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COMMUNICATION

Photo-induced ring-closure via a looped flow reactor

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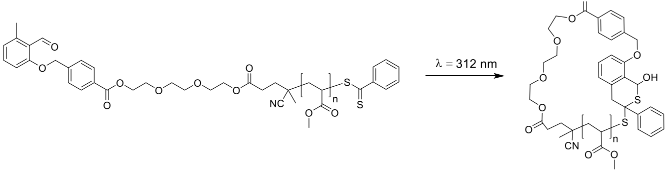
Looped flow processes are an efficient and versatile tool to synthesize complex macromolecular materials. Especially for light-induced ring closure reactions, which typically require low concentrations, looped flow processes are critical for upscaling. Here, such reactor was designed to carry out a photo-induced ring-closure reaction via a photo-enol reaction for the synthesis of cyclic polymers, leading to a reduction of required solvent in the synthesis by over a factor 40, hence giving access to a more economical and fully scalable process.

Continuous flow processes are increasingly investigated as alternative to conventional batch chemistry in the last decade. Providing a high level of control over reaction parameters, fast heat exchange and high reaction efficiencies, continuous flow approaches are of particular interest for organic synthesis, yet increasingly so in the field of advanced polymer design.[1-4] Contemporary research focusses on the use of specialized reactor set-ups for specific reactions, and on the use of reactor cascades (multistep reactions in 'one-flow') to carry out several chemical transformations in sequence.[5-7] Recently, looped flow processes – where the main reactor consists of a closed looped tubular system – have been (re)investigated for the synthesis of complex macromolecular materials.[8] Already in 1990, liquid phase (free radical) polymerizations of olefins were carried out in a 'loop reactor' on an industrial scale.[9-11] Later, emulsion polymerizations were carried out in a continuous 'loop reactor'.[12, 13] Only recently, the first 'looped flow process' for controlled radical polymerizations was reported, where well-defined multiblock copolymers were prepared via a reversible addition fragmentation chain transfer (RAFT) polymerization.[8] Yet, similar processes are also achievable with near identical efficiency via linear continuous flow processes.[7] Thus, the main potential of looped flow processes – the ability to use higher concentrations compared to a batch process – has not fully been exploited in the polymer field.

The principle of looped flow processes is based on the use of a recycle loop, whereby the solution circulates in a closed reactor circuit. Looped flow processes are not truly continuous since no outlet flow is generated. Yet, looped flow reactors have the same advantages as other continuous flow processes due to similar reactor characteristics. Thereby, they allow the gradual addition of reagents, as equivalent to the batch wise 'slow-addition' method via the use of a dropping funnel or a syringe pump. Generally, such method can be employed to reduce side reactions or to establish higher product concentrations. Hence, the productivity of the process can be increased significantly when compared to the original batch or linear continuous flow processes. Here, a looped flow reactor was designed to carry out a photo-induced ring-closure reaction generating cyclic polymers (refer to Scheme 1). Cyclic polymers are interesting because of their more compact nature compared to their linear analogues and are thus the most simplistic version of a compacted polymer chain.[14-16] Generally, cyclic polymers have a smaller hydrodynamic volume compare to their linear counterparts, but also exhibit higher glass transition temperatures, lower intrinsic viscosities and higher critical solution temperatures.[17-23] Yet, to synthesize these cyclic



Scheme 1. Light-induced ring-closure reaction between the dithioester and an *o*-methyl-substituted aromatic aldehyde endgroups of a linear methacrylate precursor polymer.

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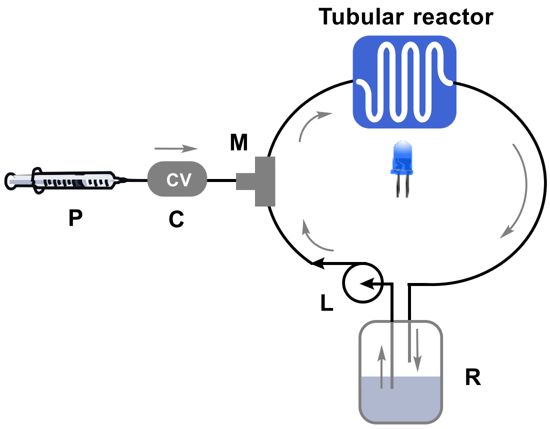
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x polymers in high purity, a highly diluted (< 0.1 g L^{-1}) reaction solution is typically required to avoid intermolecular coupling. This seriously hampers scalability when a traditional process is used and requires excessive amounts of solvent even for small product amounts. A first flow process for the synthesis of cyclic polymers has already been described, yet requires 17.3 L of solvent to produce 1 g of cyclic polystyrene.[18] While in this study, the flow reactor already helped to reach higher reaction efficiencies and made handling of large solvent volumes somewhat easier, the core problem – the sheer use of large volumes of solution – was not solved. Hence, a looped flow process is developed herein as alternative, in order to reduce the required amount of solvent by increasing the product concentration.



Scheme 2. Looped flow reactor representation for the light-induced ring-closure of an α,ω-functionalized linear precursor toward cyclic polymers.

First, a flow reactor is constructed to carry out a light-induced reaction in the reactor loop (refer to Scheme 2, Figure S1). The main feature of the looped flow reactor is the loop pump ('L'), providing a continuous recycle stream from the reservoir ('R', solvent + product) through the loop. An injection pump ('P') takes care of injecting the α,ω-functionalized linear precursor gradually into the reactor system via the use of a check valve ('C'). The injected solution is immediately diluted by the recycle stream via the use of a static mixing tee ('M'), after which it directly undergoes the light-induced ring-closure reaction under the influence of a UV lamp (peak wavelength of 312 nm). Via the difference in flow rate between the loop and the dosing from pump D, no significant volume increase in the loop is required when injection the precursor from a concentrated solution at low rate. Since the starting material concentration in this setup is at all times low – while product can accumulate – it is possible to work in the highly diluted concentration regime without the need for excessive amounts of solvent. More technical details on the setup can be found in the ESI.

For cyclization, the well-known photo-enol ring-closure reaction is used, based on a difunctional RAFT agent (see Scheme 1).[24-26] The photo-enol reaction is light triggered, which provides convenient access to reaction conditions where the reaction only takes place in the reaction loop, but not in the syringe. In addition, the photo-enol reaction is very fast, allowing for conversions on a short time scale. Using a flow reactor increases the efficiency of the light reaction even further.[27, 28] An α,ω-functionalized linear polymethacrylate (PMA) was prepared as precursor polymer via RAFT polymerization with an α-methyl benzaldehyde functional RAFT agent. To ensure a high end group fidelity, a temperature of 70°C and a low azobisisobutyronitrile (AIBN) equivalence (0.05 eq compared to the RAFT agent) were employed, while monomer conversions of less than 100% were targeted. The α,ω-functionalized linear PMA precursor was obtained with 68% conversion, a number average molecular weight of 7000 g mol^{-1} and a dispersity of 1.3. (refer to Figure 3, and ESI for more details) The slight broadening can be explained by the not ideal match between the acrylate monomer and the dithiobenzoate RAFT agent. Yet, also the presence of light cannot completely be avoided during sample preparation, leading to the presence of a high molecular weight shoulder related to the intermolecular coupling of several polymer chains. After isolation of the linear polymer, the light-induced coupling of the functional end-groups of this precursor polymer was employed to investigate the required reaction conditions. Therefore, a 5 mg mL^{-1} solution was prepared by dissolving 19 mg precursor polymer in 3.8 mL acetonitrile and by purging with argon. As reactor set-up, the looped flow reactor was employed, thus injecting the precursor polymer via a syringe pump and diluting it with pure acetonitrile via the loop pump to mimic the recycle stream. However, the reaction mixture was not recirculated back into the reactor but was collected instead for analysis. Initially, the precursor polymer was diluted by a factor 50, leading to a total precursor polymer concentration of 0.1 g L^{-1}. Despite the low concentration, the light-induced reaction is extremely fast. A complete shift of the polymer distribution to lower apparent molecular weights – caused by the smaller hydrodynamic volume of the cyclic polymer – could be observed (Figure 3), indicating the quantitative conversion already for 15 s and 30 s residence time. No significant differences could be observed between the cyclic polymer formed after 15 s and after 30 s residence time, yet to stay on the side of caution, 30 s residence time was employed for further testing. Still, an increase of the high molecular weight fraction within the distribution is

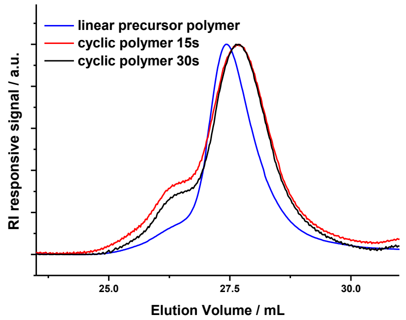


Figure 1. GPC chromatograms of the linear precursor polymer and the obtained cyclic polymers after 15 s and 30 s residence time (with a concentration of 0.1 g L^{-1}).

observed for both residence times, indicating the formation of intermolecular coupling products during the cyclization reaction.

Thus, to reduce this intermolecular coupling, different precursor polymer concentrations were tested by varying the flow rate of the injection pump. Three residual concentrations were assessed: 0.1 g · L^{-1}, 0.05 g · L^{-1} and 0.025 g · L^{-1}, of which the results are given in Table 1 and in Figure 4. The success of the intramolecular coupling is at all times clearly indicated by the shift to lower apparent molecular weights. Critically, a clear decrease of intermolecular coupling is observed when decreasing the concentration of the linear precursor. Although the differences between 0.05 g · L^{-1} and 0.025 g · L^{-1} are minimal, 0.025 g · L^{-1} was employed for further experiments to err on the side of caution and to assure maximum purity of the produced cyclic polymer.

Table 1. Results of the light-induced cyclization when employing 0.1 g · L^{-1}, 0.05 g · L^{-1} and 0.025 g · L^{-1} as precursor polymer concentrations.

Type of polymer	***Concentration* g · *L*$^{-1}$**	**M_n^{app} g · mol^{-1}**	**Đ**	**M_p^{app} g · mol^{-1}**
Precursor	/	7070	1.25	8840
Cyclic	0.1	7200	1.26	7890
Cyclic	0.05	6500	1.29	8040
Cyclic	0.025	6380	1.26	8170

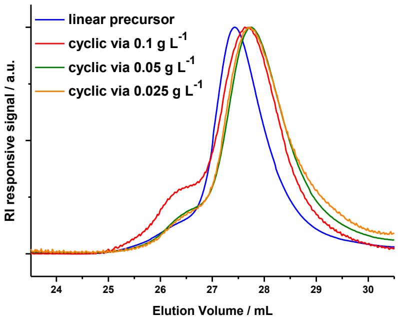


Figure 2 GPC chromatograms of the linear precursor polymer and the obtained cyclic polymers when employing 0.1 g · L^{-1}, 0.05 g · L^{-1} and 0.025 g · L^{-1} as precursor polymer concentrations.

Next, the cyclic polymers were prepared via the use of the looped flow reactor by employing the conditions derived above. Hence, a concentration of 0.025 g · L^{-1} of the α,ω-functionalized linear precursor was established by injecting the precursor polymer directly into the loop reactor. Therefore, a 5 mg · mL^{-1} precursor polymer solution was injected into the loop reactor, where it is directly diluted to 0.025 g · L^{-1}. The light-induced ring-closure takes place in the reactor loop with a residence time of 30 s by injecting the precursor polymer with a flow rate of 10 μL · min^{1}. Simultaneously, the looped pump was used to dilute the precursor polymer with the solvent/product mixture (initial solvent volume 10 mL) at a flow rate of 2 mL · min^{-1}. The reaction was allowed to proceed for 16 h 40 min, until 50 mg precursor polymer was converted into cyclic polymer in a total volume of 20 mL. The cyclic polymer was collected in a quantitative manner by evaporating the solvent/polymer mixture (refer to Figure 5). Since the precursor linear polymer and its corresponding RAFT agent are not easily available in larger quantities no further upscale was carried out. Since reaction conditions – as described above – were chosen quite conservatively and because a volume increase in the looped flow reactor could be realized without any problems, production of larger product quantities, significantly above gram scale should proceed without problems.

Compared to previously reported flow procedures, our looped flow process features clear advantages. Zhang and coworkers generated 1 g cyclic polystyrene in 17.3 L, in 3h by using a reactor with an internal volume of 200 mL. In comparison, our production rate seems rather low (50 mg in 16 h 40), yet this is rather related to the employed reactor with a loop volume of 1 mL than to the technology as noted above. Yet, the major advantage of a looped flow process is clearly the ability to reduce the required solution volumes by establishing a higher product concentration. As a consequence, we were able to reduce the required solution volumes by a factor 43 compared to the reported procedure by Zhang and coworkers (50 mg in 20 mL ~ 1 g in 400 mL compared to 17.3 L).[18] Most likely, the amount of required solution volume could be decreased even further is a shorter residence time is chosen.

Conclusions

Looped flow processes provide a continuous alternative to the batch-wise ‘slow-addition’ method, by allowing the gradual addition of reagents. Higher product concentrations can be established and thus the productivity of a process can be increased greatly. The looped flow process thus provides a straightforward upscalable procedure to all reactions limited by their concentrations, i.e. the synthesis of cyclic polymers in the present example. To synthesize these cyclic polymers in high purity, a ring-closure coupling reaction must be carried out in highly diluted reaction solutions (< 0.1 g L^{-1}). In comparison to previously reported procedures, the required solution volumes could be reduced by a factor of 43.

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