Block Copolymers

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Closed-System One-Pot Block Copolymerization by Temperature-Modulated Monomer Segregation

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***Abstract:** A biphasic one-pot polymerization method enables the preparation of block copolymers from monomers with similar and competitive reactivities without the addition of external materials. AB diblock copolymers were prepared by encapsulating a frozen solution of monomer B on the bottom of a reaction vessel, while the solution polymerization of monomer A was conducted in a liquid layer above. Physical separation between the solid and liquid phases permitted only homopolymerization of monomer A until heating above the melting point of the lower phase, which released monomer B, allowing the addition of the second block to occur. The triggered release of monomer B allowed for chain extension without additional deoxygenation steps or exogenous monomer addition. A method for the closed (i.e., without addition of external reagents) one-pot synthesis of block copolymers with conventional glassware using straightforward experimental techniques has thus been developed.*

Reversible deactivation radical polymerization (RDRP) techniques have provided access to a host of previously inaccessible, well-defined macromolecular architectures. Precision block copolymer synthesis is a common and attractive goal of RDRP that has enabled the preparation of stimuli-responsive polymers (i.e., sugar-,[1,2] temperature-,[3,4] and redox-responsive[5,6] systems), the in situ preparation of nanoparticles,[7,8] and the synthesis of functional nanomaterials.[9,10] Reversible addition fragmentation chain transfer (RAFT) is a commonly employed RDRP technique owing to its amenable experimental conditions, monomer versatility, and functional-group tolerance.[11] This controlled chain-growth procedure has led to innovative strategies to ease the synthesis of complex architectures.[12,13]

Recently, Perrier and co-workers outlined the synthesis of multiblock copolymers through iterative additions of monomers with high propagation rate constants (k_p).[14–16] This innovative method allows reactive monomers to reach quantitative conversion ($>99\%$) while high chain-end retention is maintained. As the number of terminated chains is directly related to the initiator concentration and the rate of termination, chain-end retention at high monomer conversion can be achieved by reducing the radical concentration (i.e., lowering the amount of initiator). The sequential addition of fresh monomer and initiator following near-quantitative monomer conversion for each step allowed for block copolymer chain extensions without purification between blocking steps.

We reasoned that an ideal scenario might involve a closed, one-pot method in which all reaction components (RAFT agent, initiator, and co-monomers) are present prior to a single deoxygenation step, to provide a facile strategy towards well-defined block copolymers. However, such a method would require some form of physical separation between the monomers present in the reaction vessel to prevent cross-propagation and the formation of statistical copolymers. In most other reports of block copolymer synthesis by one-pot, closed-system approaches, the second monomer is physically separated from the homopolymerization of the first monomer by a break-seal approach, in which a thin layer of breakable glass serves as a temporary barrier in elaborate custom-made glass reactors.[17] After the homopolymerization of the first monomer has reached completion, the break seal is ruptured (often by the externally stimulated rapid movement of a magnetic stir bar against the fragile glass seal), and the second monomer is allowed to mix with the polymerization solution to initiate block copolymerization. While effective, this approach requires the design and construction of rather elaborate reactors that are often only usable once.

Herein, we report a biphasic block copolymerization strategy in which a layer of frozen solvent physically separates an active solution polymerization of a high-k_p monomer from a second monomer trapped in a separate frozen layer in the same reaction vessel. This approach relies on a second monomer remaining isolated and trapped in a high-melting-point solvent at the bottom of a reaction vessel, while the first monomer is polymerized to full or near-quantitative conversion above. Subsequently, the second monomer can be released into the active polymerization solution by melting both the frozen barrier and the underlying monomer solution to allow for chain extension. This approach achieves the physical separation required to prevent significant statistical copolymerization, while still using ordinary, reusable glassware. Therefore, block copolymer formation is achieved without quenching the preceding polymerization, additional deoxygenation steps, or exogenous addition of the second monomer.

The development of a one-pot, biphasic block copolymerization strategy relies on isolating an active solution polymerization of one monomer from a second monomer reservoir to create block copolymers without purification between each polymerization or the external addition of

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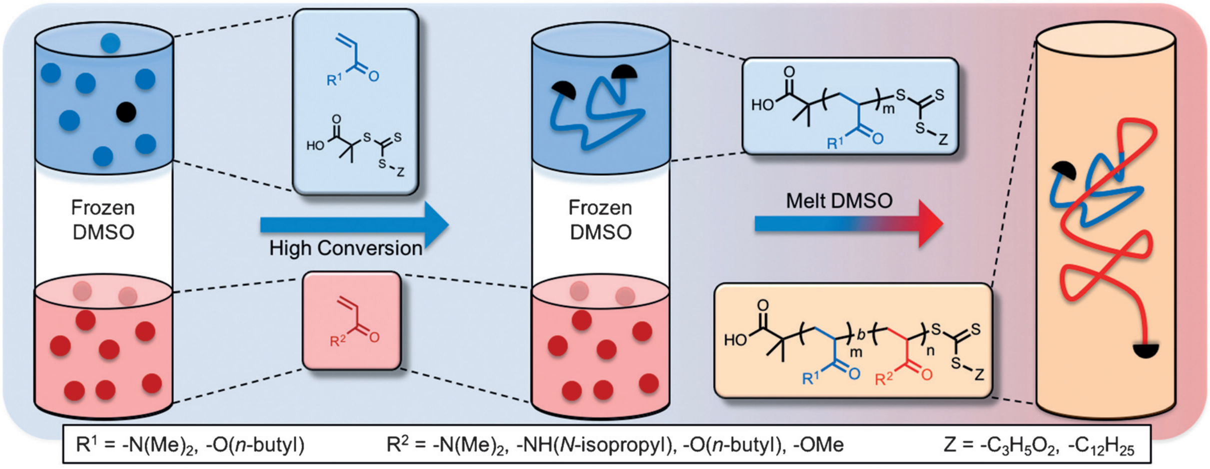
reagents. As our approach relies on the isolation of the second monomer by freezing, the solvent needs to be judiciously chosen. Specifically, it is necessary to employ two solvents that have disparate freezing points but are miscible upon heating. Moreover, the polymerization of the first monomer must have an appreciable rate at the temperatures required to keep the solvent buffer and the underlying solution of the second monomer frozen. RAFT polymerization has been shown to operate efficiently at temperatures as low as −15 °C provided that an appropriate initiator system and high-k_p monomers are employed.[18] We reasoned that carrying out a solution polymerization of the first monomer over a frozen solution of the second monomer, wherein the entire system was at a temperature between the freezing points of the two solvents, should lead to well-controlled homopolymerization of the first monomer. Subsequent melting of the underlying solution of the frozen second monomer should then lead to chain extension and block copolymer formation. For our initial studies, the first monomer was dissolved in either *N*,*N*-dimethylformamide (DMF) or water, and the second monomer was dissolved in dimethyl sulfoxide (DMSO). Furthermore, to prevent contamination of the first polymerization by dissolution of the underlying frozen solution of the second monomer, a buffer layer of pure, frozen DMSO (freezing point: 19 °C) was placed in between the two monomer phases. Without this buffer layer, we observed leaching of the second monomer and its undesirable statistical incorporation within the first block, thereby precluding precision block copolymer synthesis. Although the integrity of the resulting block copolymer relied on the frozen solvent spacer, this freezing step was rapid compared to the additional deoxygenation procedure typically required for RDRP and circumvented the need for external addition of the second monomer, which might lead to the introduction of adventitious impurities that can interfere with polymerization.

With these conditions defined, a general scheme is presented in Scheme 1. The reaction vessel is prepared and placed in the cooling apparatus (see the Supporting Information, Figure S1). The first monomer and the trithiocarbonate chain transfer agent (CTA) are dissolved in either DMF or water and exposed to redox- or photoinitiation conditions to initiate polymerization. Upon near-quantitative conversion, the polymerization vessel is warmed in a room-temperature water bath to melt the frozen DMSO/monomer layer, thereby releasing the second monomer into the active polymerization solution. The resulting homogenous solution is then heated in a water bath or irradiated with UV light for chain extension.

Our initial investigation focused on the synthesis of block copolymers of *n*-butyl acrylate (nBA) and *N*-isopropylacrylamide (NIPAM). The low temperatures required for this approach preclude the use of most thermal initiators typically employed in RAFT polymerization. However, redox-initiated RAFT polymerization has been shown to be successful under sub-ambient conditions through the use of organic reduction–oxidation pairs resulting in active radical species (e.g., potassium persulfate/sodium ascorbate[18] or cumene hydroperoxide/ascorbic acid).[19] However, these redox pairs resulted in low monomer conversion of the acrylates and acrylamides in our system. Therefore, a combination of benzoyl peroxide (BPO) and *N*,*N*-dimethylaniline (DMAn) was investigated, based on the success of this system in previous reports of room-temperature RAFT polymerization.[15,20] nBA (2.0 M), BPO, DMAn, and CTA (25:1.0:1.0:1.0) were dissolved in DMF, and the resulting solution was placed over a frozen layer of DMSO and an underlying layer of NIPAM in DMSO (1.5 M). At a temperature of 16 °C, high monomer conversion (94 % by ^{1}H NMR spectroscopy) was achieved in 24 h (Figure 1). Subsequent warming of the reaction system led to the release of NIPAM into the active polymerization solution. However, chain extension was slow (Figure 1 b), which was attributed to the depletion of the redox pair. To increase chain extension efficiency, an azo initiator was also frozen with the second monomer. The additional initiator led to more rapid chain extension, but a low-molecular-weight tail was observed by size exclusion chromatography (SEC), and the molar mass dispersity (*Đ*) increased from 1.10 to 1.35 (Figure 1 c). The inefficient chain extension was attributed to irreversible



Scheme 1. The reaction vessel is prepared such that upon full monomer conversion of the first block (blue), the frozen DMSO spacer can be melted to release a second monomer (red) for chain extension.

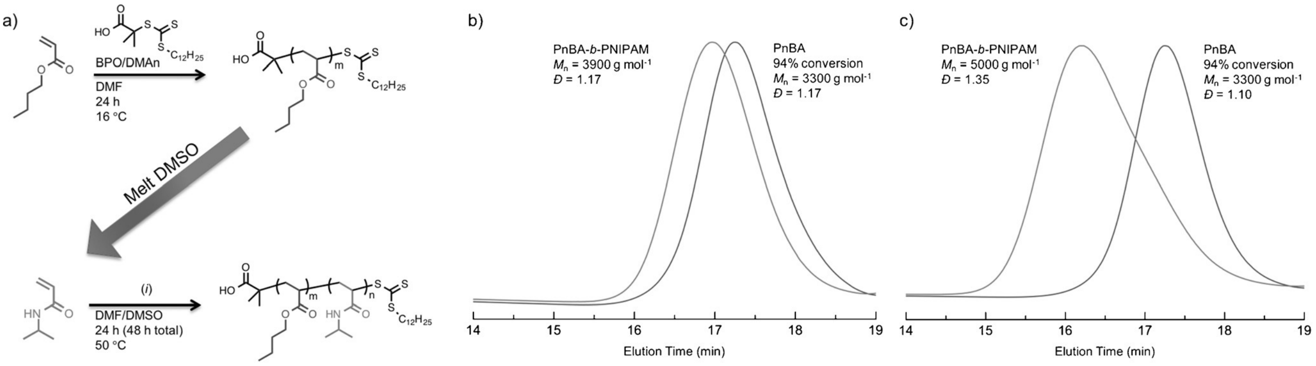


Figure 1. a) The one-pot polymerization of poly(*n*-butyl acrylate)-*b*-poly(*N*-isopropylacrylamide) required a nBA/NIPAM/CTA/BPO/DMAn ratio of 25:50:1:1:1 and achieved 94% monomer conversion (by ^{1}H NMR spectroscopy) in 24 h. i) Warming the reaction vessel released NIPAM into solution for chain extension. b) Chain extension of poly(*n*-butyl acrylate) was performed in the absence of a second initiator or c) with a CTA/V-50 initiator ratio of 1:0.01. The relatively poor blocking efficiency from PnBA to PnBA-*b*-PNIPAM suggests that an alternative initiator system is needed.

termination or CTA degradation from the high concentration of the redox pair. Although stopping at a lower conversion (80% by ^{1}H NMR spectroscopy) during polymerization of the first block afforded more uniform chain extension with the second monomer (Figure S2), the resulting block copolymers would be more accurately described as gradient-block copolymers rather than precise block copolymers. Owing to the long polymerization times and poor chain extension, a new initiator system was necessary.

Light-mediated RDRP,[21–23] specifically RAFT polymerization,[24] has shown promise for the preparation of well-defined block copolymers. Most CTAs, namely trithiocarbonates,[25–28] xanthates,[29] and dithiocarbamates,[30] can undergo photolysis of the carbon–sulfur bond under ultraviolet (UV) or near-visible irradiation (> 320 nm) to yield carbon- and sulfur-centered radicals. This process allows the polymerization to be both initiated and mediated by the CTA and can involve characteristics of RAFT and photoiniferter polymerizations.[28,31] The carbon-centered radical is responsible for initiation, whereas the sulfur-centered racial is too stable to initiate polymerization. It is primarily the photochemical energy of the light source that governs the polymerization rate (i.e., the rate of CTA end-group photolysis); therefore, high polymerization rates can be maintained at low temperatures without the need for an external initiator. This feature is advantageous in our closed one-pot system as the solid DMSO layer must not thaw during the polymerization of the first block, and high monomer conversion must be achieved on reasonable timescales. It has been shown that the intensity of the light source dictates the polymerization rate;[28] thus a high-intensity UV lamp (ca. 10 mW cm^{-2}) was employed for the preparation of the first block.

Acrylates and acrylamides both have high k_p values[11] and are capable of reaching near-quantitative conversion under mild polymerization conditions. Water-soluble *N*,*N*-dimethylacrylamide (DMA) showed a high rate of polymerization under aqueous conditions and reached full conversion (> 99% by ^{1}H NMR spectroscopy) in 3.5 h.

Table 1: Biphasic photomediated polymerizations of high-k_p acrylamide- and acrylate-based diblock copolymers.

Entry		t [h]	Conv. [%]	$M_{n,SEC}$[a] [g mol^{-1}]	$M_{n,theo}$[b] [g mol^{-1}]	$Đ$
1	PDMA	3.5	> 99	2700	2300	1.18
	PDMA-*b*-PDMA	5.0	85	11000	9000	1.09
	PDMA-*b*-PDMA	6.0	96	12900	9800	1.17
2	PDMA	3.5	> 99	3200	2300	1.20
	PDMA-*b*-PNIPAM	6.0	80	10400	10000	1.07
	PDMA-*b*-PNIPAM	8.0	> 99	12600	11700	1.06
3	PDMA	3.5	> 99	3200	2300	1.20
	PDMA-*b*-PMA	6.5	20	5500	4600	1.16
	PDMA-*b*-PMA	9.5	52	6600	6500	1.09
4	PnBA	14	94	2400[c]	2800	1.17
	PnBA-*b*-PDMA	17	57	5600	6600	1.21
	PnBA-*b*-PDMA	20	70	9600	7600	1.13
5	PnBA[d]	14	93	2800[c]	2800	1.09
	PnBA-*b*-PMA	20	42	9900	5700	1.14
	PnBA-*b*-PMA	27	65	11300	7300	1.20
6	PnBA	24	94	2800[c]	2800	1.09

[a] Absolute number average molecular weights ($M_{n,SEC}$) were determined by SEC equipped with a multi-angle light scattering detector assuming 100% mass recovery or known dn/dc, unless otherwise noted. [b] The theoretical molecular weights ($M_{n,theo}$) were determined by considering the monomer conversion from ^{1}H NMR spectroscopy. [c] The M_n values were calculated by conventional calibration with poly(methyl methacrylate) standards. [d] A photoinitiator was included during the polymerization of the first block to promote higher nBA monomer conversion. Each entry represents a biphasic one-pot polymerization.

However, the polymerization rate was slower in DMF and required 24 h to reach a similar conversion (Figure S3). Hydrogen bonding of the amide carbonyl group with water molecules has been shown to drastically increase the polymerization rate.[32]

As outlined above, upon high conversion of the first monomer, the reaction vessel was warmed to release the second monomer for chain extension. Unlike the polymerization of the preceding block, chain extension with the second monomer was achieved through irradiation with a less intense light source rather than a high-power lamp. This UV light source provided less intense irradiation (ca. 7.0 mW cm^{-2}) but afforded a uniform irradiation area suitable for the increased polymerization volume.

Acrylate- and acrylamide-based monomers provided rapid chain extension from the first PDMA block. However, the formation of an acrylamide-based diblock copolymer (e.g., PDMA-*b*-PNIPAM; Table 1, entry 2) was the most efficient. Quantitative monomer conversion of DMA in 3.5 h was followed by $>99\%$ monomer conversion of NIPAM in 4.5 h (8.0 h in total; Figure 2).

Therefore, it was possible to prepare a pristine diblock copolymer, PDMA-*b*-PNIPAM, with full conversion of each monomer in a one-pot closed system. This polymerization demonstrates chain extension devoid of monomeric impurities, with full monomer conversion of each block, and a high polymerization rate. Furthermore, chain extension with DMA to form PDMA-*b*-PDMA also afforded $>95\%$ monomer conversion in 2.5 h (6.0 h in total; Figure S4 and Table 1, entry 1). As expected, chain extension of PDMA with methyl acrylate (MA) was slower and achieved 52 % monomer conversion after 6.0 h (19.5 h in total; Figure S5 and Table 1, entry 3), but maintained a narrow molecular weight distribution ($Đ = 1.09$).

This photomediated approach was also employed to prepare a first block from an acrylate monomer. The polymerization of nBA in an upper layer of DMF reached relatively high monomer conversions (94 % by ^{1}H NMR spectroscopy) after 14 h. Both the addition of a photoinitiator, namely 2,2-dimethoxy-2-phenylacetophenone (DMPA; Figure S6 and Table 1, entry 5), and longer irradiation times (24 h; Figure S7 and Table 1, entry 6) did not result in higher monomer conversion. Furthermore, homopolymerization of another acrylate-based monomer, MA, resulted in an even lower polymerization rate (Figure S8).

Despite reaching only 94 % conversion, the PnBA macro-CTA was chain-extended by melting the frozen underlying layer of DMA or MA in DMSO, and polymerization with these high-k_p monomers resulted in good blocking efficiency. Chain extension of MA resulted in 65 % conversion in 13 h (27 h in total; Figure S7 and Table 1, entry 5). However, the formation of PnBA-*b*-PDMA was more rapid, reaching 70 % monomer conversion in 6.0 h (20 h in total; Figure 3 and Table 1, entry 4). It should be noted that the 6 % residual monomer present after the preparation of the PnBA macro-CTA inevitably resulted in its incorporation into the second block. Both monomer classes exhibit similar k_p values and tend to undergo statistical copolymerization. Therefore, the final block copolymer would contain statistical insertions of nBA within the first portion of the second PDMA or PMA block while the concentration of the second monomer is high relative to the remaining nBA. This is supported by the nBA monomer peaks present after 3.0 h of DMA chain extension.

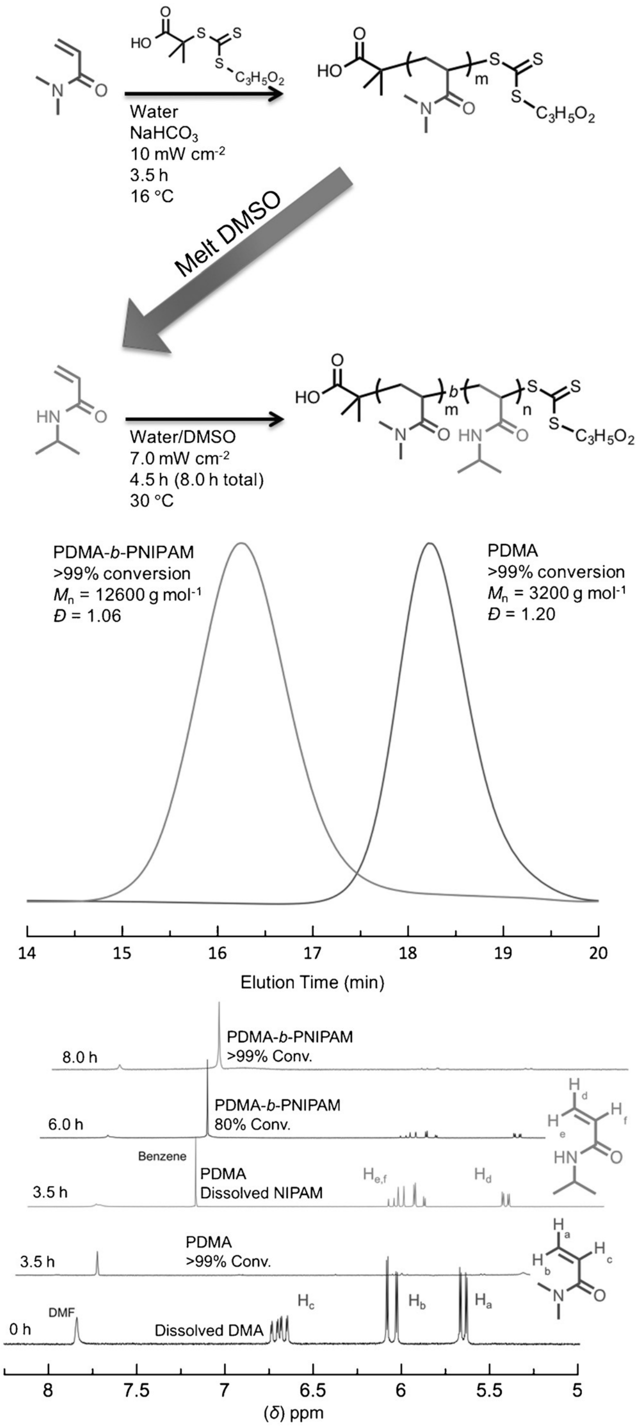


Figure 2. PDMA-*b*-PNIPAM was prepared in 8.0 h upon full monomer conversion of each block without the addition of an exogenous initiator. A clean shift in the molecular weight distribution is observed, indicative of good blocking efficacy. The ^{1}H NMR spectra highlight full monomer conversion of both DMA and NIPAM using DMF and benzene as internal standards, respectively.

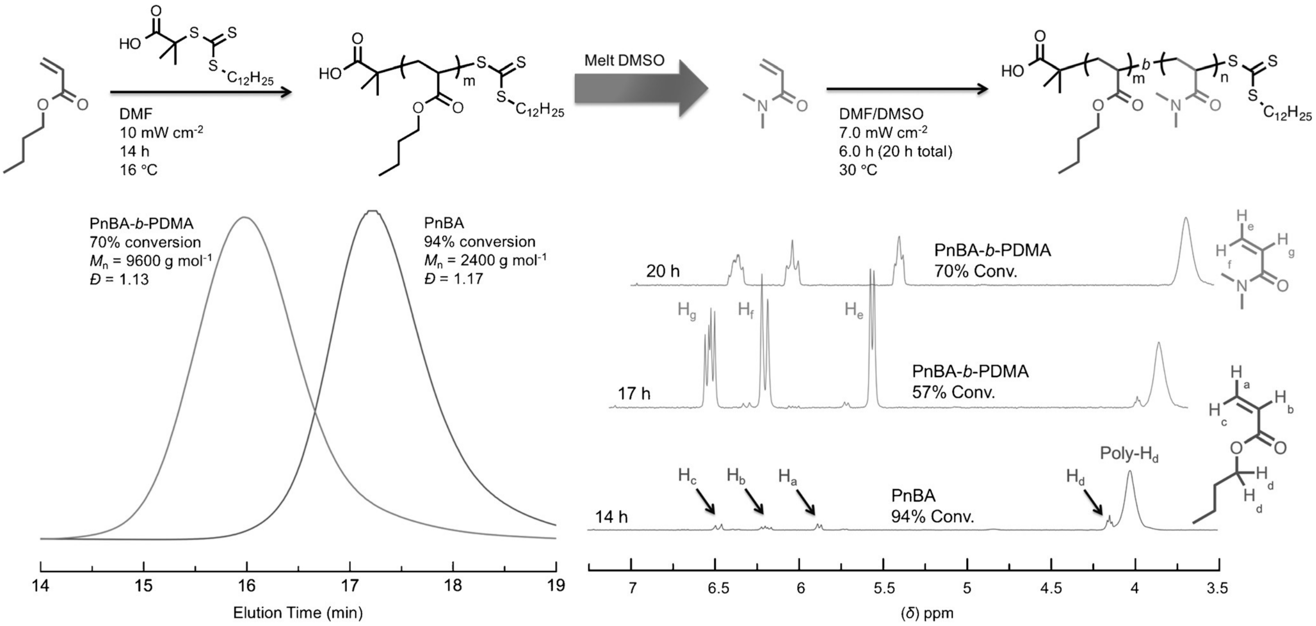


Figure 3. PnBA-*b*-PDMA was prepared in 20 h upon near quantitative conversion of nBA and subsequent chain extension of DMA. A clean shift in the molecular weight distribution is observed, indicative of good blocking efficiency. The ^{1}H NMR spectrum shows the incorporation of residual nBA monomer into the PDMA block.

Our investigation into this novel biphasic one-pot polymerization approach proved to be successful for the preparation of acrylamide- and acrylate-based diblock copolymers. This report outlines the first attempt towards block copolymer synthesis in which the incorporation of a second monomer and subsequent block copolymer formation is dictated simply by temperature-controlled phase separation. The readily controlled release of a second monomer into an active polymerization solution was achieved through the exploitation of a frozen monomer reservoir, with dissolution being triggered after near-quantitative conversion of the preceding block.

Light-initiated polymerization provided amenable reaction conditions and resulted in high livingness, corroborated by uniform chain extension upon blocking even after near-quantitative monomer conversion during the synthesis of homopolymer macro-CTAs. Importantly, this new technique is adaptable and can be manipulated to design multiblock copolymers in a one-pot process, without the addition of external materials to the polymerization vessel and without the need for exotic glassware. Furthermore, we have shown that this biphasic RAFT copolymerization strategy can be conducted without a classical photo-, redox-, or thermal initiator and therefore represents a facile approach to well-defined block copolymers. This process could also be extended to more general transformations in which the sequential addition of reaction components is required. The ability to physically separate discrete reagents in a closed-system, one-pot process transcends block copolymer synthesis and may potentially prove to be a powerful strategy towards the synthesis of other sophisticated molecules or materials.

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