DEVELOPING MICROFLUIDIC SYSTEMS FOR IN SITU CHARACTERIZATION OF
HIGH TEMPERATURE COLLOIDAL NANOPARTICLE SYNTHESIS

A Dissertation in
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by
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Abstract

While the growth process of colloidal nanoparticles is generally understood and described, relatively few studies exist which provide a quantitative description of nanoparticle nucleation and growth. This dissertation addresses that gap by developing new methods for in-situ analysis of nanoparticle growth. Syntheses are transitioned to a flow scheme using microfluidic reactors with the goal of interfacing spatially resolved analytical techniques with the microreactor. A range of microreactor systems have been presented including polydimethylsiloxane (PDMS) reactors, Teflon capillary based reactors, all glass reactors, and PDMS-glass hybrid reactors. The construction and evaluation of a translatable visible spectrometer is demonstrated. This enables absorbance spectrum to be acquired at designated spatial locations on a microreactor.

All glass microreactors were coupled to the translatable spectrometer to quantify the nucleation and growth of cadmium selenide (CdSe) nanoparticles. In-situ absorbance spectra were acquired under harsh reaction conditions of 230 – 260 °C. A kinetic model was developed to fit this data which provided insight into the reaction rates of nucleation and growth as well as a measure of the solubility in these systems. The trend of the rate constants for nucleation and growth provided an estimation of the activation energy for both processes.

Finally, isothermal titration calorimetry was used to quantify the thermodynamics of the cation exchange of CdSe nanoparticles with silver. This spontaneous process provides a method to transform the chemical identity of a nanoparticle post-synthesis. A more detailed thermodynamic understanding of the exchange will enable stronger predictive ability as well as finer control of the process.
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Chapter 1

Introduction

1.1 The Broad Impact of Nanoparticles

Nanoparticles are particles possessing a length scale less than 100 nm. These small length scales cause two major deviations from their bulk counterparts that make them useful in a variety of applications. Their small size means they have more exposed surface area, and often times they exhibit properties that differ from the bulk material. Numerous nanomaterials have been developed and their applications range from catalysis\(^1\)–\(^3\), medicine\(^4\)–\(^6\), solar energy\(^7\)–\(^9\), energy storage\(^10,11\), and many others.

In the United States alone, over $22 billion have been invested into nanomaterials research through the National Nanotechnology Initiative (NNI).\(^12\) A measure of the increasing interest in nanoparticles is shown in Figure 1-1. Thousands of articles are published each year across a broad range of disciplines. New materials and applications are constantly being developed. Not only are new base materials constantly being presented, but modifications controlling the size\(^13\)–\(^15\), shape\(^16\)–\(^19\), doping\(^20,21\), and surface chemistry\(^22\) are all of interest.
Figure 1-1. Number of publications per year with the word “nanoparticle” according to Web of Science as of October 2015.
Even though many specific syntheses have been developed and presented, there is a significant gap in the understanding of how these nanomaterials form. Often the synthesis is developed in an iterative way that relies on experience as much as an understanding of the underlying mechanisms. A more quantitative understanding of the underlying processes involved in nanoparticle synthesis will provide a more rational approach to develop syntheses. The aim of the work presented in this thesis is to develop new techniques for measuring the kinetics and thermodynamics of nanomaterial synthesis to allow a finer control over nanoparticle synthesis.

1.2 Synthetic Approaches to Nanoparticle Synthesis

Nanoparticles can be synthesized by a variety of methods. The work presented in this thesis focuses on colloidal nanoparticle synthesis synthesized by chemical conversion of precursors. Many transition metal and semiconductor nanoparticles involve elevated temperatures to achieve the desired reaction. A typical reactor setup is shown in Figure 1-2. A three-neck round bottom flask is often used in conjunction with a heating mantle and some sort of temperature measurement (either thermometer or thermocouple). The three-neck flask provides a versatile reactor that can include a condensing reflux column, controlled atmosphere for air sensitive chemistry, and a method for injection of reagents or withdrawal of sample aliquots. Two common schemes using this setup are the hot-injection\(^{23}\) and a rapid heat up of reagents\(^{24}\). In the hot-injection scheme, one of the reactants is brought up to a desired temperature while the second reactant is injected into the hot solution. The rapid heat up approach involves all the reagents being present in the flask initially and the temperature is rapidly brought up to the desired setpoint. Both approaches have successfully been used to synthesize many materials. Before discussing the advantages and disadvantages of this type of reactor for measuring the kinetics and thermodynamics of these reactions, it is important
to overview the underlying phenomena during nucleation and growth and the models that have been developed to describe them.
Figure 1-2. Photo of a typical flask synthesis system for synthesizing colloidal nanoparticles. The left neck allows injection of reagents, the middle neck refluxes solvent and maintains the atmosphere, and the right neck has a thermocouple for measuring and maintaining temperature.
1.3 Nucleation and Growth Theory

1.3.1 Classical Nucleation Theory

Nucleation is an important phenomena present in a variety of systems beyond nanoparticles that range from clouds to soda. The common driving force is a system driven past a solubility limit resulting in a metastable state that is not at its thermodynamic minimum. This supersaturated concentration is caused either via a change in the temperature or pressure of the system or via a chemical production of the component. The primary factor that determines how long this metastable state persists is how far the system is taken into supersaturation. Nucleation occurs when a small amount of the component changes phases to the more stable phase. This can occur homogeneously or heterogeneously. In the heterogeneous case impurities present in the system provide a low energy point for the supersaturated component to phase change. Homogeneous nucleation occurs on a much slower timescale and is the type of nucleation involved in nanoparticle formation. Homogeneous nucleation requires the spontaneous formation of nuclei which then become the lower energy source for heterogeneous nucleation. The path to a stable nucleus can include a combination of steps. In the case of nanoparticle growth, nuclei consist of a few atoms up to tens of atoms. These nuclei likely form via a sequential bimolecular collisions that build up a given nucleus. Two nuclei also have the potential to fuse together and grow.

The metastable phase that can exist before nucleation is a product of two competing forces. The main driving force for nucleation is already mentioned, the supersaturated concentration. This can be described as the product of the nuclei particle volume and the difference in energy between the two phases as described by Eq. 1.
\[ \Delta G_{\text{Volume}} = -\frac{4}{3}\pi r^3 \Delta G_v \quad \text{Eq. 1} \]

\( \Delta G_v \) is the difference in free energy per volume between the supersaturated phase and the nucleated phase. This term is negative for all particle sizes, implying a favorable driving force.

The second term describes the energetically unfavorable surface energy of the nuclei which is a consequence of the new interface that is generated between the two phases. This contribution is a product of the nuclei surface area with the surface energy of the newly formed interface, as shown in Eq. 2.

\[ \Delta G_{\text{Interface}} = 4\pi r^2 \gamma \quad \text{Eq. 2} \]

The general trends of Eq. 1 and Eq. 2 as well as their sum are shown in Figure 1-3. A maximum occurs in the sum of the two terms, resulting in some critical particle radius, \( r^* \). At particle sizes smaller than \( r^* \), the surface energy term dominates and favors dissolution of the particle. Above this critical radius, the decrease in system energy due to the phase change overcomes the energy increase of the interface. This results in a stable nuclei. The balance between the two terms is why some amount of supersaturation can be a metastable phase. Until a nuclei of sufficient size can grow, small nuclei below the critical radius are constantly growing and subsequently redissoolving back into the solution.
Figure 1-3. The energetic contributions to homogeneous nucleation. The volumetric free energy contribution drives the nucleation while the interfacial energy favors redissolution of the nuclei. The cubic dependence for the volumetric energy overcomes the quadratic dependence of the interface and results in a critical nuclei size, $r^*$, for stability. Nuclei below this size tend to redissolve while nuclei that exceed this size tend to be stable.
The maximum present in Figure 1-3 can be solved for to describe the free energy change required for the nucleation of a critical nucleus of size $r^*$ as shown in Eq. 3, 4 and 5.

$$\frac{d\Delta G}{dr} = 8\pi r^* \gamma + 4\pi r^*^2 \Delta G_v = 0$$ \hspace{1cm} \text{Eq. 3}

$$r^* = \frac{-2\gamma}{\Delta G_v}$$ \hspace{1cm} \text{Eq. 4}

$$\Delta G^* = \frac{16\pi \gamma^3}{3\Delta G_v^2} = \frac{4\pi \gamma r^*^2}{3}$$ \hspace{1cm} \text{Eq. 5}

This simple derivation of the Gibbs free energy change for nucleation is a useful exercise because it can provide insight into the dominant system parameters for nucleation. If the rate of nucleation ($J$) is assumed to follow an Arrhenius relationship (Eq. 6), the Gibbs energy shown in Eq. 5 can be used to qualitatively analyze the important parameters during nucleation.

$$J = A \cdot \exp\left(\frac{-\Delta G}{k_B T}\right)$$ \hspace{1cm} \text{Eq. 6}

The Gibbs-Thompson relationship (Eq. 7) describes the size dependent solubility of a solute due to the surface energy effect at small sizes.\(^{26}\) $S$ is the degree of supersaturation – the ratio of the system concentration to the maximum solubility. $\nu$ is the molecular volume. This relationship can be rearranged and substituted for $\Delta G_v$ as shown in Eq. 7.

$$\ln S = \frac{2\gamma \nu}{k_B T r}$$ \hspace{1cm} \text{Eq. 7}

$$-\Delta G_v = \frac{2\gamma}{r} = \frac{k_B T \ln S}{\nu}$$ \hspace{1cm} \text{Eq. 8}

Finally, Eq. 8 can be substituted into Eq. 5 which is then applied to the Arrhenius relationship for the rate of nucleation (Eq. 6). The result is shown in Eq. 9.
The relationship shown in Eq. 9 demonstrates that surface tension, temperature, and supersaturation play critical roles in the nucleation process.\textsuperscript{25} The latter two are most significant since they are the most easily modified system parameters. Description of the nucleation process requires control and knowledge of the system temperature and concentration.

An understanding of homogeneous nucleation is a critical first step towards developing models of particle growth. The following sections will go into other models that build onto the classical nucleation theory to describe the growth of particles from a solution.

1.3.2 LaMer Growth Model

One of the first models describing the homogeneous nucleation and growth of a monodisperse colloidal solution was developed by LaMer and Dinegar.\textsuperscript{27} The LaMer model describes the concentration of the dissolved component as it passes the solubility limit. This is shown in Figure 1-4. It divides the growth into three categories. The first phase of the reaction is the generation of dissolved atoms or monomers. LaMer studied the reaction of acids with thiosulfates which generate dissolved sulfur. As the reaction progresses, sulfur builds up in solution and exceeds the solubility. The second phase of the model happens once the concentration exceeds a critical point of supersaturation. At this point, a burst of nucleation occurs. This nucleation consumes enough reactants to bring the concentration back below the nucleation threshold, but still above the bulk solubility. In this third phase, the nucleated particles grow until the concentration reaches the bulk solubility in solution.

\[ J = A \cdot \exp\left(-\frac{16\pi\gamma^3v^2}{3k_B^3T^3(\ln S)^2}\right) \]  

Eq. 9
LaMer’s model was particularly effective at describing sulfur sols. However, a major concept from this model has been successfully extended to many systems. The separation of the growth into distinct phases has proven to be a valuable approach to synthesizing monodisperse nanoparticle colloids. That is, a burst of nucleation followed by an exclusive growth phase. Ideally nucleation ceases after the initial burst and any remaining reagents go towards growing the existing particles. Continual nucleation is undesirable and broadens the overall size distribution. The hot injection scheme of nanoparticle growth is a prime example of this separation. A rapid injection of one reagent into another allows the system to rapidly enter a deep supersaturation which causes a burst of nucleation. Not only are the kinetics generally rapid in hot injection schemes, but injection happens at an initial higher temperature while growth happens at a lower temperature due to the mixing of the two streams. This further supports the separation of nanoparticle formation into the distinct nucleation and growth stages.
Figure 1-4. Plot demonstrating the LaMer model for growth from a supersaturated solution. The concentration of the solute rapidly rises at the beginning of the reaction until a nucleation threshold is exceeded. A burst of nucleation occurs which takes the solution concentration back below the threshold followed by an exclusive growth step.
1.3.3 Ostwald Ripening

Growth still happens after a supersaturated system reaches equilibrium concentrations. Looking back at Eq. 1, Eq. 2, and Figure 1-3, we see that larger particles are more energetically favorable than smaller. Once the concentration reaches the equilibrium concentration, there are still atoms or monomers exchanging between nanoparticles and the solution. Equilibrium is just the point where that exchange is equal in both directions. Over time, monomers from smaller less energetically favorable nanoparticles go back into solution and tend to attach to larger more stable particles. This type of growth, Ostwald ripening, was first quantitatively described in 1958.\textsuperscript{28} Ostwald ripening is typically an undesirable aspect of nanoparticle growth. It has the effect of broadening the size distribution since the smaller particles shrink and the larger particles grow. Ostwald ripening can be minimized in the case of high temperature syntheses by thermally quenching quickly after the concentration reaches the bulk solubility. Quenching the solution lowers the bulk solubility and decreases diffusion to mitigate Ostwald ripening. Ostwald ripening is also a concern for samples stored at room temperature for prolonged amounts of time. Given enough time, these samples will tend to grow into fewer but larger particles.

1.3.4 Size Focusing

Work by Peng\textsuperscript{29} and Sugimoto\textsuperscript{30} has shown a way to utilize the underlying phenomena of Ostwald ripening to actually focus a size distribution rather than defocus it. Ostwald ripening occurs at a constant monomer concentration. However, Sugimoto describes how at each monomer concentration there exists a critical radius that is at equilibrium with the solution. Similar to what is described in Ostwald ripening, nanoparticles below this concentration tend to dissolve, meaning a negative growth rate, while nanoparticles above this concentration tend to grow. This is summarized in Figure
1-5A. Particles below the critical radius have a negative growth rate while particles above that radius have a positive growth rate. Monomer concentration can be adjusted throughout synthesis by injecting additional monomer into the system. This has the effect of shifting the critical radius lower than the current size distribution. As a result, the majority of nanoparticles now have a positive growth rate. The smallest nanoparticles have higher growth rates than the larger ones. This overall provides a focusing of the size distribution along with an overall particle size increase, shown in Figure 1-5B. This scheme can involve a modification of an already existing synthesis. The initial injection size can be cut down by a certain percentage and that percentage can be injected at an appropriate time into the reaction. Overall this has the potential to provide a similar size product but with a lower size distribution.
Figure 1-5. A) Illustration of the growth rate of a nanoparticle near the equilibrium critical radius. Nanoparticles below the critical radius show negative growth, dissolution, while nanoparticles above the critical concentration have a positive growth rate depending on the size above the critical radius. B) Demonstration of size focusing: the arrows indicate monomer injection. By reserving some of the monomer until a later time, the size distribution is focused during growth. Both from reference 29.
1.3.5 Two Step Watzky-Finke Autocatalytic Mechanism

The LaMer model stood alone for several decades as one of the only general mechanistic descriptions of the growth of monodisperse populations of particles. Until the work of Finke and Watzky, it was generally accepted that the burst of nucleation was the defining characteristic of monodisperse growth. Watzky et al. developed an indirect way of monitoring the growth of iridium nanoparticles (Figure 1-6A). Watzky et al. developed a special technique that was fairly specific to the iridium system being studied. A catalytic “indicator” reaction that consumed hydrogen was carried out alongside the growth of nanoparticles. By monitoring the hydrogen pressure of the headspace, insight into the nanoparticle growth rate was gained. They noticed a sigmoidal growth curve during synthesis. The only satisfactory explanation for this behavior was a new growth model where slow continuous nucleation occurs until after a certain induction time, when autocatalytic surface growth begins to dominate. This provides an example of growth that does not rely on a burst of nucleation but rather continuous nucleation. This method of measuring nanoparticle growth and the model that resulted are unique and provided valuable insight - however both the technique utilized and the model itself are only relevant for certain systems. Interestingly, the Finke and Watzky two-step mechanism has found success outside of the study of transition metal nanoparticle synthesis. It has been used to model the aggregation of proteins and yeast.
Figure 1-6. A) Example of the sigmoidal nature of the measured nanoparticle growth rate. B) Proposed growth model that includes continual nucleation and autocatalytic surface growth. The third step in the reaction shows the indicator reaction that enabled catalyst concentration to be monitored via hydrogen headspace pressure. Taken from reference 31.
1.3.6 Interparticle Growth

Typically, nanoparticle syntheses involve one or more reagents that bind to the surface of the nanoparticle that help stabilize them in solution. These are referred to as capping agents or capping ligands. The strength of the bond between the ligand and nanoparticle can vary from weak physical interactions to covalent interactions. For some growth systems, interparticle growth is a significant factor. Interparticle growth is particle growth where multiple nanoparticles combine to form a single particle. This can be via coalescence\textsuperscript{34,35} or oriented reattachment\textsuperscript{36}. The difference between the two is whether the crystal planes align before combination or not. Besson et al. extended the Finke and Watzky two step mechanism to include terms that describe particle aggregation.\textsuperscript{37} This provided a simple kinetic model that includes nanoparticle nucleation, autocatalytic growth, as well as interparticle aggregation. The aggregation was split into two types, one being between small similar nanoparticles and the second being another autocatalytic step that describes the coalescence of bulk-like large nanoparticles with small nanoparticles.

1.4 Re-examination of Flask Synthesis

With the understanding that monomer concentration is a critical aspect of nucleation, we can now reexamine the use of flasks as a tool for studying nanoparticle growth. For hot injection as well as rapid heat up, a fundamental problem exists that limits the use of flasks for characterization of the nucleation process. Both scenarios suffer from heat and mass transfer limitations. The heating mantles that warm the solution from the outer edge of the flask means that there are spatial gradients in the temperature. For the hot injection scheme, injecting the second solution causes a local spot of high concentration and lower temperature that then has to be mixed within the flask. The timescales for mixing in a flask are on the order of 1-10 seconds.\textsuperscript{38-40} In many
flask syntheses, homogeneous nucleation is complete within the first ten seconds. While these flask methods are useful platforms from a synthetic point of view, their use in characterization is limited.

Flasks also provide a limitation from an analytical standpoint. Most techniques that can offer insight into nucleation and growth require information being transmitted into and out of the system. This can include x-ray, ultraviolet, visible, or infrared electromagnetic radiation. Thick glass reactor walls, while chemically and thermally resilient, are not conducive to these interrogations. There, the flask scale synthesis of nanoparticles is not ideal for studying the processes of nucleation and growth. Heat and concentration gradients that vary with space and time as well as the analytical difficulties of a thick glass reactor mean that another avenue is necessary to provide a versatile platform for the characterization of nanoparticle formation and growth.

1.5 Microfluidics as an Alternative Reaction Platform

Microfluidics are a class of chemical reactor where reagents flow down a channel with a length scale measured in micrometers. An example device is shown in Figure 1-7. Such reactors can be made from a variety of materials using many different fabrication methods. The small nature of these reactors and the versatile fabrication methods means they can be more easily engineered to be compatible with different analytical techniques. Flask reactors tend to be made of thick curved glass which is a limitation when designing in-situ experiments.
Figure 1-7. An example microfluidic device made out of polydimethylsiloxane polymer bonded to a glass slide. Two reactors are visible on this device, the lower one is a long straight channel while the upper one involves a serpentine section to allow increased residence times. Image courtesy of the Whitesides’ group.
1.5.1 Transitioning from Batch to Steady State

One of the most significant and obvious differences between a microfluidic reactor and a flask is that the former involves the continual flow of reagents. At a constant flowrate, the microfluidic reactor operates at steady state. A batch reaction is constantly in flux as a reaction goes from beginning to end. Certain analytical techniques can be performed on a fast enough timescale to capture snapshots in a flask reactor, however, this is a limited approach. By contrast, a microfluidic reactor operating at a constant flowrate does not vary with time. During steady state operation, concentration and temperature are constant with time across the spatial coordinates of the reactor. This means the reaction progression is a function of spatial coordinate. From an analytical view, this is the most important aspect of microfluidics. A given characterization technique can be performed at a specific location along the channel length, and the results will be independent of the acquisition time of the analytical technique. Even for techniques where acquisition times may be up to an hour, the steady state nature of microfluidics can allow a successful snapshot of the reaction at a well-defined residence time. This is a significant contrast to batch syntheses. In a batch synthesis, the analytical technique must be performed on a timescale must faster than the reaction. Many nanoparticle reactions happen very quickly, with significant progress occurring in the first few seconds; in some cases complete synthesis occurs in seconds. Thus, batch reactors are simply not feasible for many syntheses from an analytical standpoint. Microfluidics do not suffer from this limitation, which makes them an ideal and potentially a universal platform for synthesis characterization. Steady state operation is the most significant advantage that transitioning to a microfluidic reactor provides, however, it is not the only one. Transitioning from big to small provides further benefits that are not present in a flask scale.
1.5.2 The Importance of the Surface Area to Volume Ratio

The general equation for convective heat transfer is shown in Eq. 10.

\[ \dot{Q} = hA\Delta T \]  \hspace{1cm} \text{Eq. 10}

The heat transfer is proportional to a heat transfer coefficient \(h\), the area of heat transfer \(A\), and the temperature difference \(\Delta T\). In the case of a chemical reactor, it is also important to consider the volume of the solution being heated. This leads us to describe the heating effectiveness of a reactor based on the surface area to volume ratio (SAVR). The general relationship of heat transfer for a characteristic length scale is described by the simple relationship shown in Eq. 11.

\[ \frac{\text{Surface area}}{\text{Volume}} \sim \frac{l^2}{l^3} = l^{-1} \]  \hspace{1cm} \text{Eq. 11}

This inverse relationship means that as the length scale decreases, the SAVR increases. A higher SAVR enables more rapid thermal equilibration. Flasks have a length scale measured in cm, while even large microfluidic channels are measured in 100s of \(\mu\)m. Consequently, the SAVR in microfluidics is multiple orders of magnitude higher than in a flask.

In flask synthesis, the reaction solution is heated by a heating mantle on the outside of the flask. Not only is the surface area for heat transfer minimal, but heat must be dispersed throughout the solution via mechanical stirring. The thermal equilibration of the reactant stream is much more rapid in a microfluidic reactor. This is a result of not only the surface area to volume effect, but also the fact that stream flow rates tend to be small. When the streams being heated up are often on the order of 1 \(\mu\)L/min, the thermal mass of the stream being heating up is extremely small compared to the entire reactor. As a result, not only is heat transfer rapid due to surface area, but it has a very minimal
effect on the temperature of the reactor walls. By finely controlling the reactor temperature, we have a fine control over the temperature of the reagents.

Rapid control over temperature makes microfluidics desirable in several ways. Overall the thermal gradients as they exist in a flask reactor are minimal. The analog of a hot injection in a microfluidic device is simply mixing two streams that have already thermally equilibrated. This is a trivial feat in a microfluidic reactor. While it would be possible to devise a more complicated hot injection flask scheme where the injected stream is preheated, it would only serve to minimize the problem of temperature gradients, not eliminate them. From an analytical and characterization perspective, a well-defined temperature is an important property. The temperature that nucleation and growth occur are very important and a microfluidic reactor provides ideal control over temperature. Hot injection procedures tend to define a temperature for the flask at injection and often a lower a temperature setpoint for after injection, because the act of injection drops the temperature of the reactor. Consequently, the temperature that nucleation happens is a very nonspecific value. Upon injection, an interface of hot and cold solution form which then must mix together. For a significant amount of time (seconds), nucleation can occur at a variety of temperatures and concentrations while the system equilibrates. In a microfluidic reactor, the mixing zone can have a well-defined temperature and any information gathered from that system is for a very specific and known temperature.

Another appeal of rapid thermal equilibration is that microfluidics open a level of complexity to the experiment unavailable by traditional means. More complex growth recipes can be designed for a microfluidic device due to the rapid equilibration. A schematic representation is shown in Figure 1-8. Zones of different temperatures can be defined for different steps of the reaction. Using a combination of heating and cooling,
steep thermal gradients can be established on a reactor. The stream could be thoroughly mixed at low temperature, rapidly brought to a high temperature in a nucleation zone, and then growth could follow in a zone of a slightly lower temperature. Secondary reactions can be carried out on the same reactor by injecting an additional reagent stream with an additional heated zone. Establishing steep thermal gradients also means the product can be rapidly quenched when the reaction is over. Reactors that are capable of separate nucleation and growth have been demonstrated for the synthesis of CdSe.42
Figure 1-8. Schematic representation of a microfluidic device with multiple heating and cooling zones. Reagents enter on the left and are thoroughly mixed at a low temperature. The reagent stream then passes through a high temperature nucleation zone followed by a lower temperature growth zone. The right half of the schematic shows the addition of another reagent stream followed by another growth process. Finally, the reagents exit the reactor at a quenched temperature.
1.5.3 Mass Transfer Considerations

The transition to a smaller length scale is not advantageous in every way. The Reynold’s number (Eq. 12) describes the ratio between inertial forces and viscous forces in a flow.

\[ N_{Re} = \frac{\rho V l}{\mu} \]  

Eq. 12

The density (\( \rho \)) and viscosity (\( \mu \)) are independent on the reactor used. However, the velocity (\( V \)) and length scale (\( l \)) for microfluidics are both much lower than flask systems. For the case of water flowing through a 100 \( \mu \)m channel, the Reynold’s number is on the order of 1. This means viscous forces and inertial forces are of a similar magnitude. Under these conditions, fluids flow with an ordered laminar behavior, which is a drawback compared to larger length scale systems. At higher Reynold’s numbers, turbulent mixing provides a mechanism to rapidly mix reagents. The result is that typical microreactor flow has fewer mechanisms to dissipate concentration gradients.

When limited to laminar flow, diffusion becomes the primary mixing mechanism. The timescale for mixing can be estimated according to Eq. 13.

\[ t_{diffusion} \sim \frac{l^2}{2D} \]  

Eq. 13

For ions in water with a diffusion coefficient (D) on the order of \( 10^{-5} \) cm\(^2\)/s, this gives an approximate diffusion time (\( t_{diffusion} \)) of 5 seconds across a 100 \( \mu \)m channel. For systems where synthesis happens in minutes, diffusion alone can provide the mixing needed. Mixing via diffusion becomes a limiting factor only at fast residence times.

Multiple approaches can be taken to address systems that require more rapid mixing. The simplest is to decrease the distance for mixing. Decreasing the channel width, even for a small section of the reactor, has the effect of decreasing the mixing
time.\textsuperscript{43} However, this approach is a limited method for decreasing the mixing time. Smaller length scales require further focusing in the case of spectroscopic techniques and will tend to lower signal levels. An alternative method of mixing is desirable for systems with faster kinetics where mixing by diffusion alone is not fast enough.

1.5.4 Multiphase Flow and Residence Time Distributions

A disadvantage of typical single phase microfluidics is that laminar flow yields a parabolic flow profile. This flow profile means that at a given point down the length of a reactor, fluid elements at different positions in the cross section have different residence times. The description of this distribution is the residence time distribution (RTD) of a laminar flow reactor (LFR), as shown in Eq. 14.

\begin{equation}
E(\theta) = \begin{cases} 
0 & \text{for } \theta < 0.5 \\
\frac{1}{2\theta^3} & \text{for } \theta \geq 0.5
\end{cases} \tag{Eq. 14}
\end{equation}

The RTD of an LFR mean that a given location along the reactor is not adequately described by a particular value of residence time, but rather a distribution of residence times. A broad RTD, such as the one for an LFR, is undesirable for characterization. However, a versatile solution does exist which addresses the issue of residence time distribution as well as mixing.

Introduction of a second phase in the reactor causes droplets of reactant to flow down the channel that are similar in concept to a plug flow reactor (PFR).\textsuperscript{44-47} The second phase can be a gas, which separates plugs of liquid by a segment of gas, or it can be a liquid, where an immiscible second fluid flows down the channel and separates the reactant into droplets. Figure 1-9 shows a comparison between the RTDs for an LFR, PFR, and a two phase microfluidic flow. The width of the RTD for the two phase
scenario is simply a function of how long the droplets are. Smaller droplets approach a plug behavior.
Figure 1-9. Comparison of RTDs for A) laminar flow reactor, B) plug flow reactor, and C) droplet reactor. The width of the RTD for the droplet case is dependent on the length of the droplet; smaller droplets behave more similar to plug flow.
Another positive aspect of two phase flow is related to mixing. The parabolic flow profile typical of a LFR is still present in two phase flow. However, when it occurs in a droplet it causes a recirculating behavior. This has been shown to mix droplets on the timescale of milliseconds.\textsuperscript{48-50} Reagents in the middle of the channel have a higher velocity while reagents near the wall have a lower velocity. The interface between the two phases causes a circulating flow to develop within the droplet. This circulating nature combined with an irregular channel design can provide rapid mixing. This is illustrated in Figure 1-10 for the case of liquid-liquid flow.

In summary, breaking the flow of reagents into plugs addresses two disadvantages inherent to microfluidics. The broad RTD typical of a single phase LFR is eliminated. In addition, the introduction of a new interface introduces a mechanism for mixing that occurs on a faster timescale than diffusion alone.
Figure 1-10. Cartoon illustration of mixing by chaotic advection. For both gas-liquid and liquid-liquid dispersions, circulating currents are produced that mix the contents of droplets faster than diffusion alone.
1.5.5 Flask Versus Microfluidics Summarized

The limitations inherent to flask synthesis have led to the hypothesis that in-situ microfluidic analysis will provide the capability to characterize nanoparticle synthesis and enable a more quantitative understanding of nanoparticle growth. The comparison between flask and microfluidics with respect to characterization is briefly summarized in Table 1-1. While flasks are perfectly adequate synthetic tools, they are not ideal from a characterization viewpoint. Transitioning to a steady state reactor means microfluidics allows the potential of capturing early residence times in systems with rapid kinetics. Microfluidic reactors provide a finer degree of control over both temperature and mixing. Additionally, a wide variety of microfabrication techniques exist that allow microreactors to be custom engineered to be compatible for a given analytical technique.
Table 1-1. Comparison of microfluidics and flasks as an analytical platform

<table>
<thead>
<tr>
<th></th>
<th>Microfluidic</th>
<th>Flask</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mass transfer</strong></td>
<td>Single phase flow – diffusion mixing on the order of seconds. Multiphase flow – mixing on the order of milliseconds</td>
<td>Concentration gradients due to slow mixing $O(10 \text{ s})$</td>
</tr>
<tr>
<td><strong>Heat Transfer</strong></td>
<td>Rapid equilibration of reactants with surroundings, spatial control of temperature</td>
<td>Heated externally, small surface area, limited by mixing</td>
</tr>
<tr>
<td><strong>In-situ analysis</strong></td>
<td>Steady state, can be customized for each analytical technique</td>
<td>Incompatible with most spectroscopic techniques, difficult to sample early residence times</td>
</tr>
</tbody>
</table>
1.6 Summary of the Dissertation

The aim of this first chapter is to give a perspective on the significance of nanoparticles, followed by a discussion of synthetic methods and the underlying processes that have been developed to describe nanoparticle growth. After identifying the limiting factors of flask synthesis, the need for a different reaction platform has been proposed. The subsequent chapters aim to develop microfluidic approaches to studying nanoparticle growth. Chapter two will provide an overview of the intersection of microfluidics and nanomaterials. An overview of the literature regarding microfluidic synthesis of nanomaterials will be presented. Several types of microfluidic reactors will be described, as well as a description of their capabilities for synthesis and analytical techniques. Chapter three will provide an overview of the literature for in-situ microfluidic techniques - both general and nanoparticle specific techniques. This will be followed by my work on the design, construction, and evaluation of a translatable visible spectroscopy system for microfluidic analysis. Chapter four will provide background on cadmium selenide (CdSe) nanoparticle synthesis, including an overview of the literature of CdSe synthesis in microreactors as well as kinetic and mechanistic studies that have been presented. This will be followed by a study that has combined microfluidics with a translatable visible spectroscopy system to study CdSe nanoparticle growth in-situ. Chapter five will present a thermodynamic study on the cation exchange of CdSe using isothermal titration calorimetry, which presents another approach to providing quantitative information regarding nanoparticle growth to enhance the synthetic control of experimentalists. Chapter six presents the conclusion of the dissertation and provides an overview of future work.
1.7 References


Chapter 2

Development of High Temperature Microfluidic Reactors

2.1 Introduction

Microfluidics can be fabricated from a number of different materials and each one has advantages and disadvantages. Each nanoparticle synthesis has unique requirements that must be carefully aligned to a given reactor platform. Reviews of the broad uses of microfluidics in the synthesis of nanomaterials have been presented elsewhere.1,2 Glass capillary reactors were some of the earliest examples, with example syntheses ranging from CdSe3,4. Glass microfluidics made using microfabrication techniques have also been demonstrated for a variety of materials. Examples of semiconductor nanoparticles synthesized using glass microfluidics include CdS5, and CdSe6,7. Transition metal nanoparticles have also been synthesized in glass microreactors.8,9 The development of soft lithography based polydimethylsiloxane (PDMS) microfluidics10,11 opened up the field to a wide range of applications. PDMS reactors have been limited to a much lower temperature than their glass counterparts, but systems have been developed for the synthesis of CdSe12, CdS12, SiO213, . Polymer capillary based reactors have also been demonstrated as a lower cost and widely available reactor platform with demonstrations for CdSe, Ag, and TiO2.14

The significant benefit multiphase flow provides for chemical synthesis has been demonstrated for a number of reactions and materials.7,12,15–18 By breaking the reactant phases into small volumes that travel down the reactor similar to plugs, the residence time distribution is improved. Multiphase flow is desirable from a synthetic, analytical,
and production standpoint. Well defined residence times as well as enhanced mass transfer result in higher quality products.

The development of microfluidic platforms also has the potential to impact the industrial side of nanomaterials. Nanoparticle syntheses tend to not scale-up well. The poor heating and mixing present at the flask scale worsens as volumes are scaled up. Microfluidics provide enhanced heating and mixing characteristics, but also counterintuitively enable successful scale-up. Scaling up production is done by having many reactors in parallel, sometimes referred to as scale-out.\textsuperscript{19,20} Scale-out preserves the benefits of microfluidics while allowing increased productions. This is especially relevant for syntheses that can be adapted to capillary based systems. Nightingale et al.\textsuperscript{21} demonstrated scaled up production of CdTe, CdSe, and mixed alloys at scales up to 145 g/day. The authors acknowledge that it would be trivial to achieve a scale of kilograms/day.

The work described here focuses on developing microreactor platforms for transition metal and semiconductor nanoparticle syntheses. One of the primary goals during this work has been developing in-situ capable reactors. The progress that has been made coupling different reactors schemes to analytical techniques will be discussed.

2.2 Experimental

2.2.1 Materials

Polydimethylsiloxane (PDMS), specifically Sylgard 184 (Dow Corning), was obtained from Ellsworth Adhesives. Perfluoromethyldecalin (PFMD) was obtained from F2 Chemicals. 1H,1H,2H,2H-Perfluorodecyltrichlorosilane (FDTS), 1H,1H,2H,2H-Perfluorodecyltriethoxysilane, 2,2,2 Trifluoroethanol, 2,2,4-Trimethylpentane, Fomblin Y
06/6, Trichloro(1H,1H,2H,2H-Perfluorooctyl)silane, triethoxymethylsilane (TEMS), tetraethylorthosilicate (TEOS), chloroauric acid, sodium citrate, ethylene glycol (EG), silver nitrate, chloroplatinic acid (CPA), polyvinylpyrrolidone (PVP, MW 55k) were obtained from Sigma Aldrich. SU8 and SU8 developer were obtained from MicroChem Corp. All chemicals were used without further purification. All water used was filtered (conductivity 18 MΩ) using an in-house system.

2.2.2 Fabrication of Polydimethylsiloxane Microreactors

The fabrication of PDMS microfluidic reactors presented here is based on soft lithography. SU8 photoresist was spin coated onto silicon wafers (University Wafers) according to the manufacturer’s recommendations for the given thickness. The following parameters are specific to SU8-3050 for a thickness of 80 µm. Approximately 3 mL of photoresist was dispensed onto a static wafer. The wafer was then accelerated to 500 rpm at 100 rpm/sec for 5 seconds, followed by 1500 rpm at 300 rpm/sec and maintained for 30 seconds. The wafer was then baked at 95 °C for 25 minutes. The wafer was then exposed using a Karl-Suss MA6 Contact Aligner using a transparency mask (CAD/Art Services) for 30 seconds at 8 mJ/cm². The transparency mask was designed using CAD software (OpenSCAD). The wafer was then baked at 65 °C for one minute and then 95 °C for 5 minutes. The photoresist was then developed in SU8 Developer for at least 5 minutes and with constant agitation until no more dissolution was visible. The wafer was then rinsed with fresh developer, followed by IPA, followed by nitrogen. A final hard bake was not employed. The wafers were then placed into a vacuum chamber along with 30 µL of trichloro(1H,1H,2H,2H-perfluorooctyl)silane. The wafer was left under vacuum for 30 minutes. This step bonds a fluorinated hydrocarbon chain the silicon surface, decreasing the surface energy and facilitating the release of the polymer mold used in the next step.
PDMS (Sylgard 184, Dow Corning) was mixed in a ratio of 10 parts base to 1 part catalyst for 1 minute. The mixture was placed in a vacuum chamber and degassed until no bubbles remained. The silicon master was placed in a close fitting petri dish and the degassed PDMS was poured over the top of the dish. The dish was then placed back in the vacuum chamber to remove any newly formed air bubbles and to ensure intimate contact between the mold outlines and the PDMS. The PDMS was cured at 70 °C for at least an hour. The PDMS device outline was traced with a razor blade and the PDMS removed from the master. Holes were punched at the inlets and outlets with 1 mm biopsy punches (Integra Miltex). The PDMS and a methanol cleaned glass slide were loaded into a TePla M4L plasma cleaner. The PDMS and glass were exposed to a 3 parts oxygen to 1 part helium plasma at 100 W and 300 mTorr for 15 seconds. The PDMS and glass were removed from the unit and put into contact immediately. The two halves were pressed together at several locations to facilitate bond formation. Once no visible bubbles existed between the two halves, the device was left to rest undisturbed for at least 2 minutes. This resting time is important to allow solidification of the PDMS-glass bond.\textsuperscript{23,24} If necessary, surface modification of the PDMS walls with other silane chemistries (discussed below) can be carried out immediately after the 2 minute rest. Teflon tubing (21 AWG light wall, Zeus Tubing) was pressed into the inlets and outlets for fluidic interfacing. Careful sizing considerations between the punch and the tubing size allow a fluid tight seal due to the durable and elastic nature of PDMS. This tubing size also allows a liquid tight slip fit over 20 gauge needles (Becton Dickinson).

2.2.3 Surface Modification of PDMS Microreactors

Functionalization of PDMS reactor walls is performed shortly after the bonding procedure. After exposure to oxygen plasma there is an excess of silanol groups that dissipate over time. The functionalization solution should be injected into the channels.
no earlier than 2 minutes after the initial bond, but no more than 5 minutes after the
bond. A 4 vol% solution of FDTS in PFMD is injected into the channels. The excess
solution is wiped away and the inlets and outlets are covered in cellophane tape. The
reactor is left undisturbed for 30 minutes. Filtered air is then passed flowed through the
microreactor for at least 10 minutes to remove the excess solution and dry the walls.

2.2.4 Capillary Microreactors

Two types of capillary microfluidic / millifluidic reactors were created that utilize
small diameter Teflon tubing (26 AWG light wall, Zeus Inc). These will be referred to as
the submerged millifluidic reactor (SMR) and the analytical millifluidic reactor (AMR). For
both reactors, flow streams were combined as needed using T-junction fittings
(Upchurch Scientific) before reaching the reactor.

The SMR consisted of 10 ft of Teflon tubing neatly coiled into a 3 inch diameter
loop and secured with ties to prevent uncoiling.\textsuperscript{14} The tubing was then submerged in a
silicone oil bath on a temperature controlled hotplate.

For the AMR reactor, a serpentine channel was milled into a flat aluminum plate
(McMaster-Carr) such that the Teflon tubing snugly fit into the cutout. Recesses were
also milled into the aluminum for silicone strip heaters (McMaster-Carr) and small
channels for thermocouples (Omega Engineering). A ¼” slot was milled out along the
middle of the aluminum plate to allow for spectroscopic measurements on small sections
of tubing along the length of the reactor. A similarly sized aluminum plate with a
matching slot was used to sandwich the tubing and silicone heaters. This assembly was
clamped together. The heaters and thermocouples were interfaced with a computer and
controlled via a LabVIEW program. For x-ray measurements, kapton tubing was slid
around the Teflon tubing at each analysis spot to provide mechanical support.
2.2.5 Continuous Synthesis of Gold Nanoparticles

The procedure for synthesizing gold nanoparticles in a flow system was adapted from the sodium citrate method of Turkevich. Stock solutions were prepared as follows. To prepare the 1% sodium citrate stock solution, 0.2 g sodium citrate was dissolved in 19.8 g water. The chloroauric stock solution was prepared by dissolving 3.63 mg chloroauric acid into 40 g water. The solutions, particularly the chloroauric acid stock solution, were stored in a cool drawer and wrapped in foil to prevent exposure to light. Immediately before an experiment, the solutions were mixed in a ratio of 19 parts chloroauric acid solution to 1 part sodium citrate solution. Mixtures were always prepared freshly and used within an hour. The solution was loaded into a syringe and the flowrate controlled using a syringe pump (NE500, New Era Pump Systems).

2.2.6 Continuous Synthesis of Silver Nanoparticles

Silver nanoparticles were synthesized using a procedure adapted from Sun et al. Two solutions were prepared. 0.212 g PVP was dissolved in ethylene glycol to form a 20 mL solution. The second solution was prepared by dissolving 0.232 g AgNO₃ in ethylene glycol to form a 20 mL solution. Each solution was loaded into a separate syringe and the flowrates controlled using a syringe pump. The two solutions were mixed using a T-junction (Upchurch) prior to entering a heated zone to minimize premature nucleation.

2.2.7 Continuous Synthesis of Platinum Nanoparticles

Platinum nanoparticles were synthesized using a procedure adapted from Song et al. Two solutions were prepared. The first was the platinum stock solution; 0.110 g of CPA was dissolved into 10 mL of EG. The PVP stock solution was prepared by dissolving 0.357 g PVP into 10 mL of EG. Each solution was loaded into a syringe and
the flowrate was controlled using a syringe pump. The two solutions were mixed in a 1:1 ratio using a T-junction (Upchurch) prior to entering a heated zone to minimize premature nucleation.

A modified synthesis was developed that was identical to the above but with 0.064 g NaOH added to the CPA solution.

### 2.2.8 Fabrication of Glass Microreactors

A general procedure for fabrication of glass microfluidics is presented here. It is based on details from a number of sources. Glass microreactors were fabricated according to a procedure developed from several sources. Borofloat 33 glass wafers (University Wafers) were first etched in 49% hydrofluoric acid for 10 seconds. Next, 150 nm of amorphous silicon was deposited using plasma enhanced chemical vapor deposition. SPR 220-7 photoresist was then spun on to a thickness of 1.5 µm and patterned using a transparency mask (CAD Art Services). The silicon was etched using reactive ion etching to expose the glass in the areas defined by the photoresist. The backside of the wafer was covered with a protective adhesive film (Nitto Denko Corp.) and the wafer was etched in 49% hydrofluoric acid for approximately 15 minutes to reach the desired etch depth of 100 µm.

The patterned wafer was bonded to a blank soda lime wafer using Crystalbond adhesive (Ted Pella Inc.) to prevent chipping during the drilling step. Holes were drilled at the inlets and outlets using 1 mm diamond drill bits (Triple Ripple, Abrasive-Tech). The patterned wafer was then separated from the soda lime blank. Next, the patterned wafer was thoroughly cleaned starting with an acetone bath to remove the photoresist, and then soaked in 45% potassium hydroxide to remove the amorphous silicon, followed by 10% hydrochloric acid to remove surface oxides. Afterwards, the patterned wafer and
A blank wafer were soaked in Nanostrip (Cyantek Corp.) for at least 30 minutes. Both wafers were sonicated in water for 30 minutes, changing the water every 3 minutes. Each wafer was scrubbed for 3 minutes using melamine foam and dried thoroughly. The patterned and blank wafers were put into contact with each other and pressed together to facilitate room temperature bonding. The wafers were sandwiched between graphite plates (Graphite Store) and bonded in a furnace at 670 °C for 6 hours. Finally, the bonded device was sectioned as necessary using a dicing saw.

Small sections of kapton capillary were epoxied at the inlets and outlets. Teflon tubing was joined to the kapton using Teflon shrink wrap.

2.2.9 Fabrication of PDMS-Glass Hybrid Microreactors

PDMS-Glass hybrid microreactors are fabricated in a procedure very similar to what is outlined in 2.2.2 for typical PDMS microreactors. Master molds were CNC milled out of aluminum. However, everything described below is applicable to silicon SU8 masters as well. The master was machined using a 0.05” end mill operated at 10.5k rpm and a feedrate of 300 mm/min. PDMS was mixed, degassed, and then poured over the master mold. The mold was then placed in a vacuum chamber to remove any newly formed air bubbles. A 1/16” thick piece of borosilicate glass (SI Howard Glass) was cleaned with methanol and then placed on top of the PDMS and pressed against the channels of the master. Bubbles must be avoided during this step. The polymer was cured at 70 °C for at least 1 hour. Holes were drilled in another 1/16” thick piece of borosilicate glass at the appropriate locations for fluidic connections. The glass was then cleaned with methanol. The PDMS was carefully removed from the master, making sure not to delaminate the glass from the PDMS. Next, the PDMS piece and the drilled glass were placed in a plasma cleaner (Harrick Plasma PDC-32G) and exposed to 10:1 He:O2 plasma at the high power setting for 5 s. The PDMS and glass were quickly placed in
contact with each other and left undisturbed for at least 2 minutes to allow the bond to form.

Kapton capillaries (Cole-Parmer) were used as inlets and outlets due to kapton's thermal stability up to 450 °C. The kapton capillaries were sized to be smaller than the holes drilled in the glass. The glass around the inlets and outlets was sanded with 150 grit sandpaper to roughen the surface. Short 1 cm long sections of capillary were then epoxied into the inlets and outlets using 5 minute epoxy (Loctite). The epoxy was mixed and left undisturbed for 5 minutes before applying. During this time the epoxy viscosity increased significantly and helped prevent epoxy flowing into the channels and clogging the reactor. Teflon shrink wrap was used to connect the kapton tubing to Teflon tubing (Zeus Inc).

2.3 Results and Discussion

2.3.1 PDMS Microreactors

An example PDMS microreactor is shown in Figure 2-1. Aqueous dispersions in a fluorinated hydrocarbon carrier phase were successfully created at frequencies up to 114 Hz. These droplets varied in volume from 1.4 – 4.0 nL in size. However, these devices had limited usefulness in the synthesis of nanoparticles. A synthesis of gold nanoparticles was attempted based on the Turkevich recipe. In flask experiments, this synthesis occurs in boiling water. Experiments were carried out aiming for a temperature setpoint of 95 °C. Over the course of these experiments, it was noted that heating these reactors to this temperature and above showed a very high failure rate. Reactors would spontaneously crack and ruin the fluidic seal of the reactor. This was the largest motivating factor for pursuing other types of microreactors.
Figure 2-1. Left) An example of a PDMS microreactor. The channels are filled with dyed water for increased visibility. Right) A zoomed in view of a flow focusing nozzle producing aqueous droplets in a PDMS reactor.
2.3.2 Capillary Microreactors

Transitioning to microreactors that utilize Teflon tubing brings a number of advantages and a few disadvantages when compared to PDMS reactors. The most obvious advantage is the simplicity of Teflon tubing based reactors. The SMR requires no special cleanroom processes or tools while the AMR only requires a mill. Therefore, these Teflon based reactors are very accessible. The next advantage is that Teflon can be used up to a temperature of 250 °C. This temperature range is relevant to many transition metal nanoparticle syntheses. In addition, Teflon is also a very chemically resistant material, which enables a long reactor life as well as minimal deposition of nanoparticles onto the reactor wall. Teflon is also the most convenient material for making liquid-liquid dispersions using fluorinated hydrocarbons. In other reaction schemes, a surface modification step is required to make fluorinated hydrocarbons wet the reactor wall. In reactors based on Teflon, this is the natural behavior. As shown in Figure 2-2, liquid-liquid dispersions have been successfully formed using a number of fluorinated liquids (PFMD, Fomblin Y, Fluorinert) as well as a number of dispersed phases (water, ethylene glycol).

A drawback to Teflon tubing based reactors is that the reactor diameter is not as controllable as microfabricated reactors. Tubing is available in set diameters with a minimum size measured in hundreds of microns. Microfabricated microreactors have tuneable channel dimensions and minimum sizes that go down to the submicron range.30,31 Additionally, while 250 °C does provide a useful temperature range for many transition metal nanoparticle syntheses, it is insufficient for many semiconductor nanoparticle syntheses. Another limitation of Teflon based reactors when compared to PDMS is optical clarity. Teflon tends to be a cloudy white, while PDMS microreactors are
transparent across the visible wavelength range. This will impact signal levels in spectroscopic experiments utilizing visible light.
Figure 2-2. Droplet flow in the submerged millifluidic reactor. A temperature controlled hotplate maintains the reaction temperature while the flowrate and length of submerged tubing control the residence time.
The Turkevich synthesis was successfully translated to a flow scheme and carried out in the SMR. Figure 2-3 shows a TEM image of gold nanoparticles synthesized with a residence time of 6 minutes. The temperature was maintained at 90 °C. This yielded nanoparticles with an average diameter of 14.5 nm. At higher temperatures gas evolved in the reactor which causes an unsteady flow in the reactor. Other syntheses were also successfully translated to the SMR. The polyol synthesis of silver nanoparticles was carried out in a droplet flow, however an undesirable side effect was observed. In flask synthesis, many syntheses occur at the boiling point of the solvent and under constant reflux. The production of gas through solvent boiling or through precursor conversion does not cause any problems and often gaseous byproducts go unnoticed. However, in a microreactor, gaseous products disturb the liquid flow and often disturb the steady state operation. For the case of polyol silver synthesis, it was observed that the reduction of silver nitrate to metallic silver had a gaseous byproduct. Analysis of the outlet gases showed that the reaction involves the production of NO₂. Thermal decomposition of AgNO₃ does not occur until almost 350 °C. Skrabalak et al. proposed a reaction pathway for the polyol synthesis that involves the reduction of metal salts via glycoaldehyde. This results in the formation of nitric acid which can thermally decompose into NO₂, H₂O, and O₂. Gaseous byproducts from a liquid-liquid flow have the convenient behavior of forming a well ordered three phase flow (immiscible phase, reactant phase, gaseous phase) that still operates at steady state. However, without any accurate method to measure the volume fraction as a function of position along the reactor, too much error is introduced to the residence time to be useful for characterization.
Figure 2-3. TEM micrograph of gold nanoparticles synthesized in a millifluidic reactor at 95 °C with a residence time of 4.5 minutes. Scale bar is 100 nm.
While the SMR was a simple reactor that allowed the adaptation of several syntheses, fundamentally it was flawed for the application of in-situ measurement. While it is possible to include on-line detection downstream, in-situ detection is near impossible while the tubing is submerged in silicone oil. This motivated the development of the AMR. Figure 2-4 shows the AMR both dismantled and in use. One of the primary goals when designing the AMR was to allow for in-situ measurement with minimal disturbance to the solution temperature. This is accomplished by using a minimal slot to allow access to sections of the reactor for spectroscopic measurements. The thermal effect of this slot can be minimized by applying a film to minimize convective heat losses. In the case of x-ray experiments, kapton was used.
Figure 2-4. Photographs of the analytical millifluidic reactor. A) The reactor disassembled showing the routing for the Teflon tubing as well as the routing for thermocouples. B) The reactor assembled. Analysis can be carried out across the middle slot.
The first synthesis and analytical combination attempted was that of platinum polyol with x-ray absorption spectroscopy (XAS) using the AMR. However, several hurdles were encountered with this combination. Like the silver polyol synthesis, platinum polyol also evolved gas as a byproduct of the reaction. Thermal decomposition of chloroplatinic acid has been shown to evolve H₂O and HCl and it is reasonable to assume those products would evolve during the polyol synthesis. A control experiment was performed where 1 vol% H₂O in ethylene glycol was passed through the AMR at 190 °C and no gas evolution was noticeable. This suggests HCl as the main component of the vapor phase rather than any water in the system. An experiment was attempted where the synthesis recipe was tuned to include an amount of NaOH to react with the HCl and avoid gas generation. This significantly decreased the production of gas bubbles in the reactor but did not eliminate the problem. It is also important to note that the addition of NaOH could significantly affect the kinetics of the reduction. While it was a useful trick to explore the proof of concept stage, it is non-ideal since it will convolute the mechanism of the reaction. An example of the impact multiphase flow has on the in-situ XAS spectra is shown in Figure 2-5. It is quite apparent that gas production is detrimental to the experiment.
Figure 2-5. X-ray absorption spectrum of in-situ platinum reduction in the analytical millifluidic reactor with gaseous byproducts.
The XAS spectra of multiphase flow resulted in un-useable and noisy data. Whether intentional or not, multiphase flow makes analytical work much more difficult. Either very fast techniques or very specialized data acquisition methods are required. For a technique such as XAS, thousands of data points are taken and each individual data point is time averaged. If this time average involves an inconsistent sampling of the phases then the data is unusable due to noise. This means multiphase flow needs to be extremely consistent (much better than 1% variability) and the droplet frequencies need to be extremely fast (hundreds of Hz) to provide a suitable average. Both of these options are difficult constraints on a reactor, therefore it is more desirable to modify the manner with which data is gathered. Either spectra must be acquired very quickly to capture single droplets, or more complicated data acquisition schemes must be developed. For the case of XAS, this would mean each data point must be selectively averaged, rather than indiscriminately. Only signal readings while the phase of interest is being analyzed should be averaged while the rest are thrown out. This would require modified software methods and is an unlikely route. The only straight forward path for combining multiphase flow and in-situ analysis is selecting techniques that can be acquired on a fast timescale.

To further explore the proof of concept of the AMR combined with XAS, the temperature was lowered to 150 °C; at this point gas formation was eliminated. By manipulating both the spatial location and the volumetric flowrate, spectra were taken at residence times ranging from 3 to 120 seconds. At 150 °C there was no visible conversion to platinum nanoparticles. Using a linear combination fit, each spectra was fit as a combination of chloroplatinic acid and platinum metal. The time dependent behavior of this fit is shown in Figure 2-6. At low temperatures the preconversion of Pt(VI) to Pt(II) is observed. This demonstrates the ability of in-situ XAS to provide insight into the
kinetics of reduction. Since no platinum metal was formed, no information was available to characterize particle growth.
Figure 2-6. XANES fitting of chloroplatinic acid reduction. By controlling flowrate and length down the reactor, XANES spectra were taken at a variety of time points. A linear combination fit of each spectra was performed using chloroplatinic acid and platinum metal. The LCF fraction equilibrated halfway between the two standards which implies the production of Pt(II). The data were fit using a modified first order kinetic equation. This yielded a rate constant of $0.055 \text{ s}^{-1}$ for the conversion of Pt(VI) to Pt(II) in ethylene glycol at 150 °C.
An important limitation of the AMR when used with XAS is the lifetime of the Teflon tubing. X-rays have been shown to embrittle Teflon materials\textsuperscript{34} and this effect was very significant at the energies and intensities for these experiments. Without the use of the kapton sheaths, the Teflon tubing would leak within the first few minutes of a given experiment. The high intensity of insertion device beamlines indicates that these experiments may be more suited to lower energy stations and high sensitivity detectors.

Gas evolution proved itself to be a problem in several different syntheses. In order to address this, a back pressure regulator (BPR) was attached to the outlet of the AMR. This eliminated gas evolution and also provided an interesting benefit. Since the boiling point of a solvent is dependent on the pressure, the inclusion of a BPR raises the boiling point for each system. In the case of water-based syntheses, such as the Turkevich synthesis, the BPR raised the maximum temperature to 170 °C. Consequently, the AMR coupled with the BPR allows a wider range of synthetic conditions than typical flask systems are capable of. Figure 2-7 shows gold nanoparticles synthesized at 160 °C and a residence time of 2 minutes. The BPR also allowed the successful synthesis of platinum nanoparticles with no gas production as shown in Figure 2-8.
Figure 2-7. TEM micrograph of gold nanoparticles synthesized in the analytical millifluidic reactor at 160 °C with a residence time of 1 minute. The use of a back pressure regulator allowed synthesis above the standard boiling point of water (100 °C) without forming a vapor phase. Scale bar is 20 nm.
Figure 2-8. TEM micrograph of platinum nanoparticles synthesized in the analytical millifluidic reactor at 210 °C with a residence time of 4.5 minutes. The use of a back pressure regulator allowed synthesis above the standard boiling point of ethylene glycol (197 °C) without forming a vapor phase. Scale bar is 20 nm.
2.3.3 Glass Microreactors

Teflon capillary based reactors are limited by the softening temperature of the Teflon. The maximum operating temperature for the systems developed here were about 210 °C. While that temperature range is useful for a number of transition metal nanoparticle syntheses, a different reactor is necessary to access the temperature ranges often found in semiconductor nanoparticle syntheses. This was the driving force behind developing the procedures to fabricate glass microreactors.

A number of different approaches were taken to fabricate glass microreactors, ranging from Cr/Au wet etch masks to deep reactive ion etching of glass wafers. The final process that was developed is illustrated in Figure 2-9. An amorphous silicon mask protected the desired areas during a hydrofluoric acid etch step. This was the only successful combination of mask material and etch process that could achieve the desired depth of 100 μm. Other mask and etch combinations did not adequately protect the surface of the wafer. It was determined that the wafer smoothness and cleanliness were critical aspects to successful bonding of a glass microfluidic device. Profilometer measurements on a clean wafer and an inadequately masked wafer are shown in Figure 2-10. Inadequate cleaning of the wafers resulted in unbonded spots around the wafer. This is unacceptable for microfluidics, where a fluid tight seal is essential. An example glass microreactor is shown in Figure 2-11. The grid of squares was part of the mask design. It provides structural support across the entire wafer while decreasing the amount of area that needs to be bonded. Overall it was found to increase the bonding success rate.
Figure 2-9. Procedure for the microfabrication of glass microfluidic reactors. The procedure utilizes amorphous silicon as a protecting mask to preserve the surface finish of the wafer.
Figure 2-10. A) Profilometer measurement of a clean glass wafer. B) A wafer that has been etched in hydrofluoric acid with a Cr/Au mask. Pinhole defects in the metallic mask lead to undesired etching and result in a roughened surface.
Figure 2-11. A photograph of a glass microreactor. Three inlets are visible on the left that combine and flow through the reactor. The reagents exit on the right.
Interfacing with glass microfluidics requires careful consideration. The main justification for working with glass reactors is the increased temperature range. However, an increased temperature range provides fewer options for interfacing fluids with the reactors. Two methods were developed, each with its own merit. The first method involves stainless steel mounts that interface flat bottom PTFE fittings to the reactor, as shown in **Figure 2-12**. The flat bottom fittings are convenient and very chemically resilient, however, they have a maximum operating temperature that is similar to the Teflon capillary reactors. Therefore, in order to both utilize the flat bottom fittings as well as access high temperature, the microreactor will require zones of different temperatures. The inlets and outlets must be maintained below the softening point of Teflon while the channels must be maintained at the desired reaction temperature. This also means reactants will experience a thermal gradient as they enter the heated zone of the reactor.
Figure 2-12. Stainless steel interfacing hardware for glass microfluidics. A) View from above B) Side view.
The complexity of multiple temperatures on a single device as well as the lack of isothermal operation motivated the development of another fluidic interface technique. Kapton capillaries were epoxied into the inlet and outlet holes to provide a high temperature resistant interface. This is shown in Figure 2-13. Kapton is thermally stable up to 450 °C. The limiting factor in this arrangement is the thermal stability of the epoxy. This scheme has been successfully used at temperatures up to 250 °C for over 10 hours with intermittent use at 260 °C. This method allows the entire reactor to be maintained at the desired setpoint. Reagent streams mix on the device after already thermally equilibrating with the reactor. This provides a truly isothermal synthesis which is not feasible on a flask scale. A photograph of an all glass microreactor synthesizing CdSe isothermally at 250 °C is shown in Figure 2-14.
Figure 2-13. Photograph of a glass microreactor with kapton tubing epoxied at the inlets and outlets. This provided a convenient interfacing method capable of temperatures up to 260 °C.
Figure 2-14. Photograph of a glass microreactor synthesizing CdSe nanoparticles at 250 °C. Reagents enter on the left and exit on the right. The solution color changes as the residence time increases and the nanoparticles nucleate and grow.
2.3.4 PDMS-Glass Hybrid Microreactors

Glass microfluidics require expensive supplies, complicated cleanroom processes, and have a limited maximum channel dimension. Microfabrication is meant for small dimensions, but feature thicknesses above 100 μm become increasingly difficult. In some applications, a method for fabricating accurate channels with dimensions of 100 – 500 μm is desirable. Johnson et al. measured the thermal decomposition of Sylgard 184 PDMS using thermogravimetric analysis.\(^{35}\) They found a 0.31% mass loss at 200 °C and a 3.3% mass loss at 300 °C. The high thermal stability of PDMS means PDMS reactors could potentially utilize temperatures up to 300 °C. However, the highest temperature demonstrated in a PDMS device in the literature is 115 °C.\(^{36}\) As described in section 2.3.1 traditional PDMS devices tended to fail catastrophically above 100 °C. This is attributed to a mismatch in coefficients of thermal expansion (CTE) between PDMS (310 ppmK\(^{-1}\)) and the soda lime glass (9.5 ppmK\(^{-1}\)). As the reactor is heated, the PDMS expands an order of magnitude more than the glass slide, leading to a bending stress in the glass slide. Eventually the stress results in the glass slide cracking and the device failing. This was addressed in two similar alternatives to the traditional PDMS reactor.

The first alternative utilized 1/8” thick borosilicate glass instead of 1 mm soda lime. The thickness of the glass gave enough mechanical strength to withstand the stresses from the CTE mismatch. Additionally, borosilicate glass has a lower CTE (3 ppmK\(^{-1}\)) and can withstand uneven heating much better than soda lime glass. However, during reactor use significant outgassing of the PDMS into the reaction mixture was observed. This led to future reactors going through a heat treatment step at 250 °C to fully outgas the PDMS. However, this produced fissures through the PDMS, as shown in
Figure 2-15. Even with this temperature limitation, this simple modification allows PDMS reactors to carry out reactors at temperatures up to 200 °C.
Figure 2-15. Photograph of a PDMS microreactor heat treated at 250 °C. Fissures form throughout the reactor, ruining the fluidic seal.
The more successful alternative utilized a thin PDMS layer sandwiched between two borosilicate glass slides; an example reactor is shown in Figure 2-16. A glass-PDMS-glass reactor is not an entirely original idea.\textsuperscript{37,38,38} However, previous work on these types of reactors has emphasized their high pressure capability and overlooked the potential for high temperature. We successfully used these microreactors to synthesize CdSe nanoparticles at temperatures up to 225 °C. However the reactor lifetime was limited to around 30 minutes. It was identified that the PDMS absorbed octadecene and slowly swelled over time. Eventually this swelling resulted in mechanical failure in the glass slide. Further work is required to expand the capabilities of these reactors to organic systems that swell PDMS. Without modification, these reactors are well suited to aqueous and ethylene glycol based syntheses.\textsuperscript{39} They should easily be able to withstand the temperatures of the polyol syntheses. Additionally, the master molds used in this work were fabricated using a CNC mill, which means these reactors can be made completely outside of a cleanroom. This provides another technique to fabricate microfluidics for researchers without access to the specialized equipment of a cleanroom.
Figure 2-16. A) Schematic breakdown of the layers of the PDMS-glass hybrid reactor. B) A photograph of a PDMS-glass hybrid reactor with kapton tubing epoxied at the inlets and outlets.
2.4 Conclusions

A number of high temperature capable reactors have been presented. Reactors capable of temperatures from room temperature to 300 °C have been presented. Flow based syntheses of transition metal nanoparticles (Pt, Au, Ag) have all been presented as well as semiconductor nanoparticles (CdSe). Preliminary in-situ data from the coupling of a flow reactor with x-ray absorption spectroscopy has been presented. The rate constant for the reduction of chloroplatinic acid in ethylene glycol was successfully measured at 150 °C.

2.5 References


Chapter 3

Development of a Translatable Spectrometer for In-Situ Microfluidic Analysis

3.1 Introduction

The goal of in-situ analysis is to study a reaction as it occurs. Traditional ex-situ methods study the before and after of a reaction. By ex-situ methods, mechanistic insight is gained by looking at the precursors and the final product to theorize how one leads to the other. However, to develop a true understanding of what is occurring during a reaction, in-situ measurements are a necessity. Sampling and quenching aliquots of reactants over time is possible and has provided some successful studies, however, the act of sampling and quenching can have an effect on the resulting product when compared to its in-situ counterpart. Additionally, it is difficult to access fast residence times (<10 seconds) via aliquot sampling.

The combination of microfluidics and in-situ analysis for studying nanoparticle formation has been demonstrated in several cases. The appeal of the microfluidic aspect is the steady state nature of operation. It is worth emphasizing the difference in terminology used to describe these studies. In-situ refers to analysis done on a reaction mixture as a reaction is occurring. Ex-situ refers to analysis of samples taken from a reaction mixture that are typically quenched and not undergoing a reaction. On-line/in-line analysis refers to analysis that is happening in real time, but typically is not in-situ. An example of on-line analysis is an analytical flow cell situated at the outlet of a flow
A number of studies have aimed to combine microfluidic reactors with x-ray based techniques. X-rays are well suited for studying local atomic environments using x-ray absorption spectroscopy as well as longer range structure using x-ray scattering.\textsuperscript{1–3} Chan et al. demonstrated x-ray absorption near edge structure (XANES) coupled with a multilayered microfluidic reactor.\textsuperscript{4} XANES provides information on the oxidation state of a target element. This combination allowed access to the kinetics of CdSe cation exchange on a millisecond timescale. Uehara et al. performed extended x-ray absorption fine structure (EXAFS) on a microfluidic reactor during the synthesis of CdSe nanoparticles.\textsuperscript{5,6} These experiments were carried out at 240 °C, showing the ability of microfluidic reactors to combine harsh reaction conditions with in-situ analysis. Polte et al. combined a microfluidic reactor with small angle x-ray scattering (SAXS) to study gold nanoparticle formation.\textsuperscript{7,8} SAXS bridges the gap between small and intermediate nanoparticle growth. This allows the study of particle nucleation and growth. SAXS also allows the measurement of particle coalescence; a phenomena out of the scope of XANES and EXAFS.

While x-ray techniques provide valuable insight into nanoparticle growth, many experiments require the use of a dedicated synchrotron facility. Ultra-violet and visible spectroscopy analysis has been integrated into microfluidic systems in variety of ways.\textsuperscript{9} Several systems exhibit distinct absorbance features that can be used to characterize growth. Quantum dots show size dependent absorbance behavior due to quantum confinement.\textsuperscript{10,11} Gold nanoparticles also have size dependent features due to a plasmon resonance in the visible range.\textsuperscript{12,13}
Much of the work combining microfluidics with UV-Vis spectroscopy involves on-line detection using a flow cell, which provides constant characterization but not in-situ insight. The flowrate can be adjusted in flow systems to adjust the residence time at the flow cell, but overall there is minimal advantage over ex-situ analysis. Wagner et al. utilized a microfluidic reactor coupled to a flow cell equipped with UV-Vis capabilities to characterize the resulting gold and silver nanoparticle products.\textsuperscript{14} Chan et al. utilized a photoluminescence flow cell downstream of a high temperature glass microfluidic reactor synthesizing CdSe nanoparticles.\textsuperscript{15} This provided on-line characterization of the nanoparticle size as well as the size distribution. However, more recently there has been demonstration of in-situ coupling of absorbance measurements to microreactors. Abolhasini et al. have recently demonstrated the growth of CdSe in a oscillatory reactor with in-situ absorbance measurement.\textsuperscript{16} A drop of reagent is passed back and forth through a heated section of Teflon capillary with integrated fiber optic connections for absorbance measurements. Lignos et al. have presented a Teflon capillary reactor that integrates in-situ absorbance and fluorescence measurements.\textsuperscript{17} They applied this scheme to the synthesis of PbS nanoparticles using droplet based flow and measured the reaction kinetics at residences times on the order of 1 second.

Stopped-flow UV-Vis absorbance is similar in concept to in-situ microfluidic analysis and has successfully been used to study a number of nanoparticle systems.\textsuperscript{18–20} Stopped-flow is particularly effective at fast residence times (<1 second); however, it is generally not compatible with high temperature syntheses.

Alternative methods of integrating detection into microreactors can involve the integration of fibers and optics directly into the reactor.\textsuperscript{21–23} However, these measurements are not compatible with high temperature nanoparticle synthesis. Jindal and Cramer demonstrated on-chip electrochromatography with a UV-Vis absorbance
scheme that keeps the microreactor and optical system separated. This utilized a chip mounted to an XYZ stage and two fibers placed perpendicular to the region of interest on the device. This was used to monitor the separation of various peptides.

The work presented here aims to develop a system capable of making absorbance measurements on a microreactor at temperatures up to 300 °C. This is achieved by keeping the reactor and measurement hardware separate. The glass microreactors developed in this thesis are independently capable of achieving 300 °C. The next step is to develop an analytical scheme that is compatible with these reactors.

### 3.2 Design Requirements

Certain requirements were identified to enable successful in-situ experiments. The first criterion was to design a fiber optic based instrument. The option of designing a translating microfluidic reactor in front of a fixed spectrometer was investigated; however, it was rejected due to limited space. Typically, only a few inches of space is available between the two halves (light source and detector) of a UVVis spectrometer. A fiber optic based system allows the light source and detector to be placed anywhere in relation to the reactor. Only the optics at the ends of each fiber need to be near the microreactor, allowing less crowding around the reactor and a more flexible setup. A fiber system also provides an adjustable distance between the optics. Again, this adds versatility to the experimental setup since an adjustable setup can accommodate a wider variety of systems.

Another important choice is whether to translate the reactor across a stationary beam, or to translate the beam across a stationary reactor. The latter was selected due to the sensitive nature of microfluidics. Movements and vibrations of inlet and outlet tubes can perturb the pressure within the microreactor. This is minimized when the
reactor is held stationary. Additionally, the microreactor not only has inlet and outlet tubing, but also wires for heaters and thermocouples. Moving the beam across a stationary reactor means that all of these components can stay still rather than risk disconnecting during movements.

Since microfluidic channels are often less than 100 μm wide, a precise positioning system is important. The analysis needs to be well centered on the microfluidic channel to avoid analytical errors. Additionally, since the residence time depends on position, an accurate placement of the beam ensures accurate knowledge of the residence time. The initial project goal defined a positioning precision of 25 μm (0.001’’). Another benefit of a modular and flexible system is that each component is easily upgraded independently. If a 25 μm precision is inadequate for future experiments, the positioning system can be swapped out while all else is held constant.

The last requirement is a spectrometer system with fast acquisition times. As described in Chapter 2, the successful meshing of multiphase flow and analytical measurements requires techniques with fast acquisition times. Rapid acquisition will allow flexible post processing of the data. Spectra from the reactant phase can be summed and averaged while spectra from the second phase can be discarded. This also provides a mechanism for quantifying the relative volumes of the phases as described in the next section.

3.2 Description of the System

A general Bill of Materials (BOM) is presented in Table 3-1 and a photograph of the translatable spectrometer system is shown in Figure 3-1. A spectrometer was selected that allowed measurement in the ultraviolet and visible light ranges, from 177 – 891 nm. A tungsten light source provides illumination from 360 nm to as high as 2400
nm. The positioning system was designed from a low-cost 2-dimensional milling table, stepper motors, and a motor control board. This system has a theoretical accuracy better than 5 μm\(^1\). 

\(^1\)1 mm per revolution of the handle with 200 steps/revolution motors gives 5 μm/step. Micro-stepping was used and provides finer resolution, however the conservative 5 μm accuracy is proposed.
Table 3-1. Bill of materials for the translatable spectrometer system

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<tr>
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<td>Fasteners</td>
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<tr>
<td>Panucatt</td>
<td>AX5MINI</td>
<td>1</td>
<td>Motor Controller</td>
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Figure 3-1. Overview of the translatable visible spectrometer and microreactor system. A) light source, B) spectrometer, C) motors, D) translating optics stage, E) microreactor, F) temperature controller, and G) syringe pumps.
An important aspect for both the spectrometer and the motor controller was the ability to control the individual elements through National Instrument’s LabVIEW software. Custom LabVIEW software allows the rapid development of experiment specific software. New types of experiments using the same hardware can be theorized and prototyped in the same day. An integrated program was developed that simultaneously controlled the spectrometer and the beam position. An overview of the software control panel is shown in Figure 3-2. The tabbed panel allows access to 4 different modes of operation described below.
Figure 3-2. Overview of the software controlling the translatable spectrometer. The integration time, scan averaging, and position settings are available at all times while a tabbed interface allows access to four different modes of operation.
**Live Update** – This tab displays a live readout of the spectrometer at the rate defined by the integration time and the number of scans to average. While the integration time can be set as low as 10 μs, the transfer speed of the spectra to the computer is limited to approximately 7 ms. The spectrometer readout can be used to fine tune the integration time and monitor steady state. The second line on the spectrometer readout is the average intensity over time. This provides some basic insight into the systems behavior over time. While the system is equilibrating this readout will approach an asymptotic value which visualizes the approach to steady state. The “Stream to file” button allows a constant stream of spectra to be saved sequentially and then output to one large file.

**Line Scan** – The line scan mode allows accurate determination of the specific location of microreactor channels or other small features. The average intensity can be plotted as a function of position (X or Z). This is useful for centering the beam on microfluidic channels. An optional setting allows a similar scan that plots the average absorbance. In some instances, this provides an enhanced contrast

**Array Scan** – This mode allows the input of an arbitrary number of points at arbitrary locations. Once the “Begin” button is pressed, the program goes to each location, acquires a spectra at that location using the integration time and number of scans settings, and then saves it to the location specified. Each file is saved with information about the spatial location and the time of the scan.

**Simple Absorbance** – The simple absorbance tab allows the acquisition and plotting of basic absorbance plots as well as the import and export of background and sample scans. This page allows a sensitive method of monitoring steady state. While

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2 The spectrometer has a special mode of operation that supports the retrieval of spectra faster than 7 ms, however, it is outside of the scope of the work presented here.
approaching steady state, background and sample scans can be acquired back to back. At steady state the absorbance spectrum from two back to back measurements should be approximately zero at all wavelengths.

### 3.3 Evaluation of the Spectrometer

#### 3.3.1 The Effect of Beam Misalignment

The method for measuring absorption and how it relates to concentration is shown in Eq. 1.

\[
A = \log \frac{I_B}{I_S} = \varepsilon CI
\]

Eq. 1

For a single beam spectrometer, two scans must be performed to measure the absorbance. \(I_B\), the background spectra, and \(I_S\), the sample spectra, must be determined separately. All conditions should be held as closely as possible between the two scans. This means path length, solvent, and temperature should all be the same for the background and sample spectra. The absorbance is related to the product of the extinction coefficient (\(\varepsilon\)), concentration (\(C\)), and path length (\(l\)).

A consistent path length is critical to determining absorbance. In the case of a translatable beam it is worth emphasizing the importance of beam centering on a channel. Misalignment has a similar effect as stray light as shown in Eq. 2.

\[
A = \log \left( \frac{I_B + I_M}{I_S + I_M} \right)
\]

Eq. 2

**Figure 3-3A** shows an example absorbance spectra alongside simulated spectra with misaligned beams. Misalignment has a significant effect on the magnitude of absorbance, which is directly related to concentration. A misaligned beam also causes distortions in the spectrum, as emphasized in **Figure 3-3B**. These two effects highlight the importance of accurate sampling of the channel.
Figure 3-3. A) Demonstration of how beam misalignment affects the absorbance spectrum. B) A scaled view of a well aligned absorbance spectra and a 75% offset spectra showing the resulting distortions. Samples were cadmium selenide nanoparticles dissolved in octadecene.
Multiplicative differences between a background and sample scan are easily accounted for in absorbance measurements. An example of a multiplicative difference is a slight difference in acquisition/integration time. This produces an additive component of the absorbance spectrum that can be easily accounted for. This is shown in Eq. 3 for arbitrary multiplicative constants B and C.

\[ A = \log \frac{B \cdot I_B}{C \cdot I_S} = \log \frac{I_B}{I_S} + \log \frac{B}{C} \]  

Eq. 3

The multiplicative constants result in a constant offset in the absorbance which can be subtracted out during data analysis.

3.3.2 Backlash Measurement

An important characteristic of any mechanical positioning system is the backlash. Backlash is a description of how closely the mechanisms of a moving system fit. In the case of the translating spectrometer, this is how closely the threaded rod and the nut of the stage fit with each other. When the direction of motion is changed, there is a measurable distance the system must travel before the two components reengage. This was measured using a dial gauge and is shown in Figure 3-4. The measured backlash was 70 μm. In microfluidics, where channels are on the order of 10-100 μm, this has the potential to be a significant offset. While it is ideal to have no backlash, it can be manually compensated for. As long as all movements are performed and reported in the same orientation, i.e. always left to right or up to down, the resulting positions will be consistent. Without compensation, backlash has the potential to cause significant error due to effectively displacing the beam as described in section 3.3.1.
Figure 3-4. Backlash measurement of the positioning system. The stage was translated forwards in increments of 0.1 mm while measuring the true displacement using a dial gauge. Zero backlash would result in the two datasets overlapping.
3.3.3 Measurement of the Positional Precision

As outlined in the design requirements, successful measurements of the absorbance on a microfluidic channel will require a positioning precision better than 25 μm. To evaluate this, the beam was translated across a stationary 400 μm aperture several times and the results recorded. This is shown in Figure 3-5. Five scans were performed and when overlaid they agree with each other to better than 25 μm. A similar type of scan is used to center the beam on a microfluidic channel. This shows that alignment can be performed with a high degree of precision.
Figure 3-5. A) Demonstration of the precision of the translating stage. Five separate scans of identical condition are shown here manually offset from each other. B) The derivative of the data from A. The dashed lines highlight a 25 μm range around the calculated maximum.
3.3.4 Beam Refraction

Accurate sampling of the microfluidic channel requires more than just an accurate positioning system. The microfluidic reactor must also be positioned perpendicular to the beam. Any deviation from perpendicular will add a displacement to the beam as shown by Eq. 4 and Figure 3-6.

\[
d = t \sin \theta \left[ 1 - \frac{\cos \theta}{\sqrt{\left(\frac{n_2}{n_1}\right)^2 - \sin^2 \theta}} \right] \tag{Eq. 4}
\]

The displacement \(d\) is a function of the thickness of the microreactor \(t\), the angle from the perpendicular plane \(\theta\), and the refractive indices of the microreactor \(n_2\) and the air \(n_1\). Even at angles of just a few degrees, a 1 mm thick microfluidic reactor can displace the beam tens of microns. This can cause a significant error on the measured absorbance spectrum in manner similar to beam misalignment.
Figure 3-6. Beam displacement caused by the refraction of a 1 mm thick microreactor at an angle away from perpendicular.
3.3.5 Beam Size Considerations

The beam size as it exits the collimating optics is about 5 mm in diameter. For traditional cuvette measurements this is an ideal size, but for microfluidic measurements 5 mm is too large. Any part of the beam that is larger than the channel contributes to stray light and affects the absorbance spectrum as described in Eq. 2. That means that stray light must be eliminated to provide quantitatively accurate spectra. Theoretically, there are a number of ways to accomplish this. The most direct option would be to utilize a smaller diameter beam. However, the beam diameter is a product of the collimating optics and physical limitations prevent the beam from being condensed further. The more indirect option is to limit the light that reaches the detector. This can be done with an aperture downstream of the sample. An aperture would mean that the entire 5 mm diameter light beam interacts with the reactor, but only the fraction of the beam defined by the aperture would reach the detector. This has the effect of limiting the beam size.

The first approach taken utilized a 200 μm circular aperture. The aperture was centered in the beam and moved with the stage. Ideally, this would allow analysis of any arbitrary point on a microreactor since the aperture moves with the beam. To verify that the aperture adequately cut off the beam to the desired dimensions, the beam size was characterized. A razor blade was placed in the beam path and the beam was translated from a position completely off of the razor blade to a position completely blocked by the razor blade (Figure 3-7A). The razor blade scan should provide a verification of the aperture size. However, as seen in Figure 3-7A, the resulting beam shape extended past the aperture. This undesired result was attributed to a slightly divergent beam.

For the case of a microfluidic channel in the path of a divergent beam, the distance between the aperture and the microreactor becomes an important variable as demonstrated in Figure 3-8. As the microreactor was moved closed to the aperture, a
more quantitatively accurate absorbance spectrum was measured. This is an unacceptable result that required addressing. The most ideal resolution in this setup was to place the reactor to a location almost touching the aperture, however, this still resulted in a separation of 1 cm between the microchannel and the aperture and resulted in quantitatively inaccurate spectra. To address this problem, an arrangement that allows the aperture to rest as close as possible to the channel is necessary.
Figure 3-7. A) Illustration of the scan performed from the perspective of the beam axis. B) The results of the razor blade scan. The dotted lines shows the width of the aperture.
Figure 3-8. The impact on the absorbance spectrum due to the distance between the aperture and the microchannel. All other conditions, including concentration, were the same between the two spectra. Samples were resazurin/resarufin in water.
To fully eliminate the effect seen in Figure 3-8, the distance between the microfluidic channel and the aperture should be zero. However, due to the thickness of the glass substrates used, the closest an aperture can get is 0.5 mm. To achieve a separation of 0.5 mm the aperture must be directly against the microreactor itself. This eliminates the possibility of using an aperture that translates with the light beam. Rather, the aperture needs to stay fixed against the stationary microreactor. This was achieved by fabricating a silicon mask that defined the locations for analysis. 400 μm holes were drilled into a silicon wafer at distances that intersect with the microfluidic channels. The silicon wafer and glass microreactor were carefully aligned and clamped to a heating mantle. Instead of sampling arbitrary points using a moving aperture, fixed points along a reactor are defined and analyzed. The silicon wafer aperture and the assembled system is shown in Figure 3-9.
Figure 3-9. A) The aluminum heating mantle designed for in-situ analysis. The slot through along the middle allows light to pass through the area of interest. B) The silicon wafer aperture with 400 μm holes drilled every 5 mm. C) The microfluidic reactor aligned on top of the silicon aperture. D) The entire assembly clamped together.
3.3.6 Thermal Expansion of the Reactor Components

The microreactor is expected to be used at temperatures up to 300 °C. For applications where micron accurate positioning is important, thermal expansion becomes an important factor. Silicon and glass have very similar coefficients of thermal expansion, 2.6 ppm·K⁻¹ and 3.3 ppm·K⁻¹, respectively. This means misalignment due to one material expanding more significantly than the other is very minimal. Holes drilled directly into an aluminum heating mantle were used at first. However, the coefficient of thermal expansion for aluminum, 22.2 ppm·K⁻¹, is significantly higher than glass. This has the potential to cause misalignment once the reactor assembly is brought up to temperature. Another useful property of silicon is the high thermal conductivity, which is similar to aluminum. This will help ensure even heating across the microfluidic reactor. As shown in Figure 3-9A, slot in the middle of the heating mantle allows the light beam to pass through unobstructed, while the silicon wafer helps minimize the thermal effects of the slot.

3.3.7 Verification of the System’s Quantitative Accuracy

In order for the translatable spectrometer system to be useful for in-situ work, it must provide accurate absorbance results. Figure 3-10 shows a comparison between the system developed here and an HP 8453 Spectrometer using a cuvette. Overall the results agree very well. The difference between the two spectra at low wavelengths is attributed to low intensity at lower wavelengths of the light source as well as the low value of absorbance for the microfluidic measurement.
Figure 3-10. Evaluation of the quantitative accuracy of the translatable spectroscopy system. Identical solutions were evaluated using a 1) 1 cm path length cuvette on an HP 8453 Spectrometer and 2) a 0.5 mm path length microfluidic reactor using the translatable spectrometer. The microfluidic spectrum shown here was adjusted to compensate for differences in path length. The sample was resazurin/resorufin in water.
3.4 Conclusions

A translatable spectrometer capable of quantitative visible spectroscopy was designed and built. It has the translational precision necessary for analysis of microfluidic channels. The precision was estimated to be better than 25 μm, which is smaller than the typical microfluidic channel. A silicon wafer aperture was implemented that allows accurate absorbance measurements at the path lengths and channel widths typical of microfluidics. The modular and open nature of the system allows different components of the system to be easily upgraded. System components can be swapped to address the engineering needs of future experiments.

3.5 References


Chapter 4

In-situ Characterization of the Formation and Growth of Cadmium Selenide Nanoparticles

4.1 Introduction

Colloidal cadmium selenide (CdSe) nanoparticles have been under study for over two decades. \(^1\) While a variety of procedures for the synthesis of CdSe and other semiconductor nanoparticles have been presented in both flask\(^2-^4\) and microreactor\(^5,^6\) schemes, there are few examples of quantitative descriptions of the formation and growth. However, CdSe nanoparticles are an ideal system for quantitative characterization. CdSe nanoparticles exhibit a size dependent absorbance spectrum that has been well characterized by multiple sources.\(^7,^8\) This information conveniently allows the determination of nanoparticle size and concentration based on the peak absorbance of the sample, making CdSe synthesis an ideal system for in-situ absorbance measurements.

Ex-situ studies have successfully been performed by a number of groups to study various aspects of synthesis. Bullen and Mulvaney measured the reaction rate for CdSe growth at 265 °C using quenched aliquots at various time points.\(^9\) They reported a rate constant of \(2.2 \times 10^{-6}\) cm/s. They also propose general observations on how ligand concentration can affect both nucleation rates as well as nuclei stability. Embden and Mulvaney performed similar measurements to study how two ligands, oleic acid and bis-(2,2,4-trimethylpentyl) phosphinic acid (TMPPA), control nanoparticle nucleation and growth.\(^10\) By tuning the relative contribution of each ligand they demonstrate control over nanoparticle size. Nolf et al. studied how ligand chain length affects the size of CdSe nanoparticles.\(^11\) They found that longer chain ligands provided a more significant
diffusional barrier which resulted in smaller nanoparticles. The important contributions of ligand effects have also been quantified via first principles methods.\textsuperscript{12} Owen et al. studied the kinetics and nucleation for CdSe nanoparticle growth that was limited by precursor conversion.\textsuperscript{13} Several examples can be found that utilize on-line analysis in a flow scheme to characterize nanoparticle growth.\textsuperscript{6,14–16} However, this provides little advantage over ex-situ flask experiments.

In-situ techniques have the potential to provide a clearer look at particle growth as it occurs as well as the potential to access faster residence times. The first example of in-situ work was presented by Qu et al. by utilizing a reflecting dip-probe based UV-Vis absorbance system placed directly into the synthesis solution.\textsuperscript{17} This allows the measurement of the absorbance spectrum throughout the entire synthesis, from residence times of 0 seconds up to 20 minutes. They also measure the temperature after injection and observe that it takes about 30 seconds to equilibrate to the growth temperature setpoint, which is a limitation of flask based analysis. Qu and coworkers proposed no quantitative description of nanoparticle growth, just general observations that align with ex-situ analysis. Abecassis et al. utilized in-situ x-ray scattering to study the aggregative growth of CdSe nanoparticles.\textsuperscript{18} More recently, Abolhasini et al have demonstrated a oscillatory droplet reactor that repeatedly passes a droplet of reagents through a heated zone that includes in-situ absorbance measurement.\textsuperscript{19} They apply this system at temperatures up to 220 °C to study the growth of CdSe nanoparticles with each oscillatory pass. However, they make no kinetic measurements using this information. Lignos et al. developed a reactor coupled with absorbance and fluorescence measurements to study another quantum dot material, PbS.\textsuperscript{20} They measured the kinetics at fast time scales (<5 seconds) to quantify the growth of PbS nanoparticles. They determined that growth was dominated by Ostwald ripening after the first second of
growth. While the majority of these examples are relevant to CdSe synthesis, a number of studies have combined in-situ analysis to study other nanoparticle systems, most often for the characterization of aggregative growth.21-23

Much of the work presented in the literature has been focused on proof of concept rather than quantitative studies. Using a combination of an all glass microreactor and a translatable spectroscopy system, the work presented here provides quantitative measures of the kinetics of particle formation and growth for cadmium selenide nanoparticles, as well as a measure of the activation energies for both processes. A unique aspect to the synthesis shown here is its isothermal nature. Reagents are preheated before mixing together on the reactor. As a result, both particle formation and growth happen at a known and controlled temperature. This is in contrast to batch synthesis where typically one reagent is injected into another producing a temperature disturbance at nucleation.

4.2 Experimental

4.2.1 Materials

1-Octadecene (technical grade, 90%), oleic acid (technical grade, 90%), cadmium oxide, selenium powder, trioctylphosphine (97%), tributylphosphine (97%), trichloro(1H,1H,2H,2H-perfluorodecyl) silane (97%), sulfuric acid, hydrogen peroxide, and 2,2,4-trimethylpentane (anhydrous) were all purchased from Sigma-Aldrich. Filtered water (18 MΩ conductivity) from an in-house system was used. All chemicals were used as received without any further purification.

4.2.2 Flask Synthesis of Cadmium Selenide

128 mg cadmium oxide (CdO), 1.2 mL oleic acid (OA), and 5 mL octadecene (ODE) were added to a three-neck round bottom flask. Rubber septum stoppers were
attached to the left and right neck while a reflux column was attached to the middle neck. A glass capillary was pushed through the right septum until it was submerged 1 cm into the liquid. A thermocouple was then inserted into the capillary. A stir plate and heating mantle were placed under the flask. The temperature was regulated using a PID controller. The mixture was heated to 130 °C under vacuum and held for 30 minutes. The atmosphere was then switched to Argon and the mixture heated to 275 °C. 40 mg of selenium (Se) powder dissolved in 0.5 mL of trioctylphosphine (TOP) was loaded into a syringe. Once the CdO was fully dissolved in the flask, the Se/TOP mixture was quickly injected into the flask. The injection caused a slight drop in temperature but recovered within the first few minutes. The reaction was carried out for 10 minutes, after which the heating mantle was removed to cool the reaction mixture. The same procedure was repeated for setpoints of 225 °C and 175 °C. Small samples (<250 μL) were taken from the reaction mixture at various times using glass Pasteur pipettes and quickly quenched in a vial of toluene to be subsequently analyzed using UV-Vis spectroscopy.

4.2.3 Fabrication of Glass Microreactor

A general procedure for fabrication of glass microfluidics is presented here, with aspects taken from multiple sources. Borofloat 33 glass wafers (University Wafers) were first etched in 49% hydrofluoric acid for 10 seconds. Next, 150 nm of amorphous silicon was deposited using plasma enhanced chemical vapor deposition. SPR 220-7 photoresist was then spun on to a thickness of 1.5 μm and patterned using a transparency mask (CAD Art Services). The silicon was etched using reactive ion etching to expose the glass in the areas defined by the photoresist. The backside of the wafer was covered with a protective adhesive film (Nitto Denko Corp.) and the wafer was etched in 49% hydrofluoric acid for approximately 15 minutes to reach the desired etch depth of 100 μm.
The patterned wafer was bonded to a blank soda lime wafer using Crystalbond adhesive (Ted Pella Inc.) to prevent chipping during the drilling step. Holes were drilled at the inlets and outlets using 1 mm diamond drill bits. The patterned wafer was then separated from the soda lime blank. Next, the patterned wafer was thoroughly cleaned starting with an acetone bath to remove the photoresist, and then soaked in 45% potassium hydroxide to remove the amorphous silicon, followed by 10% hydrochloric acid to remove surface oxides. Afterwards, the patterned wafer and a blank wafer were soaked in Nanostrip (Cyantek Corp.) for at least 30 minutes. Both wafers were sonicated in water for 30 minutes, changing the water every 3 minutes. Each wafer was scrubbed for 3 minutes using melamine foam and dried thoroughly. The patterned and blank wafers were put into contact with each other and pressed together to form a contact bond. The wafers were sandwiched between graphite plates (Graphite Store) and bonded in a furnace at 670 °C for 6 hours. Finally, the bonded device was sectioned as necessary using a dicing saw.

Small sections of kapton capillary were epoxied at the inlets and outlets. Teflon tubing was joined to the kapton using Teflon shrink wrap.

4.2.4 Surface Modification of Glass Microreactors

The channels of the glass microreactor were modified using a procedure from Chan et al. Fluorinated silanes grafted to the hydroxyl groups of the glass surface prevent nucleation on the channel walls and extend the useful lifetime of the reactor. The microreactor was submerged in a water bath held at 80 °C while piranha solution (3:1 ratio of sulfuric acid to hydrogen peroxide) was pumped through the channels. This cleans the channels and oxidizes the glass surface. The microreactor was rinsed sequentially with water, isopropanol, and 2,2,4-trimethylpentane. The reactor was then dried with filtered nitrogen. 1.5 mL of 0.66 mM trichloro(1H,1H,2H,2H-
perfluorodecyl)silane in 2,2,4-trimethylpentane was then pumped through the reactor over the course of 1 h. Next, the reactor was rinsed sequentially with 2,2,4-trimethylpentane, isopropanol, and then water, followed by drying with filtered nitrogen. Finally, the microreactor was placed in an oven overnight held at 120 °C.

4.2.5 Microfluidic Synthesis of Cadmium Selenide

The CdSe synthesis described here was adapted from Chan et al.\textsuperscript{15} The cadmium solution was prepared by heating 170 mg CdO, 3.17 mL OA, and 6.83 mL ODE to 200 °C under an argon atmosphere. Once a clear solution formed, the temperature was lowered to 130 °C and the solution was left under vacuum for one hour to remove water from the solution. The trioctylphosphine/selenium solution (TOPSe) was prepared by sonicating 39.5 mg selenium powder with 0.428 mL trioctylphosphine (TOP) until a clear solution was formed. 9.57 mL ODE was then added to the solution. The tributylphosphine/selenium solution (TBPSe) was prepared by adding 39.5 mg selenium powder to 0.244 mL tributylphosphine (TBP) and stirring until a clear solution was formed. 9.76 mL ODE was then added to the solution. All solutions were degassed before each experiment using a TA Instruments degassing station held at 80 °C and 635 mmHg vacuum for at least 30 minutes. The cadmium solution slowly solidifies at room temperature so experiments were performed within 3 hours of the degassing step. No solidification was observed during this time.

Solutions were loaded into Hamilton gastight syringes and the flowrates controlled using syringe pumps. Cadmium, selenium, and ODE streams were combined using 2 t-junctions on the microreactor (\textbf{Figure 4-1A}). Each synthesis utilized either the TOPSe solution or the TBPSe solution. The cadmium and selenium streams were pumped in a 1:1 ratio while the ODE stream was kept at 10% of the total flowrate. The dedicated ODE stream provided a way to quickly flush the reactor with pure solvent. The
concentrations of Cd, Se, and ligand (TOP or TBP) were constant for all experiments. The only differences between experiments were temperature, ligand, and total flowrate. Four temperatures were used for this study; 230, 240, 250, and 260 °C. Each ligand and temperature combination was performed at two flowrates, 5 µL/min and 2.5 µL/min, to capture a wider range of timescale.

The temperature was measured using a thermocouple inserted into the heating mantle. The microreactor was aligned with a silicon wafer aperture and clamped to the aluminum heating mantle. The silicon wafer aperture had 400 µm holes drilled at appropriate locations to define areas for analysis. The temperature was controlled using a PID temperature controller (Auber Instruments).
Figure 4-1. Schematic of the microfluidic reactor. A) Three streams are mixed and then follow a winding channel pattern to the outlet. The dotted line shows the path the visible spectrometer is translated along for analysis. B) Cross section of the channel. The main channel width of 400 μm matches the size of the aperture used during analysis. The rounded ends of the channel are due to the isotropic wet etch used to fabricate the reactor.
4.2.6 In-situ Visible Spectroscopy Measurements

Spectra were acquired using an Ocean Optics USB4000-UV-VIS spectrometer. A custom motor controlled translatable stage moved the beam across the microreactor. A silicon wafer with 400 micron holes drilled at appropriate locations served as the aperture for the channels of the microreactor. The microreactor, silicon aperture, and heating mantle were carefully aligned, clamped together, and placed in the beam. Background spectra at each temperature setpoint were collected by flushing the channels with degassed octadecene.

The peak wavelengths were determined using a peak fitting algorithm that combined a quadratic background function with a Gaussian curve to fit the relevant section of data. This was especially useful for samples at low conversion but the algorithm was used for all samples to be consistent. The peak absorbance and the half width at half maximum (HWHM) were taken directly from the absorbance data. The particle radii and concentrations were determined from this information according to the empirical formula from Jasieniak et al.⁸

4.2.7 Measurement of Residence Time Distribution

The residence time distribution of the microreactor was measured at room temperature using water and food coloring. Pure water was pumped through the reactor at a flowrate of 5 μL/min. Once the channels had been purged completely with water, the water stream was turned off while a dye stream was turned on at 5 μL/min. This causes a step change in the concentration which is then measured at the furthest downstream analysis point. Spectra were constantly acquired until the measured concentration reached steady state. The process was repeated for a flowrate of 2.5 μL/min.
4.3 Results and Discussion

4.3.1 Ex-situ Flask Studies

Ex-situ analysis on batch synthesis of CdSe nanoparticles was initially performed to have a baseline for comparison to later in-situ work. Figure 4-2 shows the nanoparticle radius as the reaction progresses for the synthesis at several temperatures. The reaction progressed more quickly at higher temperatures, as expected. At 175 °C the reaction occurred across the entire 10 minute reaction time, whereas at 275 °C the nanoparticles showed almost complete growth in the first minute. The higher temperature synthesis produced larger nanoparticles. This was an unexpected result. It is generally assumed that the activation energy for growth is lower than the activation energy for nucleation. This means that as temperature increases, the kinetics of nucleation should increase more rapidly than the kinetics of growth. The expected result from this trend is that more nucleation occurs at higher temperature and the resulting particle size should be smaller.
Figure 4-2. Nanoparticle radius over time for samples synthesized in a flask reactor at temperatures of 275, 225, and 175 °C.
4.3.2 In-situ Absorbance Measurements of Cadmium Selenide Formation and Growth

The reactor arrangement used for in-situ analysis is shown in Figure 4-3. As the reagents flow from left to right, the solution color changes. The color and intensity as measured by visible spectroscopy provide a direct quantitative measure of the particle size and concentration. A time series of in-situ absorbance spectra is shown in Figure 4-4. Each spectra is separated by 2.5 cm of channel length, which equates to 17 s for a flowrate of 5 μL/min. As the residence time increases, the peak absorbance is shifted to higher wavelengths and the peak intensity increases.

The absorbance spectra provides a measure of the average nanoparticle radius and the nanoparticle concentration. The HWHM for most spectra tended to be in the range of 25-27 nm. The broad nature of the peaks in these experiments is due to the residence time distribution in the reactor, time dependent nucleation, and thermal broadening of the peaks.

Figure 4-5 shows growth curves for both ligands at 230 °C, 240 °C, 250 °C, and 260 °C. Both ligands show larger nanoparticle formation at higher temperatures. This is the same trend observed in the ex-situ samples. At the lowest temperature, 230 °C, TBP and TOP yield similar size nanoparticles. Increasing temperature has a more dramatic effect on nanoparticle size in the TBP system than the TOP. At 260 °C the TBP ligand yields an 11% larger nanoparticle than TOP.
Figure 4-3. Photograph of a microreactor during CdSe synthesis at 250 °C. The holes in the silicon wafer aperture are visible behind the channels, with the farthest right being illuminated by the beam.
Figure 4-4. In-situ absorbance plots of CdSe synthesis at 240 °C using a trioctylphosphine ligand at a flowrate of 5 μL/min. The residence times ranged from 9 – 163 s with 17 s between spectra.
Figure 4-5. Nanoparticle radius as a function of residence time for A) trioctylphosphine and B) tributylphosphine at temperatures of 230, 240, 250, and 260 °C. Each set is a combination of the data from both flowrates.
Traditional flask synthesis involves an injection of one reagent into another. This injection helps to separate the nucleation and growth stages of the synthesis. In isothermal microfluidic synthesis, continual time-dependent nanoparticle formation is observed as shown in Figure 4-6. Under some conditions, new particle formation occurs for as long as two minutes. This is a unique perspective offered by studying nanoparticle growth in-situ using a microreactor. For each given ligand system, higher temperatures yield fewer nanoparticles. This is an expected parallel to the observation of larger nanoparticles at higher temperatures. A more quantitative explanation of the driving forces during synthesis requires kinetic modeling of the data.
Figure 4-6. Nanoparticle concentration with time for various synthesis conditions. A) TOP 230 °C B) TOP 240 °C C) TOP 250 °C D) TOP 260 °C E) TBP 230 °C F) TBP 240 °C G) TBP 250 °C H) TBP 260 °C.
4.3.3 Kinetic Model for Nanoparticle Formation and Growth

A kinetic model was developed to fit the two datasets of nanoparticle radius versus time and nanoparticle concentration versus time. Both processes were assumed to be first order. Monomer refers to CdSe monomer units in solution, as described by Liu et al.\textsuperscript{26} and Steckel et al.\textsuperscript{27} The rate limiting processes were assumed to be formation of new nanoparticles and nanoparticle growth, as described below.

\[ \frac{dN(t)}{dt} = k_1[C_M(t) - C_{M,SS}] \quad \text{Eq. 1} \]

\[ \frac{dC_M(t)}{dt} = -k_2[C_M(t) - C_{M,EQ}][N(t) \ast 4\pi r^2] - \left[ \frac{dN(t)}{dt} \right] \frac{4}{3} \pi r^3 V_m^{-1} \quad \text{Eq. 2} \]

\[ C_M(t = 0) - C_M(t) = N(t) \cdot \frac{4}{3} \pi r^3 \cdot V_m^{-1} \quad \text{Eq. 3} \]

Eq. 1 describes the rate of nanoparticle formation using a rate constant of $k_1$. The concentration driving force is the monomer concentration that is above the supersaturation concentration limit ($C_{M,SS}$). New nanoparticle formation stops once the monomer concentration reaches $C_{M,SS}$.

Eq. 2 describes the rate of monomer conversion. It is comprised of two terms. The first term describes the monomer consumption due to nanoparticle growth. The growth term is proportional to the available monomer concentration and the total nanoparticle surface area. The available monomer concentration is the concentration of monomer above the final equilibrium concentration ($C_{M,EQ}$). The second term describes the monomer consumption due to new particle formation. This term assumes that new nanoparticles rapidly grow to the current average nanoparticle radius and is a simplification of what actually occurs. This simplification fails to capture the size broadening caused by continual nanoparticle formation.
The final equation, Eq. 3, gives the relationship between particle size and monomer consumption. $V_m$ is the molar volume of CdSe nanoparticles.

An analytical solution for the model was not readily obtained. A numerical approach was used to obtain best fit values for $k_1, k_2, C_{M,SS}, C_{M,EQ}$, and $r_0$, the initial radius. For each temperature both the nanoparticle concentration and radii datasets were simultaneously fit, which includes both flowrates. Figure 4-7 shows an example fit for synthesis with TOP at 240 °C. The results for the kinetic fit of all the data are summarized in Table 4-1. As expected, the rates of particle formation and growth increase with temperature. The rate constants were fit using an Arrhenius equation to extract the activation energies, as shown in Figure 4-8. In both systems, the activation energy for nanoparticle formation is about 25 kJ/mol higher than the activation energy for growth. Additionally, both activation energies are significantly higher in the TBP synthesis than for TOP. This shows one of the significant ways ligand choice can impact nanoparticle growth.

An interesting trend is present in the supersaturation concentration threshold, $C_{M,SS}$. As temperature increases, $C_{M,SS}$ increases significantly. This shows that even though the nanoparticle formation rate constant ($k_i$) increases with temperature, the concentration driving force is lower at higher temperatures. According to the model presented, higher monomer solubility is responsible for the decreasing nanoparticle concentration observed with increasing temperature. As a result, fewer nanoparticles form at higher temperatures which subsequently grow to a larger size.
Figure 4-7. Comparison of the experimental data and kinetic fit for trioctylphosphine synthesis at a temperature of 240 °C. The resulting fit parameters are $k_1 = 8.4 \times 10^{-5} \text{s}^{-1}$, $k_2 = 9.2 \times 10^{-7} \text{cm}\cdot\text{s}^{-1}$, $C_{M,SS} = 10.4 \text{mM}$, $C_{M,EQ} = 6.1 \text{mM}$ with an initial radius of 1.1 nm.
Table 4-1. Summary of the kinetic parameters for CdSe nanoparticle formation and growth

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>$k_1$ (s$^{-1}$)</th>
<th>$k_2$ (cm·s$^{-1}$)</th>
<th>$C_{M, EQ}$ (mM)</th>
<th>$C_{M, SS}$ (mM)</th>
<th>$r_0$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOP</td>
<td>TBP</td>
<td>TOP</td>
<td>TBP</td>
<td>TOP</td>
</tr>
<tr>
<td>230</td>
<td>$6.5 \times 10^{-5}$</td>
<td>$5.2 \times 10^{-5}$</td>
<td>$8.2 \times 10^{-7}$</td>
<td>$4.3 \times 10^{-7}$</td>
<td>6.8</td>
</tr>
<tr>
<td>240</td>
<td>$8.4 \times 10^{-5}$</td>
<td>$4.7 \times 10^{-5}$</td>
<td>$9.2 \times 10^{-7}$</td>
<td>$7.1 \times 10^{-7}$</td>
<td>6.1</td>
</tr>
<tr>
<td>250</td>
<td>$1.3 \times 10^{-6}$</td>
<td>$1.1 \times 10^{-6}$</td>
<td>$1.2 \times 10^{-6}$</td>
<td>$1.3 \times 10^{-6}$</td>
<td>6.4</td>
</tr>
<tr>
<td>260</td>
<td>$1.9 \times 10^{-6}$</td>
<td>$4.3 \times 10^{-6}$</td>
<td>$1.7 \times 10^{-6}$</td>
<td>$2.6 \times 10^{-6}$</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Figure 4-8. Arrhenius plots for the rate constants of A) formation ($k_1$) and B) growth ($k_2$).
4.4 Conclusions

In-situ visible spectroscopy and isothermal nanoparticle synthesis were successfully combined to quantify the growth of CdSe nanoparticles in the temperature range of 230–260 °C. Time dependent nanoparticle formation and growth were measured and a kinetic model was developed to fit both processes. The resulting temperature dependent rate constants provided a measure of the activation energies for nanoparticle formation and growth. TBP showed significantly higher activation energies than TOP, showing one way ligand identity can impact nanoparticle growth.

Larger nanoparticles were observed at higher temperatures. This is attributed to increasing monomer solubility at higher temperature.

4.5 References

(3) Yang, Y. A.; Wu, H.; Williams, K. R.; Cao, Y. C. Angew. Chem. 2005, 117 (41), 6870–6873.


4.6 Supplemental Information

4.6.1 Peak Fitting Algorithm

The peak wavelength was determined using a peak fitting algorithm that combines a quadratic background function with a Gaussian function. An example fit is shown in Figure 4-9. This procedure was used for all results and proved especially useful for low signal levels where manually determining a precise position would be difficult.
Figure 4-9. Demonstration of the peak fitting results. A quadratic background function and a Gaussian peak are combined and fit to the experimental data. The resulting Gaussian position is used as the peak wavelength for analysis.
The peak absorbance and half width at half maximum (HWHM) were taken straight from the data using the peak wavelength. A comparison between an in-situ spectrum and a quenched room temperature spectrum are shown in Figure 4-10. The difference in peak wavelength position agrees well with the work from Qu et al.\textsuperscript{17} who measured a 25 nm difference between room temperature and 250 °C spectra for all nanoparticles sizes. Similarly, Qu et al. measured about a 30% thermal broadening which agrees well with the HWHM values shown.
Figure 4-10. Comparison of in-situ and ex-situ spectra. The peak wavelengths and half width half maximums are shown by the dotted lines and labels. The ex-situ spectrum was adjusted for path length and dilution for comparison with the in-situ spectrum.
4.6.2 Residence Time Distribution Considerations

The residence time distribution (RTD) for the reactor was measured using water and food dye. This provides only an approximation to the RTD during synthesis since there are differences in viscosity, density, and diffusivity. Two streams were utilized for the measurement. First, a stream of pure water was flushed through the system and then maintained at the desired flowrate. RTDs for 2.5 and 5 μL/min were measured. The system was allowed to equilibrate, and then the water stream was turned off and a dye stream was turned on at the desired flowrate. Ideally, this should cause minimal disturbance in the pressure at the inlets and a step function change in dye concentration. Absorbance spectra of the dye were taken at the furthest analysis point on the reactor. The normalized concentration over time in response to the step change \( F(t) \) was monitored and its relationship to the RTD \( E(t) \) is shown in Eq. 4.

\[
F(t) = \int_0^t E(t) \, dt \tag{Eq. 4}
\]

\[
E(t) = \frac{d}{dt} F(t) \tag{Eq. 5}
\]

The RTD can be estimated according to Eq. 5 but will suffer from the noisy approach of taking numerical derivatives of data. An example \( F(t) \) curve is shown in Figure while the RTDs for 5 and 2.5 uL/min are shown in Figure 4-11. Overall the RTD looks similar to plug flow with dispersion. The relatively low velocities in these experiments means that mixing by diffusion (particularly in the transverse dimensions) minimizes the negative aspect of laminar flow.
Figure 4-11. A) $F(t)$ curves for the microfluidic reactor at the flowrates used in this study.

B) Residence time distributions calculated from the data shown in A.
Chapter 5

Isothermal Titration Calorimetry Measurements of the Cation Exchange of Cadmium Selenide Nanoparticles

5.1 Introduction

The ability to chemically adjust a nanoparticle post-synthesis is a useful way of extending the usefulness of syntheses that have already been developed. Cation exchange is a method of post-synthesis modification that involves the spontaneous replacement of the cation in a crystal lattice. Cation exchange has been demonstrated in a variety of materials as a way to adjust particle composition both with\textsuperscript{1–4} and without\textsuperscript{5,6} changes to the morphology. The expertise to synthesize one material at a desired size and shape has the potential to be easily expanded to several materials.\textsuperscript{2} Cation exchange can also allow access to metastable phases.\textsuperscript{7} Not only is complete conversion possible, but minute doping has also been demonstrated.\textsuperscript{8–10} While it is not the focus of this work, anion exchange has also been demonstrated as a way to control particle composition\textsuperscript{11,12} and morphology\textsuperscript{13}.

A more thorough understanding of the kinetics and thermodynamics present in cation exchange would provide a deeper understanding of the process as well as finer control over the exchange. Mechanistic theory for the specific steps of cation exchange has been developed using both simulations\textsuperscript{14} and experimental observations\textsuperscript{15,16}. Kinetic measurements for cation exchange have been presented\textsuperscript{17}, but there has been no quantitative discussion about the thermodynamics of cation exchange. A number of developing technologies\textsuperscript{18–22} could benefit from a quantitative understanding of the thermodynamics of cation exchange.
Isothermal titration calorimetry (ITC) has the potential to shine light on the thermodynamic contributions present in the reaction. Previously, ITC has found use in studying the thermodynamics of various nanoparticle interactions. ITC possesses the sensitivity to study interactions between nanoparticle surfaces and various biomolecules including amino acids\(^{23}\) and DNA\(^{24}\). Ravi et al. studied the formation of self-assembled monolayers of alkanethiols onto gold nanoparticle surfaces.\(^{25}\) These examples demonstrate the versatility ITC possesses for applications involving nanoparticles. It is expected that the chemistry of the nanoparticle interface will play an important role in cation exchange as well. This shows the intersection previous studies could have with ITC measurements of cation exchange. Other factors that likely impact the thermodynamics of cation exchange are nanoparticle size, solvent choice, stabilizing ligand, and most obviously, cation source. ITC has the potential to provide insight into each of these aspects.

Here we present thermodynamic measurements on the cation exchange of CdSe nanoparticles with silver using ITC. An overview of the modeling is presented, as well as discussion on the choice of experimental parameters.

5.2 Experimental

5.2.1 Materials

Toluene and methanol were acquired from VWR. Silver perchlorate, silver nitrate, and copper nitrate were acquired from Sigma-Aldrich. All chemicals were used without further purification. A multi-element standard (ICP-MCS-1) was acquired from High Purity Standards.

Cadmium selenide (CdSe) nanoparticles were also acquired from Sigma-Aldrich. Six different types of Sigma-Aldrich Lumidot CdSe nanoparticles were acquired with
fluorescence emissions of 480, 520, 560, 690, 610, and 640. These samples are referred as LDXXX where XXX is the fluorescence emission wavelength, e.g. LD480. All the Lumidot samples except LD640 are hexadecylamine capped nanoparticles, while the LD640 is capped with hexadecylamine and trioctylphosphine oxide. The sizes for LD480 – LD640 as reported by Sigma-Aldrich are 2.2, 2.5, 3.3, 4.2, 5.0, and 7.0 nm, respectively. These samples were selected to provide a broad size range for investigation.

5.2.2 Measurement of Concentrations via Inductively Coupled Plasma

Inductively coupled plasma optical emission spectroscopy (ICP-OES) was used to determine the concentration of Cd and Se in CdSe nanoparticle samples. An Agilent 725 ICP-OES equipped with a radial torch and a OneNeb nebulizer was used for analysis.

Solutions for ICP analysis were prepared as follows. 50 μL of sample was transferred to a clean vial. The solvent was allowed to evaporate. 1 mL of aqua regia (1 part nitric acid and 3 parts hydrochloric acid) was added to digest the CdSe and the solution was left undisturbed for 1 hour. The sample was then diluted to 25 mL using a volumetric flask. Digestion times of 1 h and 24 h provided the same results within experimental error, so all samples utilized a 1 h digestion time.

Calibration standards were prepared by adding an appropriate amount of stock standard solution, hydrochloric acid, and nitric acid as shown in Table 5-1. Each standard solution was diluted to 25 mL using a volumetric flask. Both the samples and standards consisted of 4% aqua regia by volume.
Table 5-1. Preparation of ICP-OES calibration standard solutions.

<table>
<thead>
<tr>
<th>Label</th>
<th>Stock Solution Volume (mL)</th>
<th>Nitric Acid Volume (mL)</th>
<th>Hydrochloric Acid Volume (mL)</th>
<th>Final Cd Concentration (μM)</th>
<th>Final Se Concentration (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard 1</td>
<td>0.01</td>
<td>0.250</td>
<td>0.75</td>
<td>0.356</td>
<td>1.01</td>
</tr>
<tr>
<td>Standard 2</td>
<td>0.1</td>
<td>0.248</td>
<td>0.75</td>
<td>3.56</td>
<td>10.1</td>
</tr>
<tr>
<td>Standard 3</td>
<td>1</td>
<td>0.230</td>
<td>0.75</td>
<td>35.6</td>
<td>101</td>
</tr>
<tr>
<td>Standard 4</td>
<td>10</td>
<td>0.050</td>
<td>0.75</td>
<td>356</td>
<td>1010</td>
</tr>
</tbody>
</table>
5.2.3 Isothermal Titration Calorimetry Measurements

Isothermal titration calorimetry (ITC) measurements were performed on a TA Instruments NanoITC with 1 mL hastelloy sample and reference cells. All analyses were carried out at 25 °C. A stirring rate of 200 rpm was used for all experiments to introduce minimal noise. The experiments were generally carried out using a solvent system of 80% toluene and 20% methanol (discussed in 5.3.2), any deviation from this will be specified. Peak integration was performed using TA Instruments NanoAnalyze software. All other data analysis functions were performed using custom Mathematica programs.

5.2.4 UV-Visible Spectroscopy of CdSe Cation Exchange

The cation exchange of CdSe with silver was characterized using UV-Vis spectroscopy. The experiment was carried out in a manner similar to the ITC experiments. 3.0 mL of 0.5 mM CdSe (Se basis) was loaded into the sample vial of a dual beam spectrometer. A spectrum of the unmodified CdSe was then taken. 15 μL of 5 mM AgClO4 was injected into the vial and the solution was mixed. A spectrum of the partially cation exchanged CdSe was then measured. The process of injection and measurement was repeated until there was no observable difference in the resulting absorbance spectrum.

5.3 Results and Discussion

5.3.1 ITC Model for Cation Exchange

Isothermal titration calorimetry is traditionally used to investigate the binding thermodynamics of biomolecules (proteins, enzymes, DNA). The models typically applied to these systems do not apply to the cation exchange of CdSe. A more traditional chemical thermodynamic analysis was performed. The net reaction for cation exchange is shown in Eq 1.
Cation exchange in solution is a complex process made up of several elementary steps.\textsuperscript{26,27}

\begin{equation}
Cd - Se \leftrightarrow Cd + Se \quad \text{Eq. 2}
\end{equation}

\begin{equation}
Ag^+ \leftrightarrow Ag \quad \text{Eq. 3}
\end{equation}

\begin{equation}
2Ag + Se \leftrightarrow Ag_2Se \quad \text{Eq. 4}
\end{equation}

\begin{equation}
Cd \leftrightarrow Cd^{2+} \quad \text{Eq. 5}
\end{equation}

These include bond dissociation (Eq. 2), desolvation of the new cation (Eq. 3), bond formation (Eq. 4), and solvation of the original cation (Eq. 5). ITC measurements quantify the net reaction as shown in Eq. 1. The approach used in this study does not utilize any nanoparticle concentrations. Any concentrations presented are the concentration in the cell or syringe for compounds listed in Eq. 1. The relationship for the equilibrium constant for Eq. 1 is shown in Eq. 6.

\begin{equation}
K_{eq} = \frac{[Ag_2Se][Cd^{2+}]}{[CdSe][Ag^+]^2} \quad \text{Eq. 6}
\end{equation}

The specifics of data analysis are presented in further detail in the supplemental information. The presented equilibrium constants, $K_{eq}$, and the enthalpy of reaction, $\Delta H_R$, are in terms of Eq. 1 and Eq. 2.

5.3.2 Selection of Appropriate Solvent

Traditional ITC experiments typically utilize water as a solvent. However, without modification, CdSe nanoparticles tend to be capped in ligands that are not water soluble. With proper precautions, it is trivial to perform ITC measurements in organic solvents. The original aim was to mimic the prototypical cation exchange of CdSe in toluene using
methanolic silver nitrate. However, the heat of solution when mixing solvents ends up being the dominating thermodynamic effect in those experiments and the heat evolved from cation exchange is lost in the noise. Even injecting 10% methanol / 90% toluene solutions into pure toluene provides heat signals too large for ITC analysis. This means characterizing cation exchange using ITC will require different conditions. This led to the requirement that both the cell solution and the syringe solution would need to be identical with respect to solvent composition. Without imposing this requirement, the heat of solution is the domination effect. Several solvent systems are presented here. Initially a pure toluene system was used with the silver salt being silver perchlorate. It is the only toluene soluble silver salt; there is no similar analogue for other cation exchange relevant metals. Any work presented beyond silver perchlorate utilizes a 20% methanol / 80% toluene solvent. This provides adequate solubility of various metal salts while still keeping the CdSe nanoparticles dispersed.

5.3.3 The Importance of Control Experiments

It is worth emphasizing the importance of control experiments in ITC experiments. Typically, ITC experiments utilize control runs to quantify the thermodynamic effects of dilution, as well as any interactions between the two molecules of interest and the buffer solutions. These are then used to provide more quantitatively accurate thermodynamic information for the binding of the two molecules of interest. However, the interactions present in the cation exchange of CdSe present more significant hurdles. In several cases during this work, it has been observed that the metal salt injected into the cell shows a significant interaction, even when CdSe is not present. This points towards interactions with the cell wall or the outside of the injection syringe. An example of this is shown in Figure 5-1. The concentration ranges used in the control experiment were the same as similar cation exchange experiments. This means the
behavior during a cation exchange is the simultaneous and competing interactions of both cation exchange and binding with the cell wall. Due to the irreproducible nature of the control experiment, it was determined that this could not be compensated for. The interactions with the cell wall would overall play a less significant role if the concentrations of both the silver salt and CdSe were increased by an order of magnitude; however, this consumes too much CdSe in a given run to be useful. Overall, these factors meant AgClO$_4$ was unsuitable for ITC cation exchange measurements. Instead, AgNO$_3$ in a mixed solvent system was used.
Figure 5-1. ITC control experiment for cation exchange. A) The thermogram that results from injecting 2.5 mM AgClO$_4$ into pure solvent. B) The integrated peak data for the control experiment.
Transitioning to a mixed solvent system enabled successful thermodynamic measurements of CdSe cation exchange with silver. However, these measurements showed a significant variability from run to run. Overall the heat of reaction was predictable, but the inflection point of the sigmoid could vary +/- 10% between runs. This is shown in Figure 5-2. To address this variability, all silver cation exchange results are the average of 3 runs. The resulting integrated heat data for nanoparticle sizes (LD480 – LD640) are shown in Figure 5-3. Overall there seems to be no predictable patterns as a function of nanoparticle size.

For simple experiments where only one equilibrium reaction is occurring, the first few data points should have very similar values. However, this is not observed in this data, which implies there is another interaction occurring during the first few injections. A number of explanations that may explain this behavior are proposed here, however each requires extensive testing to evaluate. (1) The cation exchange could occur in a two-step mechanism with multiple equilibria. An example could be the accumulation of silver on the nanoparticle surface before integration into the nanoparticle. (2) Interactions between the cell wall and stirrer with the AgNO₃. While control experiments were run to evaluate this, the control experiments were inconsistent and interactions may have been missed. (3) When an experiment starts, the cell contains ligand-stabilized CdSe nanoparticles, as well as presumably free ligand in solution. The first few injections could involve the interaction of silver ions with the free ligand in solution, resulting in a multi-sigmoidal behavior. (4) Residual reagents that remain in the cell run to run. It is difficult to develop cleaning procedures that can effectively remove small deposits of CdSe and Ag₂Se nanoparticles while at the same time not harming the hastelloy of the ITC cells.
Figure 5-2. Integrated heat data for three different runs of identical conditions for the cation exchange of LD590 CdSe nanoparticles with silver.
Figure 5-3. Integrated heat data for the cation exchange of various sized CdSe nanoparticles with silver. The dashed line is the stoichiometric ratio for cation exchange (2).
The resulting fit of the data presented in Figure 5-3 with the model presented in section 5.3.1 is shown in Figure 5-4. The model yields values for $K_{eq}$ and $\Delta H_R$. From these values, the Gibbs free energy of the reaction as well as the entropic contributions to the Gibbs free energy can be determined according to Eq. 7 and Eq. 8.

$$\Delta G_R = -RT \ln K_{eq} \quad \text{Eq. 7}$$

$$\Delta G_R = \Delta H_R - T \cdot \Delta S_R \quad \text{Eq. 8}$$

The thermodynamic results are summarized in Table 5-2. No trend was observed for any parameters as the nanoparticle size changed. The average enthalpy of reaction for all nanoparticle sizes was $-141$ kJ/mol, while the average Gibbs free energy of reaction for all nanoparticle sizes was $-27.3$ kJ/mol.

The results presented here are specific for the cation exchange of CdSe with AgNO$_3$ in a solvent system of 20% methanol in toluene. It is expected that the solvent system plays a significant role in the thermodynamics of the exchange. The net reaction presented in Eq. 1 is a summary of the elementary steps shown in Eq. 2 – Eq. 5. The solvent used has a significant effect on these steps of the cation exchange, and as a result, the overall thermodynamics of the process.
Figure 5-4. Integrated heat data and corresponding model fit for the cation exchange of CdSe with silver. A) LD480 B) LD520 C) LD560 D) LD590 E) LD610 F) LD640
Table 5-2. Summary of the thermodynamic parameters for the cation exchange of CdSe samples with silver.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$K_{eq}$ (M$^{-1}$)</th>
<th>$\Delta G_R$ (kJ/mol)</th>
<th>$\Delta H_R$ (kJ/mol)</th>
<th>$T \cdot \Delta S_R$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD480</td>
<td>$5.6 \times 10^4$</td>
<td>-27</td>
<td>-146</td>
<td>-119</td>
</tr>
<tr>
<td>LD520</td>
<td>$6.9 \times 10^4$</td>
<td>-28</td>
<td>-141</td>
<td>-113</td>
</tr>
<tr>
<td>LD560</td>
<td>$1.1 \times 10^5$</td>
<td>-29</td>
<td>-141</td>
<td>-112</td>
</tr>
<tr>
<td>LD590</td>
<td>$2.1 \times 10^4$</td>
<td>-25</td>
<td>-143</td>
<td>-118</td>
</tr>
<tr>
<td>LD610</td>
<td>$1.0 \times 10^5$</td>
<td>-29</td>
<td>-133</td>
<td>-104</td>
</tr>
<tr>
<td>LD640</td>
<td>$5.4 \times 10^4$</td>
<td>-27</td>
<td>-144</td>
<td>-117</td>
</tr>
</tbody>
</table>
5.3.5 Insights into Cation Exchange From UVVis Spectroscopy

ITC measurements of the cation exchange of CdSe provide a bulk view of the thermodynamics of the exchange, however, they do not provide any insight into the mechanism of the exchange. This motivated analysis of the exchange using UVVis spectroscopy. The goal was to mimic the conditions present in the ITC experiment and characterize the solution at each injection. The results of this measurement are shown in Figure 5-5. The plasmon of the CdSe is observed to diminish with each injection, while the overall background absorbance increases at all wavelengths. This was quantified using a linear combination fit (LCF) using the initial and final spectra. The results are shown in Figure 5-6. The LCF was not forced to sum to one, however, the contributions generally held very close to a total of one. The linear trend of the LCF and the natural summation to one implies something about the mechanism of the cation exchange. The fact that each injection can be described as a combination of the pure materials (CdSe and Ag₂Se) implies that at each injection there is a population of unmodified CdSe and a population of fully converted Ag₂Se. The alternative mechanism would be that each nanoparticle undergoes a partial conversion. However, a partially converted CdSe nanoparticle would exhibit a modified plasmon absorbance. This general observation is supported by results presented elsewhere.¹⁷,¹⁵
Figure 5-5. Absorbance measurements of the cation exchange of CdSe with silver. Silver was dosed into the system in fixed amounts between spectra. The final injection shown corresponds to a stoichiometric amount of silver.
Figure 5-6. Linear combination fit of the intermediate spectra at each injection.
5.4 Conclusions

Isothermal titration calorimetry was successfully performed to quantify the thermodynamics of cation exchange in CdSe nanoparticles. A mixed solvent system was used that allowed the successful simultaneous solvation of CdSe nanoparticles and silver nitrate. No size dependence of the thermodynamic properties was observed for particles ranging from 2.2 – 7.0 nm. UV-Vis measurements at various points of cation exchange were performed and support the mechanism of individual nanoparticles tending to fully convert between phases, rather than nanoparticles of mixed composition.

5.5 References


5.6 Supplemental Information

5.6.1 Concentration of CdSe by ICP

The concentrations determined using ICP-OES for the Lumidot CdSe nanoparticles are reported in Table 5-3. The sizes as reported by Sigma-Aldrich are also provided for reference.
Table 5-3. Summary of properties of Lumidot CdSe nanoparticles.

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Diameter (nm)</th>
<th>Cd Concentration (μM)</th>
<th>Se Concentration (μM)</th>
<th>Cd:Se Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD480</td>
<td>2.2</td>
<td>11.3</td>
<td>9.0</td>
<td>1.25</td>
</tr>
<tr>
<td>LD520</td>
<td>2.5</td>
<td>12.7</td>
<td>11.7</td>
<td>1.08</td>
</tr>
<tr>
<td>LD560</td>
<td>3.3</td>
<td>18.4</td>
<td>15.3</td>
<td>1.20</td>
</tr>
<tr>
<td>LD590</td>
<td>4.2</td>
<td>21.7</td>
<td>17.9</td>
<td>1.21</td>
</tr>
<tr>
<td>LD610</td>
<td>5.0</td>
<td>19.9</td>
<td>17.1</td>
<td>1.16</td>
</tr>
<tr>
<td>LD640</td>
<td>7.0</td>
<td>17.2</td>
<td>15.6</td>
<td>1.10</td>
</tr>
</tbody>
</table>
5.6.2 Data Analysis of Cation Exchange ITC Experiments

The data is fit in a numerical fashion where a value of $K_{eq}$ and $\Delta H_R$ is proposed, the corresponding integrated heats are calculated, and then the calculated integrated heats are compared to the experimental. A least squares procedure minimizes the difference between these two data sets by varying $K_{eq}$ and $\Delta H_R$ until acceptable agreement is found between the two datasets.

The total amount of selenium and silver after each injection is known. For the case of selenium, this is the sum of all CdSe and Ag$_2$Se in the system. Similarly, for silver, the total amount of silver in the system is a combination of silver salt in solution and Ag$_2$Se. The total concentrations of selenium ([Se$_{Total}$]) and silver ([Ag$_{Total}$]) after each injection (i) can be calculated according to Eq. 9 and Eq. 10.

\[
[\text{Se}_{Total}]_i = [\text{Se}]_0 \times \left(\frac{V_c - V_i}{V_i}\right)^{i-1} \quad \text{Eq. 9}
\]

\[
[\text{Ag}_{Total}]_i = \left(\left[\text{Ag}_{Total}\right]_{i-1} \cdot (V_c - V_i) + [\text{Ag}_{Syringe}] \cdot V_i\right) \frac{1}{V_c} \quad \text{Eq. 10}
\]

Each injection displaces a small volume of reagents from the cell. This is taken into account in both Eq. 9 and Eq. 10, where $V_c$ is the cell volume and $V_i$ is the volume of an injection. $[\text{Se}]_0$ is the concentration of CdSe (Se basis) present in the cell at the beginning of the experiment. $[\text{Ag}_{Syringe}]$ is the concentration of AgNO$_3$ in the syringe.

The concentrations after equilibration are determined according to Eq. 11. First, the value for $x$ is determined, then the concentration of each species after equilibration can be easily calculated.

\[
K_{eq} = \frac{[\text{Ag}_2\text{Se}][Cd^{2+}]}{[\text{CdSe}][\text{Ag}^+]^2} = \frac{x \times x}{([\text{Se}_{Total}]_i - x) ([\text{Ag}_{Total}]_i - 2x)^2} \quad \text{Eq. 11}
\]
Once the concentration of each species has been determined, the heat of a given injection can be calculated according to Eq. 12. The net production of Ag$_2$Se is multiplied by the heat of reaction.

$$H_i = \left[ [Ag_2Se]_i \ast V_c - [Ag_2Se]_{i-1} \ast (V_c - V_i) \right] \Delta H_R$$  \hspace{1cm} \text{Eq. 12}

5.6.3 Preliminary Results of Copper Cation Exchange

The cation exchange of CdSe nanoparticles with copper was also performed, however triplicates have not yet been carried out. The copper source was copper (II) nitrate. The overall reaction is shown in Eq. 13.

$$CdSe + Cu^{2+} \leftrightarrow CuSe + Cd^{2+}$$  \hspace{1cm} \text{Eq. 13}

Preliminary results for the copper exchange are shown in Figure 5-7. The average enthalpy of reaction for all nanoparticle sizes is approximately -35 kJ/mol.
Figure 5-7. Integrated heat data for the cation of CdSe nanoparticles with copper (II). The dashed line corresponds to an enthalpy of reaction of -35 kJ/mol for the injection volume and concentration used in these experiments.
Chapter 6

Conclusions and Future Work

6.1 Conclusions of the Dissertation

The overall goal of the work presented in this thesis has been the development of new analytical tools for studying nanoparticle growth. The primary focus has been on in-situ microfluidic techniques. To this end, a number of microfluidic platforms have been developed and presented. Each platform comes with advantages and disadvantages and the take-away is that each system requires careful consideration and planning. Simple polydimethylsiloxane based reactors have been presented that are ideal for low temperature aqueous work. Teflon tubing based microreactors have been demonstrated that provide a simple low cost platform capable of synthesis up to 200 °C and pressures up to 6 bar. Several transition metal nanoparticle syntheses were successfully adapted to a flow scheme, including gold, silver, and platinum. This platform was successfully coupled with x-ray absorption spectroscopy for proof of concept kinetic measurements of the reduction of platinum salts by the polyol method. All glass microreactors were developed that are capable of harsh synthetic conditions and should prove to be a versatile analytical tool. During the work of this thesis, these reactors have been taken to temperatures up to 260 °C for the synthesis of cadmium selenide nanoparticles. While the all glass microreactors are capable of high temperatures, their cost and complexity has motivated the development of a more convenient and cheaper alternative. This resulted in the development of glass-PDMS hybrid reactors which consist of two glass slides and a thin PDMS membrane between them that defines the channels. This low cost reactor can be fabricated entirely outside of a cleanroom. This platform allows the
generation of precise channel heights of 0.1 mm and higher. This provides accurate and tune-able path lengths for in-situ spectroscopic work.

The design, construction, and evaluation of a translatable visible spectrometer have been presented. The general aim was to build a system capable of acquiring quantitatively accurate spectra on microfluidic channels. This was successfully demonstrated and the important considerations discussed. The first successful iteration of this system relies on an aperture placed directly against the microreactor channels to limit the light reaching the spectrometer. This was achieved using a silicon wafer aperture with 400 μm holes drilled at appropriate locations and aligned with the microreactor.

All glass microreactors were successfully coupled with the translatable visible spectrometer to study the formation of cadmium selenide nanoparticles. A fully isothermal synthesis was demonstrated and characterized in the temperature range of 230 – 260 °C. The impact of stabilizing ligand was studied for trioctylphosphine and tributylphosphine. The kinetics of both nucleation and growth were measured and modeled. The activation energies for nucleation and growth were calculated. The ligand choice had a significant effect on the activation energies of both nucleation and growth, as well as an effect on the monomer solubility in solution. A lower concentration driving force behind nucleation was observed at higher temperatures, which resulted in fewer but larger nanoparticles with increasing temperature. While it is generally expected that monomer solubility would increase as temperature increases, this type of study provides specific measures that are not possible in batch synthesis and are unique to isothermal operation.

Thermodynamic measurements of the cation exchange of CdSe with silver and copper were successfully carried out using isothermal titration calorimetry. A mixed
solvent system of 20% methanol / 80% toluene provided versatile solubility of both CdSe nanoparticles as well as various metal salts. The net reaction enthalpy and equilibrium constants were successfully measured, and from those the Gibbs free energy and the entropic term were calculated. There was no noticeable trend in any measured or calculated quantity for increasing nanoparticle diameters.

6.2 Future Work

6.2.1 Extensions of In-situ CdSe Characterization

The work presented in this thesis characterizing CdSe growth using a glass microreactor and a translatable spectrometer can be extended to even harsher conditions. One of the most significant advantages to a microreactor is the steady state operation providing snapshots of a reaction as it occurs, particularly at low residence times (<1 minute). The work here focused on temperatures up to 260 °C and the lowest residence time was on the order of 10 seconds. The only limitation preventing higher temperatures was the fluidic interfacing to the glass reactor. The kapton tubes were epoxied into place, with the thermally weakest link being the epoxy. Once a new method of interfacing the fluids to the reactor is developed, the new maximum usable temperature will be where the solvent starts to boil. This is expected to be 300 °C or higher.\(^3\) Glass capillaries combined with low temperature solder glass could provide a low tech but high performance fluidic seal. The experiments could then be performed in a near identical manner at higher temperatures.

Faster residence times could easily be accessed by appropriate design of the microreactor and control of the total volumetric flowrate. Similar conditions reported in this thesis but with a straight rather than serpentine channel would allow analysis at residence time increments of about 3 seconds. The flowrates used in the studies

\(^3\) The boiling point of the solvent, octadecene, is 315 °C.
presented here were moderately low (maximum 5 μL/min) and could easily be increased by an order of magnitude. This would provide reaction snapshots every 300 ms. At these timescales, it is expected that diffusion will become a limiting factor in the synthesis.

The next extension of the in-situ CdSe characterization would address diffusion limitations. Multiphase flow would increase the mixing in the system as well as provide a more well-defined residence time distribution. The starting point for this would be liquid-gas dispersion. This has been demonstrated in similar reactors for CdSe synthesis. Liquid-liquid dispersions have also been demonstrated for CdSe synthesis and provide further enhanced mixing and residence time distribution characteristics. However, since these rely on surface coating procedures as well as complex nozzle geometries, the more simple gas-liquid case should be pursued first.

The microreactor and translatable spectrometer could also be used to study other nanocrystal syntheses. The absorbance spectra of CdTe and CdS have also been characterized as thoroughly as CdSe. The nanocrystal size and nuclei concentration can be measured in a similar fashion based on the wavelength and intensity of the absorption peak. The absorbance spectrum for various sizes and shapes of gold nanoparticles have also been characterized. Another system suitable for in-situ spectroscopy measurements is gold. A flow scheme for gold nanoparticles analogous to the Turkevich method was presented in Chapter 2. This could be studied in-situ using the translatable spectrometer. Gold nanoparticle synthesis at an elevated pressure of about 5 bar was demonstrated with significantly enhanced kinetics. Systems with rapid kinetics are ideal for these studies since they are difficult to characterize using ex-situ methods.

6.2.2 Development of Multiphase Flow Control
Gas-liquid dispersions are easier to establish due to the high surface tension between the gas phase and the reactor walls. This leads to liquids preferentially wetting the wall and the gas phase forming rounded bubbles that flow down the channel. Liquid-liquid dispersions require careful control of the reactor wall surface chemistry and the two liquid phases used. However, even though gas-liquid dispersions are easier to establish from a surface tension perspective, establishing steady state for these systems is more difficult. This is due to the compressibility of the gas stream. Streams are typically controlled using syringe pumps that operate at constant volumetric flowrates. However, controlling the gas phase using a constant volumetric flowrate leads to difficulties in reactor startup.

On startup, the path of least resistance for fluid flow is for the liquid stream to backflow into the gas stream rather than down the microreactor. As the gas syringe compresses, the pressure will eventually become high enough to counteract this, leading to flow down the microreactor channel. However, as more liquid flows down the microfluidic channel, the pressure drop across the reactor increases, necessitating a higher gas stream pressure. The constantly changing pressure requirements makes volumetric flow (syringe pumps) very unsuitable for startup of gas-liquid flows.

This limitation has been partially addressed by using a syringe pump for the liquid phase and a pressure regulator for the gas phase. An example of steady state dispersed phase flow using this method is shown in Figure 6-1. Photograph of gas-liquid dispersed flow in a microreactor. A pressure regulator was used to control the gas inlet pressure. However, this requires constant manual tuning of the pressure setpoint during startup until steady state is achieved. An automated scheme for maintaining the multiphase flow would simplify startup and make the system more immune to disturbances in the flow. This could be achieved using a scheme described in Figure
6-2. A scheme for automated two phase flow control. The phase fraction is measured using an LED and photoresistor and the measured phase fraction is fed into a PID algorithm that adjusts the pressure to maintain the desired phase fraction setpoint. An LED and photoresistor could be placed near the point of two phase flow generation to monitor the flow. This could then be fed into a PID algorithm that maintains the phase fraction at a desired setpoint by constantly adjusting the pressure setpoint sent to the pump.
Figure 6-1. Photograph of gas-liquid dispersed flow in a microreactor. A pressure regulator was used to control the gas inlet pressure.
Figure 6-2. A scheme for automated two phase flow control. The phase fraction is measured using an LED and photoresistor and the measured phase fraction is fed into a PID algorithm that adjusts the pressure to maintain the desired phase fraction setpoint.
6.2.3 Extending the Capabilities of the Translatable Spectrometer

The success of the translatable spectrometer described in this thesis relied on an aperture placed directly against the microchannel. The simplest way to achieve this ended up being a silicon wafer aperture with holes drilled at appropriate locations. The wafer was then aligned and clamped to the microreactor. A similar concept could be developed that utilizes a reflective layer deposited onto the glass microreactor followed by photolithographic patterning of appropriate apertures. However, this still provides a limited number of analytical locations along the reaction. The ability to analyze arbitrary locations along a microreactor channel would provide a more versatile analytical platform.

During the development of the translatable spectrometer, it was hypothesized that the necessity for the aperture being directly against the channel was due to the light beam being slightly divergent. Another important factor is the angular alignment of the reactor in the beam. Future upgrades to the translatable spectrometer could address both of these issues. A five-axis kinematic mount coupled with a cylindrical aperture (Figure 6-3. A) A 5-axis kinematic mount that allows precision translational and angular alignment. B) A schematic of a cylindrical aperture that would decrease the effect of a divergent beam. The image of the 5-axis kinematic mount is taken from the ThorLabs website (part no. K5X1).) would eliminate the effects of a divergent beam and also allow precision alignment of the aperture. This would allow the sampling of arbitrary locations along the microreactor channel. To alleviate problems due to angular misalignment, the microreactor heating mantle could be mounted onto a stage that allows precision adjustment of pitch and yaw angles (Figure 6-4. A photograph of a pitch and yaw stage that could be used for fine tuning the angular alignment of the microfluidic reactor. The image is taken from the ThorLabs website (part no. GN2).). With these two features in
place, acquiring spectra at arbitrary locations on the microreactor would simply be a matter of tuning acquisition time.
Figure 6-3. A) A 5-axis kinematic mount that allows precision translational and angular alignment. B) A schematic of a cylindrical aperture that would decrease the effect of a divergent beam. The image of the 5-axis kinematic mount is taken from the ThorLabs website (part no. K5X1).
Figure 6-4. A photograph of a pitch and yaw stage that could be used for fine tuning the angular alignment of the microfluidic reactor. The image is taken from the ThorLabs website (part no. GN2).
Further upgrades for the translatable spectrometer could enhance the wavelength range of the apparatus. Since the microreactor and spectrometer combination is very modular, individual elements can be easily upgraded or swapped as needed. A combination deuterium and tungsten light source and ultraviolet fiber optic cables could allow for true UV-Vis spectroscopy, rather than the visible spectroscopy presented in this thesis. Microreactors compatible with UV absorbance measurements could be fabricated with minimal modifications to the procedures outlined in Chapter 2. Fused silica substrates could be used rather than borosilicate. This would provide UV transmittance down to at least 200 nm. The PDMS-glass hybrid reactors described in Chapter 2 could also be adapted for UV transmittance. Fused silica slides could replace the borosilicate slides. This would provide a low cost reactor compatible with ultraviolet and visible spectroscopy with a highly tunable path length. This could be used to study the formation of aluminum nanoparticles with a deep UV plasmon absorbance.6

6.2.4 Low-Cost Reactors Capable of In-situ X-ray Absorption Spectroscopy

Microreactors have been successfully coupled to x-ray based analytical techniques to study nanoparticle growth. X-ray absorption spectroscopy has been used to study CdSe growth7 and CdSe cation exchange8. X-ray scattering has also been combined with microreactors to study gold nucleation and growth.9,10 In all of these cases, special reactors have been developed to allow compatibility with x-ray techniques. A versatile and easily fabricated microreactor that is compatible with x-ray based analytical techniques would permit a more widespread study of nanoparticle nucleation and growth. The PDMS-glass hybrid microreactors presented in Chapter 2 have the potential to fill this application. The work presented in this thesis utilized 1.75 mm thick glass slides to form the outside layers of the microreactor. Schott D263 borosilicate glass is available in thicknesses as small as 30 μm. 100 μm D263 is easily
available and would provide more mechanical strength. One or both of the outer layers (Figure 6-5. A) Schematic showing the three layers of a PDMS-glass hybrid microreactor. B) A complete PDMS-glass microreactor with kapton capillary fixed at the inlets and outlets, could be replaced with this thinned glass. The transmittance of x-rays through 100 μm thin glass is shown in Figure 6-6. X-ray transmittance for 100 μm thick glass in the energy range of 10 - 25 keV. This simple modification has the potential to allow both transmission and fluorescence measurements through most of the relevant hard x-ray range. This x-ray compatible microreactor should enable expansion of the preliminary x-ray absorption spectroscopy data of platinum reduction presented in Chapter 2. The reduction rate of chloroplatinic acid to Pt(II) and Pt(0) could be quantified as well as the rate of production and growth of platinum nuclei using extended x-ray absorption fine structures. An additional avenue that could be taken with this analysis is combining multiphase flow with quick-EXAFS (QEXAFS).¹¹ QEXAFS acquires spectra much more quickly than traditional XAS. This would allow proper signal averaging for multiphase flow. Spectra from each phase can be sorted before being averaged.
**Figure 6-5.** A) Schematic showing the three layers of a PDMS-glass hybrid microreactor. B) A complete PDMS-glass microreactor with kapton capillary fixed at the inlets and outlets.
Figure 6-6. X-ray transmittance for 100 μm thick glass in the energy range of 10 - 25 keV.
6.2.5 Passivation Techniques for Isothermal Titration Calorimetry Measurements of Nanoparticle Ligand Exchange

Exchanging the ligands that stabilize nanoparticles provides a versatile method of modifying a particle post-synthesis to allow use in other solvent systems. However, quantitative measurement of the equilibrium that results from the exchange is difficult to measure. A quantitative understanding of the nanoparticle ligand interface would allow finer control over nanoparticle surface chemistry. Isothermal titration calorimetry presents a straightforward way to measure the enthalpy of ligand exchange as well as the equilibrium constant. However, since the cell and stirrer in ITC are generally made out of metals, injecting ligands into the system evolves large heat signals when the ligands bind with the metal of the ITC. This leads to a difficult convolution of equilibria when exchanging ligands on nanoparticles. Techniques that passivate the surfaces and eliminate this effect would extend the capability of ITC measurements involving nanoparticles.

Ravi et al. studied the binding of carboxylic acid terminated alkane thiols on gold nanoparticles.\textsuperscript{12} The problem of ligands interacting with the cell wall was encountered here as well. Their solution to this was to presaturate the cell with a solution containing the thiol for a certain amount of time, and then loading the cell with the appropriate reagents. This adequately passivated the cell wall for their experiments. The routine performed by Ravi and coworkers established a self-assembled monolayer (SAM) on the gold cell wall and prevented further interaction with the surface.\textsuperscript{13} This specific routine could be a more widely useful technique than previously thought. SAMs could be prepared on the cell wall and then the desired reagents loaded into the cell. This could
also address some of the problems presented in Chapter 5 where cation exchange reagents showed significant interaction with the cell wall.

The strong passivation of gold with thiol is specific to gold. While it is a convenient technique to passivate the cell wall, it would not be useful for passivating the stirrer of the ITC. A more traditional and material independent passivation would be coating the stirrer in Teflon. There are a variety of forms that Teflon can be acquired in. Either resin based Teflon AF or aqueous dispersion Teflon PTFE TE-3893 (DuPont) could provide a way to passivate the stirrer. After an adequate surface treatment is developed, any interactions with the stirrer could be eliminated. This opens up ITC measurements to study a variety of ligand exchange reactions as well as reactions involving metal salts, such as in cation exchange.

6.3 References


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The Pennsylvania State University, University Park, PA (August 2010 – Present)
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Publications


Conference Proceedings

• NPH Sturgis, RM Rioux, Thermodynamic Measurements of Cation Exchange in Chalcogenide Nanocrystals. AIChE Annual Meeting, November 2014, Atlanta GA
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