ORGANIC MOLECULAR CAGES AS TEMPLATES
FOR THE SYNTHESIS OF METALLIC NANOPARTICLES: FROM STABILIZATION TO
APPLICATION AND ASSEMBLY

by

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.
Thesis Abstract

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Organic Molecular Cages as Templates for the Synthesis of Metallic Nanoparticles: From Stabilization to Application and Assembly

Thesis directed by Prof. Wei Zhang

Shape-persistent 3-D covalent organic polyhedrons (COPs) with well-defined intrinsic cavities have been well studied in materials chemistry due to their applications in host-guest chemistry, chemical sensing and gas adsorption and separation. However, the use of 3-D COPs as endo-templates for the synthesis of metallic nanoparticles has not been intensely explored. The purpose of the work described within this thesis is to answer the following questions: Can discrete, purely organic hollow molecular structures be designed in such a way as to facilitate the size-controlled synthesis of metallic nanoparticles? What are the applications of such organic-inorganic hybrid structures? Is it feasible for such structures to be used as the basic repeat units for further chemical assembling into more complex architectures?

In Chapter 1, an overview is given on the current progress of templated nanoparticle synthesis as it relates to molecular structures with closed-shell interiors. The advantages of 3-D templates built in a modular fashion will be highlighted.
In Chapter 2, the templated synthesis of gold nanoparticles (AuNPs) within organic cage molecules is described. Particle growth and encapsulation within the hollow cage interior can be guided through the introduction of interior thioether groups and allows for a size-controlled synthesis of AuNPs with high solubility and excellent stability.

In Chapter 3, the application of cage-encapsulated palladium nanoparticles (PdNPs) in homogeneous catalysis is presented. Using the organic molecular cage described in Chapter 2, we demonstrate the ability to seed the growth of PdNPs and further demonstrate their activities in the Suzuki-Miyaura reaction.

In Chapter 4, the directed assembly of colloidal AuNPs by organic cage molecules is described. When substituents on the cage exterior are modified, the cage encapsulated nanoparticles can be covalently linked together to form short 1-D oligomers with variable interparticle distances. The formation of discrete and variable 2-D clusters mediated by small organic linkers will also be described.

Chapter 5 focuses on current research progress towards the synthesis of AuNPs within covalent organic frameworks (COFs). Using a similar design principle as described in previous chapters, the size-controlled synthesis of AuNPs within the void space of COFs as solid supports for heterogeneous catalysis is presented.

Chapter 6 gives a short perspective on current work and recommended future work. This chapter gives some mention to silver nanoparticle research as well as further development of nanoparticles encapsulated within organic cage frameworks (OCFs) from covalent organic polyhedron precursors.
DEDICATION

To My Family
ACKNOWLEDGMENTS

This thesis represents not only countless laborious hours at a keyboard, but is the culmination of many years of research in synthetic organic materials chemistry. Beginning first as an undergraduate researcher in the Zhang group, and into my eventual transition as a full-time graduate student under the same advisor, I feel deeply grateful and truly privileged for all of the friends, experiences and knowledge I have accumulated over the years. As such, this thesis could never have been completed without the advice, support, and generosity of my colleagues, friends, mentors and students. First and foremost I wish to thank my advisor, Professor Wei Zhang, and his wife Dr. Yinghua (Alice) Jin, for their constant mentorship, unending support, and willingness to help me develop into an independent, mature researcher. Your kindness, expertise, skepticism, passion for chemistry, and eagerness to engage in scientific discourse has been inspiring and will forever be cherished. I am deeply grateful to the following people for their contributions: Claire Waugh, Ben Tucker, Jen Tucker, Dr. Chao Yu, Dr. Philip Tayton, Dr. Kenji Okochi, Dr. Lily A. Robertson, Athena Jin, Dr. Youlong Zhu, Dr. Haishen Yang, Dr. Ya Du, and Dr. Jyothish Kuthanapillil. Your friendship, guidance, and support have been significant and will always be remembered.

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CHAPTER I

CLOSED-SHELL STRUCTURES AS ENCAPSULATING AGENTS FOR METALLIC NANOPARTICLES

1.1 Introduction

“Materials are what the world is made of. They are hugely important, and hugely interesting. They are also intrinsically complicated.”

-George M. Whitesides

The American architect Louis Kahn was once quoted as saying “even a brick wants to be something more than just a brick”.¹ For Kahn, form did not necessarily follow function and it seemed there were times when he truly believed his materials had a sense of their own vocation. One could make a similar argument about the field of biology and our understanding of biological systems: a series of seemingly simple molecules that interact with one another, associate into larger aggregates, and then further self-assemble to give some of the most sophisticated and structurally complex nanostructures known. In fact, biology is one of the principal inspirations for nanoscience. This ability for biological systems to develop into hierarchically ordered structures that impart uniquely separate functions and properties not present in the individual components is only beginning to be exploited consciously and rationally in synthetic materials. To date, the art of organic and inorganic chemical synthesis is arguably
the most sophisticated of all science and has focused on a few fundamental questions in regards to nanostructured materials: i) What are the most interesting nanostructures? and ii) How can they be synthesized and introduced into materials? The following chapters provide an approach to molecular design that utilize the tools of organic synthesis, along with the concept of molecular templates, to place atoms into molecular structures with atomic-level precision so that one day synthesized materials can be programmed into something more than what they really are.

1.1.2 Nanoparticle properties

Most carpenters will probably agree that their preferred hammer is one made out of steel, not gold. Though it would probably be a very luxurious and expensive hammer, even the most skilled carpenter would find it very difficult to get much work done with such a thing. Our everyday experience illustrates to us that the type of material we are using typically determines the properties of the material. A steel hammer is useful because it is tough and can drive nails, while a gold hammer is far too soft to be of any use other than decoration. One of the most intriguing aspects of nanoscience has been the realization that as things become small, they become different. In the nanoscale size regime (1-100 nm) the properties of materials are largely determined not by the nature of the material itself, but by its physical dimension.

Particles in the size range of 1-100 nm are referred to as nanoparticles. Such particles typically contain $\sim 10^6$ atoms or molecules bonded together, which puts their dimensions somewhere in the intermediate range between that of individual atoms and aggregates large enough to be considered bulk material.\textsuperscript{2,65} Figure 1.1 shows the situation in which a molecule with discrete energy levels, ordinarily called molecular orbitals, is occupied by a particular number of electrons. Increasing the number of atoms broadens the states, owing to the increase
in energy levels, and eventually gives rise to the well-known band structure present in a metal of freely mobile electrons (Fig. 1.1c). Nanoparticles lie somewhere in the middle (Fig. 1.1b) and have physical properties that are neither those of bulk material or molecules but instead depend strongly on particle size, shape, and interparticle distances. These differences in physical property are the outcome of high surface-to-volume ratio, quantum size effect, and electrodynamic interactions, and as a consequence provide to nanoparticles some remarkable optical, magnetic, chemical, and electronic properties. For instance, a macroscopic piece of copper has a soft, malleable and ductile character, whereas copper nanoparticles are exceptionally hard.

![Figure 1.1. Formation of a metallic band structure.](image)

Noble-metal nanoparticles, namely, palladium, silver, and gold, exhibit strong absorption bands in the visible and near-infrared (vis-NIR) domains that give them their characteristic colors. For example, colloidal gold nanoparticles are responsible for the vibrant red colors observed in stained glass windows. The optical properties of nanoparticles are governed by localized surface plasmon resonances (LSPRs), which are generated when the conduction
electrons are driven into a coherent oscillation when induced by the interacting electromagnetic field (Fig. 1.2).\(^7\)

**Figure 1.2.** Schematic of plasmon oscillation for a sphere, showing the displacement of the conduction electron charge cloud relative to the nuclei. Reproduced from reference [7].

As the incident light passes over the surface of the particle the electron cloud is displaced relative to the nucleus, giving rise to a restoring force from Coulomb attraction that brings the electrons back towards the nucleus and into a collective oscillation. Since many electrons contribute to this LSPR excitation the absorption and scattering cross sections at the surface of the particle can be very large.\(^8\) The guiding and controlling of light based on the sensitivity of the surface plasmon resonance to both the environment of the nanoparticle and its interparticle couplings is the basis for many of the applications (e.g., colorimetric sensing, plasmon enhanced luminescence upconversion, waveguides).\(^9-11\) It is for this reason that the control of the size and shape of nanoparticles with a high degree of precision is essential and a key challenge in materials science, as these parameters have a significant influence on the nanoparticles’ properties and potential applications.
1.2 Encapsulation by Closed-Shell Hollow Interior Structures

Though the potential benefits of organizing and controlling matter at the nanoscale has yet to be entirely realized, billions of years of evolution has provided natural systems with highly effective methods towards the efficient production of energy and materials through the use of nanoscale biological entities (e.g., DNA, enzymes, chlorophyll, etc.). By mimicking nature’s ability to directly control systems at the nanoscale, it is foreseeable that we too may also be able to create a more sustainable environment for future generations to come. To date, the synthesis of nanoparticles is routine and many research groups have demonstrated the synthesis of a wide variety of nanoparticles. Though many solution-phase methods exist for the synthesis of nanoparticles, many of which are based on surface capping ligands and dendritic architectures, the precise control of size and shape in the synthesis of nanoparticles is still challenging and of great importance in material science since control of bulk properties on a molecular level could lead to new and interesting properties. It is for this reason, historically speaking, that many of the more efficient methods towards the synthesis of monodisperse nanoparticles have advanced through the use of more closed-shell, hollow “ship-in-bottle” structures that restrict the particles to a specific size and shape.

1.2.1 Biomolecular Templating

In the early period of colloidal science the synthesis of nanoparticles was done using reactions in microemulsions such as reverse micelles, where vesicular assemblies are built up from low-molecular-weight molecules. However, due to the lack of a structurally well-defined cavity these classes of templates tend to produce imprecise particles. Other approaches to the formation of nanostructures with greater structural integrity emerged from biomolecular
architectures, such as proteins, as spatially well-defined host systems comprising robust outer shells and high degrees of organization.

The iron storage protein ferritin is probably the most well understood self-assembled protein cage used in the synthesis of nanoparticles.\textsuperscript{30-35} A ubiquitous intracellular protein, ferritins consist of a hydrated iron\textsuperscript{III} core encapsulated within a polypeptide based spherical shell. The iron atoms within ferritin can readily be removed from the interior cage via reductive dissolution to afford the hollow cavity analog form apoferritin. T. Ueno and co-workers exploited such a hollow cavity by encapsulating palladium nanoparticles (PdNPs) within the interior via in situ chemical reduction of Pd\textsuperscript{II} ions (Fig. 1.3).\textsuperscript{36} Interestingly, Mann and co-workers demonstrated that post-functionalization of the ferritin surface via carbodiimide-activated coupling of long chain primary amines to the carboxylic acid residues allowed for solubility in several organic solvents.\textsuperscript{37,38}

![Scheme illustrating Pd-apoferritin preparation. TEM images of Pd-apoferritin with (a) unstained sample and (b) samples negatively stained with uranyl acetate (scale bar 50 nm). Reproduced from reference [36].](image)

Several other groups have used additional biomolecular systems in a similar fashion to Pd-apoferritin formation to generate hybrid materials. For example, the hollow icosahedral bacterial
enzyme Lumazine synthase was also shown to be a suitable template for the synthesis iron oxide nanoparticles.\textsuperscript{39} Biotemplating has even been applied to virus particles,\textsuperscript{40} as such natural starting materials allow chemists to explore the chemical modification of a synthetic platform in almost unlimited quantities. Also, viruses are distinct from ferritin in that they occur in a wide range of size and morphology, which would allow for a more versatile strategy in terms of the molecular entrapment of NPs with varying sizes and surface morphology. However, the inability to alter the chemical structure of such biological templates limits their general usability. With this in mind, it is desirable to synthetically generate void spaces within molecules whereby guests will be trapped and specific reactions may occur.

1.2.2 Supramolecular DNA Assembly

A particularly attractive synthetic platform for the encapsulation of nanoparticles has been through the use of DNA as a template. As a predictable and programmable genetic code carrier, DNA acts as a precise self-assembly unit and hence an attractive template for the organization and control of matter on the nanoscale.\textsuperscript{41} To date, there is now a plethora of literature describing the programmable assembly of DNA building blocks to create both discrete two-dimensional materials,\textsuperscript{42-45} as well as three-dimensional DNA polyhedra.\textsuperscript{46-49} As host-guest interactions are common in nature, as seen in enzyme-substrate interactions, such three-dimensional DNA polyhedral (nanocages) are of particular interest for the development of higher order functional constructs.

Recently, the Mao group demonstrated the potential of using DNA nanocages as host-guest systems through AuNP encapsulation within a polyhedron void space to form core-shell structures (Fig. 1.4).\textsuperscript{50} The AuNP encapsulation was driven by the hybridization between DNA
strands immobilized on AuNPs and sequence complimentary strands on the tails of the preassembled DNA nanocages (including DNA tetrahedron, octahedron, and icosahedron).

![DNA polyhedra encapsulated AuNPs assembled into core-shell structures: tetrahedron (TET), octahedron (OCT), and icosahedron (ICO).](image)

**Figure 1.4.** DNA polyhedra encapsulated AuNPs assembled into core-shell structures: tetrahedron (TET), octahedron (OCT), and icosahedron (ICO). Reproduced from reference [50].

Given the diameters of the spherical interiors as 7.9, 12.0, and 20.6 nm for DNA-TET, OCT, and ICO, respectively, it was found that by simply adding functionalized AuNPs of the appropriate size allowed for the formation of 1:1 DNA-AuNP complexes. Additionally, it was also possible for several smaller functionalized particles to be swallowed within an appropriately larger sized nanocage. Through addition of excess single DNA strands the AuNPs could also be released from the nanocages resulting in the original empty DNA polyhedral.

Another advantage of this unique class of materials is in its ability to engineer DNA based ‘nanopeapod’ structures, as pioneered by the Sleiman group. Due to the programmability of DNA, they were able to link together triangular DNA units via double stranded linking stands (dsLS) and construct DNA nanotubes with longitudinal variation, generating alternating smaller (7 nm) and larger (14 nm) capsules along the nanotube to give a nanopeapod-type structure (Fig. 1.5). The size-selective encapsulation and precise positioning of AuNPs along the DNA nanotube was made possible simply by adding AuNPs with sizes similar to the dimensions of the
capsules (5- and 15-nm AuNPs). Since the AuNPs were functionalized only with negatively charged citrate groups, the particles themselves have no actual affinity for the DNA strands and were thus encapsulated only passively due to the dimensional similarity.

![Figure 1.5](image.png)

**Figure 1.5.** (a) Construction of triangular DNA nanotube 3 through addition of nine dsLS. (b) Size-selective encapsulation of AuNPs to give DNA nanotube 4. Reproduced from reference [51].

Furthermore, addition of intermediate-sized 10-nm AuNPs resulted in no observable size-selective inclusion demonstrating the ability for the nanopeapod to ‘sieve’ through particles and encapsulate only those with the correct dimensions. In a similar fashion to the work done by the Mao group, adding complimentary DNA eraser strands to the nanotube effectively modified and ‘opened’ the cargo capsules resulting in the release of the AuNPs.

The elegance of supramolecular DNA assembly represents arguably the pinnacle of human creativity and ingenuity as it applies to programmable self-assembly. However, materials science is still in need of an accessible strategy for imparting a specific functionality to the surface of the NP if they are to be introduced into technologies, as surface functionalization will provide the opportunity to produce nanostructures with various hierarchical architectures and well-defined geometries.
1.2.3 Metal-Organic Spheres

In recent years the use of discrete coordination cages have emerged as a promising and viable strategy for nanoparticle synthesis. Similar in nature to biological giant hollow structures, such as families of spherical viruses, coordination cages have the ability to encapsulate guest species within the confines of their cavities and are often called “molecular flasks”\(^{52}\). These closed-shell structures are well studied in terms of their host-guest chemistry\(^{53, 54}\) and are known to function as molecular-scale reaction containers by promoting reactions within their interiors.\(^{55-58}\)

In 2010, Fujita and coworkers introduced a novel method for the synthesis of highly monodisperse silica nanoparticles within the cavity of a discrete, crystalline molecular flask composed of rigid aromatic compounds connected by organometallic coordination bonds.\(^{59}\) The 4.6 nm M\(_{12}\)L\(_{24}\) metal-organic sphere 2 self-assembled as a result of mixing Pd(NO\(_3\))\(_2\) and bis(4-pyridyl)-substituted bent ligand 1 and contained a rigid, well-defined cavity that was expandable up to a diameter of 6.3 nm (Fig. 1.6).

![Synthesis of silica nanoparticles within metal-organic sphere 2. Reproduced from reference [59].](image-url)
Modification of ligand 1 with a glucose sugar resulted in a spherical container molecule with 24 pendant glucose units lining the interior cavity walls. These glucose units were then able to act as endo-templates for the reversible sol-gel condensation reaction between sugar and alkoxy silanes to give a controllable synthesis of near perfectly monodisperse silica nanoparticles (Fig. 1.7). Since the glucose units are confined within the cavity of the well-defined shell framework there was no intermolecular cross-linking between spheres after the nanoparticle synthesis as measured by diffusion-ordered NMR spectroscopy. Transmission electron microscopy (TEM) images revealed that the silica nanoparticles have diameters of around 2.8 nm, which is consistent with the diameter of the shell framework and was further confirmed directly using laser desorption ionization mass spectrometry (LDI-MS).

![Figure 1.7](image.png)

**Figure 1.7.** TEM image of silica nanoparticles within self-assembled coordination sphere 2. Reproduced from reference [59].

Furthermore, by expanding the diameter of the metal-organic sphere to 6.3 nm via an extended ligand 1c the authors were able to increase the diameter of the silica nanoparticles to 4 nm. Though the incarcerated silica nanoparticles were rather amorphous and severely disordered, the synthesis of such highly monodisperse silica nanoparticles was previously
unobtainable by traditional methods such as microemulsions.\textsuperscript{60} The structurally exact coordination sphere was later shown to template the synthesis of both titania (TiO\textsubscript{2}) nanoparticles,\textsuperscript{61} as well as core-shell nanoparticles (SiO\textsubscript{2}/TiO\textsubscript{2}, SiO\textsubscript{2}/ZrO\textsubscript{2}).\textsuperscript{62}

Contrary to biotemplates with hollow spherical shells, where chemical functionalization is very limited and quite difficult, the endohedral functionalization of metal-organic spheres is moderately simple and a variety of functional groups can be coated within the large hollow interior structure.\textsuperscript{63} Moving beyond modifications that allow for the entrapment of small molecules, Fujita and co-workers controlled the functionalization in a way that’s reminiscent of enzymes and reported the encapsulation of the small protein, ubiquitin, within a giant, self-assembled coordination cage (Fig. 1.8).\textsuperscript{64}

\textbf{Figure 1.8.} Self-assembly of ubiquitin-containing spheres 3. Reproduced from reference [64].

Through judicious attachment of ubiquitin to the interior edge of one of the 24 ligands of the M\textsubscript{12}L\textsubscript{24} sphere framework, the coordination cage was able to self-assemble around the protein. Due to the large size of the protein (3-4 nm), the 7.3 nm metal-organic sphere prohibits the encapsulation of multiple proteins, and thus after equilibrium each sphere contained only a single ubiquitin-containing ligand. Such discrete, synthetic hosts are clearly distinct from the ill-
defined host media used previously, and the synthetic accessibility and modular nature of the hosts allow for a useful range of platforms for the encapsulation of a multitude of guest species of various sizes and shapes. However, the construction of metal-organic spheres through the use of such dative metal-ligand bonding does not come without several drawbacks. For instance, due to the Lewis acidity of both the metal ions and protons, which compete to combine with the ligand, a lewis base, the integrity of the metal-organic spheres can be compromised and as such they are highly sensitive to variations in pH. Additionally, this cleavage of the metal ion-ligand coordination bonds, which can also occur as a result of elevated temperature and/or a change in solvent, gives emphasize to the feebleness of its architectural integrity and the strong desire to eliminate the use of metals and construct hollow, highly stable, purely organic 3-D spheres.

1.3 Dynamic Covalent Chemistry

The development of 3-D, purely organic cage molecules has gained significant interest in the past few decades.\textsuperscript{66-70} Much of this renewed interest is built around the structural novelty of containing a well-defined intrinsic cavity, which have found potential applications in chemical sensing, catalysis, host-guest chemistry, etc.\textsuperscript{71-75} Though efforts towards the construction of 3-D cage molecules can be dated back to the synthesis of cubane in the 1960’s by Eaton and Cole,\textsuperscript{76} the use of cage molecules in host-guest chemistry wasn’t fully realized until 1987 when Losensky and coworkers synthesized cage molecule 1 capable of encapsulating a variety of guests (Fig. 1.9).\textsuperscript{77} Since then, organic cage molecules based on purely covalent bonding has experienced a resurgence.\textsuperscript{78-80}
To date, there are a large variety of organic cage compounds developed through supramolecular chemistry, where the components interact and arrange themselves via self-assembly processes using weak noncovalent interactions that allow for self-correction (e.g., hydrogen bonding, or dative metal-ligand bonding).\textsuperscript{81-84} Covalent organic cages are much more rare and are still being explored due to the irreversible nature of most covalent bond formation, and as such have led to massive synthetic efforts to make complex cage molecules.\textsuperscript{85,86} More contemporary methods have evolved through Lehn’s idea of constitutional dynamic chemistry (CDC),\textsuperscript{87} which allows for the application of dynamic combinatorial chemistry (DCC) to be applied directly to the synthetic route. This approach allows one to generate libraries of reversibly interconverting building blocks that are under thermodynamic control thus enabling self-correction and the predominant formation of well-defined cage molecules as opposed to strong competition with oligomers and polymer side products. When dealing with only covalent reactions, such methodologies are referred to as dynamic covalent chemistry (DC\textsubscript{V}C).\textsuperscript{88}
1.3.1 Dynamic Imine Chemistry

The characteristic feature of dynamic covalent chemistry (DC\_C) is that it is an adaptive chemistry. More generally, DC\_C is a dynamic process during which the components of the system are exchanged at equilibrium until a thermodynamic minimum is met.\(^{89}\) Compared to supramolecular complexes, which are connected through weak non-covalent interactions, covalent bound molecular architectures have the advantage of ensuring a high degree of chemical and thermal stability.

Though many types of dynamic covalent bond chemistries are available through DC\_C (e.g., boronic ester,\(^{98}\) alkene,\(^{99}\) alkyne,\(^{100}\) disulfide\(^{101}\) ) the reversible condensation reaction between amino and carbonyl groups to form imine bonds remains one of the most significant. Such reaction products are referred to as “Schiff’s bases” and have the general formula \(R^1R^2C=NR^3\). Depending on the geometry of the diamine and trialdehyde (or triamine and dialdehyde) building blocks, imine-linked cage molecules have a tendency to form either \([4+6]\) tetrahedral cage or \([2+3]\) trigonal prismatic cage.\(^{80}\) The reversible nature of the imine bond corrects for kinetically introduced, undesired bond formation in favor of the most thermodynamically stable product and has enabled the synthesis of many complex molecules.\(^{90-94}\)

1.3.2 Organic Cage Molecules as Encapsulating Agents

The imine bond, while enabling the chemical synthesis of many complex molecules due to the inherent element of ‘error-checking’, also carries with it some interesting and unique properties. One such distinguishing feature of the imine bond is that it’s highly reactive\(^{95}\) and enables the efficient synthesis of shape-persistent cages with a large cavity and high surface area.\(^{74,96}\) The electron lone pair on the nitrogen is also convenient for coordination with metal
ions, as demonstrated in the molecular Solomon Knot by Stoddard.\textsuperscript{97} Due to the usefulness of the well-defined cage structure connected via imine bonds, only recently have purely organic cages molecules been explored as hollow structures for the synthesis and stabilization of metal nanoparticles. For example, the Mukherjee group elegantly demonstrated the synthesis of a shape-persistent prismatic cage that could anchor palladium nanoparticles (PdNPs) within the interior.\textsuperscript{102} The imine-based [2+3] cage was formed in high yield via the reaction of a triphenyl amine-based trialdehyde with a chiral diamine and was able to sequester palladium ions within its interior, presumably through complexation with the vicinal diamines. After reduction of Pd\textsuperscript{II} to metallic Pd\textsuperscript{0} the cage was able to serve as a novel platform for the controlled synthesis of 1.8 nm PdNPs that were shown to be highly active in the cyanation of aryl halides. Due to the robust nature of the cage architecture, the strongly bound PdNPs were found to be stable, relatively monodisperse and more importantly reusable as a catalyst through many cycles without a significant decrease in activity.

Similarly, the use of porous organic molecules as hollow interior structures for the synthesis of metal nanoparticles was also demonstrated by the Xu group.\textsuperscript{103} Using organic cage molecules synthesized by a [4+6] cycloimination reaction, it was possible to impregnate the cage with rhodium nanoparticles (Rh NPs) following the reduction of rhodium acetate in a solution of the cage monomer. The resulting ultrasmall Rh NPs (~1.1 nm) are highly stable and extremely active in both the reduction reaction of 4-aminophenol and the methanolysis of ammonia borane. Analogous to the previous palladium-impregnated cage molecules, it is assumed that such high catalytic activity is attributed to both the small size of nanoparticles and the highly accessible catalytic sites, which favors more direct contract between the NP and substrate. Given the purely
covalent nature of cage molecules, such templates are highly stable and serve as promising and amenable platforms for the synthesis of metal nanoparticles.

Lastly, the imine groups can be reduced to amines, thus removing their dynamic nature and permanently locking them into a conformation. After such reduction, the amine-linked cage molecule experience increased thermal and chemical stability and can thus be applied to a greater range of applications.

1.4 Conclusions and Perspectives

The synthesis and study of metallic nanoparticles with unique and specific shape, size, and composition has become an important area of research within the fields of nanoscience and nanotechnology. Due to their unique properties, which have inspired tremendous possibilities in terms of potential applications, the controlled synthesis of nanoparticle size, atomicity, and surface properties will undoubtedly remain active and significant. Thus, a much larger repertoire of viable platforms for the synthesis of such systems is needed, particularly if potential applications are to be explored and eventually realized.

In the past 20 years, design-led approaches have stimulated immense advances in the synthetic control of structure and rational molecular design has made permissible the development and realization of molecular architectures with atomic-level precision. For example the fervent and rapid development of shape-persistent 3-D covalent organic cages within the scope of DC₃C have witnessed widespread uses throughout catalysis, adsorption, separation, and purification. Though it remains to be seen whether function within such systems is an emergent or intrinsic property, the relationship between composition and structure will surely become an important parameter for controlling the properties of the materials. As such, there is a
fundamental need for the further development of synthetic tools so that materials by design can become a reality.

1.5 References


CHAPTER 2

Template Synthesis of Gold Nanoparticles with an Organic Molecular Cage.¹

This work has been published: McCaffrey, R.; Long, H.; Jin, Y.; Sanders, A.; Park, W.; Zhang, W. J. Am. Chem. Soc. 2014, 136, 1782-1785

2.1 Abstract

We report a novel strategy for the controlled synthesis of gold nanoparticles (AuNPs) with narrow size distribution (1.9 ± 0.4 nm) through AuNP nucleation and growth inside the cavity of a well-defined three-dimensional, shape-persistent organic molecular cage. Our results show that both a well-defined cage structure and pendant thioether groups pointing inside the cavity are essential for the AuNP synthesis.

2.2 Introduction

The size-dependent optical and electronic properties of gold nanoparticles (AuNPs) have long been of interest in the context of nanoscience and nanotechnology.²⁻⁶ In particular, AuNPs with diameters in the sub-nanometer to ~2 nm range are known to exhibit properties that are quite unique compared to those larger than 5 nm,⁷,⁸ an observation that has motivated intense interest in the design of organic architectures for the template synthesis of 1-2 nm AuNPs that can be further used in catalysis,⁹⁻¹¹ sensor devices,¹² and nanoelectronics.¹³ For instance, the integration of AuNPs into electronic devices will require the use of 1-2 nm particles.¹⁴ Since the advent of the Brust-Schiffrin method,¹⁵ there has been a wealth of literature exploring the
structure-function relationships of ligand-stabilized NPs that can be rationally designed for fundamental studies and practical applications.\textsuperscript{16-20} To date, control over NP size, shape, and distribution has advanced through the use of small organic ligands, dendritic architectures, or polymers as templates or stabilizers.\textsuperscript{4,10,21-29} Despite this recent progress, there still remain very few examples of passivating ligands allowing for a size-controlled synthesis of AuNPs.

Well-defined, discrete organic molecular cages have attracted tremendous attention\textsuperscript{30-34} due to their shape persistence, structural tunability, and thermal and chemical stability. Our group has demonstrated the modular synthesis\textsuperscript{35} of a variety of organic molecular cages and their great potential in carbon capture\textsuperscript{36,37} and fullerene separation applications.\textsuperscript{38} Furthermore, modular synthesis allows for judicious external functionalization so that molecular cages can be covalently assembled into ordered networks through the bottom-up “cage-to-framework” approach.\textsuperscript{39} We envision that discrete rigid organic molecular cages with multiple Au-binding sites inside the cavity can serve as templates for controlled synthesis of AuNPs. Such a cage template has a well-defined architecture with a spatially confined cavity that is large enough to accommodate NPs. Compared to conventional small organic or macromolecular ligands, which form thick, insulating layers on the AuNP surface, a cage template can provide a protecting shell with minimum coverage and greater encapsulated AuNP surface accessibility. Another potential advantage of such a “cage-template” approach is that exterior functionalization on the cage may enable further assembly of AuNPs in a controlled fashion as possible three-dimensional building blocks for chemically directed hierarchical assembly, which would provide a powerful platform for development of novel nanostructured materials for optical or catalytic applications. Herein, we report the first example of size-controlled synthesis of AuNPs using a discrete organic molecular cage as a template.
2.3 Results and Discussion

We designed trigonal prismatic cage 1 with internal cavity size of 1.8 – 2.1 nm (Fig. 2.1), the interior of which is functionalized with three thioether groups. We chose to use thioether as the nucleation site for the Au deposition since it has higher stability than thiol yet is known to coordinate, albeit weakly, gold colloids.\(^{27,40,41}\) AuNPs of a size similar to the cage are expected to grow inside the cavity, leading to the formation of a core/shell structure, with AuNP as the core and the cage molecule as the shell. Previously reported cage 2, with the same cavity size but lacking thioether anchoring groups, was selected as a control compound.\(^{36}\)

![Figure 2.1](image.png)

**Figure 2.1.** Structures of cages 1 and 2, and side view of a fully stretched model of cage 1. Methyl group for hexyl chain, and hydrogen for OC\(_{16}\)H\(_{33}\) and Br were used in the calculation for simplification.

Cage 1 was synthesized through dynamic imine chemistry using triamine 3 as the top and bottom panels and dialdehyde 4 with a thioether group as the three lateral edges (Fig. 2.2). Triamine 3 was prepared as previously described in the literature.\(^{37}\) Dialdehyde 4 was synthesized starting with 3,5-diiodo-\(p\)-cresol 5, which was prepared from \(p\)-cresol.\(^{42}\) Following
alkylation of compound 5, trimethylsilyl-protected terminal acetylenes were introduced before radical bromination at the methyl position. The brominated intermediate is critical in that it allows for the later introduction of pendant interior thioether groups. Desilylation of compound 7 followed by Sonogashira coupling with 3-bromo-5-iodobenzaldehyde yielded the lateral side piece 4. Imine condensation between the two building blocks 3 and 4 and subsequent reduction led to the formation of 1. Cage 1 was characterized by $^1$H and $^{13}$C NMR spectroscopy, gel permeation chromatography (GPC), and matrix-assisted laser-desorption ionization mass spectrometry (MALDI-MS).

![Chemical structure](image)

**Figure 2.2.** Synthesis of molecular cage 1.

We used a two-phase liquid-liquid approach developed by Brust et al., with tetraoctylammonium bromide (TOAB) as a phase-transfer reagent, to prepare cage-encapsulated AuNPs.$^{15}$ A solution of TOAB in CH$_2$Cl$_2$ was added to an aqueous solution of HAuCl$_4$ (10
equiv.) and stirred until the aqueous layer was colorless, indicating all AuCl₄⁻ was transferred to the organic phase. A solution of 1 (1 equiv.) in CH₂Cl₂ was added to the above biphasic mixture. Upon mixing, no obvious color change was observed in the organic phase. The mixture was subsequently reduced with an aqueous solution of sodium borohydride (190 equiv., rt). The organic phase immediately changed color from orange-red to dark brown without any precipitates, indicating efficient Au³⁺ reduction and further stabilization of the resulting AuNPs by cage molecule 1. The organic layer containing AuNP@1 complex was separated, and AuNP@1 complex was precipitated from ethanol and collected by centrifugation. The AuNP@1 complex shows good solubility in common organic solvents. The AuNPs were characterized by ultraviolet-visible spectroscopy (UV-vis), ¹H NMR spectroscopy, diffusion-ordered NMR spectroscopy (DOSY), thermogravimetric analysis (TGA), and transmission electron microscopy (TEM).

The UV-vis absorption spectra of the solution before and after reduction are shown in Figure 2.3c. All the absorption measurements were performed in CH₂Cl₂ at the same concentration (1.4 µM). In the absence of cage 1, the absorption spectrum of tetrabutylammonium tetrachloroaurate(III) in CH₂Cl₂ shows absorption peaks at λ = 250 nm, and 380 nm, arising from the ligand-to-metal charge-transfer transition (Au³⁺, red line, Fig. 2.3c). Upon addition of the cage molecule to the Au³⁺ solution, the absorption of 1 appeared as a shoulder band in the region around 275-381 nm, and the intensity of the peak at 380 nm was decreased (Au³⁺@1, purple line, Fig. 2.3c). Complete reduction of AuCl₄⁻ to zero-valent Au metal and formation of AuNPs with diameter ~2 nm were confined by the disappearance of the 250 nm band and the emergence of a featureless broad tail extending to 700 nm after the reduction (AuNP@1, green line, Fig. 2.3c).
The particle diameter and size distribution were analyzed using TEM images. All the samples were prepared using a solution of AuNP@1 in CH$_2$Cl$_2$. The solution was drop-cast onto carbon-coated 300-mesh copper grids (CF300-Cu) and allowed to air dry before the measurements. The TEM image (Fig. 2.3a) of AuNP@1 shows the formation of well-dispersed AuNPs with average diameters of 1.9 nm, which matches well with the estimated cage internal cavity size of 1.8-2.1 nm.

Thermal gravimetric analysis shows a mass loss of 56% for pure cage 1 and a mass loss of 6% for AuNP@1 complex between ambient temperature and 480 °C. Based on the above mass loss determined by TGA, we calculated that each cage molecule contains a NP composed
of roughly 150 Au atoms. This corresponds to a 1.7 nm AuNP, which is in close agreement with
the AuNP size observed by TEM.

Despite its small size, AuNP@I complex shows excellent stability. It is stable in
solutions, with no evidence of agglomeration, and without noticeable color change, over periods
of several months. More importantly, it can be evaporated to dryness overnight under high
vacuum and then re-dissolved in common organic solvents with no signs of aggregation. It
should be noted that re-dispersion of AuNPs after drying has been difficult for AuNPs with
weaker binding ligands, such as some carboxylates and multivalent thioether ligands.28,43
Presumably, the cage shell provides good solubility as well as effective coverage and protection
of the AuNPs’ surface, thus preventing their aggregation. The high solubility and stability of the
AuNP@I complex further supports the notion that NPs reside inside the cage cavity.

In the 1H NMR spectra of the above AuNP@I complex, we did not observe the phase-
transfer agent TOAB (Fig. 2.4). Interestingly, substantial broadening and shifting of not only the
protons of the thioether group but also all aromatic protons of the cage skeleton were observed.
This is in great contrast to the oligomeric ligands based on benzylic thioethers reported by Simon
and Mayor, in which no significant shifting and broadening of proton signals of ligands were
observed upon the formation of AuNP complex.26,41 Line broadening of resonances is
characteristic for ligands with thiol functionality, which have the highest affinity to Au.44,45 Line
broadening commonly occurs due to the intrinsic heterogeneous environment for the bound
ligands on the AuNPs and their restricted mobility on the NP surface.43 The considerable line
broadening and shifting of almost all protons of the cage skeleton in the present case therefore
support the notion that the cage shell is likely tightly wrapped around the AuNP, and experiences
restricted mobility and fast spin relaxation.
It has been known that multidentate thioether ligands, such as thioether dendrimers, can stabilize AuNPs to form stable and narrowly dispersed ligand-wrapped NPs.\textsuperscript{26,41,46} To further corroborate that the particle rests inside of the cage cavity and rule out the possibility of particle formation through aggregation of multiple cages on the AuNP surface, \textsuperscript{1}H diffusion-ordered spectroscopy (DOSY) NMR was performed on both free cage 1 and AuNP@1 under the same temperature and concentration (Fig. 2.5). As expected, we obtained very similar diffusion coefficients for cage 1 and AuNP@1, 2.5 and 2.4 respectively, which indicates the similar size and shape of free cage and AuNP@1. This study provides additional evidence supporting the AuNP formation is a result of a single cage encapsulation rather than intercage interactions and the simple multivalency effect of ligands.
To further confirm the role of cage scaffold and thioether groups in AuNP synthesis, we conducted two control experiments using cage 2, which lacks thioether groups, and thioether ligand 4, which lacks a cavity. First, HAuCl₄ was reduced in the presence of 2, a structural analog of cage 1 but without the three internal thioether groups. As expected, upon reduction with NaBH₄, we observed the immediate and complete precipitation of aggregated NPs under conditions similar to those used to form AuNP@1 complex. The TEM image of AuNPs obtained from the control experiment with 2 (Fig. 2.3b) showed only shapeless agglomerates, indicating that 2 is unable to serve as a template for the synthesis of AuNPs, presumably due to the lack of nucleation (i.e., Au binding) sites. In the other control experiment, the side-piece 4,
which bears a thioether group, was used as the ligand. In this case, we observed similar rapid aggregation and precipitation of AuNPs upon reduction, suggesting the poor stabilization of AuNPs by monodentate open ligand 4.

It is therefore tempting to conclude that both the thioether groups and the closed cage structure itself are playing critical roles in controlled AuNP synthesis. The thioether groups serve as the initial nucleation sites for AuNP growth and also stabilize the resulting NP. Once seeded, the Au nanocluster grows until it is confined sterically within the cage, and the three thioether groups and the six amino groups may provide stabilization through Au surface binding. The fact that the AuNP@1 complexes themselves remain isolated from one another is likely due to the long alkyl chains present around the cage exterior. The working mechanism of this cage template is very different from that of the previously reported dendrimer template, which inherently relies on multipoint interactions that conform to the surface of the particle, thus allowing it to grow until “dendritic wrapping” of the cluster becomes favorable.26 Interestingly, closer inspection of the AuNPs using high-resolution TEM shows that the particles have a periodic lattice structure giving evidence that the NPs are crystalline in structure rather than amorphous (Fig. 2.6).

Figure 2.6. TEM (200 kV) images showing the periodic lattice structure of the cage-encapsulated AuNPs.
Computational simulation of the interaction between cage 1 and AuNPs of different radii provides theoretical support for our experimental findings. The AuNPs were generated using a Au crystal cubic close-packed lattice structure with a closest Au-Au separation of 0.2884 nm. Five different AuNPs are used, with radii of 11.54, 9.99, 8.65, 7.63, and 5.77 Å, respectively. For each NP, we built a cage around it and bonded the three sulfur atoms of the cage to the Au atoms at the equator of the NP, 120° apart. The Amber 11.0 molecular dynamics program package was then used to optimize the structures of the cage/NP complexes. The force field used for the cage was the general Amber force field (GAFF) with the charge parameters computed by the AM1-BCC method, and the force field for gold was adopted from Agrawal et al. For each optimization run, the atoms on AuNPs were frozen, and the structure of the cage was optimized. The cage was first minimized for 5000 steps using the conjugate gradient method, and then it was further optimized by the simulated annealing method for 150 ps with a time step of 1 fs. During the simulated annealing, the system temperature was first raised to 1000 K for 50 ps and then gradually cooled to 0 K over another 100 ps. Finally, the annealed structure was minimized again for another 5000 conjugate gradient steps. The total energy of cage/cage and cage/gold interactions was calculated on the basis of the energy-minimized structure. Figure 2.7a shows the cage energy as a function of the encapsulated NP radius. The energy first decreases when the radius increases due to the larger van der Waals attraction between the cage and the NP. At a radius of 8.65 Å (1.7 nm diameter), the energy reaches the maximum, and the structure of the AuNP@1 complex is presented in Figure 2.7b. This is in close agreement with the 1.9 ± 0.4 nm average diameter value that we observed experimentally via TEM characterization.
2.4 Summary

In summary, a novel cage-templated strategy has been demonstrated for the controlled synthesis of AuNPs via the use of a well-defined, discrete organic molecular cage functionalized with pendant interior thioether groups. The AuNPs formed inside the cage cavity exhibit narrow particle size distribution (1.9 ± 0.4 nm) and could potentially be used as seed particles for further seed-mediated growth of nonspherical Au nanoparticles. The average particle size obtained from this cage-templated synthesis is consistent with the molecular dynamics simulation results. To the best of our knowledge, this is the first example of *in situ* AuNP growth in a confined organic molecular environment. Our results show that the successful controlled synthesis of AuNPs is attributed to the combination of a well-defined cage scaffold and the interaction between AuNPs and pendant thioether groups that serve as the nucleation and stabilization sites for AuNPs grown
inside the cage. The diversity in size and shape of cage molecules makes such a cage-template approach a versatile strategy for synthesis of AuNPs with tunable size and shape. Hierarchical NP assembly with special optical or magnetic properties can be achieved by the proper functionalization of cage exterior, which can direct their spatial arrangement. Furthermore, the abundance of available surface area from the resulting AuNPs would allow for their facile interactions with small molecules thus making AuNP@1 an interesting model complex for homogenous catalysis. Currently the scope of this cage-template strategy in NP synthesis as well as utilization of exterior functionalized molecular cages to direct AuNP assembly are being investigated in our laboratory and will be reported in due course.

2.5 Experimental Section

2.5.1 Materials and general synthetic methods

All commercially available reagents and solvents were used as received, unless noted otherwise. CH$_2$Cl$_2$ and tetrahydrofuran (THF) were purified by MBRAUN solvent purification system. All reactions were carried out under nitrogen in flame-dried glassware, unless noted otherwise. After workup, all solvents were removed by rotary evaporation. Unless otherwise indicated, the purity of the compounds was ≥95% based on $^1$H NMR spectral integration.

Flash column chromatography was performed using 100-150 times weight excess of 32-63 µm silica gel from Dynamic Absorbants Inc. Fractions were analyzed by TLC using TLC silica gel F254 250-µm pre-coated plates from Dynamic Absorbants Inc. GPC was performed using a Viscotek GPCmaxTM, a Viscotek Model 3580 Differential Refractive Index (RI) Detector, a Viscotek Model 3210 UV/vis detector and a set of two Viscotek Viscogel columns (7.8 x 30 cm, 1-MBLMW-3078, and 1-MBMMW-3078). GPC calibration was done using
monodisperse polystyrene standards and THF was used as the eluent at 30°C. UV-vis absorption measurements were recorded with an Agilent 8453 spectrophotometer. MALDI-MS was performed using a Voyage-DE™ STR Biospectrometry Workstation in linear mode using a sinapic acid matrix. High resolution mass spectrometry (HR-MS) was performed using a Waters SYNAPT G2 high-definition mass spectrometry system.

1H and 13C NMR spectra were obtained using either an Inova 500 or Bruker 300 spectrometer. CHCl3 was used as an internal reference for both 1H NMR (7.27 ppm) and 13C NMR (77.23 ppm). NMR data is reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J, Hz), number of protons.

The Amber 11.0 molecular dynamics program package47 was used to optimize the structures of the cage/nanoparticle complexes. The force field used for the cage was the general Amber force field (GAFF field)48 with the charge parameters computed by the AM1-BCC method.49 The force field parameters for gold atoms were taken from the literature report.50 For each optimization run, the atoms on gold nanoparticle were frozen and the structure of the cage was optimized. The cage was first minimized for 5000 steps using the conjugate gradient method, and then it was further optimized by simulated annealing method for 150 ps with a time-step of 1 fs. During the simulated annealing, the system temperature was first raised up to 1000 K for 50 ps and then gradually cooled to 0 K for another 100 ps. Finally, the annealed structure was minimized again for another 5000 conjugate gradient steps. The total energy of cage-cage and cage-gold interactions was calculated based on the minimized structure.

Imaging was performed using a JEOL ARM 200F, Schottky Field Emission TEM, Bright Field only. The sample was drop-cast onto an Ultrathin Carbon/Holey Support on 400-mesh Cu
grid (part number 1824) from Ted Pella (Images 45 and greater). Particle size data were obtained by analyzing the TEM images using software ImageJ.

2.5.2 Experimental procedures

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\begin{align*}
\text{5-((Hexadecyloxy)-1,3-diiodo-2-methylbenzene: To a Schlenk tube were added} & \text{3,5}-\text{iodo-}p\text{-cresol (1.0 g, 2.78 mmol), 1-bromohexadecane (0.93 g, 3.06 mmol), NaOH (120 mg, 3.06 mmol), and ethanol (35 mL) under N}_2. \text{ After refluxing for 18 h, the reaction mixture was cooled to room temperature and poured into water (50 mL). The product was extracted with diethyl ether (3 x 75 mL). The organic extracts were combined, dried over anhydrous Na}_2\text{SO}_4, \text{ and concentrated. The crude product was purified by flash column chromatography using hexanes to afford the product as a white solid (1.5 g, 94 %):} \\
& \text{1H NMR (500 MHz, CHCl}_3\text{): } \delta \text{ 7.58 (s, 2H), } \delta \text{ 3.93 (t, } J = 6.6 \text{ Hz, 2H), } \delta \text{ 2.24 (s, 3H), } \delta \text{ 1.94-1.86 (m, 2H), } \delta \text{ 1.59-1.49 (m, 2H), 1.27 (m, 24H), } \delta \text{ 0.89 (t, } J = 7.0 \text{ Hz, 3H)}; \text{13C NMR (75 MHz, CDCl}_3\text{): } \delta \text{ 155.79, 140.24, 137.46, 90.56, 73.43, 31.94, 30.04, 29.73, 29.70, 29.68, 29.66, 29.62, 29.55, 29.38, 25.99, 22.71, 19.63, 14.15; HR-MS (ESI): c} \text{alc} \text{d for C}_{23}\text{H}_{38}\text{I}_2\text{O [2M+Li}^+\text{]} \text{1175.2180; found 1175.2173.}
\end{align*}
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**Compound 6:** The general procedure for Sonogashira cross coupling was followed\textsuperscript{51,52} Using 5-(hexadecyloxy)-1,3-diiodo-2-methylbenzene (625 mg, 1.07 mmol), trimethylsilylacetylene (1.8
mL, 12.84 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (45 mg, 0.064 mmol), CuI (4 mg, 0.021 mmol), and diethylamine (35 mL), the product was obtained as a light yellow oil (542 mg, 96%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.20 (s, 2H), 4.15 (t, $J$ = 6.6 Hz, 2H), 2.22 (s, 3H), 1.84 – 1.76 (m, 2H), 1.55 – 1.47 (m, 2H), 1.39 – 1.21 (m, 24H), 0.89 (t, $J$ = 7.0 Hz, 3H), 0.25 (s, 18H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.09, 134.47, 132.52, 117.21, 101.02, 98.43, 74.27, 31.94, 30.46, 29.71, 29.69, 29.67, 29.63, 29.37, 26.17, 22.70, 20.26, 14.13, -0.08; HR-MS (ESI): calcd for C$_{33}$H$_{56}$OSi$_2$ [M+Li$^+$] 531.4025; found 531.4027.

**Compound 7, Step 1:** To a Schlenk tube were added compound 6 (513 mg, 0.98 mmol), N-bromosuccinimide (452 mg, 2.54 mmol), dibenzoyl peroxide (43 mg, 0.18 mmol) and CCl$_4$ (15 mL) under nitrogen atmosphere and the solution was refluxed for 20 h. The dark red solution was cooled to rt, filtered and rinsed with CCl$_4$. Due to the instability of the benzylic bromide the crude material was used in the following step without further purification. The physical data for the product: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (s, 2H), 4.36 (s, 2H), 4.21 (t, $J$ = 6.6 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.59 – 1.45 (m, 2H), 1.26 (s, 24H), 0.89 (t, $J$ = 7.0 Hz, 3H), 0.25 (s, 18H).

**Step 2:** To a Schlenk tube were added sodium ethanethiolate (984 mg, 1.17 mmol) and a solution of the above crude product (304 mg) in THF (10 mL). The solution was stirred at rt for 18 h and poured into H$_2$O (50 mL). After extraction with CH$_2$Cl$_2$ (3 x 25 mL), the combined organic solution was dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified
by flash column chromatography using 5% ethyl acetate/hexane to afford the product as an orange oil (233 mg, 41% over 2 steps): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (s, 2H), 4.19 (t, $J = 6.5$ Hz, 2H), 3.58 (s, 2H), 2.41 (q, $J = 7.4$ Hz, 2H), 1.82 (dt, $J = 6.6$ Hz, 2H), 1.52 (m, 2H), 1.29 (m, 29H), 0.89 (t, $J = 7.0$ Hz, 3H), 0.26 (s, 18H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 161.15, 134.16, 133.43, 128.52, 127.12, 117.51, 100.75, 98.90, 74.24, 70.79, 66.02, 34.77, 31.94, 30.46, 29.71, 29.69, 29.67, 29.64, 29.62, 29.38, 26.15, 25.18, 22.70, 14.30, 14.13, -0.12; HR-MS (ESI): calcd for C$_{35}$H$_{60}$OSSi$_2$ [M+H$^+$] 586.0942; found 586.2675.

(2,6-Diethynyl-4-(hexadecyloxy)benzyl)(ethyl)sulfane: To a Schlenk tube were added compound 7 (525 mg, 0.9 mmol) and THF (15 mL) under nitrogen atmosphere. The solution was cooled to 0 ºC using an ice bath. A solution of TBAF (1 M in THF, 1.8 mL, 1.8 mmol) was added dropwise at 0 ºC. The darkened solution was warmed to rt and stirred for 10 min. The solvent was removed by rotary evaporation, and the crude product was passed through a short column of silica gel using 25% ethyl acetate/hexane to yield the product as a slightly yellow oil (395 mg, 100%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 (s, 2H), 4.20 (t, $J = 6.6$ Hz, 2H), 3.61 (s, 2H), 3.26 (s, 2H), 2.43 (q, $J = 7.4$ Hz, 2H), 1.85 – 1.77 (m, 2H), 1.49 (dq, $J = 14.5, 7.0$ Hz, 2H), 1.38 – 1.25 (m, 24H), 1.24 (t, $J = 7.4$ Hz, 3H), 0.89 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 161.42, 134.88, 133.70, 116.67, 81.69, 79.45, 74.58, 34.69, 31.93, 30.25, 29.70, 29.66, 29.64, 29.46, 29.37, 25.89, 25.28, 22.70, 14.30, 14.13; HR-MS (ESI): calcd for C$_{29}$H$_{44}$OS [2M+H$^+$] 881.6299; found 881.6292.
**Compound 4:** The general procedure for Sonogashira cross coupling was followed. Using (2,6-diethynyl-4-(hexadecyloxy)benzyl)(ethyl)sulfane (200 mg, 0.45 mmol), 3-bromo-5-iodobenzaldyhyde (310 mg, 1.00 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (19 mg, 0.027 mmol), CuI (2.0 mg, 0.009 mmol), triethylamine (5 mL), and THF (5 ml), the compound 4 was obtained as a pale yellow solid (320 mg, 88%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.98 (s, 2H), 8.03-7.86 (m, 6H), 7.49 (s, 2H), 4.32 (t, $J = 6.3$, 2H), 3.69 (s, 2H), 2.50 (q, $J = 7.4$ Hz, 2H), 1.95-1.82 (m, 2H), 1.64-1.54 (m, 2H), 1.41-1.14 (m, 29H), 0.89 (t, $J = 6.9$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 189.83, 160.57, 139.35, 137.84, 134.60, 134.19, 131.82, 131.34, 126.18, 123.23, 116.84, 90.88, 88.24, 75.02, 34.80, 31.93, 30.61, 29.69, 29.66, 29.37, 26.46, 25.43, 22.70, 14.36, 14.14; HR-MS (ESI): calcd for C$_{43}$H$_{50}$Br$_2$O$_3$S [M+H$^+$] 807.7459; found 807.6611.

**COP-1:** To a Schlenk tube was added compound 3 (30 mg, 50 µmol) and compound 4 (60 mg, 74 µmol) in CHCl$_3$ (17 mL) under nitrogen atmosphere. TFA (0.57 µL, 7.43 µmol) was then added drop wise and the reaction was stirred at rt for 18 h. The reaction mixture was cooled at 0 °C, and DIBAL (1.50 mL, 1.0 M solution in CH$_2$Cl$_2$, 1.50 mmol) was added. The clear solution was stirred at 0 °C for 1 h. Saturated NaHCO$_3$ was added and the mixture was stirred at rt for 30
The product was extracted with CHCl₃ (3 x 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography using dichloromethane as the eluent to afford the product as a white solid (20 mg, 23%): ¹H NMR (500 MHz, C₆D₆) δ 7.60 (s, 6H), 7.46 (s, 6H), 7.36-7.17 (m, 24H), (d, J = 8.5 Hz, 12H), 4.40 (t, J = 6.0 Hz, 6H), 3.70 (d, J = 5.3 Hz, 12H), 3.29 (m, 12H), 2.52 (s, 12H), 2.14 (q, J = 7.4 Hz, 6H), 1.93 (m, 6H), 1.65 (m, 8H), 1.51 (m, 16H), 1.31 (m, 74H), 1.11-0.86 (m, 80H), 0.79 (t, J = 7.1 Hz, 18H); ¹³C NMR (101 MHz, C₆D₆) δ 161.03, 145.75, 142.72, 140.00, 139.48, 134.32, 134.08, 132.62, 131.33, 131.10, 130.08, 128.67, 125.33, 122.69, 117.61, 113.10, 111.54, 92.50, 87.15, 74.63, 46.89, 34.56, 32.04, 31.05, 30.77, 29.93, 29.85, 29.66, 29.54, 26.57, 24.96, 22.83, 22.31, 14.12, 14.07; MS (MALDI) calcd for C₄₁₃H₂₆₄Br₆N₆O₃S₃ ([M + H⁺]) 3533.10, found 3530.78.

COP-2: For synthesis of COP-2, refer our previous publication.³⁶ The physical data for COP-2:
¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, J = 8.0 Hz, 12H), 7.24 (d, J = 7.6 Hz, 12H), 7.19 (t, J = 5.7 Hz, 3H), 7.13 (t, J = 7.9 Hz, 6H), 6.99 (d, J = 1.2 Hz, 6H), 6.86 (t, J = 9.6 Hz, 6H), 6.80 (d, J = 11.0 Hz, 6H), 6.63 (dd, J = 8.1, 2.1 Hz, 6H), 4.39 (s, 12H), 4.24 – 4.10 (m, 6H), 3.97 (t, J = 6.5 Hz, 6H), 2.04 – 1.93 (m, 12H), 1.82 – 1.76 (m, 6H), 1.49 – 1.42 (m, 6H), 1.40 – 1.20 (m, 84H), 1.13 – 1.05 (m, 12H), 0.95 – 0.87 (m, 21H), 0.76 – 0.65 (m, 42H); ¹³C NMR (101 MHz, CDCl₃) δ 158.96, 148.13, 140.33, 139.03, 138.97, 137.16, 130.64, 129.32, 127.78, 126.67, 124.69, 123.84, 121.10, 117.53, 115.58, 113.98, 90.41, 88.04, 68.45, 48.05, 32.15, 31.81, 30.80, 30.59,
29.93, 29.84, 29.81, 29.59, 29.42, 29.38, 26.22, 22.92, 22.26, 14.37, 14.29; MS (MALDI) calcd for C_{204}H_{252}N_{6}O_{3} ([M+H^+] ) 2836.98: found 2837.01.

**GPC Graph of COP-1**

![Graph of COP-1 GPC](image)

**AuNP Assembly**

All reactions were carried out on a 5-10 mg scale with respect to COP-1. A solution of HAuCl_{4} (6 mg, 0.014 mmol) in deionized H_{2}O (0.5 mL) was stirred and TOAB (39 mg, 0.071 mmol) in CH_{2}Cl_{2} (0.5 mL) was added and stirred until Au(III) was transferred into organic phase (~25 min). A solution of COP-1 (5 mg, 0.0014 mmol) in CH_{2}Cl_{2} (0.5 mL) and subsequently reduced with an aqueous solution of NaBH_{4} (10 mg, 0.26 mmol) in deionized H_{2}O (0.5 mL). The resulting organic layer was dark in color and contained no precipitate. After separation, the aqueous layer was washed with CH_{2}Cl_{2} (2 x 1 mL), the organic fractions were combined and concentrated to ca. 0.2 mL without the application of heat. Ethanol (1.5 mL) was then added and the solution was centrifuged to precipitate the AuNP@1 complexes. This centrifugation
procedure was repeated until the supernatant was no longer colored (~3 times). The resulting complexes are soluble in all organic solvents and stable in solutions, even over periods of several months.

**Computational Methods**

The Amber 11.0 molecular dynamics program package\textsuperscript{47} was used to optimize the structures of the cage/nanoparticle complexes. The force field used for the cage was the general Amber force field (GAFF field)\textsuperscript{48} with the charge parameters computed by the AM1-BCC method.\textsuperscript{49} The force field parameters for gold atoms were taken from the literature report.\textsuperscript{50} For each optimization run, the atoms on gold nanoparticle were frozen and the structure of the cage was optimized. The cage was first minimized for 5000 steps using the conjugate gradient method, and then it was further optimized by simulated annealing method for 150 ps with a time-step of 1 fs. During the simulated annealing, the system temperature was first raised up to 1000 K for 50 ps and then gradually cooled to 0 K for another 100 ps. Finally, the annealed structure was minimized again for another 5000 conjugate gradient steps. The total energy of cage-cage and cage-gold interactions was calculated based on the minimized structure.

**Magnification of TEM images of AuNP lattice structure**
2.6 References


CHAPTER 3

Cage-templated Synthesis of Highly Stable Palladium Nanoparticles and Their Catalytic Activities in Suzuki-Miyaura Coupling

This paper has been submitted for publication under the same title: McCaffrey, R.; Jin, Y.; Long, H.; Park, W.; Zhang, W.

3.1 Abstract

We report a size-controlled synthesis of small palladium nanoparticles (PdNPs) with narrow particle size distribution (1.8 ± 0.2 nm) using an organic molecular cage as a template. The well-defined cage structure with thioether anchoring groups inside the cavity is critical for the formation of narrowly distributed PdNPs, offering a confined organic molecular environment and guiding NP nucleation and growth. Provided a protecting cage shell with minimum surface coverage, the resulting encapsulated PdNPs are resistant to agglomeration and stable in solution that is exposed to air. Our study shows that such PdNPs can be used as a catalyst in Suzuki-Miyaura coupling reactions with high efficiency.

3.2 Introduction

Metal nanoparticles (NPs) have been widely applied in various disciplines of modern sciences, including catalysis,1-3 diagnostic imaging,4-7 sensing,4,8 magnetic recording,9 electronics10 and optics.11 These materials often exhibit particular physical and chemical characteristics arising from their small size and high surface-to-volume ratio, which are distinct from those of bulk materials.12 The properties of metal NPs depend on their sizes, shapes and
compositions, thus the synthesis of narrowly distributed particles of a specific structure and composition has become an important research area in nanoscience. Various solution phase methods have been developed for the synthesis of nanoparticles, many of which are based on surface capping ligands and dendritic architectures.\textsuperscript{3,13,14}

Recently, the synthesis of monodisperse nanoparticles have advanced through the use of closed-shell, hollow “ship-in-bottle” structures, such as protein cage,\textsuperscript{15} supramolecular DNA assemblies,\textsuperscript{16,17} and metal-coordination complexes,\textsuperscript{18} which confine the particles to a specific size and shape. However, the size-controllable preparation of small narrowly dispersed nanoparticles remains challenging.

Our group has been interested in exploring shape-persistent 3-D organic molecular cages as templates to control over encapsulation and growth of nanoparticles. Since the advent of dynamic covalent chemistry (DC,C),\textsuperscript{19-22} the thermodynamically controlled synthesis of shape-persistent 3-D organic molecular cages have attracted tremendous attention as viable candidates for carbon capture and fullerene separation.\textsuperscript{23-25} With well-defined and permanently rigid pore structures, such a cage template\textsuperscript{26-28} can offer a protecting shell with minimum surface coverage, which would be advantageous compared to conventional small organic ligands or macromolecular ligands that form thick, insulating layers on the nanoparticle surface.\textsuperscript{29,30} Herein, we report robust organic cage-templated synthesis of narrowly distributed palladium nanoparticles (PdNPs) and their catalytic application in Suzuki-Miyaura cross-coupling reactions.
3.3 Results and Discussion

Cage 3a with large internal void and pendant interior thioether anchoring groups was synthesized through dynamic imine chemistry (Fig. 3.1),\textsuperscript{26} and characterized by $^1$H and $^{13}$C NMR spectroscopy, gel permeation chromatography (GPC), and matrix-assisted laser-desorption ionization mass spectrometry (MALDI-MS). Analogous cage 3b with methyl groups instead of thioether groups was synthesized for comparison purpose. Palladium NPs (PdNPs) were then prepared via a two-phase liquid–liquid approach adapted from Brust et al. and others in the presence of cage molecules.\textsuperscript{31-33} A solution of tetaoctylammonium bromide (TOAB), a phase-transfer reagent, in CH$_2$Cl$_2$ was added to an aqueous solution of K$_2$PdCl$_4$ (5 equiv.) and stirred until the aqueous layer was colorless, indicating all PdCl$_4^{2-}$ was transferred to the organic phase. A solution of cage 3a (1 equiv.) in CH$_2$Cl$_2$ was added to the above biphasic mixture and stirred for 45 minutes. The orange-red colored mixture deepened and was subsequently reduced with an aqueous solution of sodium borohydride (190 equiv., rt) resulting in a dark brown organic phase with no precipitation, indicating the efficient reduction of Pd$^{2+}$ and further stabilization of PdNPs by cage molecule 3a. After extraction using CH$_2$Cl$_2$, the resulting PdNP@3a complex was dried over sodium sulfate, precipitated from ethanol in order to remove excess phase transfer agent and characterized by UV–vis, HR-TEM and energy-dispersive X-ray spectroscopy (EDS).
Figure 3.1. The synthesis of cage 3a and 3b.

The UV–vis absorption spectra of the solution before and after reduction are shown in figure 1b. In the absence of cage 3a, the absorption spectrum of tetrabutylammonium tetrachloropalladate(II) in CH$_2$Cl$_2$ shows absorption peaks at $\lambda = 250$ nm, and 320 nm arising from ligand-to-metal charge-transfer transitions (Pd$^{II}$, red line, Fig. 3.2b). After the addition of cage 3a to the Pd$^{II}$ solution, the charge-transfer bands decreased in intensity and the absorption of 3a appeared as a shoulder band around 275 nm (Pd$^{II}$@3a, blue line, Fig. 3.2b). Complete reduction of PdCl$_4^{2-}$ to Pd$^{0}$ and the formation of PdNPs was confirmed by the complete absence of bands from 300-500 nm (PdNP@3a, green line, Fig. 3.2b), which correlates well with those previously reported in the literature.$^{34,35}$
Figure 3.2. Calculated cavity size of fully extended cage 3a (a); UV–Vis absorption spectra of cage 3a and palladium complexes in CH₂Cl₂ (b); HRTEM micrographs (scale bar 10 nm) of PdNP@3a (c); and size distribution of PdNP@3a complex (d).

The diameter and size distribution of resulting PdNP@3a were then analyzed by TEM micrographs (Fig. 3.2c). A solution of PdNP@3a in CH₂Cl₂ was drop cast onto carbon-coated 300 mesh copper grids (CF300-Cu) and allowed to air dry before the measurements. The TEM image (Fig. 3.2c) shows well-dispersed PdNPs with an average size of 1.8 nm (over 500 particles counted), which matches well with our computation models showing an internal cavity size of 1.8 – 2.1 nm (Fig. 3.2a, 3.2d).

The formation of such small PdNPs agrees well with the absence of a plasmon peak in the UV-Vis. Energy-dispersive X-ray spectroscopy (EDS) spectrum (Fig. 3.3) also confirms unambiguously the presence of metallic palladium: however, further characterization of the
PdNP lattice structure using power X-ray diffraction (PXRD) failed to produce any characteristic sharp peaks, indicating that the NPs are likely amorphous. These PdNP@3a complexes are stable and highly soluble in common organic solvent.

![Figure 3.3](image)

**Figure 3.3.** EDS profiles of PdNP@3a.

It is expected that the thioether groups inside the cage cavity provide preferential nucleation site for Pd and further deposition in the spatially confined cavity would provide PdNPs of a size similar to the cage. Additionally, since the high surface area and surface energy of PdNPs cause their extensive aggregation, encapsulation of PdNPs in isolated cavities also prevents agglomeration and improves their chemical and thermal stability. Control experiments in the absence of cage 3a led to the formation of a black precipitate supporting the notion that the presence of cage 3a, which contains six amino groups and three thioether groups, is necessary for the growth, size control and stabilization of PdNPs. In order to understand exactly what structural requirements are necessary for PdNP growth, we performed additional control experiments in the presence of cage 3b, where the only structural difference is that the three thioethers are replaced with methyl groups. We again observed the complete precipitation of PdNPs. Further control experiments in which only the thioether side piece 2a was used as the
stabilizing ligand also led to similar aggregation and precipitation, further suggesting the closed
cage and multidentate interaction involving thioether groups are necessary for PdNP-cage
stabilization.

![Figure 3.4](image)

**Figure 3.4.** Photographs showing the reaction mixture during various stages during the synthesis of PdNP@3a.

Traditional synthetic methods for the preparation of PdNPs rely heavily on classic
organic supports (e.g. polymers, dendrimers, micelles, etc.) to prevent NP agglomeration at the
colloidal stage. However, there is a compromise between the stability of the resulting NPs and
the available surface accessibility for substrate activation and transformation.\textsuperscript{36,37} For instance,
the El-Sayed group found that although G4 dendrimer-encapsulated PdNPs were more stable
than polymer-stabilized PdNPs, the catalytic activity was in fact lower.\textsuperscript{38} In our cage-based
supports not only can the particle size be predetermined by the cage cavity size, but further stability and resistance to agglomeration can also be achieved via the well-defined closed architecture of the cage. This is in great contrast to dendritic architectures where increases in generation lead to steric crowding on the dendrimer periphery and subsequent lowering of the PdNP activity.\textsuperscript{39}

With the successful formation of stable PdNP@\textbf{3a}, we next explored the use PdNP@\textbf{3a} in homogenous catalysis. The pursuits of novel catalytic technologies for more efficient chemical transformations have arguably been some of the most significant developments in the history of modern science. As compared to their bulk counterparts, nanoparticle based catalysts often exhibit unique and enhanced catalytic properties due to their high surface area, size reduction, and shape variation.\textsuperscript{40–51} Since palladium-mediated catalysis has been widely applied and shown great synthetic power in current organic chemistry,\textsuperscript{52} as proof-of-principle, we chose to use one of the most popular carbon-carbon (C–C) bond formation reactions, namely Suzuki-Miyaura cross-coupling reaction, to evaluate the catalytic activity of PdNP@\textbf{3a}.

The coupling reactions were carried out using phenylboronic acid (1.5 equiv.) and PdNP@\textbf{3a} (0.01 equiv.) along with various aryl iodides and aryl bromides bearing a variety of functional groups. All reactions were performed in a mixture of toluene/H\textsubscript{2}O (10:1, v/v) using Na\textsubscript{2}CO\textsubscript{3} (3 equiv.) as a base. The catalytic activity of PdNP@\textbf{3a} was first investigated using phenylboronic acid and aryl iodides at 100 °C under microwave heating (Table 1, entries 1 and 2). The reaction progress was monitored via TLC. Although conversion was good after 10–15 min of reaction, we found that increasing the reaction time to 30 min gave almost quantitative yields. To broaden the scope of the PdNP@\textbf{3a} catalyst, the same conditions were applied to a
series of aryl bromide substrates using a temperature of 140 °C. We obtained the desired coupling products in almost quantitative yields in most entries. The analysis of the crude reaction mixture by \(^1\)H NMR analysis shows little evidence of impurity formation during the coupling except entry 5, which was seen to contain 1-2% biphenyl byproduct.

**Table 1.** Results for Suzuki-Miyaura coupling of aryl halides using PdNP@3a and Pd(PPh\(_3\))\(_4\).\(^{a,b,c}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Product</th>
<th>Yield [%]</th>
<th>PdNP@3a</th>
<th>Pd(PPh(_3))(_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>98</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NC</td>
<td>NC</td>
<td>&gt;99</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td></td>
<td>96</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O(_2)N-Br</td>
<td>O(_2)N-Br</td>
<td>&gt;99(^c)</td>
<td>78(^c)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>&gt;99</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MeOOC-Br</td>
<td>MeOOC-Br</td>
<td>&gt;99</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: aryl halides (0.057 mmol), phenylboronic acid (0.087 mmol), Na\(_2\)CO\(_3\) (0.17 mmol), Pd catalyst (0.57 \(\mu\)mol, 1.0 mol%).

\(^b\)Yields are based on \(^1\)H NMR analysis of the crude products.

\(^c\)This yield decreases to 40% after exposure to air for 2.5h when using Pd(PPh\(_3\))\(_4\) while yields using PdNP@3a remain the same.
As a comparison, commercially available palladium (0) tetrakis (triphenylphosphine) catalyst (Pd(PPh$_3$)$_4$) was used under otherwise the same conditions. We found the conversion to the desired products could only be achieved in yields of 73–85% (Table 1) after 30 min. Although we observed only a modest increase in overall yields using PdNP@3a, we found that a major advantage of this cage-based catalyst is in its ability to be stored in solution under atmosphere over a period of several hours with no decrease in activity, thus highlighting its superb stability under ambient conditions. Such stability is remarkably superior to palladium tetrakis catalyst, which must be stored under inert atmosphere with very limited exposure to air. When both catalysts are stored in solution for 2.5 h (open to air), the activity of PdNP@3a remained the same while the activity of Pd(PPh$_3$)$_4$ was decreased to 40%, further corroborating the stability of the nanocatalyst. Moreover, we observed that after removal of the reaction vessel from the microwave reactor, the solution containing PdNP@3a was still colored and homogeneous giving further support to the highly stable structure of PdNP@3a.

The catalytic efficiency of PdNP@3a can be attributed to both its high solubility and largely unpassivated surface, which presumably allows for either easy substrate diffusion to the nanoparticle surface or the efficient leaching of Pd atoms from the PdNP surface due to lack of ligation.$^{37}$ Our study successfully demonstrates the use of organic cage molecules as suitable colloidal chemistry platforms for the controllable synthesis and stabilization of nanometer-sized catalytically active metallic nanoparticles. Due to their highly accessible, well-defined surface morphology and long shelf life in solution, cage-encapsulated nanoparticles show great promise as convenient and active catalysts.
3.4 Summary

In summary, we report the synthesis and stabilization of ~1.8 nm-sized PdNPs within the cavity of an organic cage molecule, which shows excellent catalytic activity in the Suzuki-Miyaura reaction. The incorporation of metallic nanoparticles within the cavities of well-defined, discrete molecular cage molecules have become increasingly attractive as novel catalytic supports given their stability and size programmability within the interior cage dimensions. Our cage-template approach will pave new avenues in the development of significantly improved or even novel catalysts for a range of different reactions through the use of different metallic nanoparticle centers. In addition, we envision that such approach could provide a powerful platform for controlled growth of novel nanostructured materials, which can be used in a range of nanotechnologies, including nanocatalytic applications.

3.5 Experimental section

3.5.1 Materials and general synthetic procedures

All commercially available reagents and solvents were used as received, unless noted otherwise. CH$_2$Cl$_2$ and toluene were purified by MBBRAUN solvent purification system. All reactions were carried out under dry nitrogen in flame-dried glassware, unless noted otherwise. After workup, all solvents were removed by rotary evaporation. Unless other indicated, the purity of the compounds was ≥95 % based on $^1$H NMR spectral integration. Flash column chromatography was performed using 100-150 times weight excess of 32-63 µm silica gel from Dynamic Absorbants Inc. Fractions were analyzed by TLC using TLC silica gel F254 250-µm pre-coated plates from Dynamic Absorbants Inc. GPC was performed using a Viscotek GPCmaxTM, a Viscotek Model 3580 Differential Refractive Index (RI) Detector, a Viscotek
Model 3210 UV/VIS Detector and a set of two Viscotek Viscogel columns (7.8 x 30cm, 1-MBLMW-3078, and 1-MBMMW-3078).

GPC calibration was done using monodisperse polystyrene standards and THF was used as the eluent at 30 °C. UV-vis absorption measurements were recorded with an Agilent 8453 spectrophotometer. MALDI-MS was performed using a Voyager-DE™ STR Biospectrometry Workstation in linear mode using a sinapic acid matrix. High-resolution mass spectrometry (HR-MS) was performed using a Waters SYNAPT G2 high definition mass spectrometry system. EDS was performed using a JEOL JSM-6480 scanning electron microscope with an elemental detection lower limit of carbon. All microwave reactions were conducted under dry nitrogen in flame dried glass tube using Discover SP microwave from CEM. ¹H and ¹³C NMR spectra were obtained from either an Inova 500 or Bruker 300 spectrometer. CHCl₃ (7.27 ppm) was used as an internal reference in ¹H NMR, and CHCl₃ (77.23 ppm) for ¹³C NMR. NMR data is reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (J, Hz), number of protons.

3.5.2 Experimental procedures

General procedure for Suzuki coupling. To a flame-dried, 10-mL microwave synthesizer reaction vessel was added: aryl halide (0.057 mmol), phenylboronic acid (0.087 mmol), and Na₂CO₃ (0.17 mmol). The vessel was sealed using a silicon cap with septum and further secured using a piece of tightly wrapped electrical tape. After degassing the vessel under vigorous vacuum/refill were added H₂O (200 µL) and PdNP@3a in toluene (2.0 mg in 2.0 mL) via syringe. The solution was degassed three times, transferred to the microwave reactor and reacted using the following conditions: 30 min, 100 °C (iodo), 140 °C (bromo), 130 PSI, 50 W. After
the reaction was complete, the solution was cooled to rt, poured into H₂O (4 mL) and extracted 3 x 2 mL using CHCl₃. The organic fractions were combined, dried over sodium sulfate and concentrated under reduced pressure.

**Entry 1 (4-methylbiphenyl):** The general procedure for Suzuki coupling described above was followed. 4-iodotoluene (12.3 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 4-methylbiphenyl (white solid, 98% based on ¹H NMR integration) using Na₂CO₃ (18 mg, 0.17 mmol), PdNP@I (2.0 mg, 0.57 µmol), H₂O (200 µL) and toluene (2.5 mL). ¹H NMR (CDCl₃, 500 MHz) δ 7.63-7.59 (m, 2H), δ 7.52 (d, J = 8.1 Hz, 2H), δ 7.45 (t, J = 7.4 Hz, 2H), δ 7.35 (d, J = 7.7 Hz, 1H), δ 7.29-7.25 (m, 2H), δ 2.42 (s, 3H); ¹³C (CDCl₃, 75 MHz): δ 141.46, 141.26, 138.24, 128.75, 128.62, 127.19, 127.17, 125.10, 21.42; HR-MS (ESI): calcd for C₁₃H₁₂ [M+H]⁺ 169.1012; found 169.1012.

**Entry 2 (3-cyanobiphenyl):** The general procedure for Suzuki coupling described above was followed. 3-iodobenzonitrile (13 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 3-cyanobiphenyl (yellow solid, >99% based on ¹H NMR integration) using Na₂CO₃ (18 mg, 0.17 mmol), PdNP@I (2.0 mg, 0.57 µmol), H₂O (200 µL) and toluene (2.5 mL). ¹H NMR (CDCl₃, 500 MHz) δ 7.88 (s, 1H), δ 7.84-7.82 (m, 1H), δ 7.66-7.63 (m, 1H),
δ 7.60-7.55 (m, 3H), δ 7.50 (t, J = 7.5 Hz, 2H), δ 7.44 (q, J = 7.5 Hz, 1H); 13C (CDCl₃, 75 MHz): δ 142.45, 138.87, 131.49, 130.71, 130.69, 129.60, 129.13, 128.39, 127.08, 118.85, 112.96; HR-MS (ESI): c alc for C₁₃H₉N [M+Li]+ 186.0896; found 186.0897.

Entry 3 (3,5-dimethylbiphenyl): The general procedure for Suzuki coupling described above was followed. 3,5-dimethylbromobenzene (10.5 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 3,5-dimethylbiphenyl (colorless oil, 96% based on ¹H NMR integration) using Na₂CO₃ (18 mg, 0.17 mmol), PdNP@1 (2.0 mg, 0.57 μmol), H₂O (200 μL) and toluene (2.5 mL). ¹H NMR (CDCl₃, 500 MHz) δ 7.60 (dd, J = 8.1, 1.1 Hz, 2H), δ 7.45 (t, J = 7.6 Hz, 2H), δ 7.38-7.33 (m, 1H), δ 7.24 (s, 2H), δ 7.03 (s, 1H), δ 2.41 (s, 6H); ¹²C (CDCl₃, 75 MHz): δ 141.5, 141.3, 138.27, 128.92, 128.78, 127.3, 127.2, 125.14, 21.45; HR-MS (ESI): c alc for C₁₄H₁₄ [M+Li]+ 189.1256; found 189.1257.

Entry 4 (4-nitrobiphenyl): The general procedure for Suzuki coupling described above was followed. 4-nitrobromobenzene (11.4 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 3,5-dimethylbiphenyl (yellow solid, >99% based on ¹H NMR integration) using Na₂CO₃ (18 mg, 0.17 mmol), PdNP@1 (2.0 mg, 0.57 μmol), H₂O (200 μL)
and toluene (2.5 mL). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.33 (d, J = 8.8 Hz, 2H), $\delta$ 7.76 (d, J = 8.8 Hz, 2H), $\delta$ 7.67-7.63 (m, 2H), $\delta$ 7.56-7.50 (m, 2H), $\delta$ 7.50-7.45 (m, 1H); $^{13}$C (CDCl$_3$, 75 MHz): $\delta$ 147.63, 147.09, 138.78, 129.15, 128.91, 127.80, 127.39, 124.11; HR-MS (ESI): calcd for C$_{12}$H$_9$NO$_2$ [M+H]$^+$ 200.0712; found 200.0711.

Entry 5 (4-acetylbiphenyl): The general procedure for Suzuki coupling described above was followed. 4-nitrobromobenzene (11.3 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 3,5-dimethylbiphenyl (white solid, >99% based on $^1$H NMR integration) using Na$_2$CO$_3$ (18 mg, 0.17 mmol), PdNP@3a (2.0 mg, 0.57 µmol), H$_2$O (200 µL) and toluene (2.5 mL). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.06 (d, J = 8.5 Hz, 2H), $\delta$ 7.71 (d, J = 8.5 Hz, 2H), $\delta$ 7.52-7.47 (m, 2H), $\delta$ 7.45-7.41 (m, 1H), $\delta$ 2.66 (s, 3H); $^{13}$C (CDCl$_3$, 75 MHz): $\delta$ 197.75, 145.78, 139.88, 135.85, 128.95, 128.91, 128.23, 127.27, 127.23, 26.68; HR-MS (ESI): calcd for C$_{14}$H$_{12}$O [M+H]$^+$ 203.1048; found 203.1045.

Entry 6 (3,5-dimethylesterbiphenyl): The general procedure for Suzuki coupling described above was followed. 4-nitrobromobenzene (15.5 mg, 0.057 mmol) and phenylboronic acid (10.4 mg, 0.087 mmol) were converted to 3,5-dimethylbiphenyl (white solid, >99% based on $^1$H NMR
integration) using \( \text{Na}_2\text{CO}_3 \) (18 mg, 0.17 mmol), PdNP@1 (2.0 mg, 0.57 µmol), H\( _2 \)O (200 µL) and toluene (2.5 mL). \(^1\)H NMR (CDCl\( _3 \), 500 MHz) \( \delta \) 8.67 (t, \( J = 1.6 \) Hz, 1H), 8.48 (d, \( J = 1.6 \) Hz, 2H), 7.68 (d, \( J = 7.2 \) Hz, 2H), 7.50 (t, \( J = 7.6 \) Hz, 2H), 7.44 (m, 1H), 4.00 (s, 6H); \(^{13}\)C (CDCl\( _3 \), 75 MHz): \( \delta \) 166.24, 141.95, 139.03, 132.30, 131.15, 129.32, 129.03, 128.23, 127.18, 52.45; HR-MS (ESI): calcd for \( \text{C}_{16}\text{H}_{14}\text{O}_4 \)[M+Li]\(^+\) 277.1053; found 277.1056.

**Cage 3a:** For synthesis of Cage 3a, refer to previous publication. \(^1\) The physical data for cage 3a:

\(^1\)H NMR (C\( _6\)D\(_6\), 500 MHz) \( \delta \) 7.60 (s, 6H), \( \delta \) 7.46 (s, 6H), 7.36-7.17 (m, 24H), \( \delta \) 6.41 (d, \( J = 8.5 \) Hz, 12H), \( \delta \) 4.40 (t, \( J = 6.0 \) Hz, 6H), \( \delta \) 3.70 (d, \( J = 5.3 \) Hz, 12H), \( \delta \) 3.29 (m, 12H), \( \delta \) 2.52 (s, 12H), \( \delta \) 2.14 (q, \( J = 7.4 \) Hz, 6H), \( \delta \) 1.93 (m, 6H), \( \delta \) 1.65 (m, 8H), \( \delta \) 1.51 (m, 16H), \( \delta \) 1.31 (m, 74H), \( \delta \) 1.11-0.86 (m, 80H), \( \delta \) 0.79 (t, \( J = 7.1 \) Hz, 18H); \(^{13}\)C NMR (101 MHz, C\( _6\)D\(_6\)): \( \delta \) 161.03, 145.75, 142.72, 140.00, 139.48, 134.32, 134.08, 132.62, 131.10, 130.08, 128.67, 125.33, 122.69, 117.61, 113.10, 111.54, 92.50, 87.15, 74.63, 46.89, 34.56, 32.04, 32.04, 31.05, 30.77, 29.93, 29.85, 29.66, 29.54, 26.57, 24.96, 22.83, 22.31, 14.12, 14.07; MS (MALDI): calcd for \( \text{C}_{213}\text{H}_{264}\text{Br}_6\text{N}_6\text{O}_3\text{S}_3 \)[M]\(^+\) 3531.50; found 3530.78.
**Compound 5:** To a Schlenk tube were added compound 4 (500 mg, 0.95 mmol) and THF (15 mL) under nitrogen atmosphere. The solution was cooled to 0 °C using an ice bath. A solution of TBAF (1M in THF, 1.9 mL, 1.9 mmol) was added dropwise at 0 °C. The darkened solution was warmed to rt and stirred for 30 min. The solvent was removed by rotary evaporation, and the crude product was passed through a short column of silica gel using 25% ethyl acetate/hexane to yield the product 5 as a slightly yellow solid (362 mg, 100%).

\[ \text{H NMR (CDCl}_3, 500 MHz) \delta 7.26 (s, 2H), \delta 4.18 (t, J = 6.6 Hz, 2H), \delta 3.24 (s, 2H), \delta 2.26 (s, 3H), \delta 1.87-1.76 (m, 2H), \delta 1.55-1.46 (m, 2H), \delta 1.40-1.19 (m, 26H), \delta 0.90 (t, J = 6.9 Hz, 3H); \text{C NMR (CDCl}_3, 75 MHz):} \delta 160.42, 135.16, 132.74, 116.39, 81.24, 79.70, 74.52, 31.93, 30.25, 29.71, 29.69, 29.64, 29.47, 29.37, 25.92, 22.70, 20.27, 14.12; \text{HR-MS (ESI):} \text{calcd for C}_{27}\text{H}_{40}\text{O} [\text{M+H}^+] 381.3152; \text{found 386.3153.}

**Compound 2b:** The general procedure for Sonogashira cross coupling was followed. Using compound 5 (152 mg, 0.40 mmol), 3-bromo-5-iodo-benzaldehyde (286 mg, 0.92 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (17 mg, 0.02 mmol), CuI (1.5 mg, 0.008 mmol), triethylamine (4 mL), and THF (1
mL), compound 2b was obtained as a colorless solid (155 mg, 52%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.98 (s, 2H), $\delta$ 8.00 (t, $J =$ 1.7 Hz, 2H), $\delta$ 7.95 (t, $J =$ 1.5 Hz, 2H), $\delta$ 7.91 (t, $J =$ 1.7 Hz, 2H), $\delta$ 7.35 (s, 2H), $\delta$ 4.28 (t, $J =$ 6.3 Hz, 2H), $\delta$ 2.34 (s, 3H), $\delta$ 1.93-1.84 (m, 2H), $\delta$ 1.63-1.58 (m, 2H), $\delta$ 1.40-1.14 (m, 26H), 0.89 (t, $J =$ 6.9 Hz, 3H); $^{13}$C (CDCl$_3$, 75 MHz): $\delta$ 189.87, 159.61, 139.34, 137.82, 134.92, 133.20, 131.70, 131.35, 126.33, 123.21, 116.57, 90.51, 88.51, 75.00, 31.93, 30.61, 29.73, 29.71, 29.69, 29.67, 29.37, 26.49, 22.70, 20.40, 14.14; HR-MS (ESI): calcd for C$_{41}$H$_{46}$Br$_2$O$_3$ [M+Li]$^+$ 751.1974; found 751.1967.

**Cage 3b:** To a Schlenk tube was added compound 2b (37 mg, 0.05 mmol) and compound 1 (20 mg, 0.033 mmol) in CHCl$_3$ (11 mL) under nitrogen atmosphere. TFA (0.38 µL, 0.005 mmol) was then added dropwise and the reaction stirred at rt for 18h. The reaction mixture was cooled at 0 °C and DIBAL (1.24 mL, 1.0 M solution in CH$_2$Cl$_2$, 1.24 mmol) was added. The clear solution was stirred at 0 °C for 1h. Saturated NaHCO$_3$ was added and the mixture was stirred at rt for 30 min. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by flash column chromatography using dichloromethane as the eluent to afford the product 3b as a white solid (13 mg, 24%). $^1$H NMR (CD$_2$Cl$_2$, 500 MHz) $\delta$ 7.54 (s, 12H), $\delta$ 7.47 (s, 6H), $\delta$ 7.27 (s, 6H), $\delta$ 7.06-6.87 (m, 12H), $\delta$ 6.68-6.48 (m, 12H), $\delta$ 4.37 (s, 12H), $\delta$ 4.30 (s, 6H), $\delta$ 4.19 (t, $J =$ 6.2 Hz, 6H), $\delta$ 2.28 (s, 6H), $\delta$ 2.02-1.94 (m, 12H), 1.86-1.78 (m, 6H), $\delta$ 1.60-0.63 (m, 153H); $^{13}$C (CD$_2$Cl$_2$, 101 MHz): $\delta$ 159.47,
145.69, 142.82, 139.71, 138.94, 134.17, 132.40, 130.88, 129.97, 128.73, 125.17, 122.39, 116.89, 91.65, 86.74, 74.64, 47.33, 31.90, 31.58, 30.73, 30.54, 30.47, 30.02, 29.70, 29.67, 29.64, 29.35, 29.29, 26.42, 22.68, 22.06, 20.09, 13.90, 13.86; MS (MALDI): calcd for C_{207}H_{252}Br_{6}N_{6}O_{3} [M+2Li]^\+ 3357.53; found 3357.19.

**GPC Graph of Cage 3a and 3b**

![Graph of Cage 3a and 3b]

**PdNP Assembly**

All reactions were carried out on a 4-8 mg scale with respect to cage 3a. A solution of K_{2}PdCl_{4} (1.8 mg, 0.0055 mmol) in deionized H_{2}O (0.5 mL) was stirred and tetraoctylammoniumbromide (TOAB) (31 mg, 0.056 mmol) in CH_{2}Cl_{2} (0.5 mL) was added and stirred until Pd(II) was transferred into organic phase (~25 min). A solution of cage 3a (4 mg, 0.0011 mmol) in CH_{2}Cl_{2} (0.5 mL) was added and the mixture was stirred at rt for 30-45 min and then subsequently reduced with an aqueous solution of NaBH_{4} (8 mg, 0.21 mmol) in deionized H_{2}O (0.5 mL). The resulting organic layer had the characteristic dark color of PdNP and contained no precipitate. After separation, the aqueous layer was washed with CH_{2}Cl_{2} (2 x 1 mL), the organic fractions were combined and concentrated to ca. 0.2 mL without the application of heat. The remaining organic solution (0.2 mL) was then transferred dropwise to a solution of ethanol (5-10 mL) and
centrifuged to precipitate the PdNP@3a complexes. This centrifugation procedure was repeated until supernatant was no longer colored (~2x). The resulting complexes are soluble in common organic solvents and stable in solution.

**Transmission Electron Microscopy (TEM)**

Imaging was performed using an FEI Tecnai F20 IVEM 200kV high resolution TEM. The sample was drop-cast from CH$_2$Cl$_2$ onto carbon-coated 300-mesh copper grids (CF300-Cu) purchased from Ted Pella. Particle size data of over 500 particles were obtained by analyzing TEM images using software ImageJ.

Representative TEM images of PdNP@3a including control experiment in the absence of cage 3a.

**PXRD Spectra of PdNP@3a**
3.6 References


Chapter 4

Assembly of Colloidal Gold Nanoparticles Directed by Organic Molecular Cages

This paper is planned for publication submission under the same title: McCaffrey, R.; Jin, Y.; Long, H.; Park, W.; Zhang, W.

4.1 Abstract

We report a series of amine-linked organic molecular cages as templates that guide the formation of well-dispersed gold nanoparticles (AuNPs) with diameters of ~$(1.6 \pm 0.4)$ nm inside the cage cavities. We envision that these cage molecules can serve not only as the templates to control AuNP growth, but also direct their further assembly in an ordered fashion. The resulting encapsulated AuNPs in the cage can be chemically directed into dimers and trimers with variable interparticle spacing and they show promise in the assembly of more sophisticated architectures through the coupling with simple organic linkers.

4.2 Introduction

Given the unique electronic, optical, and magnetic properties of zero-dimensional (0-D) nanoparticles (NPs), there have been substantial efforts in developing nanostructured materials that utilize NPs as the key components. The old adage ‘materials by design’ has been used to describe the long-standing goals and promises of materials science since its inception but explicit control over NP size and surface stoichiometry remain as a bottleneck in terms of the
fabrication of novel hybrid functional materials. Despite the successes of organizing
nanomaterials lithographically onto solid surfaces, the controlled organization of NP clusters in
solution largely remains a challenge. From the perspective of fundamental research, assembly of
NPs into one-dimensional (1-D), two-dimensional (2-D), and three-dimensional (3-D)
assemblies would give insight into coupled NP systems while also providing a platform for better
understanding what structural characteristics of NP ensembles generate useful and interesting
properties.

The development of a colloid chemistry method for assembling NPs is rapidly gaining
attention and many existing methods for mediating the assembly of NPs have been reported. For example, the positional organization of nanoparticles can be observed through various types
of interparticle interactions (e.g., electrostatic, hydrogen bonding, van der Waals, magnetic,
molecular, etc.), as well as through the use of templating agents, such as DNA scaffolds, polymer-based molecular recognition, multidentate thioether ligands, and carbon
nanotubes, the latter often utilizing strong template-NP interactions and subsequently lead to
particle organization around the predefined shape of the template. However, many of these
methods lack the ability to control the spacing between the particles and, in many cases, produce
only large uncontrollable aggregates of nanoparticles with no discernable morphology.
Colloid chemistry methods for the precise control of morphology and chemical composition of
NP materials has been gaining momentum in recent years but is a far more challenging feat
and the ability to assemble NPs with known and controlled surface functionality into discrete and
variable architectures is highly desirable.

Well-defined, discrete organic molecular cages have gained increasing attention due to
their shape persistence, structural tunability, and thermal and chemical stability. Recent
advances in dynamic covalent chemistry, particularly the imine condensation/metathesis
reaction, readily gives access to a wide variety of molecular cages that have made significant
advances in areas of chemical sensing,\textsuperscript{52} catalysis,\textsuperscript{53} gas separation and storage\textsuperscript{54,55} and self-
assembly of gold nanoparticles (AuNPs).\textsuperscript{56} However, the use of the confined nanopore within an
organic molecular cage as a template for the synthesis and stabilization of metallic nanoparticles
is a far more recent advance, with only a handful of publications being found in the literature.\textsuperscript{57-59}
Furthermore, the capacity for such a highly organized ligand shell to direct NPs chemically into
various discrete architectures and assemblies has yet to be explored at all. Previously, we
reported a cage-templated strategy for the controlled synthesis of AuNPs through the use of a
well-defined, discrete organic molecular cage functionalized with pendant interior thioether
groups.\textsuperscript{57} The AuNPs formed within the cage cavity exhibited a narrow size distribution of (1.9 ±
0.4) nm and were highly stable due to the effective coverage and protection of the AuNPs’
surface by the cage shell. We envision these cage molecules can serve not only as the templates
to control AuNP growth, but also direct their further assembly in an ordered fashion.

As such, herein we report our initial findings towards the accurate control of the surface
chemical functionalization of AuNPs using divalent organic molecular cages as means of
controlling the stoichiometry of NPs. Our results show that these complexes are promising in
operating as amenable platforms for the interlinking of gold nanoparticles (AuNPs) using wet
chemical techniques. Specifically, we demonstrate the ability to generate discrete 1-D oligomers
(e.g., dimers, trimers) with adjustable interparticle spacing through homocoupling of
nanoparticle-encapsulated cage molecules as well as the formation of small, discrete 2-D
architectures such as triangular and tetrameric assemblies that can be directed through the use of
small ethynyl-functionalized organic linkers. The aim of this approach, within the context of
nanoscience and nanotechnology, is to better understand and design, and thus better develop, such structures in order to enable their applications as novel and advanced tunable materials, particularly in systems that require precision in terms of the relative position of NPs.

4.3 Results and Discussion

For the purposes of directing AuNP-cage complexes into discrete clusters we designed a series of organic molecular cages 1a-c built from modular components that have been both endo- and exo-functionalized. In order to seed and guide the growth of AuNPs within the nanopore of the cage we used previously published endo-functionalized compound 4 as the cage side panel, as it contains the necessary thioether group for the nucleation of AuNPs. Exo-functionalization of the cage exterior was achieved using a four arm top panel comprising a tetrahedral geometry. We chose to use 4,4’,4”-((4-iodophenyl)methanetrityl)tribenzoicacid 2 as the starting building block such that after a Curtius rearrangement, it provided the tetrphenylethane-based triamine building block 3a necessary for [3+2] cage formation, while still leaving a reactive arm (iodo site) free for post functionalization. Replacement of the exo-directing haloarene on 3a via Sonogashira coupling with trimethylsilylacetylene gave ligand 3b. After further deprotection of 3b using tetra-n-butylammonium fluoride (TBAF) the arm was additionally extended via Sonogashira coupling with excess 1,4-diiodobenzene and finally terminated with trimethylsilylacetylene to afford 3c.
Figure 4.1. Synthesis of cage building blocks.

Molecular cages 1a-c were then formed through an acid catalyzed imine condensation reaction between compounds 4 and 3a-c. After reduction of the imine bond to the more stable amine using DIBAL-H, the obtained cage molecules were characterized by $^1$H and $^{13}$C NMR spectroscopy, gel permeation chromatography (GPC), and matrix-assisted laser-desorption ionization mass spectrometry (MALDI-MS). Empty molecular cages 1b and 1c were further reacted with excess TBAF in THF prior to the nanoparticle synthesis in order to form free acetylene cage analogues 1b$_2$ and 1c$_2$, as was verified by $^1$H NMR spectroscopy.

Scheme 4.2. Synthesis of cages 1a-c.
Divalent cage-encapsulated AuNPs were prepared in the presence of cages 1a, 1b, or 1c using a two-phase liquid-liquid approach developed by Brust et al., with tetraoctylammonium bromide (TOAB) as a phase-transfer agent. A solution of TOAB in CH₂Cl₂ was added to an aqueous solution of H₅AuCl₄ (5-10 equiv.) and stirred until the aqueous layer was colorless, indicating complete transfer of AuCl₄⁻ into the organic solution. A solution of the respective cage 1a, 1b, or 1c (1 equiv.) in CH₂Cl₂ was added to the above biphasic mixture and then subsequently reduced with an aqueous solution of sodium borohydride (190 equiv., rt). The resulting organic phase changed to a strongly colored dark solution without any precipitates, indicating the stable formation of AuNP-1a, AuNP-1b, and AuNP-1c. The organic layer containing the respective AuNP-1a,1b,1c complex was separated, precipitated from ethanol and collected by centrifugation. All three NP-cage complexes were analyzed by TEM and UV/Vis and seen to stabilize NPs of comparable size with average particle diameters of around 1.6 nm (Fig. 4.3a). Computational simulation of the interaction between cage 1 and AuNPs of different radii was performed and matches well with our observation thus providing a theoretical support of our experimental findings (Fig. 4.3b). Moreover, these complexes are stable in solution and show good solubility in common organic solvents, as described previously.
The synthesis of NP oligomers was explored through the homocoupling of complexes AuNP-1b₂ and AuNP-1c₂, both of which are terminated on opposite sides by ethynyl groups of distinct length and thus represent divalent unit cells. Given the immense variety of possible acetylenic coupling chemistries\textsuperscript{62} Hay coupling is the most suitable method for the coupling of organic ligand coated nanoparticles as such mild reaction conditions avoid potential incidence of particle sintering and as well as the versatility of copper-TMEDA complex in a range of different solvents.\textsuperscript{63} Initially we used empty molecular cage 1b₂ as a model complex in order to test the feasibility of generating a 1D polymer using a divalent cage platform and to optimize conditions for the homocoupling of NP-cage complexes. A series of empty cage polymerization reactions
were performed at room temperature using CH$_2$Cl$_2$ as the solvent and CuCl and TMEDA were added incrementally using 10-200 molar equivalents. Based on GPC analysis, we found that in the presence of catalyst loadings below 50 equiv. the coupling efficiency was quite poor and the reaction mixture consisted mostly of unreacted cage monomer. However, in the presence of much larger loadings (100 equiv.) we observed a significant disappearance of free cage monomer (Fig. 4.4, red line) and the appearance of a large band at lower retention volumes after 12 min indicating the formation of polymeric species (Fig. 4.4, blue line). The polymerization was further improved to > 90% conversion when stirred in an open scintillation vial in order to maximize surface area for aeration, though our results show that despite the fact that the polymerization proceeds very quickly the free cage 1b$_2$ is never completely consumed.

![Figure 4.4](image)

**Figure 4.4.** GPC graph of pure cage 1b$_2$ (red line) and cage polymer (1b$_2$)$_n$ (blue line) after 12 min.

After subjecting NP-cage complexes AuNP-1b$_2$ and AuNP-1c$_2$ to more or less the same conditions as above we monitored the evolution of each respective polymeric NP-cage complex (AuNP-1b$_2$)$_n$ and (AuNP-1c$_2$)$_n$ by transmission electron microscopy (TEM) in intervals of 5, 10, 15, and 20 min. TEM analysis distinctly shows the presence of large amorphous NP clusters after
ca. 10 min of reaction time, likely due to the insolubility of the growing NP chains. After ca. 1h the reaction mixture becomes entirely clear, containing only insoluble precipitate, further corroborating empirically the homocoupling of NP-cage complexes. As such, the reaction time was limited to 5-10 min in an effort to generate a wider fraction of shorter, more soluble species such as dimeric structures.

A crude aliquot of the reaction mixture of respective polymer complex (AuNP-1b)\(_n\) and (AuNP-1c)\(_n\) was removed, diluted and drop cast onto copper coated carbon grids for TEM analysis. Dilute mixtures of NP-cage oligomers were used in order to relate those structures derived from engineered acetylenic connectivity and rule out more spurious structures that are in close proximity due solely to high concentration. As an additional control experiment we performed the coupling reaction in the presence of AuNP-1a, which lack the proper functionality for acetylenic coupling, at more or less the same concentration and time. Though trivial amounts of clustering will always be observable due to drying effects, TEM analysis shows no relatable, average interparticle spacing of the clusters thus suggesting that the observed short oligomers in both (AuNP-1b)\(_n\) and (AuNP-1c)\(_n\) are indeed covalently connected. With that said, our results show very similar oligomeric distributions of monomer/dimer/trimer for both NP-cage polymer complexes with the shorter species (AuNP-1b)\(_n\) having a distribution of 66%, 28%, 5% while the extended analog (AuNP-1c)\(_n\) a distribution of 65%, 27%, 7%. However, despite the copious amount of alkyl chains present on each cage species, linear oligomers composed of four units were observed only rarely (< 1%) while those composed of five or more units were not seen at all. This observation could be both the result of a short coupling time as well as severe insolubility of the chains of organic ligand-wrapped NPs. Attempts at imaging potentially longer chain type structures from the precipitation formed during the reaction using TEM were
unsuccessful, which is consistent with previous results in the literature.\textsuperscript{42,43} It is worth adding that these previous studies also observed the formation of primarily dimeric and trimeric species.

From a series of TEM micrographs we measured the interparticle spacings of the observed dimers and trimers in both \((\text{AuNP-1b})_n\) and \((\text{AuNP-1c})_n\) from roughly 100-150 oligomers (measured from center-to-center of adjacent NPs) and found experimental average maxima of 3.1-3.4 nm and 4.4-4.8 nm respectively, for \((\text{AuNP-1b})_n\) and \((\text{AuNP-1c})_n\) (Fig. 4.5).

![Figure 4.5](image)

**Figure 4.5.** Representative TEM images and corresponding interparticle distances for a) \text{AuNP-cage 1b}\_2 and b) \text{AuNP-cage 1c}\_2.

The experimentally measured average maxima match well with the calculated theoretical distance of each coupled NP-cage complex as 3.2 nm and 4.6 nm respectively, for \((\text{AuNP-1b})_2\) and \((\text{AuNP-1c})_2\) (Fig. 4.6). Interestingly, we observed a second maxima spacing of 2.9-3.5 nm present in roughly 5% the \text{AuNP-1c}\_2 oligomers (Fig. 4.5b), which incidentally matches the
estimated length of the terminal end of one oligo(phenyleneethynyl) linker coordinating to the surface of another gold NP-cage complex. We also note that the observed trimeric structures with dimodal particle spacing often have a dihedral angle giving the oligomers a bent shape further supporting the notion of Au-alkynyl interfacial bonding. Precedence for such an observation can be found in the work of Peterle et al., who reported an analogous phenomenon following the covalent homocoupling of thioether dendrimers via a central oligo(phenyleneethynyl) rigid rods and attributed this to what was believed to be direct acetylene-gold bond formation.43

Figure 4.6. Calculated theoretical interparticle distances between two NPs of complexes a) (AuNP-1b)2, b) (AuNP-1c)2 and c) (AuNP-1c)-AuNP through Au-alkynyl interfacial bonding.

Currently, there is a plethora of literature describing such Au-alkynyl interfacial bonding,44-72 though the exact mechanism describing its formation is largely unknown.

Moreover, the fact that a bimodal interparticle distribution is not seen in the case of AuNP-1b2 is

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probably due to the substantially shorter length of the linker, thus making such Au-alkynyl bonding unfavorable due to the increased van der Waals interactions between neighboring NP- cage complexes.

Given the inability to generate long chain-like oligomeric structures from acetylenic chemistry, where the lack of observable higher order oligomers (e.g., tetramers, etc.) is probably hindered by uncontrollable polymerization, we expanded the scope of chemical reaction conditions applicable to our divalent cage platform in order to augment the architectural geometry of the resulting clusters. As proof-of-concept, we used halogen-based AuNP-1a as the model complex for Sonogashira cross-coupling with various small ethynyl-functionalized organic linkers, namely 1,3,5-triethynylbenzene and 1,3,6,8-tetraethynylpyrene. Given the divalent nature of AuNP-1a and in an effort to favor the formation of discrete clusters, specifically triangular and tetrameric architectures, the Au:linker ratio of the system was adjust to 3:1 and 4:1, respectively. To further encourage the formation of discrete clusters a pseudo-dilution was performed in the presence of AuNP-1a in solution of THF and Et$_3$N containing a large excess of CuI and Pd catalyst. A dilute solution of the respective linker in THF was slowly added at rt under inert atmosphere via a syringe pump. After slow addition over a period of 6-8 h, the solution was quenched and extracted and a small aliquot was removed, diluted and drop cast onto copper coated carbon grids for TEM analysis. Interestingly, we found that this system is indeed capable of generating triangular and tetrameric clusters, as shown in Figure 4.7, though the populations are low.
Given the statistical nature of coupling with a divalent building, much of the resulting assemblies exist as dimeric species or unreacted monomer, though pseudo-dilution is capable of generating such 2-D geometries. We are currently seeking out other applicable chemistries for the formation of interesting architectures (e.g., click chemistry) and possibly other ways to solubilize the larger insoluble clusters.

4.4 Summary

In summary, we report the synthesis and stabilization of ~1.6 nm-sized AuNPs within the cavities of various exo-functionalized organic cage molecules, which can then serve to chemically direct and assemble the NPs into dimers and trimers with variable interparticle spacing. These complexes also show promise in the directed assembly of discrete clusters through the use of small organic linkers. Since the ability to assemble nanoscopic components into discrete, controllable architectures with well-defined interparticle spacing is crucial for the development of nanostructured materials, NP-cage complexes can serve as amenable platforms.
for the controllable synthesis of nanoparticles and the further development of experimental systems from which interparticle interactions can be engineered.

4.5 Experimental section

4.5.1 Materials and general synthetic procedures

All commercially available reagents and solvents were used as received, unless noted otherwise. CH$_2$Cl$_2$ and THF were purified by MBBRAUN solvent purification system. 1,3,5-triethynylbenzene$^{73}$ and 1,3,6,8-tetraethynylpyrene$^{74}$ were synthesized according to previously published procedures. All reactions were carried out under dry nitrogen in flame-dried glassware, unless noted otherwise. After workup, all solvents were removed by rotary evaporation. Unless otherwise indicated, the purity of the compounds was $\geq$95% based on $^1$H NMR spectral integration. Flash column chromatography was performed using 100-150 times weight excess of 32-63 µm silica gel from Dynamic Absorbants Inc. Fractions were analyzed by TLC using TLC silica gel F254 250 µm precoated-plates from Dynamic Absorbants, Inc. GPC was performed using a Viscotek GPCmaxTM, a Viscotek Model 3580 Differential Refractive Index (RI) Detector, a Viscotek Model 3210 UV/VIS Detector and a set of two Viscotek Viscogel columns (7.8 x 30cm, 1- MBLMW-3078, and 1-MBMMW-3078). TEM was performed using a Philips CM100 operating at 80 kV. GPC calibration was done using monodisperse polystyrene standards and THF was used as the eluent at 30 °C. UV-vis absorption measurements were recorded with an Agilent 8453 spectrophotometer. MALDI-MS was performed using a Voyager-DE™ STR Biospectrometry Workstation in linear mode using a sinapic acid matrix. High-resolution mass spectrometry (HR-MS) was performed using a Waters SYNAPT G2 high definition mass spectrometry system. $^1$H and $^{13}$C NMR spectra were obtained using either an Inova 500 or Bruker 300 spectrometer. CHCl$_3$ (7.27 ppm) was used as an internal reference in
$^1$H NMR, and CHCl$_3$ (77.23 ppm) for $^{13}$C NMR. NMR data is reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (J, Hz), number of protons.

4.5.2 Experimental procedures

[Diagram]

**Compound 3a.** This compound was prepared in the following four steps, without fully characterizing all the intermediates:

**Step 1:** A solution of compound 2 (939 mg, 1.45 mmol) in CH$_2$Cl$_2$ (10 mL) and THF (3 mL) was stirred and cooled to 0°C. Oxalyl chloride (1.65 g, 13.05 mmol) was added dropwise, followed by DMF (3 drops) at 0°C. The mixture was allowed to warm to rt and stirred 1 h. The volatiles were evaporated to give a light yellow solid, which was used in the following step without purification.

**Step 2:** A solution of the above acyl chloride in acetone (40 mL) was stirred and cooled to 0°C, as a solution of NaN$_3$ (848 mg, 13.05 mmol) in H$_2$O (3 mL) was added dropwise. The mixture was stirred at 0°C for 1h. The solvent was evaporated and water (50 mL) was added. The organic was separated, and the aqueous layer was extracted with Et$_2$O (5 x mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated to give the crude product as a foamy yellow solid, which was used in the following step without further purification.
**Step 3:** To the solution of the above acyl azide in toluene (20 mL) was added benzyl alcohol (1.41 g, 13.05 mmol). The solution was refluxed for 2h, at which point TLC showed complete conversion of the acyl azide to carbamate. Ethyl acetate (100 mL) was added, and the solution was washed 1M HCl (2 x 50 mL), saturated NaHCO₃ (2 x 50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated to give the crude product as a golden brown solid, which contained excess benzyl alcohol and was hydrolyzed directly in the next step without further purification.

**Step 4:** To the solution of the above carbamate in EtOH (25 mL) was added a solution of KOH (1.22 g, 21.75 mmol) in H₂O (2 mL). The mixture was heated at 95 °C for 18h. The volatiles were removed and water (100 mL) was added. The product was extracted with Et₂O (3 x 50 mL). The combined organic fractions were washed with brine (75 mL), dried over anhydrous Na₂SO₄, and concentrated to give the crude product as a pink oil. Purification by flash column chromatography (80% EtOAc, 3% TEA in hexane) provided amine 3a as an off-white solid (490 mg, 69% over four steps): ¹H NMR (CDCl₃, 500 MHz) δ 7.51 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.6 Hz, 6H), 6.55 (d, J = 8.6 Hz, 6H), 3.59 (s, 6H). ¹³C NMR (CDCl₃, 101 MHz) δ 148.2, 144.1, 137.4, 136.3, 133.3, 132.0, 114.3, 114.2, 62.5. HR-ESI (m/z): [M+H]⁺ calcd for C₂₅H₂₂N₃I 492.0937 found 492.0930.

\[ \text{H}_2\text{N}\begin{array}{c} \text{Si} \\ [-] \\ \text{H}_2\text{N} \end{array} \text{H}_2\text{N} \begin{array}{c} \text{H}_2\text{N} \\ [-] \\ \text{NH}_2 \end{array} \]
**Compound 3b:** To a Schlenk tube was added compound 3a (200 mg, 0.407 mmol), CuI (1.5 mg, 0.008 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (8.5 mg, 0.012 mmol) in THF (3 mL) and TEA (10 mL). The solution was degassed 3x and then following the addition of TMSA (0.3 mL, 2.0 mmol) the solution was left to stir at rt overnight. After removal of volatiles the crude material was directly subjected to flash column chromatography using 80% EtOAc in hexane with 3% TEA to afford compound 3b as a white solid (184 mg, 98%): $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.32 (d, J = 8.5 Hz, 2H), δ 7.14 (d, J = 8.5 Hz, 2H), δ 6.92 (d, J = 8.6 Hz, 6H), δ 6.56 (d, J = 8.6 Hz, 6H), δ 3.60 (s, 6H), δ 0.24 (s, 9H). $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 148.9, 143.9, 137.4, 131.9, 130.9, 130.8, 120.0, 114.1, 105.3, 93.9, 62.7, 0.01. HR-ESI (m/z): [M+Li]$^+$ calcd for C$_{30}$H$_{31}$N$_3$Si 468.2448 found 468.2467.

**Compound 3c.** This compound was prepared in the following three steps, without fully characterizing all the intermediates:

**Step 1:** A solution of compound 3b (159 mg, 0.34 mmol) in THF (10 mL) was stirred and cooled to 0 °C. TBAF (0.7 mL, 0.7 mmol) was added dropwise and allowed to stir at rt for 1h. After quenching with NH$_4$Cl the product was extracted 3x CH$_2$Cl$_2$, dried over Na$_2$SO$_4$ and evaporated to give 119 mg of a golden brown solid that was used without further purification.
**Step 2:** A solution of the above terminal acetylene (119 mg) in THF (3 mL) and TEA (5 mL) was added to a Schlenk tube charged with CuI (1.0 mg, 0.006 mmol), Pd(PPh₃)₂Cl₂ (6.5 mg, 0.01 mmol) and 1,4-diiodo benzene (403 mg, 1.22 mmol). After vigorous degassing the solution was stirred at rt overnight and the volatiles removed under reduced pressure. The crude material was passed through a short silica plug using hexanes in order to remove excess 1,4-diiodobenzene and the remaining material was flushed through using 90% EtOAc/Hex with 1% TEA and then concentrated to give semi-pure product (97 mg) that was not further purified.

**Step 3:** A solution of the above aryl iodide (97 mg) in THF (3 mL) and TEA (4 mL) was added to a Schlenk tube charged with CuI (0.5 mg, 0.0016 mmol) and Pd(PPh₃)₂Cl₂ (3.4 mg, 0.005 mmol). After vigorous degassing, TMSA (117 µL, 0.82 mmol) was added and the solution was stirred overnight at rt. The solvent was evaporated and water was added (25 mL). After extracting with CH₂Cl₂ (3x 15 mL), the organic fractions were combined, dried over Na₂SO₄, and concentrated to give the crude product as a brown solid. Purification by flash column chromatography (80% EtOAc/Hex + 3% TEA) provided compound 3a as a white solid (91 mg, 47% over 3 steps): ¹H NMR (CDCl₃, 500 MHz) δ 7.44 (s, 4H), δ 7.38 (d, J = 8.5 Hz, 2H), δ 7.20 (d, J = 8.5 Hz, 2H), δ 6.95 (d, J = 8.6 Hz, 6H), δ 6.58 (d, J = 8.6 Hz, 6H), δ 3.61 (s, 6H), δ 0.27 (s, 9H). ¹³C NMR (CDCl₃, 101 MHz) δ 148.8, 144.0, 137.4, 137.3, 131.8, 131.3, 123.5, 119.9, 114.0, 114.1, 104.8, 96.1, 91.4, 88.7, 62.8, 62.7, 62.5, 0.2. HR-ESI (m/z): [M+Li]⁺: calcd for C₃₈H₃₅N₃Si 568.2761: found 568.2758.

**General Procedure for COP Synthesis.** To a solution of compound 4 (49 mg, 0.060 mmol) and compound 3a (20 mg, 0.040 mmol) in CHCl₃ (13.5 mL) was added a solution of TFA (0.47 µL, 0.006 mmol) in CHCl₃ (100 µL) slowly dropwise. The solution was stirred at rt for 18h, at which time the solution was cooled to 0°C and DIBAL-H (1.5 mL, 1.5 mmol, 1.0 M in CH₂Cl₂)
was added. After stirring at 0 °C for 1h, the reaction was quenched with MeOH (1 mL), and saturated NaHCO₃ (5 mL) was added. The mixture was stirred at rt for 15 min, and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product. Purification by flash column chromatography (CH₂Cl₂) provided the pure product COP-1a as a white solid (12 mg, 18%): ¹H NMR (CH₂Cl₂, 500 MHz) δ 7.48 (m, 28H), δ 6.99 (d, J = 8.2 Hz, 4H), δ 6.91 (d, J = 8.2 Hz, 12H), δ 6.46 (d, J = 8.2 Hz, 12H), δ 4.27 (m, 24H), δ 3.65 (s, 6H), δ 2.45 (q, J = 7.4 Hz, 6H), δ 1.27 (m, 90H), δ 0.89 (m, 18H). MS (MALDI): [M+Li]⁺ calcd for C₁₇₀H₁₉₄Br₆N₆O₃S₃ 3305.77: found 3305.56.

COP-1b: The general procedure for COP synthesis described above was followed. Compound 4 (26 mg, 0.032 mmol) and compound 3b (10 mg, 0.021 mmol) were converted to COP-1b (8 mg, 24% yield, a white solid) using TFA (0.25 µL, 0.0032 mmol), CHCl₃ (7 mL), and DIBAL-H (0.859 µL, 0.859 mmol, 1.0 M in CH₂Cl₂). The physical data for COP-1b: ¹H NMR (CH₂Cl₂, 500 MHz) δ 7.48 (m, 24H), δ 7.31 (d, J = 8.4 Hz, 4H), δ 7.18 (d, J = 8.4 Hz, 4H), δ 6.90 (d, J = 8.3 Hz, 12H), δ 6.46 (d, J = 8.3 Hz, 12H), δ 4.27 (m, 24H), δ 3.65 (s, 6H), δ 2.44 (q, J = 7.4 Hz, 6H), δ 1.25 (m, 90H), δ 0.89 (m, 18H), δ 0.25 (s, 18H). MS (MALDI): [M+Na]⁺ calcd for C₁₈₉H₂₁₂Br₆N₆O₃S₃Si₂: 3262.03, found: 3262.91.

COP-1c: The general procedure for COP synthesis described above was followed. Compound 4 (0.030 mg, 0.037 mmol) and compound 3c (14 mg, 0.025 mmol) were converted to COP-1c (3 mg, 7%, a white solid) using TFA (.28 µL, 0.0037 mmol), CHCl₃ (8.3 mL), and DIBAL-H (900 µL, 0.900 mmol, 1.0 M in CH₂Cl₂). The physical data for COP-1c: ¹H NMR (CH₂Cl₂, 500 MHz) δ 7.46 (m, 36H), δ 7.24 (d, J = 8.1 Hz, 4H), δ 6.93 (d, J = 8.3 Hz, 12H), δ 6.48 (d, J = 8.3 Hz, 12H), δ 4.29 (m, 24H), δ 3.65 (s, 6H), δ 2.45 (q, J = 7.3 Hz, 6H), δ 1.29 (m, 90H), δ 0.91 (m,
18H), δ 0.28 (s, 18H). MS (MALDI): [M+Li]⁺ calcd for C₂₀₅H₂₂₁Br₆N₆O₃S₃Si₂ 3347.13; found 3446.45.

**COP-1b₂:** To a Schlenk tube was added COP-1b (8.0 mg, 0.0025 mmol) in THF (3 mL) under nitrogen. After cooling to 0 °C, TBAF (1M in THF, 123 µL, 0.123 mmol) was added dropwise and the reaction mixture was left to stir at rt for 30 min. The reaction was then quenched with NH₄Cl (2 mL), extracted with CH₂Cl₂ (3 x 3 mL) and dried over sodium sulfite. After partially concentrating the reaction mixture (ca. 2 mL) the solution was pipetted directly into a column containing a short pad of silica gel (ca. 2 cm) using CH₂Cl₂ as the eluent to afford COP-1b₂ as a white solid (6 mg, 79%). The physical data for **COP-1b₂:** ¹H NMR (CH₂Cl₂, 500 MHz) δ 7.52 (s, 6H), δ 7.47 (s, 6H), δ 7.42-7.38 (m, 12H), δ 7.32 (d, J = 8.4 Hz, 2H), δ 7.17 (d, J = 8.2 Hz, 2H), δ 6.88 (d, J = 8.8 Hz, 12H), δ 6.43 (d, J = 8.8 Hz, 12H), δ 4.27-4.17 (m, 24H), δ 3.62 (s, 6H), δ 3.07 (s, 2H), δ 2.42 (q, J = 7.4 Hz, 6H), δ 1.76 (s, 6H), δ 1.36-1.13 (m, 93H), δ 0.91-0.80 (m, 9H).

**COP-1c₂:** To a Schlenk tube was added COP-1c (3.0 mg, 0.0009 mmol) in THF (2 mL) under nitrogen. After cooling to 0 °C, TBAF (1M in THF, 44 µL, 0.044 mmol) was added dropwise and the reaction mixture was left to stir at rt for 30 min. The reaction was then quenched with NH₄Cl (1.5 mL), extracted with CH₂Cl₂ (3 x 2 mL) and dried over sodium sulfite. After partially concentrating the reaction mixture (ca. 1 mL) the solution was pipetted directly into a column containing a short pad of silica gel (ca. 2 cm) using CH₂Cl₂ as the eluent to afford COP-1c₂ as a white solid (2 mg, 71%). The physical data for **COP-1c₂:** ¹H NMR (CH₂Cl₂, 500 MHz) δ 7.56-7.34 (m, 12H), δ 7.22 (d, J = 7.9 Hz, 4H), δ 6.90 (d, J = 8.4 Hz, 12H), δ 6.45 (d, J = 8.4 Hz, 12H), δ 4.41-4.08 (m, 24H), δ 3.62 (s, 6H), δ 3.24 (s, 2H), δ 2.42 (q, J = 7.2 Hz, 6H), δ 1.53 (s, 6H), δ 1.31-1.08 (m, 93H), δ 0.88 (m, 9H).
**AuNP synthesis**

All reactions were carried out on a 5-10 mg scale with respect to COPs 1a,1b,1c. A solution of HAuCl₄ (4 mg, 0.01 mmol) in deionized H₂O (0.5 mL) was stirred and TOAB (54 mg, 0.099 mmol) in CH₂Cl₂ (0.5 mL) was added and stirred until Au(III) was transferred into organic phase (~25 min). A solution of COP-1b (7.6 mg, 0.0025 mmol) in CH₂Cl₂ (0.5 mL) and subsequently reduced with an aqueous solution of NaBH₄ (9 mg, 0.24 mmol) in deionized H₂O (0.5 mL). The resulting organic layer was dark in color and contained no precipitate. After separation, the aqueous layer was washed with CH₂Cl₂ (2 x 1 mL), the organic fractions were combined and concentrated to ca. 0.2 mL without the application of heat. Ethanol (1.5 mL) was then added and the solution was centrifuged to precipitate the AuNP-COP-1b complexes. This centrifugation procedure was repeated until the supernatant was no longer colored (~3 times). The resulting complexes are soluble in all organic solvents and stable in solutions, even over periods of several months.

**AuNP polymerization**

The resulting AuNP-1b complex (0.0025 mmol) was taken up in CH₂Cl₂ (3 mL) and transferred into a small scintillation vial with CuCl (24 mg, 0.24 mmol) under air and rapid stirring. TMEDA (37 µL, 0.285 mmol) was then added dropwise at rt and the solution was left to stir in open air. After 5 -7 minutes, the reaction mixture was quenched with NH₄Cl (0.5 mL), extracted with CH₂Cl₂ (3 x 1 mL), and a small aliquot (ca. 0.5 mL) was removed and diluted with CH₂Cl₂ until there was almost no visible color, at which time it was drop cast onto copper coated carbon grids for TEM analysis.
Synthesis of higher order discrete NP structures

All reactions were carried out on a 5-10 mg scale with respect to AuNP-COP-1a. The resulting AuNP-1a complex (5 mg, 0.0015 mmol) was taken up in dry THF (1 mL) and transferred to a small Schlenk tube under inert atmosphere containing CuI (29 mg, 0.00015 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (106 mg, 0.00015 mmol) and dry TEA (0.3 mL). The reaction tube was degased 3x and fit with a rubber septum. A solution of 1,3,5-triethynylbenzene (0.0005 mmol, 0.33 equiv) or 1,3,6,8-tetraethynylpyrene (0.00038 mmol, 0.25 equiv.) in dry THF (1 mL) was added dropwise via syringe pump over a period of 6-8 h. The reaction mixture was quenched with NaHCO$_3$ (0.5 mL), extracted with CH$_2$Cl$_2$ (3 x 1 mL), and a small aliquot (ca. 0.5 mL) was removed and diluted with CH$_2$Cl$_2$ until there was almost no visible color, at which time it was drop cast onto copper coated carbon grids for TEM analysis.

4.6 References


CHAPTER 5

Synthesis of Gold Nanoparticles within Covalent Organic Frameworks: Research Progress

5.1 Overview of Objectives

It is well known that in the absence of a stabilizing ligand or solid support freshly prepared colloidal solutions of nanoparticles will undergo rapid aggregation and precipitation towards bulk material (Fig. 5.1). The purpose of this thesis research was to demonstrate that 3D organic molecular architectures constructed using dynamic covalent chemistry are viable, convenient ligands for the synthesis and stabilization of small nanoparticles. Moreover, these complexes are functional platforms for chemical assembly and homogenous catalysis.

Figure 5.1. Strategies to stabilize AuNPs from uncontrolled aggregation towards bulk gold.
The advantage of this strategy includes precise structure/function control, modularity, and high solubility in solution phase. Besides the use of organic cage molecules as ligands to avoid uncontrolled particle growth, another viable strategy is to stabilize NPs within a solid support. Many conventional solid support methods involve the deposition of particles on the external surface of metal oxides, however this can often lead to sintering of particles and loss of catalytic activity. Embedding of nanoparticles within a polymer or inorganic matrix is also used but it is often difficult to control the size and morphology of the particles within the irregular void spaces of the medium.

Having demonstrated the colloidal stabilization of particles within discrete molecular cages, we would now like to explore the development of nanoparticle synthesis within well-defined organic frameworks. Considering the high surface area and uniformity of extended organic framework structures, there is obvious interest in using these porous solids as hosts for the incorporation of catalytically active nanoparticles.

5.2 Introduction

Significant progress has been made in the area of novel porous materials due to their applications in gas storage and separation. To date, a large variety of porous materials can now be synthesized through reticular chemistry, a process where the molecular building blocks are designed to assemble into predetermined ordered structures.\(^1\) One of the first families of porous materials to be synthesized through reticular chemistry was metal-organic frameworks (MOFs), which are constructed through metal ions or clusters and organic ligands to give highly ordered crystalline structures.\(^2\) Though many diverse structures can be synthesized using MOFs, the high concentration of metal centers and labile coordination bonds limit practical applications and
therefore the utility of this topological design has been extended to the synthesis of purely organic porous materials connected via covalent bonds.

There are generally two types of purely organic porous materials that have been developed in the past decade, including discrete porous organic molecules and infinite porous organic polymer networks such as crystalline covalent organic frameworks (COFs), microporous organic polymers (PIMs), covalent triazine-based frameworks (CTFs), organic cage frameworks (OCFs), etc. These materials generally have low mass densities, high thermal stability, and usually possess permanent porosity, making them highly viable alternatives in gas storage and separation applications. COFs, in particular, exist as the most general 2D polymerization strategy for providing layered, well-ordered periodic networks that are connected via covalent bonds (Fig. 5.2). The high surface area and well-ordered periodicity present in COFs support these host materials as suitable supports for the deposition of catalytically active nanoparticles.

![Figure 5.2. Synthesis of a 2D polymer using reticular synthesis.](image)

In addition to applications such as gas storage materials, COFs have only recently been explored as nanoparticle holding reservoirs. In terms of catalyst supports, many research groups have explored the encapsulation of nanoparticles within MOFs, but porous organic polymers might be more suitable scaffolds due to their built-in covalent bond architecture. Currently,
nanoparticles@COFs have been used for Suzuki coupling, nitro reduction, oxidation, etc\textsuperscript{15-21} but one of the major drawbacks with such systems has been stability of COF supports in aqueous-acidic-alkaline reaction media.\textsuperscript{22-24} Furthermore, concerns regarding sintering, leaching, stability and recyclability of nanoparticles embedded within COFs has also been an issue due to weak interaction between the host material and nanoparticles.

5.3. Preliminary Results and Discussion

In order to evade the possibly weak interaction between the nanoparticles and COF support, the target diamine monomer 4 was designed to contain thioether groups as NP anchoring points, since this functionality is more stable than free thiol yet has an affinity for a variety of different nanoparticles.\textsuperscript{25-27} Starting from the bromination of 2,5-dibromo-p-xylene to give 1, the benzylic bromines were then substituted with sodium ethanethiolate to afford the thioether containing compound 2 (Fig. 5.3).

![Figure 5.3. Synthesis of COF building block 4.](image)

Further Suzuki coupling of 2 with boronic ester derivative 3 gave desired diamine 4 in 62\% yield and was characterized by $^1$H NMR and GPC. We chose to use as the secondary trialdehyde building block 1,3,5-triformylphloroglucinol 5 due to the fact that coupling between the enamine
and ketone after the imine condensation to form the β-keto-enamine is known to further stabilize the framework structure.\textsuperscript{28}

We next set out to determine the optimal conditions for COF formation (Fig. 5.4) with high specific surface area by systematically screening a series of solvothermal conditions with varying solvent combinations. Conventional thermal conditions under stirring were also explored but all obtained COF samples were found to be nonporous with BET specific surface areas ranging from 10-84 m\textsuperscript{2} g\textsuperscript{-1}, likely due to the breaking up of 2d sheets and hence lack of pore uniformity.

\textbf{Figure 5.4.} Synthetic route to COF 6 formation using a 3:2 stoichiometric ratio of 4 and 6.

The optimal solvothermal conditions were found using a mixture of 1,4-dioxane and mesitylene (2:1 v/v) as the solvent, 6 M acetic acid as the catalyst, and 150°C reaction temperature to form highly porous 6 with a BET specific surface area of 588 m\textsuperscript{2} g\textsuperscript{-1}.

The permanent porosity of 6 was evaluated by the N\textsubscript{2} adsorption/desorption isotherms of freshly activated sample at 77 K, and the pore size distribution was calculated using non-local density functional theory. As shown in figure 5.5b the pore size was found to be quite uniform with a dominant pore size of 1.25 nm. Moreover, the polymer exhibits typical type I nitrogen adsorption isotherms with BET surface area of 588 m\textsuperscript{2} g\textsuperscript{-1} (Fig. 5.5a).
Figure 5.5. (a) Nitrogen adsorption and desorption isotherms of 6 at 77 K. (b) Pore size distribution of 6.

Figure 5.6. Schematic of repeat unit within organic polymer.
Having established a synthesis of 6 that gives high surface area and well-ordered periodicity we then sought out conditions for its usability as a support structure for the synthesis of gold nanoparticles. Gold nanoparticles were used in particular due to their high chemical stability and ease of preparation and thus serve as a useful indicator of the polymers usability as a support. Due to the fact that the polymer material is insoluble in common organic solvents such as dichloromethane, acetone, ethanol, THF and DMF, we selected methanol given its ease of removal and ability to solubilize gold precursor and reducing agent.

After a small addition of methanol to the framework the insoluble suspension was then impregnated with a solution of H\text{AuCl}_4 in methanol via sonication for 15 minutes in order to evenly deposit Au(III) ions throughout the well ordered porous architecture. A solution of Na\text{BH}_4 in methanol was subsequently added and after vigorous stirring the dark solid was filtered, rinsed with methanol and dried under vacuum. TEM analysis of dilute solutions of AuNP@6 indicates very even dispersions of AuNPs throughout the porous framework as can be seen in figure 5.7b. It is presumed that such even dispersion of AuNPs throughout the network is likely due to the thioether anchoring points as well as the high porosity of the framework architecture consequently eliminating any substantial sintering or leaching of particles.

The particle size distribution within AuNP@6 was measured from the TEM micrographs using imageJ software and found to have an average particle size of 8.25 nm ± 0.8 nm (Fig. 5.7c). Closer inspection of the TEM micrograph at higher magnification elaborates on the high dispersity and narrow size distribution of the AuNPs (Fig. 5.7a). Such narrow monodispersity of nanoparticles is rare is such systems and has not been achieved with even crystalline COF material.\textsuperscript{30}
5.4 Summary

In conclusion, we have successfully prepared a thioether modified porous organic polymer capable of evenly distributing AuNPs with a relatively narrow size distribution. Given that the gold nanoparticles embedded within the void space are small, which is a pre-requisite for high catalytic activity, it seems likely that AuNP@6 would show high catalytic activity for a wide variety of heterogeneous reactions. Moreover, washing crude AuNP@6 with organic solvents before TEM analysis had no effect on particle distribution confirming both the stable loading of particles within the framework and its heterogeneity as a catalyst.
5.4 Experimental Section

5.4.1 Materials and general synthetic methods

All commercially available reagents and solvents were used as received, unless noted otherwise. 1, 3, 5-triformylphloroglucinol was synthesized following the published procedure.\textsuperscript{29} CH\textsubscript{2}Cl\textsubscript{2}, toluene, dimethylformamide (DMF) and tetrahydrofuran (THF) were purified by MBRAUN solvent purification system. All reactions were carried out under nitrogen in flame-dried glassware, unless noted otherwise. After workup, all solvents were removed by rotary evaporation. Unless other indicated, the purity of the compounds was \( \geq 95\% \) based on \( ^1\text{H} \) NMR spectral integration.

Flash column chromatography was performed using 100-150 times weight excess of 32-63 µm silica gel from Dynamic Absorbants, Inc. Fractions were analyzed by TLC using TLC silica gel F254 250-µm precoated-plates from Dynamic Absorbants Inc. GPC was performed using a Viscotek GPCmaxTM, a Viscotek Model 3580 Differential Refractive Index (RI) Detector, a Viscotek Model 3210 UV/vis detector and a set of two Viscotek Viscogel columns (7.8 x 30 cm, 1- MBLMW-3078, and 1-MBMMW-3078). GPC calibration was done using monodisperse polystyrene standards and THF was used as the eluent at 30 °C.

UV-vis absorption measurements were recorded with an Agilent 8453 spectrophotometer. MALDI-MS mass spectrometry was performed using a Voyage-DE\textsuperscript{TM} STR Biospectrometry Workstation in linear mode using a sinapic acid matrix. High-resolution mass spectrometry (HR-MS) was performed using a Waters SYNAPT G2 high-definition mass spectrometry system.
$^1$H and $^{13}$C NMR spectra were obtained from either an Inova 500 or Bruker 300 spectrometer. CHCl$_3$ (7.27 ppm) was used as an internal reference for $^1$H NMR, and CHCl$_3$ (77.23 ppm) for $^{13}$C NMR. NMR data is reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J, Hz), number of protons.

All TEM samples were prepared by drop casting dilute solutions onto carbon-coated 300 mesh copper grids (CF300-Cu). All TEM images were taken using a Phillips CM100 microscope operating at 100 kV. The Quantachrome Autosorb ASiQ automated gas sorption analyzer was used to measure N$_2$ adsorption isotherms. The sample was heated at 100 °C and kept at this temperature for at least 22 h for the activation. Ultra high purity grade (99.999 % purity) N$_2$, oil-free valves and gas regulators were used for all free space corrections and measurements. For all of the gas adsorption measurements the temperature was controlled by using a refrigerated bath of liquid N$_2$ (77 K) and ice water (273 K).

**5.4.2 Experimental procedures**

![Chemical reaction](image)

**Compound 1:** To a Schlenk tube were added 2,5-dibromo-p-xylene (1.5 g, 5.68 mmol), n-bromosuccinimide (2.12 g, 11.93 mmol), 1,1’-azobis(cyclohexanecarbonitrile) (694 mg, 2.84 mmol) and benzene (15 mL) under N$_2$. After refluxing for 16 h, the hot solution was filtered, rinsed with benzene and concentrated. The crude material was recrystallized in ethanol to afford
the product as a colorless solid (1.2 g, 51%). $^1$H NMR (500 MHz, CHCl$_3$): $\delta$ 7.67 (s, 2H), $\delta$ 4.52 (s, 4H).

**Compound 2:** To a Schlenk tube were added compound 1 (500 mg, 1.18 mmol) and THF (14 mL) under N$_2$. The solution was cooled to 0 °C and sodium ethanethiolate (300 mg, 3.54 mmol) was added in THF (6 mL). The solution was warmed to rt and stirred 2.5 h. After pouring into H$_2$O (150 mL) the product was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic fractions were combined, washed with brine (2 x 75 mL), dried with anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by flash column chromatography using CH$_2$Cl$_2$ to afford the product as a light yellow solid (422 mg, 93%). $^1$H NMR (500 MHz, CHCl$_3$): $\delta$ 7.57 (s, 2H), $\delta$ 3.78 (s, 4H), $\delta$ 2.53 (q, J = 7.4 Hz), $\delta$ 1.28 (t, J = 7.4 Hz, 6H).

**Compound 3:** To a Schlenk tube were added 4-bromo-aniline (1.72 g, 1 mmol), bis(pinacolato)diboron (3.05g, 12 mmol), potassium acetate (3 g, 30.56 mmol), Pd(dppf)Cl$_2$ (210 mg, 0.287 mmol), dppf (160 mg, 0.288 mmol), and dioxane (50 mL) under N$_2$. The solution was degassed 3 times and heated at 100 °C for 16 h. After cooling down to rt the reaction mixture was diluted with H$_2$O (150 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic
fractions were combined, washed with brine (2 x 75 mL), dried with anhydrous Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography using CH₂Cl₂ then 10% EtOAc/CH₂Cl₂ to afford the product as a colorless solid (1.27 g, 58%). ¹H NMR (500 MHz, CHCl₃): δ 7.62 (d, J = 8.5 Hz, 2H), δ 6.66 (d, 2H, J = 8.5 Hz), δ 3.86 (s, 2H), δ 1.33 (s, 12H).

**Compound 4:** To a Schlenk tube were added compound 2 (260 mg, 0.67 mmol), compound 3 (385 mg, 1.74 mmol), Pd(PPh₃)₂Cl₂ (95 mg, 0.134 mmol), K₂CO₃ (271 mg, 1.94 mmol), dioxane (10 mL) and H₂O (2 mL) under N₂. The flask was degassed 3x and heated at 100 °C for 27 h. After cooling to rt, H₂O (50 mL) was added and the product extracted with CH₂Cl₂ (3 x 25 mL). The organic fractions were combined, washed with brine (1 x 75 mL), dried with anhydrous Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography using CH₂Cl₂ then 10% EtoAc/CH₂Cl₂ to afford the product as a light yellow solid (172 mg, 62%). ¹H NMR (500 MHz, CHCl₃): δ 7.32 (s, 2H), δ 7.30 (d, J = 8.40 Hz, 4H), δ 6.78 (d, J = 8.40 Hz, 4H), δ 3.75 (s, 4H), δ 3.73 (s, 4H), δ 2.47 (q, J = 7.4 Hz, 4H), δ 1.17 (t, J = 7.4 Hz, 6H).
**Compound 6:** To a customized glass tube (outer diameter of 10 mm and inner diameter of 8 mm) was added compound 4 (40.1 mg, 0.098 mmol), compound 5 (13.7 mg, 0.065 mmol), 6 M acetic acid (0.2 ml), dioxane (2 mL) and mesitylene (1 mL). The tube was flash-frozen at 77 K in liquid nitrogen bath and evacuated to the internal pressure of about 100 mtorr, and then the tube was sealed under an open flame. The mixture was first warmed to rt and then the temperature was slowly raised to 150 °C over 2 h. The reaction was kept at this temperature was 3 days and cooled to rt over 12 hr. The orange precipitate was collected by vacuum filtration, washed with large amounts of acetone and CH₂Cl₂ and dried under vacuum to yield 6 (49 mg, 99%).

**AuNP@6:** To a 20-mL scintillation vial was added compound 6 (10 mg, 0.0065 mmol) and methanol (2 mL). Under vigorous stirring was added HAuCl₄ (9 mg, 0.023 mmol) in methanol (0.5 mL) dropwise followed by sonication for 15 min. The impregnated framework was returned under vigorous stirring and NaBH₄ (12.3 mg, 0.325 mmol) in methanol (1 mL) was added dropwise and left to stir for 5 min. The precipitate was collected by vacuum filtration and rinsed with methanol until filtrate was colorless and the resulting AuNP@6 was dried under vacuum.
5.5 References


CHAPTER 6

Summary and Future Work

6.1 Summary

Current research in the field of dynamic covalent chemistry has included the study of dynamic covalent reactions for the rapid development of novel organic functional materials such as 3-D organic molecular cages and covalent organic frameworks. In addition to forming these molecular architectures, these systems have also shown promise when extended to more functional platforms through the introduction of metallic nanoparticles. There will be significant opportunities for improved functional systems that can have potentially widespread applications throughout materials science.

6.2 Future Work

6.2.1 Research proposed toward metal nanoparticle@organic cage frameworks (NP@OCFs)

Currently most reported porous organic networks exist as extended networks that are constructed from 1-D or 2-D building blocks. Such purely organic porous materials include COFs,\(^1\) amorphous porous organic polymers,\(^2\) and porous organic molecules.\(^3\) As an alternative strategy, Jin et al. have developed a novel approach that hinges on the polymerization of 3-D cage building blocks with small organic linkers.\(^4\) Such extended cage-to-framework polymers contain a 3-D cage as the “unit cell” and have the advantage of adding dimensionality to the
framework as well as a variety of chemically different cross-linkers in order to systematically tune the framework properties. Furthermore, the networks are cross-linked by coupling chemistry and therefore can be constructed via microwave heating to afford very efficient network formation (Fig. 5.8).\(^5\)

**Figure 5.8.** Microwave-assisted Sonogashira coupling of a 3-D cage that has six bromo cross-coupling sites per molecule with an organic linker molecule to give an extended porous network.

Despite nanoparticles having been successfully imbedded within porous solids using 1-D and 2-D building blocks, there still exists the possibility that once the NP-encapsulated frameworks are subjected to catalytic reactions the integrity of the framework itself will be compromised. This is particularly true for COFs that are unstable in aqueous-acidic-alkaline media. It can be assumed that this loss of crystallinity and rigidity, which will inevitably lead to the leaching and sintering of particles and a decrease in recyclability, can largely be evaded by encapsulating the particles within the 3-D cage “unit-cell” thus keeping them contained within the porous network. Expanding upon the nanoparticle-cage encapsulation work done by McCaffrey et al.,\(^6\) it would be advantageous to utilize the NP@cage complex as the basic unit-
cell for a cage-to-framework approach. Using this approach, the nanoparticles will be tightly bound within the 3-D cage molecule and hence physically trapped within the covalently linked network once assembled (Fig. 5.9).

We envision that this ability for the network to irreversibly ‘catch’ and isolate NPs deep within the framework will expand the applications of this platform beyond heterogeneous catalysis and into fields such as nanophotonics and plasmonics, where networks of NPs of uniform size and distribution are essential.  

6.2.2 Cage-templated synthesis of silver nanoparticles (AgNPs)

Through the use of DC\textsubscript{6}C we now have access to a wide variety of distinctive 3-D cage architectures. The tools of rational design have allowed us to synthetically manufacture porous molecular landscapes that are not found in nature (e.g., naturally occurring zeolites) and can be judiciously tuned and functionalized to give particular geometries (e.g., tetrahedral blocks, cubic...
blocks, etc.). Within the scope of this work, we believe it is also possible and likely advantageous to explore the synthesis and application of nanoparticles outside of gold and palladium. Specifically, the use organic cage molecules that template the synthesis of silver nanoparticles (AgNPs) for medical purposes.

Silver metallic nanoparticles have a distinct characteristic as being antibacterial agents. The antibacterial effects of silver nanoparticles have been known for a very long time and many researchers have shown that Ag ions and Ag-based compounds are highly toxic to microorganisms.\(^9\) This is significant considering the multidrug resistance caused by current chemical antimicrobials. However, in order to improve biocompatibility and maximize the growth-inhibitory capacity of AgNPs, it is essential to reduce the particle size of the materials. Since Ag nanoparticles can be used as effective growth inhibitors in various microorganisms, the synthesis of AgNPs within organic cage molecules would be interesting models compounds for their application in medical devices and antimicrobial control systems due to their small size and unpassivated surfaces.

To evaluate efficacy of this system we have preformed preliminary studies in order to determine the possibility of synthesizing AgNPs using an organic molecular cage, specifically the thioether-based cage described previously in Chapters 2 and 3. Using a similar biphasic system containing AgNO\(_3\)/TOAB in a solution of dichloromethane/H\(_2\)O, the AgNO\(_3\) can be reduced to Ag\(^0\) after addition of NaBH\(_4\). As shown in Figure 5.10b, the organic molecular cage is able to template the synthesis of AgNP but the phenomenon of the cage template is different then as described previously. With the use of AgNPs, which are notoriously unstable,\(^ {10}\) the particle size distribution from TEM micrographs show an average particle size of 4.2 nm, a size much larger than our computational-model-estimated cage cavity size of 1.8-2.1 nm (Fig. 5.10a).
One possible explanation for these results is likely the stabilization of AgNPs via a multiple cage interaction, as shown in scheme 1. Though it appears there are indeed 1:1 AgNP-cage complexes with the desired diameters of ~2 nm (6% of total population; Fig. 5.10a), it seems the majority of the nanoparticles exist in the form of AgNP-(cage)$_n$, as shown in Scheme 1. Closer inspection by high-resolution TEM of the particle lattice structure shows that the larger AgNPs are highly epitaxial, suggesting that as the AgNP nucleates and grows it doesn’t stay confined to the cage interior but instead grows outside the cage window and fuses together with nearby neighboring nanoparticles. Similar to inter-dendrimer systems, the resulting AgNPs give a randomized population of both AgNP-cage and AgNP-(cage)$_n$. This assumption can also be supported by the broad dispersion in particle size, though the size distribution still appears to be Gaussian.
Scheme 1. Suggested mechanism for observed distribution of AgNP-cage complexes.

Though further studies are still in progress, one possibility for optimizing the synthesis of AgNPs using this system would be to eliminate the biphasic approach and attempt the growth of particles using only organic solvent. By removing the surfactant TOAB, the use of a single solvent (or co-organic solvent) would allow for the Ag to be driven into the cage solely from Ag-cage interactions, possibly eliminating the growth of AgNPs due to inter-cage interactions. This work is still in progress.

6.3 References


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