Video Article

Millifluidics for Chemical Synthesis and Time-resolved Mechanistic Studies

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Abstract

Procedures utilizing millifluidic devices for chemical synthesis and time-resolved mechanistic studies are described by taking three examples. In the first, synthesis of ultra-small copper nanoclusters is described. The second example provides their utility for investigating time resolved kinetics of chemical reactions by analyzing gold nanoparticle formation using *in situ* X-ray absorption spectroscopy. The final example demonstrates continuous flow catalysis of reactions inside millifluidic channel coated with nanostructured catalyst.

Video Link

The video component of this article can be found at http://www.jove.com/video/50711/

Introduction

Lab-on-a-chip (LOC) devices for chemical synthesis have demonstrated significant advantage in terms of increased mass and heat transfer, superior reaction control, high throughput and safer operation environment[1]. These devices can be broadly classified into chip based fluidics and nonchip based fluidic devices. Among the chip-based fluidics, microfluidics is well investigated and a topic well-covered in the literature[2-5]. Nonchip based LOC systems use tubular reactors[6]. Conventionally, microfluidic systems are used for precise control and manipulation of fluids that are geometrically constrained to submillimeter scale. We have recently introduced the concept of chip-based millifluidics, which can be used for manipulation of fluids in channels in millimeter scale (either width or depth or both of the channels are at least a millimeter in size)[7-9]. Furthermore, the millifluidic chips are relatively easy to fabricate while offering similar control over flow-rates and manipulation of reagents. These chips could also be operated at higher flow-rates, creating smaller residence times, thereby, offering the possibility for scale-up of controlled synthesis of nanoparticles with narrower size distribution. As an example, we have recently demonstrated the synthesis of ultra-small copper nanoclusters and characterized them using *in situ* X-ray absorption spectroscopy as well as TEM. Ability to obtain small residence times within millifluidic channels in combination with the use of MPEG, which is very efficient bidentate PEGylated stabilizing agent for the formation of stable colloids of copper nanoclusters[7] .

In addition to the synthesis of chemicals and nanomaterials, the millifluidics could offer, due to higher volume and concentration at the probe area, a synthetic platform that is more generalized and efficient for time-resolved kinetic studies and also achieves better signal to noise ratio than microfluidic systems[7,10]. We show the use of millifluidic chip as an example for time resolved analysis of the growth of gold nanostructures from solution using *in situ* XAS with a time resolution as small as 5 msec[11].

Also, majority of the micro reactors developed to date for catalysis applications are based on silicon[12,13]. Their expensive fabrication in addition to small volumes generated makes them unsuitable for large scale manufacturing. The two general methods for coating the channels with nanocatalysts - chemical and physical, often referred to as silicon coating procedures, are currently in vogue[14,15] . In addition to expensive micro fabrication, clogging of the channels makes micro reactor catalysis may be unsuitable for large-scale manufacturing. Although microreactors have been used for heterogeneous catalysis in micro continuous flow-through processes earlier[16-18] , the ability to control the dimension, and morphology of the embedded gold nanostructured catalysts within continuous flow channels was never explored before. We have recently developed a technology for coating the millifluidic channels with Au catalysts, having controlled nano morphology and dimensions (**Figure 5**)[11], for carrying out catalysis of industrially important chemical reactions. As an example we have demonstrated conversion of 4-nitrophenol into 4-aminophenol catalyzed by nanostructured gold coated within the millifluidic channels. Considering that a single millifluidic reactor chip can produce flow-rates of 50-60 ml/hr,[7] high-throughput and controlled synthesis of chemicals is possible either through continuous flow operation or parallel processing.

In order to capitalize on the possibilities the millifluidics offer, with few examples described as above, we also demonstrate a user-friendly millifluidic device that is portable and has the all the required components such as millifluidic chips, manifolds, flow controllers, pumps and electrical connections integrated. Such a millifluidic device, as shown in the **Figure 7**, is now available from the company Millifluidica LLC (www.millifluidica.com). The manuscript also provides protocols using the hand-held millifluidic device, as described below, for controlled synthesis of nanomaterials, time-resolved analysis of reaction mechanisms and continuous flow catalysis.

Protocol

Millifluidics set-up: Purchase a millifluidic chip (made of polyester terephthalate polymer) from Microplumbers Microsciences LLC, which has serpentine channels with dimensions of 2 mm (W) x 0.15 mm (H) x 220 mm (L). Use FEP Tubing with dimensions of 0.25 mm I.D., 1/16 in O.D., for connecting the chip to the pump. Use two different pumps for the two different experiments. Use P-Pump for the first experiment (copper nanoparticles) and the millifluidic device for the second experiment (gold nanoparticles). To minimize the problem of gas bubbles within the channels, freshly prepared $NaBH_4$ solution was left open to stand for ~10-15 min before pumping into the chip so that the gas bubbles escape from the solution. This step was followed for all of our experiments.

1. Synthesis of Ultra-small Copper Nano Clusters (UCNCs)

1. **Chemicals required:** Obtain copper(II) nitrate hydrate, sodium borohydride, sodium hydroxide pellets and O-[2-(3-mercaptopropionylamino)ethyl]-O'-methylpolyethylene glycol (MW=5,000) [MPEG] and use all chemicals without further purification. Use nanopure water (18.2 MΩ-cm) for the experiment.
2. Use P-Pump regulated under nitrogen pressure for the experiment. Test the pumps with water as solvent at different pressures prior to the experiment to correlate with the corresponding flow-rates (ml/hr). Rinse the millifluidic reactor and tubing with deionized water before initiation of the experiment.
3. Dissolve 174 mg (0.95 mmol) of copper(II) nitrate and 610 mg (0.122 mmol) of O-[2-(3-mercaptopropionylamino)ethyl]-O'-methylpolyethylene glycol in 28 ml of nanopure water and keep them in a vial to be connected with one input channel
4. Keep another solution of 111 mg (2.93 mmol) of sodium borohydride and 102 mg (2.78 mmol) sodium hydroxide in 28 ml (pH ~13) in a different vial and connect it with the other input channel.
5. Flow both the solutions simultaneously within the millifluidic reactor at different flow-rates (given below) and collect the resulting UCNCs at the outlet in glass vial. Purge the solution with nitrogen and store it under nitrogen.
6. Operate the pumps under different constant pressures of 50 mbar (6.81 ml/hr), 100 mbar (14.31 ml/hr), 200 mbar (32.7 ml/hr) and 300 mbar (51.4 ml/hr) at room temperature for the synthesis of UCNCs at different flow-rates.

While the synthesis procedure was demonstrated using the millifluidic set-up with P-Pump, it can also be carried out using the hand-held millifluidic device from Millifluidica.

2. Time Resolved *In situ* Kinetic Studies on Gold Nanoparticle Formation

1. **Chemicals required:** Obtain chloroauric acid ($HAuCl_4 \cdot 3H_2O$) meso-2,3-dimercaptosuccinic acid (DMSA) and sodium borohydride and use all chemicals without further purification. Use nanopure water (18.2 MΩ-cm) for the experiment.
2. Use high precision, fully automated, pulsation free syringe pumps to flow the liquids within the chip. Test the pumps with water as solvent at different flow-rates prior to the experiment to optimize the required flow-rate.
3. Prepare standard solutions of (i) $HAuCl_4 \cdot 3H_2O$ (10 mmol, 118.2 mg/30 ml) and (ii) DMSA (20 mmol, 109.2 mg/30 ml) with 50 mg of sodium hydroxide (pH 12) in nanopure water.
4. Feed the two solutions through two separate syringes into the millifluidic chip at a constant flow-rate of 10 ml/hr using the automated pump.
5. Couple the millifluidic chip to the synchrotron beam line using a metal stage that has access to movement in XYZ directions and collect the XAS data at different zones on the chip as the solutions were pumped through the chip.

While the *in situ* analysis procedure was demonstrated using the millifluidic set-up with P-Pump, it can also be carried out using a hand-held millifluidic device.

3. Continuous Flow Gold Catalysis

This procedure was demonstrated using a hand-held millifluidic device.

1. **Chemicals required:** Obtain chloroauric acid ($HAuCl_4 \cdot 3H_2O$), meso-2,3-dimercaptosuccinic acid (DMSA), sodium borohydride, 4-nitrophenol, 4-aminophenol and use all the chemicals without further purification. Use nanopure water (18.2 MΩ-cm) for the experiment.
2. **Catalyst preparation:** Prepare standard solutions of $HAuCl_4 \cdot 3H_2O$ (10 mmol, 118.2 mg/30 ml), DMSA (20 mmol, 109.2 mg/30 ml) and $NaBH_4$ (10 mmol, 11.34 mg/30 ml) in Nanopure water.
3. Take 10 ml each of $HAuCl_4$ and DMSA solutions into two separate vials and flow them within the chip using the hand-held millifluidic device with a uniform flow-rate of 12 ml/hr for 45 min.
4. Flow 10 mmol $NaBH_4$ within the chip at 12 ml/hr flow-rate for 15 min to reduce the Au(I) to Au(0).
5. Finally, wash the chip with nanopure water for 30 min at the same flow-rate before conducting the catalysis experiments.
6. **Catalysis reaction:** Perform the chemical conversion reaction (reduction) of 4-nitrophenol (4-NP) into 4-aminophenol (4-AP) within the gold catalyst (prepared above) coated millifluidic channel as given below.
7. Mix 15 ml of 9×10^{-5} mol solution of 4-NP with 3.3 ml of 0.65 mol $NaBH_4$ solution to form 4-nitrophenolate ion (4-NPI).
8. Pass the resultant solution over the gold catalyst deposited within chip at a constant flow-rate of 5 ml/hr to evaluate the catalytic activity. Analyze the UV-Vis spectra of the collected products within the wavelength range of 250-500 nm to confirm the conversion of 4-NP.
9. Estimate the catalytic activity of the reaction by obtaining the calibration curve of 4-NPI. Calibration curve can be acquired by plotting the experimentally observed absorption intensity (I) of 4-NPI at different standard concentrations. The peak heights (at 399 nm) for the UV-Vis absorption curves represent the absorption intensity (I) values and according to the Beer Lambert's law, any change in the peak height value would show corresponding change in its concentration. Therefore, estimate the catalytic activity by finding the difference in initial and final

concentrations of the reactant from the calibration curve. For example, if the peak height is 1 unit (**Figure 6**) it corresponds to a catalytic conversion of 90% (based on the calibration plot).

Representative Results

Well dispersed and uniform sized copper nanoclusters with a narrow size distribution were obtained using the millifluidic chip setup (Fig. 1a). The different flow-rates used for synthesis did not have a significant effect on the size of the clusters. Nevertheless, with increase in the flow-rate, there is an observable improvement in the narrowing of the size distribution. UCNCs with a best narrow size distribution were obtained at a flow-rate of 32.7 mL/hr. The size of UCNCs formed at 32.7 mL/hr flow-rate has an average diameter of 1.2 nm (Fig 1b).

The time-resolved *in situ* XAS setup is shown in Fig 2a. As described in the experimental procedure, the millifluidic chip was mounted onto a metal stage directly in the path of the monochromatized synchrotron beam and adjusted such that the beam passed through the desired zone on the chip. After optimizing the flow conditions, the precursor reagents (chloroauric acid ($HAuCl_4$) and meso 2, 3-dimercapto succinic acid (DMSA)) were dispensed and allowed to react at zone 1 (Fig. 2b). The spectra at Au L_3-edge were obtained at five different zones probed by an X-ray beam size of 0.05 mm x 0.05 mm, while flowing the precursor solutions into the channels. Based on these spectra analysis, the first changes in the precursor solution was found to take place around the zone 5 with the formation of $Au_xS_y^-$ nanoclusters[21] having an Au/S ratio close to 2 with Au(I) oxidation state. Fig. 3a shows the Au L_3-edge XANES spectra collected at different zones with the spectrum obtained at zone 3 showing the presence of the precursor, $HAuCl_4$, having Au(III) oxidation state. Fig. 4 shows the transmission electron microscopy (TEM) image of the sample of $Au_xS_y^-$ nanoclusters of 1-2 nm size collected from zone 5. Based on the EXAFS analysis and linear combination fitting with gold foil and gold sulfide reference compounds of the sample probed at zone 5, we can also confirm that the sample is a mixture of precursor gold salt (40% of $HAuCl_4$) and 60% of the $Au_xS_y^-$ nanoclusters (Fig. 3b). The formation of $Au_xS_y^-$ nanoclusters was first observed 17 sec after the start of the reaction and the reaction rate (calculated using the precursors consumption) at this point was 0.235 mmol/sec. No metallic gold nanoparticles were obtained even after 12-24 hours of the reaction and the stable colloid contained only $Au_xS_y^-$ nanoclusters. After passing $NaBH_4$ through the chip, the EXAFS analysis showed that the bond-length of the nanoclusters increased from 2.30 Å (Au-S) to 2.86 Å (Au-Au) indicating the reduction of Au(I) to Au(0) (Fig. 3c). Over prolonged time of flowing the precursors (9 h), the $Au_xS_y^-$ deposits within the millifluidic channels in the form of hemispherical microstructures (Fig. 5).

For the catalysis experiment, conversion of 4-NP to 4-AP was monitored based on the UV-Vis analysis of the products obtained in comparison with the spectra of the standards (Fig. 6a), On mixing with $NaBH_4$ one can see that the absorption spectrum of 4-NP (λ_{max} of 316 nm) was shifted to 399 nm indicating the formation of 4-NPI which on further reaction was converted to 4-AP (λ_{max} of 301 nm) by flowing it through the millifluidic channel containing the nanostructured gold deposited at the center. Conversion rate of 90.5% was observed for 4-NP to 4-AP (Fig. 6b) within the gold-deposited chip whereas the conversion was only 20% in a chip devoid of any gold. Most importantly, the gold catalyst was found to be catalytically active even after 80 hours of reaction. The results show the significance of millifluidics for continuous flow catalysis.

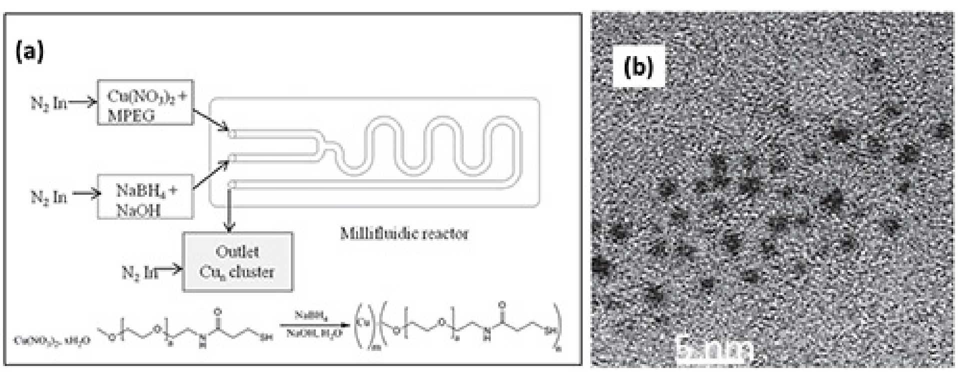

Figure 1: (a) A schematic representation of the millifluidic platform for the synthesis of UCNCs along with the reaction scheme (b) TEM image of ~ 1.2 nm UCNCs formed using the millifluidic chip with a flow-rate of 32.7 mL/h (Reproduced with permission from reference[7]).

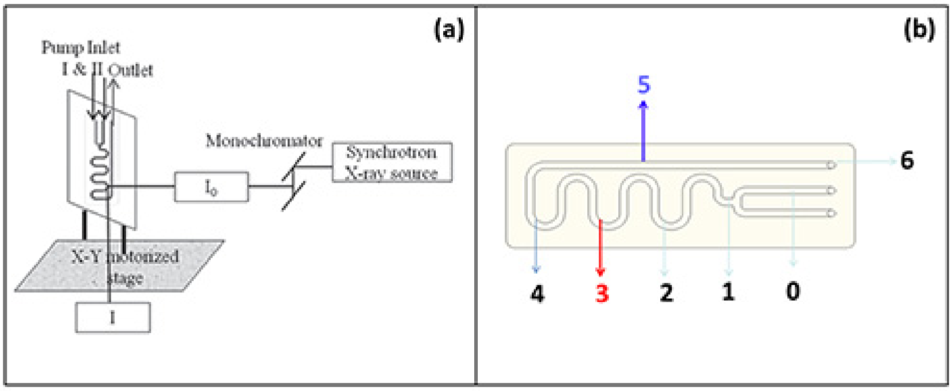

Figure 2: (a) *In situ* XAS analysis set-up for the time-resolved kinetic studies (b) Millifluidic chip with the marked zones where *in situ* XAS is performed (Reproduced with permission from ref. 7, Copyright Wiley-VCH Verlag GmbH & Co. KGaA, 2012).

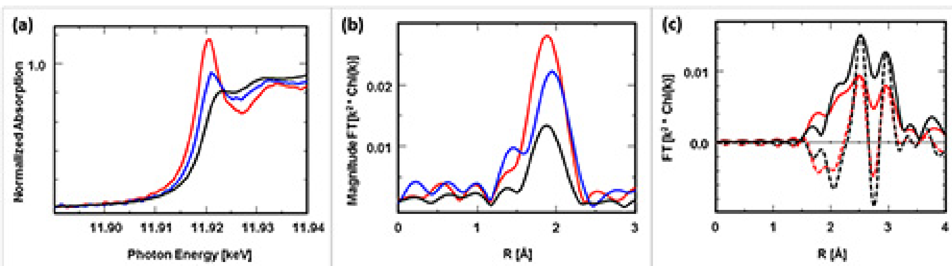

Figure 3: (a) XANES spectra showing the Au L_3 edge at zone 3 (red), zone 5 (blue) and at zone 5 after 12 hours (black) (b) EXAFS spectra at the same zones (c) EXAFS of Au foil (black) and sample after $NaBH_4$ reduction (red); (—) Fourier transform magnitude and (- - -) imaginary component of the Fourier transform (Reproduced from reference[11]).

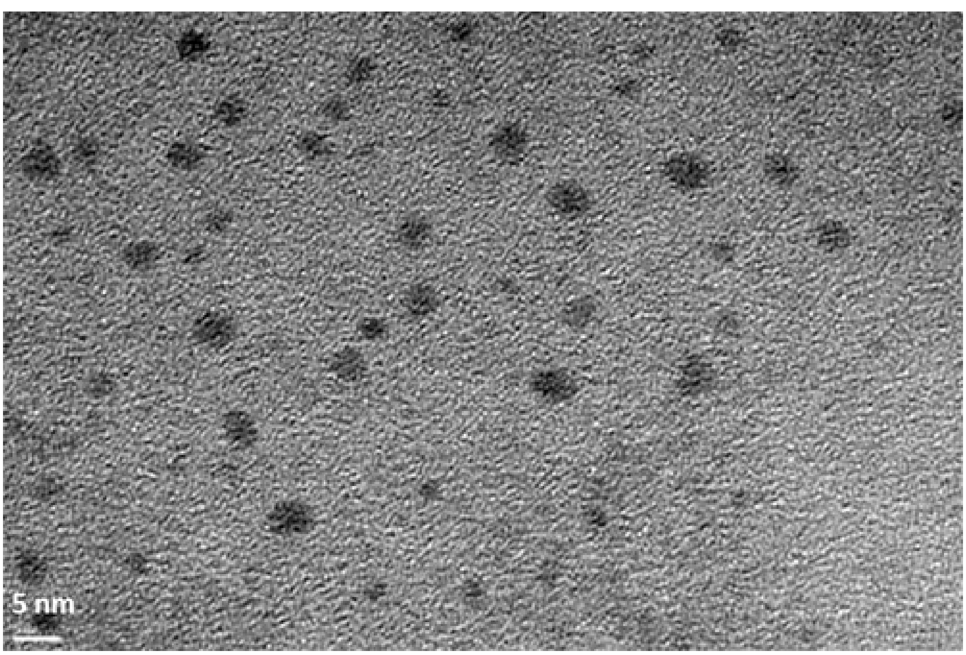

Figure 4: TEM image of $Au_xS_y^-$ nanoclusters (Reproduced from reference[11])

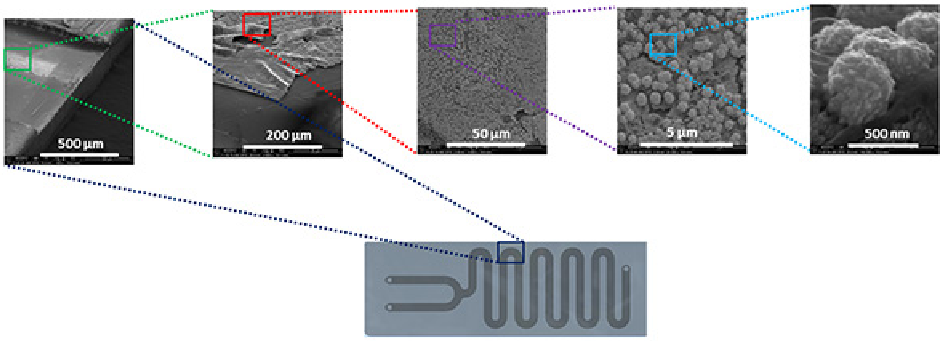

Figure 5: SEM images of the different magnifications of gold catalyst formed within the millifluidic channel after 9 h of coating time.

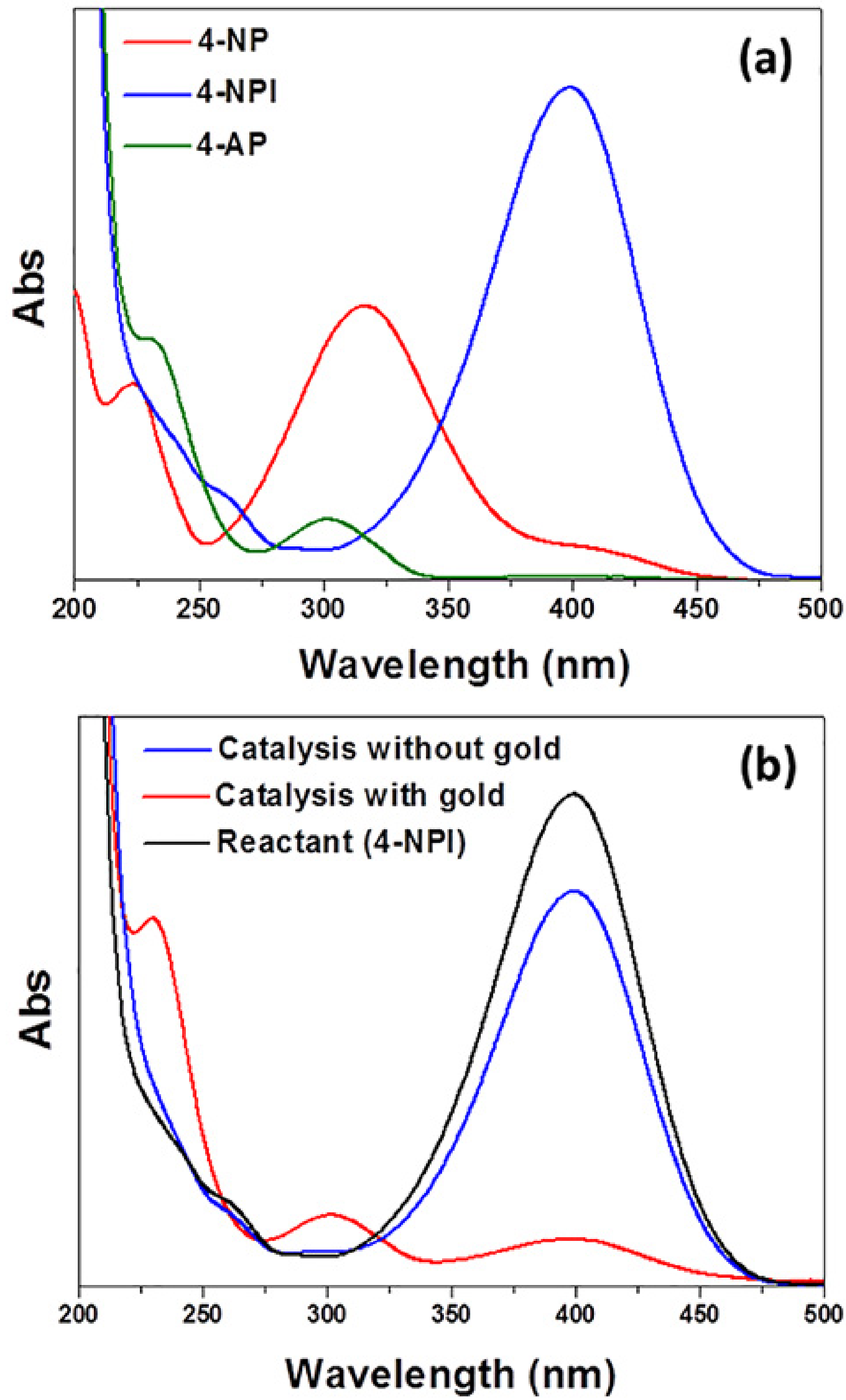

Figure 6: UV-Vis spectra of (a) 4-NP, 4-NPI, and 4-AP (b) Conversion of 4-NPI to 4-AP in a millifluidic chip reactor with and without gold (Reproduced from reference[11]).

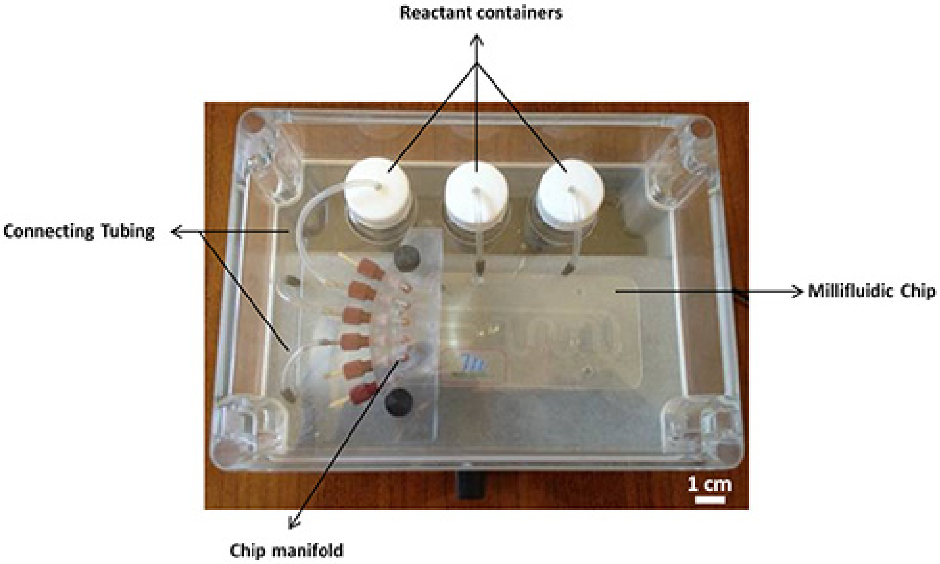

Figure 7: Hand-held millifluidic device used in the experiments.

Discussion

The UCNCs were formed by the reduction reaction of copper nitrate with sodium borohydride in the presence of the polymeric capping agent O-[2-(3-Mercaptopropionylamino)ethyl]-O'-methylpolyethylene glycol (MW=5,000) [MPEG]. The reaction was performed within the millifluidic chip reactor at different flow-rates such as 6.8 ml/hr, 14.3 ml/hr, 32.7 ml/hr, and 51.4 ml/hr to study the effect of flow-rates on the UCNCs formed. The respective residence times for the above flow-rates are 47.49, 24.44, 16.56, and 9.02 sec. The colloidal copper clusters obtained at all these flow-rates were stable up to three months under inert conditions. A narrow size distribution with average particle size of 1.2 nm was obtained for the flow-rate of 32.7 ml/hr.

One of the main advantages of using millifluidics over microfluidics for chemical synthesis in general and nanoparticle synthesis in particular is the possibility to attain high flow-rates. For example, flow-rates as high as 51.4 ml/hr were observed in our experiment whereas the typical flow-rates that are achievable with microfluidics having 10-100 µm channel sizes are in the range of 0.03-4 ml/hr[20]. It was possible to reach even higher flow-rates (*i.e.* > 3 ml/min) when the millifluidic device from Millifluidica was used. Fluidic properties arising due to such high flow-rates still retained features such as laminar flow similar to the case of microfluidics as determined experimentally as well as through numerical simulations. For example, the calculated Reynolds's numbers confirmed the laminar flow and the range of Peclet numbers demonstrated that the mixing of the two inputs is dominated by convection.

Some of the critical steps in the synthesis are identification of appropriate reduction process for metal salts and suitable surfactant as a stabilizer. In addition, design of the millifluidic channel and selection of correct flow-rates is important. Since the current millifluidic chips are made using polymers, the reactions are limited to water-based reactions and those that can be carried out at room temperature. However, by using appropriate high-temperature stable polymeric chips or borosilicate-based chips, one can carry out reactions at higher temperatures as well using organic solvents.

For the time-resolved kinetic studies, the *in situ* formation of gold nanoparticles starting from the precursor gold salt was probed in real time using *in situ* X-ray absorption spectroscopy by converting spatial resolution into time resolution. The first evidence of the formation of gold nanoparticles with Au-Au bonding was observed only after the addition of $NaBH_4$ unlike the results from the investigations by Tsukuda and coworkers[19]. They reported the formation of metallic $Au_{13}(DMSA)_8$ clusters with Au-Au bonding upon mixing of the same precursors in a traditional flask synthesis. The technique, therefore, is valuable in observing the reaction intermediates at time-resolution that is not possible in a traditional flask based reaction.

One of the greatest advantages of using millifluidic systems for time resolved kinetic study is due to the possibility to have higher concentrations that will enable better signal to noise ratio when the reactions are probed *in situ*. In the current system the limitation is that, only hard X-rays can be used to probe the reaction using XAS. In order to probe the reactions using other spectroscopy techniques such as UV-VIS spectroscopy, the millifluidic chips need to have optical windows. Again, with the existing set-up, one could only probe water-based reactions and at room temperature.

Catalysis using gold-based catalysts within batch processes is well-known and very actively pursued research. However, the same is not true for the continuous-flow catalysis. In this investigation, we demonstrate continuous flow catalytic activity of the gold catalysts formed within the millifluidic chip for the reduction of 4-NP to 4-AP[22], which was used as an example. The results showed over 90% conversion of 4-NP with gold catalyst using the continuous flow catalysis approach. One of the major advantages of this method over batch catalysis process is the reusability of the catalyst. For example, the catalyst was reused over 40 cycles (80 hr of reaction time) and still remained active.

The advantages of using the current system for continuous flow catalysis is that the channels are less likely to be clogged by the catalyst unlike those reported in the literature using microfluidic systems[23,24]. Yet another advantage is the ability to probe the catalysis reaction *in situ* as it happens in order to understand the catalysis reaction mechanism. Current limitations of the system for continuous flow catalysis are that only water based solution-phase catalysis reactions can be carried out and that too only at room temperature. Further modifications of the device are required to enable gas-phase continuous flow catalysis either at room temperature or at higher temperatures.

In summary, we demonstrate two important capabilities of millifluidic reactors. First, it can be used as a tool for continuous flow chemical synthesis and second, as a versatile probe for time resolved kinetic studies of chemical reactions. In addition, we show that a millifluidic device can be utilized both as an educational tool for learning about lab-on-a-chip devices and also as a simple, user-friendly and hand-held device for chemical synthesis and *in situ* probe for chemical reactions.

Disclosures

All authors except C.S.S.R. Kumar declare that they have no competing financial interests. C .S.S.R. Kumar is the founder of the company Millifluidica LLC.

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References

1. Song, Y., Hormes, J., & Kumar, C.S.S.R. Microfluidic Synthesis of Nanomaterials. *Small.* **4**(6), 698-711 (2008).
2. Huebner, A., Sharma, S., Srisa-Art M., Hollfelder, F., Edel, J.B., & DeMello, A.J. Microdroplets: a sea of applications? *Lab Chip.* **8**, 1244-1254 (2008).
3. Helen, S., Delai, L.C., & Rustem, F.I. Reactions in Droplets in Microfluidic Channels. *Angew. Chem. Int. Ed.* **45**, 7336-7356 (2006).
4. Marre, S, & Jensen, K.F. Synthesis of nanostructures in microfluidic systems. *Chem. Soc. Rev.* **39**, 1183-1202 (2010).
5. Theberge, A.B., Courtois, F., Schaerli, Y., Fischlechner, M., Abell, C., Hollfelder, F., & Huck, W.T. Microdroplets in microfluidics: an evolving platform for discoveries in chemistry and biology. *Angew. Chem. Int. Ed.* **49** (34), 5846-68 (2010).
6. Nicolas, L., Flavie, S., Pierre, G., Pascal, P., Annie, C., Bertrand, P., Cindy, H., Patrick, M., Samuel, M., Thomas, D., Cyril, A., Pascale, S., Laurent, P., Christopher, G., & Emmanuel, M. Some recent advances in the design and the use of miniaturized droplet-based continuous process: Applications in chemistry and high-pressure microflows. *Lab Chip.* **11**, 779 (2011).
7. Biswas, S., Miller, J.T., Li, Y., Nandakumar, K., & Kumar, C.S.S.R., Developing Millifluidic Platform for Synthesis of Ultra-small Nanoclusters (UNCs): Ultra-small Copper Nanoclusters (UCNCs) as a Case Study. *Small.* **8**(5), 688-698 (2012).
8. Li, Y., Sanampudi, A., Reddy, V.R., Biswas, S., Nandakumar, K., Yamane, D.G., Goettert, J.S., & Kumar, C.S.S.R. Size Evolution of Gold Nanoparticles in a Millifluidic Reactor. *Phys. Chem. Phys.* **13**(1), 177-182 (2012).
9. Li, Y, Yamane, D.G., Li, S., Biswas, S., Reddy, R., Goettert, J.S., Nandakumar, K., & Kumar, C.S.S.R. Geometric Optimization of Liquid-Liquid Slug Flow in a Flow-focusing Millifluidic Device for Synthesis of Nanomaterials. *Chem. Eng. J.* **217** 447–459 (2013).
10. Zinoveva, S., De Silva, R., Louis, R.D., Datta, P., Kumar, C.S.S.R., Goettert, J., Hormes, J. The wet chemical synthesis of Co nanoparticles in a microreactor system: A time-resolved investigation by X-ray absorption spectroscopy. *Nucl. Instrum. Methods Phys. Res. A.* **582**, 239−241 (2007).
11. Krishna K.S., Navin, C.V. Biswas, S., Singh, V., Ham, K., Bovenkamp, G.L., Theegala, C.S., Miller, J.T., Spivey, J., & Kumar, C.S.S.R. Millifluidics for Time-resolved Mapping of the Growth of Gold Nanostructures. *J. Am. Chem. Soc.* **135**(14), 5450-5456 (2013).
12. Kumar, C.S.S.R. Editor, Microfluidic Devices in nanotechnology-Fundamental Concepts, John Wiley (2010).
13. Kumar, C.S.S.R., Editor, Microfluidic Devices in nanotechnology-Applications, John Wiley (2010).
14. Meille, V., Review on Methods to Deposit Catalysts on Structured Surfaces. *Appl. Catal. A Gen.* **315**, 1-17 (2006).
15. Shin, W.C., McDonald, J.A., Zhao, S., & Besser, R. Etching Characteristics of a Micromachined Chemical Reactor Using Inductively Coupled Plasma. *Proceedings of the 6th International Conference on Microreaction Technology (IMRET VI)*. p357, AIChE, New Orleans, LA (2002).
16. Abahmane, L., Köhler, J.M. & Groß, G.A. Gold-nanoparticle-catalyzed synthesis of propargylamines: the traditional A3-multicomponent reaction performed as a two-step flow process. *Chem. Eur. J.* **17**, 3005-3010 (2011).
17. Abahmane, L., Knauer, A., Ritter, U., Köhler, J.M., & Groß, G.A. Heterogeneous Catalyzed Pyridine Synthesis using Montmorillionite and Nanoparticle-Impregnated Alumina in a Continuous Micro Flow System. *Chem. Eng. Technol.* **32**, 1799-1805 (2009).
18. Abahmane, L., Knauer, A., Köhler, J.M., & Groß, G.A. Synthesis of polypyridine derivatives using alumina supported gold nanoparticles under micro continuous flow conditions. *Chem. Eng. J.* **167**, 519-526 (2011).
19. Negishi, Y. & Tsukuda, T. One-Pot Preparation of Subnanometer-Sized Gold Clusters via Reduction and Stabilization by meso-2,3-Dimercaptosuccinic Acid. *J. Am. Chem. Soc.* **125**, 4046-4047 (2003).
20. Abou-Hassan, A., Sandre, O., & Cabuil, V. Microfluidics in Inorganic Chemistry. *Angew. Chem. Int. Ed.* **4**9, 6268 - 6286 (2010).
21. Jiang, D., Walter, M., & Dai, S. Gold Sulfide Nanoclusters: A Unique Core-In-Cage Structure. *Chem. Eur. J.* **16**, 4999-5003 (2010).
22. Kuroda, K., Ishida, T., & Haruta, M. Reduction of 4-nitrophenol to 4-aminophenol over Au nanoparticles deposited on PMMA. *J. Mol. Catal. A Chem.* **298**, 7-11 (2009).

23. Navin, C.V., Krishna, K.S., Theegala, C.S., & Kumar, C.S.S.R. Lab-on-a-chip devices for gold nanoparticle synthesis and their role as a catalyst support for continuous flow catalysis. *Nanotech. Rev.* In Press, doi: 10.1515/ntrev-2013-0028 (2013).
24. Shahbazali, E., Hessel, V., Noël, T., & Wang, Q. Metallic nanoparticles made in flow and their catalytic applications in organic synthesis. *Nanotech. Rev.* In Press, doi: 10.1515/ntrev-2013-0017 (2013).