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Minimizing Formaldehyde Use in the Synthesis of Gold−Silver Core−Shell Nanoparticles

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Through a careful analysis of the role of formaldehyde in the preparation of silver nanomaterials, a previously unnoticed function of the reagent has been discovered. Formaldehyde reacts with ammonium hydroxide to form a polymer that changes how silver attaches to and coats a substrate. In the case of a gold nanoparticle substrate, this polymer is responsible for creating a nonconcentric core−shell nanoparticle with a near-infrared plasmon resonance at 700 nm. In contrast, when conditions do not favor synthesis of this polymer, concentric nanoparticles are formed that have a plasmon resonance between that of gold and silver at 498 nm. Understanding this second role of formaldehyde allowed us to decrease the amount used 100-fold compared to previous methods, providing a greener synthesis. In addition, it is shown that ascorbic acid can function as a partial substitute for formaldehyde in this synthesis. This strategy may be effective at minimizing or eliminating formaldehyde from the synthesis of other core−shell nanoparticles and nanoshells, facilitating their use in medical applications.

Two approaches have proven successful in tuning the localized surface plasmon resonance (LSPR) of metal nanomaterials into the near-infrared. The first approach uses additives that alter growth rates on different facets of a metal seed, providing control of nanoparticle shape.[1] Materials obtained from these routes, notably gold nanorods, can be tuned to absorb and scatter in the near-infrared by changing their aspect ratio.[1] A second category of near-infrared active nanomaterials are produced by a stepwise process of coating one metal onto either a dielectric particle creating a nanoshell[2] or onto a second metal, creating a core−shell structure.[3,4] The LSPR wavelength of these nanomaterials has been tuned by altering the core size[5] and the coating thickness.[6] It is the promise of medical applications that has driven interest in nanomaterials that absorb light at near-infrared wavelengths, where light passes more readily through tissue.[7]

Although many types of near-infrared active nanomaterials have been described, there remains a significant need for optimization of their synthetic routes. The ideal synthetic method would be simple, reproducible, and provide a single type of nanoparticle, eliminating the need for excessive isolation and purification steps. To achieve the desired reproducibility in nanomaterial syntheses, it is essential to understand why subtle changes in reagent concentration, age,[8] and source[9,10] can lead to substantial differences in the shapes of nanoparticles obtained. Biocompatibility of these nanomaterials is another area in need of optimization because of toxicity of the reagents used in many syntheses. The use of toxic compounds in preparing nanomaterials for medical applications will complicate their testing, use, and approval. The goal of identifying more benign synthetic routes is achievable and will become more tractable as nanomaterial formation mechanisms are better understood.[11]

Given the interest in medical applications of nanomaterials, it is particularly concerning that many of the synthetic routes to nanoshells and core−shell metal nanoparticles use a large excess of the toxic reagent formaldehyde as a reducing agent. One of the early methods reported for coating silver on silica spheres made use of 1 mmol of formaldehyde for reduction of a 0.15 mM solution of silver.[5] This is a greater than 3000-fold excess if each molecule of formaldehyde is assumed to reduce one silver ion in a 2 mL reaction. This large excess is based

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on Zsigmondy's original silver nanoparticle synthesis reported in 1927[12] and is typical of coating procedures. Other reports have used a 1000-fold excess for coating silver on polystyrene beads or gold nanoparticles,[13] up to 320-fold excess for coating silver on silica nanowires,[14] a 346-fold excess to coat silver onto latex spheres,[15] and a 24 000-fold excess for layering silver onto tin-coated silica nanoparticles.[16]

Here, we describe an effort to minimize the amount of formaldehyde used for coating silver onto gold nanoparticles. We discovered that the reaction conditions commonly used for providing a silver coating also produce a polymer by reaction of formaldehyde with ammonium hydroxide. Deposition of silver onto gold nanoparticles in the presence of this polymer results in a thin asymmetric silver coating and the polymer coating also results in aggregation. The resultant core−shell nanoparticles are 19 ± 4 nm in diameter and have an intense plasmon resonance at 700 nm making this route a convenient approach to forming near-infrared active nanomaterials that are well-suited for use in phototherapy.[7] Although formaldehyde is an essential component of this polymer, we were able to reduce the amount used 100-fold compared to the 1000-fold excess previously used to coat gold.[13] Part of this minimization resulted from the discovery that ascorbic acid can be used as a reducing agent in combination with formaldehyde. Understanding this previously overlooked polymer formation is a good starting point for minimizing formaldehyde use in the synthesis of nanoshells and other core−shell nanomaterials. We expect that this will result in greener syntheses and more biocompatible nanomaterials suitable for medical applications.

Experimental Section

Hydrogen tetrachloroaurate hydrate was from Strem, ammonium hydroxide (15.14 M determined by titration) was from Fisher, aqueous formaldehyde (37 wt % with 10−15% methanol) was from Alfa Aesar, silver nitrate was from EM Science, sodium citrate dihydrate was from J.T. Baker, and ascorbic acid was from Matheson, Coleman, & Bell. All water used was Milli-Q purified. Citrate capped gold nanoparticles were synthesized following a literature procedure.[13] UV−visible spectra were collected using a Perkin-Elmer spectrophotometer with a 1 cm quartz cuvette. Mass spectrometry data were obtained with a Bruker microTOF-Q LC-MS/MS. The ESI interface was operated in the positive mode using the following settings: end plate offset, −500 V; capillary voltage, −4500 V; nebulizer gas, 1.6 bar; dry gas, 4 L/min; dry temperature, 200 °C; funnel 1, RF 350 Vpp; funnel 2, RF 350 Vpp; hexapole RF, 400 Vpp; collision energy, 10 eV; and collision RF, 300 Vpp. Transmission electron micrographs were acquired on an FEI Tecnai F-20 microscope using a CCD detector. Images were collected at an acceleration voltage of 200 kV. Samples were prepared by drop casting dilute solutions of nanoparticles onto carbon-coated (300 Å) Formvar films on copper grids (Ted Pella). Nanoparticle size was measured using ImageJ (NIH).

Standard Core−Shell Nanoparticle Synthesis. Formaldehyde (20 μL, 267 μmol) was added to H_2O (4.5 mL) in a 20 mL scintillation vial. This solution was stirred at room temperature for 15 min. Citrate-capped gold nanoparticles (0.5 mL) were added, followed by the immediate addition of $AgNO_3$ (0.2 mL of 1.1 mM). The color of the solution was pale red with a hint of purple that was observed as $AgNO_3$ was added. After 5 min of stirring, ammonium hydroxide (53 μL, 802 μmol) was added, upon which the solution immediately turned a bright yellow color. After 15 min of being stirred uncapped, the solution turned pale red, followed by green, purple, and finally blue. UV−vis in H_2O: λ_{max} = 693 nm.

Core−Shell Nanoparticle Synthesis Using Minimal Formaldehyde. H_2O (4.35 mL) was added to a 20 mL scintillation vial followed by addition of 4, 3, or 0.5 μL of formaldehyde. After 15 min of stirring uncapped, citrate capped gold nanoparticles (0.5 mL) and $AgNO_3$ (0.2 mL of 1.1 mM) were added. After 5 min, ammonium hydroxide (21.2 μL, 321 μmol) was added. After an additional 5 min, ascorbic acid (0.1 mL, 0.534 M) was added. The reaction reached completion within 1−3 days. UV−vis in H_2O: λ_{max} = 638 nm.

Results and Discussion

Here we report a detailed exploration of methods for coating a silver layer onto gold nanoparticles using formaldehyde as a reducing agent. Our starting point is a synthesis that uses a 1000-fold excess of formaldehyde based on an approach reported for coating gold nanoparticles.[13] Figure 1 shows the progress of a typical reaction when gold nanoparticles, silver nitrate, and ammonium hydroxide are added to a dilute formaldehyde solution using our standard conditions. This technique is also similar to methods reported for coating silver on silica or latex particles,[5,14,16−21] all of which stem from the method reported by Zsigmondy.[12] However, this peak at 700 nm is very unusual for core−shell nanoparticles, which typically have an LSPR intermediate between the LSPR of each individual metal.[6]

Many different types of nanoparticles are formed under the standard conditions, however, the predominant structures are core−shell nanoparticles in which the two metals appear nonconcentric in the TEM image (Figure 2). Typically, multiple core−shell nanoparticles are connected to each other by silver although isolated nanoparticles are also observed (see Figure S1 in the Supporting Information). These nanoparticles are 19 ± 4 nm in diameter while the uncoated gold nanoparticles have a 16 ± 3 nm diameter. Other nanoparticles are obtained

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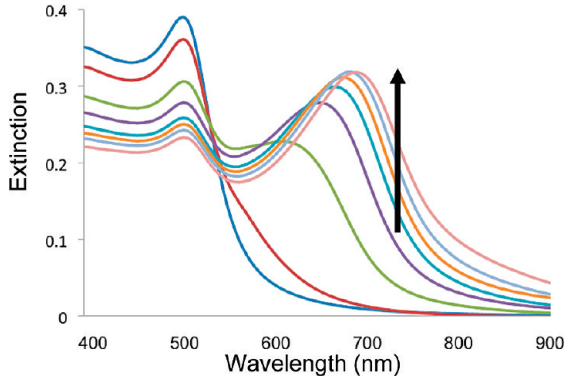

Figure 1. UV−vis spectra collected during core−shell nanoparticle synthesis using standard conditions in which 20 μL of formaldehyde was incubated with 4.5 mL of water for 15 min prior to addition of 0.5 mL of gold nanoparticles and 0.2 mL of 1.1 mM silver nitrate followed by 53 μL of ammonium hydroxide after a 5 min incubation. Arrow shows increasing time at 3, 10, 30, 50, 70, 90, 120, and 180 min after addition of ammonium hydroxide.

from these reaction conditions, including concentric core shell nanoparticles ($d = 21 \pm 4$ nm) and spherical silver nanoparticles. Concentric core−shell nanoparticles have no offset between the centers of the two metals (Figure 2a). When the centers of the two metals are substantially offset, we refer to these as nonconcentric core−shell nanoparticles (Figure 2b). In some nanoparticles, the core may be obscured by the orientation of the nanoparticle on the grid, making it difficult to reliably discern concentric from nonconcentric. Concentric core−shell nanoparticles exhibit an LSPR intermediate in wavelength between that of the two metals; for silver and gold this occurs between 400 and 520 nm; the thicker the silver, the closer to 400 nm.[6,22] Recent experiments[23] and calculations[24,25] indicate that asymmetric metal coatings on dielectric particles have a strong near-infrared LSPR. A thin 2 nm shell provides a significant change in LSPR.[24] However, asymmetric core−shell structures have also been reported without observation of a near-infrared peak.[3,4] At the same time that the 700 nm LSPR appears, there is a shift in the low wavelength LSPR peak from 522 to 498 nm (Figure 1). These two spectroscopic changes are consistent with gold nanoparticles being converted to a mixture of nonconcentric and concentric core−shell nanoparticles as seen by TEM. Specifically, the lower wavelength LSPR arises from the concentric nanoparticles and the higher wavelength LSPR arises from the nonconcentric nanoparticles.

Successful synthesis is evident by a progression of color changes ending with an intense LSPR near 700 nm and a blue color in solution. Initially, the solution of formaldehyde and water is colorless but takes on a pale red color when gold nanoparticles are added. No color change occurs on addition of silver nitrate until the pH is

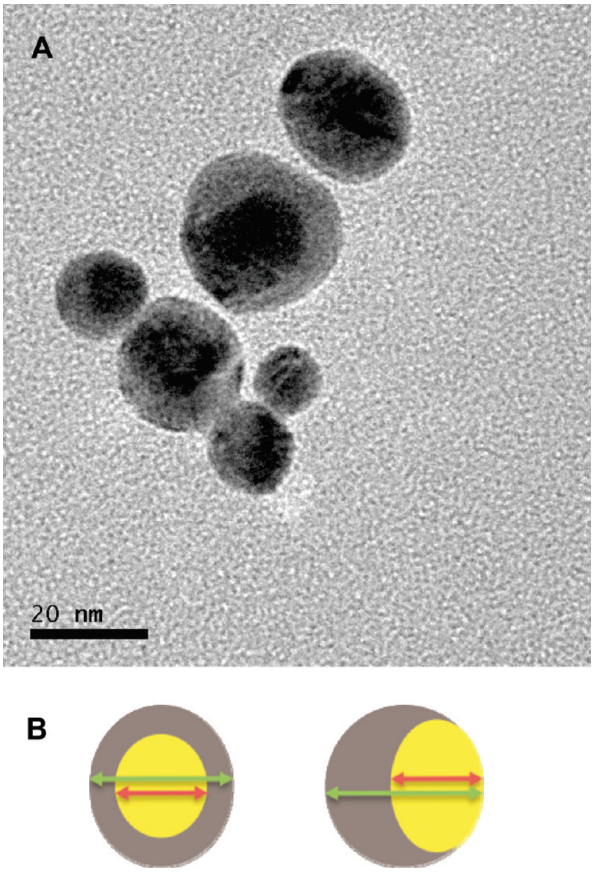

Figure 2. (a) Representative core−shell nanoparticles observed in TEM images. Scale bar = 20 nm. (b) Schematic representation of core−shell nanoparticles with concentric metals (left) and core−shell nanoparticles with nonconcentric metals (right). Red arrow indicates interior gold diameter. Green arrow indicates exterior diameter.

increased by introduction of ammonium hydroxide. At this point, the solution immediately turns yellow as silver nitrate is converted to a silver ammonia complex. In a successful reaction, the yellow color fades revealing the pale red color, followed by a slow darkening. This takes hours and results in a bluish color. If conditions allow for reduction of the silver but not for asymmetric silver coating, a similar sequence of color changes occurs, terminating at the yellow or pale red stage. We refer to this as an unsuccessful reaction. For example, when too little reducing agent is available (Figure 3, green), the solution does not progress past the yellow color, and when not enough ammonium hydroxide is used, the progression stops at the pale red color. However, in these experiments, the shift of the lower plasmon resonance below 500 nm does indicate that a reaction is occurring and that silver is coating the gold although only concentric core−shell nanoparticles are formed.

Initial efforts to replace or minimize formaldehyde to provide a greener synthesis were unsuccessful. Using 10 μL (134 μmol) of formaldehyde or less results in a much lower intensity LSPR in the near-infrared (Figure 3). Another simple approach to developing a greener route would be to replace formaldehyde, however, this approach also does not result in the desired long wavelength absorbing materials. We have explored a range of reducing agents and while

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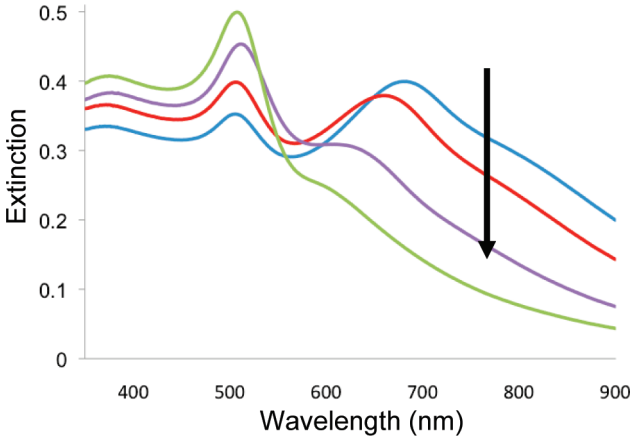
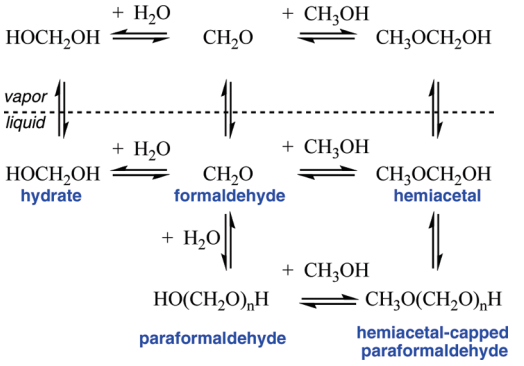


Figure 3. UV−vis spectra of formaldehyde limited reactions. Standard core−shell nanoparticle reaction conditions with varying amounts of formaldehyde: 10 μL (blue), 8 μL (red), 6 μL (purple), and 2 μL (green). Arrow shows decreasing formaldehyde concentration.

some, such as ascorbic acid, reduce silver to coat gold (see Figure S2 in the Supporting Information), none show evidence of the long wavelength LSPR.

Many of the difficulties of developing reliable, reproducible nanoshell and core−shell syntheses using formaldehyde can be explained by the complex nature of aqueous formaldehyde solutions. There is a large range in the amount of formaldehyde used for creating silver coatings between different papers (vide supra) and even within individual papers. Furthermore, the age of the solutions used can be critical in determining the nanoparticle shapes obtained.[25] In our experience, it is often difficult to obtain identical nanoparticles using the same reagent concentrations on different days, especially if the formaldehyde has been diluted (see Figure S3 in the Supporting Information). We suggest that these difficulties arise from the complex nature of formaldehyde. Although formaldehyde gas exists as a simple carbonyl compound, this is not the form commonly used in the research laboratory. The polymer paraformaldehyde is one commonly used source of formaldehyde (Scheme 1). Formaldehyde is also readily soluble in water and aqueous solutions of formaldehyde are a second commonly used form of the compound. These solutions are available up to the saturation point (reported as both 37% by weight and 40% by volume) that by convention is also called 100% formalin.[26] In aqueous solution, the hydrate of formaldehyde is the dominant form present.[27] Because of the propensity of the aqueous solutions to polymerize and to oxidize, they are sold with 10−15% methanol added as a stabilizer. Methanol reacts with formaldehyde to form a hemiacetal (Scheme 1) and under acidic conditions or at elevated temperature the acetal dimethoxymethane can also be formed (not shown). Furthermore, in methanol stabilized solutions a hemiacetal forms on the end of the paraformaldehyde, resulting in a second category of oligomers (Scheme 1). It is this methanol-stabilized

Scheme 1. Structures and Critical Equilibria for Methanol-Stabilized Aqueous Formaldehyde Solutions in Both the Liquid and Vapor Phase



aqueous formaldehyde solution that is commonly used in nanoshell and core−shell nanoparticle synthetic methods.

Because of the complex nature of formaldehyde solutions, they take hours to reach equilibrium after dilution,[28] suggesting a reason for poor reproducibility in formaldehyde-based syntheses. The simple act of diluting formaldehyde has many effects on the composition of the solution.[29] Dilution with water prior to a reaction will affect all of the solution equilbria shown in Scheme 1 as well as the vapor−liquid equilibria for each volatile component. In our standard conditions, typical of literature methods, methanol is diluted from 15% in the original reagent to ~0.06% in the final reaction mixture. As the methanol concentration decreases, the hemiacetal releases formaldehyde and methanol. Likewise, the hemiacetal-capped polymer will depolymerize to release formaldehyde and hemiacetal which in turn will release more formaldehyde. As a result, the quantity of formaldehyde hydrate available increases with dilution and becomes the predominant species.[28] Dilution of paraformaldehyde oligomers is also expected to release formaldehyde; however, the complex equilibria makes it difficult to predict the precise effect of the standard conditions on paraformaldehyde concentration and polymer length.[29] The concentration of reagents in the headspace is also difficult to predict and even simpler systems behave counterintuitively. For example, formaldehyde vapor pressure decreases as its concentration in solution increases.[30,31] When the standard synthesis is performed in a sealed vial, the reaction fails, suggesting that the liquid−vapor equilibria are also important to the success of the reaction.

The time the reaction mixture has to reach equilibrium was found to be critical to achieving a successful reaction, suggesting that formaldehyde may be involved in a complex set of reactions in addition to reducing silver. We explored various sequences of reagent addition in conjunction with

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varying incubation times in which the solution was allowed to stir without further reagent addition. For a 15 min incubation of formaldehyde with water, followed by addition of gold nanoparticles, silver nitrate, and finally ammonium hydroxide after an additional 5 min incubation the reaction reliably produces a near-infrared peak (Figure 1), whereas shorter incubations typically lead to unsuccessful reactions (see Figure S3 in the Supporting Information). Although 15 min is much less than the 5 h required for this system to reach equilibrium,[28] the changes that occur during that period of time are essential to the success of the reaction, which may explain previous observations that the age of reagents influences nanoshell shape.[8] Although the amount of formaldehyde used (267 μmol) is lower than previously reported (667 μmol),[13] a successful reaction requires very specific timing. This incubation time may be essential due to changes in paraformaldehyde concentration, formaldehyde hydrate concentration, or both. Further supporting the importance of establishing the necessary equilibria is the observation that using 15% methanol (aq) to dilute the formaldehyde instead of water dramatically slows the reaction, producing a minimal near-infrared peak (see Figure S4 in the Supporting Information). In contrast, the same amount of methanol added after the 15 min incubation in water does not slow the reaction as much. Furthermore, when the acetal of formaldehyde, dimethoxymethane, was added in place of formaldehyde, it did not produce a successful reaction for days (see Figure S5 in the Supporting Information).

Ammonium hydroxide is added to the reaction to form the easily reduced silver ammonia complex, however, the quantity required suggests a second role for ammonium hydroxide. In standard conditions, 53 μL (802 μmol) of ammonium hydroxide is used, which is a $>$3600-fold excess over the amount of silver nitrate present. Other bases, such as bicarbonate or carbonate are suitable for adjusting the reduction potential of the silver solution, however, they lead to unsuccessful reactions with no evidence of a near-infrared peak (see Figure S6 in the Supporting Information). This suggests a second role for ammonium hydroxide. Furthermore, if the amount of ammonium hydroxide is decreased and the formaldehyde is kept at 20 μL (267 μmol), the synthesis is unsuccessful (Figure 4). Although 35 μL (Figure 4, orange) provides a $>$1500-fold excess of ammonium hydroxide for reaction with silver and there is a color change associated with formation of the silver ammonia complex, only a minimal shoulder $>$500 nm is observed. This further suggests that ammonium hydroxide has a second role beyond adjusting the reduction potential. The incubation time of the reagents prior to ammonium hydroxide addition is also critical and using less than a 5 min incubation results in reduction of silver but the resultant LSPR is $<$500 nm.

Studies of hexamine synthesis suggest what the additional roles of formaldehyde and ammonium hydroxide could be. Hexamine was identified as the primary product

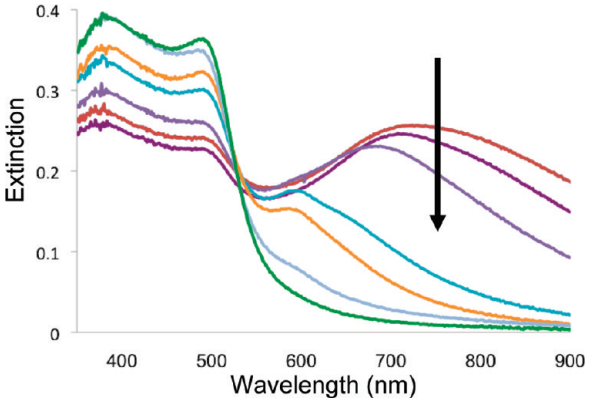

Figure 4. UV−vis spectra of ammonium hydroxide limited reactions. Standard core−shell nanoparticle reaction conditions with varying amounts of ammonium hydroxide: 55 μL (red), 50 μL (magenta), 45 μL (purple), 40 μL (light blue), 35 μL (orange) 30 μL (blue), and 25 μL (green). Arrow shows decreasing ammonium hydroxide concentration.

of the reaction between concentrated formaldehyde and concentrated ammonium hydroxide in 1859,[32] although the mechanism of formation is still not completely understood.[33] When water is removed in vacuo from an aqueous mixture of gold nanoparticles, formaldehyde, and ammonium hydroxide at the same concentrations used for the standard synthesis, hexamine is identified as the primary product by NMR and MS. This demonstrates that hexamine can form under the standard reaction conditions, which are over 200-fold more dilute than the concentrated reagents. However, hexamine itself does not function as a replacement for formaldehyde and ammonium hydroxide. That is, no near-infrared peak results when hexamine is used as a stoichiometric replacement for formaldehyde, ammonium hydroxide, or both reagents. An early study of hexamine synthesis[34] explored dilute solutions of ammonium hydroxide and formaldehyde that in later work is referred to as Henry's solution (Scheme 2). Although it can provide hexamine when heated with acid, it was later shown that Henry's solution did not itself contain substantial hexamine.[35] Instead, a portion (25%) of Henry's solution was isolated as 1,3,5-hexahydrotriazine and 75% was not identified. It was later shown that Henry's solution reacts to first form 1,3,5-hexahydrotriazine, followed by 1,3,5,7-tetraazabicyclo-[3.3.1]nonane, and finally hexamine (Scheme 2) over 100 days.[33] At dilute concentrations, hexamine does not become the predominant product until 2 weeks of reaction time have elapsed. At higher concentrations of reagents, hexamine becomes predominant in the first 2 h. Under strongly acidic conditions (pH 1) or basic (pH 12) conditions, Henry's solution provides hexamine within hours.[33] At the dilute concentrations and short reaction time used in the standard nanoparticle synthetic conditions, hexamine is not expected as a primary product, and we attribute most of the hexamine obtained to the isolation procedure of heating in vacuo.

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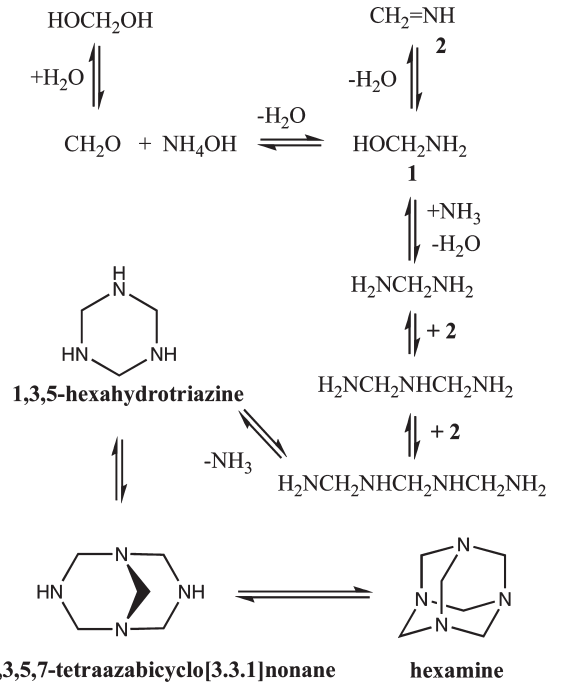
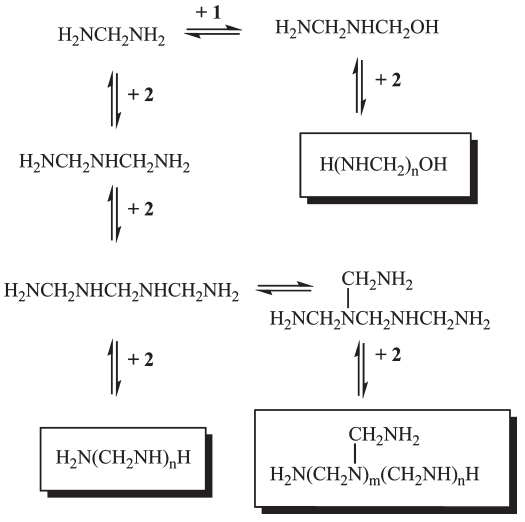
Scheme 2. Reaction of Formaldehyde and Ammonium Hydroxide to Yield 1,3,5-Hexahydrotriazine, 1,3,5,7-Tetraazabicyclo[3.3.1]nonane, and Hexamine



Scheme 3. Three Representative Polymerization Pathways



The likely initial intermediates in hexamine synthesis, methanolamine (**1**) or methenimine (**2**), are also able to polymerize as has been noted previously.[33,35] Three representative polymerization routes based on Nielson's mechanism and earlier kinetic studies[36,37] are shown in Scheme 3. The thermodynamic stability of hexamine precludes a simple isolation of these polymers. Routes similar to the one shown on the right side of Scheme 3 but with oxygen atoms replacing more nitrogen atoms are also plausible. However, the fact that the isolated product (hexamine) and the identified intermediates contain only nitrogen and no oxygen led Nielson to suggest that the predominant reactions are from pathways similar to those shown on the left side of Scheme 3. Reactions that create tertiary amine sites, such as found in hexamine, will also occur during this polymerization, leading to branched polymers. One of many possible examples of a branched polymer is shown on the bottom right of Scheme 3. Furthermore, cyclization reactions will occur during the polymerization. The specific polymerization routes that occur would be sensitive to the ratio of ammonia to free formaldehyde and therefore sensitive to paraformaldehyde and methanol concentrations. In the presence of gold nanoparticles and silver nitrate additional factors may further alter these reaction pathways. The importance of the sequence and timing of addition of ammonium hydroxide and formaldehyde in this synthesis are consistent with the idea that polymerization of formaldehyde and ammonium hydroxide must occur prior to silver coating its substrate.

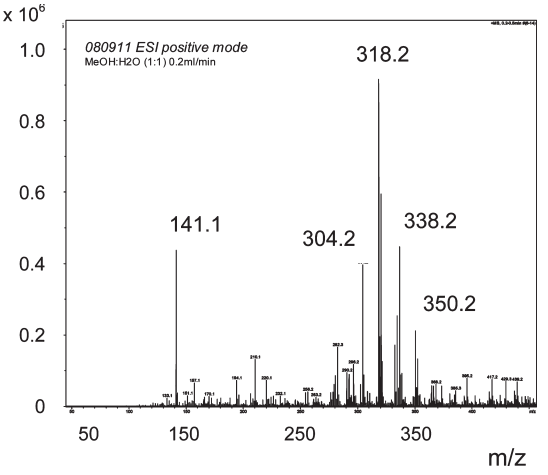


Figure 5. Mass spectrum of polymers shown in Scheme 3 that are formed during nanoparticle synthesis. Analysis of a reaction mixture of formaldehyde, ammonium hydroxide, citrate capped gold nanoparticles, and formaldehyde that was stirred for 2 h at room temperature and centrifuged.

When the reaction fractions are not isolated in vacuo, but instead the reaction mixture is studied directly by mass spectrometry, evidence of polymerization of formaldehyde and ammonium hydroxide is observed (Figure 5). An aliquot of a reaction mixture containing citrate capped gold nanoparticles, formaldehyde, and ammonium hydroxide was examined by mass spectrometry after 2 h of reaction. This reaction mixture lacks silver nitrate, which prevents core−shell nanoparticle synthesis and allows for analysis by mass spectrometry. A peak for hexamine is observed at 141.2 but peaks indicative of larger structures at 318.2, 338.2, and 350.2 are evident and cannot be explained by paraformaldehyde oligomers alone. These peaks are consistent with oligomers of formaldehyde and ammonium hydroxide although each mass observed could represent multiple branched or cyclic structures (Scheme 3), and these oligomers may reveal the polymer fraction that is most easily observed by mass spectrometry. Although hexamine is present, it is not responsible for the near-infrared activity (vide supra). Interestingly, the gold nanoparticles

(36) Wood, R. K.; Stevens, W. F. *J. Appl. Chem.* **1974**, 325–330.
(37) Ogata, Y.; Kawasaki, A. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 514–519.

in this modified reaction, lacking silver nitrate, precipitate within 2 h.

Larger polymers than those observed by mass spectrometry could be contained in the precipitate from this modified reaction; however, these were ruled out as being the polymers critical for obtaining the near-infrared peak. To confirm that the soluble fraction of the mixture contains the critical polymer, an aliquot of the soluble fraction was added to a separate modified reaction mixture. This second reaction mixture contained silver nitrate, a new aliquot of gold nanoparticles, no formaldehyde or ammonium hydroxide, but ascorbic acid instead which served as the reducing agent. Although the polymer precursors are absent from this second modified reaction mixture, adding an aliquot of the soluble fraction of the polymerization solution results in a peak at 700 nm confirming that the soluble fraction contains the necessary polymers (see Figure S7 in the Supporting Information). This approach of preparing the soluble polymer in one solution and adding it to a modified reaction mixture works optimally at a 2 h age of the polymer solution, indicating that there is a critical polymer size. If gold is not added to the original polymerization solution, near-infrared active materials are not produced. The fact that gold is required in the first step suggests that the polymerization reactions in Scheme 3 are influenced by the gold. However, if gold is completely removed from the modified reaction mixture by centrifugation at 2 h, the colorless, soluble fraction still contains the polymer necessary for producing near-infrared active core−shell nanoparticles. This indicates that although gold influences the polymerization, the critical polymer is not irreversibly attached to gold. Instead, we suggest that the polymer binds reversibly to gold by a small number of amine groups.

These dual functions of formaldehyde are responsible for the large amount of reagent required to obtain the desired core−shell nanoparticles and this discovery made it possible to minimize the amount of formaldehyde used. Initial efforts at minimizing only formaldehyde were of moderate success. That is, when 10 μL (134 μmol) or less of formaldehyde was used, only a minor near-infrared LSPR was observed (Figure 3). However, considering the polymerization pathway for formaldehyde and ammonium hydroxide, a better approach presented itself. By minimizing formaldehyde and ammonium hydroxide concurrently, a lower threshold for core−shell nanoparticle synthesis was achieved. Using 6.0 μL (80 μmol) of formaldehyde and 31.0 μL (484 μmol) of ammonium hydroxide (Figure 6, green), we observed a substantial near-infrared peak. In contrast, 6 μL of formaldehyde with 53 μL of ammonium hydroxide (Figure 1, purple) produces a minimal near-infrared peak. This is consistent with the idea that most of the formaldehyde and ammonium hydroxide react to form a polymer and that the original proposed roles of these reagents consume a small fraction of the total amount added. Limiting either formaldehyde or ammonium hydroxide without limiting the other reagent does not optimally produce the necessary polymer and only concentric core−shell nanoparticles

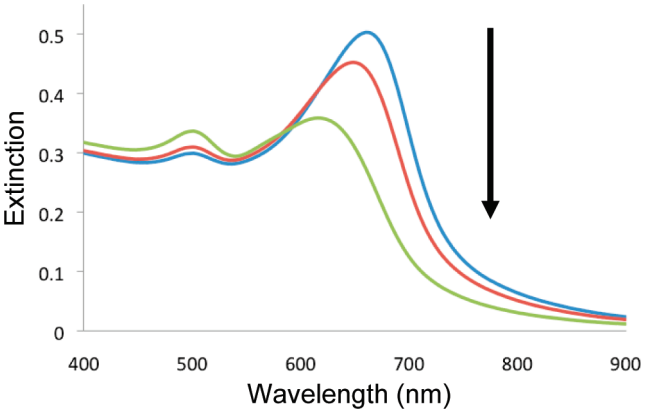


Figure 6. UV−vis spectra collected during core−shell nanoparticle synthesis using minimal formaldehyde and minimum ammonium hydroxide. Formaldehyde incubated with 4.5 mL of water for 15 min followed by addition of 0.5 mL of gold nanoparticles, 0.2 mL of 1.1 mM $AgNO_3$, and NH_4OH after 5 min. Ten microliters of formaldehyde and 53 μL of ammonium hydroxide (blue), 8 μL of formaldehyde, 42 μL of ammonium hydroxide (red), 6 μL formaldehyde, and 31 μL ammonium hydroxide (green). Arrow shows decreasing formaldehyde and ammonium hydroxide concentrations.

result with an LSPR λ_{max} = 519 nm. The minimal amount of polymer required is not known, and further minimization of formaldehyde is possible. However, optimization is complicated because the two reagents each have two distinct roles.

The question of whether a second reducing agent could replace the reducing agent function of formaldehyde while still using formaldehyde for polymer formation was next explored. Although formaldehyde cannot be completely replaced (vide supra), knowing that formaldehyde has two functions provided a new opportunity to investigate its minimization. Adding the more benign reducing agent, ascorbic acid, to the standard reaction conditions still produces a near-infrared LSPR; however, using both ascorbic acid and a full aliquot of formaldehyde does not demonstrate which reagent is responsible for the silver reduction. Instead, reaction conditions where the formaldehyde concentration was <4 μL were utilized, which is the point at which almost no near-infrared peak appears using formaldehyde alone (Figure 3). When ascorbic acid was added to reactions with <4 μL of formaldehyde, the near-infrared peak returned to full intensity (Figure 7). Reactions with 4, 3, or as little as 0.5 μL of formaldehyde all show substantial near-infrared activity, if and only if, ascorbic acid is added to supplement the formaldehyde. In contrast to the 50 μL of formaldehyde used in the original literature example,[13] this is a 100-fold decrease in formaldehyde. Note that the ammonium hydroxide used has been minimized to 21.2 μL and this is not enough for a successful synthesis when a full 20 μL of formaldehyde is available (Figure 4, green). By decreasing the formaldehyde, less ammonium hydroxide is needed to produce the same polymer.

To determine if the materials formed using minimal formaldehyde had the same core−shell structure, samples were examined by TEM (Figure 8). Similar to the standard

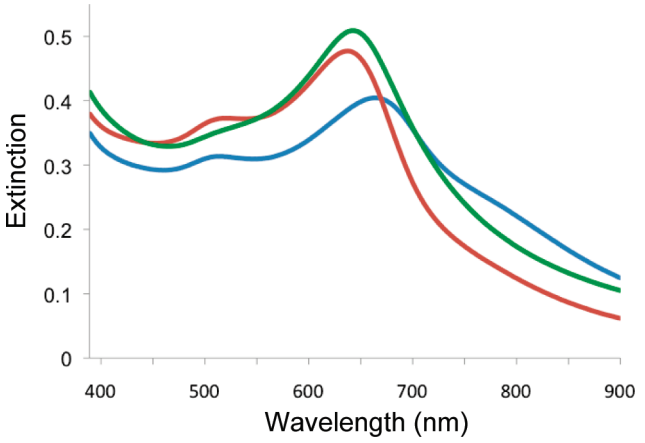


Figure 7. UV−vis spectra collected of core−shell nanoparticles synthesized using a combination of formaldehyde and ascorbic acid. Each reaction is performed under standard conditions, however, with 21.2 μL of ammonium hydroxide and 100 μL of ascorbic acid added at the end of the reaction, and with formaldehyde amounts of 4 (red), 3 (blue), and 0.5 (green) μL.

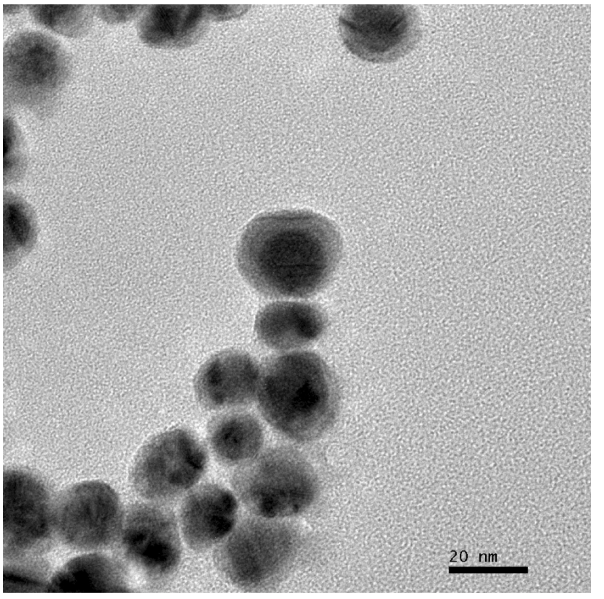


Figure 8. Representative TEM image of core−shell nanoparticles prepared using a mixture of formaldehyde and ascorbic acid. One-half a microliter of formaldehyde was incubated with 4.5 mL water for 15 min prior to addition of 0.5 mL of gold nanoparticles and 0.2 mL of 1.1 mM silver nitrate followed by 21.2 μL ammonium hydroxide after a 5 min incubation and 0.1 mL of 0.534 M ascorbic acid after an additional 5 min incubation. Scale bar = 20 nm.

synthesis, both isolated and aggregated nanoparticles with silver coatings on gold cores and a mixture of both concentric and nonconcentric nanoparticles are observed. Their appearance is similar and the average size of these particles is similar ($d = 22 \pm 4$ nm) to those obtained from the standard conditions (see Figure S8 in the Supporting Information). Although an asymmetric coating appears in both routes, others have reported similar core−shell structure without a near-infrared peak.[3,4] Therefore, asymmetry alone cannot explain the optical properties. The polymer that is formed must either directly or indirectly influence the optical properties. One possibility is that the polymer attaches selectively to certain faces of the metal surfaces, resulting in oriented cross-linking that causes the near-infrared peak. Alternatively, the polymer itself may be contributing the shift of the LSPR. That is, the polymer coating, possibly loaded with metal, acts as an asymmetric dielectric coating that alters the LSPR position. Similar types of geometries with similar thicknesses[24] have been observed with nanoeggs that absorb strongly in the near-infrared.[23] Under the minimal formaldehyde conditions, the final LSPR appears at 638 nm, 60 nm lower than from the standard high formaldehyde conditions, despite the fact that the amount of gold and silver used is the same. This is consistent with the polymer coating being responsible for the near-infrared shift and less polymer causing less of a shift. Likewise, when both formaldehyde and ammonium hydroxide were minimized, there was also a shift to lower wavelength (Figure 6). We rule out silver alone as the cause of the long wavelength LSPR because increased silver nitrate concentration did not change the long wavelength LSPR. Higher silver nitrate concentration did, however, decrease the wavelength of the low wavelength LSPR, as expected for a thicker symmetric coating in gold nanoparticles.

To examine the effect that aggregation has on the optical properties, we examined the use of sonication to separate the core−shell nanoparticles. Within 1 h of preparation, sonication can be used to disrupt the particles as evidenced by partial loss of the near-infrared LSPR band (see Figure S9 in the Supporting Information). Although there is a return of the LSPR over time, the intensity is not as high as before. This is consistent with weak polymer attachment altering the optical properties of the particles. As the samples age, sonication is no longer able to disrupt the near-infrared peak. Increased points of attachment between the polymer and the nanoparticle surface cause this irreversibility at later times. Eventually, after days or weeks, the nanoparticles precipitate because of cross-linking, although these precipitates can be resuspended by sonication without a change in the near-infrared activity. The precise values of the LSPR are also influenced by the dielectric constant of solvent which includes some methanol and any unreacted formaldehyde and ammonium hydroxide.

As nanomaterials become adopted for larger-scale applications, it is important to optimize their syntheses to reduce the potential environmental impact of their production. Considering that these polymers are expected to release formaldehyde as they decompose, as hexamine does,[38] their use in medical applications should be approached with caution. The persistent use of high concentrations of formaldehyde since Zsigmondy's original synthesis suggests that the properties of this polymer or similar polymers could favorably influence the metal coating process. Therefore, finding a suitable replacement for this polymer could help to minimize the use of formaldehyde and allow a switch to more benign reducing agents.

(38) Tada, H. *J. Am. Chem. Soc.* **1960**, *82*, 255–263.

Conclusions

The observation that previous synthetic routes for nanoshell and core−shell nanoparticles utilize a large excess of formaldehyde suggested an opportunity for minimizing the quantity of formaldehyde used. However, the synthesis of gold-core, silver-shell nanoparticles that are active in the near-infrared requires the polymer that forms by reaction of formaldehyde and ammonium hydroxide. Until a replacement polymer is found, formaldehyde is required to obtain the desired optical properties. However, formaldehyde use can be reduced 100-fold from prior routes using the strategy described here and this minimization strategy can be applied to other nanoparticle syntheses.

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Supporting Information Available: Figure S1, TEM images of concentric and nonconcentric core−shell nanoparticles prepared under standard conditions; Figure S2, UV−vis spectrum of core−shell nanoparticles synthesized using ascorbic acid; Figure S3, UV−vis spectra collected using various formaldehyde incubation times; Figure S4, UV−vis spectra of core−shell nanoparticles synthesized using 20 μL formaldehyde incubated with 4.5 mL of 15% MeOH for 15 min; Figure S5, UV−vis spectra of core−shell nanoparticles synthesized using dimethoxymethane; Figure S6, UV−vis spectra of core−shell nanoparticles synthesized using sodium carbonate; Figure S7, UV−vis spectra of nanoparticles synthesized by a two-step method using a separate polymerization mixture; Figure S8, TEM images of core−shell nanoparticles prepared using 0.1 mL of 0.534 M ascorbic acid and 0.5 μL formaldehyde; Figure S9, UV−vis spectra of nanoparticles after sonication (PDF).This material is available free of charge via the Internet at http://pubs.acs.org.