

Lab on a Chip

Accepted Manuscript

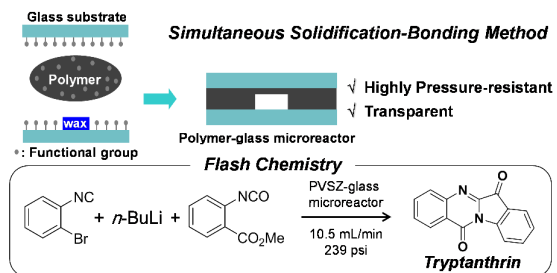


This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



Polymer-glass microreactors fabricated by simultaneous solidification-bonding technique are transparent and pressure-tolerant for flash chemistry under high pressure condition.

ARTICLE

Pressure-tolerant polymer microfluidic device fabricated by simultaneous solidification-bonding method and flash chemistry application

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Wurong Ren,^a Heejin Kim,^b Hyune-Jea Lee,^b Jun Wang,^a Hao Wang^a and Dong-Pyo Kim^{*b},

Pressure-tolerant polymer-glass microfluidic reactors with excellent bonding strength have been fabricated by simultaneous solidification-bonding (SSB) method, in which a viscous and reactive matrix polymer was cast on the glass substrate with pre-patterned wax as a sacrificial template. Elaborate interfacial chemistry between the matrix polymer and the functionalized glass surface was designed to achieve simultaneous solidification and chemical bonding under UV or/and mild thermal condition (<200 °C with no pressure). Highly pressure-tolerant microchannels were obtained by complete removal of the liquid wax template at 80 °C. The versatility was demonstrated by fabricating microreactors from various polymers with different interfacial chemistry, which were all stable at 1000 psi with the highest burst pressure of 2000 psi. In particular, the burst pressure of fluoropolymer-glass microreactor withstood two orders of magnitude higher than the microchannel made by conventional method. Finally, the polymer-glass microfluidic device was used for synthesis of a natural product of Tryptanthrin by flash chemistry under high pressure induced condition (synthetic yield: 90%, flow rate: 10.5 mL/min, reaction time: 14 ms). The transparent microfluidic device can be used as a useful platform for miniaturizing spectroscopic tools for chemical analysis study under high pressure conditions.

Introduction

Microfluidic systems have attracted a lot of interests in the area of chemistry due to their unique characteristics such as miniaturized reaction volume, large surface to volume ratio, and efficient mass and heat transfer capability.¹⁻⁵ Fabrication of a microfluidic device involves a series of steps of microchannel creation, bonding, connecting and interconnecting to and from inlet/outlet. To date, fabrication methods such as photolithography,⁶ soft lithography⁷ and laser ablation⁸ have been used to fabricate microfluidic devices from various materials. In general, microfluidic devices made of elastic polydimethylsiloxane (PDMS) and other plastics have been widely used due to their low cost and easy fabrication.⁹ Despite their successful applications of these kinds of relatively low pressure-tolerant microfluidic devices to biological area and others, most of these microfluidic devices have suffered from mechanical, chemical, and thermal stability problems that restrict their applications in chemical syntheses.¹⁰ Therefore, durable and economic microfluidic devices that can overcome swelling and leaking problems under high pressure are increasingly needed for microreaction applications.

The bonding step of sealing the channel layer with no leaking is one of the most critical steps for durable microfluidic devices, which requires skilful techniques, and is quite challenging due to lack of reliable and reproducible protocol. In particular, glass,

silicon and ceramic microfluidic devices require a high temperature process for the bonding such as fusion bonding (>600 °C), anodic bonding (>300 °C), and adhesive bonding (>200 °C).^{11,12} Some polymer-based chips such as polyimide⁸ and Teflon¹³ film laminated reactors also need a fusion bonding at 320 and 260 °C, respectively. Facile bonding under mild conditions, on the other hand, often results in insufficient bonding strength and poor material durability as in polydimethylsiloxane (PDMS) microfluidic chips.^{9,10} Functional polymers with UV or/and thermally reactive groups such as SU8 photoresist¹⁴ and inorganic polymer polyvinylsilazane (PVSZ)¹⁵ are also used for microfluidic devices and the devices are sealed by a post-curing method after molding the polymer into solidified channel shape under partial curing conditions.

The serial process of solidification followed by bonding mostly results in weak bonding strength and low reproducibility with leaking failure (refer to ESI,† Scheme S1), because a considerable amount of functional groups is consumed during the initial solidification step, which lowers the interfacial chemical reactivity, leading to the weak bonding. Besides, conformal contact is difficult to achieve with the solidified pieces. Therefore, a simultaneous solidification-bonding process would be desirable to achieve excellent bonding strength with high pressure tolerance in polymer based microfluidic devices.

Herein, we present simultaneous solidification-bonding (SSB) method for the fabrication of pressure-tolerant polymer-glass microfluidic reactors with excellent bonding strength, in which a viscous and reactive matrix polymer is cast on the glass substrate with pre-patterned wax as a sacrificial template (Fig. 1(a)). Elaborate interfacial chemistry between the matrix polymer and the functionalized glass surface was designed to achieve simultaneous and robust chemical bonding and solidification under UV or/and mild thermal condition (<200 °C with no pressure). Highly pressure-tolerant microchannels are obtained by complete removal of the liquid wax template at an elevated temperature. This simultaneous solidification-bonding method leads to a microfluidic device that tolerates a burst pressure that is one order of magnitude higher than that achieved with the conventional sequential solidification and bonding process (refer to ESI,† Scheme S1). We demonstrate the utility of this polymer-glass microfluidic device in the synthesis of a natural product of Tryptanthrin by flash chemistry under high pressure induced condition.

Experimental

Materials

Polydimethylsiloxane (PDMS) base polymer and curing agent (Sylgard 184) were supplied by Dow Corning. Methacryl Polyhedral Oligomeric Silsesquioxane (POSS, MA0735) was purchased from Hybrid Plastics. Paraffin wax (ASTM D 87, mp 58–62 °C), 2,2-dimethoxy-2-phenyl-acetophenone (DMPA), 3-(trimethoxysilyl)propyl methacrylate (MPTMS), trichlorovinylsilane (TCVS), trichloromethylsilane (TCMS), 3-glycidoxypropyltrimethoxysilane (GPTMS), triethoxylvinylsilane (TEVS), triethoxymethylsilane (TEMS), poly(ethylene glycol) dimethacrylate (PEGDMA) were purchased from Sigma-Aldrich. Polyvinylsilazane (HTT1800) was purchased from Kion company. Fluoropolymer (MD 700) was purchased from Fluorolink. Norland optical adhesive (NOA 81) was purchased from Norland Products. INC. Duralco 4525 was purchased from Cotronics Corporation. SU8-50 was purchased from MicroChem. AZ 1512 was purchased from Clariant industries (Korea) Ltd. Glass substrate was purchased from Marienfeld Laboratory Glassware. 2-Bromophenyl isocyanide was synthesized according to previous report.¹⁶ *n*-BuLi, methyl 2-isocyanatobenzoate, tetrahydrofuran, hexane were purchased from Sigma-Aldrich and were used without further purification.

Fabrication of microreactors by simultaneous solidification-bonding method

Pre-patterning of wax on glass substrate: PDMS mold with required channel design was prepared according to previous report.¹⁷ Glass substrate was cleaned by acetone, isopropyl alcohol, and DI water, and dried up by air gun. Then, AZ 1512 sacrificial layer was spin coated on glass substrate (2500 rpm, 30 s) and baked at 95 °C for 5 min to dry up the solvent. Next, inlet and outlet holes were punched on AZ coated glass substrate, and a reversible bonding between PDMS mold and glass was formed by placing plasma treated PDMS mold on AZ coated glass substrate. The paraffin wax was melt and infused automatically into the PDMS mold-glass substrate through a punched hole and kept in oven at 80 °C for 30 min to allow the wax to fully infiltrate the whole channel driven by capillary force. Finally, we carefully took out the wax filled PDMS mold-glass substrate from oven, and then peeled off the PDMS mold after solidification of wax by cooling to room temperature and cleaned the AZ sacrificial layer by acetone.

Chemical functionalization of glass surface: The surface of wax pre-patterned glass was functionalized by two methods depending on the silane used. In case of vinyl functionalized glass substrate by vapour method, both a wax patterned glass substrate and a small container containing one drop (about 30 µL) of TCVS were put in a desiccator and kept for 12 h at room temperature. In case of methacrylate functionalized glass substrate by liquid method, MPTMS was dissolved in toluene (50 wt%), and the solution was spin coated onto wax pre-patterned glass substrate at 2000 rpm for 30 s, then the glass substrate was baked at 50 °C for 12 h to stabilize the functional group. Similarly, epoxy terminated glass substrate was prepared from GPTMS, methyl terminated glass substrate was prepared from TEMS, methyl/methacrylate terminated glass substrate was prepared from a mixture of MPTMS and TEMS with various ratios, methyl/vinyl terminated glass substrate was prepared from TCVS and TCMS.

PVSZ microreactor: PVSZ solution was prepared by mixing PVSZ with 10% UV curable POSS as hardener and 1% DMPA for enhancing the crosslinking kinetics. Several drops of PVSZ solution was put on the vinyl functionalized wax pre-patterned glass substrate, which was covered by another vinyl functionalized bare glass. Next the glass-PVSZ-glass laminated structure was exposed to UV irradiation for 10 min to solidify the polymer, and followed by thermal treatment at 200 °C for 1 h to complete the curing reaction. And the wax template pattern was melted by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene until no detection of wax by GC-MS analysis.

Fluoropolymer microreactor: Fluoropolymer solution was prepared by mixing fluoropolymer with 1% DMPA as a photo initiator. Several drops of fluoropolymer solution were spread on the methacrylate functionalized wax patterned glass substrate, which was covered by another methacrylate functionalized bare glass. Next the glass-fluoropolymer-glass laminated structure was exposed to UV irradiation for 10 min to solidify polymer, and followed by thermal treatment at 80 °C for 1 h to enhance the thermal stability. The wax template was removed by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene.

PEGDMA microreactor: PEGDMA solution was prepared by mixing PEGDMA with 1% DMPA as a photo initiator. Several drops of PEGDMA solution was spread on the methacrylate functionalized wax pre-patterned glass substrate, which was covered by another methacrylate functionalized bare glass. Next the glass-PEGDMA-glass laminated structure was exposed to UV irradiation for 10 min to solidify polymer, and followed by thermal treatment at 80 °C for 1 h to enhance the thermal stability. The wax template was removed by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene.

NOA 81 microreactor: NOA 81 was used directly. Several drops of NOA was spread on the wax pre-patterned glass substrate with vinyl group, this was covered by another glass. Next the glass-NOA-glass laminated structure was exposed to UV irradiation for 10 min to solidify polymer, and followed by thermal treatment at 80 °C for 1 h to enhance the thermal stability. The wax template was removed by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene.

SU8 microreactor: SU8-50 was used directly. Several drops of SU8-50 was put on the epoxy functionalized wax patterned glass substrate, which was baked at 50 °C for 12 h to remove solvent in SU 8, then it was covered by another epoxy functionalized bare glass. Next the glass-SU 8-glass laminated structure was exposed to UV irradiation for 10 min to solidify polymer, and followed by thermal treatment at 80 °C for 1 h to enhance the thermal stability. The wax

template was removed by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene.

Duralco microreactor: Duralco 4725 and hardener were mixed together in a weight ratio of 8:1. Several drops of Duralco 4725 were spread on the wax pre-patterned glass substrate with epoxy group, which was covered by another bare glass. Next the glass-Duralco-glass laminated structure was kept at room temperature for 24 h for curing the polymer, and followed by thermal treatment at 80 °C for 1 h to enhance the thermal stability. The wax template was removed by heating at 80 °C to readily remove by applying vacuum from the open outlet, and washed with acetone and toluene.

Fabrication of microreactor with built-in micromixer pattern: For making microreactor with built-in structure, PDMS mold with the mixer microstructure was used to pattern wax on glass substrate, the surface functionalization of glass substrate as well as simultaneous solidification-bonding of microreactor were identically performed as aforementioned description to fabricate a microreactor.

Flash chemistry application of microreactor

A microreactor consisting of two T-junctions (T1, T2) and two parts of microreaction (R1, R2) was used for flash chemistry. A solution of 2-bromophenyl isocyanide in tetrahydrofuran (0.1 M) and a solution of *n*-BuLi in hexane (0.42 M) were introduced to T1. The resulting solution was passed through R1 (300 μm x 150 μm x 40 mm) and was mixed with a solution of methyl 2-isocyanatobenzoate in tetrahydrofuran (0.22 M) at T2. The resulting solution was passed through R2 (300 μm x 150 μm x 5 mm). After a steady state was reached, the product was collected for 30 sec while being quenched with 2 mL of saturated NH₄Cl aqueous solution. For ¹H NMR yield, 4-iodoanisole was used as an internal standard. The combined organic extracts were dried over Na₂SO₄ and concentrated, then, ¹H NMR spectrum was measured. The crude product was purified by silica gel chromatography (hexane:ethyl acetate=7:1) to give Tryptanthrin as a bright yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.64 (d, J = 8.1 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.86 (t, J = 8.2 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 182.7, 158.3, 146.8, 146.5, 144.5, 138.5, 135.3, 130.9, 130.4, 127.7, 127.4, 125.6, 123.9, 122.1, 118.1 ppm; GCMS (EI) *m/z* calcd for C₁₅H₈N₂O₂: 248.1, found: 248.1.

Characterization and device tolerance test

Pressure-tolerance test of microreactor: All the burst pressure test of fabricated microreactors was conducted with the same size of microchannel (500 μm x 50 μm x 30 mm, glass substrate: 75 x 25 x 1 mm). The inlet of microreactor was connected to a high pressure pump (PrimeLine™ HPLC Pumps), and the outlet was blocked by a screw. Then water was injected into the microchannel (flow rate: 0.5 mL/min) until leaking of microreactor occurred. Three sets of identical experiments were conducted for burst pressure test for average values with deviation range. The back pressure in the microreactor for flash chemistry application was conducted by connecting the inlets with high pressure pump and kept the outlet open, and then hexane was injected into microreactor with very high flow rate (1–10 mL/min). The inlet and outlet of microreactor were connected to PFA tubing by using stainless steel framework for pressure tolerance test or chemical synthesis.

Characterization: The microchannels were observed by scanning electron microscopy (SEM, SNE-1500/JEOL) and optical microscopy (SV 32, Sometech). The dimensional change of microchannel was calculated by comparing the channel width of

PDMS mold and the corresponding PVSZ microreactor observed from optical microscopic image. To test the mixing performance of microchannel with built-in mixer, dye solution (methylene blue, 0.1 wt%) and DI water were injected into Y shaped channel at flow rate of 5 μL/min through two inlets, the color change in microchannel was observed by optical microscopic, and analyzed by ImageJ software (ImageJ, Calcium Group, UK)

Results and discussion

Fabrication of microfluidic device

For the device fabrication, the surface of glass substrate is first pre-patterned according to microchannel design using a molding technique (Fig. 1(a)). Wax as a sacrificial template offers a facile formability to desired shape, a dimensional stability during molding, and an easy removal of the wax after solidifying matrix materials, unlike polylactide,¹⁸ sugar,¹⁹ gelatin²⁰ and other templates^{21–23} that are difficult to shape and remove. The diverse wax patterns on glass substrates can easily be obtained by micromolding method using various PDMS molds that can be made by soft lithography and auto CAD design techniques (refer to ESI,† Scheme S2).⁷ Due to capillary force, the liquid wax (melting point 58–62 °C) readily infiltrates various channels (3–80 cm of length) into the PDMS mold through the predrilled holes in glass substrates. After solidification of liquid wax by cooling to room temperature, the PDMS mold can be removed to leave the patterned wax template on the substrate. A long and serpentine design of wax pattern (400 μm width, 50 μm height, 20 cm length) on glass substrate, for instance, can readily be obtained as shown in Fig. 1(b) and 1(c), which shows red color emanating from the photoresist, AZ, layer beneath the wax pattern. Notably, the sacrificial AZ layer on the glass substrate facilitates demolding due to its moderate bonding to PDMS mold. In addition, the AZ layer is critically helpful to trim the spilled thin wax layer that would impede direct chemical bonding between polymer and glass substrate (refer to ESI,† Fig. S1 and S2), by lift-off development step.

The reactive matrix polymer utilized first in this work is polyvinylsilazane (PVSZ) inorganic polymer that has a vinyl group in fabricating a pressure-tolerant microreactor due to its excellent chemical and thermal stability that is well-documented.²³ The wax-patterned glass substrate is then functionalized with vinyl group by placing with an open vial containing one drop (about 30 μL) of trichlorovinylsilane (TCVS) into a desiccator for 12 h at room temperature, as reported²⁴ (refer to ESI,† Fig. S3). Subsequently, the PVSZ mixed with UV and thermal curing initiators was gently cast onto the vinyl functionalized glass substrate with pre-patterned wax template, with another vinyl-functionalized glass substrate placed on the polymer to produce a thin polymer layer between the two glass substrates. The sandwiched PVSZ was solidified by UV irradiation for 10 min, and further stabilized by subsequent thermal annealing at 200 °C for 1 h. It is pointed out that the 52–55 μm thick viscous and reactive PVSZ matrix polymer layer (channel roof 2–5 μm thickness) cast on the wax template pattern was simultaneously solidified and bonded to the glass substrates, thereby sealing the microchannel by consecutive UV and thermal cross-linking reaction. Eventually, the wax template was removed and completely washed out with toluene at 80 °C until no wax was detected by GC-MS analysis, although the wax melted down and partly evaporated through inlet and outlet in glass substrate during thermal curing stage.

The resulting transparent PVSZ microchannel was clearly visualized when filled with green dye solution (Fig. 1(d), 1(e) and Fig. S2). There was little dimensional shrinkage (less than 1%) from the original PDMS mold presumably due to adhesion of the thin wax pattern on the glass surface that prohibited the intrinsic shrinkage upon cooling. This simultaneous solidification-bonding technique resolved long-lasting problems such as tricky conformal contact and weak bonding strength in the conventional sequential solidification and bonding process. Applicability of the SSB method to uneven substrate surface is another advantage, as demonstrated with a rough glass cover for which the conventional process leads to incomplete sealing with leaking failure (refer to ESI,† Fig. S4).

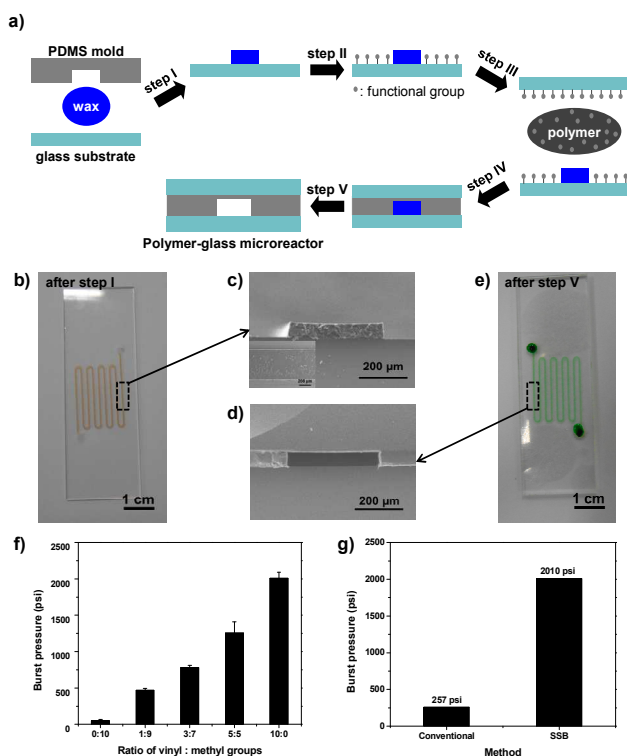


Fig. 1 a) General schematic of simultaneous solidification-bonding (SSB) method to fabricate a microreactor. Step I: pre-patterning of wax template on glass substrate; Step II: chemical functionalization of glass surface; Step III: casting the matrix polymer on glass substrate; Step IV: simultaneous solidification-bonding between the matrix polymer and the glass substrates; Step V: removal of wax template. b) Optical image of wax pattern (400 μm x 50 μm x 20 cm) on glass substrate. SEM images of c) cross-sectional and top-view (inset) of the wax pattern, d) fabricated PVSZ microchannel (400 μm x 50 μm). e) Optical image of PVSZ microchannel filled with green dye (400 μm x 50 μm x 20 cm). f) Burst pressure of PVSZ-glass microreactor for various ratios of vinyl/methyl functional group on glass substrate. g) Burst pressure comparison between PVSZ-glass microreactor fabricated by the SSB method and that by the conventional sequential method.

To gain an understanding of the way the interfacial chemistry affects the bonding strength, the ratio of reactive vinyl group to non-reactive methyl group on glass substrate was manipulated by varying the ratio of trichlorovinylsilane (TCVS) to trichloromethylsilane (TCMS) in the treatment solution as follows; 0:10, 1:9, 3:7, 5:5 and 10:0. For the check of bonding strength, the burst pressure of the PVSZ microchannel was measured that was pressurized with water through open inlet with closed outlet. In general, a low ratio of TCVS to TCMS or

a large amount of non-reactive $-\text{CH}_3$ groups led to a low burst pressure; a high ratio of TCVS to TCMS or more reactive $-\text{C}=\text{C}-$ groups yielded a higher burst pressure due to a stronger chemical bonding between substrate and matrix polymer, as shown in Fig. 1(f). When the surface is functionalized only with $-\text{CH}_3$ group (vinyl/methyl = 0:10), the burst pressure was 51 psi. As the vinyl/methyl ratio was increased from 1:9 to 5:5, the burst pressure also increased from 469 psi to 1258 psi. When treated only by $-\text{C}=\text{C}-$ functional groups, the burst pressure reached 2010 psi (137 atm) which compares with the burst pressure of 257 psi for the microchannel fabricated by conventional solidification and bonding process in a sequential manner, indicating an increase that is nearly one order of magnitude higher in bonding strength (Fig. 1(g)). Moreover, the SSB method allowed highly reliable reproducibility to fabricate the PVSZ polymer-glass microreactor with nearly zero failure or leak problem, while the conventional bonding method often suffered from incomplete or weak bonding and channel blocking problem.

Any desired form of microchannels with different design can be produced by micromolding the wax sacrificial template pattern into the desired PDMS mold in fabricating the chemically and physically robust inorganic polymer based microfluidic devices. A series of PVSZ microchannels with serpentine shape, Y or T shape, and logo 'CAMC' shape in the range of 3-80 cm length were fabricated, as shown in Fig. 2(b). Furthermore, the PVSZ microchannel with built-in herringbone mixer microstructure was also fabricated using the SSB method and the corresponding PDMS mold (refer to ESI,† Fig. S3). A Y-shaped channel only with 3 cm of herringbone mixer pattern yielded excellent mixing efficiency when injected by two types of laminar liquids (refer to ESI,† Fig. S3(b) and S3(c)), which is consistent with previous report.^{25, 26} However, a plain channel with no mixer pattern required much a longer length to reach similar level of mixing.

The versatility of SSC method for various reactive polymers

To demonstrate fabrication versatility of SSB method, microchannels were fabricated with a number of commercially available polymers: fluoropolymer (MD 700), negative photoresist (SU 8), poly(ethylene glycol)dimethacrylate (PEGDMA), norland 81 (NOA 81) adhesive and Duralco 4525 adhesive (Fig. 2 and refer to ESI,† Fig. S6). Depending on the curing chemistry of matrix polymers, the glass substrates were accordingly functionalized with silane compounds. The glass substrate was modified with methacrylate group, for instance, for reacting with methacrylate group of MD 700 and PEGDMA matrix polymers, with epoxy group for coupling with epoxy group of SU 8 polymer and Duralco 4525 adhesive, and with vinyl group for thiol-ene cross linking of NOA 81 adhesive (Fig. 2(a), 2(b) and refer to ESI,† Fig. S6). The bonding strengths of these microchannels fabricated by SSB method were also estimated by burst pressure that ranged from 1034 psi for fluoropolymer to up to 1931 psi for Duralco 4525 adhesive polymer (Fig. 2(c)). In particular, the bonding strength of fluoropolymer based microchannels is higher by two orders of magnitude when compared with 36 psi of burst pressure for the channel made by conventional sequential method²⁷ and 35 psi by fusion bonding method²⁸ (refer to ESI,† Tab. S1). The effective chemistry of the SSB method was also demonstrated in the fluoropolymer-glass microchannels by varying surface coverage with methacrylate/methyl ratios of 0:10, 1:9, 3:7, 5:5 and 10:0, indicating tunable bonding strength similar to the PVSZ polymer-glass microchannels (Fig. 2(d)).

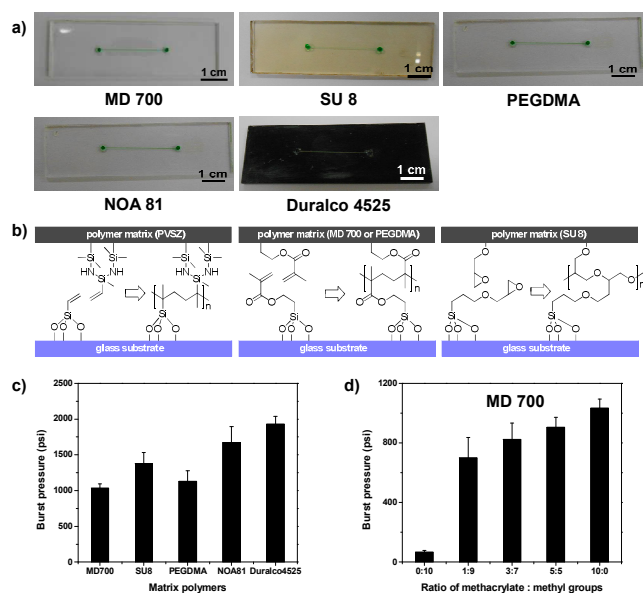


Fig. 2 a) Optical images of various polymer-derived microreactors fabricated by the SSB method. b) Chemical principle of the interfacial bonding between the functionalized glass and the polymer matrix such as PVSZ (left), MD 700 or PEGDMA (center) and SU 8 and NOA 81 (right). The chemical bonding for NOA 81 was based on radical thiolene coupling reaction. c) Burst pressure of various microreactors made of different matrix polymers. d) Burst pressure of fluoropolymer-glass microreactor for various ratios of methacrylate/methyl functional group on glass substrate.

Flash chemistry application of pressure-tolerant microreactor under high pressure condition

The pressure-tolerant microchannels fabricated by the SSB method would be useful in a number of areas. One such area is flash chemistry,²⁹⁻³¹ a new synthetic concept in a fast but controlled manner which offers an integrated scheme for bringing together the generation of highly reactive species and their reactions in a time scale of one second or less. The ultra-fast reaction with short-lived reactive intermediate at extremely fast flow rates can be handled by continuous-flow microreactor systems that have reliable tolerance under induced high back pressure. Typically, the flash chemistry was conducted in metal tube-type microfluidic devices because of their good stability against high pressure as well as chemicals and temperature. The metal tube-type microreactor has several drawbacks such as opaqueness, difficulty on construction of sophisticated microstructure, and limited design of microchannel. We envisaged that transparent polymer microfluidic devices with excellent pressure tolerance could be employed for the reactions that require highly pressurized condition as in flash chemistry, and further extended into the area of in-situ analysis such as micro total analysis systems.

Here, the high pressure-tolerant PVSZ polymer-glass microreactor with excellent chemical stability was effectively employed to synthesize a well-known antibacterial, antiparasitic, and antineoplastic drug, Tryptanthrin,¹⁶ by utilizing an unstable intermediate (aryllithium bearing isocyanide group) at extremely high flow rate (several mL/min). Notably, these kinds of highly reactive intermediates are quite unstable only with a very short life time, and the reactions in a conventional batch process could be conducted only at very low temperature such as $-78\text{ }^{\circ}\text{C}$.³²

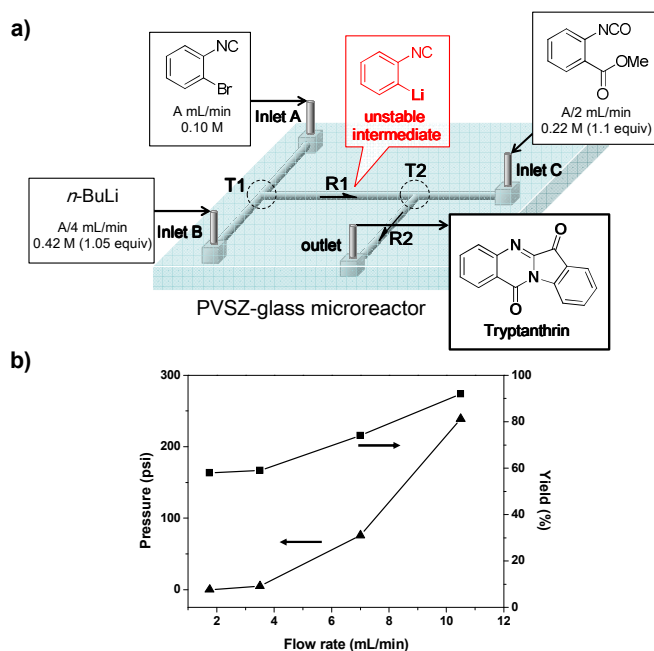


Fig. 3 a) Continuous-flow synthesis of Tryptanthrin using pressure-tolerant PVSZ-glass microreactor that consists of two T-junctions (T1 and T2, 300 μm width and 100 μm height) and two reaction parts R1 (300 μm width, 150 μm height and 40 mm length), R2 (300 μm width, 150 μm height and 5 mm length) b) Synthetic yield and flow induced pressure as a function of total flow rate of three inlets at R2.

Therefore, the continuous-flow microreactor developed here is a most suitable tool to perform chemical transformations of reactive species that are impossible to handle in flasks. In this work, a transparent PVSZ polymer-glass microreactor with three inlets and two T-shaped junctions was devised and fabricated by the SSB method as shown in Fig. 3(a). Reagents of *o*-bromophenyl isocyanide and *n*-BuLi were mixed at the first T-junction (T-1) to generate a highly reactive intermediate, *o*-lithiophenyl isocyanide, it was immediately reacted by mixing with phenyl isocyanate at the second T-junction (T-2) to produce a drug compound at room temperature. The ratio of the flow rate was kept at 4:1:2 for starting substrate, *n*-BuLi, and electrophile, respectively. When the flow rate was relatively slow (1 mL/min for starting substrate), the yield of the product was not satisfactory (58%), presumably due to the decomposition of the highly reactive aryllithium intermediate²⁹⁻³¹ (Fig. 3(b) and refer to ESI,† Tab. S2). The fast reaction involves generation of unstable short-lived reactive species and their subsequent in-situ utilization by transferring to another location before they are decomposed in ms-scale of time. Upon increasing the flow rate of starting substrate to 6 mL/min, the synthetic yield of desired product, Tryptanthrin, was improved up to 90% isolated yield with the total flow rate of 10.5 mL/min and 14 ms of reaction time for the unstable intermediate. To the best of our knowledge, this is the first report on the use of polymer-based microfluidic chip device for flash chemistry that has been performed only by opaque metal tube-type microreactor, as well as on the synthesis of Tryptanthrin in microfluidic device. Our synthetic method is much superior to the reported method using flask, in terms of mild reaction temperature and short reaction time with high isolated yield of the product.³¹ The induced pressure in the microreactor gradually increased with increasing flow rate, finally reaching 239 psi that only metal-tube or ceramic capillary would have

endured. Moreover, the transparency of PVSZ-glass microreactor enabled us to observe the bright yellow color of the unstable intermediate that changed to reddish brown due to its decomposition within several tens of ms at low flow rates (refer to ESI,† Fig. S7). Therefore, the highly pressure-tolerant property of PVSZ-glass microreactor is indispensable to accomplishing this kind of flash chemistry.

Conclusions

We have introduced a general strategy for resolving long-lasting bonding difficulties in polymer microfluidics devices by simultaneous solidification and bonding of microchannel with the aid of a sacrificial wax template. The SSB method to fabricate highly pressure-tolerant microreactors involves steps of pre-patterning wax template on glass substrate, chemical functionalization of glass surface, simultaneous solidification and bonding between the matrix polymer and the glass substrate, and sacrificial removal of wax template. This user-friendly method with no use of sophisticated facilities allows fabrication of polymer based microreactors under mild conditions, leading to high success-yield, excellent bonding strength, and various channel design with no conformal contact difficulty. The versatility of this SSB method was demonstrated by fabricating microreactors from a variety of polymers with different interfacial chemistry, which were all stable at 1000 psi with the highest burst pressure of 2000 psi for PVSZ-glass microreactor. In particular, the fluoropolymer-glass microreactor can withstand a burst pressure that is two orders of magnitude higher when compared to the microchannel made by conventional method. The PVSZ-glass microreactor was successfully utilized to perform flash chemistry under highly pressurized condition with the synthetic yield of 90% at the total flow rate of 10.5 mL/min and reaction time of 14 ms. Finally, it is believed that this pressure-tolerant microfluidic device is a useful platform to investigate flash chemistry and to miniaturize spectroscopic tools for chemical analysis into micro total analysis systems (micro-TAS).

Acknowledgements

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2008-0061983).

Notes and references

^a Science and Technology on Advanced Ceramic Fibers and Composites Laboratory, College of Aerospace Science and Engineering, National University of Defense Technology, Changsha 410073, People's Republic of China.

^b National Center of Applied Microfluidic Chemistry, Department of Chemical Engineering, Pohang University of Science and Technology, Environ. Eng. Bldg., San31, Hyoja-dong, Nam-gu, Pohang, Gyungbuk, 790-784, Korea. dpkim@posetech.ac.kr

Wurong Ren worked at Professor Kim's lab under co-advisor program. Wurong Ren and Heejin Kim contributed equally to this work.

† Electronic Supplementary Information (ESI) available: [Detailed fabrication scheme of SSB method, CVD process, microreactor with various channel dimensions, detailed chemistry and the whole set-up.] See DOI: 10.1039/b000000x/

- 1 A. J. deMello, *Nature*, 2006, **442**, 394-402.
- 2 B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300-2318.
- 3 A. Abou-Hassan, O. Sandre and V. Cabuil, *Angew. Chem. Int. Ed.*, 2010, **49**, 6268-6286.
- 4 K. Jähnisch, V. Hessel, H. Löwe and M Baerns, *Angew. Chem. Int. Ed.*, 2004, **43**, 406-446.
- 5 A. M. Nightingale and J. C. deMello, *Adv. Mater.*, 2013, **25**, 1813-1821.
- 6 T. Ito and S. Okazaki, *Nature*, 2000, **406**, 1027-1031.
- 7 Y. Xia and G. M. Whitesides, *Angew. Chem. Int. Ed.*, 1998, **37**, 550-575.
- 8 K. I. Min, T. H. Lee, C. P. Park, Z. Y. Wu, H. H. Girault, I. Ryu, T. Fukuyama, Y. Mukai and D. P. Kim, *Angew. Chem. Int. Ed.*, 2010, **49**, 7063-7067.
- 9 D. C. Duffy, J. C. McDonald, O. J. A. Schueller and George M. Whitesides, *Anal. Chem.*, 1998, **70**, 4974-4984.
- 10 J. N. Lee, C. Park and G. M. Whitesides, *Anal. Chem.*, 2003, **75**, 6544-6554.
- 11 C. Iliescu, H. Taylor, M. Avram, J. Miao and S. Franssila, *Biomicrofluidics*, 2012, **6**, 016505.
- 12 S. G. Pedro, M. Puyol, D. Izquierdo, I. Salinas, J. M. Fuente and J. Alonso-Chamarro, *Nanoscale*, 2012, **4**, 1328-1335.
- 13 T. W. Haas, H. Fadaei, David Sinton, *Lab Chip* 2012, **12**, 4236.
- 14 M. Hashimoto, R. Langer and D. S. Kohane, *Lab Chip*, 2013, **13**, 252-259.
- 15 T. H. Yoon, S. H. Park, K. I. Min, X. Zhang, S. J. Haswell and D. P. Kim, *Lab Chip*, 2008, **8**, 1454-1459.
- 16 A. V. Lygin and A. Meijere *Org. Lett.*, 2009, **11**, 389-392.
- 17 D. Qin, Y. Xia and G. M. Whitesides, *Nature protocols*, 2010, **5**, 491-502.
- 18 A. P. Esser-Kahn, P. R. Thakre, H. Dong, J. F. Patrick, V. K. Vlasko-Vlasov, N. R. Sottos, J. S. Moore and S. R. White, *Adv. Mater.*, 2011, **23**, 3654-3658.
- 19 L. M. Bellan, S. P. Singh, P. W. Henderson, T. J. Porri, H. G. Craighead and J. A. Spector, *Soft Matter*, 2009, **5**, 1354-1357.
- 20 L.M. Bellan, M. Pearsall, D. M. Cropek and R. Langer, *Adv. Mater.*, 2012, **24**, 5187-5191.
- 21 A. Asthana, K. Kim, J. Perumal, D. M. Kim and D. P. Kim, *Lab Chip*, 2009, **9**, 1138-1142.
- 22 S. h. Chao, R. Carlson and D. R. Meldrum, *Lab Chip*, 2007, **7**, 641-643.
- 23 W. Ren, J. Perumal, J. Wang, H. Wang, S. Sharma and D. P. Kim, *Lab Chip*, 2014, **14**, 779-786.
- 24 Y. H. Tennico, M. T. Koesdjojo, S. Kondo, D. T. Mandrell and V. T. Remcho, *Sensor Actuat. B-Chem*, 2010, **143**, 799-904.
- 25 A. D. Stroock, S. K. W. Dertinger, A. Ajdari, I. Mezic, H. A. Stone and G. M. Whitesides, *Science*, 2002, **295**, 647-651.
- 26 Q. Fang, D. P. Kim, X. Li, T.H. Yoon and Y. Li, *Lab Chip*, 2011, **11**, 2779-2784.
- 27 T. J. A. Renckens, D. Janeliunas, H. Vliet, J. H. Esch, G. Mulac and M. T. Kreutzer, *Lab Chip*, 2011, **11**, 2035-2038.
- 28 T. W. de Haas, H Fadaei and David Sinton, *Lab Chip*, 2012, **12**, 4236-4239.

Journal Name

ARTICLE

- 29 J. Yoshida, A. Nagaki and T. Yamada, *Chem. Eur. J.*, 2008, **14**, 7450-7459.
- 30 J. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896-9904.
- 31 H. Kim, A. Nagaki and J. Yoshida, *Nature Commun.*, 2011, **2**, 264.