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Elemental Bismuth Nanoparticles : Mechanistic Studies Concerning Reduction of a Bi(III) Precursor Leading to Nanoparticle Formation in a Bottom-Up, High Payload Synthetic Approach

Colin J. Hiatt
Portland State University

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Elemental Bismuth Nanoparticles: Mechanistic Studies Concerning Reduction of a
Bi(III) Precursor Leading to Nanoparticle Formation in a Bottom-Up, High Payload
Synthetic Approach

by

Colin J. Hiatt

An undergraduate honors thesis submitted in partial fulfillment of the

requirements for the degree of

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Thesis Adviser

Dr. Andrea M. Goforth

Portland State University

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Abstract

Nanoparticle X-ray contrast agents have garnered significant attention over the past decade. While gold nanoparticles (AuNPs) have held most of that attention, being one of the most widely studied and understood materials mechanistically, as well as synthetically, bismuth has gained significant ground as an alternative material to gold. This is owing to the low cost of bulk elemental bismuth and bismuth compounds, bismuth's high X-ray opacity, as well as its generally accepted biological tolerance, making bismuth a very suitable candidate for medical X-ray contrast applications. In the research presented, an ultra-high payload, glucose-assisted, elemental bismuth nanoparticle (BiNP) synthetic protocol is examined. In order to make more directed modifications to future BiNP synthetic work that would allow greater control over particle morphology, size control, as well as particle stability, greater understanding into the subtle and intricate chemical interactions governing kinetic parameters must be obtained. In an attempt to gain the necessary mechanistic understanding required to make such synthetic modifications, several studies were carried out. This thesis represents a small step, with the aforementioned synthesis, in that direction and also suggests future studies that can be implemented in order to gain further mechanistic insight.

Table of Contents

	<i>Page</i>
<i>Abstract</i>	<i>i</i>
<i>List of Figures</i>	<i>iii</i>
<i>Introduction</i>	<i>1-10</i>
1.1 <i>Research Motivation (significance)</i>	<i>1</i>
- 1.1.1 <i>Medical X-ray Contrast Agents</i>	<i>1</i>
- 1.1.2 <i>Nanomaterials Explored</i>	<i>3</i>
1.2 <i>Bismuth Nanoparticles</i>	<i>5</i>
- 1.2.1 <i>Bismuth as an Alternative Material for NP XCAs</i>	<i>5</i>
- 1.2.2 <i>Bismuth Nanoparticle Synthetic Approaches</i>	<i>5</i>
<i>Relevant Chemistry and NP Mechanistic Insights</i>	<i>10-15</i>
2.1 <i>Chemistry of Borane Morpholine</i>	<i>10</i>
2.2 <i>Mechanistic Studies</i>	<i>11</i>
<i>Experimental Section</i>	<i>15-20</i>
3.1 <i>Materials and Instrumentation</i>	<i>15</i>
- 3.1.1 <i>Materials</i>	<i>15</i>
- 3.1.2 <i>Instrumentation and Analysis</i>	<i>16</i>
3.2 <i>Methods</i>	<i>17</i>
<i>Results and Discussion</i>	<i>20-36</i>
4.1 <i>Temperature-Control UV-vis Study</i>	<i>20</i>
4.2 <i>Glucose Molar Equivalence: A Kinetic Advantage</i>	<i>22</i>
4.3 <i>Carbonyl/Polyol Screening</i>	<i>26</i>
4.4 <i>Acetone Derivatives: Series Screening</i>	<i>30</i>
<i>Conclusions</i>	<i>36</i>
<i>Future Work</i>	<i>37</i>
<i>References</i>	<i>39</i>
<i>Appendix A</i>	<i>42</i>
<i>Appendix B</i>	<i>43</i>

List of Figures

		<i>Page</i>
<i>Figure 1</i>	Four commonly administered tri-substituted iodobenzene X-ray contrast agents	1
<i>Figure 2</i>	TEM images of pH dependence on morphology and size distribution of BiNPs in a glycine buffered synthesis	6
<i>Figure 3</i>	TEM, ^1H NMR, and FTIR analysis of a glucose-assisted BiNP synthesis	8
<i>Figure 4</i>	Analysis of X-ray attenuation properties exhibited by the glucose/PPD-capped BiNPs with respect to concentration	9
<i>Figure 5</i>	Structure of borane morpholine with transition state when reacted with carbonyl-containing species	10
<i>Figure 6</i>	UV-vis spectroscopic data concerning the kinetic nature of nucleation and particle formation of BiNPs in PPD	21
<i>Figure 7</i>	Plot of reaction time versus molar equivalents of added glucose	23
<i>Figure 8</i>	Reaction scheme of $\text{Bi}(\text{NO}_3)_3$ in the presence of acetone and borane morpholine	24
<i>Figure 9</i>	Isomeric equilibrium between α -D-glucose, D-glucose, and β -D-glucose	25
<i>Figure 10</i>	First of two reaction series screened for reactivity with borane morpholine and $\text{Bi}(\text{NO}_3)_3$	27
<i>Figure 11</i>	Reaction time data for series 1	28
<i>Figure 12</i>	FTIR spectra for four species from series 1	29
<i>Figure 13</i>	Reaction series 2, consisting of acetone derivatives and glucose	30
<i>Figure 14</i>	Reaction time data for series 2	31
<i>Figure 15</i>	Dimeric equilibrium of 1,3-dihydroxyacetone	32

<i>Figure 16</i>	¹ H NMR spectra for acetone reaction with borane morpholine	33
<i>Figure 17</i>	¹ H NMR spectra for 1,3-dihydroxyacetone reaction with borane morpholine	35

Introduction - Background and Significance

1.1 Research Motivation (significance)

1.1.1 Medical X-ray Contrast Agents - X-ray contrast agents (XCAs) consist of atoms, molecules, or ionic compounds, that are capable of attenuating X-ray radiation and are used for the purpose of imaging structures or soft-tissue that are typically transparent under X-ray radiation. A patient receives XCAs internally, sometimes carrying unwanted side effects due to a patient's physiological response to the XCA. XCAs currently in use are barium sulfate (BaSO_4), which is used for gastrointestinal (GI) imaging, and heavily iodinated small organic molecules (*Figure 1*), which are used for imaging the circulatory and renal systems.¹

Iopamidol

Ioxogallic Acid

Diatrazoic Acid

Iodixanol

Figure 1 Four commonly used XCAs containing tri-substituted iodobenzene rings. The carboxylic acid, amide, and alcohol functionalities aid in water solubility. Adapted from [2].

BaSO_4 is a water insoluble salt that is typically administered orally or rectally. The white chalky suspension coats a patient's GI tract making it visible on an X-ray.

Even though ionic barium is fairly toxic, BaSO_4 passes through a patient's GI tract without absorption into the circulatory system, bypassing any unwanted side effects. On the other hand, iodine based XCAs are typically water-soluble compounds. As a result, iodinated XCAs are injected directly into a patient's circulatory system, allowing imaging of various circulatory structures.

Complications associated with such established XCAs are typically mild to moderate negative medical side effects, such as edema. Less commonly, patients can experience serious, and sometimes fatal, reactions to XCAs, including anaphylaxis and even cardiac arrest. The Food and Drug Administration reported 920 XCA-related deaths between 1978 and 1994, out of approximately 170 million contrast-medium enhanced radiological studies.¹ While this constitutes only a very small percentage of the total number, it still represents a significant problem associated with traditional XCAs that must be addressed.

In recent years, there has been a significant demand within the medical community for replacements to traditional XCAs. Functionalized heavy transition-metal complexes and nanomaterials are quickly becoming encouraging prospects in this field for a variety of reasons. Heavy transition-metal complexes, utilizing novel ligand design, allow for highly tunable electronic properties. As a result, such complexes can respond to a wide range of incident radiation, facilitating fluorescence or phosphorescence, enabling their use as imaging contrast agents³ or as components to optoelectronic devices.⁴ These complexes have also found utility in medicinal applications, such as anticancer agents.⁵ However, when considering contrast agents for imaging applications, specifically medical X-ray imaging,

nanomaterials have garnered the most attention, owing to their high X-ray attenuation.

1.1.2 Nanomaterials Explored - Nanoparticles (NPs) are of particular interest due to the fact that they are comprised of a tightly packed network of atoms with hydrodynamic radii up to 100 nm. The high surface area-to-volume ratio of such particles leads to a large fraction of their atoms being present on the NP surface, enabling them for applications in heterogeneous catalysis,^{6,7} lubricating oil additives,⁸ as well as electronic and optical display devices,⁹ among many other viable applications. More importantly, these factors contribute to their overall X-ray attenuation, making NPs potentially better candidates for application in medical X-ray imaging.

X-ray imaging utilizes a phenomenon known as attenuation. Attenuation of a given material decreases the intensity of incident radiation due to absorption and/or scattering of photons. The photoelectric effect (emission of an electron from a low-lying orbital of an atom due to interaction with a photon), Compton scattering (direct momentum transfer from an X-ray photon to a bound electron, effectively scattering the photon with reduced energy), and pair production (creation of an elementary particle and its antiparticle due to photon interaction with a nucleus) are typically seen as the primary causes for attenuation in matter.¹⁰

For nanomaterials used in medical imaging applications, however, the amount of radiation that a given material can absorb is of primary interest. Radiation absorption of a material is dictated by a parameter known as the X-ray attenuation

coefficient (μ), which is represented by the following expression:

$$\mu = \frac{\rho Z^4}{AE^3} \quad (1)$$

where ρ is the density of the attenuating material, Z is the atomic number of the X-ray absorbing atoms, A is the atomic mass of those atoms, and E is the energy of the incident X-ray radiation. Inorganic nanocrystals, typically heavy transition-metals (*e.g.* noble metals such as gold), are generally comprised of higher Z atoms than XCAs that are currently being administered. Since μ is directly proportional to Z^4 , the fraction of attenuated radiation increases exponentially with the atomic number of the attenuating element.²

A variety of elements and compounds have been investigated for use as NP XCAs. Studies have shown that inorganic NP XCAs tend to have characteristically longer circulation times and optimal chemical stabilities, both of which have enabled studies involving site-directed imaging.^{11,12} PEGylated erbium-doped ytterbium oxide particles and particles containing a tantalum oxide core, as well as a variety of other materials have been investigated for such applications.¹²⁻¹⁴ However, the majority of the research concerning NP XCAs have focused on gold nanoparticles (AuNPs), owing to the highly studied nature of their synthesis and application. AuNPs are more easily synthesized and exhibit many desirable electronic properties, lending to their continued research as XCAs, as well as components for a wide variety of other applications.^{11,15-19} However, gold is expensive and there still remains some risk of toxicity due to the tendency of AuNPs to bioaccumulate.¹¹

1.2 Bismuth Nanoparticles

1.2.1 Bismuth as an Alternative Material for NP XCAs - Bismuth (Bi) is an attractive alternative to gold for medically applied XCAs due to its high atomic number ($Z = 83$), low cost,²⁰ and generally accepted biological tolerance.^{21,22} Furthermore, bismuth nanomaterials should be, theoretically, much more X-ray opaque than contrast agents that are currently being administered due to the high Z value of bismuth. When comparing this parameter with that of other X-ray opaque atoms currently in use (*e.g.* iodine (I), $Z = 53$; barium (Ba), $Z = 56$; gold (Au), $Z = 79$) to that of bismuth, the direct proportionality of μ to Z^4 seen in equation 1 demonstrates the advantage bismuth nanomaterials should have in terms of X-ray opacity.

Bismuth has a relatively long-standing history of known biological tolerance and medicinal use, and is generally administered at high doses. As an example, Pepto Bismol contains milligram quantities of complexed bismuth(III) subsalicylate in a single dose. This suggests that elemental bismuth nanomaterials would make for a safe alternative to currently administered XCAs.²² Unlike AuNPs, elemental bismuth nanoparticles (BiNPs) undergo oxidation and hydrolysis in water, possibly leading to better systematic clearance, by decomposing over time into smaller molecular or ionic Bi(III) species, and avoiding bioaccumulation.²¹ However, this property also lends to difficulty in synthetic preparation as well as stabilization in aqueous media.

1.2.2 Bismuth Nanoparticle Synthetic Approaches - Of the BiNP preparations that have been reported, the majority are carried out in an air-free environment and

generally yield hydrophobic particles. Morphological control is usually accomplished with the use of organic solvents and surfactants that have either poor or unknown biocompatibility.^{22,23,24} Furthermore, purification of these nano-materials is often challenging due to the necessity of removing the excess of said potentially toxic reagents, such as tris[bis(trimethylsilyl)amino]bismuth ($\text{Bi}(\text{N}(\text{SiMe}_3)_2)_3$), prior to their application in biological systems.²¹⁻²⁴

In recent years, there have been two notable synthetic preparations developed by our research group that mitigate the challenges faced in aqueous synthesis of BiNPs. The first is a pH-dependent, glycine buffered synthetic approach.²¹ In this preparation bismuth nitrate pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$) is suspended in an aqueous glycine buffer solution with a pH maintained at a range of 8-10 pH units and temperature at 40°C. Upon reaching temperature, sodium borohydride (NaBH_4) is added to solution, which is immediately followed by the addition of the particle

Figure 2: TEM images of BiNPs synthesized using pH-dependent, glycine buffered synthetic preparation demonstrating the effect of pH on size and morphology control, as well as on reaction kinetics. **(a)** pH < 9; reaction time ~1s; aggregation of particles with a large size distribution; **(b)** pH > 9; reaction time 1-10m; greater control over size and morphology is achieved with a slight increase in pH.²¹

surfactant, dextran. Size and morphological control for this preparation is highly dependent upon the pH of the reaction system (*Figure 2*).

Dynamic light scattering (DLS) measurements of the colloids synthesized at pH > 9 were used to confirm an average hydrodynamic diameter of the purified particles, which was found to be ~60nm. Compared to a core size of ~19.5nm (measured by TEM), this represents a ratio of ~3.4 vol% bismuth core-to-dextran surface coating. This core-to-surface coating ratio inevitably results in poor X-ray attenuation for the particles, even under heavy concentration.²¹

Fourier transform infrared (FTIR) spectroscopy was then used to analyze the surface chemistry of the particles, indicating dextran as the sole surfactant. While this synthesis represents a major step forward in aqueous synthetic preparation for colloidal BiNPs, the particles' instability in environments with a pH outside of 8-10 and tendency to photodegrade, coupled with their poor X-ray opacity, present further challenges when concerning their potential biological application.²¹

In an attempt to overcome the challenges of stability with pH and photodegradation, a second method for synthesis of aqueous BiNPs was generated. In this synthesis, $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ suspended in 1,2-propanediol (PPD) is added to a solution containing α -D-glucose in PPD. A solution of borane morpholine in PPD is added, initiating the reaction. When the solution reaches a deep black color (~60s), the reaction is quenched in nanopure water (npH_2O). After centrifugation and purification, the particles are resuspended in npH_2O or ethanol (EtOH), making them ready for analysis.²⁵

In this synthesis, there is more of a temperature dependence on the size

distribution and the morphology of the particles. Early on in the development of this synthetic approach, ethylene glycol was used as the solvent with borane trimethylamine as the reducing agent. It was found that as temperature of the reaction increased, the morphology of the particles changed in response. More specifically, the “roughness” of the particles decreased, yielding more spherical particles versus the rhombohedral shape that is common to crystalline bismuth. However, in response to an increase in reaction temperature, size distribution increased. Therefore, it was determined that 80°C was the optimal temperature that yielded a more consistent size distribution with particle morphology that was bordering between spherical and rhombohedral. With this temperature constraint applied to the current synthesis, we see the same constant size distribution, however, the particle morphology is primarily rhombohedral (*Figure 3a*).

Figure 3: (a) TEM image of glucose/PPD-capped BiNPs demonstrating size and shape consistency achieved with this synthetic approach; (b) Top: ^1H NMR spectra of PPD, α -D-glucose, and glucose/PPD-capped BiNPs; Bottom: FTIR spectra of PPD, α -D-glucose, and glucose/PPD-capped BiNPs. Analysis of the surface chemistry shows the surfactant (α -D-glucose) and the reaction solvent (PPD) capping the BiNPs in a 5:1 molar ratio, respectively, where in the synthesis the molar ratio of glucose-to-PPD was 1:5.²⁵

Analysis of the surface chemistry with ^1H NMR and FTIR confirmed the presence of α -D-glucose as well as PPD on the surface of the particles in a 5:1 molar

ratio (Figure 3b). DLS measurements gave an average hydrodynamic diameter of $\sim 86\text{nm}$ while TEM measurements yielded an average core diameter of $\sim 74\text{nm}$, giving a core-to-surface coating ratio of $\sim 64\%$ by volume. The increase in the core-to-surface coating ratio demonstrates attenuation, as a function of concentration, with variation of X-ray tube voltages that stays relatively consistent (Figure 4).²⁵

Figure 4: CT attenuation evaluation of glucose/PPD-capped BiNPs. **(a)** CT images of varying concentrations (1-65mM bismuth) of BiNPs in solution; **(b)** Attenuation as a function of concentration with variation in X-ray tube voltage (80-140 kV); **(c)** Attenuation rates of BiNPs, bismuth(III) cations, and iodine with variation in X-ray tube voltage (80-140 kV).²⁵

When comparing the relative stability of glucose/PPD-capped particles with the dextran-capped particles, the former demonstrated a similar response when exposed to solutions of varying pH; the particles show greater stability in the slightly basic region of 8-10. Much like the dextran-capped particles, the glucose/PPD-capped particles decomposed readily in acidic environments. It should be noted that these particles appear to have a longer shelf life than the dextran-capped particles, in that they can be maintained for months without any signs of decomposition or photodegradation.²⁵

While there has been a great deal accomplished in the way of aqueous BiNP synthetic preparations, as well as techniques for developing aqueously stable BiNPs,

there remains much to learn. For example, in the last synthetic preparation discussed, the function of certain species (*i.e.* α -D-glucose) in the reaction system remains unclear. Furthermore, the mechanism for reduction of bismuth(III) by borane morpholine is not well understood. To that end, the focus of the research discussed hereafter is to develop further understanding into the subtle intricacies that lend to the overall success of this reaction. With greater understanding of the mechanism for this synthesis, more subtle and directed modifications can be applied to future syntheses, allowing greater control over physical and chemical parameters.

Relevant Chemistry and NP Mechanistic Insights

2.1 Chemistry of Borane Morpholine - In the synthesis being examined, borane morpholine (*Figure 5a*) is used as a reducing agent for the synthesis of BiNPs. Borane morpholine is a mild reducing agent, typically used in the reduction reactions of aldehydes and ketones.^{26,27} It has also seen use as a component for reducing metal salts in electroplating applications, as well as for NP synthetic preparations.^{19,25,28-30}

Concerning reduction of aldehydes and ketones, it is thought that the rate-determining step involves the attack of borane morpholine on the carbonyl with a corresponding hydride shift from

Figure 5: (a) molecular structure of borane morpholine; (b) generally accepted transition state of morpholine borane in reaction with an aldehyde/ketone.

boron to carbon.²⁶ *Figure 5b* shows the generally accepted transition state in which

bonding interaction occurs between boron and the keto-oxygen, as well as bonding interaction between the hydride and carbonyl-carbon. There are a number of competing theories as to what occurs beyond this transition state. One such theory is that upon nucleophilic attack of the keto-oxygen on the boron, a corresponding displacement of morpholine occurs, giving the following complex: $R_2C^+OB\cdot H_3$ (R = alkyl group or H). This is followed by a fast hydride transfer to the carbonyl-carbon giving a species with the following formula: R_2CHOBH_2 .^{26,27} Furthermore, this can lead to further reaction with another of the same carbonyl species to give $(R_2CHO)_2BH$.²⁷ However, addition of more carbonyl typically yields no reaction. This can then proceed according to various different pathways when introduced to water, typically resulting in H_2 gas evolution, generation of a hydroxyborane species, and formation of the corresponding alcohol.

Borane morpholine is also used to reduce metal salts in electroplating applications, as well as for NP synthesis. For NP synthesis, one advantage to using borane morpholine is that it is a more mild reducing agent, which lends to greater control over NP nucleation and morphology.^{19,25} Use of stronger reducing agents in NP synthesis (*i.e.* $NaBH_4$ or $LiAlH_4$) often results in significantly more rapid nucleation which can then lead to unstable colloids that aggregate and precipitate out of solution. For the case of NP synthesis, it is important to maintain kinetic control over the reaction such that control over size distribution, as well as morphology, can be achieved.

2.2 Mechanistic Studies - As previously established, there is increasing interest in the

research on elemental metal NPs due to the multiple possible applications utilizing both the physical and chemical properties exhibited by such materials. However, these properties are dependent on the particles' shape and size, surface (*i.e.* ligand coordination/surface-stabilization), and arrangement either in suspension or when supported by other materials.³¹ In order to achieve the desired properties, precise and accurate control in the synthesis of NPs is needed. Despite the extensive research and vast progress that has been made in the field of NP synthesis, size and morphology control, and the limited mechanistic understanding to achieve this control, remain challenges to this field.²⁴

It is understood that solution-based nanoparticle synthesis requires the presence of a species to act as a surface-stabilizer (surfactant), thereby avoiding particle aggregation. Typically, the nature of such surfactants and their ratio to the NP precursor allows for size and shape control in particle growth.³¹ Their role within the synthesis, however, is often times not well understood. More specifically, it is not clear as to whether these species act simply as surfactants, capping the NPs and preventing particle aggregation while contributing to the overall stability of the particles in solution, or if they actually have a role in the synthetic transformations that take place in the early stages of reaction. Such interactions could be coordination to the precursor or to other intermediates that are involved in the NP formation process, or as catalytic species, reducing the activation energy of reduction.

In recent years, there have been many investigations into the mechanism of NP formation in various synthetic systems. One such study by Lagunas *et al.* reports a

proposed mechanism for the formation of colloidal cobalt NPs (CoCNPs) from a dicobalt octacarbonyl ($\text{Co}_2(\text{CO})_8$) precursor.³¹ In this study, it was found that species typically considered to be simple surfactants actually have a direct influence on the rate and kinetics of the decomposition of the $\text{Co}_2(\text{CO})_8$ precursor. In order to achieve these findings, spectroscopic analysis (primarily infrared spectroscopy due to decarbonylation of the cobalt) of the solution where NP formation took place was conducted. Coupled with high-resolution transmission electron microscopy (HR-TEM), this provided a rich and more detailed account of the reaction progress towards NP formation. As a complement, density functional theory (DFT) calculations on some of the proposed organometallic intermediary species were done to help interpret spectroscopic results.³¹

Another study by Dudin *et al.* reported on the mechanism of electrochemical nucleation and growth of AuNPs on single-walled carbon nanotubes (SWNTs).¹⁶ In this study, increased densities of NPs were observed at greater cathodic (reduction) potentials. Furthermore, it was found that NP size initially increased with deposition time with constant particle surface coverage. At the highest driving forces, however, NP density appeared to decrease with deposition time, confirmed by atomic force microscopy (AFM), revealing both large and small particle sizes at longer times. This property was attributed to electrochemically induced Ostwald Ripening, in that larger particle formation occurs at the expense of smaller particles. Overall, this study suggested that nucleation was more so progressive in nature, as well as highly directional, occurring only on the SWNT network.¹⁶ This study does not incorporate the use of capping ligands, however, it provides more understanding into NP

nucleation and growth in correlation to the electronic parameters it's dependent on.

Finally, Wang *et al.* reported a mechanistic study in which a bismuth precursor, sodium bismuthate ($\text{NaBiO}_3 \cdot 2\text{H}_2\text{O}$), in either ethylene glycol or glycerol was subjected to high temperatures ($180\text{--}200^\circ\text{C}$) in a pressure sealed vessel for a period of 24 hours. Such conditions allowed for the reduction of the bismuth precursor through the following mechanistic steps:

Scheme 1

where ethylene glycol is oxidized to acetaldehyde in step 1, which is followed by reaction of NaBiO_3 to produce elemental bismuth with sodium acetate, acetic acid, and water as reaction byproducts. In this synthesis, ethylene glycol serves as both solvent and reducing agent, forming an intermediate (acetaldehyde) that is capable of reducing bismuth(V) to bismuth(0). In other cases, polyvinylpyrrolidone (PVP), acetone, and water were added to the synthesis in order to control morphology of the product.³²

For this preparation, particle growth is thought to occur based on the Ostwald ripening process. It was determined that nanoparticles were formed in solution according to the above mechanism, where some were able to grow into larger crystals, subsequently acting as seeds for the growth of nanowires or nanospheres. Further research proposed that growth of the nanocrystals was dependent on the identity of the surface-capping molecules in the system. For example, adsorption of ethylene glycol or PVP on the nanocrystalline surface through Bi-O interactions

could significantly decrease the growth rate of these nanocrystals, resulting in highly anisotropic growth.³²

The three studies explored represent only a small fraction of the variety of synthetic systems seen in NP production, demonstrating that there are very fine and subtle intricacies involved in not only the reduction mechanism, but as well as in the mechanism of formation in NP syntheses. It was shown that surface-stabilizing agents play a role in the mechanism of NP formation. However, they can also be quite active in the process of reduction of the precursor, as well. These studies provide insight into the finer details of NP synthetic mechanistic studies that must be considered.

Experimental Section

3.1 Materials and Instrumentation

3.1.1 Materials - Bismuth(III) nitrate pentahydrate, 98% ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$) and borane morpholine, 97% (morbor) were supplied through Acros. α -D-glucose, anhydrous, 96% (Glc), acrylic acid, 99% (HOAc), 1,3-dihydroxy-acetonedimer, 97% (DHDMK), and 1-propanol, 99.5+%, HPLC grade (nPrOH) were all supplied from Aldrich. Glacial acetic acid (HOAc) was supplied from AmaChem. 1,2-propanediol (PPD) was supplied from ChemProducts. Chloroform-D, 99.6 atom% D (CDCl_3) was supplied from TCI America. Deuterium oxide, 99.9 atom% D (D_2O) was supplied from Cambridge Isotope Laboratories, Incorporated. Acetone (DMK) was used as supplied from the chemistry stockroom at Portland State University. All reagents and solvents were used as received from their respective suppliers and stored as

per manufacturer recommendation.

3.1.2 Instrumentation and Analysis

TIME MEASUREMENTS - All time measurements were performed using a Samsung HMX-W200 pocket camera, in which reactions were visually monitored from beginning to end. Reaction timing began when borane morpholine was introduced to the system, while reaction completion was determined to occur when solution color change ceased.

ULTRAVIOLET-VISIBLE (UV-vis) SPECTROSCOPY - Time-based UV-vis spectroscopic measurements were performed on a Varian Cary 100 Bio UV-vis spectrophotometer equipped with temperature-control capabilities. Cuvettes containing PPD and $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ were set in the temperature-controlled heating block and were heated to 80°C. A solution containing solubilized borane morpholine was then added to the cuvette and mechanically mixed via micropipette, upon which the scan was started.

FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPY - FTIR measurements were performed on a Thermo Scientific Nicolet iS10 FTIR spectrophotometer equipped with a single-bounce diamond ATR attachment. Samples were prepared by concentrating the reaction mixture via rotary-evaporation, removing reaction solvent and any remaining volatile organics prior to measurement.

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY - ^1H NMR spectroscopy was performed on a Bruker 500 Hz AVANCE-III NMR spectrometer using a standard pulse sequence (zg30) and Bruker automation software. Spectra

were processed using the MestReNova 7 analysis software package. Samples were prepared by first concentrating the reaction mixture via rotary-evaporation. Upon concentration, depending on solubility, ~50-75 μL of sample were transferred to a borosilicate NMR tube with a micropipette and filled to a final volume of ~500-600 μL with CDCl_3 or D_2O .

3.2 Methods

Ultra-High Payload Elemental Bismuth Nanoparticle Synthetic Preparation - 54 g of α -D-glucose was suspended in 84 mL of 1,2-propanediol (PPD) and heated to ~40-60°C. 4 mL of 250 mM bismuth nitrate pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$) solution in PPD was then added to the glucose/PPD solution and further heated to 80°C. A final addition of 12.2 mL of 250 mM morpholine borane solution in PPD was added rapidly. The mixture was allowed to react for approximately 60 seconds, during which the solution became dark black, indicating BiNP formation. The reaction was terminated by pouring the solution into a beaker containing up to 200 mL of npH_2O at 0°C. The BiNPs were then isolated and purified by centrifugation and dialysis, respectively.

Temperature-Control UV-vis Study - The reaction mixture was scaled down by a factor of ~67 in order to conduct the temperature control UV-vis study. Mechanical stirring was achieved by repeated depression and release of a pipette plunger with a micropipette in solution, all other solution additions and reaction temperatures followed standard protocol. The instrument was set to scan for a period of 20 minutes, taking absorbance measurements every 6 seconds at $\lambda = 400$

nm.

Glucose Molar Equivalence Trials - Each reaction was scaled down by a factor of 10 in the interest of waste and reagent management. This resulted in a total reaction volume of ~10 mL. α -D-glucose at 0, 1, 2, 3, 6, 12, and 30 molar equivalents to Bi(III) was transferred to individual scintillation vials containing 8.4 mL of PPD and set to temperature. Following the original synthetic protocol, 0.4 mL of 250 mM $\text{Bi}(\text{NO}_3)_3$ in PPD was transferred to each reaction vial when temperature was in the range of 40-60°C. When reaction vial reached the synthetic temperature of 80°C, 1.2 mL of 250 mM borane morpholine in PPD was added, initiating the reaction. Each reaction was monitored by video to establish total reaction time.

Carbonyl/Polyol Screening - In individual 20 mL scintillation vials, a fraction of a gram of each substrate, listed in *Appendix B1*, was added to ~10 mL of PPD and stirred while heating to 80°C. ~1 mL of 250 mM $\text{Bi}(\text{NO}_3)_3$ in PPD was then added to the reaction flask and stirred for several minutes, any visible changes in solution upon addition were noted. Borane morpholine was then added in an approximately equivalent mass amount as the substrate. Changes in the reaction mixture were noted and recorded.

A series based on results from the carbonyl/polyol screenings was developed that included the following substrates: acetone, acetic acid, acrylic acid, glycine, 3-mercaptopropionic acid, L-cysteine, α -D-glucose, and fructose. For reactivity trials, 1 mmol of each substrate was transferred to a 20 mL scintillation vial containing ~8 mL of 1-propanol and heated to 80°C with mechanical stirring. When solution reached reaction temperature, 1 mmol of borane morpholine suspended in 2 mL of

1-propanol was then added. Aliquots were taken at 1 minute, 1 hour, and 4 hours, and concentrated for spectroscopic analysis. Following reaction with borane morpholine, ~0.3 mmol of $\text{Bi}(\text{NO}_3)_3$ was then added, with reaction time data and qualitative observations noted.

Acetone Derivatives - Individual reactivity trials of each of the 5 compounds tested in the following series was done: acetone, acetic acid, acrylic acid, 1,3-dihydroxyacetone dimer, and α -D-glucose. First, reactivity of the substrate with borane morpholine was tested, followed by a scaled down (by a factor of 10) model of the synthesis in which each substrate was tested with the bismuth precursor and borane morpholine under normal synthetic conditions.

For borane morpholine reactivity trials, approximately 1 mmol of each substrate was transferred to a 20 mL scintillation vial containing 8 mL 1-propanol. The vial was then sealed and set to stir and heat at 80°C. When the solution reached reaction temperature, 1 mmol of borane morpholine solubilized in 2 mL 1-propanol was added via syringe. A separate syringe needle was placed in the injection point to avoid pressure buildup upon borane morpholine addition. Aliquots were taken at 5 minutes and 1 hour for analysis.

Each of the 5 substrates were tested at 3, 6, 12, and 30 molar equivalents to $\text{Bi}(\text{III})$. For each reaction the desired amount of substrate was added to 8 mL of PPD in a 20 mL scintillation vial and sealed. The reaction was then set to heat and mechanical stirring at 80°C and ~700-800 rpm, respectively. When solution temperature reached the range of 40-60°C, 0.408 mL of a 250 mM solution of $\text{Bi}(\text{NO}_3)_3$ in PPD was added to the reaction vial via syringe injection. Upon solution

temperature reaching 80°C, 1.230 mL of a 250 mM solution of borane morpholine in PPD was added to the reaction vial via syringe injection, using a separate syringe needle to mitigate pressure buildup. Each reaction was monitored by video to judge overall reaction time.

Results and Discussion

4.1 Temperature-Control UV-vis Study - In ascertaining the role of glucose in the reaction, it was important to determine what would occur with its absence from the reaction system. Previous studies in our lab have indicated that no observable reaction took place without the presence of glucose.² However, this falls contrary to literature precedence, in which borane morpholine and other amine borane reducing agents have demonstrated utility in metal electroplating applications.²⁸⁻³⁰ Although electrochemical potentials vary to a large extent with metal-containing salts and with various reducing agents, it stands to reason that the differences in electrochemical potential should not be a limiting factor, especially with the incorporation of heat energy to aid in slightly reducing any thermodynamic energy barrier.

Of the several trials performed in which glucose was left out of the standard reaction system, all demonstrated bismuth(III) reduction taking place in a much larger interval of time than the 60 seconds required for the synthetic preparation. Initial observations put this interval in the range of 35-45 minutes. Reduction was indicated by a slowly progressing color change from colorless → transparent brown → black. It should be noted that the large discrepancy of this interval is due to the

inherent error of judgment in determining the end of a reaction by visual observation alone.

Measurements of radiation absorption via UV-vis spectroscopy were conducted to better quantify reaction times, specifically monitoring absorption at 400 nm (*Appendix A1*). However, due to absorbance values increasing beyond 1.0, reaction time data could not be collected in this manner. Therefore, scans were limited to twenty minutes per run, with scans taken at six-second intervals in order to minimize inconsistencies and systematic error in the measurements. In this way,

Figure 6: Combination of three UV-vis spectra on the synthesis of BiNPs with glucose absent from the reaction system. The compounded scan showcases three distinct regions: **0-8 min** - initial reduction of Bi(III); **8-16 min** - beginning nucleation of elemental bismuth atoms demonstrating a linear relationship with respect to time; **16-20** - particle formation and continued nucleation demonstrating an exponential relationship with respect to time.

it became possible to just observe the trends in nucleation and overall particle formation (*Figure 6*). There exist three distinct regions of interest within the corresponding plot: a flat or region occurring from 0-8 minutes, a linear region occurring from 8-16 minutes, and an exponential region from 16 minutes onward

(linear and exponential trendlines-*Appendix A2*). From these data, several inferences can be made. First, the “zero-region” can confidently be assigned to initial reduction of bismuth(III) that subsequently leads to the nucleation, or the linear region. While cationic bismuth(III) is able to absorb radiation, as seen in *Figure 4c*, it is thought that absorption capacity is limited to X-ray or higher energy radiation, while remaining inactive to low-energy UV radiation. If this were not the case, then it would follow that one would expect to see absorbance in the “zero-region.”

Second, the linear region is thought to correspond to initial nucleation of elemental bismuth atoms. Lastly, the exponential region is thought to correspond with particle growth, as well as continued nucleation. Overall particle formation is thought to occur via the Ostwald ripening process in which larger particle formation occurs at the expense of smaller particles. While this assertion has not been sufficiently studied, this does appear to be a reasonable conclusion, based on the UV-vis data. Once nucleation occurs to enough of a degree, the distance between multiple nuclei would be significantly lessened, which would allow for better chance of aggregation, leading to rapid particle growth. Furthermore, with continued nucleation taking place and the existence of growing particles, it follows that this would be a much more rapid process than that of nucleation itself, hence the exponential increase in absorbance.

4.2 Glucose Molar Equivalence: A Kinetic Advantage - With a bit more understanding as to how nucleation and particle formation take place with respect to time, elucidating the utility of glucose in terms of kinetic parameters was the logical next

step. A number of trials were implemented in which the amount of glucose introduced to the reaction system gradually increased from 0 to 30 molar equivalents. However, first determining the total reaction time with the absence of glucose was of primary concern. Using a digital recording device, several trials were carried out in which the reaction could be monitored and a reasonable approximation could be made for the total reaction time. The reaction start time corresponded to the time of addition of the reducing agent and the end time was determined to be when color change (or darkening) of the reaction mixture appeared to cease, which was at the discretion of the observer. This inherently leads to inconsistencies in the time data collected, in that determination of the reaction endpoint is subjective. Regardless, it still yields a reasonable approximation and can be used in conjunction with more visual reaction time determinations.

Figure 7: Plot of reaction time to molar equivalents of glucose to bismuth(III). The plot demonstrates an overall decrease, or exponential decay, in total reaction time in connection with added amounts of glucose to the reaction system.

Further trials were carried out at 1, 2, 3, 6, 12, and 30 molar equivalents of glucose to bismuth(III) and rerun at least once for result confirmation. *Figure 7* corresponds to a plot of reaction time versus molar equivalents of glucose to bismuth(III), where reaction times of multiple runs are averaged. From this plot, it can be reasonably concluded that addition of increasing quantities of glucose provides a kinetic advantage, in what is thought to be glucose acting “catalytic” in nature.

The “catalytic” role of glucose was first hypothesized after observation of a reaction carried out for demonstration purposes. In this reaction, a 50/50 solution of acetone-to-water (by volume) containing unsolubilized $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ is reacted with borane morpholine (*Figure 8*), initiating rapid reduction of bismuth(III) and

Figure 8: Reaction scheme in which $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$, in the presence of acetone, is reacted with borane morpholine, resulting in rapid reduction of bismuth(III) to elemental bismuth.

resulting in a suspension of elemental bismuth that quickly aggregates and precipitates out of the system. While not directly analogous to the reaction system being investigated, this reaction provides a line of inquiry into the structural nature of glucose during the reaction.

In solid form, glucose exists predominantly as the α -isomer. However, when solubilized in aqueous media, glucose stands in equilibrium between its three dominant forms: α -D-glucose, D-glucose, and β -D-glucose (*Figure 9*). At 25°C in H_2O ,

for example, α -D-glucose is present at $\sim 36\%$, β -D-glucose at $\sim 64\%$, while the intermediate straight-chain aldehyde form, D-glucose, is at $<< 1\%$.³³ Looking at

Figure 9: Isomeric equilibrium of glucose showing the most abundant species and relative equilibrium populations in H₂O at 25°C.³³

standard synthetic conditions, 30 molar equivalents of glucose are present in the reaction system. Under the assumption that relative equilibrium concentrations of glucose in PPD are similar to that in H₂O while also taking into consideration the reaction temperature of 80°C, which by Le Châtelier's principle would shift equilibrium toward formation of the aldehyde form, it is speculated that the relative equilibrium concentration of D-glucose would be closer to 1% of the total concentration. Therefore, under those circumstances D-glucose would be at a 3:1 molar ratio with bismuth(III). In that case, it could then be hypothesized that D-glucose is the active catalytic species of glucose in the reaction.

D-glucose as the active catalytic species is considered a possibility due to the aldehyde functionality, enabling reaction with borane morpholine, generating an intermediary alkoxyborane species that can facilitate more rapid reduction of bismuth(III) while also enabling coordination to the reduced bismuth particle surface. This hypothesis concerning carbonyl functionality was tested by the introduction of a variety of carbonyl-containing substrates to the reaction system.

Furthermore, the comparison of these results to the reactivity of polyols was done in order to provide insight into the mechanism, as the α - and β -isomers of glucose are, in themselves, polyols.

4.3 Carbonyl/Polyol Screening: Quest for a Carbonyl - Aside from glucose, a total of thirty-one different substrates were screened (*Appendix B1*). Substrates containing multiple functionalities were included such as thiol, amine, aromatic, carboxylic acid, and ether, all in combination with either carbonyl or polyol functionality. Each substrate's response to borane morpholine and to the combination of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and borane morpholine was monitored.

Screening results were quite varied and displayed general trends in terms of reactivity with respect to functionality. By far, substrates containing organosulfur functionality were most reactive when in the presence of bismuth(III) and borane morpholine, exhibiting rapid reduction that typically resulted in a stable black suspension, often times carrying a yellowish hue. However, this type of reactivity was to be expected due to the vast array of literature precedence that has established bismuth's high affinity for sulfur. Carboxylic acid-containing substrates generally exhibited moderate-to-high reactivity, typically forming dark black colloids that would eventually aggregate and precipitate out of solution. Polyol-containing substrates on the other hand, typically displayed mild-to-no reactivity in the presence of bismuth(III) and borane morpholine, with exceptions found in maltose and D-fructose. In comparing to the series of controls in which glucose was removed from the synthetic system where the reaction still proceeded but produced

unstable macroscale particles, the results with the polyols were not entirely surprising. Digital images of screening samples, several hours after reaction endpoint, can be found in *Appendix B2*.

From these results, a more controlled series of substrates was determined (*Figure 10*). This series was based on acetone as the model for rapid reduction, in which each substrate chosen can be viewed as a derivative of the one that came before. α -D-glucose and D-fructose were also included in this study, as glucose is used in the accepted synthetic protocol, while separate unpublished studies have been conducted in our lab on the efficacy of fructose in the synthetic system.

Figure 10: First of two series-screening, comprised mainly carboxylic acid-containing substrates, to determine reactivity trends based on structural similarity and varying functionality.

For this particular series study, 1,2-propanediol was replaced with the structurally and nearly chemically similar 1-propanol, merely for the purpose of concentrating the reaction solution as to avoid over saturation of solvent signal during spectroscopic analysis. Three separate reactions were carried out with each substrate and borane morpholine at a 1:1 molar ratio for a period of 1 minute, 1 hour, and 4 hours. Aliquots of each system were analyzed prior to the addition of $\text{Bi}(\text{NO}_3)_3$, at which time the reduction of bismuth(III) was timed, results of which are shown in *Figure 11* below.

Figure 11: Reaction time data for first series screening trials; **DMK** - acetone, **HOAc** - acetic acid, **HOAc** - acrylic acid, **Gly** - glycine, **HOTpr** - 3-mercaptopropionic acid, **Cys** - L-cysteine, **Glc** - α -D-glucose, **Frc** - D-fructose.

Of the trials conducted, results appear to be relatively consistent with the initial screening trials with the exception of the results obtained for acetone, L-cysteine, α -D-glucose, and D-fructose. As a whole, substrates containing carboxylic acid functionality appeared to react the fastest, displaying an overall decrease in time for reduction of bismuth(III) as the length of time of interaction between the substrate and borane morpholine is decreased. However, what came as a surprise was the lack of reactivity of acetone, α -D-glucose, and D-fructose in the 4 hour and 1 hour trials. Even more surprising were the inconclusive results obtained for L-cysteine, where during initial reactivity screenings demonstrated thorough reduction of $\text{Bi}(\text{NO}_3)_3$ but displayed quite the opposite during these trials.

In conducting FTIR analysis on the aliquots taken before addition of $\text{Bi}(\text{NO}_3)_3$, an important factor, in terms of reactivity, was discovered (*Figure 12*). In the stacked FTIR spectra, the top scan represents the substrate (clean), the middle scan is after 1 minute of reaction, while the bottom scan is after 1 hour of reaction. There

are a couple of noteworthy features presented in this data. The first is the decrease in intensity in the carbonyl band at $\sim 1600\text{--}1700\text{ cm}^{-1}$ in acetic acid (**12b**) and acrylic acid (**12c**), and the complete lose of the band in acetone (**12a**). This corresponds directly with the reactivity profile of borane morpholine with carbonyl-containing compounds, as discussed in section 2.1. The band between $2400\text{--}2200\text{ cm}^{-1}$ seen in **12b**, **12c**, and in the middle scan of **12a**, which corresponds to the BH_n stretching frequency of borane-type compounds³⁴ appears to be correlated to the successful reduction of ionic bismuth.

Figure 12: Representative FTIR spectra of four select series screening trial runs. For each spectrum: **Top** - scan of unreacted substrate; **Middle** - scan after 1 minute of reaction with borane morpholine then addition of $\text{Bi}(\text{NO}_3)_3$; **Bottom** - scan after 1 hour of reaction with borane morpholine then addition of $\text{Bi}(\text{NO}_3)_3$. (a) acetone screening; (b) acetic acid screening; (c) acrylic acid screening; (d) glucose screening.

Acetone, α -D-glucose, and D-fructose displayed no reactivity with addition of $\text{Bi}(\text{NO}_3)_3$ in the 1 and 4 hour trials, while definite reduction is observed in the 1 minute reaction trials. All other substrates, with the exception of L-cysteine, displayed reduction of bismuth(III) in all trials. Therefore, a correlation between the

existence of the IR-band corresponding to the BH_n stretching frequency and reduction of bismuth(III) can be drawn. However, there still remain inconsistencies in this correlation, that being in the spectra of α -D-glucose. The BH_n stretching band is not present in any of the spectra. This may be in part due to the abundance of hydroxyl linkages present in α -D-glucose that could be saturating the spectra to the point that the BH_n stretching band cannot be seen. Regardless of this discrepancy, these results appear to support the hypothesis of a potential intermediary alkoxyborane species and that the presence of a carbonyl has an important role in generation of this seemingly short-lived intermediary species.

4.3 Acetone Derivative Screening - In order to gain perspective on the proposed intermediary alkoxyborane species, the initial series that underwent screening was further modified to include only carbonyl/polyol containing functionality (*Figure 13*), removing any amine- and organosulfur-containing substrates. In this way, unnecessary variables are removed and therefore results concerning reactivity with respect to time should bear more of a trend with respect to structure and size.

Figure 13: Acetone derivative series. Modification of original series includes the addition of 1,3-dihydroxyacetone dimer, while removing glycine, 3-mercaptopropionic acid, L-cysteine, and D-fructose.

Before proceeding to discover what kind of structural features may be present in the proposed intermediary alkoxyborane species, the first line of inquiry was to see the response of the reaction with respect to increasing amounts of substrate. Time data from glucose-free synthetic trials were obtained as a baseline measurement for subsequent time data from the substrates being screened (*Figure 14*). Trials were conducted with 3, 6, 12, and 30 molar equivalents of added substrate.

Figure 14: Plot of reaction time versus increasing amounts of substrate in the synthetic system. A clear trend of decreased reaction time is observed with increasing amounts of added substrate. Furthermore, there appears a loose trend in decreasing overall reaction time to substrate size, with the exception of time data for glucose.

A clear trend is observed in terms of reaction time to added amounts of substrate. Reaction times of individual substrates decrease with an increase in the amount of substrate added to the reaction system. This trend falls in accord with findings from the glucose molar equivalence study, in which a near exponential decay, in terms of reaction time, was seen with increasing amounts of glucose. Furthermore, an overall decrease in reaction time with respect to substrate size can be seen, as well. This would imply that increasing substrate size has an inherent

effect on the overall reactivity. However, glucose appears to fall out of this trend. Further study into this phenomenon will have to be conducted in order to determine the cause.

Following this study, acetone and 1,3-dihydroxyacetone dimer were taken from this series for more extensive study with the goal of determining what structural features and functionality may be facilitating the above reactivity trend. From the plot above, the reactivity of acetone versus that of 1,3-dihydroxyacetone dimer is significantly different. It is possible that structural differences, that being of a simple dimethyl ketone versus a six-member heterocycle containing two sets of vicinal diol linkages, may cause this difference in reactivity. However, in solution, 1,3-dihydroxyacetone dimer exists in equilibrium between the dimer and its relatively unstable monomeric form (*Figure 15*).³⁵ Taking the monomeric form into consideration yields differences in only the 1,3-diol linkages, making for a reasonable comparative study.

Figure 15: Dimeric equilibrium of 1,3-dihydroxyacetone dimer (**I**) and 1,3-dihydroxyacetone (**II**).³⁵

To determine structural effects, both substrates were subjected to the same reaction conditions: a 1:1 molar ratio of each substrate to borane morpholine (~0.5 mmol each) in 10 mL of 1-propanol; solutions set to 80°C with mechanical stirring. For acetone, aliquots were taken at 30 seconds, 60 seconds, and 120 seconds of reaction time to accommodate for potential reagent evaporation. Each aliquot was

concentrated via rotary evaporation, followed by sample preparation for ^1H NMR analysis (Figure 16). It can be asserted from the spectra below that borane morpholine is being consumed, marked by the decrease in relative intensity of the corresponding signals. Furthermore, the signal corresponding to borane (δ +1.00-1.98 ppm) is gradually losing signal as the reaction proceeds, lending further evidence to the consumption of borane morpholine.

Figure 16: ^1H NMR spectrum of (a) acetone, (b) borane morpholine, (c) 30s aliquot, (d) 60s aliquot, and (e) 120s aliquot. In c, d, and e, the signals corresponding to borane morpholine are noticeably decreasing in relative intensity, while new signals are starting to appear. The triplet at δ +0.86 ppm, the multiplet at δ +1.52 ppm, and the triplet mixed in with the doublet of triplets at δ +3.51 ppm can be assigned to the solvent, 1-propanol. However, the appearance of the triplet at δ +3.69-3.71 ppm could suggest the formation of a propyl borate-type species.

One aspect not present in the spectra is the characteristic signals corresponding to the presence of an isopropyl borate-type compound thought to be the intermediary species for the acetone reaction. Its presence would be confirmed

by a multiplet at δ +4.29-4.31 ppm, corresponding to the successful addition of a hydride at the carbonyl-carbon position of acetone, and a doublet at δ +1.16-1.18 ppm corresponding to the methyl groups. Signals corresponding to 1-propanol are present, however, which would indicate that its removal from the reaction mixture was incomplete. This may also suggest that what solvent was not removed during the workup procedure may in fact be coordinated to boron, resulting in a propyl borate-type species. This thought is suggested due to the emergence of a triplet at δ +3.69-3.71 ppm, which would correspond to the protons on the carbon adjacent to the alcohol oxygen. However, more thorough workup techniques (*i.e.* chromatographic separation) would need to be employed, followed by further analysis by not only ^1H NMR, but by ^{11}B NMR, as well.

Similar analysis was carried out on the reaction of 1,3-dihydroxyacetone dimer (*Figure 17*), however, aliquots were taken at different time intervals: 1 minute, 5 minutes, and 10 minutes. The different time intervals were implemented to ensure equilibrium stabilization from the dimer to the monomeric form of 1,3-dihydroxyacetone, which would allow for more thorough interaction with borane morpholine. From the spectrum for 1,3-dihydroxyacetone (**17a**), it would appear as if the monomeric form is the prominent species when in solution, supported by the prominence of the strong singlet at δ +4.71-4.73 ppm, which corresponds to the protons at the α -carbons on either side of the carbonyl-carbon. It is quite clear from the spectrum for the 1-minute aliquot (**17c**) that 1,3-dihydroxyacetone, whether the dimer or the monomer, is no longer present in either form in the reaction system.

Figure 17: ^1H NMR spectrum of (a) 1,3-dihydroxyacetone dimer, (b) borane morpholine, (c) 1 min aliquot, (d) 5 min aliquot, and (e) 10 min aliquot. Similarly seen in the spectra for the reaction acetone with borane morpholine, spectra c, d, and e, display a noticeable decrease in the corresponding signals for borane morpholine. Again, solvent signals remain prominent, while the triplet at δ +3.69-3.71 ppm suggests the possibility of the formation of a propyl borate-type species.

Much like the spectra for the reaction with acetone, it would appear as if reaction solvent was not sufficiently removed. However, there is also suggestion of a propyl borate-type species in this set of spectra, suggested by the signal at δ +3.69-3.71 ppm. It could seem reasonable to speculate the formation of an alkoxyborane-type species consisting of 1,3-dihydroxyacetone and solvent ligands, however, the necessary chemical shift for the hydride added to the carbonyl-carbon (a doublet at δ +3.50 ppm) is not visible in the spectra. It may be a case of oversaturation of the solvent molecules bound to boron, which would indefinitely eclipse the signal for the hydride at the carbonyl-carbon position of 1,3-dihydroxyacetone. Further

studies are required in order to confirm or disprove the existence of an alkoxyborane species.

Lastly, there appears to be no change in the spectra from *17c-e*, suggesting that the reaction was rather rapid and ended around the time the 1 minute aliquot was taken. This is most certainly in support of the incredibly rapid reaction seen with 1,3-dihydroxyacetone in the presence of $\text{Bi}(\text{NO}_3)_3$ and borane morpholine in the initial time trials for this series.

Conclusions

From the research presented, a number of assertions can be made concerning the nature of the synthetic preparation examined. First, kinetic parameters that dictate the nature of morphology and size distribution of BiNPs in this synthetic scheme are governed by very subtle and intricate reaction conditions. It was the goal of this research to attempt at uncovering some of these conditions in order to elucidate aspects of the mechanism in which bismuth(III) is reduced by borane morpholine. It has been found that size, structure, and functionality of substrates introduced into the reaction system play a key role in the process of bismuth(III) reduction. However, the nature of these aspects is still unknown.

It was initially hypothesized that glucose in its straight-chain aldehyde form played some catalytic role, facilitating the rapid reduction of bismuth(III) in conjunction with borane morpholine. However, there are discrepancies in this hypothesis. Most notable is the relative population of the straight-chain D-glucose. While in aqueous media at 25°C, that population is at significantly less than 1% of

the total concentration of glucose, as stated previously. This presents problems in that the probability of such an interaction between borane morpholine and D-glucose, which is a very short-lived intermediate in the isomeric equilibrium, is significantly low, such that the possibility of interaction becomes exceedingly less likely to occur. Therefore, it must be speculated that the nature of glucoses reactivity comes with the 1,2- and/or 1,3-diol interactions with borane morpholine.

While the studies presented did not represent a complete look into the mechanism of the glucose-assisted synthesis of BiNPs, great progress was made in understanding small intricacies of reactivity. Furthermore, these studies aided in setting a strong foundation for future study into elucidation of the mechanism for reduction and particle formation of BiNPs that will lead to more directed modifications for future synthetic preparations.

Future Work

There are a few obvious studies to initiate that would go a long way in discovering the mechanistic details of the glucose-assisted synthesis of BiNPs. The first study will involve solvent switches, which will seek to determine the importance of diol interactions within the system. A variety of diols and polyols will be screened, observing solubility of the bismuth(III) precursor, as well as overall reactivity when introducing borane morpholine to the reaction system.

Another study will involve the switching of reducing agents to determine structural and electronic parameters of various amine borane reducing agents. The lability of the coordinating ligand would allow for the observation of kinetic

parameters and may potentially lead to synthetic modifications that yield more efficient control over these parameters.

Following the mechanistic study presented by Wang *et al.*,³² $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and 1,2-propanediol will be subjected to a high pressure and temperature reaction in which full analysis of the end result will be done to determine changes in reaction species. This should lead to a proposed mechanism for that particular reaction. This study would be complimented by a solid-phase reaction in which solid $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and borane morpholine will be mixed at low reaction temperatures, the result of which will be analyzed in conjunction with the high pressure/temperature reaction results.

Lastly, studies involving ^{11}B NMR in tandem with ^1H NMR will be carried out in order to determine the nature of borane reactivity. To that end, understanding how borane interacts with the small variety of species present in the glucose-assisted BiNP synthesis, will strongly aid in the determination of mechanistic parameters.

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Appendix A

Time Resolved UV-vis Studies

A1 - Scan wavelength determination:

Scan of absorbance versus the wavelength range of 400-800nm. Each absorbance band corresponds to time. As time increases, absorbance increases as a result.

A2 - Linear and exponential regions of Figure 6

Left: linear region of Figure 6 in which from the interval of 8-16 minutes it is believed to be initial nucleation which occurs linearly with respect to time; **Right:** exponential region of Figure 6 in which it is believed to be particle formation occurring through what is suspected to be the Oswald ripening process and occurs exponentially with time.

Appendix B1**Carbonyl/Polyol-Containing Molecules for Reactivity Screening**

Appendix B2

Images of Reaction Endpoint for Screening Trials

**Note - Some of the substrates could not be included due to unforeseen complications during reaction that lead to the scrapping of the reaction mixture before picture could be taken.*