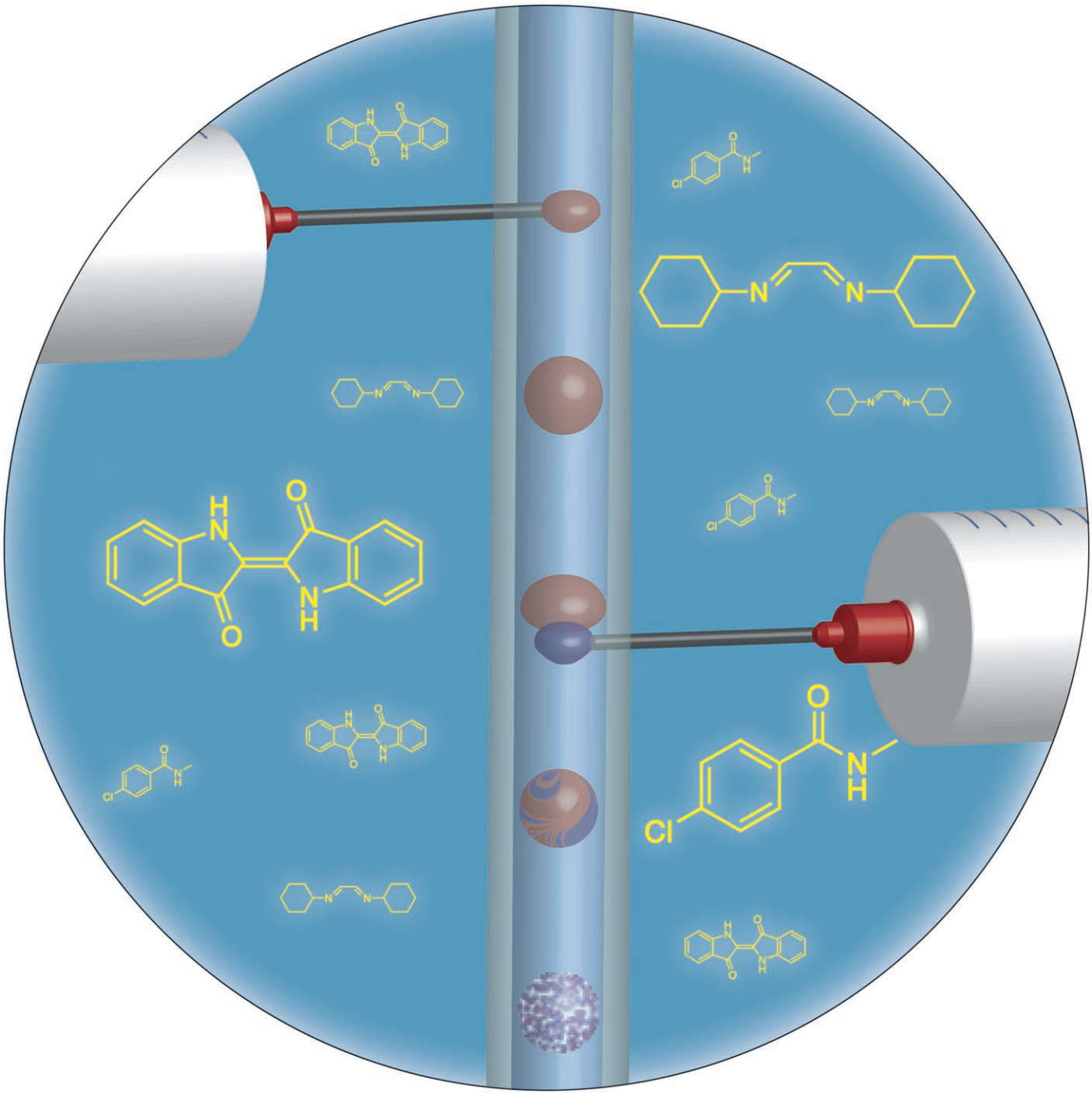
Communications

DOI: 10.1002/anie.200503925



A major drawback to the synthesis of solid products within microreactors is the clogging of the reactor channels. In their communication on the following pages, D.T. McQuade and co-workers report a solution to this problem by using a monodisperse droplet flow to isolate the solid particles from the walls of the reactor tubing.

Microreactors

DOI: 10.1002/anie.200503925

Solving the Clogging Problem: Precipitate-Forming Reactions in Flow**

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Techniques developed in recent decades have done little to change the fundamental processes of chemistry. Reaction vessels of a century ago continue to be the standard reactors of today. Recently, however, increasing attention has been paid to chemical reactions performed in microreactors.[1] Reactions are performed in these microfluidic devices by flowing reactants through channels that generally range in size from 10 to 500 μm. On account of its small proportions, a flat microchannel with a width of 100 μm has a specific surface-area-to-volume ratio that is 200 times larger than that of a 100-mL flask and over 3000 times larger than a tank that occupies a cubic meter.[2] This increased surface-area-to-volume ratio allows for better molecular-diffusion and heat-transfer properties, which allow faster and more-selective chemical reactions.[3]

From an industrial standpoint, microreactors are advantageous because they eliminate the need to scale up a reaction. Whereas in traditional process chemistry bench-top syntheses must be redesigned for industrial compatibility, a method known as numbering-up involves the addition of microreactors to achieve the desired throughput.[4] As every reactor is identical to the pilot reactor, there is no need to change dimensions or conditions. Other advantages include increased safety,[5] lower costs, and more environmentally friendly chemistry owing to efficient reactions that require less solvent.

Despite the numerous advantages of microreactors, they are not without their drawbacks.[6] Researchers in an academic setting have been slow to embrace these systems because of their cost and inflexibility.[7] The manufacture of a single microreactor can be a very time- and cost-intensive process, and once a microreactor has been developed, there is rarely any opportunity to make variations to the device.[8] Another commonly cited concern is the clogging of the channels that occurs upon precipitate formation.[9] The handling and processing of solids make up a significant proportion of laboratory and industrial processes, and current microreactor technology is not yet ready to handle these syntheses efficiently.[10] There has recently been an increased effort to deal with this problem, although many industrial solutions come at a large expense. A less expensive approach incorporates a periodic purging step to flush out solids that have formed on the channel walls.[11] However, this method is not effective if significant solid buildup occurs before purging. A more attractive alternative involves performing reactions in droplets that travel through the microreactor channels inside a carrier phase.[12]

Fluid fields generated in microfluidic devices can control reagent mixing[13] and allow the formation of an emulsion upon the collision of two immiscible liquids. We have recently reported a simple microfluidic device that can replicate these flow phenomena.[14] Our device is composed of syringe pumps, syringes, needles, and ordinary laboratory tubing—all of which are relatively inexpensive and commercially available (Figure 1). Development of our microreactor to facilitate chemical syntheses would potentially ameliorate some of the problems still plaguing microreactors, namely their cost and channel clogging. By utilizing disperse-phase droplets as individual reactors, we can confine the solid products to these droplets, thus keeping them away from the tubing walls and avoiding clogged channels. Herein, we present the results of the first chemical syntheses performed in our microreactor and show that our device is practical and efficient for the production of solids in a microfluidic device.[15]

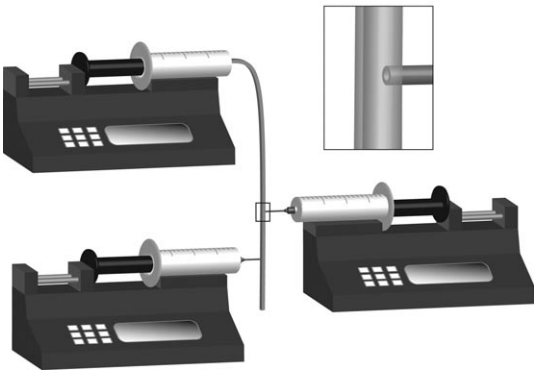

Figure 1. Basic design of our microfluidic reactor. The top-left syringe pump contains the carrier phase, the right pump contains the first disperse phase, and the bottom-left pump contains the second disperse phase. Reagents are injected through a 30-gauge blunt-edge needle (see inset).

By nature of its design, our microfluidic device is versatile, bearing the essential features of the reactor illustrated in Figure 1. Additional fluid junctions may be added as needed simply by inserting a needle anywhere along the tubing.

To demonstrate the suitability of our device for the synthesis of solid particles, we chose a simple system in which aqueous reagents combine to form a solid precipitate. Having successfully demonstrated the ability to synthesize solids by

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[**] This work was supported by NSF Sensors (CTS-0329899), ARO MAP-MURI, Cornell Center for Materials Science, and the Beckman Foundation.

interfacial polymerization in a two-flow system,[14] we took advantage of the versatility of our device and added a third fluid flow. In each case, an inert carrier fluid was employed as the continuous phase, and disperse-phase reagents were injected into the tubing through separate syringe pumps located downstream from the carrier-phase source. Reagent mixing occurred in one of two ways. If both disperse phases are immiscible with the carrier phase, the mixing of the reagents is initiated by the collision of two different reagent-phase droplets (Figure 2a). This type of mixing was observed when mineral oil was used as the carrier phase. On the other hand, reagents that are miscible with the carrier phase are injected coaxially as the final reagent. In this case, the mixing is caused both by infusion of the second reagent into the first and by diffusion from the carrier phase into the disperse phase (Figure 2b). In both of these cases, chaotic advection could be induced by passing the fluid stream through winding tubing (Figure 2c).[16] We used 30-gauge (0.15 mm i.d.) blunt-edge needles for reagent introduction to obtain spherical droplets (Figure 1, inset); beveled needles do not result in clean snap-off of the droplets.

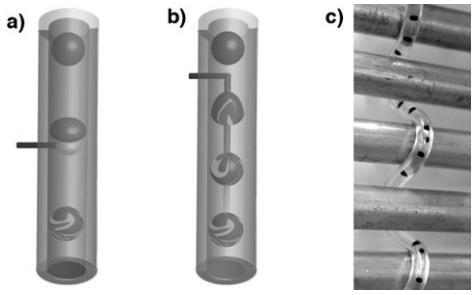


Figure 2. Reagents are mixed inside the tubing by droplet–droplet collision (a) or infusion followed by diffusion (b). Mixing can be enhanced by chaotic advection induced by passing the reaction stream through winding tubing (c).

A number of research groups have employed fluorinated solvents as carrier phases for microfluidic processes to minimize the possibility of side reactions.[17] These solvents, however, can be expensive and are rarely used as common laboratory reagents. Instead, we chose mineral oil, hexane (mixture of isomers), and toluene as relatively inert and readily available carrier phases.

The first reaction we performed was the synthesis of indigo (**1**), which involves a base-catalyzed aldol condensation between acetone and 2-nitrobenzaldehyde (**2**; Scheme 1). The synthesis of this dye was appealing not only because it results in the precipitation of a solid, but also because the product stains the poly(vinyl chloride) (PVC) tubing upon contact, which provides an easy means of determining the effectiveness of our method for isolating the solid from the channel walls. We found that a mineral oil flow rate of 3 mL min^{-1} produces sufficiently small droplets that are confined to the center of the tubing. Figure 3 illustrates the differences observed when indigo is synthesized in the presence and absence of a carrier phase.

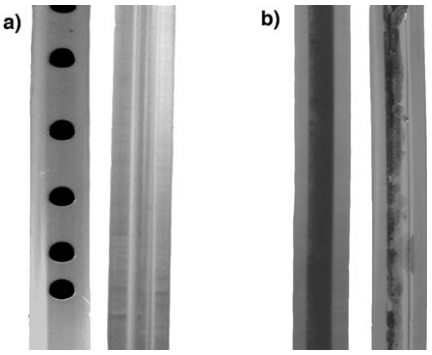
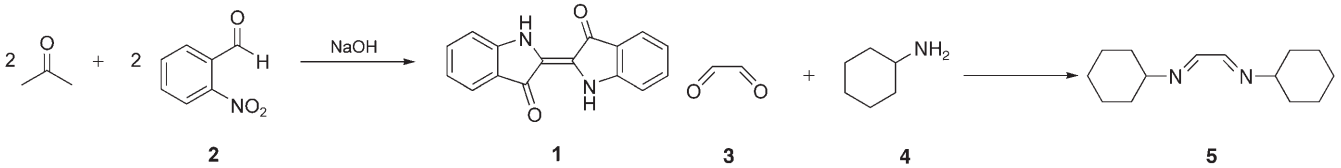


Figure 3. Demonstration of the effectiveness of the carrier phase in the formation of solids. Comparison of the tubing during (left tube) and after (right tube) the synthesis of indigo in the presence (a) and absence (b) of a mineral oil carrier phase.

The reagent collision shown in Figure 2a and b induces some mixing of the reagents. It has been shown that a further enhancement is observed when the droplets are flowed through a winding channel, which causes mixing by chaotic advection.[16] We observed a qualitatively similar phenomenon when we wound our tubing through a series of parallel horizontal bars. When the indigo synthesis was performed inside this tubing, the indigo formation (observed by a color change) occurred more rapidly than it did in straight tubing. Characterization was not performed for this reaction due to well-established purification issues.[18]

This method of producing solids in microreactors by using a monodisperse droplet flow can be extended to carrier phases other than mineral oil. The reaction of glyoxal (**3**) with cyclohexylamine (**4**) results in the precipitation of *N*,*N*′-dicyclohexylethylenediimine (**5**; Scheme 2). When mineral oil is used as the carrier phase, the droplet–droplet phenomenon shown in Figure 2a is observed. However, as **5** is soluble in mineral oil, product recovery is difficult. In contrast, the use of hexane (mixture of isomers) as the carrier phase allows both the formation of solid in the monodisperse flow as well as easier extraction of the solid. Owing to the decreased viscosity and density of the hexane carrier phase relative to mineral oil, higher flow rates are required to achieve the



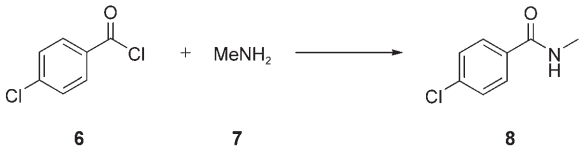
2 **1** **3** **4** **5**

Scheme 1. Synthesis of indigo (**1**).

Scheme 2. Synthesis of *N*,*N*′-dicyclohexylethylenediimine (**5**).

desired flow type. We found that a flow rate of at least 12 mL min^{-1} for the hexane phase yields desirable conditions for the formation of solid without channel blockage, although a rate as low as 5 mL min^{-1} acts as an efficient purging system by keeping the channel walls free of solids.

The final microfluidic reaction we studied was the conversion of 4-chlorobenzoyl chloride (**6**) and methylamine (**7**) into 4-chloro-*N*-methylbenzamide (**8**; Scheme 3). This



6 **7** **8**

Scheme 3. Synthesis of 4-chloro-*N*-methylbenzamide (**8**).

highly exothermic reaction was performed in our microreactor with no safety concerns. The small dimensions of the device not only mitigated the violence with which the reaction took place, but they have also increased the yield of **8** (Table 1). The use of toluene as the carrier phase for this reaction further demonstrates the versatility of our system.

Table 1: Synthesis of solids in our microfluidic device.

Product	System	Yield [%][a]	Purity [%][b]	STY[c]	Rel. STY
5	flow	97.0	94.5	11.44	25.55
5	batch	99.4	96.6	0.4478	1.00
8	flow	87.6	>99	9.150	20.43
8	batch	76.9	>99	0.7140	1.59

[a] Crude yields are reported for **5**; purified yields are reported for **8**. [b] The purities were determined from ^{13}C satellites in the ^{1}H NMR spectra. The purities of the crude product are reported for **5**; the purities of the purified product are reported for **8**. [c] Space–time yields are reported in mol m^{-3} min^{-1}.

Batch syntheses were carried out as a control by stirring the reagents for the same amount of time as the microreactor experiments were allowed to run. As indicated in Table 1, the yields for the microreactor products are comparable to—if not greater than—those for the batch reactions. Also, space–time yields (STY) for the solids formed by microscale flow were much higher than those for solids formed in the macroscale batch reactions. High yields were obtained in the microfluidic system even when one reagent was miscible with the carrier phase. Although we expected lower yields as a result of the miscible reactant flowing into both the carrier and reactant phases, this was not observed, which suggests that diffusion is fast enough in our system to ensure reagent mixing.

In summary, we have reported a practical method for producing solids in microreactors. As demonstrated by the indigo synthesis, by performing these reactions in a monodisperse droplet flow, the solid particles are effectively isolated from the walls of the tubing. Our device not only allows the practical synthesis of solids in microfluidic devices, it also retains the advantages of traditional microreactors. Its ease of use, the widespread availability of many of its components, and its versatility provide further benefits. Future work with our microfluidic device includes temperature-controlled experiments as well as multistep syntheses in a single device.

Experimental Section

1: Mineral oil (15 mL, 3 mL min^{-1}) was used as the carrier phase in 0.0625 inch (1.59 mm) internal diameter (i.d.) PVC tubing. NaOH (1 M in water, 3 mL, 0.6 mL min^{-1}) was injected into the center of the carrier phase. **2** (0.66 M in acetone, 3 mL, 0.6 mL min^{-1}) was introduced into the tubing further downstream. The pumps were allowed to run for 5 minutes while the product was collected over an ice–water bath.

5: Hexane (mixture of isomers, 60 mL, 6 mL min^{-1}) was used as the carrier phase in 0.066 inch (1.68 mm) i.d. polyethylene (PE) tubing. **3** (0.40 M in water, 12 mL, 1.2 mL min^{-1}) was injected into the center of the carrier phase. **4** (4.368 M in water, 2.4 mL, 0.24 mL min^{-1}) was introduced into the tubing further downstream. The pumps were allowed to run for 10 minutes while the product was collected at room temperature. Evaporation of the solvent yielded a white solid.

8: Toluene (70 mL, 7 mL min^{-1}) was used as the carrier phase in 0.066 inch (1.68 mm) i.d. PE tubing. **7** (1.44 M in water, 3 mL, 0.3 mL min^{-1}) was injected into the center of the carrier phase. **6** (1.0 mL, 0.1 mL min^{-1}) was introduced into the tubing further downstream. The pumps were allowed to run for 10 minutes while the product was collected at room temperature. Evaporation of the solvent and recrystallization from MeOH/H_2O afforded needles of white solid.

Received: November 5, 2005
Published online: January 13, 2006

Keywords: aldol reaction · flow reactions · microreactors · synthesis design

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