SYNTHESIS AND SUPRAMOLECULAR CHEMISTRY OF 2,4,9-TRITHIAADAMANTANE DERIVATIVES

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SYNTHESIS AND SUPRAMOLECULAR CHEMISTRY OF 2,4,9-TRITHIAADAMANTANE DERIVATIVES

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ABSTRACT

This dissertation describes the synthesis and supramolecular chemistry of 7-substituted-2,4,9-trithiaadamantanes. The structurally well-defined molecular building block was prepared by a multi-step synthesis from dimethyl malonate or diethyl malonate. A new synthetic method for the formation of a 2,4,9-trithiaadamantane ring system was developed using the combination of Lawesson’s reagent and a Lewis acid. The method improved the reaction yields to 35-40%. The ethyl or methyl ester group attached to position 7 of the 2,4,9-trithiaadamantane ring was converted to other functionalities depending upon the applications. These functional groups include a carboxylic acid, an alcohol, an aldehyde, a long chain amide, and alkynes. Additionally, the introduction of a diazomethylcarbonyl group or an azidocarbonyl group produced the photolabile molecular surface anchors. 2,4,9-Trithiaadamantan-7-yl-ethyne facilitated the synthesis of molecular wires via the Sonogashira cross coupling reaction with various phenyl halides. 1,4-Bis((7-2,4,9-trithiaadamantyl)ethynyl) benzene, 1,4-bis(7-2,4,9-trithiaadamantyl) butadiyne, S-{4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-phenyl} thioacetate and 4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-pyridine, were prepared.

2,4,9-Trithiaadamantane-7-carboxylic acid octadecylamide (TPCONHC\textsubscript{18}) was used as a ligand for stabilizing gold nanoparticles. Ligand exchange reaction of
triphenylphosphine-stabilized gold nanoparticles with TPCONHC\textsubscript{18} produced tripodal ligand-stabilized gold nanoparticles of an average size of 88.2 ± 21.6 nm. Gold nanoparticles prepared by the Brust-Schiffrin method using a 1:1 ligand to gold ratio are about 86.3 ± 14.2 nm.

The inclusion complex of 2,4,9-trithiaadamantane-7-carboxylic acid (TPCOOH) in \(\beta\)-cyclodextrin was studied by \(^1\)H NMR and 2D nuclear overhauser effect spectroscopy (NOESY), host induced circular dichroism spectroscopy (CD), and tandem mass spectrometry. The \(^1\)H NMR, MS-MS and the NOESY data show that the TPCOOH guest forms a 1:1 inclusion complex with the host \(\beta\)-cyclodextrin. The NOESY experiments also showed that TPCOOH is oriented in the complex with the thiolactyl end preferentially located at the larger opening of \(\beta\)-cyclodextrin. The orientation of the guest in the host molecule is also confirmed by the induced CD of the ligand which shows a positive Cotton effect. An association constant of 663 ± 20 M\(^{-1}\) was determined by \(^1\)H NMR titration for the complex at room temperature in D\(_2\)O.
DEDICATION

To my parents, my wife and my brothers and sisters
I would like to express my special thank to my adviser, Dr. Jun Hu, for his guidance, support and patience throughout my doctoral study. I thank my dissertation committee members, Dr. Michael J. Taschner, Dr. Christopher J. Ziegler, Dr. David A. Modarelli, Dr. Weipeng Zheng and Dr. Rex Ramsier for their comments and suggestions. Dr. Michael J. Tashcner has been very helpful in solving specific organic synthesis problems; I take this opportunity to express gratefulness. I would like to thank the Ziegler and Youngs research groups for obtaining and solving the X-ray crystallograph presented in this work. My colleagues have created a very good work place atmosphere, they deserve the praise from me. My special thanks go to my colleagues, Debanjan Sarkar and Mark Rigby for their linguistic helps and for proof reading the draft of this dissertation.

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CHAPTER I

INTRODUCTION

The chemistry of soft metals and molecular materials has become a challenging topic in materials research. Synthetic capabilities of organic chemistry allow the rapid development of the field. As a result, a great number of new materials have been prepared. Stable molecular layers prepared by the self assembling method have been studied towards various applications. The best examples of self-assembly observed in nature are protein folding and the formation of DNA double helices.\(^1\) Self-assembled monolayers (SAMs) are highly ordered arrays of molecules of long-chain alkanes that chemisorb on the surfaces of solid materials. SAMs are generally formed by strong induced chemisorption of a selected head group onto a noble metal surface spontaneously. The most widely studied head group-metal pair is thiols and Au(111) surfaces. The thiols on a Au(111) SAMs, pioneered by Nuzzo and Allara,\(^2\) are usually prepared by immersing a bare gold surface into a diluted thiol solution (Scheme 1.1). Although the preparation of SAMs in solution is the most common approach, SAMs can be prepared from vapor as well. The driving force for the formation of the SAMs is the strong chemisorption of sulfur atoms onto a gold surface. In addition, the strong
interchain van der Waals interactions ensure tight packing and stability of the monolayers.

SAMs of long-chain alkanethiols have been the center of attention due to the chemical characteristics of the thiol functionality and gold metal, which acts as a solid material. The thiol head group acts as an anchor that connects long-chain alkanes to the gold surface via a strong chemical interaction furnishing highly packed SAMs. A major drawback of alkanethiols is their air and thermal instability.\(^1\) Although, thiolates bind more strongly to the noble metal surfaces, thioethers are less prone to oxidative transformations.\(^3\) Disulfides,\(^4\) dialkyl sulfides,\(^5\) thioethers,\(^6\) thioacetate groups,\(^7\) and tetradsentate thioether ligands\(^8\) have been studied as alternatives to thiols for the preparation of SAMs on gold surfaces.

1.1 Objective and Approach

The aim of this dissertation is to design, synthesize, characterize and exploit the applicabilities of a novel molecular surface anchor, 7-substituted-2,4,9-trithiaadamantane (Figure 1.1). This rigid, stable, and well-defined building block is expected to imitate its thiol analogues towards applications in supramolecular chemistry. This new surface anchor consists of three sulfur atoms at positions 2, 4, and 9 of the adamantane ring system. This molecule is predicted to be inert to most chemical environments allowing the formation of stable SAMs. The three sulfur atoms in a well-defined structure should produce strong interactions between the anchor and the metal surfaces. The synthetic approach of this compound is based on the thionation and
Scheme 1.1 Schematic representation of self-assembling of thiolates onto a gold surface

Figure 1.1 Chemical structure of 7-substituted-2,4,9-trithiaadamantane
cyclization of trialdehydes. The introduction of different functional groups to position 7 of the 2,4,9-trithiaadamantane ring should facilitate different molecules for various applications.

1.2 Layout of Dissertation

Chapter II discusses the historical review of the synthesis and applications of 7-substituted-2,4,9-trithiaadamantane. In this section, several synthetic aspects will be discussed. This chapter also describes the synthesis of the key intermediate, 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester and its derivatives. Chapter III and Chapter IV focus on the applications of the 2,4,9-trithiaadamantane building block. Chapter III discusses the utilization of a 2,4,9-trithiaadamantane moiety as a stabilizing ligand of gold nanoparticles while Chapter IV describes the host-guest chemistry between β-cyclodextrin and 2,4,9-trithiaadamantane-7-carboxylic acid. Chapter V of the dissertation concludes all aspects of this work as well as provides some potential applications of these novel compounds.
2.1 Introduction

2.1.1 Thionation of Carbonyl Compounds

Organosulfur compounds have been of interest in the chemical community due to their rich chemistry. The importance of these compounds plays major roles in many fields of chemistry. Sulfur-containing carbohydrates have great prospects for the discovery of new therapeutics.\(^1\)\(^2\) The uses and metabolisms of different sulfur-containing drugs have been studied.\(^9\)\(^10\) Furthermore, the unique properties of sulfur atoms toward soft metals, e.g. gold, promote the studies of surface chemistry. Bain et al. reported the studies of surface characters of self-assembled monolayers (SAMs) of thiols,\(^11\)\(^12\) dialkyl sulfides and disulfides\(^5\)\(^13\) on gold surfaces.

The synthesis of organosulfur compounds usually involves the chemistry of carbonyl compounds. Generally, the thionation of carbonyl compounds requires the reaction of phosphorus pentasulfide in hot toluene, xylene or pyridine and involves a great excess amount of the reagent. The reaction yields are variable and
usually very low. Recently, many organosulfur compounds have been prepared by thionation of carbonyl compounds using Lawesson’s reagent (LR).\textsuperscript{14,15} LR was prepared from the reaction of phosphorus pentasulfide and anisole or the reaction of red phosphorus, elemental sulfur and anisole. LR is now commercially available and is usually packed under an argon atmosphere.

2.1.1.1 Mechanism of the Thionation Reaction by Lawesson’s Reagent

In a solution, Lawesson’s reagent is in equilibrium with highly reactive dithiophosphine ylide (Scheme 2.1). The more reactive form reacts with electron deficient carbonyl carbons. The reaction between carbonyl groups and dithiophosphine ylide is similar to the renowned Wittig reaction by forming thiaoxaphosphetane that eventually decomposes to yield thiocarbonyl compounds (Scheme 2.1). The reaction mechanism of this process is shown in Scheme 2.1.

The driving force of this reaction is mainly the formation of P-O bonds, which are much stronger than P-S bonds, as a by-product. It was reported that the isolated by-product from the reaction of Lawesson’s reagent is in a trimer form, \(p\)-methoxy-phenylmetathiophosphonate (Scheme 2.2)

2.1.1.2 Thionation of Carbonyl Compounds with Lawesson’s Regent

Thiocarbonyl compounds are very unstable compared to their analogous carbonyl compounds. This is because thiocarbonyl compounds do not possess a strong carbon-sulfur double bond. The carbon atom and the sulfur atom of thiocarbonyl compounds
Scheme 2.1 Reaction mechanism of Lawesson’s reagent with carbonyl compounds

Scheme 2.2 Formation of \( p \)-methoxyphenylmetathiophosphonate
fail to establish a strong double bond due to their incompatibility between a 2-p orbital of the carbon and a 3-p orbital of the sulfur. In carbonyl compounds, a 2p-2p orbital interaction between carbon and oxygen forms a strong double bond that is 192 kcal/mol, while the carbon-sulfur double bond is only 128 kcal/mol.16

Aldehydes and ketones react readily with Lawesson’s reagent producing thioaldehydes and thioketones. However, thioaldehydes are unstable in the monomeric forms. Thioformaldehyde was observed only in photoelectron spectroscopy. Thioaldehydes can be observed only in dimers, trimers, polymers or enol forms (Scheme 2.3).16 Several thioketones have been isolated as a result of the reaction of ketones with Lawesson’s reagent. Some ketones react with Lawesson’s reagent in refluxing toluene and benzene. Examples of thiolketones synthesized by thionation reaction with Lawesson’s reagent are presented in Table 2.1.

![Scheme 2.3 Different forms of thioaldehydes](image)

8
Esters and lactones react with Lawesson’s reagent to give thiono, and dithio esters. Esters usually require stronger reaction conditions than lactones. Like esters and lactones, amides and lactams also react with Lawesson’s reagent producing the corresponding thio derivatives. Some reported syntheses of thio derivatives of esters, lactones, amides and lactams are shown in Table 2.1.

2.1.2 Transition-metal-catalyzed Cross Coupling Reactions of Alkynes

The synthesis of conjugated acetylenes has gained much attention because the corresponding compounds are useful in organic materials applications such as molecular wires, rectifiers. Most of these compounds are prepared by cross coupling reactions to sp carbons. Several transition metals catalyze cross coupling reactions so effectively that many cross coupling reactions proceed under very mild conditions. Alkynylmagnesium, alkynylboron, alkynylcopper, alkynyltin and alkynylzinc reagents are among the most widely studied reagents for transition-metal-catalyzed cross coupling reactions. Scheme 2.4 depicts the reaction mechanism of transition-metal-catalyzed cross coupling reactions of alkynes. The transmetallation of alkynylmetal reagents to a catalyst proves to be the vital step of this reaction. The reactivity order of organic halides towards cross coupling reactions is I>Br>OTf>>Cl.

Palladium-catalyzed cross coupling reactions have been vital to organic synthesis for the past few decades. Unlike palladium, nickel does not catalyze cross coupling reactions of alkynes adequately because it reacts with alkynes producing corresponding polymers and lowers the reaction yields. Palladium-catalyzed cross coupling reactions of alkynylzinc reagents, which can be prepared from anhydrous zinc chloride and
Table 2.1 Examples of thio derivatives of ketones, esters, lactones, and amides synthesized by the reaction with Lawesson’s reagent

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Product" /></td>
<td>97</td>
<td>14,20</td>
</tr>
<tr>
<td><img src="image2" alt="Product" /></td>
<td>96</td>
<td>21</td>
</tr>
<tr>
<td><img src="image3" alt="Product" /></td>
<td>95</td>
<td>22</td>
</tr>
<tr>
<td><img src="image4" alt="Product" /></td>
<td>85</td>
<td>23</td>
</tr>
<tr>
<td><img src="image5" alt="Product" /></td>
<td>98</td>
<td>23</td>
</tr>
<tr>
<td><img src="image6" alt="Product" /></td>
<td>38</td>
<td>24</td>
</tr>
</tbody>
</table>
Scheme 2.4 Reaction mechanism of transition-metal-catalyzed cross coupling reactions of alkynes, i: oxidative addition, ii: transmetallation, iii: reductive elimination

alkynylmagnesium or alkynyllithium reagents, with alkenyl or aryl halides produce the corresponding alkynes effectively. Entries 1 and 2 in Table 2.2 are examples of the cross coupling reactions of alkynylzinc reactions.

Palladium-catalyzed cross coupling reactions of alkynyltin reagents are known as Stille couplings or Migita-Kosuki-Stille couplings. The reactivity order of organotin compounds is alkynyl>vinyl>aryl>>alkyl. Therefore, only the alkynyl group in Me₃SnCCTMS is transferred to palladium. The transmetallation step of alkynyltin compounds is relatively slow. This type of reactions is represented in Table 2.2, entries 3 and 4.
Alkynyl Grignard reagents undergo palladium-catalyzed cross coupling reactions with alkenyl or aryl halides. The cross coupling reaction of alkynylborane reagents is known as the Suzuki cross coupling reaction. The preparation of alkynylborane reagents is similar to the previous alkynylmetal reagents. The transmetalation of alkynylborane reagents is not very feasible due to the low nucleophilicity of organoboron. However, the negatively charged alkynylborane complexes react readily with organic halides. Entries 5 and 6 of Table 2.2 are examples of palladium-catalyzed cross coupling reactions of alkynyl Grignard reagent and the Suzuki cross coupling reaction respectively.

The palladium-catalyzed cross coupling reactions have been applied to the Stephens-Castro reaction of alkynylcopper reagents with aryl or vinyl chloride in refluxing pyridine. This latest approach works much more effectively and is widely used as a tool to prepare conjugated alkynes because it requires mild conditions to proceed. This reaction involves the cross coupling reaction of alkynylcopper reagents with organic halides. Alkynylcopper reagents are usually prepared in situ from terminal alkynes in a base such as an amine in the presence of a cocatalyst copper iodide. Palladium-catalyzed Stephens-Castro cross coupling reaction is shown in Table 2.2, entries 7 and 8.

2.1.3 2,4,9-Trithiaadamantane-7-carboxylic Acid Methyl Ester and Its Derivatives

The synthesis of 7-substituted-2,4,9-trithiaadamantane (7-sub-TP) has been originally reported by Lindgren and later by Krittredge et al. Lindgren’s approach synthesized a 2,4,9-trithiaadamantane by means of thionation of trialdehydes using
hydrogen sulfide in an acidic alcohol as a reagent. Krittredge’s approach is an improved protocol of Lidgren’s approach. However, both works reported product yields of the reactions as 10-15%, while the procedures were found to be irreproducible. Moreover, the purification process reported by Krittredge, in which the product was isolated by semi-prep HPLC, was impractical. Hydrogen sulfide as a reagent is also an unpleasant option due to its toxicity and strong odor.

The major challenge of this work is the discovery of a more effective, environment-friendly and inexpensive reagent for the preparation of 7-substituted-2,4,9-trithiaadamantanes. The aim of this study is to utilize LR as a thionation reagent for the synthesis of 7-sub-TP’s (Scheme 2.5). The preparation of the desired compounds should be more reproducible and the yields of the reactions should be improved.

2.1.4 The Preparation of Photolabile Molecular Surface Anchors

Recently, the utilization of 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone (TPCOCHN$_2$) as a surface anchor for the preparation of photo-labile SAMs on a gold surface was reported.$^{27}$ The trithiaadamantane moiety of TPCOCHN$_2$ served as a chelating ligand for the polycrystalline Au (111) surface and the diazomethylcarbonyl group displayed typical photo-induced Wolff rearrangement reactivity on a gold surface. Subsequent dark reactions at the UV-exposed surface allowed effectively for photolithographic chemical patterning on the gold surface effectively. The high chemical stability of the surface anchor and the high reactivity of the end groups in the
Table 2.2 Palladium-catalyzed cross coupling reactions of alkynylmetal reagents with organic halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynylmetal</th>
<th>Organic Halides</th>
<th>Conditions</th>
<th>Products</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClZnC ≡ R</td>
<td>R₁ R₂ X</td>
<td>Pd(PPh₃)₄, r.t., THF</td>
<td>R₁ R₂</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>R ≡ CZnCl</td>
<td>HHC ≡ CHCl</td>
<td>Pd(PPh₃)₄</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Bu₃Sn ≡ Ph</td>
<td>O₂N-Ph</td>
<td>PhPd(PPh₃)₂I, HMPA, 20°C</td>
<td>O₂N-Ph</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Bu₃Sn ≡ SiMe₃</td>
<td>R⁻SiMe₃</td>
<td>Pd(PPh₃)₄, LiCl, THF, r.t.</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>BrMg ≡ SiMe₃</td>
<td>R⁻SiMe₃</td>
<td>Pd(PPh₃)₄, Benzene/THF</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Ph⁻Br⁻Br⁻Br⁻</td>
<td>Ph⁻Br⁻Br⁻Br⁻</td>
<td>Pd(PPh₃)₄</td>
<td>Ph⁻Br⁻Br⁻Br⁻</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>PhC≡CH</td>
<td>O₂F⁻CO₂Et⁻CO₂Et</td>
<td>PdCl₂(PPh₃)₂, cat. CuI, 2,6-toluidine</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>SiMe₃</td>
<td>Ar⁻X</td>
<td>PdCl₂(PPh₃)₂, cat. CuI, NEt₃, or Pyridine</td>
<td>Ar⁻SiMe₃</td>
<td>35</td>
</tr>
</tbody>
</table>
corresponding SAMs provided a robust solution for photolithographic attachment of organic and biomolecules on gold films (Scheme 2.6). In addition to the SAM applications, it was found that this tridentate ligand coordinates several transition metals and metal clusters, which show much potential for the use in supramolecular coordination assemblies and homogeneous catalyst development. An effective synthesis of 2,4,9-trithiaadamantane derivatives will provide essential materials for the future explorations of this new ligand for transition metals.

2.1.5 Synthesis of 2,4,9-Trithiaadamantan-7-yl-ethyne and Molecular Wires

Oligophenyleneethylenes (OPEs) are considered as prototypes of molecular wires. Many different types of OPEs have been synthesized and reported. The systems consist of a conjugated phenyleneethylene building block and sulfur containing moieties at both ends (Scheme 2.7). Sulfur-containing end groups, mostly thiols, serve as connectors between molecular wires and metal electrodes. These molecules are often called “molecular alligator clips”. In this study, a new type of molecular connector has been discovered (Scheme 2.7). A well-designed, rigid and stable building block is predicted to self assemble onto metal surfaces, e.g. gold, preferably at the low energy polycrystalline (111) surface. Previous work has shown that this 2,4,9-trithiaadamantane structure mimics bulk metal surfaces and forms metal clusters with three ruthenium atoms. Each sulfur atom coordinates to one ruthenium atom, while all three ruthenium atoms are attached to one another.
Scheme 2.5 Synthesis of 7-substituted-trithiaadamantane

Scheme 2.6 Photolabile surface anchors
Scheme 2.7 Free-standing molecular wires
The syntheses of various molecular wires have been reported.\textsuperscript{36,38,39} The formation of a conjugated building block utilizes the Sonogashira cross coupling reaction.\textsuperscript{40} Desired oligophenyleneethylenes are usually prepared from the corresponding alkynes. In this study, 7-methoxycarbonyl-2,4,9-trithiaadamantane was synthesized and shown to have promising results in self-assembling onto noble metal surfaces. The 2,4,9-trithiaadamantane moiety serves as an anchor to metal contact and the substituent at the 7-position can be varied depending upon the desired applications.

The objective of this work is to construct molecular wires consisting of 2,4,9-trithiaadamantane portions as end groups of the so-called alligator clips. The methyl ester group of the precursor needs to be transformed into an ethynyl group to facilitate Sonogashira cross coupling reactions.

2.2 Experimental Section

2.2.1 General Procedures

All \textsuperscript{1}H NMR (300 MHz) and \textsuperscript{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer unless otherwise noted. NMR spectra were recorded in CDCl\textsubscript{3}. \textsuperscript{1}H and \textsuperscript{13}C Chemical shifts are reported in parts per million relative to the residual CHCl\textsubscript{3} (7.27 ppm) and to the CDCl\textsubscript{3} signal (77.23 ppm) respectively. \textsuperscript{1}H NMR multiplicity is reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Nicolet NEXUS 870 FT-IR spectrometer equipped with a Thunderdome Attenuated Total Reflectance (ATR) accessory. Data were reported in wavenumbers (cm\textsuperscript{-1}). X-Ray data were measured at 100 K, unless otherwise noted, (Bruker KRYO-FLEX) on a Bruker SMART APEX
CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (\(\lambda = 0.71037\) Å) operated at 2000 W.

Unless otherwise noted, materials were obtained from Aldrich, Acros’s or Fisher Scientific and used without further purification. All solvents were reagent grade. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride and benzene were distilled from calcium hydride under argon prior to use. Other reagents were purified by procedures described in the literature. All glassware used was flame dried or oven dried and cooled in the desiccators. Air– and moisture-sensitive reactions were performed under argon gas (99.99%). The products were purified by vacuum distillation, flash chromatography, preparative TLC, and recrystallization. All the reactions were monitored by thin-layer chromatography (TLC). TLC was performed with 0.2 mm precoated silica gel w/UV 254 on polyester backed plates (Sorbent Technologies). Preparative thin-layer chromatography was performed on 1.0 mm \(\times\) 20 cm \(\times\) 20 cm glass supported silica gel plates (Analtech INC.). EM Science silica gel 60 Å (particle size 35-75um) was used for flash chromatography.

2.2.2 Synthesis of Diallyl Dimethyl Malonate (1)

Sodium metal (11.5 g, 0.50 mol) was added to freshly distilled methanol (300 mL) in a 500-mL round bottom flask. The mixture was stirred while cooling with an ice bath. When the sodium metal had completely dissolved, dimethyl malonate (57.0 mL 0.50 mol) was slowly added. Allyl bromide (45.0mL, 0.51 mol) was added dropwise over 90 min. After the addition was completed, the mixture was then refluxed while stirring for an additional 30 min. The mixture was allowed to cool down to ambient temperature
with an ice bath. After an acidification of the mixture with glacial acetic acid, the mixture was filtered to remove any insoluble salt and the volume of the solvent was reduced to about 50 mL. The mixture was mixed with water (50 mL), and subsequently extracted with diethyl ether (3x30 mL). The collected organic layer was dried over sodium sulfate and then evaporated giving light yellow oil. The product was ready for the next reaction without further purification. Repeating this procedures for the synthesis and purification, pure diallyl dimethyl malonate was obtained as light yellow viscous oil (76 g, 0.36 mol, 72%). $^1$H NMR $\delta$: 2.60 (d, 4H, $J = 7$ Hz, $CH_2$), 3.68 (s, 3H, OCH$_3$), 5.08 (t, 4H, $J = 3$ Hz, CH=C$_2$H$_2$), 5.60 (m, 2H, $J = 8$ Hz, CH$_2$=CH$_2$) ppm; $^{13}$C NMR $\delta$: 37, 52, 58, 119, 132, 171 ppm; FTIR (ATR): 1733 (C=O), 2954 (aliphatic CH), 3080 (allylic CH) cm$^{-1}$.

2.2.3 Synthesis of Diallyl Methyl Acetate (2)

A solution of diallyl dimethyl malonate (20.3g, 96 mmol) in dimethyl sulfoxide (70 mL) was mixed with sodium chloride (6.2g, 106 mmol), and water (5.7g, 317 mmol). The mixture was refluxed for 25 h. The reaction was monitored by thin layer chromatography. After the reaction reached completion as shown by TLC, water (150 mL) was added to the reaction mixture and a distillation apparatus was attached to the reaction flask. Steam distillation of the mixture yields colorless liquid floating atop the aqueous layer, which can be extracted with diethyl ether (3x30 mL). The collected organic layer was dried over sodium sulfate. The vaporization of the solvent gives pure diallyl methyl acetate as clear, colorless liquid (11.2 g, 73 mol, 76%). $^1$H NMR $\delta$: 2.62 (d, 2H, $J = 7$ Hz, CCH$_2$), 3.68 (s, 3H, OCH$_3$), 5.09 (t, 2H, $J = 3$ Hz, HC=CH$_2$), 5.73 (m,
1H, J = 7 Hz, H₂C=CH) ppm; ¹³C NMR δ: 36, 45, 51, 117, 135, 175 ppm; FTIR(ATR): 1737 (C=O), 2951 (aliphatic CH), 3079 (allylic CH) cm⁻¹.

2.2.4 Synthesis of Triallyl Methyl Acetate (3)

n-Butyllithium (40 mmol, 1.6 M in hexane) was added dropwise to an ice-cooled solution of diisopropylamine (5.6 mL, 40 mmol) in tetrahydrofuran (60 mL). The mixture was stirred at 0°C for 15 min and then cooled to –78°C with an acetone-dry ice bath. To this reaction mixture, diallyl methyl acetate (5 g, 32 mmol) in tetrahydrofuran (50 mL) was added dropwise using a dropping funnel. After the reaction had been stirred for 30 min, allylbromide (3.6 mL, 41.6 mmol) in hexamethylphosphoramide (7.8 mL, 45 mmol) was then added dropwise through a dropping funnel. The resulting mixture was stirred at -78°C for 2 h and then slowly allowed to warm up to 0°C. The mixture was neutralized by an addition of a saturated solution of ammonium chloride (40 mL) and was extracted with ether (3x30 mL). The combined organic layers were washed with 5% hydrochloric acid (2x50 mL), brine (50mL) and dried over magnesium sulfate. The product was further purified by distillation to give pure triallyl methyl acetate (105°C at 5 torr, 5.7 g, 92 %). ¹H NMR δ: 2.35 (d, 2H, J = 7 Hz), 3.64 (s, 1H, OCH₃), 5.05 (d, 2H, J = 9 Hz, HC=CH₂), 5.68 (m, 1H, J = 9 Hz, H₂C=CH) ppm; ¹³C NMR δ: 39, 49, 51, 118, 133, 176 ppm; FTIR (ATR): 1733 (C=O), 2950 (aliphatic CH), 2980 (aliphatic CH), 3077 (allylic CH) cm⁻¹.
2.2.5 Synthesis of 2,4,9-Trithiaadamantane-7-carboxylic Acid Ethyl Ester (TPCOOEt, 4)

2.2.5.1 Synthesis of Triallyl Ethyl Acetate (5)

The procedures for the above synthesis of triallyl methyl acetate were followed closely. Diethyl malonate was used as a precursor instead of dimethyl malonate. After the distillation of the product, triallyl ethyl acetate was obtained in a comparable yield to the synthesis of triallyl methyl acetate. $^1$H NMR $\delta$: 1.26 (t, 3H, $J = 7$ Hz, CH$_2$CH$_3$), 2.35 (d, 6H, $J = 7$ Hz, CH$_2$), 4.15 (q, 2H, $J = 7$ Hz, OCH$_2$), 5.02 (t, 6H, $J = 9$ Hz, HC=CH$_2$), 5.75 (m, 3H, $J = 9$ Hz, CH$_2$=CH) ppm.

2.2.5.2 Thionation with Hydrogen Sulfide in Ethanolic Hydrogen Chloride

A solution of triallyl ethyl acetate (3 g, 14 mmol) in absolute ethanol (100 mL) in a 500-mL round bottom flask was stirred and cooled to -78$^\circ$C in a dry ice-acetone bath. Ozone was bubbled through the cooled mixture until the light blue color persisted. The ozone line was then disconnected and replaced by an argon line to remove excess ozone by purging for 10 min. Dimethyl sulfide (3.6 mL, 49 mmol) was added to the reaction mixture at -78$^\circ$C. The mixture was allowed to slowly warm up to ambient temperature. The solvent was removed by a rotatory evaporator. The resulting yellow oil was dissolved in an ice-cooled solution of hydrogen chloride gas in absolute ethanol (100 mL). To this mixture, hydrogen sulfide was bubbled through while stirring and cooling. After the mixture was stirred for 30 min, the ice bath was removed and the mixture was stirred at room temperature for an additional 15 min. The volume of the solvent was reduced to about 30 mL on a rotatory evaporator. Water (100 mL) was added. The
resulting mixture was extracted with methylene chloride (3x30 mL). The organic layer was collected, dried over magnesium sulfate and evaporated. Crude NMR spectra of the viscous oil show the presence of 2,4,9-trithiaadamantane-7-carboxylic acid ethyl ester, but the product was not purified due to a low product yield.

2.2.5.3 Thionation with Lawesson’s Reagent and Boron Trifluoride

A solution of triallyl ethyl acetate (3 g, 14 mmol) in freshly distilled methylene chloride (100 mL) in a 500-mL round bottom flask was stirred and cooled to -78°C in a dry ice-acetone bath. Ozone was bubbled through the cooled mixture until the light blue color persisted. The ozone line was then disconnected and the excess ozone was removed by argon flow for 10 min. Dimethyl sulfide (3.6 mL, 49 mmol) was added to the reaction mixture at –78°C. The mixture was allowed to slowly warm up to ambient temperature. The solvent was removed by a rotatory evaporator. Methylene chloride (100 mL) was added to the yellow, viscous liquid. To this mixture, Lawesson’s reagent (20 g, 49 mmol) and boron trifluoride (6.2 mL, 49 mmol) were added respectively. The mixture was then refluxed for 100 h. The progress of the reaction was followed by thin layer chromatography. After the reaction is completed as shown by TLC, additional methylene chloride was added (100 mL). The mixture was washed with 5 M potassium carbonate solution (3x50 mL). The organic layer was collected, dried over magnesium sulfate and evaporated. The resulting viscous oil was purified by column chromatography using 25% ethyl acetate in hexane to furnish pure 2,4,9-trithiaadamantane-7-carboxylic acid ethyl ester (1.3 g, 35%). M.P. 155–157°C. 1H NMR (CDCl₃): δ 1.27 (t, 3H, J = 7 Hz, CH₃), 2.89 (d, 6H, J = 3 Hz, CH₂), 4.17 (q, 2H, J = 7
Hz, OCH₂), 4.32 (s, 3H, broad, SCH) ppm; ¹³C NMR (CDCl₃): δ 14, 38, 40, 41, 61, 175 ppm; IR (ATR): 1724 (C=O), 2922 (aliphatic CH) cm⁻¹. HRMS: calcld for C₁₀H₁₂O₂S₃Na⁺: 285.00536, found 285.00435.

2.2.6 Synthesis of 2,4,9-Trithiaadamantane-7-carboxylic Acid Methyl Ester (TPCOOMe, 6)

2.2.6.1 Thionation with Lawesson’s Reagent and Boron Trifluoride

To a solution of methyl triallyl acetate (I) (2.85 g, 13.70 mmol) in methylene chloride (100 mL) at −78°C was bubbled through an ozone/oxygen mixture from an ozone generator until the reaction mixture displayed a light blue color. Excess ozone was removed by bubbling argon through the reaction mixture for 10 min. Dimethyl sulfide (3.5 mL, 41.10 mmol) was added to the reaction mixture at −78°C and the resulting reaction mixture was allowed to slowly warm up to ambient temperature. To the above reaction mixture, methylene chloride (100 mL), Lawesson’s reagent (5.54 g, 13.70 mmol) and boron trifluoride (5.80 mL, 41.10 mmol) were added respectively. The reaction mixture was then refluxed for 100 h. Additional methylene chloride was added (100 mL) during the reflux. The reaction mixture was then treated with aqueous K₂CO₃ (3 mL, 5.0 M) while cooling. The organic layer was then washed with water and dried over magnesium sulfate and evaporated. The resulting mixture was purified by column chromatography using 30% methylene chloride in hexane to give 2,4,9-trithiaadamantane-7-carboxylic acid ethyl ester (1.23 g, 38% yield). M.P. 149–151°C.

¹H NMR δ: 2.92 (d, 2H, J = 3 Hz, CH₂), 3.76 (s, 1H, OCH₃), 4.33 (s (broad), 1H, SCHS) ppm; ¹³C NMR δ: 38, 40, 41, 52, 175 ppm; FTIR (ATR): 1740 (C=O), 2923 (aliphatic
CH), 2944 (aliphatic CH) cm$^{-1}$. HRMS: calcd for C$_9$H$_{12}$S$_3$Na$^+$ 270.989158 found 270.98971.

2.2.6.2 Thionation with Phosphorus Pentasulfide Suspended on Alumina

The thionation reagent is a combination of phosphorus pentasulfide (P$_4$S$_{10}$, 6 g) and alumina (Al$_2$O$_3$, 10 g). The mixture was prepared by grinding in a mortar and pestle until a fine powder was obtained. 1 g of this reagent contains 0.8 mmol of phosphorus pentasulfide.

A solution of methyl triallyl acetate (3 g, 16 mmol) in freshly distilled methylene chloride (200 mL) was stirred and cooled to -78°C in a dry ice-acetone bath. Ozone was bubbled through the cooled mixture until the light blue color persisted. The ozone line was then disconnected and the excess ozone was removed by argon flow for 10 min. Dimethyl sulfide (4.2 mL, 34 mmol) was added to the reaction mixture at –78°C. The mixture was stirred for 3 h while slowly warming up to ambient temperature. The solvent was removed by a rotatory evaporator yielding a yellow viscous gel. To the flask containing a yellow gel, dry acetonitrile (200 mL), a mixture of phosphorus pentasulfide and alumina (19 g, 16 mmol of P$_4$S$_{10}$) was added slowly while stirring and cooling, CAUTION: An exothermic reaction may be observed. The reaction should be handled with great care. The mixture was then refluxed under an argon atmosphere for 24 h. During the reflux, the progress of the reaction was closely followed by thin layer chromatography. After completion of the reaction, the reaction mixture was allowed to cool to ambient temperature. Alumina and solid byproducts can be removed by vacuum filtration and the solvent was evaporated. 2,4,9-trithiaadamantane-7-carboxylic acid
ethyl ester was obtained by recrystallization from ethyl acetate and hexanes (1.2 g, 30%).

2.2.6.3 Thionation with Phosphorus Pentasulfide Suspended on Silica Gel

The thionation reagent was prepared by mixing phosphorus pentasulfide and silica gel (6 portions of phosphorus pentasulfide and 10 portions of silica gel) in the same manner as the preparation of phosphorus pentasulfide and alumina mixture. 1 g of the reagent contains 0.8 mmol of phosphorus pentasulfide.

The procedures of this reaction were similar to the procedures explained in section 2.2.6.2 and can be described briefly herein; the ozonolysis reaction was carried out in dry methylene chloride at -78°C. The ozonides were reduced by an addition of dimethyl sulfide at -78°C and the reaction mixture was stirred at room temperature for 3 h. The thionation/cyclization reaction was carried out in a refluxing acetonitrile for 24 h. After filtration, the product can be obtained as off white crystals by recrystallization from ethyl acetate and hexanes. The product yields of this approach and the reaction with P₄S₁₀/Al₂O₃ were relatively similar, around 20%.

2.2.7 Synthesis of 2,4,9-Trithiaadamantane-7-carboxylic Acid (TPCOOH, 7)

Hydrolysis of 2,4,9-trithiaadamantane-7-carboxylic acid ethyl ester (175 mg, 0.66 mmol) was carried out in a mixed solvent of tetrahydrofuran:methanol:water (2 mL, 3:3:1) with lithium hydroxide monohydrate (140 mg, 6.6 mmol) in a 10-mL pear-shaped flask connected to a reflux condenser. The reaction mixture was stirred at room temperature for 1 h and refluxed for additional 15 min. The reaction mixture was
allowed to cool to ambient temperature, diluted with water (2 mL), acidified to pH ~ 2
with aqueous hydrochloric acid (6 M), and stored in a 5°C refrigerator overnight.
Filtration and vacuum drying overnight afforded a light yellow solid of 2,4,9-
trithiaadamantane-7-carboxylic acid (140 mg, 90% yield). M.P. 235-237°C; \( ^1 \text{H NMR} \delta: 2.96. \) (d (broad), 2H, \( CH_2 \)), 4.36 (s (broad), 1H, \( CH \)) ppm; \( ^{13} \text{C NMR} \delta: 202, 42, 39, 38 \) ppm; FTIR (ATR): 1695 (C=O), 2920 (aliphatic CH), 2933 (aliphatic CH), 2700-3200 (broad, OH) cm\(^{-1}\). HRMS: calcd for C\(_8\)H\(_{10}\)O\(_2\)S\(_3\)\(\cdot 2\) found 233.9847.

2.2.8 Synthesis of 2,4,9-Trithiaadamantane-7-carbonyl Azide (TPCON\(_3\), 8)

To an ice-cooled solution of 2,4,9-trithiaadamantane-7-carboxylic acid (140 mg, 0.59 mmol) in methylene chloride (2 mL) was added thionyl chloride (1.5 mL, 3.0 mmol, 2.0 M in methylene chloride) dropwise and the resulting reaction mixture was refluxed for 2 h. After evaporation of the solvent and excess of thionyl chloride under vacuum, a yellow crystalline of 2,4,9-trithiaadamantane-7-carbonyl chloride (TPCOCl, 9) was produced. The yellow crystals were dissolved in acetone (2 mL) and a solution of sodium azide (47 mg, 0.72 mmol) in water (1 mL) was added while stirring and cooling with an ice bath. After stirring at 0°C for 2 h, 10 mL of water was added to the reaction mixture and the mixture was extracted with methylene chloride. The organic layer was collected and dried over sodium sulfate. After the solvent was removed by a rotatory evaporator, 2,4,9-trithiaadamantane-7-carbonyl azide was produced as a white crystalline solid (141 mg, 91% from 8). The compound is sensitive to light and heat and must be kept in a cool and dark place. M.P.: 106-107°C (decomposed). \( ^1 \text{H NMR} \delta: 2.87 \)
(d (broad), 2H, \(CH_2\)), 4.34 (t (broad), 1H, \(SCHS\)) ppm.; \(^{13}\text{C} \) NMR \(\delta\): 39, 40, 41, 42, 48, 182 ppm.; FTIR (ATR): 1698 (C=O), 2148 (N=N\(_2\)), 2922 (aliphatic CH) cm\(^{-1}\).

2.2.9 Synthesis of 1-(2,4,9-Trithiaadamantan-7-yl-2-diazo-ethanone (TPCOCHN\(_2\), 10)

To an ice-cooled solution of TPCOCl (43 mg, 0.17 mmol) in diethyl ether (5 mL), a freshly prepared etheric solution of diazomethane (ca. 1 mmol, 8 mL) was slowly added while stirring and cooling with an ice bath. After stirring at 0\(^\circ\)C for 2 h, 10 mL of water was added to the reaction mixture and the mixture was extracted with methylene chloride. The organic layer was collected and dried over sodium sulfate. After the solvent was removed by a rotatory evaporator, 1-(2,4,9-Trithiaadamantan-7-yl-2-diazo-ethanone was produced as a white crystalline solid (141 mg, 91% from 7). The compound is sensitive to light and heat and must be kept in a cool and dark place. M.P.: 106-107\(^\circ\)C (decomposed). \(^{1}\text{H} \) NMR \(\delta\): 2.82 (d, 6H, \(CH_2\)), 4.36 (t, 3H, \(SCHS\)), 5.48 (s, 1H, \(CHN_2\)) ppm.; \(^{13}\text{C} \) NMR \(\delta\): 39.4, 39.9, 40, 41, 44, 196 ppm.; FTIR (ATR): 1726 (C=O), 2105 (-N\(_2\)), 2849, 2917 (aliphatic CH), 3078 (CH-N\(_2\)) cm\(^{-1}\).

2.2.10 Synthesis of 2,4,9-Trithiaadamantan-7-yl-methanol (TPCH\(_2\)OH, 11)

A flame-dried, 25 mL round-bottomed flask, equipped with a Teflon\textsuperscript{®}-coated magnetic stir bar and a septum with an argon inlet, was charged with a solution of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester (270 mg, 1.10 mmol) in 5 mL of dry toluene. After the flask was cooled with an ice bath, a solution of diisobutyl aluminum hydride in hexane (1.60 mL, 1.5 M, 2.4 mmol) was slowly added. The resulting reaction mixture was stirred at 0\(^\circ\)C until the disappearance of the starting material as indicated by
TLC monitoring. The solution was quenched by 2 mL of methanol and allowed to reach ambient temperature. The resulting mixture was filtered through a celite pad to give 240 mg (97%) of 2,4,9-Trithiaadamantan-7-yl-methanol. M.P. 198-200°C (lit. 199-200°C); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.53 (s, 1H, OH), 2.58 (d, 6H, \(J = 3\) Hz, CH\(_2\)), 3.38 (s, 2H, OCH\(_2\)), 4.33 (s (broad), 3H, CH); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 32, 40, 42, 73; FTIR (ATR): 2866 (aliphatic CH), 2917 (aliphatic CH), 3316 (broad, OH) cm\(^{-1}\).

2.2.11 Synthesis of 2,4,9-Trithiaadamantane-7-carbaldehyde (TPCHO, 12)

To a stirred solution of oxalyl chloride (0.07 mL, 0.83 mmol) in 3 mL dichloromethane in a three-necked round bottomed flask (25 mL) was added dimethyl sulfoxide (0.12 mL, 1.66 mmol) dropwise through a dropping funnel while the reaction temperature was maintained at -78 °C via an acetone dry-ice bath. The solution mixture was stirred at -78 °C for additional 5 min after the addition. A solution of 2,4,9-trithiaadamantan-7-yl-methanol (240 mg, 1.09 mmol) in 5 mL of dichloromethane was added to the dropping funnel and was added dropwise to the above reaction mixture. After the reaction mixture was stirred at -78 °C for 45 min (reaction monitored by TLC), triethylamine (5 mL) was added. The resulting reaction mixture was allowed to warm up to room temperature while stirring. The reaction was quenched with water (20 mL) and extracted with dichloromethane three times (3 x 10 mL). The crude produce was obtained after removal of the solvent under reduced pressure. The aldehyde was used in the next step without further purification due to its chemical instability. M.P. 159-162°C (decomposed); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.77 (d, 6H, \(J = 3\) Hz, CH\(_2\)), 4.37 (s (broad), 3H,
SC\(\text{H}\), 9.3 (s, 1H, \textit{CHO}). \(^{13}\text{C}\) NMR (CDCl\(_3\)): \(\delta\) 38, 39, 42, 202; FTIR (ATR): 1713 (C=O), 2754 (CHO), 2847 (CHO), 2917 (aliphatic CH), 2946 (aliphatic CH) cm\(^{-1}\).

2.2.12 Synthesis of 2,4,9-Trithiaadamantan-7-yl-ethyne (TPCCH, 13)

Sodium hydride (60 mg, 1.4 mmol, 60% dispersed in mineral oil) was dispersed in dry toluene (10 mL) in a 50 mL round bottom flask which was equipped with a magnetic stirrer and cooled in an ice bath. Dimethyl (2-oxopropyl) phosphonate (22 mg, 1.3 mmol) was added slowly. The solution was stirred for an additional hour after the addition. A solution of methanesulfonyl azide (17 mg, 1.4 mmol) in a mixed solvent of toluene and THF was added to the above reaction mixture. The resulting reaction mixture was allowed to slowly warm up to ambient temperature and stirred for additional 2 h. The reaction mixture was filtered through a celite filter cake to give yellowish oil of dimethyl (1-diazo-2-oxopropyl) phosphonate, which was used for the next step without further purification.

To a mixture of aldehyde TPCHO and potassium carbonate (0.63 mg, 2.0 mmol) in 2 mL of dry methanol, the solution of dimethyl (1-diazo-2-oxopropyl) phosphonate (1.2 equivalents) in dry methanol was added. The resulting reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with dichloromethane (20 mL) and extracted with additional portions of dichloromethane (2 x 20 mL). The combined organic layers were washed with sodium bicarbonate (20 mL, 5%). After evaporation of the solvent, the crude product was purified by column chromatography to yield 7-ethynyl-2,4,9-trithiaadamantane (160 mg) in 78% yield from 2,4,9-trithiaadamantan-7-yl-ethyne. M.P. 273-274°C; \(^1\text{H}\) NMR (CDCl\(_3\)): \(\delta\) 2.27 (s, 1H, C\text{CH}, ). 2.88
(d, 6H, J = 3 Hz, CH₂), 4.28 (s (broad), 3H, SCH) ppm.; ¹³C NMR (CDCl₃): δ 27, 39, 44, 69, 90 ppm.; FTIR (ATR): 2100 (C≡C), 2907 (aliphatic CH), 2944 (aliphatic CH), 3259 (C≡CH) cm⁻¹.; HRMS: calcd for C₉H₁₀S₃⁺ 213.993911 found 213.9930.

2.2.13 Synthesis of 1,4-Bis((7-2,4,9-trithiaadamantyl)ethynyl) Benzene (TPCCBzCCTP, 14)

A mixture of 2,4,9-trithiaadamantan-7-yl-ethyne (13) (50 mg, 0.16 mmol), diiodobenzene (26 mg, 0.08 mmol) and tetrakis(triphenylphosphine)palladium(0) (9 mg, 8 µmol) in a 25-mL round bottom flask equipped with a condenser was degassed by several freeze-pump-thaw cycles. In another 25-mL round bottom flask, piperidine (5 mL) was degassed by three freeze-pump-thaw cycles and then transferred to the above reaction mixture under argon. The resulting mixture was then heated by a water bath at 60° C and stirred at this temperature for 2 h. The solution was cooled to ambient temperature and quenched with a saturated aqueous solution of NH₄Cl (10 mL). The resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated by a rotatory evaporator under a reduced pressure. The solid residue was purified by recrystallization in dichloromethane to yield 14. (38 mg, 80%). M.P. 282-284°C (decomposed); ¹H NMR (CDCl₃): δ 2.96 (6 H, d, J = 3 Hz), 4.33 (3 H, s), 7.35 (2 H, s); ¹³C NMR (CDCl₃): δ 28, 40, 44, 81, 97, 122, 131; FTIR (ATR, cm⁻¹): 2232 (C≡C), 2915 (aliphatic CH), 2936 (aliphatic CH). HRMS: calcd for C₂₄H₂₂S₆Na⁺ 524.993788 found 524.99334.
2.2.14 Synthesis of 1,4-Bis(7-2,4,9-trithiaadamantyl) Butadiyne (TPCCCCTP, 15)

To an ice-cooled solution of 2,4,9-trithiaadamantan-7-y1-ethyne (40 mg, 0.20 mmol), bis(triphenylphosphine)palladium(II) (10 mg, 10 µmol), CuI (2 mg, 10 µmol) in tetrahydrofuran (5 mL), was added diisoproylamine (0.5 mL). The resulting mixture was stirred at the room temperature for 30 min and at refluxing temperature for an additional 2 h. The flask was cooled with an ice bath and the reaction was treated with a saturated solution of ammonium chloride (10 mL). The mixture was mixed with water (50 mL) and extracted with methylene chloride (3x20 mL). The combined organic layer was washed with a brine solution and dried over sodium sulfate and removed by a rotatory evaporator. The resulting solid was recrystallized from methylene chloride yielding a white solid of 1,4-bis(7-2,4,9-trithiaadamantyl) butadiyne (32 mg, 75%) M.P. 359-361°C (decomposed); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.88 (d, 2H, \(J = 3\) Hz, \(CH_2\)), 4.28 (s (broad), 1H, \(SCH\)) ppm.; \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 27, 39, 44, 65, 84 ppm.; IR (ATR): 2850 (aliphatic CH), 2917 (aliphatic CH) cm\(^{-1}\). HRMS: calcd for C\(_{18}\)H\(_{18}\)S\(_6\)+ 425.972721 found 425.9747.

2.2.15 Synthesis of \(S\-{4-[7-2,4,9-trithiaadamantylethynyl]-phenyl}\) Thioacetate (TPCCBzSCOMe, 16)

A mixture of 2,4,9-trithiaadamantan-7-yl-ethyne (50 mg, 0.23 mmol), \(S\)-4-iodophenyl thioacetate (65 mg, 0.23 mmol) and tetrakis(triphenylphosphine)-palladium(0) (30 mg, 26 µmol, 10% mol equivalents) in a flame-dried 25-mL round bottom flask equipped with a condenser was degassed by a mechanical pump. The flask was then filled with an argon atmosphere. Dry piperidine (5 mL) in another 25-mL
round bottom flask was degassed by a 3 cycles of freeze-pump-thaw process. Both
flasks were cooled with an ice bath. Piperidine was transferred to a flask containing the
solid mixture. The resulting mixture was allowed to warm up to ambient temperature.
The solution was then stirred at 50°C for 3 h. The flask was allowed to slowly cool to
room temperature. A saturated solution of ammonium chloride (10 mL) was added to
the reaction mixture. The mixture was extracted with methylene chloride (3x10 mL).
The combined organic solvent was washed with water (10 mL), brine solution (10 mL),
and dried over sodium sulfate. The resulting solid was purified by recrystallization from
methylen chloride. TPCCBzSCOMe was obtained as a light yellow solid (68 mg, 81%)
$^1$H NMR (CDCl$_3$): $\delta$ 2.43 (s, 3H, OCH$_3$), 2.97 (s, 6H, CH$_2$), 4.33 (s, 3H, SCH), 7.36 (d,
2H, $J = 8$ Hz), 7.44 (d, 2H, $J = 8$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 28, 29, 30, 80, 124, 127,
132, 134, 193; IR (ATR, cm$^{-1}$): 1707 (C=O), 2229 (C≡C), 2852 (aliphatic CH) 2928
(aliphatic CH) cm$^{-1}$.

2.2.16 Synthesis of 4-(7-2,4,9-trithiaadamantylethynyl) Iodobenzene (TPCCBzI, 17)

A mixture of 2,4,9-trithiaadamantan-7-yl-ethyne (55 mg, 0.26 mmol), 1,4-
diiodobenzene (420 g, 1.3 mmol, 5 equivalents) and tetrakis(triphenylphosphine)-
palladium(0) (30 mg, 26 µmol, 10% mol equivalents) in a flame-dried 25-mL round
bottom flask equipped with a condenser was degassed by a mechanical pump. The flask
was then filled with an argon atmosphere. Dry piperidine (5 mL) in another 25-mL
round bottom flask was degassed by 3 cycles of freeze-pump-thaw process. Both flasks
were cooled with an ice bath. Piperidine was transferred to a flask containing the solid
mixture. The resulting mixture was allowed to warm up to ambient temperature and
stirred at 50°C for 3 h. The flask was allowed to slowly cool to room temperature. A saturated solution of ammonium chloride (10 mL) was added to the reaction mixture. The mixture was extracted with methylene chloride (3x10 mL). The combined organic solvent was washed with water (10 mL) and a brine solution (10 mL) and dried over sodium sulfate. The resulting solid was purified by recrystallization from methylene chloride. 4-(7-2,4,9-trithiaadamantylethynyl) iodobenzene was obtained as a light yellow solid (84 mg, 78%) M.P. 215-216°C (decomposed); ¹H NMR (CDCl₃): δ 2.95, (d, 6H, J = 3 Hz, CH₂), 4.32 (s (broad), 3H, SCH), 7.14 (d, 2H, J = 8 Hz, ICCHCH), 7.65 (d, 2H, 8 Hz, ICCH) ppm.; ¹³C NMR (CDCl₃): δ 28.59, 40.01, 44.83, 80.82, 94.21, 96.66, 122.62, 133.46, 137.67 ppm; FTIR (ATR): 2851 (aliphatic CH), 2916 (aliphatic CH), 3052 (aromatic CH) cm⁻¹.

2.2.17 Synthesis of 4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-pyridine (TPCCBzCCPy, 18)

A Sonogashira cross coupling reaction of 4-(7-2,4,9-trithiaadamantylethynyl) iodobenzene (30 mg, 67 µmol) and 4-ethynyl pyridine hydrogen chloride (20 mg, 0.14 mmol) in piperidine (2 mL) was carried out following the procedure described in section 2.2.15. Tetrakis(triphenylphosphine)palladium(0) (8 mg, 6.7 µmol) was used as a catalyst. The preparation of 4-(7-2,4,9-trithiaadamantylethynyl) iodobenzene was described in section 5.2.8. The solvent was transferred to a solid mixture while cooling to prevent any exothermic reactions. The reaction mixture was stirred under an argon atmosphere at the refluxing temperature for 3 h. The general work up procedure as described previously in section 2.2.13 was strictly followed. The product, 4-[4-[7-2,4,9-
trithiaadamantyl-ethynyl]-phenylethynyl]-pyridine, was obtained as a yellow solid by recrystallization from methylene chloride (21 mg, 76%). M.P. $^1$H NMR (CDCl$_3$): $\delta$ 2.97 (d, 3H, $J = 3$ Hz, CH$_2$), 4.33 (s (broad), 3H, SCH), 7.43 (d, 4H, $J = 8$ Hz, ArH), 7.51 (d, 2H, $J = 8$ Hz, NCHCH), 8.63 (s, 2H, NCHCH) ppm.; $^{13}$C NMR (CDCl$_3$): $\delta$ 29, 40, 45, 81, 88, 98, 122, 124, 126, 131, 132, 150 ppm.; FTIR (ATR): 2219 (C≡C), 2881 (aliphatic CH), 2915 (aliphatic CH), 2930 (aliphatic CH) cm$^{-1}$. HRMS: calcd for C$_{22}$H$_{17}$NS$_3$H$^+$ 392.059585 found 392.05932.

2.3 Results and Discussion

2.3.1 7-Substituted-2,4,9-trithiaadamantane

The synthesis of 7-ethoxycarbonyl-2,4,9-trithiaadamantane was originally reported by Lingrend in 1976$^{34}$ and later by Kittredge et al. in 2002.$^3$ The synthesis of this key species can be divided into two steps: namely the synthesis of triallyl ethyl acetate and the thionation/cyclization step. Triallyl ethyl acetate$^{42}$ was synthesized via a multi-step approach starting from commercially available diethyl malonate. The first step of the sequence was to add the first allyl group to an $\alpha$-carbon from the carbonyl carbon. Sodium ethoxide in dry ethanol and allyl bromide were used as a base and as a reagent respectively. The second allylation was carried out in the same manner. Both reactions were trivial and resulted in very high yield reactions without any difficulties in the work up process. The product was usually pure enough for the next reaction as shown by both $^1$H and $^{13}$C NMR. The decarboxylation reaction of diallyl diethyl malonate was carried out by reacting with sodium chloride in a refluxing dimethyl sulfoxide. This reaction is a key step for the whole sequences as it requires a lengthy refluxing time, which is usually
100 hours, to complete. After the reaction reached completion, diallyl ethyl acetate was collected by steam distillation. The steam was generated internally by water into the reaction mixture. The distillate is a mixture of diallyl ethyl acetate floating on a water layer, which is collected by extraction with diethyl ether. If the reaction was completed, as shown by TLC, the organic layer is mostly the desired product, diallyl ethyl acetate. On the other hand, if TLC showed that there is a trace amount of starting material, diallyl diethyl malonate, in the reaction mixture, the distillate usually is a mixture of both starting materials and product. The introduction of steam distillation has shown that the separation of diallyl ethyl acetate is more feasible than via the reported procedure, in which extraction with diethyl ether of the product from the reaction mixture was sufficient to purify the product. It was found that the combined ether extracts was still contaminated with dimethyl sulfoxide even after excessively washing it with water. Steam distillation has proved a better option of purifying diallyl methyl acetate. The synthesis of triallyl methyl acetate is illustrated in Scheme 2.8. The reaction mechanisms for Krapcho decarboxylation of diallyl dimethyl malonate and diallyl diethyl malonate are shown in Scheme 2.9.

Triallyl ethyl acetate was then treated with lithium diisopropylamide and reacted with allyl bromide. After the work up, distillation of the crude product gives pure triallyl ethyl acetate as a colorless liquid. This compound has a very distinctive and strong odor. It should be kept cool and dark as the color of the compound becomes yellow if kept exposed to the light and heat for a long period of time.

Triallyl ethyl acetate is a major key intermediate for the synthesis of 7-substituted-2,4,9-trithiaadamantane. However, the drawback of the synthetic pathway is the
decarboxylation reaction step. The product yield of this reaction is relatively low, presumably due to the basic hydrolysis of the ester group. Moreover, a trace amount of starting material was often observed in the product leading to problems in the work up. Hence, the lengthy reaction at a very high temperature should be avoided. Considering Krapcho conditions (Scheme 2.9), methyl ester groups should proceed much faster than bulkier ethyl esters.

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Scheme 2.8 Synthesis of triallyl methyl acetate
Scheme 2.9 Krapcho conditions for decarboxylation of diallyl diethyl malonate (top) and diallyl dimethyl malonate (bottom)

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According to the previous synthetic procedure of diethyl malonate, diallyl dimethyl malonate was produced in a comparative yield to diallyl diethyl malonate. The reaction was processed in methanol using sodium methoxide instead of ethanol and sodium ethoxide. The decarboxylation reaction of diallyl dimethyl malonate proceeded faster than its ethyl analogue. It required only 25 h for the reaction to reach completion. Additionally, the product yield of this step is better due to a shorter reaction thus minimizing unwanted hydrolysis of the ester group. Triallyl methyl acetate was obtained from the third allylation with lithium diisopropylamide and allyl bromide.

The formation of the building block, 2,4,9-trithiaadamantane-7-carboxylic acid ethyl ester was first studied following reported procedures closely (Scheme 2.10). The ozonolysis reaction of triallyl ethyl acetate was carried out in dry ethanol. Ozonides were initially reduced by the treatment with triphenylphosphine. The corresponding aldehydes were treated with hydrogen sulfide in ethanolic hydrogen chloride. This approach introduced triphenylphosphine oxide as byproducts of the reduction of the ozonides. Difficulties in the workup process had been encountered. Crude \(^{1}\)H NMR spectra showed the distinctive peaks at 2.9 and 4.3 ppm for the protons on the adamantane ring, indicating that the product was produced, but in a very small amount. The desired product cannot be isolated by simple purification techniques, i.e. column chromatography, or recrystallization. Dimethyl sulfide had been introduced as a direct replacement of triphenylphosphine to help ease the workup. The resulting reaction mixture was cleaner; however, the product yield was not significantly improved. Thionation of aldehydes with hydrogen sulfide was believed to be unsuccessful. Moreover, hydrogen sulfide gas is difficult to handle.
Lawesson’s reagent (LR)\textsuperscript{46} has been used widely as a thionation reagent. Even though it is costly compared to its analogue, phosphorus pentasulfide, its improved solubility in common organic solvents has attracted much attention. In 2001, Wu and coworkers\textsuperscript{47} reported the synthesis of acetal thia-cage compounds using Lawesson’s reagent as a reducing agent of ozonides and a thionation reagent. Desired compounds were obtained by a direct replacement of oxygen atoms on oxa-cages by sulfur atoms. The reactions did not require any extreme conditions as they were carried at ambient temperature. These conditions were applied to the synthesis of the 2,4,9-trithiaadamantane building block, but the reactions were unsuccessful even it was carried out at elevated temperature. The first assumption was that this desired reaction, thionation/cyclization, required an acid to drive the reaction to completion. A Lewis

\[ \text{Scheme 2.10 Lindgren’s approach: synthesis of 2,4,9-Trithiaadamantane-7-carboxylic Acid Ethyl Ester} \]
acid, boron trifluoride etherate, was introduced and with Lawesson’s reagent proved to be a good combination for the thionation/cyclization reaction. The reactions were carried out at the refluxing temperature of methylene chloride. The purification of the product required chromatography and recrystallization from ethyl acetate/hexanes is often necessary. This approach had improved the reaction yields greatly to about 40% compared to the previously reported 10-15%. Both triallyl ethyl acetate and triallyl methyl acetate seem to produce the corresponding products in the same range of percent yields (Scheme 2.11).

The mechanism of this reaction is still unclear. Boron trifluoride is vital to the formation of the trithiane ring system. Lawesson’s reagent is the sulfur source and boron trifluoride etherate is an acid source. The driving force of this reaction is the formation of a strong P=O bond as byproducts while forming thioacetal bonds into a six-membered ring structure. The active species of Lawesson’s reagent is believed to be an

\[ \text{LR}
\]

\[ \text{LR/BF}_3
\]

\[ \text{reflux in CH}_2\text{Cl}_2
\]

35-40%

Scheme 2.11 Thionation with Lawesson’s reagent and Boron trifluoride etherate
ylide form. A negatively-charged sulfur atom attacks an electropositive carbonyl carbon, while an oxygen atom attacks a positively-charged phosphorus atom forming a Wittig-like structure. The similar process takes place with other aldehyde groups leading to the formation of a trithiane ring structure. A proposed mechanism of this process is shown in Scheme 2.12. X-ray data of TPCOOEt are shown in Figure 2.1 and Table 2.3.

The mechanism does not include boron trifluoride etherate because its role in this reaction is not certain. Nonetheless, it is assumed that the acid plays a role in the cyclization step by coordinating to oxygen atoms of aldehydes, rather than the thionation step. This is because the thionation would be more feasible than the second step due to the formation of a stable phosphine oxide as previously mentioned.

The exploration for a possible thionation reagent is the aim of this work. Thionation/cyclization using a combination of Lawesson’s reagent and boron trifluoride etherate proves to be a worthwhile discovery, but the cost of Lawesson’s reagent together with its high molecular weight has made this reaction an expensive one. Attention was then turned to the more conventional phosphorus pentasulfide. Phosphorus pentasulfide is a solid and is not soluble in most organic solvents. It is, however, partially soluble in acetonitrile and becomes soluble when the temperature is increased. The ozonolysis product of triallyl methyl acetate treated with phosphorus pentasulfide in a refluxing acetonitrile produced a small amount of the desired 7-methoxycarbonyl-2,4,9-trithiaadamantane (~10%). To increase the reaction yields as well as to ease the workup, phosphorus pentasulfide was dispersed in basic alumina. Both solids were mixed by grinding them using a traditional pestle/mortar. It is reported that the optimum ratio of the mixture of alumina to $P_2S_5$ is $10:6$. In addition, the
Scheme 2.12 A proposed mechanism of a formation of 2,4,9-trithiaadamantane
reaction required 0.34 mole P₂S₅/Al₂O₃ per 1 mole of reaction aldehyde (or ketone). Surprisingly, the reaction reached completion in a very short period of time. A well-stirred reaction mixture in refluxing acetonitrile required only 25 hours as indicated by TLC. TLC also showed that if the reaction was allowed to proceed longer, a byproduct was observed more clearly as the spot become darker. The workup of the reaction from the new approach was relatively simple. Filtration of the reaction mixture usually removes most of undesired sulfur byproducts. Recrystallization of the remaining viscous liquid from ethyl acetate and hexanes furnished quite good quality product. A second recrystallization may be needed if the product is not pure enough as shown by NMR.

The same approach has been applied to less expensive silica gel (Scheme 2.13). Following the same treatments, a combination of phosphorus pentasulfide and silica gel was as effective as using a combination of phosphorus pentasulfide and alumina. The product yields from these two new thionation reagents are somewhat lower than the combination of Lawesson’s reagent and boron trifluoride etherate in methylene chloride. The yield ranges between 20 to 25%. Given that phosphorus pentasulfide is inexpensive and the reaction time is greatly shorter, the new approach is worth noting.

2.3.2 Photolabile Molecular Surface Anchors

The self-assembly and photolithographic surface patterning of a new tripodal ligand was inspired by Kittredge et al.³ Prior to their work, the synthesis of trithiaadamantane derivatives was reported. However, there was no report on the utilization of this new ligand for nanotechnology applications. The improved synthesis
Figure 2.1 An ORTEP diagram with thermal ellipsoids at 50% probability level of TPCOOEt. Hydrogen atoms are omitted for clarity.

Scheme 2.13 Thionation with phosphorus pentasulfide/alumina or phosphorus pentasulfide/silica gel
Table 2.3 Crystal data and structure refinement for TPCOOEt

| Identification code          | C_{10}H_{14}O_2S_3 |
| Empirical formula           | C_{10}H_{14}O_2S_3 |
| Formula weight              | 262.39             |
| Temperature                 | 373(2) K           |
| Wavelength                  | 0.71073 Å          |
| Crystal system              | Triclinic          |
| Space group                 | Pī                 |
| Unit cell dimensions        | \begin{align*} a &= 7.909(8) \, \text{Å} \quad \alpha = 89.828(17)^\circ. \\
                        b &= 7.965(8) \, \text{Å} \quad \beta = 71.899(16)^\circ. \\
                        c &= 9.707(9) \, \text{Å} \quad \gamma = 89.830(16)^\circ. \end{align*} |
| Volume                      | 581.2(10) Å³       |
| Z                           | 2                  |
| Density (calculated)        | 1.499 Mg/m³        |
| Absorption coefficient      | 0.614 mm⁻¹         |
| F(000)                      | 276                |
| Crystal size                | 0.10 x 0.10 x 0.10 mm³ |
| Theta range for data collection | 2.21 to 28.35° |
| Index ranges                | \begin{align*} -10 \leq h \leq 10, -10 \leq k \leq 10, -12 \leq l \leq 11 \end{align*} |
| Reflections collected       | 5210               |
| Independent reflections     | 2640 (R(int) = 0.2427) |
| Completeness to theta = 28.35° | 91.0 %            |
| Absorption correction       | None               |
| Refinement method           | Full-matrix least-squares on F² |
| Data / restraints / parameters | 2640 / 0 / 136     |
| Goodness-of-fit on F²       | 1.138              |
| Final R indices [I>2sigma(I)] | R₁ = 0.1033, wR₂ = 0.2885 |
| R indices (all data)        | R₁ = 0.1310, wR₂ = 0.3260 |
| Largest diff. peak and hole | 1.396 and -1.514 e. Å⁻³ |
of 7-substituted-2,4,9-trithiaadamantanes and a new method of introducing a trithiane moiety into an adamantane cyclic structure were well discussed in section 3.3.1. The key intermediate, 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester, contains two parts, namely; a stable adamantane moiety and an ester group. With the adamantane portion acting as an anchor, the ester group can feasibly be transformed into any desired functional group. In this specific case, a photolabile group, such as a diazomethylcarbonyl group and azidocarbonyl group, is desired.

The hydrolysis of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester with lithium hydroxide was carried out in a solvent combination of tetrahydrofuran, methanol and water. This solvent system was preferred because of the poor solubility of the starting material in water. After the neutralization with hydrochloric acid, the reaction produced a quantitative yield of a resulting acid, 2,4,9-trithiaadamantane-7-carboxylic acid, as light yellow crystals. 2,4,9-Trithiaadamantane-7-carbonyl chloride was obtained from a reaction of 2,4,9-trithiaadamantane-7-carboxylic acid with thionyl chloride in refluxing methylene chloride. Yellow crystals of the acid chloride were obtained after the evaporation of the solvent and excess of thionyl chloride. This should be used for the next reaction without purification due to its low stability. 2,4,9-Trithiaadamantane-7-carbonyl chloride in cold tetrahydrofuran was mixed with a low concentration of freshly prepared diazomethane in diethyl ether. Slow evaporation of solvents furnished yellow crystals of 1-(2,4,9-trithiaadamantan-7-yl)-2-diazo-ethanone. The crystals are light and heat sensitive and should be kept in a cold and dark place to avoid decomposition. This synthetic pathway involves handling of explosive materials and should be dealt with a great care. Diazomethane is explosive especially if it is highly
concentrated. In addition, 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone is unstable and believed to be explosive because of its α-diazoketone functional group. The syntheses of 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone and 2,4,9-trithiaadamantane-7-carbonyl azide are shown in Scheme 2.14.

Photolithographic patterning of 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone takes advantage of an α-diazoketone group, which undergoes the Wolff rearrangement reaction, while the trithiaadamantane serves as a molecular anchor for the self-assembled monolayers. In order to avoid explosive materials, the α-diazoketone group can be replaced by its analogous α-diazidoketone. The α-azidoketone can undergo photo-initiated Curtius rearrangement. The synthesis of 2,4,9-trithiaadamantane-7-carbonyl azide was very similar to one of 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone. Sodium azide in acetone was mixed with a cold solution of 2,4,9-trithiaadamantane-7-carbonyl chloride in tetrahydrofuran. Yellow crystals of 2,4,9-trithiaadamantane-7-carbonyl azide were obtained in a quantitative yield. This compound is sensitive to heat and light and should be stored in a dark and cool place. Reaction mechanisms for Wolf rearrangement reaction and Curtiss rearrangement reaction of 1-(2,4,9-trithiaadamantan-7-yl-2-diazo-ethanone and 2,4,9-trithiaadamantane-7-carbonyl azide are illustrated in Scheme 2.15.

2.3.3 Molecular Wires

The conversion of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester to 2,4,9-trithiaadamantan-7-yl-ethyne was carried out via 2,4,9-trithiaadamantane-7-carbaldehyde. Ohira-Bestmann rearrangement\textsuperscript{49,50} of the aldehyde, TPCHO, should feasibly
Scheme 2.14 Synthesis of photoactive surface anchors
Scheme 2.15 Wolf rearrangement (top) and Curtuis Rearrangement (bottom)
lead to the desired 2,4,9-trithiaadamantan-7-yl-ethyne. The synthesis of TPCHO was carried out by the reduction of TPCOOMe with diisobutylaluminium hydride (DIBAL-H) followed by the Swern oxidation of the corresponding alcohol to the desired aldehyde, TPCHO. The reduction of TPCOOMe was carried out in cold, dry toluene. The reaction was initiated at -78°C, then allowed to warm up to 0°C and maintained at this temperature until the reaction reached completion as shown by TLC. It was observed that the only obtained product was the desired TPCH₂OH. The reaction was quenched by a slow addition of cold methanol at 0°C. The stirred mixture became solidified and formed a clear gel. The mixture was filtered through a celite pad and the solid was washed several times with methylene chloride as the solubility of the product is very poor. The TPCH₂OH was obtained by recrystallization of a white solid from methanol. The product yield of this reaction was not very high because of the difficulties in the workup of the reaction of DIBAL-H, and other aluminium hydrides.

The Swern oxidation of TPCH₂OH was carried out at -78°C in dry methylene chloride. After the reaction was quenched with triethylamine, the mixture was extracted with methylene chloride. The product was obtained as yellow crystals after the removal of the solvent. TPCHO was usually pure enough as proved by IR and ¹H NMR and was quickly used in the next reaction due to its poor chemical stability.

Dimethyl (1-diazo-2-oxopropyl)phosphonate was prepared from dimethyl 2-oxopropylphosphonate by the reaction with methanesulfonyl azide using sodium hydride as a base in dry toluene. This compound should be prepared freshly before each use because it is unstable. Dimethyl (1-diazo-2-oxopropyl)phosphonate was treated with potassium methoxide generated from dissolving potassium carbonate in methanol
producing (diazomethyl) phosphonate in situ. The reaction of the aldehyde, TPCHO, with (diazomethyl) phosphonate took place in methanol at the room temperature. 7-(2-diazovinyl)-2,4,9-trithiaadamantane was generated and underwent the Ohira-Bestmann rearrangement at the ambient conditions. This reaction produced the desired 7-ethynyl-2,4,9-trithiaadamantane quantitatively. This reaction is suitable for the preparation of desired alkyne because it proceeds at very mild conditions. Neither strong bases nor acids were used. As it has been shown that the 2,4,9-trithiaadamantane moiety does not tolerate very strong bases and tends to decompose if treated with \( n \)-butyl lithium. Figure 2.2 and Table 2.4 show X-ray data for TPCCH. The synthetic sequence for the synthesis of TPCCH is depicted in Scheme 2.16. Scheme 2.17 illustrates reaction mechanism of the preparation of 7-ethynyl-2,4,9-trithiaadamantane.

1,4-Bis(7-2,4,9-trithiaadamantyl) butadiyne (TPCCCCTP, 15) is a dimer of 7-ethynyl-2,4,9-trithiaadamantane. It was originally obtained as a by-product in Sonogashira cross coupling reaction between TPCCH and 1,4-diisotetrafluorobenzene. White crystals were produced as a major product along with a very small amount of unexpected 1(7-2,4,9-trithiaadamantylethynyl) 2,3,5,6-tetrafluorobenzene. This compound was then prepared by the reaction of TPCCH using Pd(0) and Cu(I) as catalysts. Due to its rigid backbone, this compound has very poor solubility in most solvents. However, it is slightly soluble in methylene chloride.

Oligophenyleneethylenes containing a 2,4,9-trithiaadamantane moiety were prepared from a key intermediate, TPCCH, and desired phenyl halides via the Sonogashira cross coupling reaction. Several molecular wires based on this design have been constructed. The first group of molecular wires were designed to have symmetrical
Scheme 2.16 The synthesis of 2,4,9-trithiaadamantan-7-yl-ethyne
Scheme 2.17 Reaction mechanism of the Ohira-Bestmann rearrangement of TPCHO
Figure 2.2 An ORTEP diagram with thermal ellipsoids at 50% probability level showing the molecular structure of TPCCH
Table 2.4 Crystal data and structure refinement for TPCCH

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<tr>
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<td>β = 93.959(3)°</td>
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<td>c = 9.4622(16) Å</td>
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<td>224</td>
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<tr>
<td>Crystal size</td>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Extinction Coefficient</td>
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</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.594 and -0.587 e. Å⁻³</td>
</tr>
</tbody>
</table>
structures containing the 2,4,9-trithiaadamantane moiety at both ends. The preparations were attempted by coupling TPCCH with 1,4-diodobenzene and 1,4-diodotetrafluorobenzene respectively. 1,4-Bis((7-2,4,9-trithiaadamantyl)ethynyl)benzene (TPCCBzCCTP, 14) was synthesized as the only product of the Sonogashira cross coupling reaction between TPCCH and 1,4-diodobenzene. However, the reaction of TPCCH and 1,4-diodotetrafluorobenzene did not yield the desired product. As mentioned previously, TPCCCCTP and a small amount of 1(7-2,4,9-trithiaadamantylethynyl) 2,3,5,6-tetrafluorobenzene were isolated instead. It is believed that fluoride atoms as substituents on a benzene ring withdraw electrons from the aromatic ring generating an electron-deficient phenyl halides. It is assumed that the product of the transmetallation of TPCCArCu (Ar = tetrafluorobenzene) was protonated leading to the formation of 1(7-2,4,9-trithiaadamantylethynyl) 2,3,5,6-tetrafluorobenzene. Additionally, TPCCCCTP was obtained as a product of the reductive elimination (Scheme 2.18).

Asymmetric molecular wires were designed to contain a 2,4,9-trithiaadamantane at one end of the wire while the other end is capped with another type of molecular anchors. In this study, molecular wires with a pyridinyl and a thioacetate groups are prepared. The synthetic sequences began with the preparation of 4-(7-2,4,9-trithiaadamantylethynyl) iodobenzene (TPCCBzI, 17). The reaction between TPCCH and 1,4-diodobenzene was carried out in the same conditions as a standard procedure of the preparation of symmetric molecular wires. The amount of 1,4-diodobenzene was used in excess compared to TPCCH, usually 10 fold more because of its low cost, to prevent the formation of a symmetric molecular wire, TPCCBzCCTP. The product for
one cross coupling reaction at only one end was isolated quantitatively, indicating that
the second cross coupling reaction at the other end of the molecule was insignificant.

$S\{-4-[7\-2\-4\-9\-\text{trithiaadamantylethynyl}]\-\text{phenyl}\}$ thioacetate (TPCCBzSCOMe) was
synthesized by Sonogashira cross coupling reaction of TPCCH with $S\-4\-\text{iodophenyl}$
thioacetate (AcSBzl) using the similar conditions to the previous compounds (Scheme
2.19). The reaction was trivial and produced a high product yield.

4-(7-2,4,9-trithiaadamantylethynyl) iodobenzene is a precursor for the synthesis of
asymmetric molecular wires. TPCCBzI underwent a Sonogashira cross coupling
reaction with 4-ethynylpyridine hydrogen chloride yielding a molecular wire with
different end groups, 4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-pyridine
(TPCCBzCCPy). This compound was isolated as a yellow solid. It has poor solubility in
common organic solvents, but is somewhat soluble in methylene chloride. It should be
noted that an addition of a base, in this case an amine, should be performed at a low
temperature because 4-ethynylpyridine reacts violently with a base and decomposes
under ambient conditions. The schematic illustration of the synthesis of 4-[4-[7-2,4,9-
trithiaadamantylethynyl]-phenylethynyl]-pyridine is shown in Scheme 2.20.

2.4 Summary

The focus of this section of the dissertation was on the design and synthesis of new
molecular surface anchors. 2,4,9-Trithiaadamantane-7-carboxylic acid methyl ester was
prepared from triallyl methyl acetate. Triallyl methyl acetate was used as a direct
replacement of triallyl ethyl acetate because the reaction time in the decarboxylation
of diallyl dimethyl acetate, 25 h, is shorter than diallyl diethyl malonate, which is 100 h.
Scheme 2.18 Sonogashira cross coupling reaction of TPCCH and aryl halides: i, oxidative addition; ii, transmetallation; iii, reductive elimination
Scheme 2.19 Synthesis of molecular wires
Scheme 2.20 Synthesis of 4-[4-[7,2,4,9-trithiaadamantylethynyl]-phenylethynyl]-pyridine
The change of this group did not induce any changes in terms of reaction yields. After the ozonolysis of the triallyl compound and the reduction of ozonides, thionation and cyclization reactions were performed using a combination of Lawesson’s reagent and boron trifluoride etherate in refluxing methylene chloride. This approach improved the reaction yield from 10-15% to 35-40%. Additionally, the purification process of this reaction was less complicated than the similar reaction performed in the reported procedures.\textsuperscript{3,34} Phosphorus pentasulfide supported on either alumina or silica gel was also used as a thionation/cyclization reagent. This reaction was carried out in refluxing acetonitrile and yielded the product around 20-25%.

2,4,9-Trithiaadamantane-7-carboxylic acid methyl ester was used as a molecular precursor for the preparation of photolabile molecular surface anchors. 1-(2,4,9-Trithiaadamantan-7-yl-2-diazo-ethanone and 2,4,9-trithiaadamantane-7-carbonyl azide were synthesized via the reaction of diazomethane and sodium azide with 2,4,9-trithiaadamantane-7-carbonyl chloride respectively. The product yields for both compounds after a three-step reaction were high, usually over 90%.

2,4,9-Trithiaadamantane-7-yl-ethyne was prepared from the Ohira-Bestmann reaction of 2,4,9-trithiaadamantane-7-carbaldehyde, which was synthesized by a two step reaction from 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester. TPPCH was used as a precursor for preparation of molecular wires. Symmetric and asymmetric molecular wires were synthesized by a series of Sonogashira cross coupling reactions. All molecular wires are poorly soluble in most organic solvents, but are fairly soluble in methylene chloride.
The results indicate that the newly-developed tripodal ligand can be chemically tuned to various functionalities by taking advantage of an ester group of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester. Though, the 2,4,9-trithiaadamantane moiety does not tolerate strong bases and tends to decompose, it is stable various chemical conditions.
CHAPTER III

TRIPODAL LIGAND-STABILIZED GOLD NANOPARTICLES

3.1 Historical Background

Gold has been known and used for various purposes since ancient times. It is believed that the first gold mine was started at least the 4th millennium BC. The Egyptians in Nubia operated gold mining extensively and gold became the sign of wealth and power. Gold colloids were used long before its modern chemistry was developed. The ruby red color of the colloids was evident in stained glasses and ceramics.

The beginning of the chemistry started from the middle of the nineteenth century, when Michael Faraday carried out the preparation of gold colloids. He reduced tetrachloroaurate with white phosphorus producing the deep-red solutions of gold colloids. Later, at the beginning of the twentieth century, Osward began studying colloid science and pointed out that the properties of metal particles in the nanometer range are solely determined by the surface atoms. He also came to the conclusion that metal particles should mimic novel properties with respect to their bulk metal.
3.1.1 Stabilization of Metal Colloids

The preparation of metal colloids, especially gold nanoparticles in this case, has gained much interest due to the small sizes of the particles. In a solution, small particles will be pulled together by van der Waals interaction causing the coagulation of the particles. In order to prepare the stable particles, forces are needed to overcome the van der Waals interaction to avoid the aggregation of the particles. Therefore, the introduction of the stabilizing ligands is required. Different types of stabilization of metal colloids are discussed herein.

3.1.1.1 Electrostatic Stabilization

Ionic compounds dissolved in a solution, usually an aqueous solution, can generate electrostatic stabilization. Likewise, metal colloids dissolved in an aqueous solution will form separate layers of different charges around the particles. Therefore, the Coulombic repulsion is generated between the two layers of the same electronic charges. If the electric potential between the two layers is high enough, the coagulation of the particles can be avoided as a result of the repulsion. Nonetheless, this type of particles is sensitive to ionic strength and any systems that interrupt the double layer system can cause an aggregation of colloids.\textsuperscript{54,55} Figure 3.1 illustrates the stabilization of metal colloids by an electrostatic force while the plot of energy versus the interparticular distance is shown in Figure 3.2.
Figure 3.1 Two particles stabilized by Coulombic repulsion between two similar electric layers.

Figure 3.2 Plot of energy ($V_T$) versus interparticular distance ($d$) for electrostatic stabilization.

\[ V_T = V_{\text{Steric}} + V_{\text{Van der Waals}} \]
3.1.1.2 Steric Stabilization

The stabilization of metal colloids by steric stabilization is usually the use of macromolecules to protect metal colloids, such as polymers and oligomers. The adsorbed macromolecules can prevent colloids from aggregation. Once the interparticle distance is decreased, adsorbed molecules are restricted, hence the entropy is reduced. This process causes the free energy of the system to increase and therefore the thermodynamically unfavorable process. Another effect is the increase of the local concentration of stabilizing molecules at the interparticle space once two particles are moving closer to each other (the shaded area in Figure 3.3). This results in an osmotic repulsion as the solvent is reestablishing the concentration by diluting the area and hence separating the particles. The stabilization of metal colloids by this phenomenon applies to both organic and aqueous media, while the electrostatic stabilization applies to only aqueous media. Figure 3.4 shows the plot of energy of the colloids versus the interparticular distance.

3.1.1.3 Electrosteric Stabilization

Metal colloids stabilized by this approach are usually the colloids prepared from ligands with ionic headgroups. Ionic surfactants acting as stabilizers provide enough steric repulsion between long hydrophobic alkyl chains together with the Coulombic repulsion between the ionic headgroups. Examples of gold nanoparticles stabilized by this means are water soluble gold nanoparticles stabilized by Ph₂PC₆H₄SO₃Na.
Figure 3.3 Steric stabilization of metal particles; the shaded area represents the local increase of the concentration of stabilizing macromolecules.

Figure 3.4 Plot of energy ($V_T$) versus interparticular distance ($d$) for electrosteric stabilization.

\[ V_T = V_{\text{Steric}} + V_{\text{Electrostatic}} + V_{\text{Van der Waals}} \]
3.1.1.4 Ligand Stabilization

Metallic nanoparticles can be prepared by the stabilization of the metal core by ligands. These ligands stabilize the particles using the coordination chemistry principles of metal cores and heteroatoms as ligands. Stabilizing ligands are usually amines, \textsuperscript{61,62,63} phosphines, \textsuperscript{64,65,66} thiols, \textsuperscript{67,68} thioethers. \textsuperscript{69} The detailed discussion of the preparation of gold nanoparticles by means of ligand stabilization will be described in the next section. Figure 3.5 is an illustration of gold nanoparticles stabilized by ligands.

![Figure 3.5 A schematic representation of ligand-stabilized gold nanoparticles](image-url)
3.1.2 Preparation of Gold Nanoparticles

3.1.2.1 Citrate Reduction

The preparation of gold nanoparticles by the reduction of gold(III) with citrate was originally introduced by Turkevitch in 1951.\textsuperscript{70} This approach produces gold nanoparticles of approximately 20 nm in size. Frens\textsuperscript{71} later developed the procedure to produce gold nanoparticles of different sizes. This was succeeded by controlling the reducing agent to gold ratio. By varying the trisodium citrate to gold ratio, gold nanoparticles of sizes ranging from 16 to 147 nm were obtained. This method is still popular nowadays when gold nanoparticles with loosely-packed ligands are desired.

3.1.2.2 Triphenylphosphine-stabilized Gold Nanoparticles Prepared by The Schimd Method

The preparation of Schmid’s cluster, \([\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6]\), was reported in 1981. This type of gold nanoparticles was obtained by the reduction of \(\text{Ph}_3\text{PAuCl}\), which was prepared by the reduction of \(\text{HAuCl}_4\) with triphenylphosphine,\textsuperscript{72} by gaseous diborane, \(\text{B}_2\text{H}_2\).\textsuperscript{73} The reaction was usually carried out in either benzene or toluene at a refluxing temperature. This process produces gold nanoparticles of very narrow dispersity (1.4 \(\pm\) 0.4 nm). Gold nanoparticles prepared by this method are quite stable due to rather strong Au-P bonds. Water soluble phosphane-stabilized gold nanoparticles were also prepared by the ligand exchange reaction of \(\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6\) with water soluble ligands, \(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3\) producing gold nanoparticles of 15-20 nm.\textsuperscript{49} The gold nanoparticles can be isolated, dried and redissolved again in water.
3.1.2.3 The Brust-Schiffrin Method

The stabilization of gold nanoparticles with alkanethiols was first reported by Mulvaney and Giersig.\textsuperscript{74} Gold nanoparticles were prepared by the displacement of stabilizing citrate ligands with alkanethiols of different chain lengths. The Brust-Schiffrin method for preparation of thiol-stabilized gold nanoparticles was reported in 1994.\textsuperscript{75} Gold nanoparticles prepared from this method are thermally and air-stable. The colloids can be chemically functionalized just like common organic compounds. They can be isolated, dried and redissolved in most organic solvents repeatedly. Moreover, this method allows the preparation of gold nanoparticles with a narrow size distribution. The preparation of gold nanoparticles from this method uses the thiols that bind strongly to gold due to the soft properties of both gold and sulfur. This technique is carried out by the introduction of gold(III) salt, HAuCl$_4$, from an aqueous solution into an organic solvent, usually toluene, by a phase transfer reagent. To the organic solution containing stabilizing thiols, and gold(III) salt with a phase transfer reagent was rapidly added a freshly-prepared solution of sodium borohydride. The color of the organic solution changes from orange to deep brown instantly. After an additional stirring, the isolated black solid of gold nanoparticles were dissolved in an organic solvent and then precipitated with pentane or hexanes to furnish gold nanoparticles with a narrower size distribution. The chemical reaction is illustrated in Scheme 3.1.

3.1.2.4 Gold Nanoparticles Stabilized by Other Sulfur Ligands

There are several sulfur-containing ligands for stabilizing gold nanoparticles such as disulfides,\textsuperscript{76,77} xanthates\textsuperscript{78} and trithiols.\textsuperscript{79} It was reported that gold nanoparticles
stabilized by disulfides or thioethers are not stable.\textsuperscript{80,81} However, the use of polydentate thioether ligands prepared produced gold nanoparticles that can be redissolved in organic solvents.\textsuperscript{82}

3.1.2.5 Other Ligands

The well known and most popular methods for preparation of gold nanoparticles have been discussed. However, there are several other methods of preparation of gold nanoparticles using different stabilizing ligands that have not been mentioned. The Brust-Shiffrin method was applied to prepare phosphane-stabilized gold nanoparticles. The formula of the gold nanoparticles was estimated to be $\text{Au}_{101}(\text{PPh}_3)_{21}\text{Cl}_6$.\textsuperscript{83} The reduction of a Au(IV) salt by NaBH$_4$ in a mixture of tri-$n$-octylphosphine oxide (TOPO) and octadecyl amine (1:0.57 molar ratio) at 190$^\circ$C resulted in the controlled growth of stable gold nanoparticles.\textsuperscript{84}

Polymers can also be used as stabilizers for gold nanoparticles. The most commonly used polymers for the stabilization of gold nanoparticles are poly($N$-vinyl-2-pyrrolidone) (PVP) and poly(ethylene glycol).\textsuperscript{85} Nanoparticles-polymer composite can be obtained by many different methods. However, two approaches are generally used. The first technique is the synthesis of gold nanoparticles \textit{in situ} in the polymer matrix.\textsuperscript{86} The latter is done by blending of pre-made gold nanoparticles into pre-synthesized polystyrene polymer bound to a thiol group.\textsuperscript{87} The reduction of gold salt in polymers mostly uses NaBH$_4$.

Dendrons and dendrimers as stabilizers for gold nanoparticles have just gained much interest in the past few years. Fox described the preparation of metal-core-organic-
Scheme 3.1 Formation of gold nanoparticles by reduction of Au(III) with NaBH₄ in the presence of an alkanethiols.

The gold nanoparticles were prepared by the Brust-Schiffrin reduction of gold salt in the presence of arylpolyethers terminated ester or carboxylate groups. The other end of the polymers is attached to a thiol group. Similar approach of preparation of gold-core dendrimers was reported by Astruc. In the latter case, tri- and nonaferocenyl thiol dendrons were utilized as stabilizers for gold nanoparticles. The gold nanoparticles were prepared either by the Brust-Schiffrin method or the replacement of dodecanethiolate ligands with thiolated dendrons.
It should be noted that gold nanoparticles can be prepared from several different methods using various ligands as stabilizers. However, most ligands are based on the coordination chemistry between gold and other electronegative atoms, such as phosphorus and sulfur. Stabilizers for gold nanoparticles can be prepared as derivatives of these two popular anchors. Different ligands of the same binding atom lead to gold nanoparticles of different properties.49

3.1.3 Characterization of Gold Nanoparticles

The most common technique for characterization of gold nanoparticles is transmission electron microscopy (TEM), which gives images of gold nanoparticles. The core of gold nanoparticles can also be examined by scanning tunneling microscopy (STM), atomic force microscopy (AFM), small-angle X-ray scattering (SAXS) and X-ray diffraction.

3.1.4 Physical Properties

3.1.4.1 The Surface Plasmon Band

It has been predicted that gold nanoparticles in the diameter range 1-10 nm, which is between the sizes of small molecules and bulk gold metal, would display electronic structures, reflecting the electronic band structures of gold nanoparticles. The resulting properties of gold nanoparticles depend on their size, interparticular distance, nature of organic shell, and shape of the nanoparticles.90 The quantum effect becomes evident when the de Broglie wavelength of valence electrons is in the same order as the particle size. The particle therefore behaves as a zero-dimension quantum dot. The electrons are
trapped in metal boxes but are able to move freely producing a collective oscillation frequency of the plasma resonance band at around 530 nm. This effect gives rise to the deep ruby red color, which can be observed in stained glasses.86

The main characteristics of surface plasmon band are as follows. First, the plasmon band appears at around 520 nm. Secondly, the intensity of the surface plasmon band decreases as the size of gold nanoparticles deceases. This applies mainly to the particles with metal core of 1.4 – 3.2 nm. This is due to the quantum size effect that becomes stronger in the gold nanoparticles of 3.0 nm and smaller. This also causes a blue shift.91 Lastly, the structure of surface plasmon band is due to the unoccupied levels of conduction band with gold nanoparticles with core diameter of 1.1 to 1.9 nm.92,93 Furthermore, bulk gold and gold nanoparticles with gold core smaller than 2 nm do not show a surface plasmon band.

However, surface plasmon band characteristics of gold nanoparticles can be altered by other chemical conditions associated with gold nanoparticles itself. The shape of gold nanoparticles, medium dielectric and temperature can cause changes in surface plasmon band. The refractive index of the solvent can cause a shift of $\lambda_{\text{max}}$. The shell of stabilizing ligands can also cause either a red or blue shift because it alters the refractive index of the whole system. This is especially more evident for gold nanoparticles stabilized by thiolates, as the strong ligand field of thiolates interact with the electron cloud of the gold nanoparticles.

The surface plasmon band of gold nanoparticles is also affected by the ionic charge of the gold core of gold nanoparticles. It was reported that excess electrons in gold core can cause a blue shift while a lack of electrons induces a red shift.94,95
3.1.4.2 Fluorescence

The fluorescent characteristics of gold nanoparticles are of a great interest in biophotonics and materials sciences.\(^{96,97}\) The study was carried out by preparing gold nanoparticles capped with a fluorescent tag at the end group of stabilizing ligands. Most common capping fluorescent groups are pyrenyl,\(^{98}\) polyoctylthiophenyl,\(^{99}\) and fluorenyl.\(^{100}\) The resonant energy transfer in fluorescent ligand-capped gold nanoparticles was studied. It was reported that the radiative and non radiative rates depend solely on the sizes and shapes of gold nanoparticles as well as the distance between a fluorescent group and gold core.

3.1.5 Applications

A large number of applications of gold nanoparticles have been reported. Examples of applications will be discussed herein. Molecular recognition using gold nanoparticles as templates were previously reported.\(^{99,100,101,102}\) Alkanethiolate-stabilized gold nanoparticles, in which amidoferrocenyl-alkylthiol replaces the existing alkanethiols, was reported to recognize \(\text{H}_2\text{PO}_4^-\) and \(\text{HSO}_4^-\) as their \(\text{n-Bu}_4\text{N}^+\) salts using the variation of ferrocenyl redox potential. The gold nanoparticles act as receptors for these ions.\(^{101}\) Amide-functionalized gold nanoparticles were used as a sensor for anions.\(^{102}\) Gold nanoparticles functionalized with 15-crown-5 were studied as sensors for \(\text{K}^+\) and \(\text{Li}^+\) ions.\(^{103,104}\)

The utilization of gold nanoparticles towards biological applications has been widely studied. The functionalization of gold nanoparticles with nucleotides is a potential source of the programmability of DNA base-pairing. This approach has been
predicted as a source of DNA library. One of the pioneer works that used gold nanoparticles as templates for DNA sensing was studied by Alivasatos and Schultz. In this study, DNA was used as a template to prepare nanocrystal molecules consisting of gold nanoparticles. The DNA attached to the gold nanoparticles retained their chemical properties and hybridized with its complementary DNA. Moreover, gold nanoparticles were also functionalized towards immuno-sensing and sugar sensors applications. Biodevices for diagnostics based on antibody-attached gold nanoparticles, interact with their conjugate antigens. This technique uses the advantage of strong surface plasmon band of gold nanoparticles for bioassay applications. Mannose-encapsulated gold nanoparticles have been shown by TEM to specifically bind FimH adhesion of bacterial type 1 pili in Escherichia coli. This modified gold nanoparticles bind much stronger than free mannose. This approach leads to the competition assay of detecting specific proteins on the cell surface using carbohydrate-conjugated gold nanoparticles.

Bulk gold metal has gained very little attention for catalysis in contrast to its neighbors silver and platinum. However, gold nanoparticles possess some catalytic activities. In 1989, Haruta observed the oxidation carbon monoxide to carbon dioxide by metal oxide-supported gold nanoparticles. Inorganic oxides are for example: Fe₂O₃, TiO₃ or Co₃O₄. Several reviews have provided with great details of catalytic applications of gold nanoparticles.

3.1.6 Formation of Tripodal Ligand Stabilized Gold Nanoparticles

Self-assembly of a 2,4,9-trithiaadamantane head group as a molecular surface anchor was recently studied. The purpose of the study was to prepare and modify
photoactive self-assembled monolayers. The study shows that the 2,4,9-trithiaadamantane moiety can serve as a molecular surface anchor for self-assembling of desired molecules onto flat gold surfaces. Furthermore, the tripodal ligand acts as a model to study on how this tripodal ligand binds metal while the other study shows how the three sulfur atoms of the trithiaadaman tane ring coordinate to three ruthenium atoms.\textsuperscript{37} This provides a model of chemical structure of self-assembled monolayers of this ligand on gold surfaces.

As mentioned previously, self-assembly of 2,4,9-trithiaadamantane derivatives has been studied mostly on flat gold surfaces and the formation of ruthenium clusters. It is predicted that the head group linked with a long chain alkyl groups should provide stabilized gold(0) clusters and form gold nanoparticles just like alkyl thiols and thioethers. The advantage of this type of ligand is the extreme chemical stability of the 2,4,9-trithiaadamantane head group and the ease in handling the ligand. It possesses a distinct odor, however, it is much less unpleasant than alkyl thiols. Following the Brust-Schiffirin method, the reduction of a gold(IV) salt in the presence of a 2,4,9-trithiaadaman tane derivative in an organic solvent should facilitate organic-soluble gold nanoparticles.

The Schmid’s triphenylphosphine gold nanoparticles should also undergo a ligand exchange reaction with a 2,4,9-trithiaadamantane derivative leading to the formation of tripodal ligand-stabilized gold nanoparticles. This is due to the stronger affinity between gold and sulfur than gold and phosphorus. The pictorial illustration of tripodal –ligand-stabilized gold nanoparticles is presented in Figure 3.6.
3.2 Experimental Section

3.2.1 General Procedures

All air and/or moisture sensitive reactions were conducted under an Argon atmosphere. Unless otherwise stated, all reagents were purchased from Aldrich or ACROS and used as received. Pure water (Milli-Q) with a resistivity of higher than 4 MΩ was used. Anhydrous toluene was distilled from sodium benzophenone ketyl under an Argon atmosphere. Glassware was oven-dried at 110 °C or flame-dried if necessary. IR spectra were recorded on a Nicolet Nexus 870 FT spectrometer equipped with an ATR accessory. Data were reported in wavenumber (cm⁻¹). All ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer unless otherwise noted. NMR spectra were recorded in CDCl₃. ¹H and ¹³C Chemical shifts are reported in parts per million relative to the residual CHCl₃ (7.27 ppm) and to the CDCl₃ signal (77.23 ppm) respectively. ¹H NMR multiplicity is reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. UV-vis absorption
spectra were recorded on an OceanOptics PC2000 spectrometer. TEM was performed with a JEOL Transmission Electron Microscope (1200 EX II) at an accelerating voltage of 120 kV.

3.2.2 Synthesis of 2,4,9-Trithiaadamantane-7-carboxylic Acid Octadecylamide (TPCONHC\textsubscript{18}, \textit{19})

To an ice-cooled solution of 7-hydroxycarbonyl-2,4,9-trithiaadamantane (TPCOOH, \textit{7}) (0.200 g, 0.85 mmol) in dry dichloromethane (5 mL), is added thionyl chloride (0.7 mL of 2 \textit{M} solution in dichloromethane, 1.30 mmol) slowly. The resulting mixture was stirred and refluxed for 1 h. After the reaction mixture was allowed to reach room temperature, the solvent was removed by a rotatory evaporator and later a vacuum pump. A light yellow crystal of 7-chlorocarbonyl-2,4,9-trithiaadamantane (TPCOCl) was obtained and dissolved in 5 mL dry tetrahydrofuran immediately due to concerns over the stability of an acid chloride functional group. A solution of TPCOCl in tetrahydrofuran was cooled by an ice bath, and a solution of \textit{n}-octadecylamine (0.230 g, 0.85 mmol) in dry tetrahydrofuran (5 mL). The reaction mixture was stirred and refluxed. After 1 h, the reaction was finished as confirmed by thin layer chromatography. The mixture was left to reach room temperature before cooling with an ice bath. The resulting mixture was neutralized with saturated sodium bicarbonate and extracted with dichloromethane (20 mL) three times. The organic layer was dried over anhydrous sodium sulfate. Evaporation of solvent furnished yellow crystals of 2,4,9-trithiaadamantane-7-carboxylic acid octadecylamide (TPCONHC\textsubscript{18}) (0.373 g, 90%). \textit{1}\textit{H} NMR $\delta$: 0.89 (t, 3H, CH\textsubscript{3}), 1.24 (s (broad), 30H, (CH\textsubscript{2})\textsubscript{15}), 1.52 (m, 2H, NHCH\textsubscript{2}CH\textsubscript{2}),
The Schmid’s procedure for preparation of ClAuP(C₆H₅)₃ has followed closely as described. Hydrogen tetrachloroaurate (532 mg, 1.35 mmol) is added into a round bottom flask equipped with a magnetic stirring bar and a septum. The flask was evacuated and then filled with argon. This process was repeated three times. Degassed ethanol (95%, 20 mL) was added under an argon atmosphere. To this solution, a solution of triphenylphosphine (725 mg, 2.74 mmol) in degassed ethanol (95%, 30 mL) was added under an argon atmosphere. A white precipitate was formed immediately. After the reaction mixture was stirred for 5 min, a precipitate was collected by a vacuum filtration. This precipitate was recrystallized in methylene chloride and pentane yielding white crystals of ClAuP(C₆H₅)₃ (614 mg, 1.24 mmol, 92%).

Sodium borohydride (8.76 g, 0.23 mol) was suspended in 1,2-dimethoxyethane (35 mL) in a 500-mL, three-necked round bottom flask containing a magnetic stir bar. The flask was equipped with a dropping funnel containing boron trifluoride diethyl ether (35 mL, 0.22 mol) and a cooling finger containing methanol and dry ice. The whole system was operated under an argon atmosphere. Boron trifluoride diethyl ether was added dropwise into a stirred mixture of sodiumborohydride in 1,2-dimethoxyethane and the
atmosphere of diborane gas was driven by a gentle flow of argon passed a cooling finger through a Teflon tubing to a dry ice-methanol trap before entering the flask containing gold clusters. 112

A flow of cold diborane generated in situ as described above was bubbling into a solution of ClAuP(C₆H₅)₃ (477 mg, 0.96 mmol) in dry benzene (80 mL) in a 500-mL round bottom flask equipped with a refluxing condenser. The temperature of the mixture was elevated to 50° C and stirred for 40 min. The solution became dark after about 10 min of bubbling. The excess diborane was removed from a system by a flow of argon. The gold nanoparticles were collected by filtration. The resulted gold nanoparticles were dissolved in 20 mL methylenechloride and then precipitated by a slow addition of pentane (50 mL). The precipitates were collected and dried by a vacuum pump yielding triphenylphosphine-stabilized gold nanoparticles (80 mg).

3.2.5 Preparation of TPCONHC₁₈-stabilized Gold Nanoparticles by Direct Reduction Reaction

The preparation of gold nanoparticles by the direct reduction of gold clusters with sodium borohydride by Brust 113 was closely followed. The general procedure of the preparation of TPCONHC₁₈-stabilized gold nanoparticles is as followed; to a solution of tetraoctyl ammonium bromide (TOAB) (236 mg, 0.44 mM) in dry toluene (5 mL) in a round-bottomed flask, was added a solution of hydrogen tetrachloroaurate trihydrate (73 mg, 0.22 mmol) in Milli-Q water (7 mL). The resulting was stirred for 20 min. A solution of TPCONC₁₈ (105 mg, 0.22 mM) in dry toluene (5 mL) was added. The mixture was stirred for an additional 10 min. Freshly prepared solution of sodium
borohydride (98 mg, 2.57 mmol) in Milli-Q water (25 mL) was added rapidly at one portion to the stirred mixture. The orange aurate solution became dark brown. The stirring was continued for 12 h. The mixture was extracted with 30 mL dichloromethane and the collected organic layer was washed with water (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate. Evaporation of solvents yielded a black solid, which was later dispersed in methanol. The black solid was collected by the filtration washed with water followed by methanol. The washing process was repeated ten times to ensure the removal of the phase transfer reagent. The gold nanoparticles were obtained as a black solid. The reactions conditions are shown in Table 3.1. Figure 3.7 illustrates the experimental set up for the synthesis of gold nanoparticles by a direct reduction method.

Figure 3.7 Experimental setup for the synthesis of gold nanoparticles by direct reduction method
3.2.6 Preparation of TPCONC$_{18}$-stabilized Gold Nanoparticles by Ligand Exchange Reaction between TPCONC$_{18}$ and Triphenylphosphine-stabilized Gold Nanoparticles

Triphenylphosphine-stabilized gold nanoparticles (15 mg) were dissolved in deuterated dichloromethane (0.7 mL) in a 5-mL NMR tube. $^1$H NMR spectra were recorded as a standard. TPCONC$_{18}$ (10 mg) was added to the gold nanoparticles solution, $^1$H NMR spectra were recorded at 1, 16 and 18 h respectively. The final solution of gold nanoparticles was obtained as a solution of TPCONC$_{18}$-stabilized gold nanoparticles.

3.2.7 Ultraviolet Visible Spectroscopy of Gold Nanoparticles

All gold nanoparticles solutions were prepared by dissolving solid gold nanoparticles in methylene chloride to obtain a final concentration of 0.1 µM. UV-vis spectra were recorded on an OceanOptics PC2000 spectrometer. The spectra were plotted using the data analysis software Origin (Microcal™ software, Inc.).

3.2.8 Transmission Electron Microscopy (TEM) of Gold Nanoparticles

Transmission electron microscopy of gold nanoparticles was obtained from a JEOL transmission electron microscope (1200 EX II) at an accelerating voltage of 120 kV. The samples were prepared by placing a drop of gold nanoparticles solution on a carbon Cu grid and are allowed to dry at the ambient environment. The particle sizes and size distribution were measured and determined by counting particles from a TEM picture and plotted using spreadsheet software.
Table 3.1 Reaction compositions for the synthesis of tripodal-stabilized gold nanoparticles of different ligand-metal core ratios

<table>
<thead>
<tr>
<th>TPCONC&lt;sub&gt;18&lt;/sub&gt;: Au</th>
<th>S:Au</th>
<th>Au(mg)/H&lt;sub&gt;2&lt;/sub&gt;O(mL)</th>
<th>TPCONC&lt;sub&gt;18&lt;/sub&gt;(mg)/toluene(mL)</th>
<th>NaBH&lt;sub&gt;4&lt;/sub&gt;(mg)/H&lt;sub&gt;2&lt;/sub&gt;O(mL)</th>
<th>TOAB(mg)/toluene(mL)</th>
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<tr>
<td>2:1</td>
<td>6:1</td>
<td>5/1.5</td>
<td>13/1</td>
<td>6/1</td>
<td>14/0.5</td>
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<tr>
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<td>3:1</td>
<td>73/7</td>
<td>105/5</td>
<td>98/25</td>
<td>236/5</td>
</tr>
<tr>
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<td>1:1</td>
<td>28/2.5</td>
<td>12/1</td>
<td>32/8</td>
<td>78/2</td>
</tr>
<tr>
<td>1:10</td>
<td>0.1:1</td>
<td>21/2</td>
<td>3/2</td>
<td>28/7</td>
<td>67/2</td>
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<tr>
<th>TPCONC&lt;sub&gt;18&lt;/sub&gt;: Au</th>
<th>S:Au</th>
<th>Au(mg)/H&lt;sub&gt;2&lt;/sub&gt;O(mL)</th>
<th>TPCONC&lt;sub&gt;18&lt;/sub&gt;(mg)/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;(mL)</th>
<th>NaBH&lt;sub&gt;4&lt;/sub&gt;(mg)/H&lt;sub&gt;2&lt;/sub&gt;O(mL)</th>
<th>TOAB(mg)/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;(mL)</th>
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<td>3:1</td>
<td>22/2.5</td>
<td>31/1.5</td>
<td>29/7</td>
<td>69/1.6</td>
</tr>
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</table>
3.3 Results and Discussion

The tripodal ligand used as a stabilizer for gold nanoparticles in this work was prepared by a three-step reaction of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester (Scheme 3.2). TPCOOME was hydrolyzed with lithium hydroxide monohydrate in a solvent mixture of tetrahydrofuran, methanol and water. The corresponding acid was obtained after the neutralization of the reaction mixture with hydrochloric acid. The acid, TPCOOH, is partially soluble in water and solely soluble in acetone. TPCOOH was then treated with thionyl chloride in methylene chloride yielding a yellow crystal of the subsequent acid chloride, TPCOC1. TPCOC1 was treated with octadecyl amine in refluxing tetrahydrofuran to furnish 2,4,9-trithiaadamantane-7-carboxylic acid octadecylamide, TPCONHC\textsubscript{18}. The ligand was obtained as a flaky grey solid. Like other derivatives of 2,4,9-trithiaadamantane, TPCONHC\textsubscript{18} has poor solubility in most organic solvents. Chloroform and methylene chloride seem to be the best suited solvents for this compound.

The preparation of triphenylphosphine-stabilized gold nanoparticles in this study was conducted referring closely to the Schmid’s procedure.\textsuperscript{111} Though various procedures for preparing triphenylphosphine-stabilized gold nanoparticles have been reported,\textsuperscript{114} Schmid’s procedure is the best known protocol. The gold nanoparticles were prepared by the reduction of triphenylphosphinechloro aurate(I), ClAuP(C\textsubscript{6}H\textsubscript{5})\textsubscript{3}. The reaction of hydrogentrichloro aurate(III) with triphenylphosphine in methanol produced triphenylphosphinechloro aurate(I) qualitatively in just a few minutes. Triphenylphosphine was used in at least three fold excess than HCl\textsubscript{4}Au as it also acted
as a reducing reagent for the reduction of Au(III) to Au(I). The product was collected as white crystals that are needle-like in shape.

Triphenylphosphinechloro aurate(I) was dissolved in dry and warm benzene bubbled through a flow of cold diborane generated \textit{in situ} in another flask. A stream of diborane was cooled by a cold finger filled with dry ice and methanol. After a flow of diborane was let into the solution for a few minutes, the colorless solution of triphenylphosphinechloro aurate(I) became dark as black particles were observed. The reduction was allowed to continue for about 40 min and to cool down soon after. The gold nanoparticles were a black solid, which were not soluble in benzene at room temperature. Hence, the precipitates were isolated from the solvent. Triphenylphosphine gold nanoparticles are unstable, therefore they should be dealt with great care and kept cold and under an argon atmosphere. $^1$H NMR spectra of the gold nanoparticles showed a broad peak ranging from about 6.5 to 8.0 ppm. There was also a peak at around 7.5 ppm, which is believed to be protons of gold clusters, ClAuPPh$_3$. This unreduced species can be removed by repeated precipitation of the gold nanoparticles in methylene chloride with pentane. However, after several attempts of the purification method, gold nanoparticles decomposed leading to more of this cluster in the solution. Thus, the gold nanoparticles were precipitated from methylene chloride with pentane only once. The gold nanoparticles were readily soluble in methylene chloride and chloroform. NMR spectra of triphenylphosphine-stabilized gold nanoparticles are depicted in Figure 3.8.
Scheme 3.2 The synthesis of 2,4,9-trithiaadamantane-7-carboxylic acid octadecylamide

In this study, tripodal ligand-stabilized gold nanoparticles were prepared by two different approaches: a direct reduction and a ligand exchange reaction. The first case is known as the famous Brust-Schiffrin method (Scheme 3.3), in which the aurate salt was transferred to an organic solvent by a phase transfer reagent and reduced in the presence of stabilizing ligands. As described in section 3.1, the most common reducing agent for the preparation of gold nanoparticles is sodium borohydride. The latter approach was performed by an addition of a tripodal ligand into a solution of triphenylphosphine-stabilized gold nanoparticles. The stronger affinity of sulfur, compared to phosphorus, towards gold should lead to the displacement a stabilizing ligand.
AuCl₄⁻ was transferred from an aqueous solution into an organic solvent using tetraoctylammonium bromide as a phase transfer reagent. The resulting solution of aurate and a tripodal ligand, 2,4,9-trithiaadamantane-7-carboxylic acid octadecylamide, in toluene became orange. Initially, the ligand, TPCONHC₁₈ was not completely soluble in toluene, but it became readily soluble after mixing with a phase transfer reagent. The mixture was stirred for about 20 min to ensure the thoroughly mixed solution. The addition of freshly prepared sodium borohydride solution is required to be carried out in one step. This will allow the reduction to occur uniformly. A black solution of tripodal ligand stabilized gold nanoparticles was obtained in a few minutes. The reaction, however, was stirred for an additional 12 h. Gold nanoparticles were collected as a black solid. The purification of gold nanoparticles was performed by placing a solid on a filter membrane a washing the solid with water and methanol respectively. This process was repeated several times to ensure the complete removal of a phase transfer reagent. Proton NMR confirms if the trace amount of a phase transfers reagent is still present in the solution of gold nanoparticles. The gold resulting nanoparticles can be redispersed in most organic solvents many times with only little decomposition, if any, of the gold nanoparticles yielding an insoluble black precipitate. Proton NMR spectra of tripodal stabilized gold nanoparticles, of which the TPCONHC₁₈:Au ration is 1:10, in $d$-chloroform prepared from the Brust-Schiffrin method is shown in Figure 3.9. Protons in alkyl chains of ligands give rise to a broad peak ranging from 0.8 to 1.8 ppm. Gold nanoparticles prepared by the same method with different ligand to Au ratios did not show the similar broad peak as presented in Figure 3.10. The $^1$H NMR of gold nanoparticles of 1:1 ligand:Au ratio shows broad peaks of an
aliphatic proton region, however, the peaks do not have a distinct broadening characteristics observed in the larger nanoparticles.

Triphenylphosphine-stabilized gold nanoparticles were prepared as a precursor for the preparation of tripodal ligand-stabilized gold nanoparticles via the ligand exchange reaction of the gold nanoparticles and a tripodal ligand, TPCONHC\textsubscript{18} (Scheme 3.4). The study was conducted by adding the ligand, TPCONHC\textsubscript{18}, into a solution of triphenylphosphine-stabilized gold nanoparticles dissolved in deuterated chloroform. The reaction was monitored by proton NMR. The procedure is better known as NMR titration. As the reaction progresses, \textsuperscript{1}H NMR spectra were recorded periodically. It is clearly shown that the broad peak at around 7 ppm of triphenylphosphine-stabilized gold nanoparticles becomes narrow and a peak of free triphenylphosphine (7.6 ppm) becomes more immense. After the reaction reached 18 h, the spectra clearly shows only two sharp peaks (Figure 3.11 (d)). The more intense peak represents the protons from free triphenylphosphine, however, it is still unclear what the other peak at 7.4 ppm represents. Additionally, it was observed that aliphatic proton peaks at the region of 1-1.5 ppm becomes broadened as a function of time. This explains that the formation of tripodal ligand-stabilized gold nanoparticles takes place as a result of the ligand exchange reaction. Although the peaks are not significantly broadened, the study has already shown that gold nanoparticles of low ratio of ligand to Au(0) do not show very broad peak. Only gold nanoparticles with high ratio of Au to ligand (10 to 1) show the expected broadened peaks. In the solution of gold nanoparticles with the lower Au to ligand ratio, it is believed that more free ligands are present in the solution. Hence, the \textsuperscript{1}H NMR spectra shows peaks with characteristics of free ligands at an aliphatic region,
rather than bound ligands. Figure 3.11 represents a $^1$H NMR titration of the ligand exchange reaction between triphenylphosphine-stabilized gold nanoparticles and TPCONHC$_{18}$.

UV-visible absorption bands of solutions of gold nanoparticles in methylene chloride were recorded. All gold nanoparticles that were prepared from TPCONHC$_{18}$ show a surface plasmon band with the maximum at around 530 nm. However, the gold nanoparticles prepared from the ligand:Au ratio of 1:10, shows intense surface plasmon band at around 530 nm. Gold nanoparticles of different ratios have the surface plasmon band of the same shape, but their intensities are varied. It is observed that gold nanoparticles with higher gold content show more intense surface plasmon band than the ones with higher ligand content. Figures 12 and 13 show UV-vis spectra of different gold nanoparticles.

![Scheme 3.3 The Brust-Schiffrin method for preparation of TPCONHC$_{18}$-stabilized gold nanoparticles](image)

Scheme 3.3 The Brust-Schiffrin method for preparation of TPCONHC$_{18}$-stabilized gold nanoparticles
Scheme 3.4 Schematic representation of the synthesis of triphenylphosphine-stabilized gold nanoparticles and its ligand exchange reaction with TPCONHC₁₈

Figure 3.8 ¹H NMR spectra of triphenylphosphine-stabilized gold nanoparticles in d-chloroform
Figure 3.9 $^1$H NMR spectra of tripodal ligand-stabilized gold nanoparticles prepared by the Brust-Schirifin method
Figure 3.10 $^1$H NMR spectra of TPCONHC$_{18}$ (bottom) and TPCONHC$_{18}$-stabilized gold nanoparticles (top) with 1:1 ratio of TPCONHC$_{18}$:Au
Figure 3.11 $^1$H NMR titration of a ligand exchange reaction between triphenylphosphine-stabilized gold nanoparticles and TPCONHC$_{18}$; a) triphenylphosphine-stabilized gold nanoparticles, b) the reaction after 1 hour, c) the reaction after 16 hours and d) the reaction after 18 hours
Gold nanoparticles with different TPCONHC\textsubscript{18}:Au ratios were also prepared by the Brust-Schiffrin method. Moreover, the gold nanoparticles with 1:1 TPCONHC\textsubscript{18}:Au ratio were also prepared by the same method using methylene chloride as a solvent. The surface plasmon bands of these gold nanoparticles were observed to have a similar nature to the ones mentioned previously.

The size distribution of gold nanoparticles was studied by transmission electron microscopy. TEM micrographs show that the sizes of gold nanoparticles prepared from two different methods; the ligand exchange method and the Brust-Schiffrin method, are in the same range. Gold nanoparticles prepared from the ligand exchange reaction of triphenylphosphine-stabilized gold nanoparticles with TPCONHC\textsubscript{18} have an average size of 88.2 ± 21.6 nm (Figure 3.14). The Brust-Schiffrin method using 1:1 TPCONHC\textsubscript{18} to Au(0) ratio also produced gold nanoparticles of around 86.3 ± 14.2 nm in diameter (Figure 3.15). It can be concluded that the ligand exchange approach produced gold nanoparticles of the same properties as 1:1 gold nanoparticles. Moreover, it is predicted that the size of triphenylphosphine-stabilized gold nanoparticles changed during the ligand exchange reaction process. This can be supported by different sizes of gold nanoparticles (88.2 ± 21.6 nm) from triphenylphosphine-stabilized gold nanoparticles (1.4 nm). This phenomena is expected since several reports have discussed this effect previously.\textsuperscript{115,116,117} An alteration of reaction conditions may lead to the possible control of diameter of gold nanoparticles from the ligand exchange reaction. Another batch of gold nanoparticles prepared by the Brust-Schiffrin method with high TPCONHC\textsubscript{18} to Au(0) ratio was also obtained. The gold nanoparticles of 1:10 TPCONHC\textsubscript{18}:Au(0) ratio has very large diameter. TEM shows that the average size of
the latter gold nanoparticles are 0.71 ± 0.19 µm. The size distribution of the gold nanoparticles is somewhat wide. These large gold nanoparticles were believed to be unstable. However, the gold nanoparticles were surprisingly stable as they were dried producing a black solid and then redissolved in methylene chloride repeatedly. It is clearly shown that the 2,4,9-trithiaadamantane moiety as a head group for stabilizing gold nanoparticles can lead to large gold nanoparticles that are soluble in organic solvents.

3.4 Summary

Tripodal-stabilized gold nanoparticles have been prepared by two different methods; a direct reduction reaction and a ligand exchange reaction. Gold nanoparticles from a ligand exchange reaction were obtained from freshly prepared triphenylphosphine-stabilized gold nanoparticles. The progress of the ligand exchange reaction at various times was studied by NMR titration. Tripodal-stabilized gold nanoparticles were also prepared from direction reduction reactions with sodium borohydride. The reactions were carried out at different ligand-gold core ratios yielding different sizes of gold nanoparticles. Transmission electron microscopy of gold nanoparticles shows that the sizes of gold nanoparticles are relatively big compared to thiolate-stabilized gold nanoparticles prepared from the similar procedures.
Figure 3.12 UV-vis absorption bands of gold nanoparticles prepared by different methods

Figure 3.13 UV-vis absorption bands of gold nanoparticles of different ligand:Au ratios
Figure 3.14 TEM analysis (a: normal, b: magnified) of TPCONHC\textsubscript{18}-stabilized gold nanoparticles prepared by the ligand exchange reaction with a 1:1 TPCONHC\textsubscript{18}:Au ratio
Figure 3.15 TEM analysis of TPCONHC$_{18}$-stabilized gold nanoparticles prepared by the Brust-Schiffrin method with a 1:1 TPCONHC$_{18}$:Au ratio
Figure 3.16 TEM analysis of TPCONHC$_{18}$-stabilized gold nanoparticles prepared by the Brust-Schiffrin method with a 1:10 TPCONHC$_{18}$:Au ratio
CHAPTER IV

FORMATION OF AN INCLUSION COMPLEX OF A NEW TRANSITION METAL LIGAND IN β-CYCLODEXTRIN

4.1 Introduction

4.1.1 Cyclodextrins and Their Inclusion Complexes

Supramolecular chemistry involves the study of intermolecular interactions among involving molecules. The chemical interactions usually include weak chemical bonds, such as hydrogen bonding, van der Waal, and hydrophobic-hydrophilic interactions, but do not involve covalent bonds. These interactions are also classified as the host-guest type interactions. Among studied host-guest systems, cyclodextrins are probably the most popular candidates comparing to other hosts. This is because they are produced in large amount a year from starch and their production costs have been consequently dropped. Their biodegradability also plays a very important role in the selection for host-guest systems.

Cyclodextrins (CDs) are cyclic oligosaccharides containing varied numbers of glucopyranose units. Each D-(+)-glucopyranose unit is linked by an α-(1→4)-bond type. The numbers of repeating glucopyranose units range from 6 to 13 but the most widely studied cyclodextrins contain 6, 7 and 8 glucopyranose units (Figure 4.1). Cyclodextrins
that contain 6, 7, and 8 glucopyranose units are called α, β, and γ-cyclodextrins respectively. This nomenclature is preferred and widely used because the systematic nomenclature is more complicated. These three major cyclodextrins possess a conical cylinder, more specifically a doughnut shape (Figure 4.1). The interior of the cone is hydrophobic because of its alkyl backbone. The exterior surface, however, is hydrophilic due to the presence of hydroxyl groups (Figure 4.2). The secondary hydroxyl groups are aligned at the bigger end of the doughnut structure, while all flexible primary hydroxyl groups are aligned at the smaller rim. However, the larger cyclodextrins with 9 or more glucopyranose units do not exhibit this structural character. The lack of intramolecular hydrogen bonding at C-2 and C-3 leads to collapsed structures and the absence of cylindrical shapes. The volumes and diameters of the internal cavity and other characteristics of α, β, and γ-cyclodextrins are presented in Table 4.1.

When cyclodextrins are dissolved in an aqueous medium, the apolar cavity is filled with water molecules. This interaction is unfavorable due to the hydrophobic-hydrophilic repulsion. If appropriate small organic molecules are dissolved in the aqueous cyclodextrin solution, they will displace high energy water molecules in the internal cavities. This process is also known encapsulation and produces “inclusion complexes.” In solution, this process is in equilibrium. The formation of inclusion complexes and the association constant are presented in equation 4.1. CD represents cyclodextrin, G represents guest and K is the association constant. A pictorial illustration of the complexation is shown in Figure 4.3.
Figure 4.1 Structures of β-cyclodextrin

Table 4.1 Characteristic of cyclodextrins

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of glucose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>molecular weights</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
</tr>
<tr>
<td>solubility in water, g 100 mL⁻¹ at r.t.</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
</tr>
<tr>
<td>[α]₀ at 25°C</td>
<td>150±0.5</td>
<td>162.5±0.5</td>
<td>177.4±0.5</td>
</tr>
<tr>
<td>cavity diameter (Å)</td>
<td>4.7–5.3</td>
<td>6.0–6.5</td>
<td>7.5–8.3</td>
</tr>
<tr>
<td>height of torus (Å)</td>
<td>7.9±0.1</td>
<td>7.9±0.1</td>
<td>7.9±0.1</td>
</tr>
<tr>
<td>outer periphery diameter (Å)</td>
<td>14.6±0.4</td>
<td>15.4±0.4</td>
<td>17.5±0.4</td>
</tr>
<tr>
<td>volume of cavity (Å³)</td>
<td>174</td>
<td>262</td>
<td>427</td>
</tr>
</tbody>
</table>
Figure 4.2 Hydrophobic and hydrophilic sites of cyclodextrins

Figure 4.3 Formation of an inclusion complex in an aqueous solution
4.1.2 Formation of an Inclusion Complex of a Tripodal Ligand in β-Cyclodextrin

Cyclodextrins are one of the best known chiral natural hosts for small organic molecules and it has been the subject of numerous detailed supramolecular chemistry studies.\textsuperscript{119} The fruits of these inquiries include advanced materials for formulations, drug delivery, chiral separations and catalysts for asymmetric synthesis. Many enzyme mimics based on modified cyclodextrins have been developed, yet a catalyst based on the host cyclodextrin’s chiral cavity and a guest transition metal complex active site is yet to be developed. We recently developed a new transition metal ligand based on 2,4,9-trithiaadamantane derivatives. The trithiaadamantane structure represents a $C_{3v}$ chelating ligand and it complexes with several transition metals and metal clusters such as Au, Pt and Ru\textsubscript{3}.\textsuperscript{35} From a structural point of view, the shape of this ligand fits well into the $\beta$-cyclodextrin cavity and the formation of the inclusion complex should break the $C_{3v}$ symmetry of the ligand by the chiral host.\textsuperscript{120,121} The resulting guest-host complex is potentially a new type of asymmetric transition metal ligand suitable for the development of new materials and for chiral catalysis and separation. To develop such an inclusion complex based transition metal ligand, it is necessary to investigate the structure and properties of the 2,4,9-trithiaadamantane/$\beta$-cyclodextrin inclusion complex.
β-Cyclodextrin is perhaps the best known natural host for small organic molecules in the cyclodextrin family.\textsuperscript{1} Among the various known guest compounds of β-cyclodextrin, adamantane derivatives exhibit excellent binding stabilities due to the close match of the structure of the adamantane framework to the inner cavity of β-cyclodextrin such that the distance dependent van der Waals-London dispersion forces can be maximized.\textsuperscript{122,123,124} 2,4,9-Trithiaadamantane-7-carboxylic acid differs from adamantane in that the three carbon atoms at the 2, 4, and 9 positions of the adamantane carbon framework are substituted by sulfur atoms (Figure 4.1). The substitutions produce two major structural perturbations in the adamantane framework: (1) The six membered ring containing the sulfur atoms is enlarged due to the larger van der Waals radii of sulfur than that of carbon; (2) The compound becomes more polar because of the new C-S polar bonds. X-Ray crystal structure and quantum mechanical calculations indicated that the structural perturbation should lead to a tight size match between the 2,4,9-trithiaadamantane guest and the β-cyclodextrin host. The increased polarity of the thioacetal end should increase the water solubility of the compound and reduced the hydrophobicity of the guest. In addition, the thioacetal end is significantly larger than the carboxylic acid end. The graduation in the molecular shape of the guest is comparable to that of the inner cavity of β-cyclodextrin. Therefore, it was hypothesized that 2,4,9-trithiaadamantane derivatives should be selectively oriented in the complex with the larger end at the larger open of β-cyclodextrin to minimize the unfavorable intermolecular forces.
Figure 4.4 2,4,9-Trithiaadamantane-7-carboxylic acid and β-cyclodextrin

4.2 Experimental Section

4.2.1 General Procedures

All $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer unless otherwise noted. NMR spectra were recorded in CDCl$_3$. $^1$H and $^{13}$C Chemical shifts are reported in parts per million relative to the residual CHCl$_3$ (7.27 ppm) and to the CDCl$_3$ signal (77.23 ppm) respectively. $^1$H NMR multiplicity is reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Nicolet NEXUS 870 FT-IR spectrometer equipped with a Thunderdome ATR accessory. Data were reported in wavenumbers (cm$^{-1}$).

Unless otherwise noted, materials were obtained from Aldrich, ACROS and Fisher Scientific and used without further purification. All solvents were reagent grade. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride and benzene were distilled from calcium hydride under argon prior to use. Other reagents were purified by procedure described in the literature. All glassware used was flame dried or oven dried and cooled in the desiccators. Air– and
moisture-sensitive reactions were performed under argon gas (99.99%). The products were purified by vacuum distillation, flash chromatography, preparative TLC, and recrystallization. All the reactions were monitored by thin-layer chromatography (TLC). TLC was performed with 0.2 mm precoated silica gel w/UV 254 on polyester backed plates (Sorbent Technologies). Preparative thin-layer chromatography was performed on 1.0 mm × 20 cm × 20 cm glass supported silica gel plates (Analtech INC.). EM Science silica gel 60 Å (particle size 35-75um) was used for flash chromatography.

4.2.2 Synthesis of Materials

The detailed procedures for the synthesis of TPCOOMe and TPCOOH are described in sections 2.2.6 and 2.2.7 respectively.

4.2.3 Circular Dichroism Study

The CD spectrum was obtained with a JASCO J-500A spectropolarimeter. The concentration of TPCOOH and β-CD were 10 mM and 11 mM respectively in 35% absolute ethanol and 65% doubly distilled water. The CD spectrum was recorded through a 10 mm quartz cuvet. The experiment was carried out at ambient conditions. The original data was converted into a binary file and imported into the Origin (Microcol™ software, Inc.) for generating the graph.

4.2.4 2D \(^1\)H-\(^1\)H NOESY Experiments

The 2D \(^1\)H-\(^1\)H NOESY\(^{125}\) (Nuclear Overhauser Enhancement Spectroscopy) experiment was performed on the complex at 30° C using a Varian INOVA 400 MHz
spectrometer. A $\pi/2$ pulse width of 7 $\mu$s was used along with a mixing time of 100 ms; 16 transients were collected for each of the 2*256 $t_1$ increments. Linear prediction was used in the F1 dimension to improve the quality of the data. The data was zero filled to a 2048×1024 data matrix before Fourier transformation. Data processing was done using Varian’s VNMR software on a SUN workstation.

4.2.5 $^1$H NMR Studies

NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer at 298 K. In the NMR titration measurements, the samples were prepared by varying the ratio of TPCOOH to $\beta$-cyclodextrin in D$_2$O (1~10×10$^{-3}$ M). The NMR samples were allowed to thoroughly mix and equilibrate overnight in NMR tubes before the spectra were acquired.

4.2.6 Titration and Calculation of The Stability Constant K

The NMR titration of the association constant of the inclusion complex was carried out in D$_2$O at 20° C. The NMR samples were prepared from a stock solution of TPCOOH in acetone (1.15 mM). The TPCOOH solution (0.700 ml) was placed in a set of NMR tubes using a micropipet and the solvent acetone was subsequently evaporated under vacuum. The solutions of $\beta$-cyclodextrin were prepared in hot D$_2$O and cooled to room temperature before being transferred to the NMR tube by micropipet. The NMR samples were sonicated and allowed to mix thoroughly. The final volumes of the NMR samples were 0.700 ml. The $^1$H NMR spectra of the samples were recorded and the chemical shifts of $H_a$ and $H_b$ of $\beta$-cyclodextrin were summarized in Table 4.2. The
concentrations of β-cyclodextrin ([β-CD]₀) in the samples were plotted against the chemical shift changes (δᵢ) of the Hₐ and Hₜ of the TPCOOH (Figure 7). The binding constant was determined through the nonlinear curve fitting according to equation 6 derived from Conners’ method as outlined below.

\[
G + H \rightleftharpoons GH
\]  

(4.1)

\[
K = \frac{[GH]}{[G][H]}
\]  

(4.2)

<table>
<thead>
<tr>
<th></th>
<th>[G]</th>
<th>[H]</th>
<th>[GH]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>[G]₀</td>
<td>[H]₀</td>
<td>0</td>
</tr>
<tr>
<td>Equilibrium</td>
<td>[G]₀-[GH]</td>
<td>[H]₀-[GH]</td>
<td>[GH]</td>
</tr>
</tbody>
</table>

\[
K = \frac{[GH]}{([G]₀-[GH])([H]₀-[GH])}
\]

\[
\frac{1}{K} = \frac{[G]₀[H]₀}{[GH]} - [G]₀ - [H]₀ + [GH]
\]  

(4.3)

Because

\[
\delta_{\text{obs}} = \frac{\delta_c[G] + \delta_{GH}[GH]}{[G]₀} \quad \text{(4.4)}
\]

\[
[GH] = \frac{[G]₀\delta_t}{\delta_c}; \quad \delta_t = \delta_{\text{obs}} - \delta_c \text{ and } \delta_c = \delta_{GH} - \delta_c
\]  

(4.5)
From (4.3) and (4.5)

\[
[H]_0 = \frac{1}{K} \left[ G \right]_0 \left( \frac{\delta_c}{\delta_i} - 1 \right)
\]

(4.6)

4.3 Results and Discussion

The formation of inclusion complex between TPCOOH and β-cyclodextrin was evident in the 1H NMR experiments. TPCOOH dissolves slightly in water. When β-cyclodextrin was present in the solution, its solubility increases visibly. Thus, a 1:1 mixture of TPCOOH and β-cyclodextrin (3.5×10^{-3} M) formed a clear solution in D_2O in an NMR tube. At the low concentration limit, this change in the solubility of TPCOOH in water is attributed to the molecular interactions between water insoluble TPCOOH and water soluble β-cyclodextrin. The 1H NMR spectrum of the resulting solution showed significant changes in the chemical shifts of TPCOOH and β-cyclodextrin. Similar phenomena in cyclodextrin inclusion complexes have been observed previously and studied extensively.127 Accordingly, we attributed these spectral changes to the dynamic exchanges between uncomplexed species and the intimately included TPCOOH in β-cyclodextrin in the aqueous solutions. It is worth noting that we did not observe significant line broadening due to the complexation, indicating that the complexation equilibrium is at the fast exchange limit of the NMR time scale at the room temperature. The simultaneous observation of changes in the chemical shift of the
Table 4.2 $^1$H NMR chemical shifts and the corresponding changes of H-3 and H-5 of β-cyclodextrin for the inclusion complex of TPCOOH and β-cyclodextrin

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio(TPCOOH/β-CD)</td>
<td>0.00</td>
<td>0.30</td>
<td>0.50</td>
<td>0.70</td>
<td>1.00</td>
<td>1.50</td>
<td>2.00</td>
<td>3.50</td>
<td>4.50</td>
</tr>
<tr>
<td>δHb (ppm)</td>
<td>0</td>
<td>2.898</td>
<td>2.903</td>
<td>2.897</td>
<td>2.894</td>
<td>2.895</td>
<td>2.894</td>
<td>2.894</td>
<td>2.889</td>
</tr>
<tr>
<td>ΔδH3 (ppm)</td>
<td>0</td>
<td>-0.067</td>
<td>-0.097</td>
<td>-0.135</td>
<td>-0.175</td>
<td>-0.177</td>
<td>-0.177</td>
<td>-0.179</td>
<td>-0.180</td>
</tr>
<tr>
<td>ΔδH5 (ppm)</td>
<td>0</td>
<td>-0.054</td>
<td>-0.080</td>
<td>-0.101</td>
<td>-0.121</td>
<td>-0.123</td>
<td>-0.122</td>
<td>-0.124</td>
<td>-0.125</td>
</tr>
<tr>
<td>ΔδHa (ppm)</td>
<td>0</td>
<td>0.241</td>
<td>0.239</td>
<td>0.237</td>
<td>0.228</td>
<td>0.225</td>
<td>0.224</td>
<td>0.225</td>
<td>0.220</td>
</tr>
<tr>
<td>ΔδHb (ppm)</td>
<td>0</td>
<td>-0.052</td>
<td>-0.047</td>
<td>-0.053</td>
<td>-0.056</td>
<td>-0.055</td>
<td>-0.056</td>
<td>-0.056</td>
<td>-0.061</td>
</tr>
</tbody>
</table>
Table 4.3 Chemical shifts of TPCOOH and the corresponding changes of H_a and H_b of TPCOOH as a function of concentration of β-cyclodextrin in D_2O

<table>
<thead>
<tr>
<th>Entry</th>
<th>[β-CD] (mM)</th>
<th>δ_Ha (ppm)</th>
<th>δ_Hb (ppm)</th>
<th>Δδ_Ha (ppm)</th>
<th>Δδ_Hb (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>4.487</td>
<td>2.841</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.26</td>
<td>4.502</td>
<td>2.845</td>
<td>0.015</td>
<td>0.004</td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
<td>4.503</td>
<td>2.843</td>
<td>0.016</td>
<td>0.002</td>
</tr>
<tr>
<td>4</td>
<td>0.58</td>
<td>4.509</td>
<td>2.851</td>
<td>0.022</td>
<td>0.010</td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>4.515</td>
<td>2.854</td>
<td>0.028</td>
<td>0.013</td>
</tr>
<tr>
<td>6</td>
<td>1.15</td>
<td>4.525</td>
<td>2.862</td>
<td>0.038</td>
<td>0.021</td>
</tr>
<tr>
<td>7</td>
<td>1.64</td>
<td>4.532</td>
<td>2.866</td>
<td>0.045</td>
<td>0.025</td>
</tr>
<tr>
<td>8</td>
<td>2.30</td>
<td>4.546</td>
<td>2.870</td>
<td>0.059</td>
<td>0.029</td>
</tr>
<tr>
<td>9</td>
<td>3.84</td>
<td>4.565</td>
<td>2.876</td>
<td>0.078</td>
<td>0.035</td>
</tr>
<tr>
<td>10</td>
<td>11.5</td>
<td>4.602</td>
<td>2.907</td>
<td>0.115</td>
<td>0.066</td>
</tr>
<tr>
<td>11</td>
<td>23.0</td>
<td>4.602</td>
<td>2.907</td>
<td>0.115</td>
<td>0.066</td>
</tr>
</tbody>
</table>
Figure 4.5 $^1$H NMR spectra of TPCOOH (bottom) and the TPCOOH/β-cyclodextrin inclusion complex (upper) in D$_2$O at room temperature

β-cyclodextrin at H-3 and H-5 also indicated the binding interaction dominated by the inclusion of the TPCOOH guest inside the host β-cyclodextrin cavity.

The formation of the inclusion complex between TPCOOH and β-cyclodextrin was confirmed by electrospray tandem mass spectrometry. When a solution of TPCOOH and β-cyclodextrin in water was electrospray ionized, the corresponding 1:1 complex peak was observed (m/z = 1368 D) in the negative ion mass spectrum. The nature of this ion was confirmed by collision activation of the mass selected ion at m/z =1368 D, which fragmented preferentially into the pseudo-molecular ion of β-cyclodextrin m/z =1133 in the MS/MS spectrum (Figure 4.6).
Figure 4.6 Electrospray MS/MS spectrum of the inclusion complex of TPCOOH and β-cyclodextrin
The detailed host-guest interactions of the TPCOOH/β-cyclodextrin inclusion complex were analyzed using 2D $^1$H-$^1$H NOESY experiment. NOESY has been widely used to obtain through space interaction in 3D supramolecular complexes. The presence of cross-peak A between resonances $H_a$ of TPCOOH and $H$-3 of β-cyclodextrin indicates that these protons are close to each other. Note that the resonance $H_a$ does not exhibit a correlation with the remaining β-cyclodextrin protons. The resonance $H_b$ of TPCOOH exhibits NOE cross-peaks with the resonances of $H$-5(B) and $H$-3(C). This can be attributed to the fact that the $H_b$ protons are in close proximity to both $H$-3 and $H$-5 protons. These interactions are only possible only if the carboxylic acid end group of TPCOOH is included into the smaller end of the β-cyclodextrin cavity and the thioacetal end is located in the bigger rim of the cavity as illustrated in Equation 4.7.

The 2D NOESY study of the inclusion complex was confirmed by CD (circular dichroism) spectroscopy. TPCOOH is an achiral molecule which displays an absorption band at 267 nm. Cyclodextrin is a chiral molecule which does not absorb in the UV-vis region. As shown in Figure 4.8, the TPCOOH and β-cyclodextrin mixture shows a distinctive positive Cotton effect near the UV-vis absorption peak of TPCOOH. Because TPCOOH is $C_{3v}$ symmetric and β-cyclodextrin is $C_7$ symmetric, TPCOOH must be orientated predominately in one direction in the host as indicated by the 2D NOESY spectrum in order to display the characteristic host-induced CD spectrum.128
Figure 4.7 2D NOESY spectrum of TPCOOH and β-cyclodextrin inclusion complex
Figure 4.8 Induced positive Cotton effect observed for the TPCOOH and $\beta$-cyclodextrin inclusion complex in water
The formation of the inclusion complex induces upfield shifts of the resonances for both H-3 and H-5 of β-cyclodextrin. The resonances of TPCOOH shifted down field. The stoichiometry of the complex was calculated by using the anomeric proton H-1 of the host as the internal reference. Plotting the changes in chemical shifts of H-3 and H-5 against the guest/host ratio (r), we obtain two linear lines which have steep slopes at low guest concentration, and level off when the guest/host ratio \( r \geq 1 \), indicating the complex to be 1:1 stoichiometry for TPCOOH and β-cyclodextrin (Figure 4.9). Quantitative analysis of the association constant of the guest and host was achieved by NMR titration in similar experiments. In these experiments, the total concentration of β-cyclodextrin (host) was varied while the total concentration of TPCOOH (guest) was held at constant. NMR spectra of the solutions were recorded. To determine the binding constant (K), the increasing total concentration of β-cyclodextrin ([β-CD]₀) was plotted against the chemical shift change (δᵢ) and the binding constant was determined according to the model described in the equation (4.6).

\[
[H]₀ = \frac{1}{K} - [G]₀ \left( \frac{δᵢ}{δ_c} - 1 \right) \left( \frac{δᵢ}{δ_c} - 1 \right)
\] (4.6)

The binding constant (K) can be estimated from equation (4.6) by performing a nonlinear curve fitting using the data analysis software Origin (Microcal™ software, Inc.). [H]₀ is an initial concentration of the host, [G]₀ is an initial concentration of the guest, δᵢ is the difference between an observed chemical shift of the guest and a chemical shift of the free guest and δᵢ is the difference between a chemical shift of the completely complexed guest and the free guest. As indicated shown in Figure 4.10, an
association constant of $6.63 \times 10^2 \text{ M}^{-1}$ was obtained. Because the host solubility reaches saturation when its concentration approaches 0.01 M, the two data points at higher $\beta$-cyclodextrin concentration were removed from the fitting process.

Figure 4.9 The changes in chemical shifts for H-3 and H-5 of $\beta$-cyclodextrin as a function of guest/host molar ratios in $\text{D}_2\text{O}$ solutions
Figure 4.10 Determination of guest-host association constant from NMR titration

4.4 Summary

In this study, the inclusion complex of 2,4,9-trithiaadamantane-7-carboxylic acid (TPCOOH) in β-cyclodextrin was investigated. The formation of a structurally well defined inclusion complex of 2,4,9-trithiaadamantane-7-carboxylic acid with β-cyclodextrin in pure water by multiple spectroscopic methods, particularly NMR spectroscopy was demonstrated. The NMR and MS-MS studies showed that the guest and host molecules formed a 1:1 inclusion complex. The guest molecule was found to be predominantly oriented with the carboxylic acid end towards the small open and the trithiaacetal end towards the large open of the conically shaped β-cyclodextrin inner cavity by 2D NOESY NMR spectroscopy. Finally, an association constant of 663 M⁻¹ was determined by ¹H NMR titration for the complex at room temperature in neutral D₂O, which rendered TPCOOH to be one of the best guests for β-cyclodextrin. The well
defined structure and the high binding constant of the inclusion complex provided
exceptional hope for the future developments of new supramolecular materials for
separation and catalysis based on this new guest-host complex.
CHAPTER V

CONCLUSIONS AND FUTURE PLANS

5.1 Conclusions

The synthesis of 7-methoxycarbonyl-2,4,9-trithiaadamantane was extensively studied. Existing methods were improved by altering some reaction conditions. The combination of Lawesson’s reagent with boron trifluoride etherate proved to be a vital part for the thionation/cyclization reactions of an ozonized triallyl methyl acetate. Less expensive phosphorus pentasulfide dispersed in either basic alumina or silica gel proved to be an effective choice for the thionation reactions in refluxing acetonitrile. Although the later methods produced the desired product in a lower yield compared to the LR/BF₃ approach, the required purification of the product was simpler.

Several derivatives of 2,4,9-trithiaadamantane-7-carboxylic acid methyl ester were prepared for different applications. All derivatives of the key intermediate were prepared by chemical transformation of the methyl ester group at the position 7 of the 2,4,9-trithiaadamantane ring, while retaining the stable ring system. The introduction of photolabile functionalities, diazomethylcarbonyl and azidocarbonyl groups, into the ring was obtained by trivial nucleophilic substitution reactions of 2,4,9-trithiaadamantane-7-carbonyl chloride with diazomethane and sodium azide respectively. These two
compounds were utilized for the fabrication of photoactive SAMs described previously by Liu.\textsuperscript{106}

2,4,9-Trithiaadamantane-7-carbaldehyde was prepared by the reduction of an ester group with diisobutylaluminium hydride yielding a corresponding primary alcohol, 2,4,9-trithiaadamantan-7-yl-methanol. The alcohol was oxidized by Swern oxidation. The aldehyde underwent the Ohira-Bestmann rearrangement producing an alkyne, 2,4,9-trithiaadamantan-7-yl-ethyne. The resulting terminal alkyne was a precursor for the preparation of oligo(phenyleneethylene)s. Sonogashira cross coupling reaction of the terminal alkyne with selected phenyl iodides gives various oligo(phenyleneethylene)s. 1,4-Bis((7-2,4,9-trithiaadamantyl)ethynyl) benzene, 1,4-bis(7-2,4,9-trithiaadamantyl) butadiyne, \( S\{-4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-phenyl\}\) thioacetate and 4-[4-[7-2,4,9-trithiaadamantylethynyl]-phenylethynyl]-pyridine were prepared by the method mentioned above. These compounds have poor solubility due to their rigid structure.

With the rigid, stable 2,4,9-trithiaadamantane head group, 2,4,9-trithiaadamantane-7-carboxylic acid octadecylamide was used as a stabilizer for gold nanoparticles. The tripodal ligand-stabilized gold nanoparticles prepared from both Brust-Schiffrin and ligand exchange reaction methods are around 86.3 ± 14.2 nm in size. However, the gold nanoparticles prepared by the same method with different ligand to aurate ratio, 10:1, produced bigger gold nanoparticles. The sizes of the latter particles range from 0.71 ± 0.19 \(\mu\)m. Tripodal ligand-stabilized gold nanoparticles prepared by ligand exchange reaction of triphenylphosphine-stabilized gold nanoparticles are 88.2 ± 21.6 nm. Tripodal ligand-stabilized gold nanoparticles were studied by nuclear magnetic
resonance, UV-visible spectroscopies. The sizes of gold nanoparticles were obtained from a transmission electron microscope.

The formation of an inclusion complex between 2,4,9-trithiaadamantane-7-carboxylic acid and β-cyclodextrin was studied. Mass spectroscopy and NMR study prove that the 1:1 inclusion complex was formed. An association constant of 663 M\(^{-1}\) was obtained by an NMR titration method. Circular dichroism showed the host-induced CD phenomena of the complex. 2D NOESY NMR study of the inclusion complex proved that the bigger end of the 2,4,9-trithiaadamantane building block was oriented towards the bigger rim of β-cyclodextrin, while the carboxylic end groups pointed towards the smaller rim. These results demonstrate the formation of a well oriented inclusion complex.

5.2 Future Plans

The scope of future development of this project shall be focused on the following directions:

- The large-scale production of the key intermediate, 7-methoxycarbonyl-2,4,9-trithiaadamantane, can be considered. The current laboratory-scale operations lead to an expensive compound. The cost of reagents, reaction time should be taken into account. If this key compound can be synthesized in a much lower cost, more applications involving this platform may gain more interest.

- More studies on the utilization of the molecular surface anchor as a stabilizer of gold nanoparticles can be extended. As the gold nanoparticles are stable, various modifications of the gold nanoparticles for more applications should be
noted. Chemical transformations of an ester group at the position 7 of an adamantane structure offer the flexibility to change the chemistry of the shell of gold nanoparticles. Biocompatible materials as well as biomolecules e.g. proteins, carbohydrates, DNAs can be attached to the surface anchor leading to the formation of gold nanoparticles for biological applications.

- The surface anchor can also be used in self-assembling applications on flat metal surfaces e.g. gold. Photochemistry of photoactive SAMs can also be performed on a gold surface. Future study can be focused on photolithography of biomolecules on a flat surface. Fabrication of biomaterials and electronic materials using this surface anchor can be an interesting challenge.

In conclusion, the newly developed surface anchor can be applied to other applications requiring a sulfur-containing surface anchor. The surface anchor may, or may not, be suitable to most applications, however, it should be considered along with other similar models due to its rigid, stable and well-defined structure.


34. Lindgren, G. Chemica Scripta. 1976, 9, 220.


51. Oswald, W. *Colliod-Zeitschrift*, 1907, 1, 291.


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131
90. Schaaf, T. G.; Shafigullen, M. N.; Khoury, J. T.; Vezmar, I.; Whetten, R. L.;
    Cullen, W. G.; First, P. N.; Guttierrez-Wing, C.; Ascencio, J.; Jose-Yacamun, M. J.


94. Imahori, H.; Arimura, M.; Hanada, T.; Nishimura, Y.; Yamazaki, I.; Sakata, Y.;


103. Alivisatos, A. P.; Johnsson, K. P.; Peng, X.; Wislon, T. E.; Loweth, C. J.; Bruchez,


106. Haruta, M.; Tsuboda, S.; Kobayashi, T.; Kagehiama, H.; Genet, M J.; Delmon, B.


