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ARTICLE

Flash-Synthesis of Low Dispersity PPV via Anionic Polymerization in Continuous Flow Reactors and Block Copolymer Synthesis

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Low dispersity poly[2-methoxy-5-(3',7'-dimethyloctyloxy)]-1,4-phenylenevinylene (MDMO-PPV) with well-defined end-groups is made available by performing the anionic polymerization in a continuous tubular reactor under flash chemistry conditions. The anionic polymerization was carried out via the sulfinyl (Vanderzande) precursor route, following a protocol previously established. Flash flow chemistry allowed now to not only control the microstructure, but also the disperisty of the PPV efficiently. Further, this is the first time that premature termination of PPV anionic polymerization could be observed. Only at ultra-low reaction times in the order of tens of miliseconds products can be observed that have not reached full monomer conversion, redering this type polymerization one of the fastest polymerizations known. Due to the efficient mixing in the tubular reactors, dispersities of 1.2 could be reached at such low residence times, which is unachievable in conventinal batch-wise chemistry. In a second step, a block copolymer was formed of the precursor PPV and *tert*-butyl acrylate (*t*BuA), which is further converted into an amphiphilic block copolymer of PPV with poly(acrylic acid) (PAA). Self-assembly of the PPV-*b*-PAA block copolymer in a continuous tubular reactor resulted in micelles with a number average diameter of 170 nm.

Introduction

Conjugated polymers play a very important role in many different disciplines in chemistry due to their remarkable (opto)electronic properties.[1] These polymers have large domains of delocalized, polarizable π-electrons which make them excellent candidates for use in electronic devices such as light-emitting diodes (LEDs), organic photovoltaics (OPVs) and field-effect transistors (FETs).[2,3,4] Poly(*p*-phenylene vinylene) PPV and its derivatives are among the most common types of conjugated polymer materials due to their robustness, high reproducibility and relatively simple reaction scale up.[5] PPVs have lost some significance in the last years due to new generations of conjugated polymers being developed. Yet, the susbtantial improvements of controlled synthesis procedures and subsequent characterization promoted PPV for use in a variety of complex polymer architectures. Despite their use in optoelectronics being decreased, PPVs remain interesting and are ideal candidates for the use in biomedical applications due to their excellent fluorescent properties, high reproducibility in synthesis and non-toxic character. [6,7]

In the last decades, many efforts have been made to synthesize PPVs in a controllable manner. Among other conjugated polymers they stick out as they are readily synthesized in chain growth rather than step-growth polymerization. This allows to create them – in principle – with well-defined end-groups and chain lengths. Especially the so-called precursor routes take an important role here. In these methods, disubstituted xylenes are activated by a base to form a quinodimethane derivate that can then undergo polymerization. Conjugation of the polymer chain is only achieved in a last step, when the polarizer group is also eliminated. Different precursor routes were established, depending on the choice of the so-called leaving group and polarizer. The symmetrical premonomers are employed in the Gilch[8], Wessling[9,10], Xanthate[11,12] and dithiocarbamate[13,14] routes. Remarkably, an asymmetric premonomer is used in the sulfinyl (also known as Vanderzande) route, which makes it possible to completely decouple the polymerization process from the elimination of the polarizer group, **Error! Reference source not found.**. [15,16,17] This results in polymers with very low defect levels and thereby leading to the synthesis of distinct polymer materials with excellent optical properties.[18,19] Another remarkable advantage of the Vanderzande route is that the polymers can be formed either via radical or anionic polymerization, depending on the choice of solvent and base.[20,21] Both pathways enable the formation of a *p*-quinodimethane system after the addition of a base. In the anionic route however, the base not only forms the active monomer species but also deprotonates an anionic chain initiator, after which chains will grow until all the monomer has been consumed. In this way, specific functional groups can be introduced during the anionic polymerization. The anionic polymerization pathway is preferred due to its living character, while the radical pathway is known for its high molecular weight polymers and greater tolerance to reaction conditions. To

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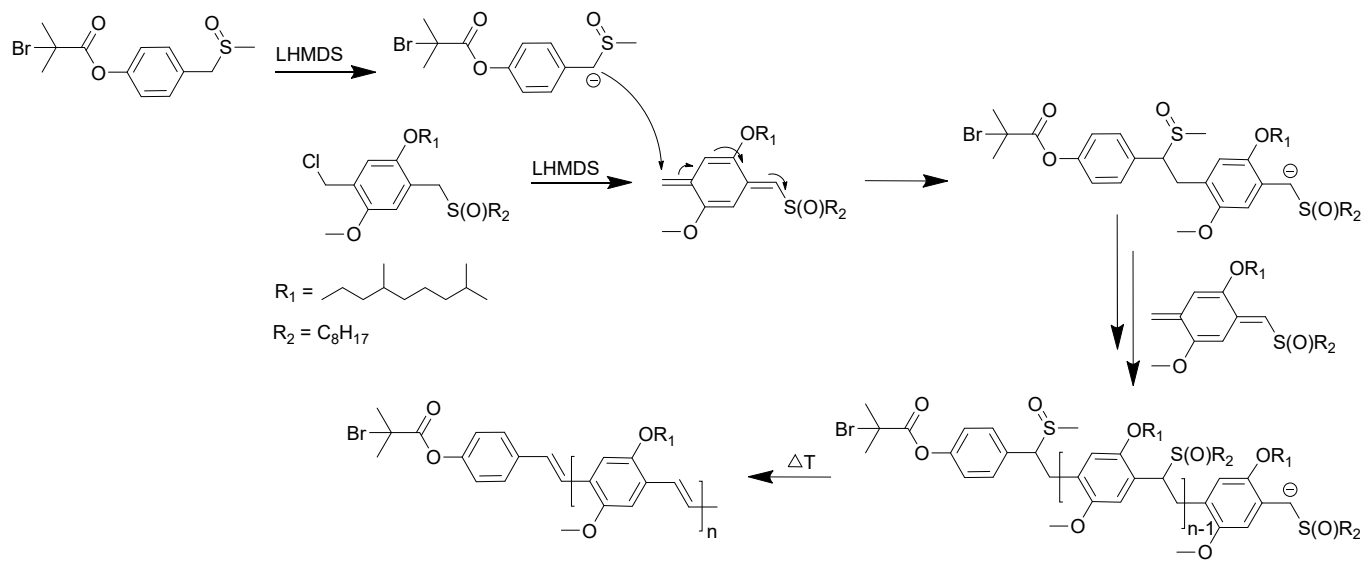


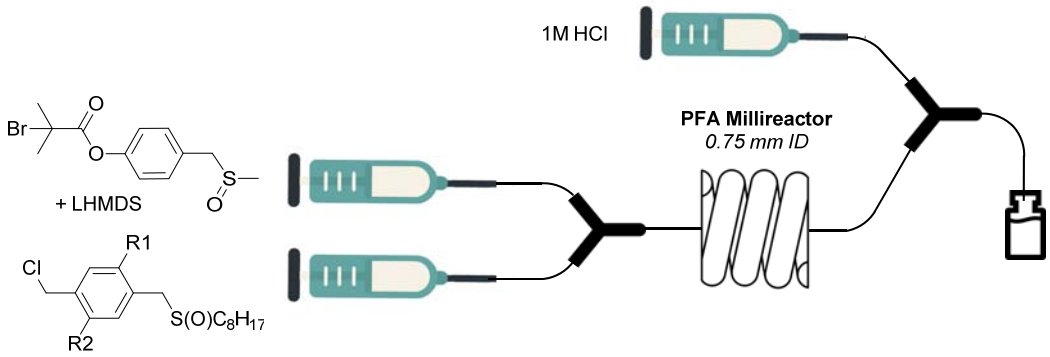
Scheme 1: Mechanism of the anionic sulfinyl polymerization of the MDMO premonomer

exclusively follow the anionic pathway, the sterically hindered lithium hexamethyldisilazide (LHMDS) must be used as the base and THF is typically chosen as the solvent due to its aprotic character and its ability to stabilize the anionic chain ends. [22,23] The full mechanism of the anionic polymerization is given in Scheme 1.

Although more control over the reaction is gained by using the anionic polymerization route, it is still a challenge to tune the desired polymeric properties, such as the molecular weight and the dispersity since the reaction is extremely fast. Previous studies had already shown that polymerizations proceed on the timescale of mixing of all components, and hence reaches full conversion below 1s even at dry ice temperature conditions. In order to tune polymer properties more efficiently, continuous flow techniques can be employed. Continuous flow reactors feature distinct advantages, such as the possibility to obtain materials on scale with high reproducibility.[24] Most importantly though they allow to mix reactants very quickly and with high reproducibility. Previous research already showed the possibility to radically polymerize conjugated PPVs in a continuous flow reactor, but tubular reactors have, to the best of our knowledge, not yet been used for the anionic polymerization of PPV.[25,26] As demonstrated by work of Takahashi and Nagaki, anionic polymerizations are advantageous to perform in continuous flow reactors.[27] Mixing of the starting materials has been identified as the largest limitation with respect to molecular weight distribution control in classical batch synthesis.[28] Efficient mixing can be ensured by the constant motion of the reagents which indicates that the concentration gradient is minimized in continuous flow processing.[29,30] Also, as explained by Yoshida and Nagaki, fast reactions generally greatly benefit from what they termed “flash chemistry”, due to the control that is gained by reducing the residence time.[31] Further, flow flash chemistry allows to perform reactions that usually would require very low temperatures at room temperature, removing the need for tedious temperature control. The flow rate and therefore also the residence time can be easily varied and perfectly controlled, therefore regulation over the dispersity and molecular weight of the polymers can be gained and especially the very short reaction times are of high value for the PPV polymerization, even on timescales below one second.[32,33] Batch chemistry is not able to provide such reaction process control on this timescale, and in fact flash chemistry has been identified as one key method to control the dispersity of a polymer product.[34,35] Flow chemistry is also typically used because its superiority towards batch reactors in terms of mass-and heat transfer. Highly controlled and fast heat transfer can be accomplished due to the small reactor volumes related to the size of the reactor channels, leading to a high surface to volume ratio of continuous flow reactors in comparison with batch reactors.[36] This leads to almost ideal isothermal reaction conditions throughout the whole reactor, whereby less side reactions and polymers with highest performance are achieved.[37] Furthermore, flow processing leads to highly reproducible reaction conditions and the scale up of the reaction can be in most cases easily achieved. The scale up of the reaction can be done by simply letting the reaction run for a longer period of time (scale-out principle) or, reactors could be placed in parallel in order to produce more polymer material at the same time (numbering up principle).[29]

On the other hand, with respect to PPV synthesis, microflow chemistry is also limited in the sense that PPV is inherently difficult to dissolve, and leads quickly to reactor fouling. Only low concentrations can be tolerated in flow channels. Also, lithium bases can quickly lead to blockages of the reactor, which is why such synthesis has not been reported before.

The formation of highly tailored PPVs via living anionic polymerization make them readily available for further applications like the development of (amphiphilic) block copolymers, synthesized via single electron transfer living radical polymerization (SET-LRP) or atom transfer radical polymerization (ATRP).[38,39,40] As classical ATRP is mostly carried out at elevated temperatures, which enables premature



Scheme 2: Schematic representation of the precursor MDMO-PPV polymerization in continuous flow.

elimination of the precursor polymer and could hinder block copolymer formation, executing polymerizations under milder reaction conditions – as typically described for SET-LRP – is preferred when using PPV macroinitiators. When PPV, most of the time strongly hydrophobic, is extended with a water-soluble polymer, amphiphilic block copolymers can be obtained that are able to self-assemble. Previous work has already shown that amphiphilic PPV-containing block copolymers show excellent self-assembly and payload uptake, and that these are ideal inherently-fluorescent carriers for potential biomedical application.[41] Such nanoaggregates are able to penetrate into cancer cells and release their encapsulated drug payload. Interestingly, the block copolymers show fluorescence, however, when self-assembled, the fluorescence is quenched due to the organization of the conjugated chain segments. Only upon cell uptake the fluorescence becomes visible again. This is a useful feature that can be employed to closely monitor the cell uptake, and later to determine the fate of the micelle materials over a longer period of time. For most to-date studied drug delivery systems similar questions are under investigation, mostly with the drawback that materials themselves are invisible to confocal microscopy – in contrast to the herein proposed PPV. Dyes can be attached to classical micelles. Yet, they often deplete either quickly under irradiation, or are toxic. PPV on the other hand has a high light stability, high fluorescence brightness and is non-toxic.

In here, the synthesis of low dispersity MDMO-PPV via the anionic sulfinyl precursor route in continuous flow reactors will be discussed. So far it had not been possible to achieve narrowly dispersed materials of this kind, and to the best of our knowledge, this is the first report on low dispersity PPV made in a consistent and reproducible fashion. Improved control over the molecular weight and low dispersity MDMO-PPV polymers are obtained by the use of flash chemistry, and hence display one of the cases where the engineering approach to a reaction – here flow chemistry with very low residence times – yields a synthetic result that otherwise would be inaccessible. Reactions are all performed at room temperature (ignoring adiabatic heat up), for simplicity of the process and to use the advantage of the flash chemistry concept. Optimization of the precursor polymer from the MDMO premonomer in continuous flow reactors will be highlighted as well as the design of the reactor and the reaction conditions. Block copolymers synthesis is described for the production of micelles in continuous tubular reactors, streamlining the synthesis of PPV-containing block copolymers under highly reproducible conditions.

Experimental section

Materials

All materials and reagents were purchased from Fisher, VWR or Sigma Aldrich and were used without further purification. THF and DMF were dried on a MD-SPS 800 system. tert-Butyl acrylate was distilled over basic alumina and tris[2-(dimethylamino)ethyl]amine (Me6TREN) was synthesized according to literature procedure.42

General flow reactor setup for the polymerization of the precursor MDMO-PPV

Error! Reference source not found. represents the general flow reactor setup for the polymerization of the precursor MDMO-PPV. The continuous tubular flow reactions were performed in a self-made PFA tubular reactor with an internal diameter of 0.75 mm and varying reactor volumes from 1.7 µL (dead volume Y-Piece) to 0.5 mL. The polymerization reactions were performed at room temperature. The reagent solutions (premonomer, initiator and base) were injected into the reactor through two gastight syringes (SGE) and a Y-piece (PEEK Y for 1/16" OD tubing, thru-hole = 0.020") to ensure mixing of both solutions. An extra gastight syringe (SGE) containing 1M HCl was added via a Y-piece at the end of the reactor and serves as a quenching line. The flow rates were controlled via two syringe pumps (Chemyx) and vary between 1 ml·min^{-1} and 31 ml·min^{-1} (for each syringe), the residence times corresponding to these flow rates depend on the reactor used. The end of the reactor was connected to a vial which could be easily switched in order to collect different samples for screening of the residence time and reactor volume.

Results and Discussion

Polymerization of MDMO-PPV in flow reactors

The ability to polymerize PPVs exclusively via the anionic precursor route has been extensively investigated for batch polymerization,

but due to the fast polymerization, control over molecular weight and dispersity could not really be achieved so far. Some molecular

Table 1: Overview of the different reactors and residence times of the MDMO precursor polymer synthesized via the first reactor set-up in continuous flow.

Residence time [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	$Đ$	Residence time [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	$Đ$	Residence time* [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	$Đ$
	1 mL reactor				0.5 mL reactor				Only Y-piece		
60	1900	2700	1.4	20	2200	3400	1.6	0.10	1900	2600	1.4
40	1900	2700	1.4	10	2100	3300	1.6	0.05	1900	2600	1.4
30	1900	2700	1.4	5	2100	3300	1.6	0.026	1900	2600	1.4
15	1900	2600	1.4	2	2200	3200	1.4	0.020	1900	2600	1.4
10	1800	2600	1.4	1	2200	3200	1.5	0.017	1900	2600	1.4

*residence times are estimated from the flow rate and the dead volume of the Y-piece, the [MDMO premonomer]/[initiator]/[LHMDS] ratio = 1/0.2/1.3

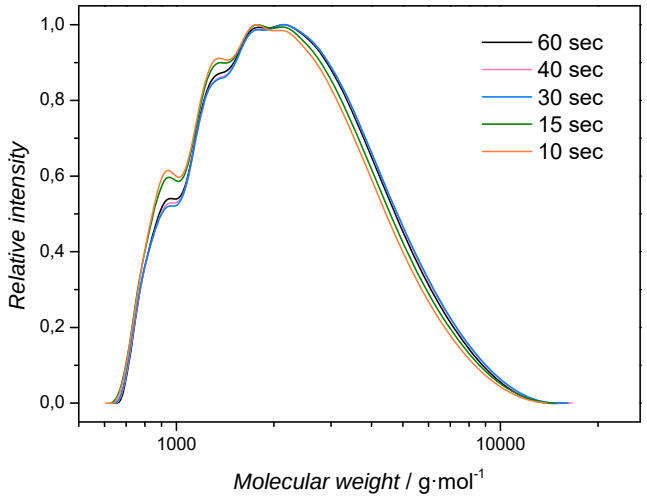


Figure 1: Molecular weight distributions obtained for PPV precursor polymers synthesized in the 1 mL reactor.

weight control could be realized, yet dispersities were typically high, and no example is known yet where a polymerization could be quenched before reaching full conversion. It is also due to this limitation, that until recently even the mechanism of PPV polymerization was under debate.

We hypothesized that this limitation could be overcome in continuous flow reactors, where residence times are better controlled, and mixing is achieved on much faster timescale. First, the MDMO-premonomer and initiator were combined in one syringe in THF and another syringe was filled with LHMDS in THF. The base needs to deprotonate the premonomer and the initiator. A small further excess (0.1 eq) was added to make sure that the deprotonation goes to completion. Both syringes were combined in a Y-piece after which it was connected to a 1 mL reactor. At the exit of the reactor (the same was done in all following experiments), the reaction mixture is directly quenched with 1 M HCl solution to stop any further reaction and thus to rule out that further polymerization occurs in the vessel in which the product is collected. PPV precursor polymer was successfully formed, but unfortunately, varying the residence times did not show any variation in the molecular weight or dispersity. After this experiment 4 different reactor designs were tested, the first one with a 1 mL reactor volume, the second one with 0.5 mL and two designs without any reactor, only a Y-piece or a static mixing tee, see **Error! Reference source not found.**. Due to the fast reaction kinetics of this polymerization a rather small reactor volume was chosen to start with, the 1 mL reactor with a Y-piece. PPV precursor polymer could be synthesized successfully but varying the residence time did not reveal any variation in molecular weight nor dispersity, **Error! Reference source not found.**. Since the variation in residence times was still quite low (between 60 and 10 seconds), it was chosen to reduce the reactor volume to 0.5 mL in order to go to ever shorter residence times (from 20 seconds to 1 second). It is clearly evident that even at a residence time of 1 second the precursor PPV polymer is formed, but still (almost) no variation in polymer length was achieved. Since the reactor volume had almost no influence on the polymeric properties, a design was chosen without any tubular residence unit at all, and hence only consisted of a Y-piece to bring both solutions together. The same results were still seen as for the designs with a reactor connected, despite the residence time being practically zero after mixing. Lastly, also a design with a static mixing tee could not change the molecular weight or dispersity of the precursor PPV polymers.

Since the reactor design or mixing units couldn't provide a solution, the composition of the starting solutions was changed. Monomer and base cannot be mixed, as this triggers spontaneous polymerization, even in absence of the dedicated initiator. Thus, the system was changed to the first syringe only containing the premonomer in THF solution and the second syringe containing the initiator and base LHMDS in THF. In this way, the LHMDS base could already activate/ deprotonate the initiator before it encountered the monomer. In this way, the initiation of the anionic polymerization will be faster and be decoupled from the mixing process. Initiation and chain growth can happen immediately when active quinodimethane monomer is formed. With this setup, PPV precursor polymer could be synthesized successfully in a 0.5 mL reactor with a number average molecular weight (M_n) of 3400 g·mol^{-1} and a dispersity of 1.4 (determined using SEC). To examine if the different

compositions of the syringes influenced the polymerization length, again different reactor lengths were investigated, see **Error! Reference source not found.**. Three reactor designs were tested, a 0.5 mL reactor, 0.13 mL reactor and a design with only a Y-piece to bring both solutions together. With the 0.5 mL reactor volume, the residence time could be easily varied between 10 and 0.5 seconds (flow rate varied between 3 mL·min^{-1} and 60 mL·min^{-1}). The molecular weights that were obtained range from 3400 g·mol^{-1} to 3000 g·mol^{-1} and the dispersities decreased

Table 2: Overview of the different reactors and residence times of the MDMO polymer synthesized in continuous flow

Residence time [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	Đ	Residence time [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	Đ	Residence time* [sec]	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	Đ
0.5 mL reactor				0.13 mL reactor				Only Y-piece			
10	3400	4700	1.4	2	3100	4600	1.5	0.05	3900	5200	1.3
5	3100	4600	1.5	1	3100	4400	1.4	0.026	3800	5200	1.4
2.5	3200	4500	1.4	0.5	3000	4000	1.3	0.013	3900	5200	1.3
1	3000	3900	1.3	0.25	3000	3700	1.2	0.0064	3800	4800	1.3
0.5	3100	3800	1.2	0.12	2800	3500	1.2	0.0032	3200	3800	1.2

*residence times are estimated from the flow rate and the dead volume of the Y-piece, the [MDMO premonomer]/[initiator]/[LHMDS] ratio = 1/0.2/1.3

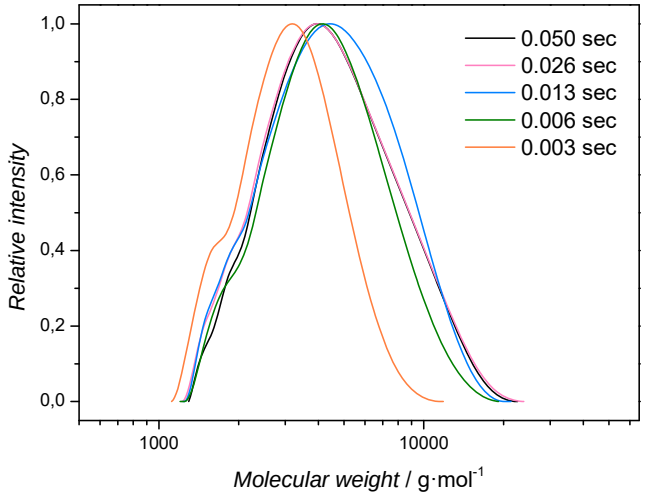


Figure 2: Molecular weight distributions for the PPV precursor polymers synthesized with only the Y-piece were determined via SEC without the impurities at low molecular weight.

from 1.5 to 1.2. Thus, when the residence time is lowered, the molecular weight and the dispersity decrease as well, even if only in limits. At higher flow rates (lower residence times), shorter polymer chains were formed because the polymer chain has less time to grow and more chains are initiated. Remarkably, in literature this trend is not visible for the anionic polymerizations of PPV in batch and this is the first report to the best of our knowledge where a premature termination of the PPV chain growth could be observed.[43] In batch polymerization, it is seen that even at "0" minutes of reaction time polymer is formed to high conversion, indicating once more how fast this polymerization is. Encouraged by these results, the residence time was further reduced. A shorter reactor with an internal volume of 0.13 mL was employed. In this way, the residence times could be varied between 2 seconds and 0.12 seconds (flow rate varied between 3.9 mL·min^{-1} and 63.7 mL·min^{-1}) leading to molecular weights that range from 3100 g·mol^{-1} to 2800 g·mol^{-1} with a dispersity decreasing from 1.5 to 1.2. Still at these low residence times PPV prepolymer can be formed, showing that the reaction is even faster than anticipated. Again, the same trend of decreasing molecular weight and dispersity with decreasing residence times is seen, even if within rather narrow limits. It should be mentioned here that the determination of monomer conversion in PPV polymerization is non-trivial due to the inherent instability of the monomer once it is formed in the elimination step. Thus, shorter chain lengths must serve as sufficient proof for reaching lower conversions before chain growth is terminated.

The previous results show that even at very low residence times PPV precursor polymer is already formed with high conversion. Therefore, in the next step the two reagent solutions were connected with a Y-piece and the polymer sample was directly collected without a tubular reactor unit. The residence times were changed from 0.05 seconds to 0.0032 seconds (residence times are estimated from the flow rate and the dead volume of the Y-piece) displaying the same trend as seen in the previous experiments, namely the molecular weight that decreases from 3900 g·mol^{-1} to 3200 g·mol^{-1} and the dispersity ranges from 1.4 to 1.2, see **Error! Reference source not found.**. This shows that the process is a true flash chemistry reaction, not necessitating any residence unit to produce PPV precursor polymer in flow. Mixing of reactants is the only rate determining step.[28] Having said that, a reaction time of only 3.2 msec is truly remarkable for any polymerization to occur, explaining also why previous attempts at flow polymerization had not been successful. When being carried out at higher starting

Table 3: Variation of the initiator concentration of the MDMO precursor polymerization in continuous flow.

equiv initiator	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	Đ	equiv initiator	M_n [g·mol^{-1}]	M_w [g·mol^{-1}]	Đ
0.5 mL reactor				0.13 mL reactor			
0.25	6600	8600	1.3	0.25	4800	6800	1.4
0.20	6300	8200	1.3	0.20	4700	6400	1.3
0.15	6900	9500	1.4	0.15	5900	8600	1.5
0.10	7500	10800	1.4	0.10	6700	10200	1.5
0.05	7800	12000	1.5	0.05	6900	11000	1.6

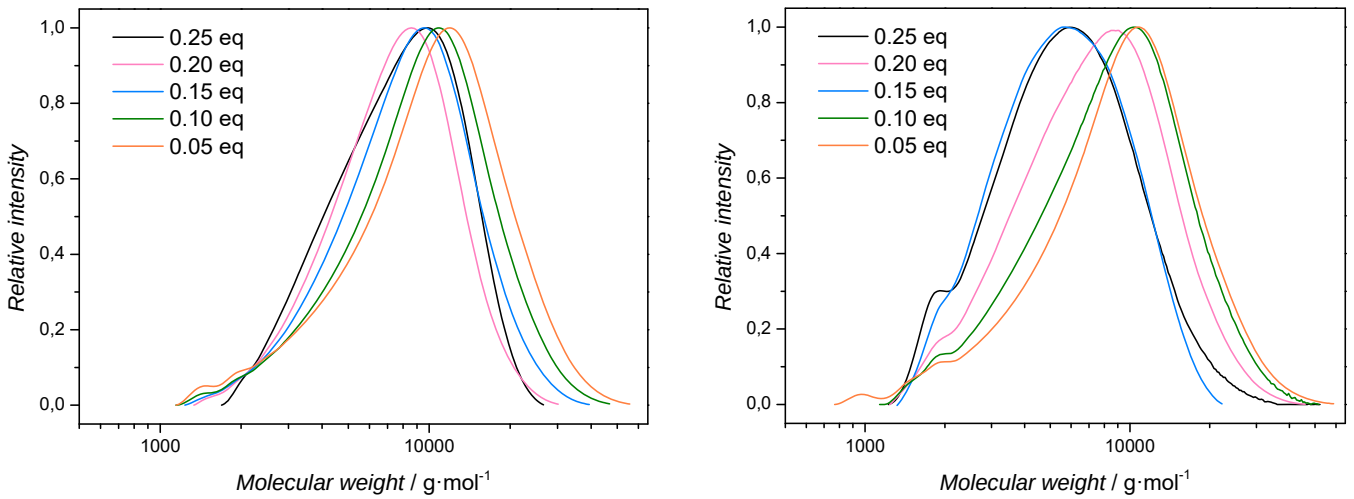


Figure 3: Variation of the initiator concentration in the MDMO precursor polymerization in continuous flow for (left) a 0.5 mL tubular reactor and (right) a 0.13 mL tubular reactor.

monomer concentration, the exotherm cannot be dissipated, and the reaction accelerates further, leading to fouling and reactor blockages. As for the polymerization itself, it is of only small consequence if a reactor residence unit is used or not (even though not negligible). All reactors show the same decrease in molecular weight and dispersity within an experimental series. Even if the reaction is finished when exiting the mixer unit, no further polymerization occurs anymore, explaining why all three reactors summarized in Table 2 show similar results. Yet, we found that a residence unit does have a beneficial effect (as seen by the inter-reactor variation summarized in Table 2), probably by increasing back pressure and hence leading to more stable flow conditions. It may be interesting to elucidate the exact influence of mixer geometries and backpressure. Yet, the results obtained here are already satisfactory and much more precise than any synthesis effort before, and hence this will be subject of a forthcoming study.

Varying the molecular weight is usually achieved by changing the initiator concentration.[28] Also here, batch reactions showed only limited success in controlling the residual polymer chain length. For our flow setup, these experiments were performed in 2 reactors since the length of the reactor has a small influence on the molecular weight, as described above in **Error! Reference source not found.**.

First, the 0.5 mL reactor with a residence time of 0.5 seconds was chosen since this reactor type and residence time gave low dispersities. Concerning the testing for different initiator concentrations, different amounts of initiator are brought in separate syringes and consecutively connected to the reactor. When the initiator concentration is reduced, the molecular weight should increase because less chains will be initiated and therefore longer chains are formed. This trend is also seen in this experiment where the initiator concentration was varied from 0.25 equivalents (relative to the monomer) to 0.05 equivalents. For this variation, the molecular weight increases from 6600 g·mol^{-1} to 7800 g·mol^{-1} and the dispersity ranges from 1.3 to 1.5, see l.h.s. of **Error! Reference source not found.**. The same trend is seen when a 0.13 mL reactor with a residence time of 0.25 seconds was used to investigate the molecular weight changes when the initiator concentration was varied. For this reaction setup, the molecular weight increases from 4800 g·mol^{-1} to 6900 g·mol^{-1} and the dispersity ranges from 1.3 to 1.6 (with initiator concentrations decreasing from 0.25 equivalents to 0.05 equivalents), see r.h.s. of **Error! Reference source not found.**. As can be observed, the molecular weights are lower than for the 0.5 mL reactor (like it was also the case when the different reactor volumes were investigated), and the same trend of increasing

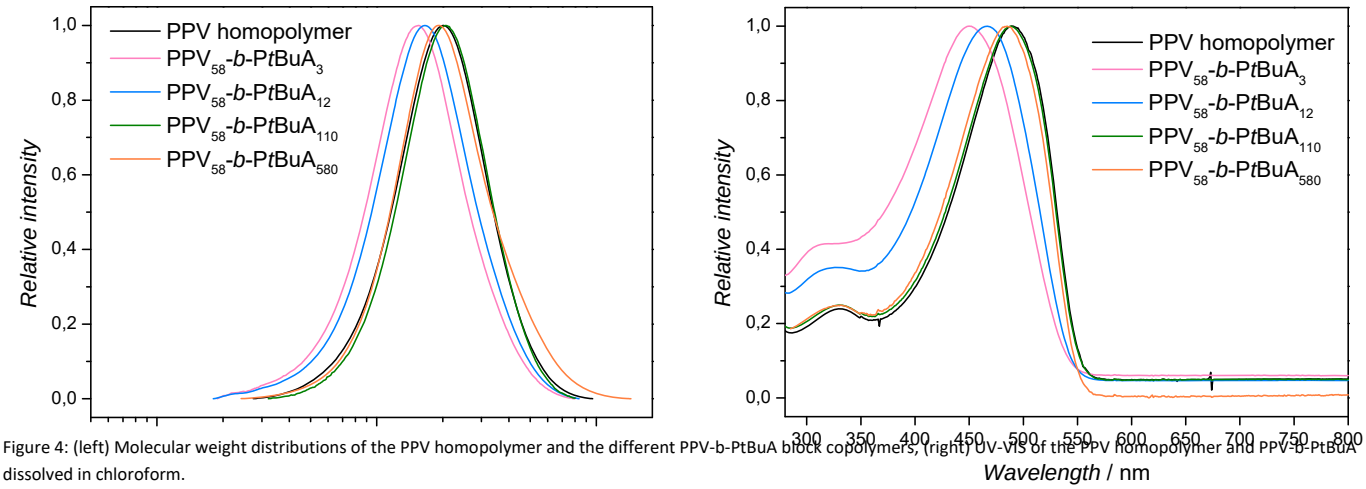


Figure 4: (left) Molecular weight distributions of the PPV homopolymer and the different PPV-b-PtBuA block copolymers, (right) UV-VIS of the PPV homopolymer and PPV-b-PtBuA dissolved in chloroform.

Table 4: Overview of the molecular weight, dispersity and λ_{max} of the PPV-b-PtBuA block copolymers

PPV/Pt-BuA DP [a]	$M_{n,T}$ [b] g·mol^{-1}	M_n [c] g·mol^{-1}	M_w [c] g·mol^{-1}	Đ	λ_{max} [e]
58 [d]		16700	21700	1,30	489
58/3	17100	12500	17100	1,37	450
58/12	18200	13400	18400	1,37	467
58/110	30800	17500	22000	1,26	489
58/580	90900	17200	23500	1,36	485

[a] DP shows the theoretical degree of polymerization, [b] $M_{n,T}$ is the theoretical molecular weight calculated via ^{1}H NMR, [c] M_n is the number average molecular weight, M_w the weight average molecular weight and Đ represents the dispersity of the molecular weight distribution. Measurements were performed via SEC. [d] DP for the PPV homopolymers is calculated from the M_n measured via SEC, [e] λ_{max} was determined using chloroform as solvent.

molecular weight and broadening of the dispersity is visible with the decrease of the initiator concentration. The broadening of the dispersity and the increase in molecular weight is often seen in batch reactions when the amount of initiator is reduced.[28] Obviously, the variation in molecular weight, even with the small reactor, is not as large as one would expect from the initiator to monomer concentration ratios. Less initiator decelerates the overall initiation rate (given by the concentration of initiator and monomer), hence leading to conditions where initiation and propagation progressively occur simultaneously. This corrupts the molecular weight control, and also leads to the observation of progressively broader distributions being produced. Yet, within limits the molecular weight can be changed, while retaining the low dispersity of the polymer. Interestingly, in recent years increasing

attention is given in the polymer synthesis field to controlling the dispersity of polymers, as this affects physical properties and self-assembly behaviour of polymers significantly.[35] In this sense, the choice of flow rate and/or mixing of the reaction streams gives access to PPVs with controllable dispersity, which may pose a significant advantage in future studies.

Block copolymer synthesis in batch

Now that PPV polymers with different molecular weights are readily available, chain extensions can be performed to form block copolymers. This serves as a facile application of the method, but also is used to further underpin the well-controlled flash polymerization procedure. Only if high endgroup fidelity is obtained in the initiation, successful block copolymer formation will be achievable. The second block can be grown from the Br end-group introduced via the anionic initiator on the PPV precursor polymer by SET-LRP (see Scheme 1). This approach had been described before, but then for more disperse PPVs. The Br-containing end-group is effectively build in in the polymer, as can be observed by NMR (see SI). For SET-LRP, tert-butyl acrylate (*t*BuA) is chosen as the second block, as it allows to hydrolyse the acrylate block later to form amphiphilic material.[44] In order to perform the SET-LRP with *t*BuA, tris[2-(dimethylamino)ethyl]amine (Me_6TREN) and DMF were added to the precursor polymer. This mixture was admitted to 5 freeze pump thaw cycles before it was transferred into the glovebox where Cu(0) was added and the mixture was stirred for 4h at 50°C. At the end of the reaction, the mixture was taken out of the glovebox and exposed to air which quenches the reaction. Next, the block copolymer was first dissolved in a small amount of chloroform and applied on a plug with basic alumina to remove all copper species. Afterwards the block copolymer was purified by precipitation in a cold methanol/water (4/1) mixture. After filtration the purified block copolymers were obtained and analysed using SEC. Since it can be expected that the acrylate has polymerized to full conversion in this time, different PPV to acrylate monomer concentration ratios were employed to vary the block copolymer composition.

As expected, a shift in the SEC chromatograms is observed for the chain extensions. Unfortunately, the elongation itself is not clearly visible for the series of PPV-*b*-P*t*BuA block copolymers, see **Error! Reference source not found.** (left). This is somewhat unusual, but has been observed before, especially for PPV polymers. It can be explained by the low change in hydrodynamic volume when the block copolymer is formed. PPV-*b*-P*t*BuA is a rod-coil like block copolymer, where PPV is the rod-like polymer and *t*BuA is the coil-like polymer. When these polymers are connected, the coil-like *t*BuA polymer is convoluted around the rod-like PPV polymer, making it difficult to follow any change in block length via size exclusion chromatography. SEC is simply not able to separate these polymers correctly. Further, since PPV is fluorescent, light scattering cannot be used for the determination of M_w, and Mark-Houwink parameters for the PPV homopolymer were used, also leading to a slight misinterpretation of the results. Other methods for testing the success of the reactions had thus to be found. Examination on the presence of the *t*BuA polymer can be done via ^{1}H NMR analysis. The ^{1}H NMR graphs indicate clearly the presence of the protons originating from the *t*BuA polymer block. The protons of the tertiary butyl group are present at 1.44 ppm, and the protons of the acrylate backbone are located at 2.22 ppm together with the two methyl groups originating from the initiator chain-end (see SI). The ^{1}H NMR spectra can also be used to quantitatively analyse the degree of polymerization of the SET-LRP and therefore also an estimation of the molecular weight can be made, see

(the calculation of the molecular weight can be found in the SI). Degrees of polymerization for the second block were achieved ranging from 3 till 580, corresponding to molecular weights ranging from 17 100 g·mol^{-1} to 90 900 g·mol^{-1}.

Another way to elucidate if the block copolymer is present is by performing a FT-IR measurement. In the SI, the comparison is made between the spectra of the MDMO precursor polymer and the precursor PPV-*b*-P*t*BuA block copolymer. The C=O ester peak (1728 cm^{-1}) of the acrylate is clearly present in the spectrum of the block copolymer. To further analyse the block copolymers their λ_{max} was measured using UV-VIS spectrometry, **Error! Reference source not found.** (right). It can be noticed that there is only a small change in the λ_{max} of the different block copolymers and the PPV homopolymer,

. This is also seen before in batch polymerizations of PPV with *t*BuA.[44] The (small) shift in λ_{max} occurs due to the tangling of the *t*BuA polymer around the fluorescent PPV polymer, like discussed above, therefore the absorbance is slightly quenched. This quenching is another confirmation the *t*BuA polymer is connected to the PPV polymer and the PPV-*b*-P*t*BuA block copolymer is formed. Yet, NMR and FT-IR can not distinguish between a polymer blend and a block copolymer, even if a block copolymer is the only reasonable explanation, since no other ATRP initiator (and hence source of Br) was present in the polymerization other than the PPV polymer.

Self-assembly of the block copolymer into micelles in a tubular reactor

A solid confirmation for the existence of a block copolymer is self-assembly. In order to form micelles, amphiphilic block copolymers that can undergo self-assembly in solution need to be synthesized. The amphiphilic block copolymer can be obtained from the PPV-*b*-P*t*BuA when the *tert*-butyl acrylate block is hydrolysed into poly(acrylic acid) (PAA). Hydrolysis is straightforward to perform and is hence not further detailed here. Self-assembly of the obtained amphiphilic block copolymers was again performed in a 2 mL tubular reactor with a static mixing tee. Previously, we had found that continuous flow reactors allow for a more precise self-assembly of micelles compared to batch protocols.[45] Two gastight syringes were used, the first one contained the PPV-*b*-PAA block copolymer that was dissolved in THF with a concentration of 10 $mg \cdot mL^{-1}$, the second syringe contained water. Both solutions were added to the tubular reactor with a different flow rate (0.2 $mL \cdot min^{-1}$ for the block copolymer solution and 1.8 $mL \cdot min^{-1}$ for water), obtaining a THF/water ratio of 10/90 v/v%. Self-assembly of the block copolymer resulted in PPV-*b*-PAA micelles with an average number diameter of 170 nm and an overall dispersity of 0.232, see SI. These micelle diameters are in the same range as for example the diameter of PPV-*b*-PHEA found in literature, in a tubular flow reactor and in batch for higher dispersity PPV polymers.[45,41] Further, the quenching of the UV-VIS absorbance upon micelle formation was visible, providing the profluoresence that was employed before in cell uptake studies. The λ_{max} of the micelles was blue shifted to 408 nm (measured in THF as the solvent), which is also within expectation. This makes these micelles excellent candidates for further studies in the field of drug delivery systems. With the new ability to control the length of the polymers better and by being able to influence the dispersity of the PPV block, more detailed studies in the morphology of the obtained micelles can commence, which will be beneficial for cell uptake studies, and for potential drug delivery applications.

Conclusions

A flash chemistry approach to the anionic polymerization of MDMO-PPV via precursor Vanderzande-route polymerization in continuous flow reactors is presented. The polymerization was accomplished in very fast reaction times on the timescale of milliseconds and polymers with low dispersity of 1.2 were achieved for the first time. The molecular weight of the PPV polymers could be changed by tuning the reactor setup or changing the amount of initiator used for the polymerization. The dispersity of the polymer can in principle be used for controlling the PPV polymer dispersity. A second polymer block was coupled to the PPV precursor polymer via SET-LRP. In this way PPV-*b*-P*t*BuA was obtained which could in a next step be converted into amphiphilic PPV-*b*-PAA. Due to the good self-assembly properties of this amphiphilic block copolymer, micelles with a number average diameter of 170 nm were obtained, likewise in a continuous tubular reactor. The resulting micelles quench their UV-VIS absorbance, which makes them excellent candidates for the use in the biomedical field as pro-fluorescent drug delivery systems. The formation of well-defined micelles is used to show the well-controlled conditions of the PPV polymerization step. As mentioned, the main advantage of the flow process is to reduce the dispersity of the PPV to levels typically observed for living or controlled polymerization, as much as giving more insights on the mechanism and kinetics of the precourser polymerization.

Conflicts of interest

There are no conflicts to declare.

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