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Convergent synthesis of polyamide dendrimer using a continuous flow microreactor

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Abstract

Dendrimers are nanoscale macromolecules that have highly branched, core-shell structures. Higher generation dendrimers have close-packed peripheral functional groups and a hollow interior. The chemistry of the core and the terminal functionalities can be tailored according to the specific application. These structural characteristics provide room for the design of dendrimers to meet a wide set of supra-molecular recognition and hosting tasks. Dendrimers are synthesized in a stepwise manner to higher generations using a number of chemical reactions, so carrying out the synthesis in a conventional reactor is time-consuming. Therefore the dendrimer products are expensive. In this work, convergent synthesis of dendrimer was carried out in a continuous flow microreactor. Pure dendrons and dendrimers could be synthesized using the microreactors within seconds of residence time. In comparison, the conventional flask synthesis took several hours for a similar yield. The reaction kinetics of G1 dendron synthetic process was conducted using the microreactor and compared with the flask synthesis. The data indicated the reaction is in fact a fast one which suggested the flask synthesis is hindered by mass transfer.

Keywords: Synthesis; Polyamide dendrimer; Microreactor; Reaction kinetics study

1. Introduction

Dendrimers [1,2] are highly-branched molecules with fractal morphologies. The word dendrimer originates from Greek dendron, meaning tree. Higher generation dendrimers are featured with close-packed peripheral functionalities and hollow interiors. This unique architecture provides dendrimers with the capability to encapsulate small guest molecules into their interiors and conjugate functional molecules on the surface. Also the chemistry of the core and the surface can be tailored according to specific applications. Dendrimers can be synthesized with a great precision, thus ideally, a certain generation of dendrimer has a single size and molecular weight rather than a broad molecular weight distribution that is the characteristic of a typical polymer [3]. These structural characteristics provide room for the design of dendrimers to meet a wide set of potential applications including catalysis, sensors, drug delivery, light harvesting, MRI imaging and gene transfer techniques [4–6]. However, the synthesis of dendrimer is a tedious and time-consuming process, some reactions take days to complete in a conventional reactor. Therefore, a limiting factor on the application of dendrimers is the cost of their production. For dendrimers to realize their full potential, processes must be developed that provide higher throughput, higher efficiency and better uniformity.

Two conceptually different approaches to dendrimer synthesis exist. The divergent approach, arising from the independent discover in parallel works from Tomalia et al. [3] and Vögtle and coworkers [7], initiates growth at the core of the dendrimer and continues outward by the repetition of coupling and activation steps. Convergent synthesis, first reported by Fréchet et al. in 1989 [8], initiates growth from the exterior of the molecule, and progresses inward by coupling end groups to each branch of the monomer. In both approaches, dendrimer generations are created by the iterative repetition of a sequence of reactions. Thus, it is critical to increase the throughput of each reaction step.

Microreactors are well recognized for their ability to provide uniform and fast mixing, enhanced mass and heat transfer due to their short diffusional pathways and large interfacial areas per unit volume (10,000–50,000 m^2/m^3) which is much higher than 100 m^2/m^3, the surface-area-to-volume ratio of conventional reactors [9]. These two features of microreactors are keys to improving yield and selectivity, specifically for

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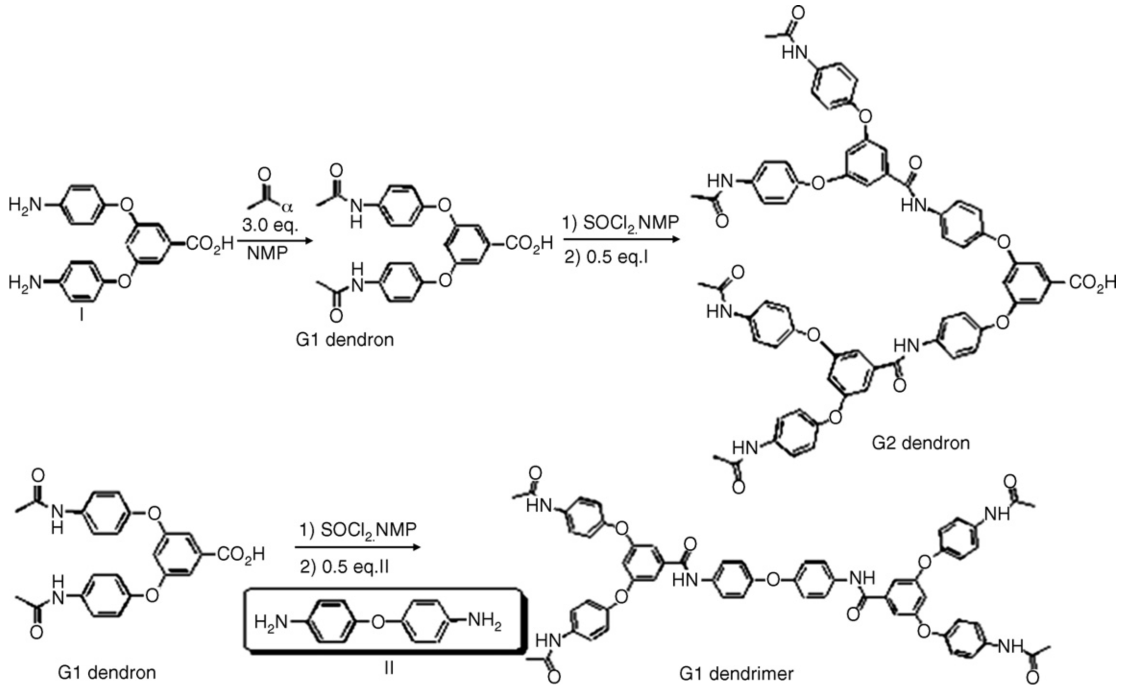

Scheme 1. Reactions of the convergent synthesis of dendrons and dendrimers.

mass-transport controlled reactions, highly exothermic or endothermic reactions, and reactions with inherently unstable intermediates. In addition to the benefits mentioned above, another attractive advantage is the ability to "number-up" laboratory-scale reactors by simply arraying the identical microreactors without a need for further process development and parameterization.

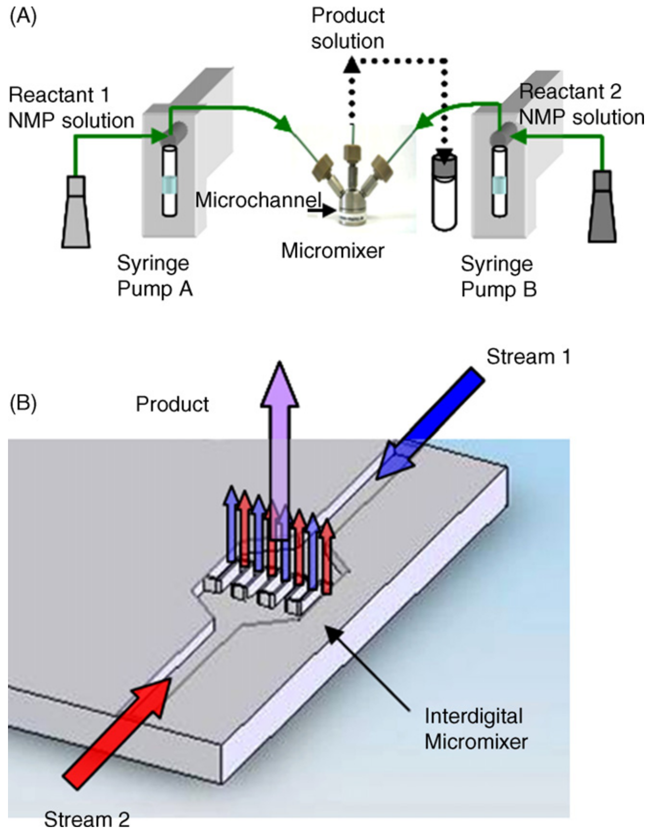

Fig. 1. (A) A schematic diagram of the continuous flow microreactor. (B) mixing via an interdigital micromixer.

In this paper, we reported the application of microreactor on the convergent synthesis of dendrimers. This study focused on the feasibility of synthesis and investigated the reaction kinetics polyamide dendrimers and dendrons via a continuous flow microreactor. The reactions for the convergent synthesis are illustrated in Scheme 1 [10]. The convergent approach used 3,5-bis(4-aminophenoxy)-benzoic acid (compound **1**) as building blocks and *N*-methyl-2-pyrrolidinone (NMP) as solvent. Thionyl chloride was used as an activating agent, while 4,4′-oxydianiline served as a core molecule for the synthesis of dendrimers. The synthesis of each generation dendron – except for dendron generation 1 (G1) – includes two steps: activation by thionyl chloride and coupling with building block 1. The synthesis of each dendrimer consists of two similar steps: activation by thionyl chloride and coupling with core 2. This synthesis strategy has been fulfilled in a conventional flask by Washio, with the exception of G1 dendrimer. The reported synthetic reactions for each generation of dendron and dendrimer required cooling and inert gas protection, and typically took 4–6 h to complete in a flask.

2. Experimental

2.1. Setup

A schematic diagram of the microreactor setup is given in Fig. 1A. The micromixer (Institut für Mikrotechnik Mainz) consists of a mixing element, interdigital microchannels, in the center of a substrate made of thermally grown silicon dioxide. The mixing element is housed within a stainless steel container.

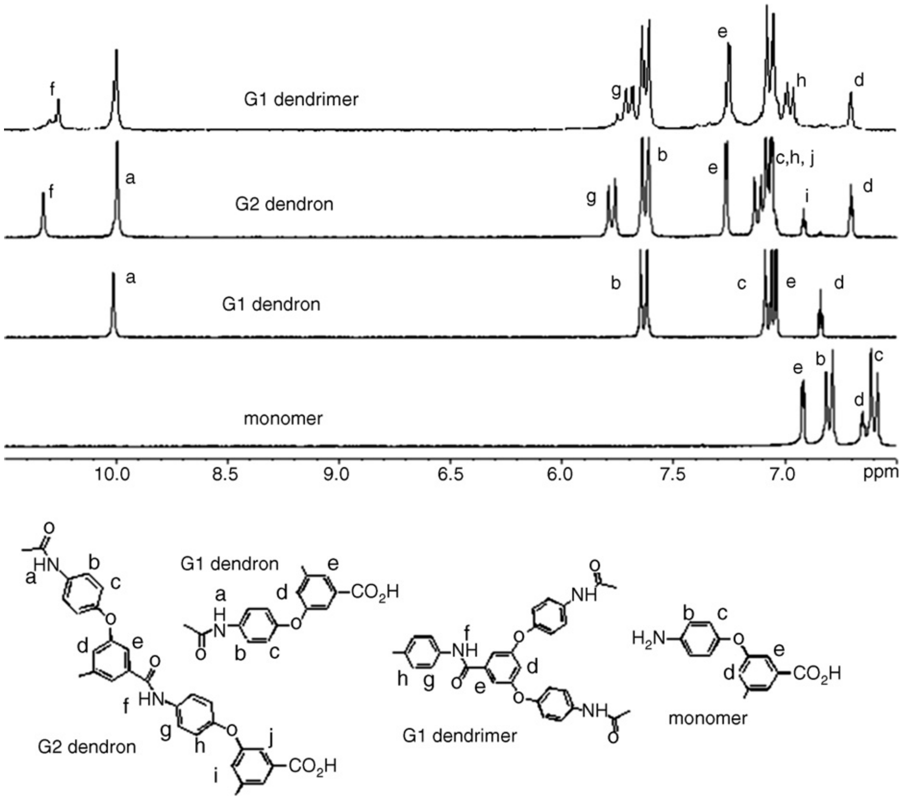

Fig. 2. ^{1}H-NMR spectra and corresponding molecular structures of the monomer, dendrons G1, G2 and dendrimer G1 synthesized via a micromixer.

Each microchannel has a dimension of 30 μm in width and 100 μm in height. Fig. 1B illustrates the principle of mixing via an interdigital micromixer. Two streams of reactants were simultaneously delivered to the interdigital micromixer at a flow rate of 0.026 ml/s through two programmable syringe pumps. The mixture of product and un-reacted reactants from the microreactor passed through a PEEK tubing (ID of 750 μm), and was collected at tubing outlet by pouring directly into water to precipitate. A double-jacked beaker that was connected with a constant temperature circulator was used for temperature control. For the study of the synthesis feasibility of dendrons and dendrimers, temperature was set at 30 °C with a residence time in the tubing of 17 s. For the study of reaction kinetics of dendron G1, temperature and residence time were varied and indicated in the results and discussion section. All chemicals, except thionyl chloride (from Sigma–Aldrich), were purchased from TCI America, and were used as received.

2.1.1. Synthesis of dendron G1

Solutions of 3,5-bis(4-aminophenoxy)-benzoic acid (monomer) dissolved in NMP (concentration of 0.4 mol/L) and 3 eq. of acetyl chloride dissolved in NMP (concentration of 1.2 mol/L) were introduced into microchannels by syringe pumps. The mixture was poured into water directly to form precipitate. The precipitate was collected and dried at 120 °C.

2.1.2. Synthesis of dendron G2

Solutions of dendron G1 dissolved in NMP (concentration of 0.323 mol/L) and 1.04 eq. of thionyl chloride dissolved in NMP (concentration of 0.336 mol/L) were introduced into microchannels. The intermediate was collected at the outlet of tubing. Then solutions of the intermediate and 0.48 eq. of monomer that has been dissolved in NMP (concentration of 0.078 mol/L) were fed into micromixer by syringe pumps at a flow rate of 0.026 ml/s. The mixture was poured into water directly to form precipitate. The precipitate was collected and dried at 120 °C.

2.1.3. Synthesis of dendrimer G1

Solutions of dendron G1 dissolved in NMP (concentration of 0.2 mol/L) and 1.5 equivalent of thionyl chloride dissolved in NMP (concentration of 0.3 mol/L) were introduced into microchannels by syringe pumps at a flow rate of 0.026 ml/s. The intermediate was collected at the outlet. Then solutions of the intermediate and 0.5 eq. of the core molecule that has been dissolved in NMP (concentration of 0.05 mol/L) were fed into micromixer by syringe pumps at a flow rate of 0.026 ml/s. The mixture was poured into water directly to form precipitate. The precipitate was collected and dried at 120 °C.

2.2. Measurement

The dried products were analyzed by ^{1}H NMR and mass spectrometry to determine the structures and purity of the products from the microreactor and from the conventional batch reactor. NMR spectra were recorded by a Bruker nuclear magnetic resonance spectrometer (300 MHz). Deuterated dimethyl sulfoxide (DMSO-d_6) was used as solvent. Mass spectra were collected

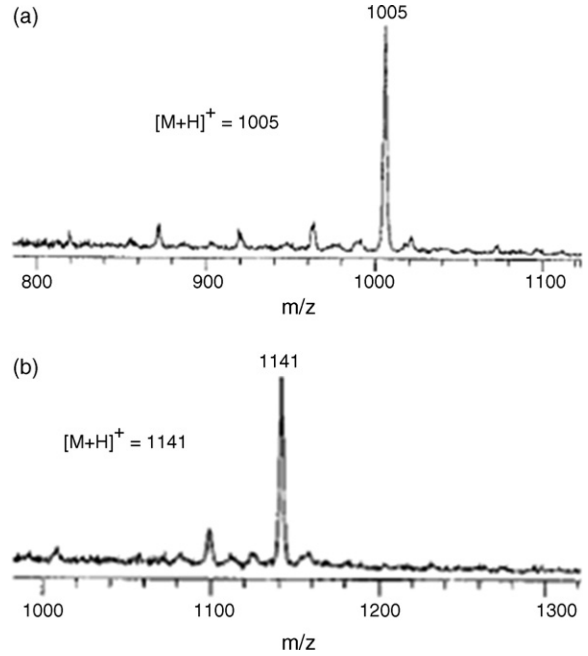

Fig. 3. Mass spectra of dendrimer G1 (a) and dendron G2 (b).

using a JEOL MSRoute mass spectrometer with positive FAB ionization.

3. Results and discussion

3.1. Syntheses of dendrons G1, G2 and dendrimer G1 via micromixer

The ^{1}H NMR spectra of dendrons G1, G2 and dendrimer G1 synthesized via the microreactor along with the spectrum of the monomer are shown in Fig. 2. The disappearance of the monomer peaks and the appearance of new peaks indicated the conversion of monomers into G1 dendrons. Compared the spectrum of G2 dendron with that of G1 dendron, the appearance of new peaks at 10.32 (f), 7.76 (g), and 6.91 (i) indicated that dendron G2 was obtained through the microreactor. Compared the spectrum of G1 dendrimer with that of G1 dendron, the signal assigned to the protons of position d shift from 6.84 to 6.71 ppm, position "e" from 7.04 to 7.25 ppm and the signals in 10.26 (f), 7.71 (g) and 6.98 (h) appear after the coupling reaction, indicating the formation of G1 dendrimer.

The mass spectra in Fig. 3 show the signals at $m/z = 1005$ and 1141, indicating the successful synthesis of dendrimer G1 (calculated molecular weight of 1004) and dendron G2 (calculated molecular weight of 1140), respectively.

3.2. Reaction kinetics study of dendron G1 via a micromixer

G1 dendron synthesis was studied in more detail using the continuous flow microreactor and compared with the results from a flask reactor. The experimental procedures are similar to what described above. The change of residence time from 0.6 to 17 s was realized by changing the length of the outlet tubing, meanwhile kept the flow rate of each reactant stream the same as 0.026 ml/s for all runs. The reaction under two reaction temperatures, 15 and 25 °C, was performed. ^{1}H NMR was used to analyze the products to identify the components and to calculate the conversions and yields.

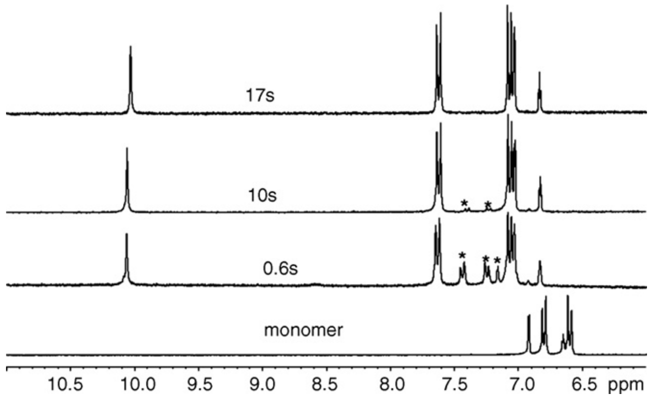

Fig. 4. NMR spectra of G1 dendron products synthesized via a microreactor at different residence times under a temperature of 15 °C.

Figs. 4 and 5 show the NMR spectra of G1 dendron products at different residence times under temperatures of 15 and 25 °C, respectively. Apparently, this reaction is rather fast as evidenced by the disappearance of the monomer NMR peaks and the appearance of the G1 dendron NMR peaks for a mere 0.6 s residence time. The majority of the reactants was converted to the desired product, G1, within residence times of 17 s and 2.5 s at 15 and 25 °C, respectively. 93% and 87% yields were achieved within 0.6 s at these two reacting temperatures with a small fraction of intermediates that had only one branch reacted. The peaks labeled with "*" are assigned for intermediate having only one branch reacted.

For analysis of the reaction kinetics, we focused on two peaks, the peak of the desired product at 7.65 ppm and the peak of the intermediate (with only one branch reacted) at 7.4 ppm. The peak areas of the two peaks were calculated to follow the course of the reaction. We assume a nearly 100% conversion of monomer was achieved after 0.6 s since the monomer NMR peaks disappeared completely. The yield is defined as the ratio of the peak area of the desired product to the sum of both peak areas. The yield as a function of residence time is illustrated in Fig. 6.

A controlled reaction was carried out in a flask at a temperature of 25 °C and same reaction conditions as that of using a microreactor. Samples were taken out from the reactor period-

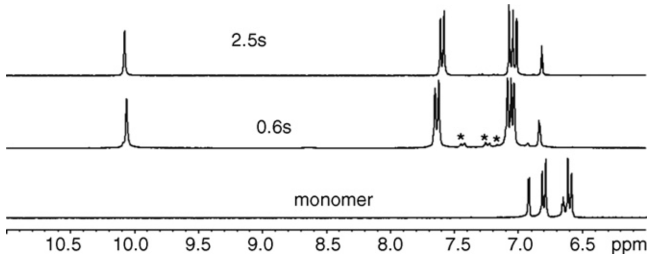

Fig. 5. NMR spectra of G1 dendrons synthesized via a microreactor at different residence times under a temperature of 25 °C.

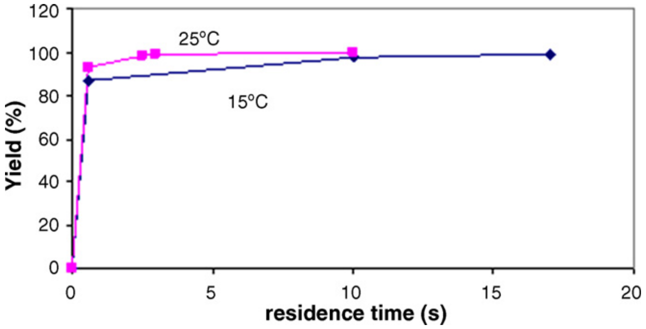

Fig. 6. Yield of G1 dendron as a function of residence time at reaction temperatures of 15 °C and 25 °C.

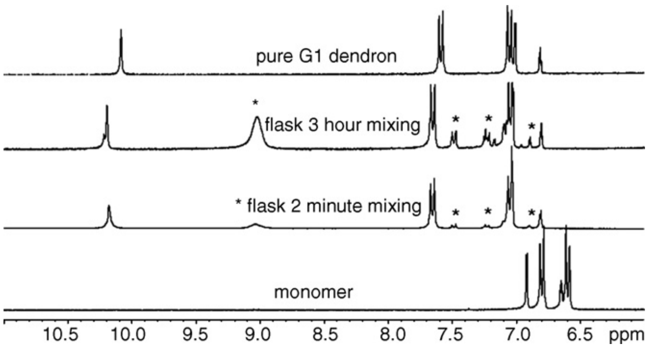

Fig. 7. Comparison of NMR spectra of G1 dendron products synthesized via a conventional flask stirring for 2 min and 3 h with that of pure G1 dendron and monomer.

ically to be analyzed. The NMR results (in Fig. 7) showed that side products and intermediate, which is labeled by "*", still existed after 3 h of stirring. These data indicated that the G1 dendron synthesis is in fact a fast reaction. The rather slow conversion from the flask synthesis is likely a result of poor mass transfer.

4. Conclusions

We have successfully synthesized polyamide dendrons and dendrimers using a continuous flow microreactor. The microreactor demonstrated several advantages over a conventional batch reactor. One of the most attractive advantages is that pure dendrons and dendrimers could be synthesized within few seconds of residence time in contrast to hours of stirring in a flask. Therefore, the continuous flow microreactor could potentially reduce the production cost, which will enhance the opportunities for the application of dendrimers in various fields. In addition, the required reaction conditions are easier to implement. For example, for the synthesis performed in a flask, the mixture needs to be stirred at low temperature (i.e. 0 °C as reported) at the beginning of the mixing, and with a continuous supply of nitrogen gas, to avoid side reactions. In contrast, the pure dendrons and dendrimers can be synthesized at a constant temperature without the need of nitrogen stream with high yield for synthesis performed in a microreactor. The reaction kinetics results of G1 dendron synthesis indicated that the reaction is a fast one. The rather slow conversion from the flask synthesis is likely a result of poor mass transfer. Rapid, continuous flow, high yield and selectivity, and most importantly, a facility for numbering-up the process for industrial production scale, microreactor-based synthesis of dendrimers appears to be a promising approach.

Acknowledgement

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