

Akihiro Abe · Kwang-Sup Lee
L. Leibler · Shiro Kobayashi
Editors

Controlled Polymerization and Polymeric Structures

Flow Microreactor Polymerization,
Micelles Kinetics, Polypeptide Ordering,
Light Emitting Nanostructures

259

Advances in Polymer Science

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The series *Advances in Polymer Science* presents critical reviews of the present and future trends in polymer and biopolymer science. It covers all areas of research in polymer and biopolymer science including chemistry, physical chemistry, physics, material science.

The thematic volumes are addressed to scientists, whether at universities or in industry, who wish to keep abreast of the important advances in the covered topics.

Advances in Polymer Science enjoys a longstanding tradition and good reputation in its community. Each volume is dedicated to a current topic, and each review critically surveys one aspect of that topic, to place it within the context of the volume. The volumes typically summarize the significant developments of the last 5 to 10 years and discuss them critically, presenting selected examples, explaining and illustrating the important principles, and bringing together many important references of primary literature. On that basis, future research directions in the area can be discussed.

Advances in Polymer Science volumes thus are important references for polymer scientists, or scientists interested in polymer science - as an introduction to a neighboring field, or as a compilation of detailed information for the specialist.

Review articles for the individual volumes are invited by the volume editors. Single contributions can be specially commissioned.

Publisher's Note

The present volume of *Advances in Polymer Science* is a collection of substantial review articles on interesting and valuable subjects from different areas of Polymer Science. The volume was not originally planned as a topical volume. The articles were invited and reviewed by the Series Editors of *Advances in Polymer Science* on an independent basis. The collected articles were put together for publication by the publisher.

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Akihiro Abe · Kwang-Sup Lee · L. Leibler ·
Shiro Kobayashi
Editors

Controlled Polymerization and Polymeric Structures

Flow Microreactor Polymerization, Micelles
Kinetics, Polypeptide Ordering, Light
Emitting Nanostructures

With contributions by

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Controlled Polymerization in Flow Microreactor Systems

Aiichiro Nagaki and Jun-ichi Yoshida

Abstract Flow microreactors are expected to make a revolutionary change in chemical synthesis in various fields of polymer synthesis. In fact, extensive studies on cationic polymerization, anionic polymerization, radical polymerization, coordination polymerization, polycondensation, and ring-opening polymerization using flow microreactor systems have opened new possibilities in polymer chemistry and the polymer industry. This article provides, in a concise form, a current overall picture of polymerization using flow microreactors.

Keywords Controlled polymerization · Fast mixing · Flow · Microreactor · Molecular weight control · Molecular weight distribution control · Residence time control · Temperature control

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1 Introduction

Microtechnology is no longer the field of electronics, but is now moving into many different areas of science and engineering, including mechanics, optics, and fluids, because it provides better efficiencies while also answering the demands of society for conservation of resources and energy. Following remarkable advances in microfabrication technology, microtechnology has been used in the field of chemistry since the 1990s. Microdevices that are used for chemical reactions are called microreactors and are reactors with micrometer-sized channels in which chemical reactions are carried out.

Microreactors are normally set up as flow-type reactors (flow microreactors) with a continuous flow of a solution through the reaction chamber. Nowadays, chemical synthesis in flow microreactors is receiving significant research interest from both academia and industry [1–24]. Recent investigations have revealed significant features of flow microreactor systems involving fast mixing, stemming from short diffusion paths and fast heat transfer by virtue of high surface-to-volume ratios, which are advantageous for increasing the selectivity of chemical reactions [25–28]. Short residence time in a microchannel is beneficial for controlling highly reactive intermediates [29–45]. By taking advantages of such features of flow microreactor systems, various chemical reactions for organic synthesis have been developed [46–56].

Polymerization reactions that convert small molecules into macromolecules by repeating chemical reactions are a fascinating field in the application of flow microreactors. Extensive studies on cationic polymerization, anionic polymerization, radical polymerization, coordination polymerization, polycondensation, and ring-opening polymerization using flow microreactor systems have been carried out so far. Reviews on various polymerization methods in microreactors have been reported by Hessel et al., Wilms et al., Steinbacher and McQuade, and Bally et al. [57–61]. The main objective of this article is to provide, in a concise form, a current overall picture of polymerization using flow microreactors, especially from the viewpoint of industrial applications. Because of space limitations, polymer particle synthesis will not be discussed here. Serra and Chang have published an excellent review on synthesis of polymer particles with an improved control of their sizes, size distributions, morphologies, and compositions using microreactors [62].

1.1 Characteristic Features of Flow Microreactors

Flow microreactors can influence the very essence of chemical reactions because of the following characteristic features derived from their small size and flow nature:

1. *Fast mixing* [63, 64]: Many chemical reactions involve combining two substances, and for this reason mixing to achieve homogeneity in solution is very important, especially for fast reactions. Mixing occurs due to molecular

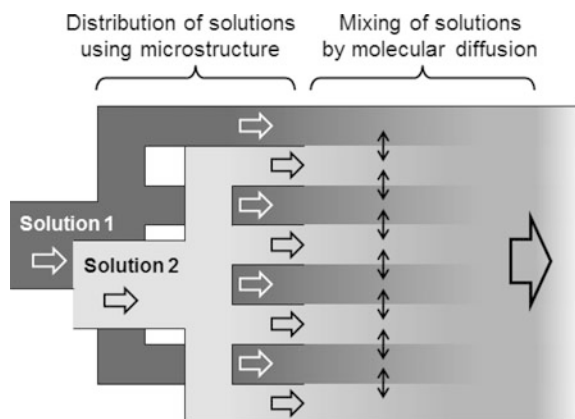


Fig. 1 Working principles of a multilamination-type micromixer

diffusion. According to the theory of molecular diffusion, the time needed for molecular diffusion is proportional to the square of the length of the diffusion path. Therefore, the marked shortening of the diffusion path in a microreactor results in a mixing speed that is unobtainable in a macroreactor. The working principle of a typical micromixer (i.e., a multilamination-type micromixer [65]) is shown in Fig. 1. The solutions to be mixed are distributed into several segments of flows of small width by using the microstructure. Mixing takes place through the interfaces of the segments of flow by virtue of the short diffusion path.

2. *Temperature control*: Heat is transferred between the interior and exterior of a reactor via the reactor surface according to the theory of heat transfer. Therefore, area per unit volume of the reactor is a crucial factor for heat transfer. Generally, volume is equal to the length cubed, and surface area is equal to length squared. When the length is shortened, the surface-to-volume ratio increases. Thus, a feature of microspaces compared to macrospace is that they have larger surface-to-volume ratios (Fig. 2). Because microreactors have a greater surface area per unit volume than macroreactors, heat transfer occurs rapidly in a flow microreactor, enabling fast cooling and heating and, hence, precise temperature control.

Another characteristic feature of microreactors derived from their much greater surface-to-volume ratios is that they make phase-boundary reactions such as gas–liquid, liquid–liquid, or solid–liquid reactions more efficient. This feature of flow microreactors is also advantageous for photochemical [66–75] and electrochemical [76–86] reactions, which have received significant attention from the viewpoint of environmentally benign syntheses.

3. *Residence time control*: The length of time that the solution remains inside the reactor is called the residence time. In flow reactors, the residence time increases with the length of the channel and decreases with the flow speed. In flow microreactors, the residence time can be greatly reduced by shortening the length of the microchannels. This feature of flow microreactors is extremely

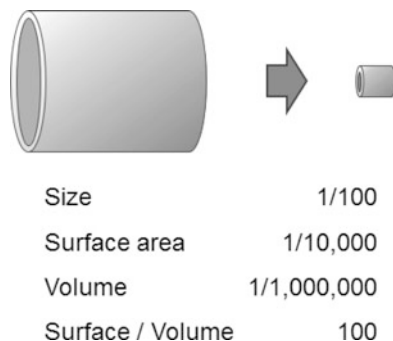


Fig. 2 Numerical aspects of decreasing size

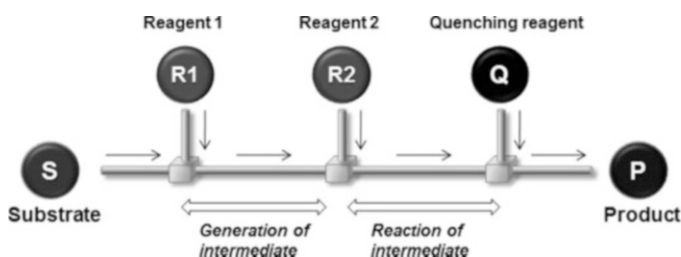


Fig. 3 Principle of generation and reaction of unstable short-lived reactive intermediates based on residence time control in a flow microreactor

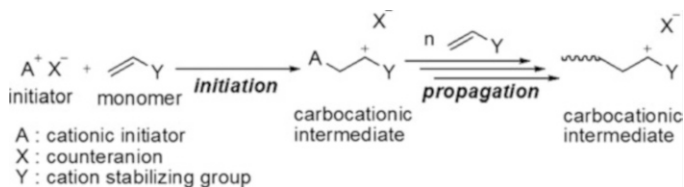
useful in controlling reactions involving unstable short-lived reactive intermediates. Unstable reactive species can be transferred to another location to be used in the next reaction before they decompose (Fig. 3). By taking advantage of this feature, chemical transformations that are very difficult or impossible in macroreactors can be achieved in microreactors [87–90].

1.2 Cationic Polymerization

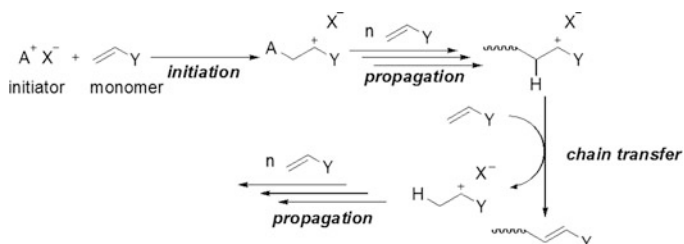
1.2.1 Basic Principles of Cationic Polymerization of Vinyl Monomers

Cationic polymerization [91, 92] is one of the most fundamental methods of synthesizing polymers. Although there are several types of cationic polymerization, the most important is cationic polymerization of vinyl monomers having a cation stabilizing group (Y) (Scheme 1).

The initiation usually involves the addition of a cationic species (A^+) to a vinyl monomer to produce a carbocationic intermediate associated with a counter anion (X^-), which is derived from the initiator. In general, proton acids or carbocations generated from their precursors by acid-promoted ionization reactions [93–95], are



Scheme 1 Cationic polymerization of vinyl monomers

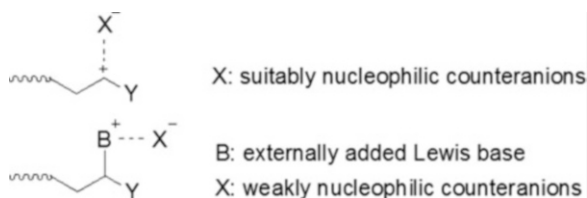


Scheme 2 Chain transfer as a side reaction in cationic polymerization of vinyl monomers

used as initiators. The carbocationic intermediate thus obtained adds to another molecule of the monomer to give the next carbocationic intermediate, which adds to another monomer (propagation step). The carbocationic intermediates are usually highly reactive and unstable. They undergo a number of side reactions such as chain transfer and termination. Chain transfer to monomer is the most problematic with regards control of molecular weight and molecular weight distribution. Namely, the β -proton of the carbocationic intermediate is inherently acidic because of the positive charge on the carbon. On the other hand, monomers used in cationic polymerization are inherently nucleophilic or basic. Therefore, the proton abstraction from the carbocationic intermediate by the monomer is inevitable and very difficult to suppress (Scheme 2).

1.2.2 Controlled/Living Cationic Polymerization of Vinyl Monomers Based on Cation Stabilization

One of the most important breakthroughs in cationic polymerization is the discovery of living cationic polymerization. The inherent and serious drawback of cationic vinyl polymerization is instability of the carbocationic intermediates, which causes the chain transfer leading to the formation of polymers of broad molecular weight distribution. Higashimura, Sawamoto, and coworkers proposed and verified experimentally that living cationic polymerization can be attained by stabilizing the carbocationic intermediate by nucleophilic interaction with a suitably nucleophilic counter anion or an externally added Lewis base (B) (Scheme 3) [96–98].



Scheme 3 Stabilization of the carbocationic intermediate by nucleophilic interaction with a suitably nucleophilic counteranion or an externally added Lewis base

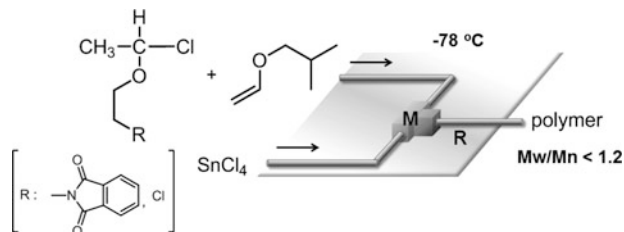
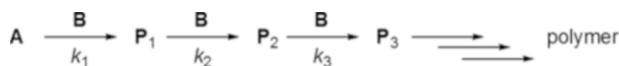


Fig. 4 Flow microreactor system for controlled/living cationic polymerization of vinyl ether initiated by SnCl_4 . M interdigital multilamination micromixer, R microtube reactor

In both methods the positive charge of the carbocationic center is reduced and thereby the acidity of the β -proton is reduced to suppress the chain transfer. As a result, good molecular weight control and molecular weight distribution control are attained. On the basis of the principles, a number of initiating systems have been developed for living cationic polymerization [99].

1.2.3 Controlled/Living Cationic Polymerization of Vinyl Ethers Based on Cation Stabilization Using Flow Microreactor Systems [100]

Living cationic polymerization of vinyl ethers initiated by the SnCl_4/RCl catalytic system can be carried out in a continuous microreactor system consisting of an interdigital multilamination micromixer (channel width = 40 μm) and a microtube reactor (Fig. 4). A solution of a monomer and an initiator's precursor is mixed with a solution of SnCl_4 using the micromixer at -78°C and the resulting mixture allowed to react in the microtube reactor at the same temperature. For example, isobutyl vinyl ether (IBVE) can be polymerized using functionalized initiators to obtain end-functionalized polymers of narrow molecular weight distribution (weight-average molecular weight/number-average molecular weight, $M_w/M_n < 1.2$). Block copolymerization of IBVE and n -butyl vinyl ether (NBVE) can also be successfully achieved using a microreactor system consisting of two micromixers and two microtube reactors to obtain the corresponding copolymer of narrow molecular weight distribution ($M_w/M_n < 1.3$).



Scheme 4 Polymerization as a competitive consecutive reaction

1.2.4 Controlled/Living Cationic Polymerization of Vinyl Ethers Without Stabilizing Carbocationic Intermediates Using Flow Microreactor Systems

One of the major drawbacks of the controlled/living cationic polymerization based on stabilization of the carbocationic intermediates is slow propagation. Because the concentration of the active propagating species is very low because of the equilibrium between active species and dormant species, overall polymerization reactions are much slower than those without the equilibrium. Another important drawback of the controlled/living polymerization is the use of additives such as Lewis bases. Such additives remain in polymer products and are generally rather difficult to remove from the polymer products.

Recently, it has been demonstrated that good control of molecular weight and molecular weight distribution can be attained by using microreactor systems without stabilizing the carbocationic intermediates. The concept of this new technology (flow-microreactor-system-controlled polymerization) is described in the following section.

Concept of Flow-Microreactor-System-Controlled Polymerization Technology

Control of molecular weight and molecular weight distribution in polymerization can be seen as control of competitive consecutive reactions as shown in Scheme 4, where A is an initiator and B is a monomer.

In the first step, initiator (A) reacts with monomer (B) to produce the first carbocationic intermediate P_1 . In the second step, P_1 reacts with another monomer to produce the second carbocationic intermediate P_2 . Further reactions lead to polymer formation. If the initiation step to give P_1 is faster than the propagation steps, there is a chance to obtain good molecular weight control and molecular weight distribution control based on monomer/initiator ratios. However, this is the case only when the reactions are slower than the mixing and the reactions proceed in a homogeneous solution. If reactions are faster than mixing, a significant amount of P_2 (and P_n , where $n > 2$) is formed before initiator A is consumed, even if $k_1 \gg k_2$. In this case, it is meaningless to define concentrations of A and B based on the total volume of the solution because the solution is not homogeneous and the product selectivity is not determined by kinetics. This problem is similar to the problem of disguised chemical selectivity for competitive consecutive reactions [101] and can be solved by extremely fast micromixing. In fact, the enhancement of product selectivity of competitive consecutive reactions [102] such as Friedel–Crafts reactions [103, 104], [4+2] cycloaddition reactions [105, 106],

lithiation of dibromobiaryls [107–110], iodination of aromatic compounds [111, 112], and the reaction of a Grignard reagent with $B(OMe)_3$ [113] by virtue of extremely fast micromixing using flow microreactor systems has been reported. These successful results suggest the possibility of molecular weight and molecular weight distribution control by using flow microreactor systems.

In flow-microreactor-system-controlled polymerization, extremely fast mixing of an initiator solution and a monomer solution leads to selective initiation. Propagation proceeds on the basis of the monomer/initiator ratio under homogeneous conditions, and therefore polymers are obtained with good control of molecular weight and molecular weight distribution. Minimization of local deviations in temperature by fast heat transfer through the wall of a microreactor by virtue of the high surface-to-volume ratios is also important because polymerization processes are usually highly exothermic.

“Cation Pool”-Initiated Polymerization of Vinyl Ethers Using Flow Microreactor Systems

Flow-microreactor-system-controlled cationic polymerization requires extremely reactive initiators, and highly reactive organic cations can serve as effective initiators for this method. Usually, organic cations such as carbenium ions and onium ions are generated by an acid-promoted reversible process from their precursors. Yoshida and coworkers have developed the “cation pool” method [114, 115] in which organic cations are generated irreversibly by low temperature electrolysis and are accumulated in relatively high concentration in the absence of nucleophiles. *N*-acyliminium ions [116], alkoxy-carbenium ions [117–121], diarylcarbenium ions [122, 123], and glycosyl triflate [124] have been generated and accumulated by this method. Yoshida and coworkers reported that *N*-acyliminium ion pools serve as extremely reactive initiators for cationic polymerization in flow microreactors [116].

A pool of an *N*-acyliminium ions is generated by low-temperature electrochemical oxidation of its precursor, a α -silyl-substituted *N*-acylamine. Cationic polymerization of NBVE using the *N*-acyliminium ion as an initiator in a conventional batch reactor gives the polymer in a quantitative yield after quenching with *i*-Pr₂NH/CH₂Cl₂, but the molecular weight distribution is broad ($M_n = 5,700$, $M_w/M_n = 2.56$). The reverse addition sequence (the *N*-acyliminium ion to the monomer) gives rise to a similar molecular weight distribution (quantitative yield, $M_n = 13,100$, $M_w/M_n = 2.25$). The simultaneous addition of a monomer solution and a solution of the *N*-acyliminium ion does not improve the molecular weight distribution control (quantitative yield, $M_n = 24,500$, $M_w/M_n = 2.43$). The molecular weight, however, strongly depends upon the method of mixing because the rate of the polymerization is so fast. In contrast, the use of a flow microreactor system consisting of two micromixers (M1 and M2) and two microtube reactors (R1 and R2) shown in Fig. 5 leads to excellent control of molecular weight and its distribution ($M_n = 6,700$, $M_w/M_n = 1.14$) [125]. Solutions of *N*-acyliminium ion (because the yield of *N*-acyliminium ion from precursor is estimated to be about 80% based on the

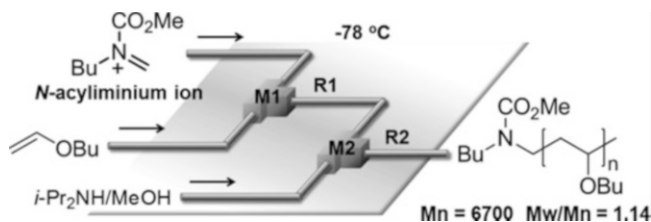


Fig. 5 Flow microreactor system for polymerization of vinyl ether initiated by *N*-acyliminium ion (cation pool). *M1*, *M2* micromixers; *R1*, *R2* microtube reactors

Table 1 Cationic polymerization of NBVE initiated by *N*-acyliminium ion using a flow microreactor system

Run	Monomer (equiv.)	Flow rate (mL/min)	Temperature (°C)	M_n	M_w/M_n
1	10	5.0	-78	1,500	1.40
2	25	5.0	-78	2,900	1.26
3	35	5.0	-78	4,400	1.17
4	50	5.0	-78	6,700	1.14
5	50	3.0	-78	5,600	1.35
6	50	1.0	-78	6,200	2.84
7	50	5.0	-48	8,200	1.30
8	50	5.0	-27	5,500	1.34
9	50	5.0	0	6,500	1.61

reactions with various nucleophiles, 1.2 equiv. of precursor is used when 1.0 equiv. of *N*-acyliminium ion is needed for polymerization) and NBVE are introduced to *M1* by the syringe pump technique at -78°C . Then, the reaction mixture is introduced to a microtube reactor (*R1* in Fig. 5) ($\phi = 1.0$ mm, 10 cm), in which the polymerization takes place. In the final stage, *i*-Pr₂NH/CH₂Cl₂ is introduced at *M2* to quench the polymerization. The polymerization takes place quite effectively and is complete within the residence time of 0.05 s to give the polymer with narrow molecular weight distribution ($M_n = 6,700$, $M_w/M_n = 1.14$). The molecular weight can be controlled by changing the monomer/initiator ratio. The molecular weight (M_n) increases linearly with the amount of NBVE, indicating that chain transfer reactions do not play a significant role in this system.

The effect of the flow rate on molecular weight distribution (Table 1, runs 4–6) indicates the importance of mixing, because it is known that mixing efficiency decreases with a decrease in the flow rate in the micromixer [65]. Reaction temperature is also important for controlling molecular weight distribution, as demonstrated by an increase in M_w/M_n with an increase in temperature (runs 4 and 7–9). A high level of molecular weight control can also be achieved by control of the initiation process by fast micromixing. Precise control of polymerization temperature also seems to be responsible for the remarkable control.

The polymer end is “living” within the residence time of 0.5 s at -78°C , and can be effectively trapped by allyltrimethylsilane. Moreover, the “cation pool”-initiated

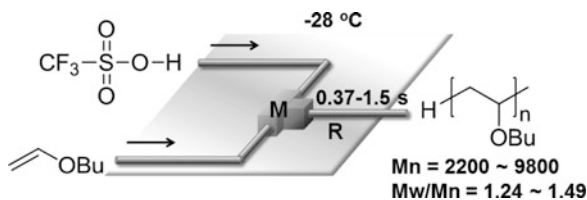


Fig. 6 Flow microreactor system for polymerization of vinyl ethers initiated by TfOH. *M* T-shaped micromixer, *R* microtube reactor

polymerization using a microreactor system can be applied to other vinyl ethers such as IBVE and *tert*-butyl vinyl ether (TBVE) to obtain the corresponding polymers (M_w/M_n of 1.12 for IBVE and 1.50 for TBVE), though the corresponding polymerization using batch macroreactors results in much poorer molecular weight distribution control (M_w/M_n of 4.31 for IBVE and 2.29 for TBVE).

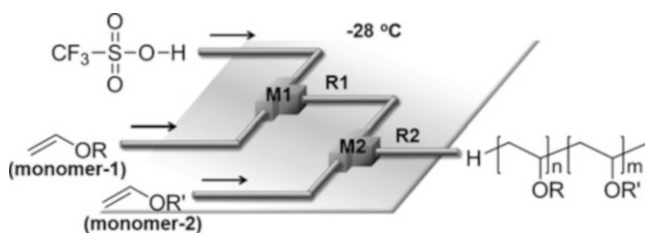
Brønsted-Acid-Initiated Polymerization of Vinyl Ethers Using Flow Microreactor Systems

Proton addition is one of the most simple and straightforward methods for the initiation of cationic polymerization. Brønsted acids are effective for this purpose. However, if we use a weak Brønsted acid, i.e., a conjugate acid of a strong nucleophilic anion, the addition of a Lewis acid is necessary to establish a reversible activation of a covalent end group for effective propagation. On the other hand, if we use a strong Brønsted acid, i.e., a conjugate acid of an extremely weak nucleophilic anion, the addition of a Lewis base is required to stabilize the carbocationic propagating polymer ends [98]. In the absence of a Lewis base, highly ionic polymer ends are too reactive and participate in transfer reactions by loss of β -protons, leading to a very broad molecular weight distribution.

Trifluoromethanesulfonic acid (TfOH) is an effective initiator for cationic polymerization. For example, TfOH-initiated polymerization of IBVE in 1,2-dichloroethane using a batch macroreactor [126] is complete within 10 s at -25°C . The molecular weight distribution is, however, rather broad and ranges from 2.73 to 4.71, presumably because of chain transfer reactions due to high reactivity of the polymer ends. By employing flow microreactor systems consisting of a T-shaped micromixer and a microtube reactor, however, cationic polymerization using a strong Brønsted acid such as TfOH can be accomplished in a highly controlled manner without adding a Lewis base (Fig. 6) [127]. The polymerization is complete within the residence time of 0.37–1.5 s at -25°C (almost quantitative yields). The degree of molecular weight distribution control strongly depends on the inner diameter of the mixer and the flow rate, as depicted in Table 2. M_w/M_n decreased with a decrease in the mixer inner diameter, presumably because faster mixing is achieved by a mixer of smaller diameter. M_w/M_n also decreases with an increase in the flow rate, probably because the increase in flow rate enhanced the mixing efficiency. High level of

Table 2 TfOH-initiated polymerization of isobutyl vinyl ether (IBVE) in a microreactor system

T-shaped inner diameter (μm)	Flow rate (mL/min)		M_n	M_w/M_n
	NBVE	TfOH		
250	2	2	2,900	2.30
	3	3	2,400	2.34
	4	4	1,600	1.61
	5	5	1,500	1.22
	6	6	1,500	1.22
	7	7	1,500	1.19
	8	8	1,500	1.22
	500	5	5	2,000
6		6	1,500	1.82
7		7	1,400	1.67
800	6	6	2,500	2.27

**Fig. 7** Flow microreactor system for block copolymerization of vinyl ether initiated by TfOH. *M1*, *M2* micromixers; *R1*, *R2* microtube reactors

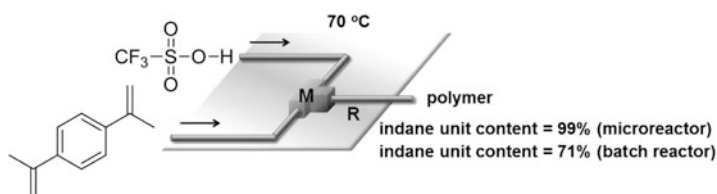
molecular weight distribution control can be attained even at -25°C . It is important to note that very low temperatures such as -78°C , which might be an obstacle to industrial-scale applications, are not required.

One of the advantages of controlled/living polymerization is that the method allows flexible synthesis of structurally defined block copolymers composed of different monomers, offering greater opportunities for synthesis of organic materials with interesting properties.

An example of microreactor systems for block copolymerization is shown in Fig. 7. The first monomer IBVE is mixed with TfOH in the first micromixer (*M1*). Introduction of the second monomer (NBVE or EVE) at the second micromixer *M2* results in the formation of the polymer of higher molecular weight with narrow molecular weight distribution [128]. Block copolymerization can be carried out with any combination and with either order of monomer addition, as shown in Table 3, demonstrating that the present method serves as a flexible method for the synthesis of block copolymers. Therefore, flow-microreactor-system-controlled polymerization can serve as a powerful method for synthesis of structurally well-defined polymers and copolymers in industry.

Table 3 Block polymerization of vinyl ether initiated by TfOH using the flow microreactor system

Monomer-1	Monomer-2	M_n	M_w/M_n
IBVE	–	1,500	1.18
IBVE	NBVE	2,300	1.43
IBVE	EVE	2,400	1.54
NBVE	–	1,000	1.24
NBVE	IBVE	1,700	1.45
NBVE	EVE	1,900	1.55
EVE	–	860	1.16
EVE	IBVE	2,100	1.54
EVE	NBVE	2,100	1.41

**Fig. 8** Flow microreactor system for cationic polymerization of 1,4-diisopropenylbenzene initiated by TfOH. *M* T-shaped micromixer, *R* microtube reactor

1.2.5 Cationic Polymerization of Diisopropenylbenzenes Using Flow Microreactor Systems

Polyindanes have received significant research interest because of their remarkable thermal resistance. Extensive work on the synthesis of 1,1,3-trimethyl-substituted polyindanes by cationic polymerization of 1,4-diisopropenylbenzenes and their thermal properties has been carried out by Nuyken and coworkers [129, 130]. The polymers of high indane-unit content serve as useful materials because of their high thermal resistance and low dielectric constants. The use of flow microreactor systems is effective for increasing the indane-unit content. In fact, indane-unit content (99%) was much higher in the flow microreactor system than that (71%) for the batch macrosystem under similar conditions (70°C , $[1,4\text{-diisopropenylbenzene}] = 0.1\text{ M}$, $[\text{TfOH}] = 2\text{ M}$) (Fig. 8) [131]. The characteristic features of flow microreactor systems including fast mixing and uniformity of the temperature seem to be responsible.

1.3 Anionic Polymerization

1.3.1 Controlled/Living Anionic Polymerization of Vinyl Monomers

Living anionic polymerizations have received significant attention since Michael Szwarc's first report in 1956 [132]. Anionic polymerization [133–137] serves as an important and powerful method for macromolecular engineering, permitting the preparation of highly defined block copolymers, star polymers, and further complex architectures, because the anionic polymer ends are living even in the absence of a capping agent [138, 139]. In fact, the anionic growing polymer ends (usually organolithium species) can be utilized for end-functionalization reactions with various electrophiles and block copolymerization with other monomers. A major drawback of conventional anionic polymerization in polar solvents in batch macroreactors is the requirement for low temperatures, such as -78°C [140]. Such a requirement causes severe limitations in the use of this highly useful polymerization in industry. Using nonpolar solvents, the polymerization can be conducted at higher temperatures, but much longer reaction time is needed for completion. It is also problematic that the use of individually manufactured laboratory equipment is frequently necessary.

Kinetic studies on anionic polymerization in a continuous flow mode have also been reported by Szwarc and coworkers [141, 142], Schulz and coworkers [141, 142], and Muller and coworkers [143, 144]. However, preparative anionic polymerizations in continuous flow mode have not been studied until recently.

1.3.2 Controlled/Living Anionic Polymerization of Styrenes

Anionic polymerization of styrenes is a highly useful technique for the synthesis of polystyrenes with precisely adjustable molecular weights and molecular weight distributions and is applied for the synthesis of structurally well-defined polymers such as end-functionalized polymers and block copolymers.

Controlled/Living Anionic Polymerization of Styrenes in Polar Solvent Using Flow Microreactor Systems [145]

In a conventional anionic polymerization of styrenes in polar solvents in a batch macroreactor, major drawbacks include the requirement of low temperature such as -78°C . In contrast, Nagaki et al. reported that controlled anionic polymerization of styrene can be conducted under easily accessible conditions such as 0°C in a polar solvent using a flow microreactor to obtain the polystyrene with narrower molecular weight distribution ($M_n = 1,200\text{--}20,000$, $M_w/M_n = 1.09\text{--}1.13$) (Fig. 9) [146]. Moreover, the molecular weight can be easily controlled by changing the flow rates of monomer and initiator solutions. Furthermore, these methods can be

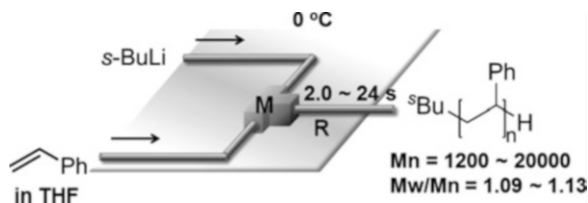


Fig. 9 Flow microreactor system for anionic polymerization of styrene in THF. *M* T-shaped micromixer, *R* microtube reactor

applied to styrene derivatives having silyl, methoxy, alkynyl, and alkylthio groups on the benzene ring. Wurm et al. also reported the anionic polymerization of styrene at 20°C using a flow microreactor [147]. Polystyrenes in a broad range of molecular weight with a narrow molecular weight distribution can be obtained within several seconds ($M_n = 1,700\text{--}70,000$, $M_w/M_n = 1.09\text{--}1.41$). It should be noted that strict dryness of the apparatus and high vacuum techniques is needed in the classical batch methods but that such experimental effort can be significantly reduced by using flow microreactors. Residual impurities and moisture can be removed by purging the reactor with solutions of a monomer and an initiator before a solution of the desired polymer product is collected at the outlet of flow microreactors.

Integration of chemical reactions enhances the power and speed of organic and polymer synthesis, and recently it has been recognized that flow microreactors enable space-integration of reactions [148–153]. On the basis of livingness of the polymer end, structurally well-defined polymers such as end-functionalized polymers and block copolymers can be synthesized using integrated flow microreactor systems consisting of two micromixers and two microtube reactors. For example, functionalization of a living polymer end using chlorosilanes such as chlorotrimethylsilane and chlorodimethylvinylsilane is effectively achieved by using integrated flow microreactor systems to obtain polystyrenes bearing the silyl group at the terminal. Block copolymerization can also be achieved using the integrated flow microreactor system at 0°C and 24°C to obtain structurally defined block copolymers composed of two different styrenes in quantitative yields (Fig. 10).

End-functionalization with epoxides is also popular because epoxides have high reactivity toward nucleophiles by virtue of ring strain. Use of functionalized epoxides enables a further transformation after deprotection. For example, polymerization of styrene followed by end-functionalization with the various glycidyl ethers having acetal structures such as ethoxy ethyl glycidyl ether (EEGE), 1,2-isopropylidene glyceryl glycidyl ether (IGG), and *trans*-2-phenyl-1,3-dioxane glycidyl ether (PDGE) can be accomplished using a flow microreactor system (Fig. 11) [154]. The acetal and ketal protecting groups in the glycidyl ethers are stable toward the highly reactive carbanionic living polymer ends but they can be easily cleaved under acidic conditions to afford multihydroxyl end-functionalized polymers (Fig. 12).