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ARTICLE TYPE

$Sn(OTf)_2$ catalyzed continuous flow ring-opening polymerization of ε-caprolactone

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A simple PTFE tubular microreactor based platform was developed to conduct metal-catalytic ring-opening polymerization of cyclic monomers. $Sn(OTf)_2$ catalyzed ε-caprolactone polymerization with benzyl alcohol as initiator was the model system for investigation. In contrast to the batch reactor, better control of reaction conditions, faster polymerizations and narrower molecular weight distributions of resultant poly(ε-caprolactone) were achieved in the continuous flow mode. The structure of product was characterized by ^{1}H NMR, SEC and MALDTI TOF MS. The kinetic study elucidated the living/control nature of $Sn(OTf)_2$ catalyzed continuous flow ring-opening polymerization of ε-caprolactone.

Well-defined aliphatic polyesters, such as poly(ε-caprolactone) (PCL) and poly(lactide) (PLA), have aroused much interest for their outstanding biodegradability, biocompatibility and the potential to be prepared from renewable bioresources.[1-3] They are identified as the good candidates for tissue engineering scaffolds,[4, 5] controlled drug delivery systems,[6] and microelectronics.[7]

Metal-, enzyme-, and organo-catalytic ring-opening polymerization (ROP) of cyclic monomers is the main synthetic protocol to aliphatic polyesters.[8-10] In the past two decades, although great progress has been made, the problems about uncontrolled properties and high cost of polyesters remained.[11] It is attributed to the low catalyst activity, the inevitable intermolecular/intramolecular transesterification side reactions and the traditional batchwise engineering challenges.[11] Where do we go from here?

One opportunity is to create a new polymerization platform to polyesters that enables (i) continuous processing with superior control of reaction conditions, (ii) accelerating polymerization rates, (iii) depressing the side reactions, and (iv) easy to scale up to industrial manufacturing.

Gross *et al*. firstly employed enzyme immobilized microreactor to conduct ε-caprolactone (CL) polymerization[12, 13] Faster polymerizations and higher number-averaged molecular weights (M_n) of PCL were revealed with comparison to using batch reactor. Moreover, the monomer conversion and the end-group fidelity could be maintained in microreactor even under "water saturated" conditions. This attracted work illuminated the promising alternative strategy to polyesters by using microflow system.

Microreactor has displayed considerable benefits over traditional batch mode.[14] Improved heat transfer efficiency, faster reaction rate, lower waste generation and safer experimental condition could be achieved in microreactor with huge surface-to-volume ratio.[15] Furthermore, microfluidic reaction could be varied easily and scaled up from laboratory to industry.[16] Almost all kinds of polymerizations have been explored in microreactor,[17] including traditional radical polymerization,[18] atom transfer radical polymerization (ATRP),[19] single electron transfer living radical polymerization (SET-LRP),[20] reversible addition fragmentation chain transfer (RAFT) polymerization,[21] anionic polymerization,[22] cationic polymerization[23] and ring-opening polymerization (ROP).[12, 13, 24] Currently, the microflow chemistry research continues rapidly growing, involving nanoparticle,[25] hydrogel,[26] microcapsule[27] and biomedical research.[28]

Inspired by the pioneering publications about microfluidic polymerizations, we take a research project to establish a new metal-catalytic continuous flow ROP platform to well-defined aliphatic polyester. The metal-free polymerizations by enzyme[29-31] or organocatalyst[32-38] have accomplished noteworthy achievement in synthesis of polyester, which preferred in biomedical and microelectronic applications. However, their disadvantages are extensive reaction times and rigorous purification of reagents and products.[39] Up to date, the commercial clinical polymeric biomaterial is widely prepared via metal-catalytic routes.[40]

Metal-complexes are one class of powerful catalysts for living/controlled ROP, including alkali-,[41] alkaline earth-,[42] poor metal-,[43] transition metal-[44] and rare earth metal-complexes.[45, 46] Among of them, stannous (II) 2-ethylhexanoate ($Sn(Oct)_2$),[47-52] authorized by FDA, was widely studied and used due to its commercial availability, simplicity to handle, toleration to moisture and solubility in common solvents. However, $Sn(Oct)_2$ showed catalytic activity at more than 120 ^oC for a long-term reaction time. The undesirable intermolecular/intramolecular transesterification resulted in the broad molecular weight distribution.[53] The stannous (II) trifluoromethane sulfonate ($Sn(OTf)_2$) was developed by Hedrick *et al*. as high performance

catalyst for living/controlled ROP of cyclic monomers at mild temperatures.[54] Poly(β-hydroxybutyrate),[54] PLA[55], poly(δ-valerolactone) (PVL)[56], and functional polycarbonates[39] were successively prepared by utilizing $Sn(OTf)_2$. However, the polymerization was a time consuming process ranging from 18 to 48 h. Moreover, the molecular weight distribution of resultant polyester was uncontrolled when increasing the reaction temperature.[54]

Recently, our group contributed a series works about microfluidic epoxidation of soybean oil and ROP of cyclic monomers.[16, 31, 58, 59, 60] In this article, we developed a metal-catalytic continuous flow polymerization platform to well-defined aliphatic polyester, by assembling a simple plug PTFE tubular microreactor and revisiting the classical $Sn(OTf)_2$ catalyst. Superiorities are exhibited in comparison with using batch reactor including (i) better control of reaction conditions, (ii) faster polymerization and (iii) narrower molecular weight distribution. We hope that this inexpensive and feasible continuous flow system can be extended to fabricate block, graft and branched functional polyesters with controlled properties.

Taking into account of the feasibility of assembling, heat transfer property, chemical resistance and running cost, we assembled a simple bench-top plug PTFE tubular microreactor with T-type mixer (Fig. 1).[20] $Sn(OTf)_2$ catalyzed ROP of CL in the presence of BnOH as initiator was exemplified as the model system for investigation.

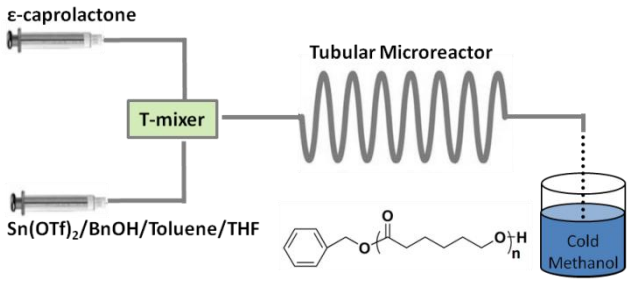

Fig. 1 Schematic bench-top plug PTFE microreactor system for $Sn(OTf)_2$ catalyzed ROP of CL with benzyl alcohol as initiator.

In the pioneering work of Hedrick *et al*., $Sn(OTf)_2$ catalyzed CL polymerizations were carried out at 20 °C, 40 °C, 65 °C and 110 °C in the batch mode.[54] The polymerization time was as long as 18 h at 65 °C. Although 99% polymer yield was obtained for 3 h at elevated temperature of 110 °C, the polydispersity index (PDI) was broadened into 1.30. To circumstance these disadvantages, we developed a continuous flow polymerization platform to enable faster polymerization and controlled PDI. We firstly conducted ROP of CL with targeted degree of polymerization (DP_{target}) of 10 in microreactor at 80 °C. The monomer conversions in a flow reaction are influenced by variation of the residence time, which could be easily and exactly tuned by adjusting the flow rate. About 90.1% CL conversion was accomplished for 40 min in microreactor, whereas 81.8% in batch mode. The kinetic study of continuous flow polymerization was carried out. As depicted in Fig. 2, the semilogarithmic plots of conversion as a function of time in both microreactor and batch reactor showed good linear correlations, which indicated the living/controlled polymerization characteristic. The slope in microreactor was larger than that in batch reactor.[12, 13] This is governed by more efficiently mixing of reactants through the mixer, strengthened heat transfer efficiency and shorter mass transport path length in the confined volume of microreactor.[14-16] Gross *et al*. reported that the apparent rate constant of enzymatic ROP of CL in microreactor (kapp=0.027 s^{-1}) was 27 times larger than in batch reactor (kapp=0.001 s^{-1}). In contrast, $Sn(OTf)_2$ catalyzed CL polymerization in PTFE tubular microreactor was not increased significantly. We assumed that it can be attributed to the limited mixing efficiency of simple T-type mixer.

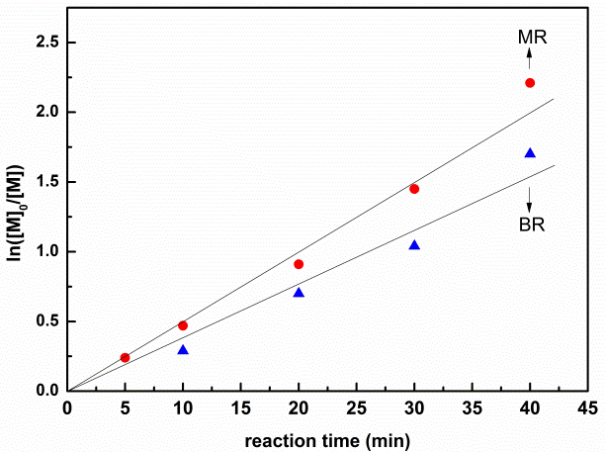

Fig. 2 Semilogarithmic kinetic plots for CL polymerization with DP_{target}=10 at 80 °C in microreactor and batch reactor.

The structure of resultant PCL in continuous flow was carefully characterized by ^1H NMR and MALDI TOF MS. Four main characteristic peaks were assigned to the protons in the PCL backbone (H^f, H^g, H^j, H^k and H^p) in Fig. S1. The typical triplet at 3.58 ppm was belonged to the methylene (H^a) adjacent to the OH. The signals of benzyl protons (H^r) appeared at around 7.29 ppm. Methylene (H^q) adjacent to the benzene was shown at 5.05 ppm. The end-group fidelity was calculated to be 97% by comparison the integrals between H^q and H^a. Less than 3% polymers were supposed to be trace water initiated PCL.[60] MALDI TOF MS provided more detailed information about polymer structure. Two series main peaks cationized by K^+ and Na^+ were clearly observed by separation of 114 m/z (Fig. S2), which corresponded to the molecular weight of the CL repeat unit. Additionally, the obtained molecular weights were exactly agreed with the theoretical values of benzyl-terminated PCL.

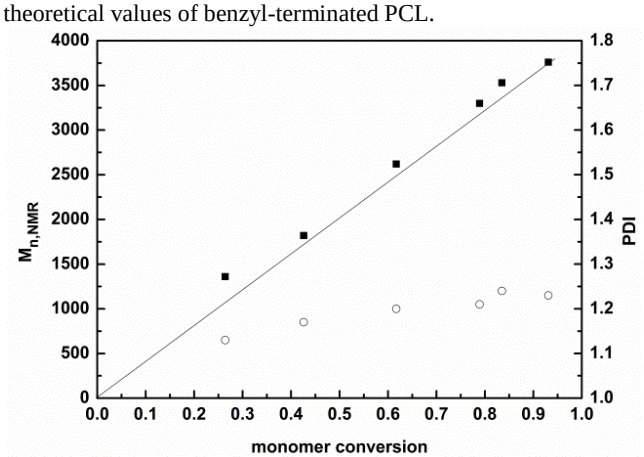

Fig. 3 Number-average molecular weight ($M_{n,NMR}$) and PDI versus monomer conversion for CL polymerization with DP_{target}=30 at 110 °C in microreactor.

To investigate the versatility of this metal-catalytic continuous flow polymerization platform, polymerization with DP_{target} of 30 was performed at elevated temperature of 110 °C. PCL ($M_{n,NMR}$=3760 g/mol) with 93.1% monomer conversion was generated for 80 min in microreactor. A linear increase of $M_{n,NMR}$ with respect to full conversion was reached in Fig. 3. And the $M_{n,NMR}$ values fairly agreed with the $M_{n,theo}$ calculated by the feed ratio of [CL]/[BnOH] and the monomer conversion.

The molecular weight distribution of the resultant PCL was uncontrolled at 110 °C in batch reactor.[54] Asymmetrical broad SEC peaks of PCL with $DP_{NMR,BR}$=13 (PDI=1.30) and $DP_{NMR,BR}$=30 (PDI=1.32) prepared in batchwise system were clearly observed in Fig. 4. It was resulted from the diffusing efficiency decrease and the intermolecular/intramolecular transesterification side reactions in batch reactor during the polymerization. These problems could be overcome by employing microreactor. Counterpart samples with $DP_{NMR,MR}$=11 (PDI=1.15) and $DP_{NMR,MR}$=32 (PDI=1.24) in microreactor exhibited symmetrical monomodal SEC traces. The PDI values in microreactor kept below 1.25, as depicted in Fig. 3. The effective mixing of reactants and less hotspots enabled high control of molecular weight distribution in the microfluidic system.

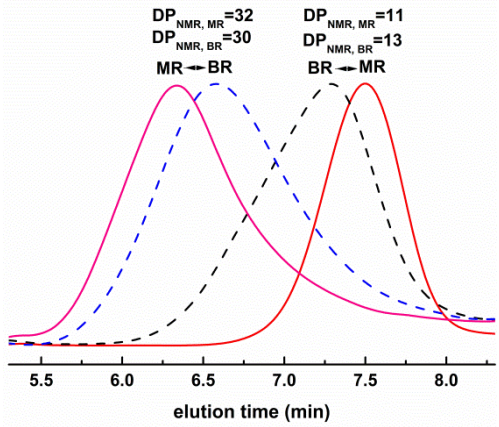

Fig. 4 SEC of PCL with DP_{target}=10 at 80 °C (40 min in microreactor and 80 min in batch reactor) and DP_{target}=30 at 110 °C (80 min in microreactor and batch reactor).

Conclusions

In the present work, we successfully established a metal-catalytic continuous flow polymerization platform to prepare well-defined polyester. Simple PTFE tubular microreactor with T-type mixer was easily assembled and used to perform $Sn(OTf)_2$ catalyzed ring-opening polymerization of ε-caprolactone with benzyl alcohol as initiator. Compared with traditional batch reactor, better control of reaction conditions, faster polymerizations and narrower molecular weight distributions were achieved in the continuous flow mode. This work can be readily extended to other catalytic ROP of cyclic monomer systems to prepare block, graft and branched polymers with controlled properties.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of experimental section, ^{1}H NMR and MALDI TOF MS of product]. See DOI: 10.1039/b000000x/

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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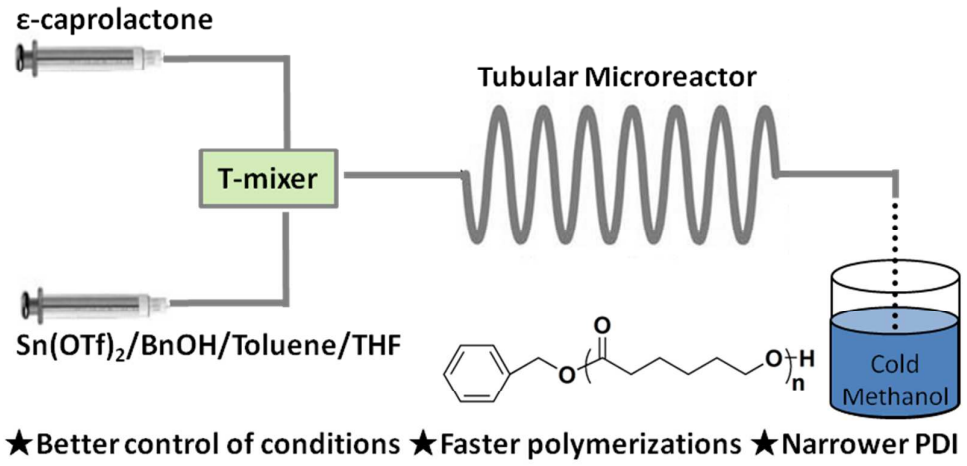

A PTFE tubular microreactor based platform to conduct $Sn(OTf)_2$ catalyzed ring-opening polymerization (ROP) was developed to well-defined aliphatic polyester. Benzyl alcohol initiated ε-caprolactone (CL) polymerization in toluene/THF was the model system for investigation. In contrast to the batch reactor, better control of reaction conditions, faster polymerizations and narrower molecular weight distributions of resultant poly(ε-caprolactone) (PCL) were achieved in the continuous flow mode. The structure of product was characterized by ^1H NMR, SEC and MALDTI TOF MS. The kinetic study revealed the living/control nature of the continuous flow ROP of CL.