15
Polycondensation

Takeshi Honda and Hideaki Maeda

15.1
Introduction

Microfluidic systems (microreactors) provide great benefits, such as precise fluid-manipulation [1] and high controllability of rapid and difficult to control chemical reactions (see Part 2, Bulk and Fine Chemistry). Advantages of microreaction technology have been utilized in polymer chemistry; notable examples include the synthesis of fine solid polymeric materials [2, 3] and excellent control of exceptionally reactive polymerization through mainly radical and cationic polymerization reactions (see Chapters 13–15). Other polymerizations using microreaction technology are still in their infancy, which include step polymerization, that is, polycondensation and polyaddition and other non-radical polymerizations.

Step polymerization is generally achieved by a condensation (or addition) reaction between two distinct homobifunctional monomers or by self-polycondensation (or self-polyaddition) of a heterobifunctional monomer. Popular and classical examples, which are mainly synthesized using a batchwise system, include polyesters, polycarbonates, polyamides and polysiloxanes for polycondensation and polyureas and polyurethanes for polyaddition [4]. These are industrially important polymers used as solid materials in various fields. In addition, the polymerization mechanisms are effective in providing structural variation to the main chain of the polymer [5]. In particular, biopolymers which are mainly produced through condensation of biomolecules such as amino acids and saccharides are extremely attractive in biotechnological fields, attributable to variations of biopolymer structures that strongly affect the physicochemical and biological functions [6]. However, control of polymer structural properties such as the degree of polymerization and the shape of solid polymeric material is often difficult. Microprocess engineering is considered to be a strong potential technology for offering solutions to such problems. Recently, several studies in step polymerization using microreactors have shown the efficient production of fine microscale solid materials and high controllability of polymerization reactions. In this chapter, we introduce step polymerizations and other non-radical polymerizations in microfluidic systems.

Micro Process Engineering, Vol. 2: Devices, Reactions and Applications.
Edited by V. Hessel, A. Renken, J.C. Schouten, and J.-I. Yoshida

ISBN: 978-3-527-31550-5

15.2
Synthesis of Fine Solid Material in a Microreactor

Polymerization reactions are often utilized for the production of microscale solid materials such as particles/beads, disks, rods, capsules, fibers, membranes and monoliths for various purposes. In the field of microreactions, preparation of a solid polymeric material was the first reported step polymerization using microfluidic system [7]. In the past few years, the microfluidic system has provided various interesting solid materials through manipulation of microfluids [3]. There are many reports on radical polymerization and among the examples are styrene and acrylate polymerization. In this chapter, we introduce several techniques for the production of microstructures using polycondensation.

15.2.1
Synthesis of Polymer Membranes

Many researchers have studied the interfacial science and technology of laminar flow in microfluidics [8]. Interfacial polymerization and the subsequent formation of solid microstructures, such as membranes and fibers in a laminar flow system, are very interesting techniques because the bottom-up method through polymerization is suitable for the formation of miniature structures in a microspace [3]. The development of such microstructure systems plays an important role for the integration of various microfluidic operations and microchemical processing [9]. For instance, membrane formation in a microchannel and further modification has a strong potential for useful functions such as microseparation, microreaction and biochemical analysis [8–10]. Here, we will introduce several reports on polyamide and protein membrane formation through interfacial polycondensation in a microflow.

Beebe's group succeeded in stably forming a laminar flow interface of immiscible liquids in a microchannel using partial chemical modification of the channel surface (Figure 15.1a) [7]. By including 1,6-diaminohexane in the aqueous phase and adipoyl chloride in the organic phase, they were able to form a polyamide membrane (nylon membrane) at the cross-junction of the microchannel through interfacial polycondensation as shown in Figure 15.1b. The pore size of the resulting membrane was less than 200 nm. Kitamori and coworkers reported preparation of a chemically modified nylon membrane using similar interfacial polycondensation inside a microchannel [9]. Microfluidic manipulation for two- or multilayered laminar flow (organic–aqueous–organic three-layer flow) also allowed the formation of parallel dual-membrane structures in a channel (Figure 15.1c and d). Furthermore, they provided enzymatic catalysis function on the inner membrane surface by immobilizing peroxidase. Substrate permeation and subsequent enzymatic reaction were performed through the integrated membrane in the microchannel. They expect potential application of parallel dual membranes for multiple-analyte determinations based on different enzyme immobilization on each membrane, or for efficient multiple chemical syntheses. Subsequently, in this

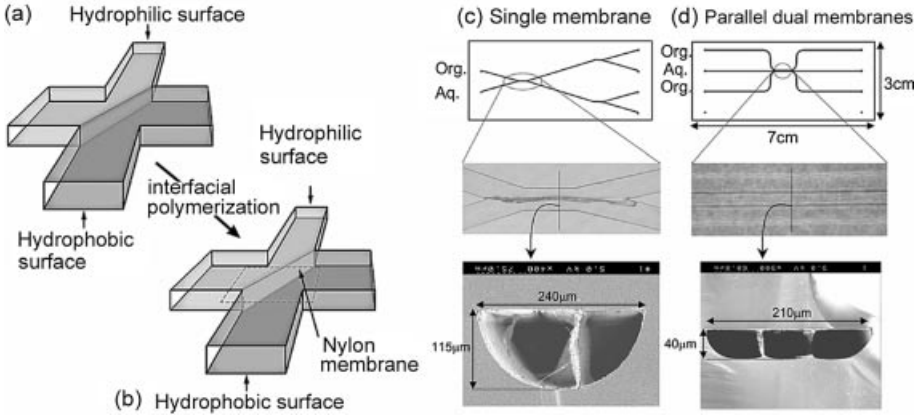


Figure 15.1 The left part shows the fabrication of a semipermeable polyamide membrane. (a) Schematic illustration of a surface-patterned channel. (b) Schematic illustration of a polymer membrane fabricated inside the channel by interfacial polymerization. The right part shows channel patterns and top and cross-sectional views of the nylon membrane prepared inside the microchannel. (c) Single membrane formed under organic–aqueous two-layer flow; (d) parallel dual membranes formed under organic–aqueous–organic three-layer flow. Reprinted in part with permission from (a, b) B. Zhao *et al*., *J. Am. Chem. Soc*. 2002, *124*, 5284–5285, Copyright 2002 American Chemical Society, and from (c, d) H. Hisamoto *et al*., *Anal. Chem*. 2003, *75*, 350–354, Copyright 2003 American Chemical Society.

membrane preparation method, Vadgama's group analyzed the influence of microfluidic device geometry and carrier-liquid flow rates in detail and mentioned the possibility of utilizing the inner-channel membrane in various applications such as sample separation, mass transport control, enzyme immobilization and cell immobilization [10].

Recently, our group developed a preparation method for a protein polymeric membrane in a microchannel using laminar flow, leading to the development of an enzyme-immobilized microreactor. Immobilization of enzymes can be achieved by the formation of an enzyme polymeric membrane on the inner wall of the microchannel [11]. Polymerization is based on enzyme–enzyme crosslinking through a condensation reaction between the enzyme amino group and the crosslinker aldehyde group. The axial dual microtube system shown in Figure 15.2 realizes the formation of concentric laminar flow in the PTFE tube. By using an enzyme solution for the outer stream and a crosslinker such as glutaraldehyde for the central stream, crosslinking polymerization rapidly progresses at the interface of the concentric laminar flow. Consequently, a cylindrical membrane is formed on the inner wall of the microtube (Figure 15.2). It is expected that the use of this technology for membrane formation in a microchannel can be extended to a broad range of functional proteins. Such broad applicability may lead to the construction of a flexible technology platform for screening and designing a potential protein-immobilized microreactor.

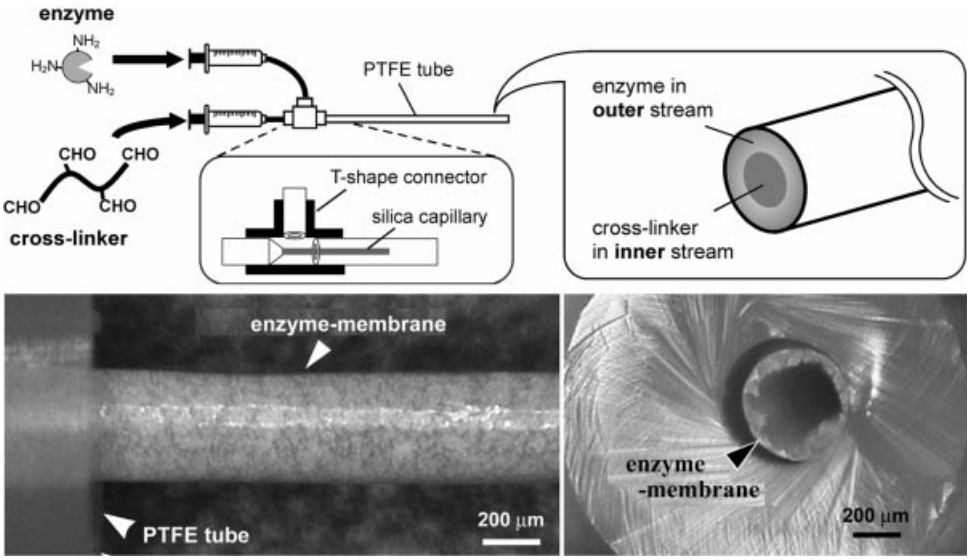


Figure 15.2 Schematic illustration of the procedure for preparation of an enzyme membrane in a microtube (top). Crosslinking polymerization was performed in a concentric laminar flow. The crosslinker solution was supplied to the substrate polytetrafluoroethylene (PTFE) tube through the silica capillary, corresponding to a central stream in the concentric laminar flow. A solution of enzyme was poured from the other inlet of the T-shaped connector and formed an outer stream of the laminar flow. Charge-coupled device (CCD) camera images (bottom) of cylindrical enzyme membrane (dry state) exposed from the PTFE tube, which forms on the inner wall of the tube (left), and sectional view of the tube obtained with enzyme membrane (right). From T. Honda *et al*., *Adv. Synth. Catal*. 2006, *348*, 2163–2171; Copyright 2006 Wiley-VCH Verlag GmbH, Weinheim, reproduced by permission.

15.2.2
Syntheses of Various Solid Materials by Polycondensation

Microcapsule syntheses have been cited in several reports on various solid materials using non-radical polymerization in a microfluidic system. Microencapsulation technology has many industrial applications, particularly in the biomedical engineering field [12]. Here, we briefly introduce microcapsule preparations in microfluidic systems through polymerization other than radical polymerization (for more details on microcapsule preparation in microfluidic system, see Part 4, Functional Materials).

Park's group performed addition reaction and subsequent polycondensation in laminar flow using a microcapillary system and produced melamine resin microcapsules with a narrow particle size distribution [13]. Whitesides and coworkers reported on the preparation of nylon microcapsules by precise manipulation of microfluids using a three-dimensional axisymmetric flow-focusing device [14]. On the other hand, McQuade's group developed a very simple microfluidic system that consisted of plastic microtubing and small-gauge needle forming T-junctions in the

middle of the tube channel [15]. Using this device, they created polyamide-coated microcapsules through rapid interfacial crosslinking polymerization based on condensation. Furthermore, they created hierarchical capsules composed of oligomeric and crystalline diphenylsilanediol through siloxane condensation using the same microfluidic system [16]. All the studies described above showed the advantages of a microfluidic system in controlling interfacial polymerization, microcapsule size and size distribution.

15.3
Solution-phase Polymerization Controlled in a Microreactor

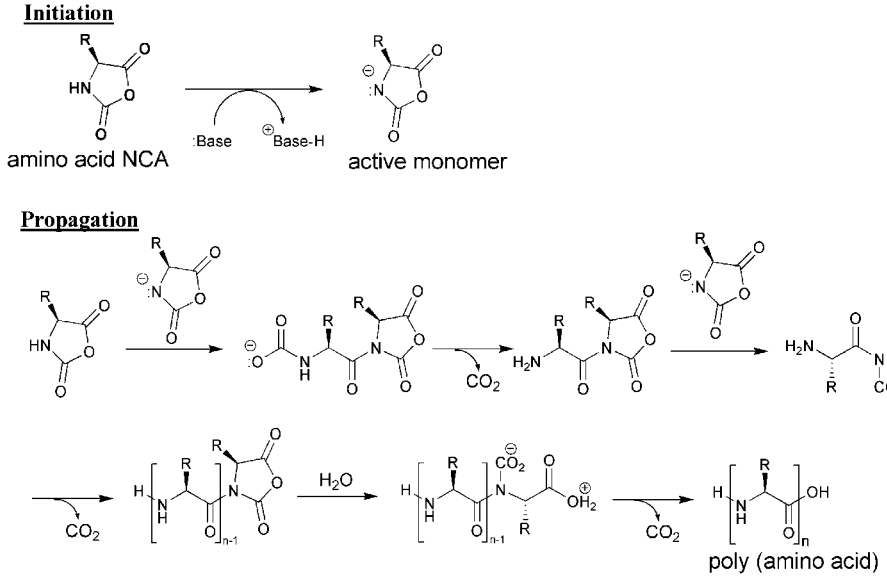
Currently, there are few applications of step and non-radical polymerization (except for cationic polymerization by Yoshida's group (see Chapter 14) in the solution phase to microreactor systems. In this section, we focus on controllable amino acid polymerization using a microreactor.

15.3.1
Amino Acid Polymer Synthesis

Amino acid-based polymers [17] have been widely recognized as functional biopolymers for cell adhesion, gene/drug delivery, morphological control of inorganic materials and as liquid crystal materials [18–21]. However, it is usually effort and time consuming to synthesize and screen useful polymers because of the difficulty in controlling polymer properties such as average molecular weight and molecular weight distribution. Therefore, there have been strong demands for high-throughput and combinatorial synthesis systems that could permit high polymerization reaction control. Taking into account the properties of microfluidic systems, microreaction technology was applied to biopolymer synthesis using an amino acid *N*-carboxyanhydride (NCA) [22].

As shown in Scheme 15.1, when using a tertiary amine as an initiator, the reaction is initiated by deprotonation of NCA. The resulting NCA anion rapidly attacks another NCA molecule, forming a dimer with a nucleophilic carbamate group in the same way as step polymerization. *N*-Carbamic acid is detached as carbon dioxide during the propagation reaction.

It is assumed that initiation steps are important in controlling the polymerization of NCA because deprotonation of NCA and NCA anion attack are known to be relatively fast reactions. One of the key factors for controllable polymerization is sufficiently-rapid and homogeneous mixing for initiation reaction [23]. Conventional batchwise systems tend to generate locally concentration gradients of the reagents as compared with a microscale reactor. When the reaction is more rapid than mixing, heterogeneous mixing causes uneven reaction. Rapid and efficient mixing by a micromixer offers a solution to such a problem. In microfluidic chemical reactions, a micromixer is often employed for effective mixing [24]. A microreactor system containing a micromixer as shown in Figure 15.3 was used for NCA polymerizations.



Scheme 15.1 Mechanism of NCA polymerization initiated by a base such as a tertiary amine. The base here is triethylamine (TEA). From T. Honda *et al.*, *Lab on a Chip* 2005, *5*, 812–818. Reproduced by permission from the Royal Society of Chemistry.

The amino acid-NCA used was N^{ε}-Benzyloxycarbonyllysine-NCA [Lys-(*Z*)-NCA] as monomer of the lysine-polymer (poly-Lys).

Mixing of NCA and TEA basically depends on diffusion through the interface of the two solutions. The micromixer creates a multilayered laminar flow. This system increases the interfacial area of the two fluids (NCA and TEA) and shortens the diffusion length, resulting in increased mixing efficiency of the reactants. Figure 15.4

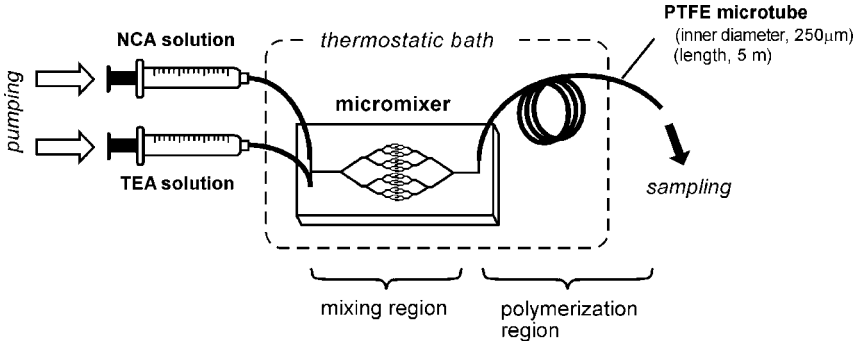


Figure 15.3 Microreaction system used in NCA polymerization reaction. The system consists of a polydimethylsiloxane (PDMS) micromixer and PTFE microtubes. From T. Honda *et al.*, *Lab on a Chip* 2005, *5*, 812–818. Reproduced by permission from the Royal Society of Chemistry.

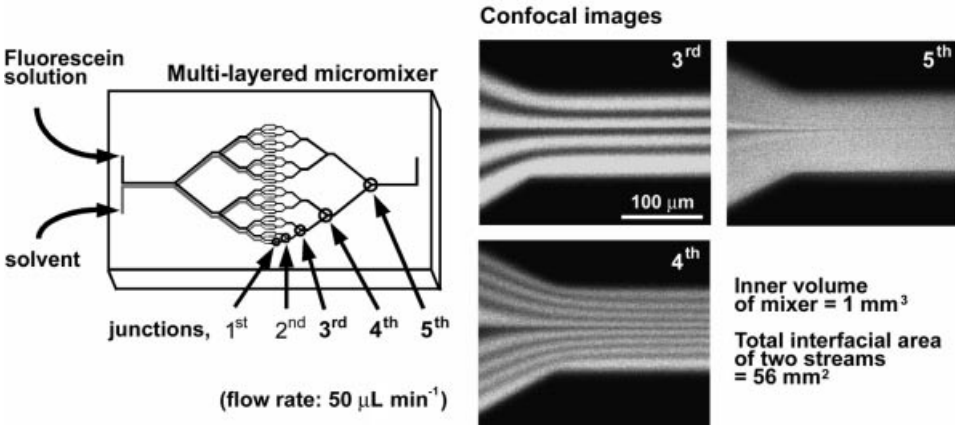


Figure 15.4 The confocal images show the sequential formation of multilayered laminar flow in the micromixer. Bright layers (streams) are fluorescein solution.

shows a preliminary experiment on efficient mixing of fluorescein using a micromixer [25]. The resulting large specific interfacial area provides rapid and efficient mixing. In addition, stable formation of laminar flow in a microchannel is considered to lead to a more controllable mixing as compared with the turbulent flow mixing in a batchwise system.

By using a syringe pump, accurate manipulation of residence time is easy with pumping control. This system allows simple and reproducible control of the polymerization time, which is estimated based on residence time in the microreactor. Figure 15.5 shows gel filtration chromatography (GFC) spectra for poly-Lys synthesized in a microreactor system at different flow rates. A decrease in flow rate caused an increase in the molecular weight of sample as a result of the increase in the time required for polymerization to occur. This result reveals that the polymer size is simply governed by the flow (pumping) rate in the microreactor system. The control of average molecular weight is important in polymer production because polymer size often affects the physicochemical and biological functions of the polymers, particularly the biopolymers. For instance, poly-Lys functions are recognized in drug (and gene) delivery, cell adhesion and cytotoxicity depending on polymer size [26, 27]. Therefore, a simple size-control system via continuous flow control has high potential application for rapid synthesis of polymer libraries with desired polymer size [24, 28].

The microfluidic system also seems to provide polydispersity control. In polymerization using NCA solution of various concentrations, the polydispersity index (PDI) increased linearly with increasing NCA concentration in a batchwise system (Figure 15.6). The PDI is a measure of molecular weight distribution expressed as the weight-average molecular weight (M_w) divided by the number-average molecular weight (M_n). This increase in molecular weight distributions can be due to increased uneven mixing such as local generation of a concentration gradient of the reagents. In contrast, there was only a very slight increase in the PDI of polymers in the microfluidic reaction. In a situation wherein control of polymerization is difficult,

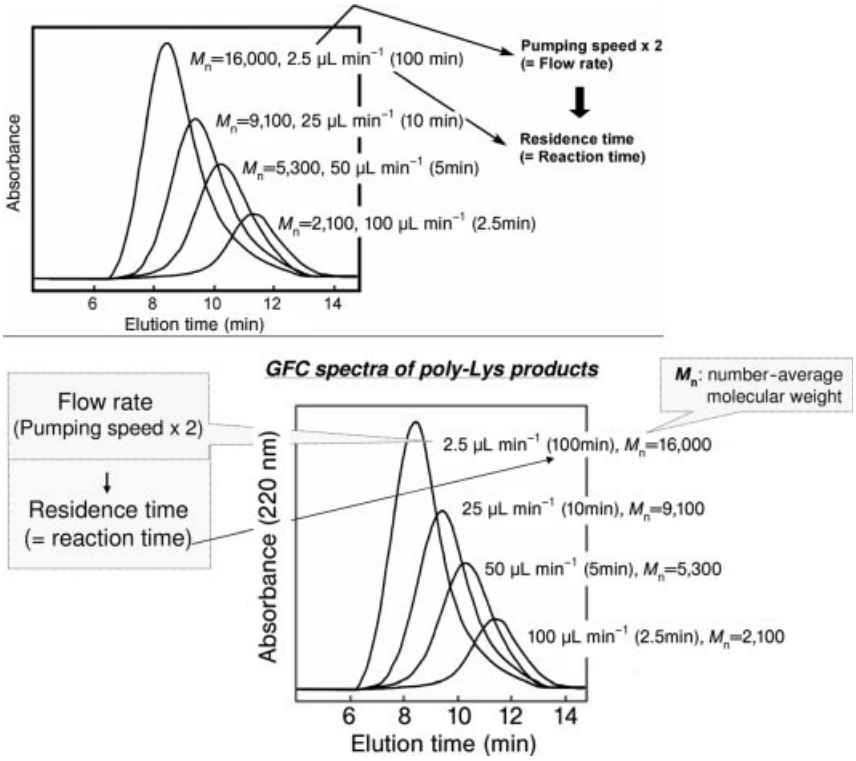


Figure 15.5 GFC analysis of poly-Lys produced by the microreactor. The number-average molecular weights (M_n) of THE respective samples increased with decrease in flow rate. From T. Honda *et al.*, *Lab on a Chip* 2005, *5*, 812–818. Reproduced by permission from The Royal Society of Chemistry.

the microreactor system can take a significant role in controlling polydispersity. Control of polydispersity was thought to be attributable to micromixing in the microreactor. Because in the microreactor the multi-laminar flow micromixer was replaced by a simple T-shaped connector as shown in Figure 15.6, a broad molecular weight distribution of the polymer was obtained. The difference in interfacial areas of the resulting laminar flow is directly related to the efficiency of mixing based on diffusion of the reactants. In the T-shaped connector system, poorer mixing due to reduction of interfacial area is considered to cause an increase in polydispersity.

The benefit of microfluidic reaction for NCA polymerization is not just confined to Lys-NCA. For example, in glutamate-based NCA, a similar result was obtained, that is, lower PDI of polyglutamate synthesized by the microreactor compared with batchwise reaction. Furthermore, the similar polydispersity control of NCA copolymerizations, which is known to be more uncontrollable due to the difference in the reactivities of individual NCAs [29], was achieved successfully [22].

When using a biopolymer with less well known functions, the polymer size should be carefully selected and polydispersity should be controlled as narrow as possible because

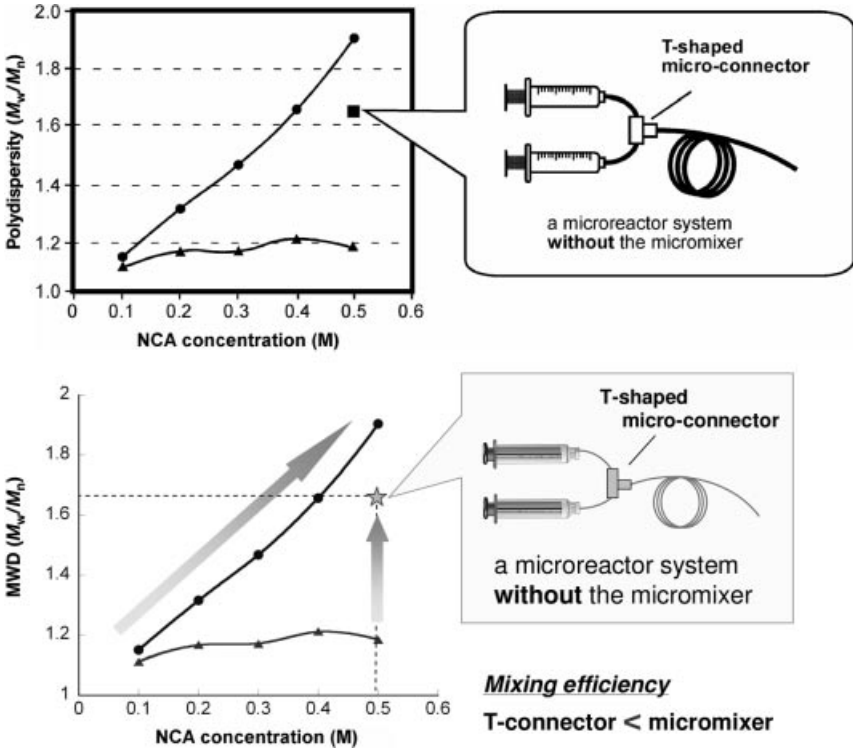


Figure 15.6 Comparisons of polymer properties in batchwise (circles) and microfluidic (triangles) systems at various Lys-(*Z*)-NCA concentrations. The square indicates polydispersity of polymer prepared using a microreactor without the micromixer. From T. Honda *et al*., *Lab on a Chip* 2005, *5*, 812–818. Reproduced by permission from the Royal Society of Chemistry.

the molecular weight of the polymer often affects polymer function. It is expected that such requirements can be satisfied by utilizing microfluidic reactions capable of high controllability of polydispersity and simple molecular weight control of biopolymers.

15.3.2
Combinatorial and High-throughput Technologies in Microfluidic Polymerization

Present-day investigations on the discovery of drugs and functional materials are directed towards the development of the rapid creation of chemical libraries by using high-throughput and combinatorial synthesis methods. Applications of such combinatorial and high-throughput technology in polymerization are shown in polymerization kinetic research, elucidation of reaction mechanisms, discovery of polymerization catalysts, preparation of polymer libraries and optimization of reaction parameters [30, 31]. These technologies have been widely developed. Examples in particular are automated (robotic) batchwise reaction system such as multi-well

microtiter plate system, in various polymerization applications including polycondensation, free and controlled radical, ring-opening, coordination and supermolecular polymerizations [31]. On the other hand, the development of flow-through processes as a high-throughput and combinatorial system for polymerization has been rather slow. However, continuous microflow technology provides facile automation, reproducibility, safety, process reliability and rapid and highly controlled production of compounds with minimum workup [32], and thus may become important in the near future [24]. In non-radical (and non-cationic) polymerization, microreaction studies of high potential for such system architecture include controllable NCA polymerization described in the above section and rapid monitoring polyethylene synthesis through anionic coordination polymerization proposed by Miller's group [33]. Continuous microfluidic systems, providing high controllability for polymerization reactions and facile on-line production and monitoring systems, are considered to lead to the construction of a flexible technology platform for screening and designing potential polymer materials.

15.4 Conclusion

For the production of general-purpose polymers entailing annual production of several tens of thousands of tons, the microreactor system needs numbering-up because the reaction scale of a microreactor is extremely small compared with the conventional batch reactor. Polymer production using a microreactor system is considered to be more suitable for custom-made and/or on-demand production systems with a large number of small-scale parallel operations in highly controlled conditions. This strategy may find application in answering specific needs of customers with flexibility and may offer advantages from the economic and environmental points of view. At present, microreaction studies, in particular radical and cationic polymerizations, appear to have strong potential for such system architecture, in which the development of highly controlled reaction systems and efficient production of fine solid materials using accurate microfluidic manipulation have been progressing. Other polymerizations in microfluidic reactions will also be a growing field. Putting together combinatorial/high-throughput technology and good control of polymerization reactions, various useful polymers (and polymeric architectures) and useful reagents such as catalysts can be progressively discovered and created. In addition, further investigations of structure–property relationships and polymerization mechanisms are expected to be fruitful.

Reactions occurring in microfluidic systems have characteristic benefits for polymerization reactions. First, microreactors provide accurate control of the reaction conditions such as temperature, reaction (residence) time and mixing. Second, microfluids based on laminar flow provide precise manipulation. This technology only allows the production of various solid polymeric materials which are synthesized under microfluidic control conditions. Third is ease in parallel operation and on-line processing. This advantage imparts upon the microreactor great potential as a

high-throughput and combinatorial system. In addition, we have considered shearing force, a hydrodynamic property generated characteristically in microfluids and a microreactor-specific property for polymerization reactions. Previously, we have shown that the polymer chain can expand and orient by shearing force in a microfluidic system using DNA as a model [34]. Such behavior of polymers demonstrates the utility of microreactors as a novel reaction apparatus for polymers. Microfluidic technology which manipulates and controls the conformation and orientation of polymer molecules may be extended to new polymerization reactions such as graft polymerization and polymer modification.

References

1 G. M. Whitesides, The origins and the future of microfluidics, *Nature* **2006**, *442*, 368–373.

2 V. Hessel, H. Löwe, C. Serra, G. Hadziioannou, Polymerizationen in mikrostrukturierten Reaktoren: Ein Überblick, *Chem. Ing. Tech.* **2005**, *77*, 1693–1714.

3 J. L. Steinbacher, D. T. McQuade, Polymer chemistry in flow: new polymers, beads, capsules and fibers, *J. Polym. Sci., Polym. Chem.* **2006**, *44*, 6505–6533.

4 M. E. Rogers, T. E. Long, S. R. Turner, in *Synthetic Methods in Step-growth Polymers* (eds M. E. Rogers, T. E. Long), John Wiley & Sons, Ltd, Chichester, **2003**, Chapter 1.

5 G. Odian, *Principles of Polymerization*, 4th edn, John Wiley & Sons, Ltd, Chichester, **2004**, Chapter 2, pp. 39–197.

6 D. Cunliffe, S. Pennadam, C. Alexander, Synthetic and biological polymers – merging the interface, *Eur. Polym. J.* **2004**, *40*, 5–25.

7 B. Zhao, N. O. L. Viernes, J. S. Moore, D. J. Beebe, Control and applications of immiscible liquids in microchannels, *J. Am. Chem. Soc.* **2002**, *124*, 5284–5285.

8 J. Atencia, D. J. Beebe, Controlled microfluidic interfaces, *Nature* **2005**, *437*, 648–655.

9 H. Hisamoto, Y. Shimizu, K. Uchiyama, M. Tokeshi, Y. Kikutani, A. Hibara, T. Kitamori, Chemicofunctional membrane for integrated chemical processes on a microchip, *Anal. Chem.* **2003**, *75*, 350–354.

10 J. Gargiuli, E. Shapiro, H. Gulhane, G. Nair, D. Drikakis, P. Vadgama, Microfluidic systems for in situ formation of nylon 6,6 membranes, *J. Membr. Sci.* **2006**, *282*, 257–265.

11 T. Honda, M. Miyazaki, H. Nakamura, H. Maeda, Facile preparation of an enzyme-immobilized microreactor using a crosslinking enzyme membrane on a microchannel surface, *Adv. Synth. Catal.* **2006**, *348*, 2163–2171.

12 G. T. Vladisavljevic, R. A. Williams, Recent developments in manufacturing emulsions and particulate products using membranes, *Adv. Colloid. Interface Sci.* **2005**, *113*, 1–20.

13 T. Sawada, M. Korenori, K. Ito, Y. Kuwahara, H. Shosenji, Y. Taketomi, S. Park, Preparation of Melamine resin micro/nanocapsules by using a microreactor and telomeric surfactants, *Macromol. Mater. Eng.* **2003**, *288*, 920–924.

14 S. Takeuchi, P. Garstecki, D. B. Weibel, G. M. Whitesides, An axisymmetric flow-focusing microfluidic device, *Adv. Mater.* **2005**, *17*, 1067–1072.

15 E. Quevedo, J. Steinbacher, D. T. McQuade, Interfacial Polymerization within a simplified microfluidic device: capturing capsules, *J. Am. Chem. Soc.* **2005**, *127*, 10498–10499.

16 J. L. Steinbacher, R. W. Y. Moy, K. E. Price, M. A. Cummings, C. Roychowdhury, J. J. Buffy, W. L. Olbricht, M. Haaf, D. T. McQuade, Rapid self-assembly of core–shell organosilicon microcapsules within a microfluidic device, *J. Am. Chem. Soc.* **2006**, *128*, 9442–9447.

17 F. Sanda, T. Endo, Syntheses and functions of polymers based on amino acids, *Macromol. Chem. Phys.* **1999**, *200*, 2651–2661.

18 A. Bargellesi, G. Damiani, W. M. Kuehl, M. D. Scharff, Synthesis of immunoglobulin by substrate attached mouse myeloma cells, *J. Cell. Physiol.* **1976**, *88*, 247–251.

19 I. L. Shih, Y. T. Van, M. H. Shen, Biomedical applications of chemically and microbiologically synthesized poly (glutamic acid) and poly(lysine), *Mini Rev. Med. Chem.* **2004**, *4*, 179–188.

20 K. M. Hawkins, S. S. S. Wang, D. M. Ford, D. F. Shantz, Poly-L-lysine templated silicas: using polypeptide secondary structure to control oxide pore architectures, *J. Am. Chem. Soc.* **2004**, *126*, 9112–9119.

21 E. G. Bellomo, P. Davidson, M. Imperor-Clerc, T. J. Deming, Aqueous cholesteric liquid crystals using uncharged rodlike polypeptides, *J. Am. Chem. Soc.* **2004**, *126*, 9101–9105.

22 T. Honda, M. Miyazaki, H. Nakamura, H. Maeda, Controllable polymerization of *N*-carboxy anhydrides in a microreaction system, *Lab Chip* **2005**, *5*, 812–818.

23 A. Nagaki, K. Kawamura, S. Seiji, T. Ando, M. Sawamoto, J. Yoshida, Cation pool-initiated controlled/living polymerization using microsystems, *J. Am. Chem. Soc.* **2004**, *126*, 14702–14703.

24 J. Yoshida, Flash chemistry using electrochemical method and microsystems, *Chem. Commun.* **2005**, 4509–4516.

25 Y. Yamaguchi, K. Ogino, K. Yamashita, H. Maeda, Rapid micromixing based on multilayer laminar flows, *J. Chem. Eng. Jpn.* **2004**, *37*, 1265–1270.

26 M. A. Wolfert, L. W. Seymour, Atomic force microscopic analysis of the influence of the molecular weight of poly(L)lysine on the size of polyelectrolyte complexes formed with DNA, *Gene Ther.* **1996**, *3*, 269–273.

27 S. Choksakulnimitr, S. Masuda, H. Tokuda, Y. Takakura, M. Hashida, *In vitro* cytotoxicity of macromolecules in different cell culture systems, *J. Control. Release* **1995**, *34*, 233–241.

28 T. Wu, Y. Mei, J. T. Cabral, C. Xu, K. L. Beer, A new method for controlled polymerization using a microfluidic system, *J. Am. Che. Soc.* **2004**, *126*, 9880–9881.

29 Y. Shalitin, E. Katchalski, Amine initiated copolymerization of *N*-carboxy-amino acid anhydrides, *J. Am. Chem. Soc.* **1960**, *82*, 1630–1636.

30 C. Guerrero-Sanchez, R. M. Paulus, M. W. M. Fijten, M. J. de la Mar, R. Hoogenboom, U. S. Schubert, High-throughput experimentation in synthetic polymer chemistry: from RAFT and anionic polymerizations to process development, *Appl. Surf. Sci.* **2006**, *252*, 2555–2561.

31 R. Hoogenboom, M. A. R. Meier, U. S. Schubert, Combinatorial methods, automated synthesis and high-throughput screening in polymer research: past and present, *Macromol. Rapid Commun.* **2003**, *24*, 16–32.

32 A. Kirschning, G. Jas, Applications of immobilized catalysts in continuous flow processes, *Top. Curr. Chem.* **2004**, *242*, 209–239.

33 C. A. Nielsen, R. W. Chrisman, R. E. LaPointe, T. E. Miller, Novel tubing microreactor for monitoring chemical reactions, *Anal. Chem.* **2002**, *74*, 3112–3117.

34 K. Yamashita, Y. Yamaguchi, M. Miyazaki, H. Nakamura, H. Shimizu, H. Maeda, Direct observation of long-strand DNA conformational changing in microchannel flow and microfluidic hybridization assay, *Anal. Biochem.* **2004**, *332*, 274–279.