

Student-Fabricated Microfluidic Devices as Flow Reactors for Organic and Inorganic Synthesis

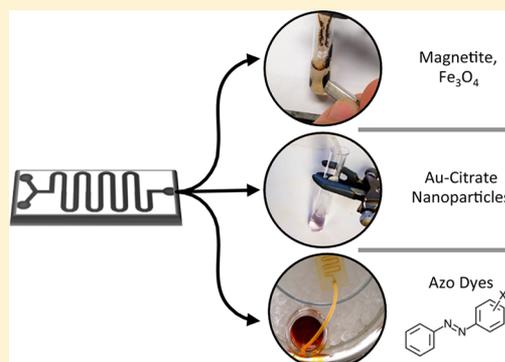
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S Supporting Information

ABSTRACT: Flow synthesis in microfluidic devices has been rapidly adapted in the pharmaceutical industry and in many research laboratories. Yet, the cost of commercial flow reactors is a major factor limiting the dissemination of this technology in the undergraduate curriculum. Here, we present a laboratory activity where students design and fabricate homemade microfluidic flow reactors using thermoplastic molds and soft lithographic methods, and conduct inorganic syntheses of magnetite particles and gold–citrate nanoparticles, as well as a two-step organic synthesis of azo dyes. The success of these reactions can be quickly assessed by colors or physical characteristics, which makes optimizations of reactor designs and reaction conditions possible on-the-spot. The activity also successfully integrates some important concepts in chemical engineering, organic and inorganic synthesis, nanomaterial chemistry, and analytical chemistry

KEYWORDS: Upper-Division Undergraduate, Analytical Chemistry, Chemical Engineering, Interdisciplinary/Multidisciplinary, Laboratory Instruction, Green Chemistry, Inquiry-Based/Discovery Learning, Laboratory Equipment/Apparatus, Nanotechnology, Synthesis



Microfluidic devices, also known as *lab-on-a-chip*, have gained tremendous popularity in technological fields, such as bioanalytical,^{1,2} medical diagnostic,³ and pharmaceutical^{4,5} industries and research laboratories in the past two decades. These devices, fabricated from a large variety of materials, from glass to polymers to papers,⁶ allow for complex tasks, such as separation, sensing, mixing, and synthesis, to be carried out in miniaturized devices at the microliter scale. The reduced sample size, ease in controlling parameters, and low costs are some highly attractive features in these devices.

Several articles have been published in recent years featuring microfluidic devices with the intention to introduce this versatile technology to the undergraduate and the graduate chemistry curricula.^{7–13} Most of these articles focused on using homemade devices made from silica glass or polymers, such as poly(dimethylsilane) (PDMS), to illustrate simple chemical principles. Teerasang et al. designed and fabricated chips using photolithography to perform electrophoresis to separate food coloring dyes in microfluidic channels.¹² Some commercial microfluidic devices have also been applied toward a quantitative acid–base titration experiment for pedagogical purposes.¹¹ These efforts have promoted the adaptation of microfluidic-based devices in various upper-division laboratories in many institutions, and even in high-schools.^{8,9} Yet, curriculum demonstrating the unique strength and versatility of continuous flow synthesis has yet to be developed.

Microreactors have been widely adapted in pharmaceutical industry and in some research laboratories in recent years.^{4,5} These reactors feature the advantage of high surface-area-to-

volume ratios, which significantly increases the interfacial contact area of reactants in the confined narrow channels or tubing. These geometric advantages also allow for more efficient heat transfer. In light of promoting green chemistry and sustainable practices, flow reactors, with the capability to incorporate catalysts in the flow channels and in-line analysis, highlight several aspects of the “12 Principles of Green Chemistry”,¹⁴ such as maximizing atom economy, increasing energy efficiency, and use safer reaction conditions. The design of flow reactors are highly versatile, which allows for both single-step and multistep syntheses to be conducted.¹⁵

With experiences in organic and inorganic laboratories, students are usually very familiar with chemical synthesis conducted in stirred batch processes. Therefore, it is highly desirable to introduce flow synthesis to the undergraduate curriculum. A few activities featuring flow synthesis have been published in the *Journal* in recent years,^{16–18} primarily for organic synthesis using commercial microflow-reactors or macroscopic specialty glassware. Commercially available instruments (e.g., Thalenano, FutureChemistry, Syrris, etc.) with prices ranging from \$40,000 to \$80,000 per unit may not be a suitable option for financial reasons. Therefore, we present this project exploring the design, fabrication, and optimization of a polymeric microfluidic device using a soft lithographic method to perform both organic and inorganic syntheses. Layout of such apparatus is shown in Figure 1. We chose reactions that yield products that are easily characterized by physical

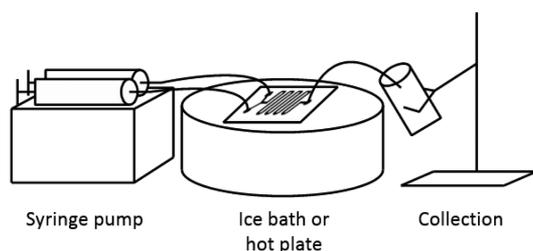


Figure 1. Layout of the synthesis assembly in a microfluidic flow reactor.

properties, such as colors and magnetism. Inorganic syntheses include making magnetic iron particles and gold–citrate nanoparticles; organic synthesis includes making a series of azo dyes. Since each student performs the synthesis in his/her own microfluidic reactor, multiple reactions with varying conditions can be conducted and compared among students. Relating to their numerous synthesis experiments done in batch in prior *Organic* and *Inorganic* laboratories, the advantages in speed and ease in parameter controls in flow synthesis are demonstrated.

EXPERIMENTAL OVERVIEW

This project is intended for two 4-h lab periods in an upper division chemistry course (*Advanced Analytical Chemistry*, in our case). Before starting with the project, students are required to complete a prelab exercise (see Supporting Document) to familiarize themselves with concepts in microfluidic devices and flow chemistry. Device fabrication and solution preparation can be accomplished in one lab period, and reactions can be performed in assembled devices in the following period. If time allows, batch synthesis can be conducted in parallel for comparison.^{19–21} Students are encouraged to make multiple chips to ensure success in device fabrication. They are encouraged to vary mold patterns, device dimensions (e.g., chip thickness, channel width, and border width, etc.), PDMS curing temperatures (hence, chip rigidity), and substrate materials (glass cover slide or another PDMS slab). Parameters reported here are optimized from various trials.

EXPERIMENTAL DETAILS

Fabrication of Microfluidic Flow Reactors

Microfluidic pattern designs can be created in PowerPoint and/or photo editing software. The polystyrene thermoplastic sheets (Shrinky-Dinks, Frosted Ruff N' Ready, K&B Innovations, North Lake, WI) are triple printed on a laser printer. The printed sheets are cut and baked in an oven for 3–5 min at 180 °C. Degassed PDMS mixture (Dow Corning Sylgard 184 Silicone Encapsulant) is poured onto the Shrinky-Dinks mold in a Petri dish, and cured at 50 °C for 1–2 h. Inlet and outlet holes are created using a biopsy punch (Miltex Biopsy Dermal Punch, 14 gauge) on the cured PDMS block. The PDMS surface and microscope slide substrate are oxidized with a handheld Tesla coil for enhanced binding. Sixteen gauge \times 1.5 in. needles are attached to the tubing (SURFLO Winged Infusion Set), inserted, and adhered to the PDMS piece with a 5 min epoxy. All reagents are injected into the microfluidic device using a syringe pump (Chemyx Fusion 100).

Magnetic Particles

Magnetic particles are made in a simple two-inlet Y-junction flow reactor as shown in Figure 2. Synthesis of magnetic iron

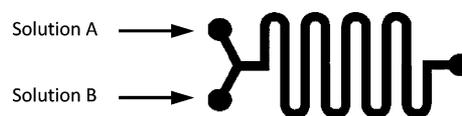


Figure 2. Two-inlet flow reactor design.

particles was adopted from Berger et al.¹⁹ An iron solution, containing FeCl_2 and FeCl_3 at 1:2 mol ratio (solution A) and a diluted ammonia solution (solution B) are injected from two 1 mL syringes at a flow rate of 0.2 mL/min. The resulting magnetic iron particles are collected at the outlet and tested with a magnet.

Au–Citrate Nanoparticles (Au-NPs)

Synthesis of Au-NPs was adapted from Ftouni et al.,²² also done in chips shown in Figure 2. The chip is placed on a hot plate at 60 °C with a HAuCl_4 solution (solution A) and a sodium citrate solution (solution B) injected at a flow rate of 0.025 mL/min. The resulting citrate-capped Au-NPs are collected for absorption measurements.

Azo Dyes

Synthesis of azo dyes is a two-step reaction which involves the formation of a diazonium salt, a highly reactive compound, as an intermediate. The chip is placed in an ice-bath cooled Petri dish with an aniline solution (solution A), a sodium nitrite solution (solution B), and an aromatic compound solution (e.g., phenol or salicylic acid) (solution C) injected from respective inlets, shown in Figure 3, at a flow rate of 0.09 mL/

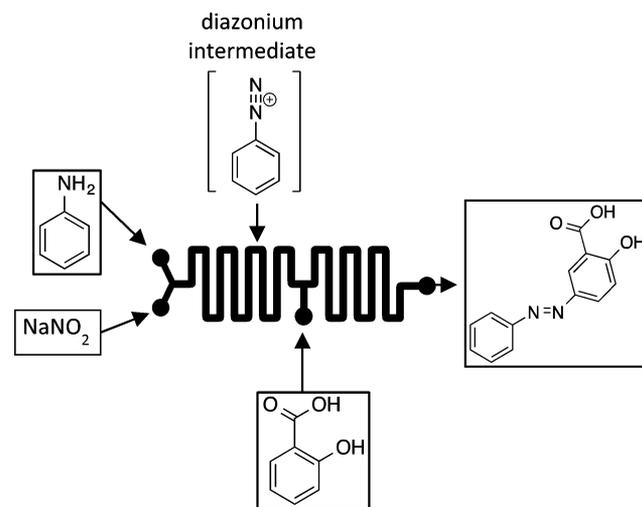


Figure 3. Three-inlet flow reactor with reagents for azo dye synthesis.

min. The resulting dye is acidified until it crashes out of solution. The solid product is analyzed with IR absorption spectroscopy and UV–visible absorption spectroscopy.

HAZARDS

Always wear safety goggles when working in the laboratory. Use of laboratory gloves is strongly recommended throughout the experiment, especially when working with PDMS, strong acids and the bases. Uncured PDMS mixture should be poured in a well-ventilated area. Extra caution should be taken when using razor blades, biopsy punches, and Tesla coil. The azo products will stain both skin and cloth. Disposal must follow proper waste disposal regulations.

RESULTS AND DISCUSSION

Diffusion and Laminar Flow in Microfluidic Channels

Diffusion is a crucial form of mass transfer important to many chemical and engineering fields, yet often left out in the undergraduate chemistry curriculum. Most batch reactions, often mechanically stirred, use convection as primary form of mass transfer. The reaction kinetics are limited by the chances of molecular collisions among reagents. Flow synthesis, fundamentally different from stirred batch reaction systems in mass transfer, provides a great opportunity to elucidate the concept of diffusion, and to highlight the advantage of confined geometry in microreactors. Another key concept demonstrated through this activity is laminar flow. Laminar flow is defined by fluid flowing in orderly layers parallel to the walls of the container. This behavior is clearly illustrated in these PDMS flow reactors. As shown in the zoomed-in image of the channels in Figure 4, as a result of reacting diazonium ion with aromatic

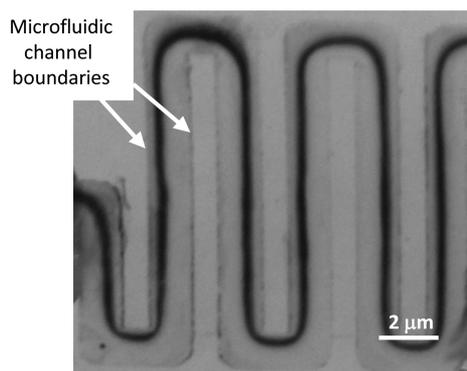


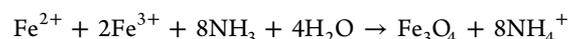
Figure 4. Image of dye-stained microfluidic channels illustrating reactions primarily occurring at the interface of two reactants in the channel.

compound in the second step of the azo dye synthesis reaction, the center of the channels are stained. Students observed this is due to the reaction primarily occurring at the interface of the two reactants when they flow in a laminar pattern. This is an alternative demonstration of laminar flow to the often-demonstrated mixing of food coloring dyes of primary colors to make a secondary color at the interface in the center of the channels.⁹

In the prelab exercise where students have to learn these concepts through reading suggested references, students use a simplified one-dimensional diffusion equation, which had been previously introduced in heterogeneous electrochemistry topics in analytical courses, to estimate the diffusion distance of a molecule in the channel. Assuming a 30 s residence time, a molecule could diffuse 150–350 μm laterally depending on the diffusion coefficient of the molecule. This calculation is crucial to illustrate to students the advantage of conducting flow synthesis in microreactors with submillimeter channel diameters to ensure high efficiency in mixing via diffusion alone.

Magnetic Particles

In batch preparation, stoichiometry is important in the formation and stabilization of magnetic iron particles.¹⁹ Therefore, the iron solution is adjusted to produce similar stoichiometry for reactions in the microfluidic devices. The magnetic particles generated are magnetite, Fe_3O_4 , which forms a colloidal suspension in aqueous media:



In the microfluidic flow reactor, the magnetite particles begin to form almost immediately when the two reactant solutions meet in the channel. The size of the particles, although visible, is small enough not to clog the channels, as seen in Figure 5a. The dark brown particles are tested to be magnetic when a magnetic field is applied to the collected solution (Figure 5b).

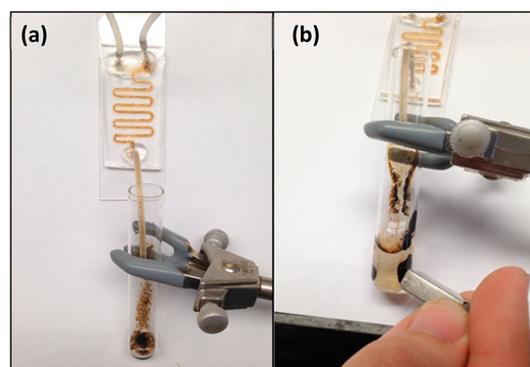


Figure 5. (a) Magnetite particles formed in a microfluidic flow reactor; (b) particles are magnetic when tested with a magnet.

This reaction is very straightforward with a high success rate. The magnetic property of the product makes it easy to characterize quickly. The product can be further modified by adding a surfactant, such as tetramethylammonium hydroxide, $(\text{CH}_3)_4\text{NOH}$, to produce ferrofluid.¹⁹ If available, microscopic characterizations can also be incorporated, and the effect of flow rate may be a parameter to evaluate.

Au–Citrate Nanoparticles

The synthesis of citrate-capped Au-NPs has been widely used as a model reaction to introduce nanomaterial synthesis to the chemistry curriculum.^{20,23} In batch synthesis, Au–citrate NPs are produced by bringing HAuCl_4 to a boil, followed by addition of sodium citrate. Colloidal Au has also been reported to be made in flow reactors.^{22,24,25} In a flow reactor, a variety of factors, such as temperature, residence time, and ratio of reactants, have been shown to affect the resulting sizes and shapes of the Au-NPs. Depending on particle size and shape, colloidal Au displays a surface plasmon resonance peak, λ_{max} between 500 and 600 nm, which gives rise to the pink to purple color of the resulting nanoparticle solutions. An increase in nanoparticle size often results in a red-shift in optical spectra with a broader peak.²³ Therefore, Au-NPs can be easily characterized without the need for an electron microscope, and the effects on particle size by reactants ratios, flow rates, and temperature can be assessed. The small reaction volumes in these PDMS microreactors allow for efficient heat transfer. To avoid turbulent flow when solution boils in the channels, we choose reaction temperature below 60 $^\circ\text{C}$.

The effect of the ratio of sodium citrate to HAuCl_4 on particle size is illustrated in Figure 6, where a clear correlation is observed in absorption spectroscopy. As the ratio increases, there is a decrease in both the peak width (triangles) and the observed λ_{max} (squares in Figure 6b). On the basis of the positions of λ_{max} we estimate the Au-NPs to be 70–90 nm in diameter.²⁶ Figure 6 shows that an increase in sodium citrate to HAuCl_4 ratio results in a measurable blue-shift and narrower

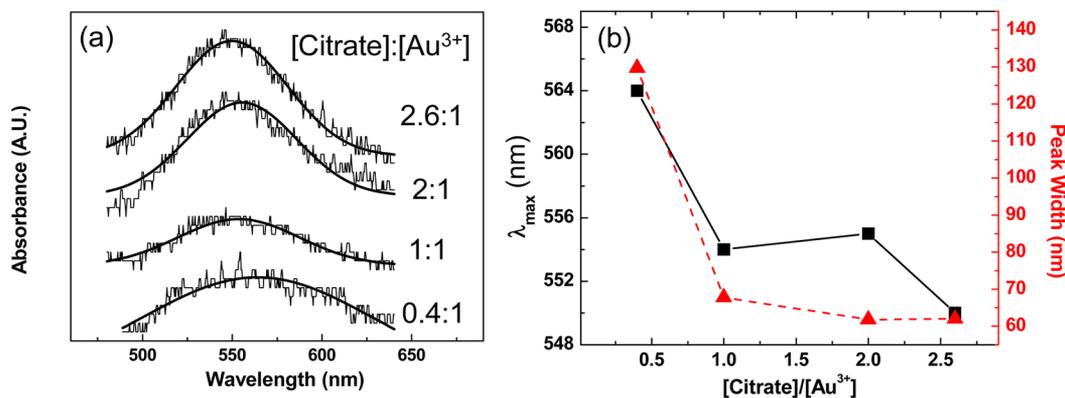


Figure 6. (a) Absorption spectra of Au–citrate nanoparticles made in PDMS flow reactors with various ratios of reactants; (b) correlations between Au plasma peak positions (squares) and plasma peak width (triangles) and reactant ratios.

peaks in the spectra, which is indicative of a decrease in particle sizes; this is in good agreement with literature.²²

Azo Dyes

The colors of the azo dye products allow for quick and easy initial assessment of the success of the reactions. A multistep synthesis also allowed students to demonstrate their creativity in chip design.

The azo dye synthesis reaction highlights three advantages of synthesis in the flow. First, multistep syntheses can be performed simply by modifying the chip design. Second, efficiency in heat transfer is demonstrated in the cooling condition with an ice bath. The small reactant volume again makes rapid cooling possible. Lastly, by merging the two-step reaction on one reactor chip, we improve the safety of the reaction. The azo reaction is done at colder temperatures to keep the reactive intermediate, a diazonium salt, stable. When the reactive intermediate is made in the flow, we avoid manually handling the reactive, unstable intermediate.

A wide variety of dyes can be made with different combinations of aniline derivatives and aromatics.²¹ Figure 7

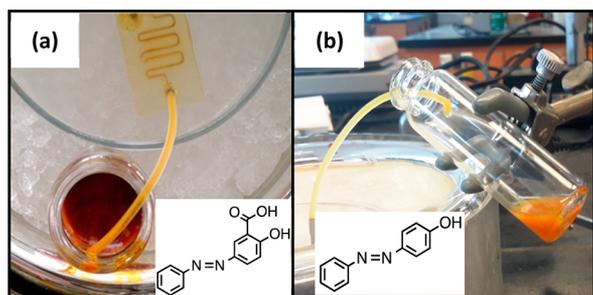


Figure 7. Synthesis of azo dyes: (a) 2-hydroxy-5-(2-phenyldiazenyl)benzoic acid, and (b) 4-(2-phenyldiazenyl)phenol in PDMS flow reactors.

shows the production of two aniline-based compounds made from salicylic acid (Figure 7a) and phenol (Figure 7b) as activated aromatic compounds. Both reactions yield vivid colors, which give rise to corresponding absorbance peaks in the visible range. The products are also characterized with FTIR spectroscopy and confirmed against spectra from commercial standards (see sample spectra in Supporting Information).

Finally, we note a few limitations of these homemade flow reactors. Like any reactions conducted in the flow, reactants

must be introduced in liquid form, either neat or in a solvent. The solubility of products in this solvent also needs to be considered to avoid clogging the channels. PDMS has limited chemical compatibility as reported by Lee et al.²⁷ The reference helps to determine the feasibility of conducting certain reactions in these devices. Lastly, channel staining is sometimes observed after multiple reactions, as shown in Figure 4, which makes these chips less reusable. Yet, due to their ease in fabrication, these devices can be considered disposable.

To give students a glimpse of the highly intertwining STEM field, this project integrates components that are conventional labeled as “analytical”, “organic”, “inorganic” or “engineering”, and breaks down the boundaries in-between. Most students successfully identified reaction mechanism, drew schematics, and characterized compounds using analytical tools in this project, which demonstrated their ability to utilize knowledge acquired in prior courses. Students manipulated various parameters in chip design and observed their impacts in synthesis products which was a rare exposure to the engineering process of optimization. The prelab exercise was also viewed very positively because students were proud that they could learn a new field on their own and carry out the project based on their newly acquired knowledge.

CONCLUSION

The highly interdisciplinary project presented here exposes students to a powerful and cutting-edge technology, synthesis in microfluidic reactors. The engineering aspects of design, fabrication, and device optimization is something chemistry students rarely experience in the undergraduate curriculum. Throughout this activity, students are excited to successfully conduct experiments in their homemade devices, in contrast to commercial instruments costing thousands of dollars. Pedagogically, the integration of important concepts in chemical engineering, organic and inorganic synthesis, nanomaterial chemistry, and analytical chemistry is also a highlight of the activity.

ASSOCIATED CONTENT

Supporting Information

Detailed instructor’s notes, written material used by students, sample product spectra, and CAS numbers of all chemicals used. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Lindsey Niederhaus, Melanie Townsend, Alex Sorum, David Bergstrand, and our CHM 481 students in Spring 2012 and Fall 2013 classes for suggestions and for piloting parts of this laboratory module.

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