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COMMUNICATION

Flow Photochemistry for Single-Chain Polymer Nanoparticle Synthesis

Or Galant,[a] Hasan Barca Donmez,[a] Christopher Barner-Kowollik*[b] and Charles E. Diesendruck*[a]

[a] O. Galant, H.B. Donmez, Prof. C.E. Diesendruck
Schulich Faculty of Chemistry & The Interdepartmental Program in Polymer Engineering,
Technion – Israel Institute of Technology, Haifa, 3200003, Israel
E-mail: charles@technion.ac.il

[b] Prof. Dr. C. Barner-Kowollik
Centre for Materials Science, School of Chemistry and Physics
Queensland University of Technology (QUT)
2 George Street, Brisbane, QLD 4000, Australia
E-mail: christopher.barnerkowollik@qut.edu.au

Supporting information (SI) for this article is given via a link at the end of the document.

Abstract: Single chain polymer nanoparticles (SCNP) constitute an attractive polymer architecture that potentially provides functions exclusively seen in folded biomacromolecules. The generation of SCNPs, however, is limited by the requirement of a high dilution chemical step, necessitating the use of large reactors in order to produce reasonable quantities of material. Herein, the chemical folding of macromolecules into SCNPs is achieved in both batch and flow photochemical processes by the previously described photodimerization of anthracene units in polymethylmethacrylate (100 kDa) under UV irradiation at 366 nm. When employing flow chemistry, the irradiation time is readily controlled by tuning the flow rates, allowing for the precise control over the intramolecular collapse process. In addition, we demonstrate that the flow system provides a route at least 4 times more efficient for SCNPs formation, reaching higher intramolecular cross-linking ratios 5 times faster compared to batch operation. Thus, we provide a new path towards the synthesis of larger quantities of SCNPs and thus their applications in different fields of soft matter materials science.

The pursuit of advanced macromolecular architectures is one of the key driving forces in polymer synthesis, as they form the basis of functional materials in a range of applications.[1–3] One of the most interesting constructs, referred to as single chain polymer nanoparticles (SCNPs), is prepared by intramolecular chemical folding of polymer chains into single chain nanostructures.[4–8] While research into SCNPs is still emerging, SCNPs have already excelled in a variety of applications such as sensors,[9] catalysts,[10] nanoreactors,[11] drug delivery systems,[12] viscosity modifiers,[13,14] mechanochemically resistant materials[15,16] and plastics with unique mechanical properties.[17,18] Many chemistries, covalent and non-covalent, have been successfully used for the preparation of SCNPs.[19–22] The general strategy for SCNP formation is the polymerization of typically two (or more) monomers into a linear chain, followed by a post-polymerization treatment in dilute conditions, typically below 1 mg mL^{-1} to promote intramolecular cross-linking and avoid network formation. Some specific chemistries were able to overcome this limitation, allowing for the preparation of scalable amounts of SCNP under mild and more concentrated conditions. Proven strategies include the use of collapse reactants with very short life-time,[23] tuning the side-chain polarity to reduce intermolecular interactions,[24] adding reactants to kinetically control the collapse chemistry or to exploit confinement effects to increase the quantum yield of photochemically induced folding reactions.[25,26] These individual successes gave access to larger amounts of SCNPs constituted of specific monomers, but they do not give access to the rich chemistry already developed for SCNPs. Research on the fundamental properties of SCNPs as well as their possible applications requires access to larger amounts of SCNPs with variable chain compositions and side chains, and under the current synthetic limitations, very large reaction volumes are required, making the synthetic process cumbersome and not environmentally friendly. As an example, we have demonstrated that SCNP assemblies in the solid state present extremely high stretchability above T_g, as well as improved strength, modulus and toughness,[18,27] however, 5 L reactors were required to generate sufficient material for even simple mechanical and thermomechanical characterization using small samples.

Over the past decade, flow chemistry has found increased scope and displays several useful advantages when applied to organic syntheses,[28] including in the context of polymerizations where controlled and unique chain architectures are desired.[29–31] Flow chemistry systems hold many advantages over batch production, such as high surface-to-volume ratios, controlled quantities and lifespan of highly reactive species as well as facile scalability that can provide a pathway to commercial production.[32] Therefore, flow chemistry systems can be used to address some of the limitations of batch production of SCNPs, while providing all the advantages of control over reaction conditions and kinetics. Amongst different chemical reactions, flow chemistry systems have shown significant advantages in photochemical syntheses.[33] Batch photochemical synthesis presents issues in adequately distributing the light in the desired intensity, potentially creating numerous by-products due to over exposure required to achieve higher yields. Therefore, photochemical intramolecular collapse was chosen as a proof-of-concept for the flow production of SCNPs. Numerous photochemical processes have been developed for the preparation of SCNPs such as the photodimerization of styrylpyrene units and radical-mediated thiol−yne coupling.[26,34,35] Herein, SCNPs are prepared by the photodimerization of pendant anthracene units,[36–41] originally demonstrated by Berda and co-workers.[42] In batch production, the process was carried out by irradiating a dilute solution of the linear polymer at 0.1 mg mL^{-1} in

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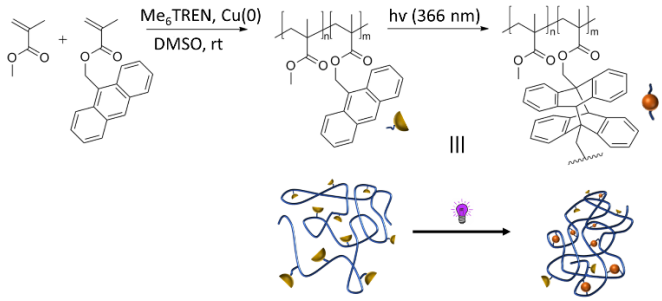
a quartz cuvette. This extremely low concentration meant that only very small amounts of these SCNPs could be produced per volume. Here, we reproduce the batch approach and compare it to an in-house built flow system, both tailored for this process and exploit the possible advantages in terms of production yield, as well as the known advantages of photochemical efficiency typically seen in flow photochemistry.[43,44]

9-Anthracenylmethyl methacrylate (AnM) was prepared by reaction of 9-anthracenemethanol with methacryloyl chloride (refer to experimental section in the SI). Single electron transfer living radical polymerization (SET-LRP) was subsequently carried out to generate a linear copolymer composed of methylmethacrylate (MMA) and AnM (9.4 mol%). Characterization by triple-detector SEC provided accurate weight average molecular weight (Mw) and dispersity, and ^{1}H-NMR was used to calculate the monomer composition (Table 1). SCNP formation was carried out via anthracene photodimerization by both batch and flow system approaches, upon irradiation with a UV light source (366 nm) at dilute solutions (0.5 mg mL^{-1}) in THF (Scheme 1).



Scheme 1. SCNP preparation strategy used in the current study. Me_6TREN = Tris[2-(dimethylamino)ethyl]amine.

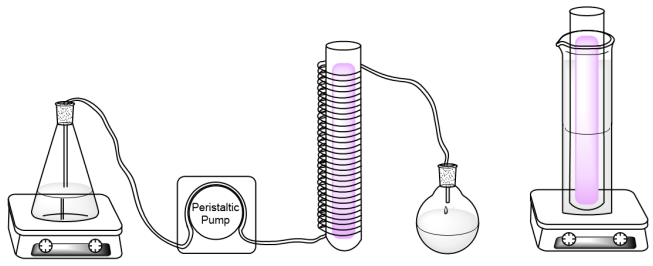


Figure 1. Flow (left) and batch (right) photochemistry systems, using a UV light source at 366 nm.

In this photochemical process, the degree of intramolecular cross-linking (CL) is controlled by the time the solution is exposed to the UV source. Therefore, 5 different flow rates were examined – 100, 150, 200, 250 and 300 µL s^{-1} (6, 9, 12, 15 and 18 mL min^{-1} respectively, representing productivity of 0.18, 0.27, 0.36, 0.45 and 0.54 g per h) which is the amount of SCNPs material in grams produced per hour. The samples are marked as **100FL**, **150FL**, **200FL**, **250FL** and **300FL**, respectively. The same original polymer solution was percolated through high purity perfluoroalkoxy (PFA) tubing, which was tightly wrapped around a ca. 50 cm long UV lamp, cooled to ambient temperature (Figure 1). The solution volume exposed to UV source is ca. 90 mL, the residence times at these flow rates are 15.5, 12.25, 8.67, 6.5 and 5.5 min respectively. Each flow system was run for variable time intervals, until 400 mL of SCNP solution was collected, the volume required in batch to cover the lamp. In the batch studies, the time intervals tested were the same as the ones required in the flow system to produce the same amount of material, therefore allowing a comparison in similar productivities. The exposure times in batch were 22, 27, 33, 44 and 67 min, reflecting the required collection time of 400 mL at flow rates 18, 15, 12, 9 and 6 mL min^{-1} respectively. Additional batch reactions were carried out using shorter exposure times (5.5, 6.5, 8.67, 12.25 and 15.5 min) to obtain also results with similar UV exposure time to the material that passes in the flow system at different flow rates. The batch experiment samples are marked **5B**, **6B**, **8B**, **12B**, **15B**, **22B**, **27B**, **33B**, **44B** and **67B**. In all cases, 400 mL solution (0.2 g of material) was collected and analyzed by triple-detector SEC and ^{1}H-NMR.

Table 1. Data for linear copolymer and SCNPs from SEC and NMR analyses.

Sample	Productivity [g h^{-1}]	Exposure time [min]	M_w [kDa] [a]	$Đ$ [a]	R_η [nm] [a]	Peak elution volume [mL] [b]	AnM CL [mol%] [c]
Linear	N/A	0.0	101.2	1.5	7.2	29.16	0.0
300FL	0.54	5.5	100.5	1.4	7.1	29.98	4.0
250FL	0.45	6.5	100.3	1.5	6.9	30.06	4.5
200FL	0.36	8.67	100.1	1.4	6.5	30.13	5.0
150FL	0.27	12.25	100.7	1.4	6.4	30.38	5.5
100FL	0.18	15.5	100.2	1.4	6.2	30.60	6.7
5B	2.2	5.5	103.0	1.5	7.2	29.38	n.m. [d]
6B	1.8	6.5	100.8	1.3	7.3	29.42	n.m.
8B	1.4	8.67	101.8	1.4	7.3	29.51	n.m.
12B	1.0	12.25	100.2	1.3	7.3	29.55	n.m.
15B	0.8	15.5	102.3	1.6	7.3	29.62	n.m.
22B	0.54	22	100.7	1.3	7.3	29.69	3.1
27B	0.45	27	100.8	1.2	7.2	29.75	3.5
33B	0.36	33	101.3	1.2	7.3	29.79	3.9
44B	0.27	44	100.6	1.3	6.9	29.85	4.4
67B	0.18	67	100.5	1.2	6.4	30.14	5.8

[a] Weight average molecular weight, polydispersity and hydrodynamic radius are calculated from triple detector SEC. See the SI for details.
[b] From UV detector trace at 254 nm.
[c] Calculated from ^{1}H-NMR spectra.
[d] n.m. – not measured.

The linear polymer and the series of SCNPs were characterized by triple-detector SEC to track the change in properties as a function of intramolecular collapse. As expected, polymers produced using smaller flow rates elute at larger elution volumes, as the exposure to the UV-source is increased leading to higher intramolecular CL ratio, causing a decrease in hydrodynamic radius while the polydispersity index (Đ) remains

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approximately the same (Figure 2A, 2C and Table 1). Although changing the flow rates changes the exposure time only by a few minutes, given the larger surface exposure to the UV-source, the variation in SCNP hydrodynamic volume is clear. The actual CL degree was readily assessed by ^{1}H-NMR spectroscopy and showed good correlation with the SEC results and the flow rate in the flow production system (Table 1). At the slowest flow rate, 6 mL min^{-1}, the calculated degree of intramolecular CL reached 6.7 mol% (based on max 9.4 mol%), while at the fastest flow rate, 18 mL min^{-1}, the degree of intramolecular CL reached 4.0 mol% (refer to Figures S4 and S8). The intramolecular process was also followed by UV-vis spectroscopy, monitoring the disappearance of π-π* absorption bands of anthracene, achieved by connecting the flow system to a spectrophotometer, or even directly from the photodiode array (PDA) detector trace in the SEC (Figure 2B and 2D). These results correlate well with the NMR spectra, but are significantly easier and more quickly obtained.

Similarly, the batch experiments show the expected trends: The peak's elution volume increases as irradiation time increases. However, hydrodynamic radius and Đ show larger variances, with less clear trends (Table 1). This is plausibly a consequence of the longer and less controlled exposure to the UV-source. From ^{1}H-NMR spectroscopy data, the intramolecular CL degree for **22B** and **27B**, the least exposed batch samples, are lower than those obtained in the highest flow rates tested with the flow system. Only when exposed for 33 min in batch (**33B**), a CL degree (3.9 mol%) comparable to the fastest flow rate (18 mL min^{-1} **300FL**) which was exposed to UV-source for only 5.5 min was obtained. Importantly, while 0.2 g of SCNPs with this CL ratio are produced in 33 min by batch, in 300FL, the same amount is obtained after 22 min, i.e., the flow system is 50% more effective than the batch system, in addition to being safer, tunable and more controlled. For the slowest flow rate, **100FL**, preparation time of 400 mL SCNPs solution takes 67 min and provides SCNPs with 6.7 mol% CL degree; while in batch, after 67 min the CL degree reaches only 5.8 mol %. Figure 3 summarizes the benefits in SCNPs productivity by photochemical flow compared to batch. Naturally, achieving higher intramolecular CL degrees requires longer reaction times, and therefore lower productivity for both approaches. However, for batch, the productivity is lower, especially for higher conversions (cross-link densities). In addition, we found that the intramolecular CL degree increases linearly with UV irradiation time for both batch and flow production; however, the slope of this fit is an order of magnitude higher in flow, 0.25 versus 0.06 for batch, indicating it is much easier to reach high CL densities using the flow system. Even though the HPFA tubing absorbs and scatters some of the UV light (unlike in batch, where the solution is exposed to the UV source with no 'barrier'), it is clear that production using a flow system provides a critically advantageous route for SCNPs synthesis, especially if higher CL densities are desired. This large advantage is a consequence of the higher surface-area-to-volume ratio. Given the low thickness of the tubing, the diluted solutions are exposed to a more homogeneous and concentrated photon flux for a shorter time period. On the other hand, in a photochemical batch reactor, most of the reagent in the solution is located far from the lamp for most of the time and given the high extinction coefficient of reactants and products, only a tiny amount of photons arrive at those points.[42,44] The batch test carried out in this study is an almost ideal one, in which the reactor is closely encircling the lamp, but even in these conditions, increasing the exposure time leads to a much slower increase in conversion (Figure 3b, represented as CL ratio). Increasing the reaction volume with the same lamp would lead to even lower conversion for the same productivity and even larger differences between batch and flow production. On the other hand, the reaction conversion (intramolecular CL) in the flow system is controlled solely by the selected flow rate and the time of operation merely determines the amount of SCNPs received. Increasing the total time, leads to a significant increase in product amount, while maintaining the same CL ratio, unlike in batch where each experiment could lead to different CL degrees due to slight differences in reaction time or stirring rate.

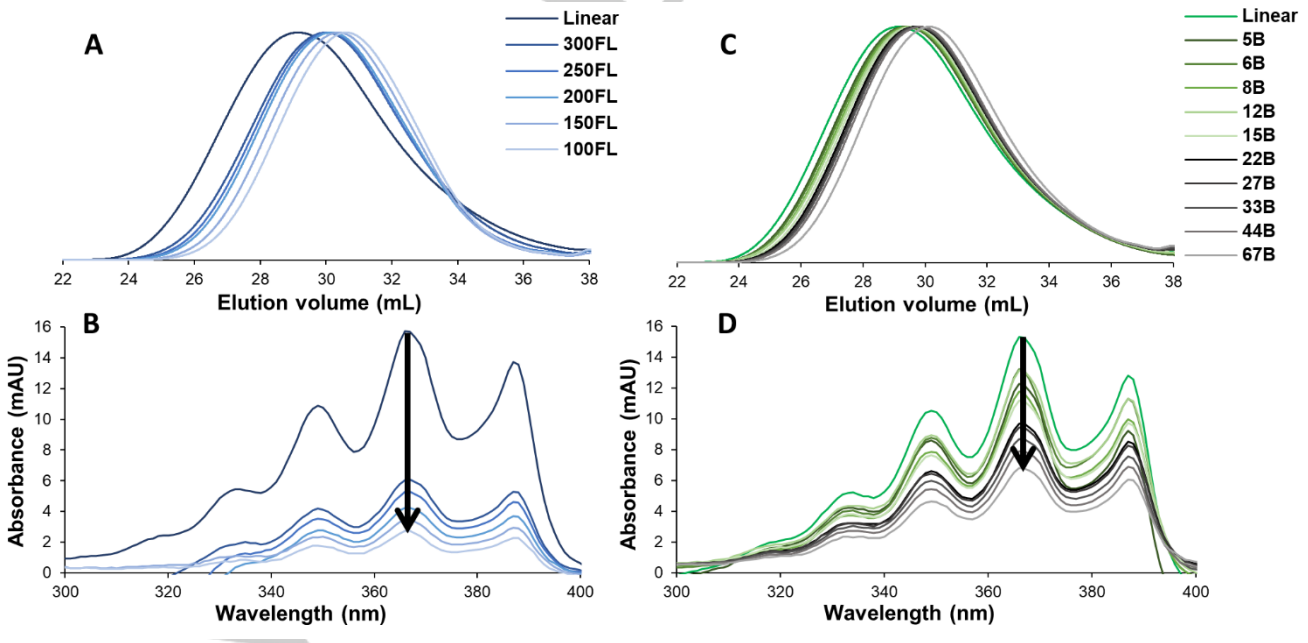

Figure 2. SEC (UV-detector, 254 nm channel) and UV-Vis spectra from the SEC-UV-Vis photodiode array detector of the linear copolymer and SCNPs at different flow rates and exposure times (batch) obtained from flow (A, B) and batch (C, D) systems, respectively.

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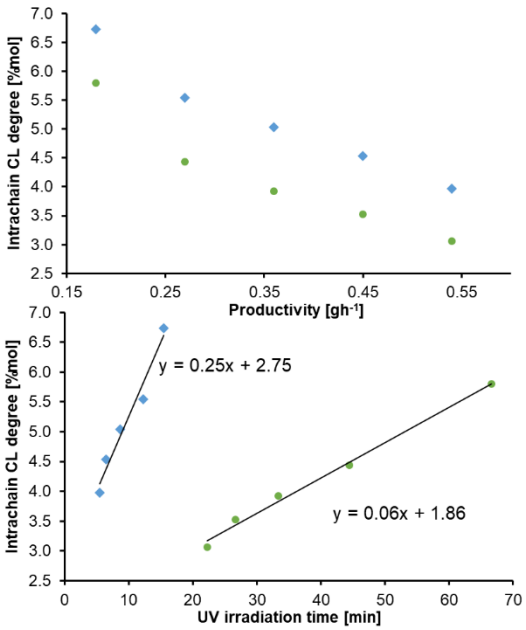

Figure 3. Intramolecular CL degree as a function of SCNP productivity (in grams per hour) (top) and UV irradiation time (bottom) in flow (blue, ♦) and batch (green, ●) systems using a polymer containing 9.4% AnM.

Given the positive results observed with the original polymers, we explore a second set of polymers, where the number of AnM moieties in the backbone is doubled to 20 mol%. Berda and co-workers demonstrated that higher ratios of AnM in the linear precursor lead to a relatively higher degree of intramolecular CL as a function of irradiation time.[42] This effect can be benefited from in flow-chemistry, as the photon density is - on average - higher throughout the solution as compared to batch systems,[43] generating a larger fraction of excited anthracenes. When comparing the dimerization conversion, between the two flow experiments, it can be seen that when 20 mol% AnM is used (refer to the SI, Table S1), the CL ratios increase, relative to the polymer with 9.4 mol% AnM by a factor of 3.4 for the fastest flow rate (300 μL s^{-1}), although this effect is less pronounced at slower flow rates (longer reaction times), given these results are closer to full conversion. In contrast, the majority of the batch results present ca. 2.7 times higher CL ratio compared to the polymer containing 9.4 mol% AnM after the same irradiation time, and, more importantly, it seems that equilibrium is reached at lower relative conversions (refer to the SI, Figure S18).

In summary, we pioneer the continuous production of SCNPs in photoflow. We demonstrate that flow systems for SCNP synthesis present critical advantages over batch mode, including faster reaction kinetics, improved chemical yield at shorter and longer times, a safer production line, better control over the folding chemistry, in addition to faster and continuous production, allowing access to larger quantities of SCNPs. The UV irradiation time was significantly reduced using flow chemistry: the fastest flow rate tested (18 mL min^{-1}, 5.5 min exposure time) produced SCNPs with intramolecular CL rates that required 33 (9.4 AnM %) or 44 min (20 AnM%) UV exposure when carried out in batch. The intramolecular collapse was readily followed using SEC, UV-vis and ^{1}H-NMR spectroscopy. Our technology allows access to larger scale, controlled and safe production of SCNPs using different chemistries. In addition, through adequate evaporation and solvent recovery, this process can be made environmentally benign. The exploration of continuous solvent recovery in combination with flow is currently under investigation and will be reported in due time.

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Keywords: Polymer nanoparticles • Cross-linking • Intramolecular collapse • Flow chemistry • Photochemistry

[1] T. Aida, E. W. Meijer, S. I. Stupp, *Science* **2012**, *335*, 813–817.
[2] T. P. Moneypenny, H. Liu, A. Yang, I. D. Robertson, J. S. Moore, *J. Polym. Sci. Part A Polym. Chem.* **2017**, *55*, 2935–2948.
[3] T. Yamamoto, Y. Tezuka, *Polym. Chem.* **2011**, *2*, 1930–1941.
[4] A. M. Hanlon, C. K. Lyon, E. B. Berda, *Macromolecules* **2016**, *49*, 2–14.
[5] E. Blasco, B. T. Tuten, H. Frisch, A. Lederer, C. Barner-Kowollik, *Polym. Chem.* **2017**, *8*, 5845–5851.
[6] J. A. Pomposo, I. Perez-Baena, F. Lo Verso, A. J. Moreno, A. Arbe, J. Colmenero, *ACS Macro Lett.* **2014**, *3*, 767–772.
[7] A. Latorre-Sánchez, J. A. Pomposo, *Polym. Int.* **2016**, *65*, 855–860.
[8] J. Chen, E. S. Garcia, S. C. Zimmerman, *Acc. Chem. Res.* **2020**, *53*, 1244–1256.
[9] M. A. J. Gillissen, I. K. Voets, E. W. Meijer, A. R. A. Palmans, *Polym. Chem.* **2012**, *3*, 3166–3174.
[10] E. Huerta, P. J. M. Stals, E. W. Meijer, A. R. A. Palmans, *Angew. Chem. Int. Ed.* **2013**, *52*, 2906–2910.
[11] H. Rothfuss, N. D. Knöfel, P. W. Roesky, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2018**, *140*, 5875–5881.
[12] I. Perez-Baena, F. Barroso-Bujans, U. Gasser, A. Arbe, A. J. Moreno, J. Colmenero, J. A. Pomposo, *ACS Macro Lett.* **2013**, *2*, 775–779.
[13] M. E. Mackay, T. T. Dao, A. Tuteja, D. L. Ho, B. Van Horn, H. C. Kim, C. J. Hawker, *Nat. Mater.* **2003**, *2*, 762.
[14] S. Aharonovich, C. E. Diesendruck, *React. Funct. Polym.* **2018**, *131*, 237–242.
[15] A. Levy, F. Wang, A. Lang, O. Galant, C. E. Diesendruck, *Angew. Chem. Int. Ed.* **2017**, *56*, 6431–6434.
[16] A. Levy, R. Feinstein, C. E. Diesendruck, *J. Am. Chem. Soc.* **2019**, *141*, 7256–7260.
[17] O. Galant, S. Bae, F. Wang, A. Levy, M. N. Silberstein, C. E. Diesendruck, *Macromolecules* **2017**, *50*, 6415–6420.
[18] O. Galant, S. Bae, M. N. Silberstein, C. E. Diesendruck, *Adv. Funct. Mater.* **2019**, 1901806.

[19] A. Sanchez-Sanchez, J. A. Pomposo, *Part. Part. Syst. Charact.* **2014**, *31*, 11–23.

[20] S. Mavila, O. Eivgi, I. Berkovich, N. G. Lemcoff, *Chem. Rev.* **2016**, *116*, 878–961.

[21] C. K. Lyon, A. Prasher, A. M. Hanlon, B. T. Tuten, C. A. Tooley, P. G. Frank, E. B. Berda, *Polym. Chem.* **2015**, *6*, 181–197.

[22] O. Altintas, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2016**, *37*, 29–46.

[23] A. M. Hanlon, R. Chen, K. J. Rodriguez, C. Willis, J. G. Dickinson, M. Cashman, E. B. Berda, *Macromolecules* **2017**, *50*, 2996–3003.

[24] E. H. H. Wong, G. G. Qiao, *Macromolecules* **2015**, *48*, 1371–1379.

[25] Y. Zheng, H. Cao, B. Newland, Y. Dong, A. Pandit, W. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 13130–13137.

[26] H. Frisch, J. P. Menzel, F. R. Bloesser, D. E. Marschner, K. Mundsinger, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2018**, *140*, 9551–9557.

[27] S. Bae, O. Galant, C. E. Diesendruck, M. N. Silberstein, *Macromolecules* **2018**, *51*, 7160–7168.

[28] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.

[29] M. H. Reis, F. A. Leibfarth, L. M. Pitet, *ACS Macro Lett.* **2020**, *9*, 123–133.

[30] M. Van De Walle, K. De Bruycker, J. P. Blinco, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2020**, *59*, 14143-14147.

[31] D. J. Walsh, D. A. Schinski, R. A. Schneider, D. Guironnet, *Nat. Commun.* **2020**, *11*, 3094.

[32] D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389.

[33] L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry, K. I. Booker-Milburn, *Chem. - A Eur. J.* **2014**, *20*, 15226–15232.

[34] I. Perez-Baena, I. Asenjo-Sanz, A. Arbe, A. J. Moreno, F. Lo Verso, J. Colmenero, J. A. Pomposo, *Macromolecules* **2014**, *47*, 8270–8280.

[35] E. Verde-Sesto, A. Blázquez-Martín, J. A. Pomposo, *Polymers* **2019**, *11*, 1903.

[36] N. C. Yang, D. M. Shold, B. Kim, *J. Am. Chem. Soc.* **1976**, *98*, 6587–6596.

[37] G. W. Breton, X. Vang, *J. Chem. Educ.* **1998**, *75*, 81.

[38] R. R. Islangulov, F. N. Castellano, *Angew. Chem. Int. Ed.* **2006**, *45*, 5957–5959.

[39] Y. Zheng, M. Micic, S. V. Mello, M. Mabrouki, F. M. Andreopoulos, V. Konka, S. M. Pham, R. M. Leblanc, *Macromolecules* **2002**, *35*, 5228–5234.

[40] H. Bouas-Laurent, A. Castellan, J. P. Desvergne, R. Lapouyade, *Chem. Soc. Rev.* **2000**, *29*, 43–55.

[41] A. Kislyak, H. Frisch, M. Gernhardt, P. H. M. Van Steenberge, D. R. D'hooge, C. Barner-Kowollik, *Chem. – A Eur. J.* **2020**, *26*, 478–484.

[42] P. G. Frank, B. T. Tuten, A. Prasher, D. Chao, E. B. Berda, *Macromol. Rapid Commun.* **2014**, *35*, 249–253.

[43] J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.

[44] B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558–7564.

[45] K. Gilmore, P. H. Seeberger, *Chem. Rec.* **2014**, *14*, 410–418.

10.1002/anie.202010429

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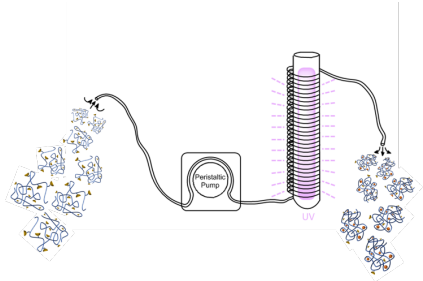

Macromolecular Chain Compaction in Flow. The preparation compact single chain architectures (single chain nanoparticles (SCNPs) requires high dilution conditions in traditional batch synthesis. Herein, we pioneer the use of flow systems to generate SCNPs as a highly efficient alternative.