

Nanoreactors to Synthesize Well-defined Polymer Nanoparticles: Decoupling Particle Size from Molecular Weight

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Considerable attention has been directed toward the synthesis of polymer nanoparticles via reversible addition–fragmentation chain transfer (RAFT) in a dispersed aqueous medium (e.g., emulsion, miniemulsion).^{1–5} The major advantages of performing polymerizations in dispersed aqueous media over bulk or solution include the following: the process is free of organic volatile compounds and environmentally friendly, cheap and can be used for a broad range of monomers, polymers can be made with high conversions, the heat transfer is highly efficient, and the resulting polymer is in a low viscosity environment and thus easy to process. Therefore, RAFT-mediated dispersion polymerization represents the ideal and cost-effective way to commercialize the technology with applications ranging from coatings with desired structure–property relations, delivery of drug-containing nanoparticles for biomedicine, colloidal crystals for diagnostic kits and nanoreactors for environmentally friendly organic reactions.⁶

Initial RAFT-mediated dispersion polymerization of styrene using highly reactive RAFT agents (e.g., cumyl dithiobenzoate) gave poor control of the molecular weight distribution (MWD) and the resulting latex was invariably unstable leading to a red layer.¹ The problem was the inefficient transportation¹ and superswelling⁷ of the RAFT agent to the growing polymer particles. Miniemulsions provided the solution to producing polymer nanoparticles with a controlled and narrow MWD, since all components were located within the stabilized droplets, but the particle size could not be controlled and usually resulting in broad distributions.^{2,8} The other drawbacks of miniemulsions were the high levels of surfactant and hexadecane, which was used to inhibit Oswald ripening.

This led researchers to alternative methods to control the MWD and particle size distribution (PSD) in RAFT-mediated emulsion polymerizations. One method, through the use of amphiphilic MacroCTA, led to stable particles with controlled PSDs but with limited control over the polydispersity index (PDI) of the MWD.^{3,4,9} However, these techniques could only dial-up the particle size through altering the MacroCTA amount. Recent work by Urbani and Monteiro, showed through the use of a thermoresponsive diblock copolymer nanoreactor with a small MacroCTA RAFT agent (Scheme 1), polymer particles were produced with excellent control over the MWD and PSD in RAFT-mediated water dispersion polymerizations.¹⁰ The size of the polymer particles with narrow PSDs could be controlled by increasing the ratio of monomer (e.g., styrene) to MacroCTA. However, this earlier work did not fully exemplify the unique feature of our nanoreactor methodology. In this work, we aim to demonstrate that our nanoreactor methodology can produce well-defined polymer

nanoparticles of any particle size (on the nanoscale), and for each size independently produce any molecular weight. Essentially, we aim to decouple the particle size from molecular weight. Achieving this would enable the production of nanoparticles with finely tuned properties to meet the growing demand for engineered nanoparticles in many applications.⁶

To achieve this goal, we used a nanoreactor that acts to control the polymerization and acts as a template to control the final particle size. A specially designed diblock copolymer (an “nanoreactor assembler”) containing a thermoresponsive block (i.e., poly(*N*-isopropylacrylamide), PNIPAM) facilitates the formation of well-defined particles, which we term “nanoreactors”, above its lower critical solution temperature (LCST ~ 36 °C)¹¹ was represented in Scheme 1.¹⁰ The other block should consist of a water-soluble component to provide the nanoreactors with stabilization against coagulation. Above the LCST, the nanoreactor assembler also provides a highly efficient method to entrap through physisorption and protect any reactive component (e.g., MacroCTA RAFT agent) or another molecule of interest covalently bound to a similar thermoresponsive polymer (or oligomer), and then release it on demand by lowering the temperature below the LCST. As demonstrated in this work, these nanoreactors can serve as templates (encapsulating a MacroCTA) to tune and control the particle size and molecular weight in radical polymerizations.⁶

We entrapped a RAFT agent bound to a PNIPAM oligomer of 18 units (i.e., MacroCTA) in the nanoreactor. This was accomplished by mixing poly(*N*-isopropylacrylamide-*b*-dimethylacrylamide) or P(DMA₆₈-*b*-NIPAM₇₃), MacroCTA, and hydrophobic monomer (styrene, STY) in water below the LCST of the NIPAM block to form a two-phase solution—the top homogeneous phase consisting of styrene and the bottom homogeneous phase consisting of water and all other components.¹⁰ Upon heating the solution above the LCST of the thermoresponsive block, the diblock self-assembled into nanoreactors while at the same time entrapping, through physisorption, the MacroCTA, and therefore the bottom phase became heterogeneous with nanoreactors dispersed in water. There was very little swelling of styrene into the nanoreactors since styrene was found to be immiscible with PNIPAM.¹² After the addition of radical initiator, the MacroCTA required the addition of only a few styrene units before the nanoreactors superswelled¹³ encapsulating nearly all styrene monomer from the top layer, resulting in the rapid and controlled polymerization.^{4,10}

We could predetermine the final particle size, first, by controlling the size of the nanoreactor and, second, the amount of styrene to be encapsulated in the nanoreactor. The amount of nanoreactor assembler in water controlled the initial size of the nanoreactors. Experiments studying the effect of the amount of nanoreactor assembler on the size of the nanoreactors is given in Figure 1. Increasing the amount of nanoreactor assembler from 0.05 to 0.2 g decreased the size from 30 to 18 nm. The molecular weight can also be controlled independent of the particle size by varying the amount of MacroCTA (see Figure 2).

To create well-defined polymer nanoparticles, the nanoparticle assembler, PNIPAM₁₈-SC(=S)SC₄H₉ (MacroCTA), styrene (STY), ammonium persulphate (APS) and water were mixed in one pot at room temperature, and then heated to 70 °C well above the LCST of the PNIPAM block to form nanoreactors. The RAFT-mediated polymerization of styrene (0.16 g) within our nanoreactors (0.2 g, size ~ 18 nm—see Figure 1) at 70 °C (experiment 1, Table 1) formed well-defined polymer reaching

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greater than 99% conversion rapidly in only 40 min with predictable molecular weight and narrow distribution ($M_n = 61\,300$ and $PDI = 1.20$ as determined by UV detection at 262 nm). UV-SEC analysis detected only polystyrene and thus provided an accurate measure of the resulting molecular weight distribution. The number-average molecular weight (M_n) increased linearly with conversion (x) and was close to theory (See Supporting Information), suggesting that nearly all nanoreactors were nucleated. The dispersion after cooling to room temperature gave a particle diameter of 38 nm with a relatively narrow particle size distribution of 0.13 and an N_c of 1.03×10^{18} particles/L at the end

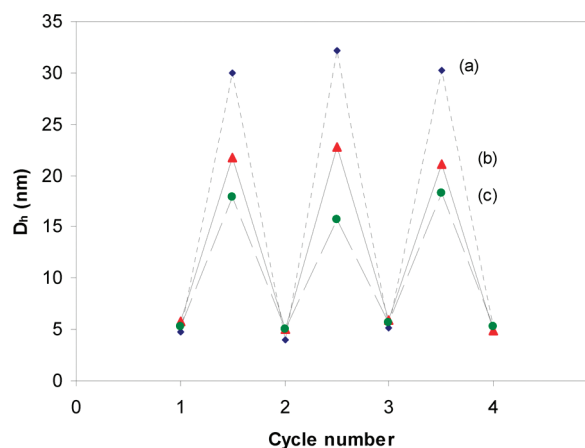


Figure 1. Particle size of nanoparticle assembler, P(DMA₆₈-*b*-NIPAM₇₃), in water (5 g) at 25 and 70 °C determined by dynamic light scattering. Key to curves: (a) 0.05 g of nanoparticle assembler, (b) 0.1 g of nanoparticle assembler, and (c) 0.2 g of nanoparticle assembler. The solution was equilibrated for 5 min at each temperature prior to measurements.

of the polymerization. Increasing the MacroCTA (experiments 2–4, Table 1) resulted in a concomitant decrease in M_n at full conversion, while maintaining low molecular weight PDIs and more importantly a similar particle size of ~40 nm (with low particle size PDIs) and N_c .

Decreasing the amount of nanoreactor assembler from 0.2 to 0.1 g resulted in an increase in the nanoreactor size from 18 to 22 nm (Figure 1). This should therefore produce larger but fewer particles. Polymerization within these nanoreactors at increasing MacroCTA (experiments 5–8, Table 1) produced monodisperse nanoparticles of approximately 50 nm (with low particle size

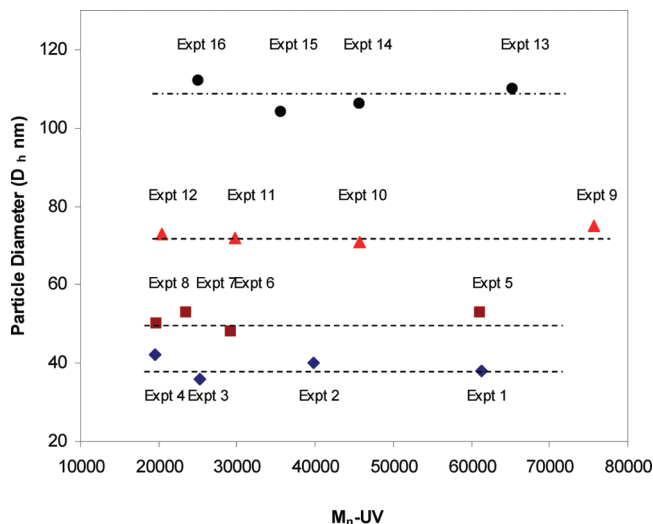


Figure 2. Nanoparticle templates used to obtain the desired polymer molecular weight and resulting nanoparticle size at full conversion (see Table 1 for details).

Scheme 1. Designer Thermoresponsive Nanoreactors for the Template “Living” Radical Polymerization of Styrene To Obtain Monodisperse Nanoparticles with Independent Control over Particle Size and Molecular Weight

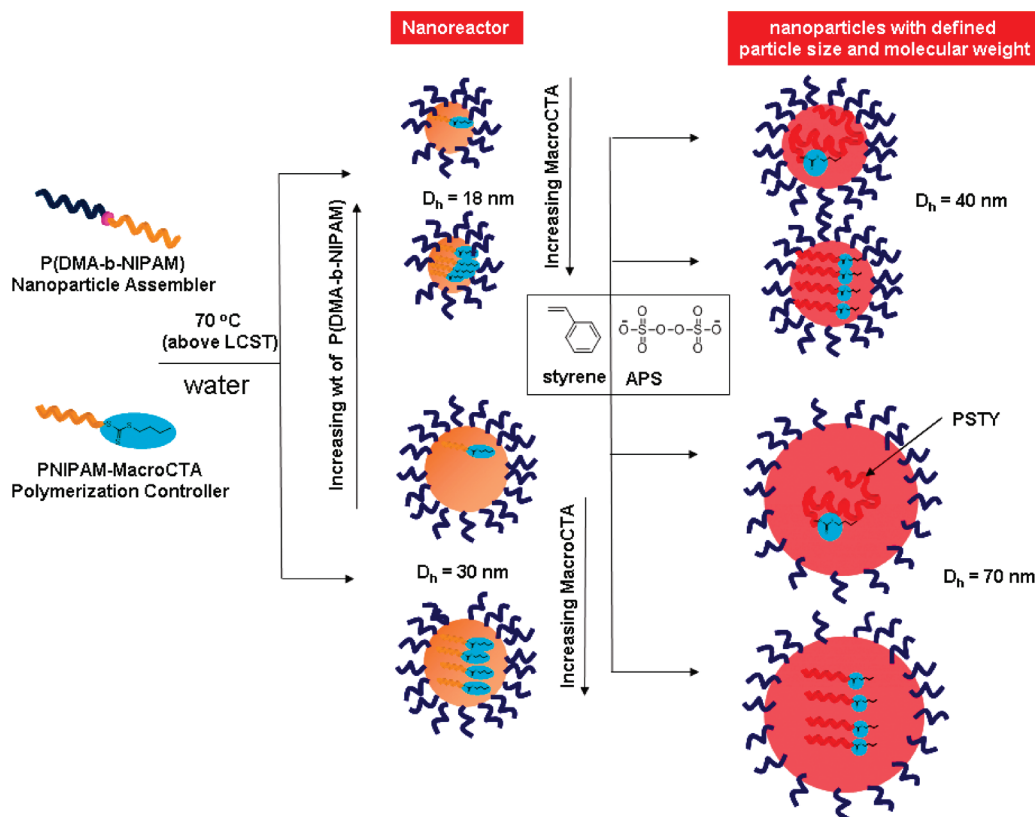


Table 1. Kinetic Data for the RAFT-Mediated Polymerization of STY (0.16 g) in the Presence of MacroCTA, PNIPAM₁₈-SC(=S)SC₄H₉, and Nanoparticle Assembler, P(DMA₆₈-*b*-NIPAM₇₃)^a

expt	STY and diblock ^b (g)	CTA ^c (g)	time (min)	convn (x)	M_n UV ^d	MWD (PDI)	M_n Theory	D_h (nm) (PDI) ^e	N_c (no. of particles/L)
1	diblock = 0.2; STY = 0.16	0.005	40	0.99	61 300	1.20	66 000	38 (0.13)	1.03×10^{18}
2		0.010	40	0.99	39 700	1.20	34 000	40 (0.09)	8.87×10^{17}
3		0.015	30	0.99	25 200	1.20	23 300	36 (0.10)	1.22×10^{18}
4		0.020	60	0.99	19 400	1.18	18 000	42 (0.12)	7.66×10^{17}
5	diblock = 0.1; STY = 0.16	0.005	30	0.99	61 200	1.20	66 000	53 (0.18)	3.81×10^{17}
6		0.010	60	0.94	29 300	1.17	32 080	48 (0.08)	5.13×10^{17}
7		0.015	40	0.99	23 500	1.15	23 300	53 (0.07)	3.81×10^{17}
8		0.020	60	0.99	19 800	1.15	18 000	50 (0.07)	4.54×10^{17}
9	diblock = 0.05; STY = 0.16	0.005	90	0.99	75 700	1.16	66 000	75 (0.07)	1.35×10^{17}
10		0.010	120	0.99	45 600	1.15	34 000	71 (0.04)	1.59×10^{17}
11		0.015	75	0.99	29 700	1.13	23 300	72 (0.03)	1.52×10^{17}
12		0.020	90	0.99	20 400	1.11	18 000	73 (0.05)	1.46×10^{17}
13	diblock = 0.1; STY = 0.77	0.020	21 h	0.81	65 200	1.20	64 400	110 (0.03)	1.84×10^{17}
14		0.030	120	0.83	45 700	1.15	45 100	106 (0.02)	2.05×10^{17}
15		0.040	120	0.85	35 700	1.11	34 700	103 (0.02)	2.17×10^{17}
16		0.060	120	0.84	25 000	1.10	23 600	101 (0.06)	1.74×10^{17}

^aThe reaction was initiated with ammonium persulfate (APS) (0.87 mg) in Milli Q water (5 g) at 70 °C. ^bDiblock = P(DMA₆₈-*b*-NIPAM₇₃) nanoparticle assembler. ^cCTA = PNIPAM₁₈-SC(=S)SC₄H₉, MacroCTA. ^d M_n and PDI determined from SEC using the UV detector at 262 nm. ^ePolydispersity index (PDI) for the particle size distribution calculated from the standard deviation of the hypothetical Gaussian distribution (i.e., $PDI = \sigma^2/Z_D^2$, where σ is the standard deviation and Z_D is the Z average mean size).

PDI's close to 0.07, and N_c 's of approximately 4×10^{17} particles/L and with excellent control over the molecular weight distributions (M_n 's were close to theory and with low molecular weight PDI's < 1.2). Decreasing the amount of nanoparticle assembler to 0.05 g (nanoparticle size of approximately 30 nm – Figure 1) after polymerization gave a narrow nanoparticles size distribution centered close to 70 nm ($N_c \sim 1.5 \times 10^{17}$ particles/L) and again excellent control over the molecular weight distribution (experiments 9–12, Table 1). In order to obtain larger particles with similar control over the molecular weights, we used a greater amount of styrene in the presence of 0.1 g of nanoparticle assembler to give nanoparticles of approximately 105 nm with narrow particle size and molecular weight distributions (experiments 13–16, Table 1).

In summary, we showed by heating a nanoparticle assembler above its LCST, stabilized nanoparticles formed that acted as a template for the RAFT-mediated polymerization of styrene. This novel process allowed the production of monodisperse nanoparticles of desired size (20–110 nm) containing monodisperse polymer of desired molecular weight (20–80K), in which the size and molecular weight were independently controlled. This work demonstrates the potential to produce monodisperse polymer nanoparticles with virtually any size on the nanoscale and with any molecular weight, and holds promise for well-defined nanoparticles in many applications.

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Supporting Information Available: Text giving details of the synthesis of polymers and polymer nanoparticles, figures showing MALDI–TOF and ¹H NMR spectra, tables of kinetic data, and figures giving absolute molecular weight size exclusion chromatograms, plots of kinetic data and particle sizes and

particle size distributions, and TEM pictures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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