WARWICK
THE UNIVERSITY OF WARWICK

Original citation:
Lotierzo, Andrea, Schofield, Ryan M. and Bon, Stefan A. F.. (2017) Toward sulfur-free RAFT polymerization induced self-assembly. ACS Macro Letters . pp. 1438-1443.

Permanent WRAP URL:
http://wrap.warwick.ac.uk/96172

Copyright and reuse:
The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions. Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:
"This document is the Accepted Manuscript version of a Published Work that appeared in final form in ACS Macro Letters copyright © American Chemical Society after peer review and technical editing by the publisher.
To access the final edited and published work
http://pubs.acs.org/page/policy/articlesonrequest/index.html ."

A note on versions:
The version presented here may differ from the published version or, version of record, if you wish to cite this item you are advised to consult the publisher's version. Please see the 'permanent WRAP URL above for details on accessing the published version and note that access may require a subscription.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk

warwick.ac.uk/lib-publications

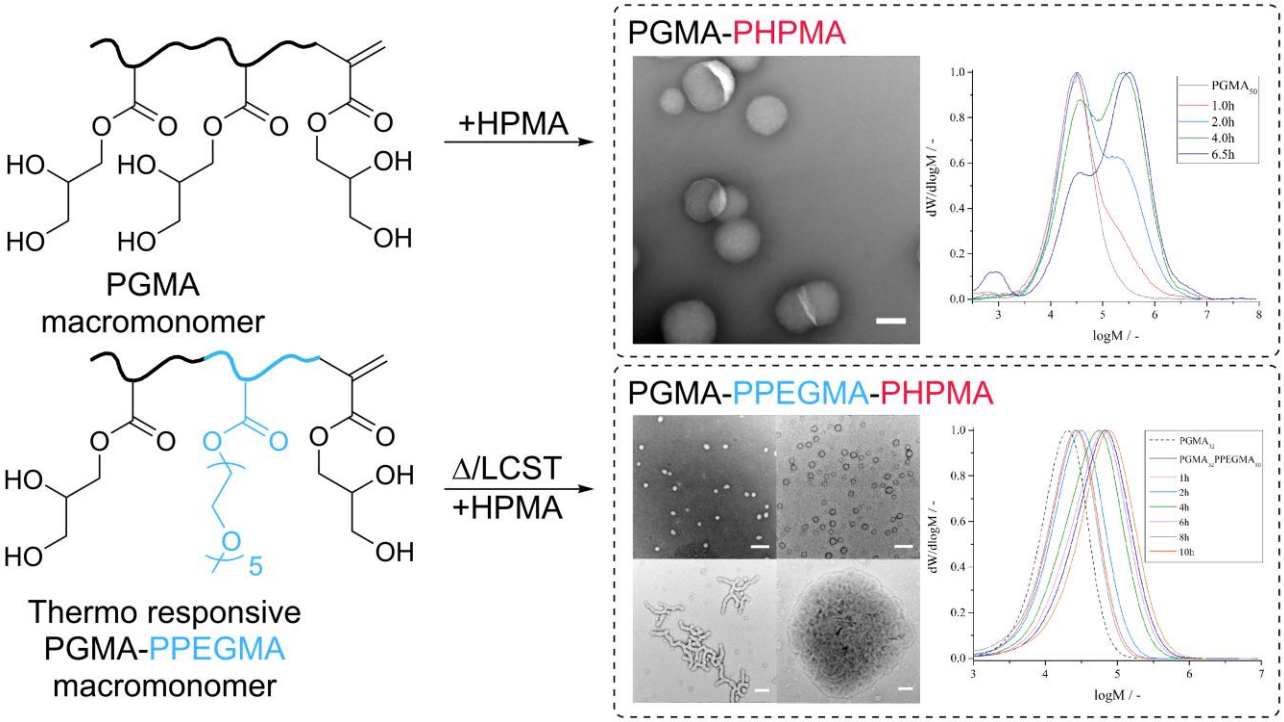
Toward Sulfur free RAFT Polymerization Induced Self-assembly

Andrea Lotierzo, Ryan M. Schofield, Stefan A. F. Bon*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, U.K.
www.bonlab.info

ACS Macro Lett. 2017, 6, 1438–1443

DOI: 10.1021/acsmacrolett.7b00857



Toward Sulfur-Free RAFT Polymerization Induced Self-Assembly

Andrea Lotierzo, Ryan M. Schofield, Stefan A. F. Bon*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, U.K.

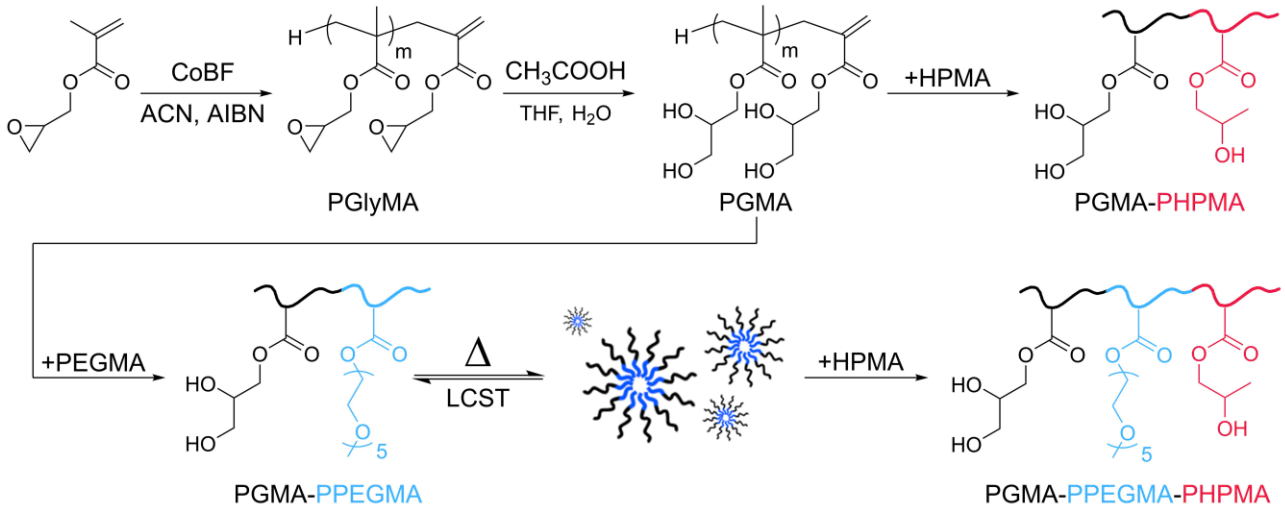
ABSTRACT: Polymerization induced self-assembly (PISA) using methacrylate-based macromonomers as RAFT agents is an unexplored, attractive route to make self-assembled colloidal objects. The use of this class of RAFT-agents in heterogeneous polymerizations is however not trivial, because of their inherent low reactivity. In this work we demonstrate that two obstacles need to be overcome, one being control of chain-growth (propagation), the other monomer partitioning. Batch dispersion polymerizations of hydroxypropyl methacrylate in presence of poly(glycerol methacrylate) macromonomers in water showed limited control of chain-growth. Semi-continuous experiments whereby monomer was fed improved results only to some extent. Control of propagation is essential for PISA to allow for dynamic rearrangement of colloidal structures. We tackled the problem of monomer partitioning (caused by uncontrolled particle nucleation) by starting the polymerization with an amphiphilic thermoresponsive diblock copolymer, already "phase-separated" from solution. TEM analysis showed that PISA was successful and that different particle morphologies were obtained throughout the polymerization.

Control of macromolecular chain architecture using radical polymerizations has undergone a step-change from the development of "reversible-deactivation radical polymerization" (RDRP).[1–3] Accessible routes towards synthesis of amphiphilic polymers has catalyzed scientific studies into the self-assembly behavior of such polymers in liquids. Control over the dynamics of the self-assembly process and the resulting morphologies of the polymeric colloidal objects has been of considerable interest.[4–6] Polymerization induced self-assembly (PISA) is an emerging area that couples control of chain-growth and thus molecular architecture with dynamic self-assembly of the produced macromolecules into colloidal structures. [7–14] PISA is a heterogeneous polymerization technique, typically performed under dispersion or emulsion polymerization conditions. When this is done a lyophilic polymer is chain-extended in a suitable solvent where the second block gradually becomes insoluble. This drives the assembly of the copolymer chains into colloidal objects, which can be seen as a particle nucleation event. One of the key aspects of PISA is that the formed colloidal objects can dynamically rearrange into different morphologies (e.g., spheres, worms and vesicles) throughout the polymerization process.[12,13] These dynamics can be further exploited when thermo-responsive polymers which exhibit a volume-phase transition, for example lower critical solution temperature (LCST) behavior, are used.[15–19] This allows for temperature-induced morphological transitions, decoupled from the polymerization process.

PISA has been mostly carried out using reversible addition-fragmentation chain transfer (RAFT) polymerization in a variety of different solvents,[9,20–24] using organo-sulfur based RAFT agents and a wealth of monomers.[11] Other RDRP methods such as nitroxide-mediated radical polymerization (NMP),[12,25] atom transfer radical polymerization (ATRP),[26,27] single electron transfer living radical polymerization (SET-LRP)[28] and organotellurium-mediated living radical polymerization (TERP)[29] have also been applied to PISA. These approaches can overcome the inherent limitations of RAFT polymerizations that use organo-sulfur compounds (i.e. yellow color and sulfur odor).

RAFT polymerization using sulfur-based chemistry was developed on the back of the discovery that methacrylate-based macromonomers could undergo the degenerative RAFT mechanism. Moad and coworkers demonstrated that "living" radical polymerizations using these macromonomers as RAFT agents was possible, facilitated by monomer starve-fed emulsion polymerization conditions (Scheme S1).[30] The slow feed of monomer was the key to achieve control of chain growth. Recently, Haddleton *et al*. showed that multi-block methacrylic copolymers could be made using the same seeded starved emulsion polymerizations.[32] Zetterlund and co-workers attempted to replace the conventional sulfur-containing RAFT agents with the macromonomers in batch dispersion PISA.[33] The latter, despite resulting in both limited conversion and lack in control of chain-growth, indicated a potential pathway to PISA by sulfur-free RAFT.

In this work we provide an understanding of the reaction conditions necessary to attain control of the PISA process using methacrylate-based macromonomers as RAFT agents. This was be done by exploring the chain-extension of poly(glycerol methacrylate) (PGMA) and thermoresponsive poly(glycerol methacrylate)-block-poly(poly(ethylene glycol) methyl ether methacrylate) (PGMA-PPEGMA) macromonomers in water with hydroxypropyl methacrylate (HPMA). We show that in



Scheme 1. Synthetic pathway for the synthesis of poly(glycerol methacrylate) (PGMA) macromonomers and poly(glycerol methacrylate)-block-poly(poly(ethylene glycol) methyl ether methacrylate) (PGMA-PPEGMA) and their subsequent chain-extension with HPMA in aqueous PISA.

order to achieve control of chain-growth nucleation needs to be decoupled from the polymerization process and, as already shown by previous literature,[30,32] seeded starve-fed conditions are required. To the best of our knowledge, the dynamic rearrangement of the colloidal structures obtained under such polymerization conditions is novel, hereby demonstrating that PISA with methacrylate macromonomers is feasible.

Firstly, we will describe the macromonomer synthesis, then the optimized PISA process, after which we will discuss the mechanistic aspects on why the chosen reaction conditions are required.

Water soluble PGMA macromonomers were obtained from the hydrolysis of glycidyl methacrylate macromonomers (PGlyMA) synthetized by means of catalytic chain-transfer polymerization (CCTP) (Scheme 1). CCTP is based on the use of certain low-spin Co(II) complexes as efficient chain transfer agents in the polymerization of methacrylates (Scheme S2).[30,34,35] The advantages are the high chain transfer constant (C_T) values (~40 K using bis[(difluoroboryl) dimethylglyoximato]cobalt(II) (CoBF) for the CCTP of methyl methacrylate in bulk)[36] and that the catalyst is not consumed during the reaction, leading to little metal contamination in the final product. In this work different amounts of catalyst, CoBF, were adopted in the solution polymerization of glycidyl methacrylate in acetonitrile in order to fabricate macromonomers with varied number average degree of polymerization (*DP*) (Table S1). Polymers with dispersities ($Đ_M$) of about 2 were obtained for [CoBF]/[GMA] < 4.61×10^{-6}, which were in in a similar range of what previously reported ($Đ_M$ ~ 1.7/1.8).[37]

Thermoresponsive $PGMA_{32}PPEGMA_{10}$ macromonomers were prepared by chain-extension of a $PGMA_{32}$ macromonomer in water with a second hydrophilic monomer, PEGMA 300, which exhibits a lower critical solution temperature (LCST) behavior in water.[38] The chain-extension was conducted under solution polymerization conditions in water by feeding the monomer (Scheme 1). GPC analysis showed an upward shift in the molecular weight distribution with control of chain-growth (Figure 1).

Table 1. Experimental conditions for the chain-extension of PGMA and PGMA-PPEGMA macromonomers with HPMA in aqueous PISA.

Run	$PGMA_{DP}$	$PPEGMA_{DP}$	F [a]/h^{-1}	Initiator	T /°C
1	32	10	9.3	Fed[b]	80
2	50	/	Batch	Batch	70
3	50	/	25.0	Batch	70
4	27	/	15.3	Batch	70
5	32	/	9.3	Fed[b]	80

[a]Feed rate = $mol_{HPMA}*mol_{macromonomer}^{-1}*h^{-1}$. [b]10% of initiator present from the start. See supporting material for additional experimental details (Table S1).

In order to carry out PISA, this thermoresponsive diblock macromonomer, i.e. PGMA32PPEGMA10, was added to water and heated to 80 °C, above its LCST (Figure S2). This resulted in the formation of a colloidal dispersion, which was used as a seed. HPMA monomer was fed to chain-extend (run 1, Table 1). Essentially the reaction was operated under starved seeded emulsion/dispersion polymerization conditions similar to those originally reported by Moad *et al.*[30] and recently by Haddleton and coworkers.[32] Instead in this work, colloidal particles which were the result of the self-assembly of the thermoresponsive macromonomers were adopted instead of latex particles made of macromonomer chains. Control of chain-growth as function of monomer conversion was accomplished (Figure 1, Figure S3). We did, however, ob-

serve a small increase in dispersity ($Đ_M$) from about 2 to around 2.5 (Table S2).

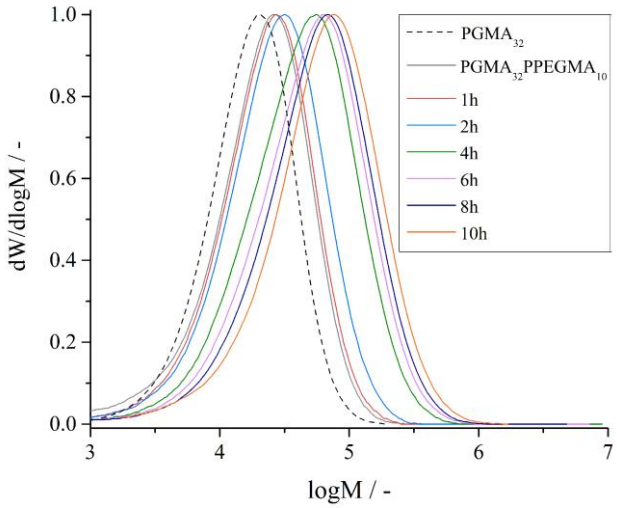


Figure 1. Evolution of the molecular weight distribution during the chain-extension of $PGMA_{32}PPEGMA_{10}$ with HPMA (run 1, Table 1).

DLS measurements indicated the formation of narrowly dispersed 40 nm particles after 2h which grew in size up to 6 h, after which the dispersity broadened and larger colloidal structures appeared (Figure S4). Negative stain transmission electron microscopy (TEM) analysis showed that indeed sphere-like objects were formed after 2h (Figure 2a). This morphology dynamically changed into branched wormlike structures as observed after 8 h (Figure 2c). Note that the overall viscosity of the system markedly increased at this stage. Finally, after 10 h (with a noticeable drop in viscosity of the dispersion) the system rearranged again away from worm-like structures into larger spherical aggregates. To date we still do not know if these objects have a full or hollow core (i.e. vesicles). As a final observation, the colloidal morphologies appear to be less defined than the ones formed in sulfur-RAFT mediated PISA. This could be potentially related to the higher dispersity of the block copolymers made in this work, >2, but this aspect is still under investigation.

Our approach to use a thermo-responsive macromonomer to generate a colloidal seed as the starting point for the PISA process was successful, as demonstrated above. Conventional organo-sulfur RAFT PISA is however usually carried out in batch conditions, with all the monomer present from the start, and employing a lyophilic macro-RAFT agent. For this reason, we tried to simplify our system to match the standard PISA conditions.

A $PGMA_{50}$ macromonomer was used as water-soluble macro-RAFT agent and chain-extended with HPMA in batch aqueous dispersion polymerization (Scheme 1; run 2, Table 1). Note that PGMA-PHPMA block copolymers have been widely studied in aqueous dispersion PISA using benzodithioate transfer agents, showing effective chain-extension and access to higher order morphologies.[13,39,40] In our case, polymerizations using these batch conditions resulted in low monomer conversion, no observable chain-extension (Figure S5A), and a lot of coagulation along with the formation of a milky white suspension. This result was not unexpected though. Methacrylate macromonomers have a much lower reported chain-transfer coefficient in comparison to the widely adopted dithioesters or trithiocarbonates macro-RAFT agents (typically C_T is at least 10 for well controlled RAFT processes).[41] C_T for a ω-unsaturated methacrylate macromonomer (DP ≈ 24) has been previously estimated to be ~ 0.21 in methyl methacrylate polymerization.[31] As a measure for control of chain growth one can use the kinetic chain length, ν (Equation 1).[42] Note that for ideal "living" conditions ν should have a value ≤ 1, this to allow for control of monomer sequence. The comparatively low C_T values for methacrylate-based macromonomers cause the downfall of a batch PISA process. When using sulfur-based RAFT agents higher monomer concentrations are tolerated.

$$\nu \approx \frac{k_p[M]}{2k_t[R^\bullet]+k_{tr}[MM]} \approx \frac{k_p[M]}{k_{tr}[MM]} \approx \frac{1}{C_T}\frac{[M]}{[MM]} \quad (1)$$

where k_p, k_t and k_{tr} are respectively the propagation, termination and transfer-to-macromonomer rate coefficients, [M], [MM] and [R•] are respectively the monomer, macromonomer and radical concentrations.

For this reason, PISA was re-attempted by feeding the monomer at a slow rate (F = 25.0 h^{-1}) over 6 hours, meeting the required condition of having low overall monomer concentration (run 3, Table 1). Figure 3 shows the molecular weight distributions at different stages of the polymerization. Unexpectedly, the results show that the molecular weight of the forming diblock polymer did not grow linearly with conversion but rather experienced a "jump" in molecular weight which did not appear to increase significantly over the reaction timescale. This means that values of ν must be considerably > 1. Strikingly, the jumping in molecular weight was similar to what was recently shown by Zetterlund *et al*, where batch conditions were adopted (like in run 2, Table 1) resulting in high ν and hence favoring high monomer insertions at the macromonomer ω-end.[33] In our case, similar results were obtained even by applying semi-batch conditions. The experiment was then repeated, lowering the feeding rate to F = 15.3 h^{-1} and using a macromonomer with lower *DP*, $PGMA_{27}$, therefore increasing [MM] (run 4, Table 1). Again, analogous results were obtained, suggesting limited control on chain-growth (Figure S5B). The apparent bimodality of the molar mass distributions is easily explained as the macromonomer has a low reactivity as evident from the low value of C_T. As a result, the timescales of full monomer conversion and complete macromonomer incorporation are out of sync, as d[M]/d[MM] = ν.

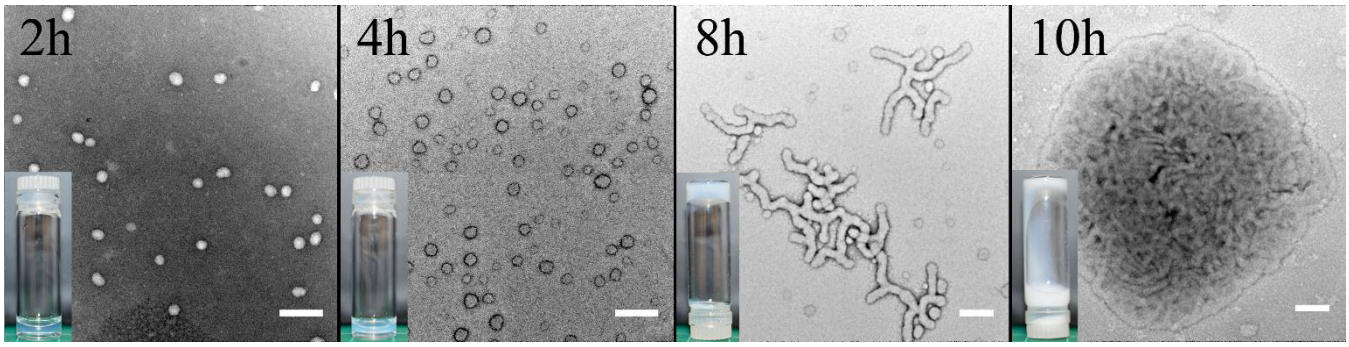


Figure 2. Negative stain TEM pictures of samples taken at 2, 4, 8 and 10 h during the HPMA chain-extension of a $PGMA_{32}PPEGMA_{10}$ macromonomer in water (Run 5, Table 1); scale bars: 200 nm. Inset: pictures of the samples appearance before 50-fold dilution for TEM analysis.

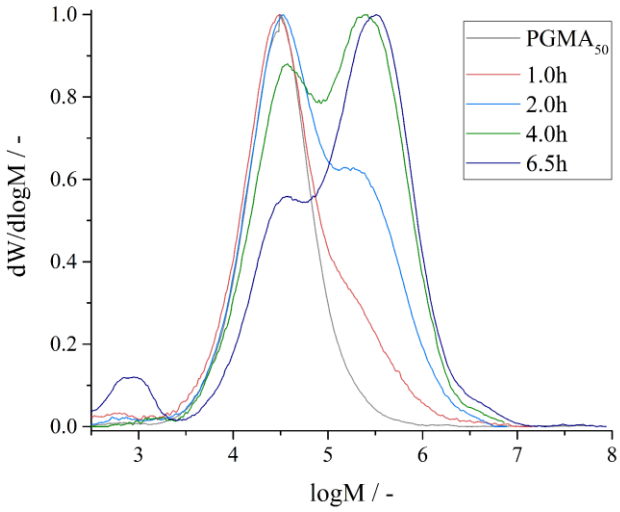


Figure 3. Evolution of the molecular weight distribution during the chain-extension of a $PGMA_{50}$ macromonomer with HPMA in aqueous dispersion polymerization (run 3, Table 1).

Dynamic light scattering (DLS) measurements showed that in these experiments large colloidal objects ($d_Z \approx 140$-250 nm) were formed after 30 minutes (Figure S6), indicating a conventional particle nucleation process as a direct result of loss of control in chain-growth. These results were again in contrast to what is reported for the aqueous chain-extension of a sulfur-based $PGMA_{47}$ macro-RAFT agent.[39] In fact, in the latter case, micellar nucleation occurred with the formation of $PGMA_{47}PHPMA_{90}$ in correspondence with the observation of 20 nm colloidal objects.

Our DLS and GPC data essentially suggested that in runs 2-4 (Table 1) the chain-extensions were not "living"; multiple insertions of HPMA occurred at the macro-CTA ω-end after every macromonomer activation, hence leading to a jump in molecular weight. The observations clearly stated that values of $\nu >> 1$ did not fit with the low overall concentration of monomer throughout polymerization. We believe that every time a radical-activated macromonomer species is formed (Scheme S1), the extent of the addition of HPMA is such that the resulting diblock copolymer is surface active. This results in the formation of new particles. Once this happens, HPMA from the water phase will diffuse and swell these particles, increasing the monomer concentration locally at point of polymerization. The observed high values for the kinetic chain length and thus loss of control of chain growth are hence explained. Note that this experimentally will be amplified in case of inhibition/retardation phenomena at the start of the polymerization process (for example due to presence of inhibitor). Monomer accumulation can however be minimized. This was done by reducing the feed rate of monomer further and increasing the reaction temperature to 80°C (run 5, Table 1; same reaction conditions as run 1). This indeed showed some improvements (Figure S7). Nevertheless, a "jump" of molecular weight was still visible so that large colloidal objects at the beginning of the reaction were still formed (Figures S6 and S8).

The results from all of these experiments show that there is a fine balancing act in experimental conditions needed to alleviate the effects of the local monomer concentration influenced by monomer feed rate and partitioning events. The system is further complicated by difficultiesin controlling particle nucleation. This essentially infers that PISA with control of propagation starting from a solution of macromonomers may not be possible. However, when operating in seeded polymerization conditions, this particle nucleation event leading to loss of control of chain growth is skipped.

In summary, we have shown the successful application of methacrylate-based macromonomers as RAFT agents in polymerization induced self-assembly (PISA). Seeded emulsion polymerization conditions, in this work the seed being self-assembled amphiphilic macromonomers, demonstrate both control of chain-growth and dynamic transformations of the block copolymer colloidal structures. Our results show that PISA is practically not successful starting from a macromonomer solution. In the latter, particle nucleation and the associated monomer partitioning obstruct the PISA process. We believe that our results open up routes to the production of waterborne polymer dispersions of intricate particle morpholo-

gy, with the big advantage that conventional organo-sulfur based RAFT agents can be omitted.

ASSOCIATED CONTENT

Supporting Information. Materials and methods. Reaction schemes for the macromonomer synthesis and its chain extension *via* RDRP polymerization. ^{1}H-NMR traces of the PGMA and PGlyMA macromonomers. Additional GPC traces and DLS data for HPMA chain-extensions. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* s.bon@warwick.ac.uk. Web: www.bonlab.info

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Dulux Australia is acknowledged for financial funding (AL). The authors would also like to thank Dr. Saskia Bakker and the University of Warwick Advanced BioImaging Research Technology Platform for the help with TEM analysis and staining procedures.

REFERENCES

(1) Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. Rapid and Quantitative One-Pot Synthesis of Sequence-Controlled Polymers by Radical Polymerization. *Nat. Commun.* **2013**, *4*, 1–9.

(2) Braunecker, W. A.; Matyjaszewski, K. Controlled/living Radical Polymerization: Features, Developments, and Perspectives. *Prog. Polym. Sci.* **2007**, *32* (1), 93–146.

(3) Jenkins, A. D.; Jones, R. G.; Moad, G. Terminology for Reversible-Deactivation Radical Polymerization Previously Called "controlled" radical Or "living" radical Polymerization (IUPAC Recommendations 2010). *Pure Appl. Chem.* **2009**, *82* (2), na.

(4) Mai, Y.; Eisenberg, A. Self-Assembly of Block Copolymers. *Chem. Soc. Rev.* **2012**, *41* (18), 5969.

(5) Discher, D. E. Polymer Vesicles. *Science (80-.).* **2002**, *297* (5583), 967–973.

(6) Srinivas, G.; Discher, D. E.; Klein, M. L. Self-Assembly and Properties of Diblock Copolymers by Coarse-Grain Molecular Dynamics. *Nat. Mater.* **2004**, *3* (9), 638–644.

(7) Delaittre, G.; Nicolas, J.; Lefay, C.; Save, M.; Charleux, B. Surfactant-Free Synthesis of Amphiphilic Diblock Copolymer Nanoparticles via Nitroxide-Mediated Emulsion Polymerization. *Chem. Commun.* **2005**, *1* (5), 614.

(8) Ferguson, C. J.; Hughes, R. J.; Nguyen, D.; Pham, B. T. T.; Gilbert, R. G.; Serelis, A. K.; Such, C. H.; Hawkett, B. S. Ab Initio Emulsion Polymerization by RAFT-Controlled Self-Assembly. *Macromolecules* **2005**, *38* (6), 2191–2204.

(9) Boissé, S.; Rieger, J.; Belal, K.; Di-Cicco, A.; Beaunier, P.; Li, M.-H.; Charleux, B. Amphiphilic Block Copolymer Nano-Fibers via RAFT-Mediated Polymerization in Aqueous Dispersed System. *Chem. Commun.* **2010**, *46* (11), 1950.

(10) Warren, N. J.; Mykhaylyk, O. O.; Mahmood, D.; Ryan, A. J.; Armes, S. P. RAFT Aqueous Dispersion Polymerization Yields Poly(ethylene Glycol)-Based Diblock Copolymer Nano-Objects with Predictable Single Phase Morphologies. *J. Am. Chem. Soc.* **2014**, *136* (3), 1023–1033.

(11) Canning, S. L.; Smith, G. N.; Armes, S. P. A Critical Appraisal of RAFT-Mediated Polymerization-Induced Self-Assembly. *Macromolecules* **2016**, *49* (6), 1985–2001.

(12) Groison, E.; Brusseau, S.; D'Agosto, F.; Magnet, S.; Inoubli, R.; Couvreur, L.; Charleux, B. Well-Defined Amphiphilic Block Copolymer Nanoobjects via Nitroxide-Mediated Emulsion Polymerization. *ACS Macro Lett.* **2012**, *1* (1), 47–51.

(13) Blanazs, A.; Ryan, A. J.; Armes, S. P. Predictive Phase Diagrams for RAFT Aqueous Dispersion Polymerization: Effect of Block Copolymer Composition, Molecular Weight, and Copolymer Concentration. *Macromolecules* **2012**, *45* (12), 5099–5107.

(14) Charleux, B.; Delaittre, G.; Rieger, J.; D'Agosto, F. Polymerization-Induced Self-Assembly: From Soluble Macromolecules to Block Copolymer Nano-Objects in One Step. *Macromolecules* **2012**, *45* (17), 6753–6765.

(15) Jia, Z.; Bobrin, V. A.; Truong, N. P.; Gillard, M.; Monteiro, M. J. Multifunctional Nanoworms and Nanorods through a One-Step Aqueous Dispersion Polymerization. *J. Am. Chem. Soc.* **2014**, *136* (16), 5824–5827.

(16) Kessel, S.; Urbani, C. N.; Monteiro, M. J. Mechanically Driven Reorganization of Thermoresponsive Diblock Copolymer Assemblies in Water. *Angew. Chemie - Int. Ed.* **2011**, *50* (35), 8082–8085.

(17) Truong, N. P.; Whittaker, M. R.; Anastasaki, A.; Haddleton, D. M.; Quinn, J. F.; Davis, T. P. Facile Production of Nanoaggregates with Tuneable Morphologies from Thermoresponsive P(DEGMA-Co-HPMA). *Polym. Chem.* **2016**, *7* (2), 430–440.

(18) Urbani, C. N.; Monteiro, M. J. Nanoreactors for Aqueous RAFT-Mediated Polymeriz Ations. *Macromolecules* **2009**, *42* (12), 3884–3886.

(19) Sebakhy, K. O.; Kessel, S.; Monteiro, M. J. Nanoreactors to Synthesize Well-Defined Polymer Nanoparticles: Decoupling Particle Size from Molecular Weight. *Macromolecules* **2010**, *43* (23), 9598–9600.

(20) Ratcliffe, L. P. D.; McKenzie, B. E.; Le Bouëdec, G. M. D.; Williams, C. N.; Brown, S. L.; Armes, S. P. Polymerization-Induced Self-Assembly of All-Acrylic Diblock Copolymers via RAFT Dispersion Polymerization in Alkanes. *Macromolecules* **2015**, *48* (23), 8594–8607.

(21) Fielding, L. A.; Lane, J. A.; Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. Thermo-Responsive Diblock Copolymer Worm Gels in Non-Polar Solvents. *J. Am. Chem. Soc.* **2014**, *136* (15), 5790–5798.

(22) Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. A Vesicle-to-Worm Transition Provides a New High-Temperature Oil Thickening Mechanism. *Angew. Chemie Int. Ed.* **2017**, *129*, 1772–1776.

(23) Dong, S.; Zhao, W.; Lucien, F. P.; Perrier, S.; Zetterlund, P. B. Polymerization Induced Self-Assembly: Tuning of Nano-Object Morphology by Use of CO2. *Polym. Chem.* **2015**, *6* (12), 2249–2254.

(24) Khor, S. Y.; Truong, N. P.; Quinn, J. F.; Whittaker, M. R.; Davis, T. P. Polymerization-Induced Self-Assembly: The Effect of End Group and Initiator Concentration on Morphology of Nanoparticles Prepared via RAFT Aqueous Emulsion Polymerization. *ACS Macro Lett.* **2017**, *6* (9), 1013–1019.

(25) Qiao, X. G.; Lansalot, M.; Bourgeat-Lami, E.; Charleux, B. Nitroxide-Mediated Polymerization-Induced Self-Assembly of Poly(poly(ethylene Oxide) Methyl Ether Methacrylate-Co -Styrene)- B -Poly(N -Butyl Methacrylate- Co -Styrene) Amphiphilic Block Copolymers. *Macromolecules* **2013**, *46* (11), 4285–4295.

(26) Sugihara, S.; Armes, S. P.; Lewis, A. L. One-Pot Synthesis of Biomimetic Shell Cross-Linked Micelles and Nanocages by ATRP in Alcohol/water Mixtures. *Angew. Chemie - Int. Ed.* **2010**, *49* (20), 3500–3503.

(27) Kim, K. H.; Kim, J.; Jo, W. H. Preparation of Hydrogel Nanoparticles by Atom Transfer Radical Polymerization of N-Isopropylacrylamide in Aqueous Media Using PEG Macro-Initiator. *Polymer (Guildf).* **2005**, *46* (9), 2836–2840.

(28) Kapishon, V.; Whitney, R. A.; Champagne, P.; Cunningham,

M. F.; Neufeld, R. J. Polymerization Induced Self-Assembly of Alginate Based Amphiphilic Graft Copolymers Synthesized by Single Electron Transfer Living Radical Polymerization. *Biomacromolecules* **2015**, *16* (7), 2040–2048.

(29) Kitayama, Y.; Kishida, K.; Minami, H.; Okubo, M. Preparation of Poly(n-Butyl Acrylate)-B-Polystyrene Particles by Emulsifier-Free, Organotellurium-Mediated Living Radical Emulsion Polymerization (Emulsion TERP). *J. Polym. Sci. Part A Polym. Chem.* **2012**, *50* (10), 1991–1996.

(30) Krstina, J.; Moad, C. L.; Moad, G.; Rizzardo, E.; Berge, C. T.; Fryd, M. A New Form of Controlled Growth Free Radical Polymerization. *Macromol. Symp.* **1996**, *111*, 13–23.

(31) Hutson, L.; Krstina, J.; Moad, C. L.; Moad, G.; Morrow, G. R.; Postma, A.; Rizzardo, E.; Thang, S. H. Chain Transfer Activity of ω-Unsaturated Methacrylic Oligomers in Polymerizations of Methacrylic Monomers. *Macromolecules* **2004**, *37* (12), 4441–4452.

(32) Engelis, N. G.; Anastasaki, A.; Nurumbetov, G.; Truong, N. P.; Nikolaou, V.; Shegiwal, A.; Whittaker, M. R.; Davis, T. P.; Haddleton, D. M. Sequence-Controlled Methacrylic Multiblock Copolymers via Sulfur-Free RAFT Emulsion Polymerization. *Nat. Chem.* **2016**, *9* (2), 171–178.

(33) Zhou, D.; Kuchel, R. P.; Zetterlund, P. B. A New Paradigm in Polymerization Induced Self-Assembly (PISA): Exploitation of "non-Living" Addition–fragmentation Chain Transfer (AFCT) Polymerization. *Polym. Chem.* **2017**, *8* (29), 4177–4181.

(34) Heuts, J. P. A.; Smeets, N. M. B. Catalytic Chain Transfer and Its Derived Macromonomers. *Polym. Chem.* **2011**, *2*, 2407.

(35) Gridnev, A. A.; Ittel, S. D. Catalytic Chain Transfer in Free-Radical Polymerizations. *Chem. Rev.* **2001**, *101* (12), 3611–3659.

(36) Haddleton, D. M.; Maloney, D. R.; Suddaby, K. G.; Muir, A. V. G.; Richards, S. N. Catalytic Chain Transfer Polymerisation (CCTP) of Methyl Methacrylate: Effect of Catalyst Structure and Reaction Conditions on Chain Transfer Coefficient. *Macromol. Symp.* **1996**, *111*, 37–46.

(37) McEwan, K. A.; Slavin, S.; Tunnah, E.; Haddleton, D. M. Dual-Functional Materials via CCTP and Selective Orthogonal Thiol-Michael Addition/epoxide Ring Opening Reactions. *Polym. Chem.* **2013**, *4* (8), 2608.

(38) Kotsuchibashi, Y.; Ebara, M.; Aoyagi, T.; Narain, R. Recent Advances in Dual Temperature Responsive Block Copolymers and Their Potential as Biomedical Applications. *Polymers (Basel).* **2016**, *8* (12), 380.

(39) Blanazs, A.; Madsen, J.; Battaglia, G.; Ryan, A. J.; Armes, S. P. Mechanistic Insights for Block Copolymer Morphologies: How Do Worms Form Vesicles? *J. Am. Chem. Soc.* **2011**, *133* (41), 16581–16587.

(40) Mable, C. J.; Derry, M. J.; Thompson, K. L.; Fielding, L. A.; Mykhaylyk, O. O.; Armes, S. P. Time-Resolved SAXS Studies of the Kinetics of Thermally Triggered Release of Encapsulated Silica Nanoparticles from Block Copolymer Vesicles. *Macromolecules* **2017**, *50* (11), 4465–4473.

(41) Keddie, D. J. A Guide to the Synthesis of Block Copolymers Using Reversible-Addition Fragmentation Chain Transfer (RAFT) Polymerization. *Chem. Soc. Rev.* **2014**, *43* (2), 496–505.

(42) Moad, G.; Solomon, D. H. *The Chemistry of Free Radical Polymerization*, 2nd editio.; Elsevier Science Inc.: Oxford, UK, 1995.