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Review Article

A Short Review of Gold-Alkane Thiolate Nanoclusters: Functionalizations, Properties, and Biomedical Applications

Tatenda Justice Gunda[1]*, Bachir Yaou Balarabe[1] and Irédon Adjama[2]

[1]*School of Engineering and Technology, National Forensic Sciences University, India*

[2]*School of Pharmacy, National Forensic Sciences University, India*

***Corresponding Author:** Tatenda Justice Gunda, School of Engineering and Technology, National Forensic Sciences University, India.

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Abstract

A brand-new class of nanoclusters based on thiolates is emerging with fascinating properties as well as behavior (e.g. dispersibility, surface functionalization, color, etc.). Such nanoclusters can be defined as small nanoparticles with properties similar to those of molecules, and thus can be considered to bridge the gap between the nanoparticle and the atom by combining their properties. There are a number of applications where thiols can be used as protective ligands for the stabilization and functionalization of metal nanoparticles, such as silver and gold. Nanoclusters (NCs) have a core-shell structure where the core is made up of a few Metal Oxide (MO) atoms, but it's surrounded by M-thiolate molecules that form a shell(s) around the core in order to prevent particle aggregation. Therefore, thiolate molecules serve as capping agents on particle surfaces to prevent particle aggregation. As well as being used for drug delivery, alkane thiolate NCs can also be used for photobacterial activity, photodynamic therapy delivery of DNA plasmids into target cells, as well as for increasing magnetic resonance imaging through photodynamic therapy. It has also been found that gold nanoparticles can penetrate cells and are not toxic in any way whatsoever. In this paper, we discuss the use of alkane thiolate nanocluster functionalized-gold nanoparticles in biomedicine due to their excellent biocompatibility and attractive chemical and physical properties.

Keywords: Alkane Thiolate; Nanocluster; Functionalization; Toxicity; Imaging; Photobacterial; Antimicrobial; Cytotoxicity

Introduction

A cluster is a small agglomeration (aggregation) of molecules and atoms; we use the term small to describe particles of matter that are made up of a few to thousands of units, each having a diameter measured on a nanometer scale (0.000000001 m) [1]. Unlike their bulk equivalents, they have a number of features that make them distinct from one another. Nanoclusters are not all stable in general, and some are more stable than others. A nanocluster's stability is determined largely by its atom content, the scaffolding around it, and the number of electrons it contains. Surface agents that decrease surface tension are needed in the first and second phases to avoid particle agglomeration and coalescence. The atomic cluster beams were developed by Heer and his colleagues in the 1990s by supersonically expanding atomic cluster sources into a vacuum using an inert gas [2]. In addition to this, magic number stability was also observed in thiolated clusters such as Au25(SR)18, Au38(SR)24, Au102(SR)44, and Au144(SR)60 [3]. These magical clusters are determined by the number of atoms or the size of their centers. As described by Hakkinen., *et al*. a nanocluster is stable if its number of valence electrons meets the shell closure of its atomic orbitals ($1S^2$, $1P^6$, $1D^{10}$, $2S^2$ $1F^{14}$, $2P^6$ $1G^{18}$, $2D^{10}$ $3S^2$ $1H^{22}$) [4,5]. Since gold (Au) and silver (Ag) can bind sulphur so easily, thiols or thiolates are widely used (Figure 1). For decades, scientists have studied how to control particle size

and shape and correlate their optical and structural properties. As a result of recent developments in the scientific community, scientists' attention has been turned to nanoclusters made up of M-thiolates [6-8]. Thiolates in nanocluster form are a new class of nanomaterials that exhibit properties and behaviors that differ from those of M-nanoparticles (e.g., in terms of dispersibility, surface functionalization, color) [9-12]. The thiolate molecules act as capping agents on the particle surface in order to prevent particle aggregation and to prevent particle separation. In contrast, the NC, on the other hand, has a core-shell structure, which consists of a few MO atoms that form a core, which is surrounded by M-thiolate units which form shells around the core [13]. A number of studies have been conducted that utilized coordinating groups like phosphines to stabilize M thiolate nanoclusters. There have been many different names that have been given to nano-clusters since they were first discovered, ranging from superatoms to nano molecules to molecular nanoparticles to quantum clusters to monolayer shielded nanoparticles (indicating that, due to the small minuscule size of these nanoparticles, their surface was protected and covered with a monolayer of the surface protecting molecules rather than just being capped with a few of them as is the case with nanoparticles) [14]. Monodispersity, one of the most advanced NC synthesis processes, has enabled x-ray crystal structure identification of Au102 (mercaptobenzoic acid) 44 NCs [15]. When compared to the bulk and nanoparticles of the corresponding NCs, it is observed that there is a significant variation in the structure of the identified NCs. This paves the way for further research into their unique properties in the future. Due to these outstanding properties, it has the potential to be used in a wide range of fields, including drug screening, sensing, image-guided cancer therapy, gene delivery, solar light harvesting, diabetic medicine, water purification, imaging, and diagnostics, which all have great applications in the near future [16-20]. Further concerns arise when thiolates and metals dominate the system. There are well-known self-assembling reactions involving alkanethiols and metals. When M cations react with alkanethiol, polymeric complexes (M+ alkanethiols) form with a lamellar structure that is twice as long as the alkane chain in the reaction, as well as two-dimensional (2D) self-assembly monolayers (SAMs) [13,14]. NCs protected by thiolates have a strong bond between the metal atoms and the thiolate ligands. Due to their exceptional stability in solution, the NC community has been working hard to develop efficient synthetic techniques for thiolate-protected metal NCs. In this way, atomically precise thiolated NCs have been produced [11]. In recent reviews, surface chemistry engineering of noble metal clusters, controllable synthesis, and catalytic applications of nanoclusters have been discussed [21-25]. We discuss in this paper the application of alkane thiolate nanocluster functionalized-gold nanoparticles in biomedicine as a result of their excellent biocompatibility and attractive chemical and physical properties.

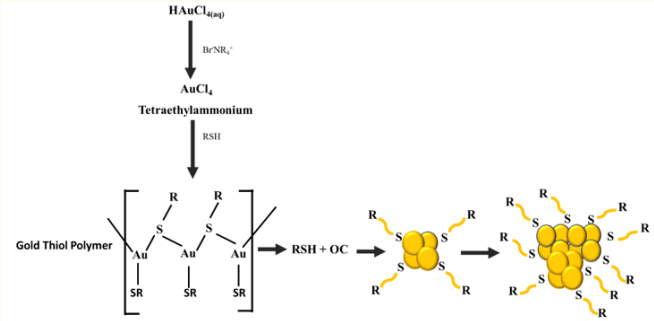

Figure 1: Synthesis of a thiol gold nanocluster where the R group can the alkane by using the Brust-Schiffrin method.

Nanoclusters functionalisation

Silver and gold nanoparticles can be stabilized and functionalized with thiols as protective ligands. The reason is that they are highly attracted to metal surfaces that are exposed. Surface-protecting ligands, such as thiols, have been studied since the first monolayers on gold surfaces were self-assembled a century ago [26,27]. The binding strength of a thiolate to gold is extremely close to the binding strength of two gold atoms together. In this development, thiolate ligands appear to have the ability to alter the current gold-gold contact, resulting in the formation of a gold-sulphur interface [28]. A covalent interaction between gold and thiols makes thiols an excellent protective ligand in the synthesis and functionalization of metal nanoparticles [14]. Consequently, thiolate-protected metal NCs are expected to become more prevalent in the future (or thiolated NCs for short) [26]. In Figure 2 below, the stages for protecting metal are outlinedThe most widely used ligands for synthesizing, stabilizing, and functionalizing metal NCs are those with thiols. There are many thiol-containing compounds (such as mercaptobenzoic acid and lipoic acid), thiol-containing peptides

(such as tri-peptide, and glutathione), thiol-containing polymers (such as SH-PEG), and thiol-containing amino acids (such as cysteine). In addition to being functional ligands for metal NCs, they have the potential to be used in a number of medical applications [26].

The thiol-terminated ligands on the surface of Au NCs may enhance their stability, according to Yuan., *et al*. In recent studies, negatively ionized thiolate ligands on Au25 NCs co-located with positively charged or neutrally charged thiolate ligands exhibit distinct optical absorptions at approximately 780 and 980 nm. In addition to the surface charge anisotropy of the thiolated Au NCs, multiple charged ligands may have contributed to the observed absorption. Figure 2 illustrates this. New avenues for exploring the physical world may be opened up by choosing the right surface ligand for metal NCs [11]. NCs with alkane thiolated caps can be examined using Atomic Force Microscopy. Using AFM tips functionalized with force spectroscopy, we can determine the chemical interactions between alkane thiolate NCs and other materials. As shown in figure 2, one substance is attached to an AFM tip, while the other is attached to a substrate.

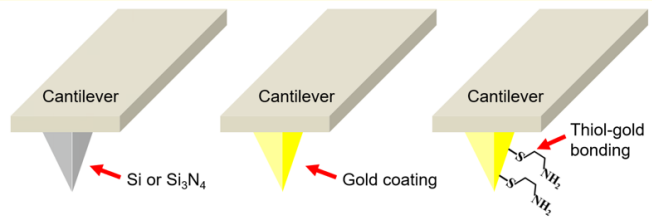

Figure 2: Chemically functionalized Atomic Force Microscopy.

Surface modification

Nanomaterial surfaces and biomolecules interact in order to facilitate the conjugation of biomolecules to nanoparticles. As a consequence, the use of nanoparticles for desirable purposes will require appropriate surface modification. As far as biological applications of Au NPs are concerned, surface modification can be classified into the following categories:

- The use of nanoclusters for therapeutic purposes is becoming increasingly popular. There is a common perception that drug distribution is a major concern; therefore, alkane thiolate nanocluster conjugates are essential because they reduce the length of time a drug is removed from the circulation via the reticuloendothelial system (RES). A longer circulation time for the nanocluster in the system is required in order for it to remain active.
- Additionally, the surface modification of alkane thiolate nanoclusters is likely to improve the nanoparticles' adhesion to the targeted and therapeutic compounds intended to be targeted by the nanoparticles.
- As well as improving the stability of alkane thiolate nanoclusters, surface functionalization can also prevent or reduce the aggregation of alkane thiolate nanoclusters.
- A further concern is the cytotoxicity of the original capping ligands on specific alkane thiolate nanoclusters, such as alkane and thiols; surface modification of the nanocluster is an acceptable cure. As synthesized alkane thiolate nanoclusters, their surface ligands are generally incompatible with human health. In contrast, alkane thiolate nanoclusters, which are chemically inert and do not interact materially with biomolecules, are considered safe and biocompatible [29].

Metal core modification

There may be novel optical, electrical, or physicochemical properties in metal NCs with modified metal cores. One of the most recently developed metal core modification methods is heteroatom doping, which can be controlled by using a chemical procedure that has been finely constructed. A number of effective approaches have been developed over the past decade in order to produce metal nanocrystals with atomic precision, especially thiolate-protected Au nanocrystals [11]. Thiolate-protected metal NCs have a strong bond between their metal atoms and their thiolate ligands. As thiolate-protected metal NCs are extremely stable in solution, the NC community has been working hard to develop efficient synthetic approaches. Consequently, a series of atomically precise thiolated NCs were produced (Figure 3).

Biomedical applications of gold-thiolated nanoclusters

It has been more than a decade since there has been significant progress in the development and use of noble metal nanoparticles that have diameters ranging from 2 to 100 nm in biomedical applications [19,26,30]. Here is a list of some of the applications

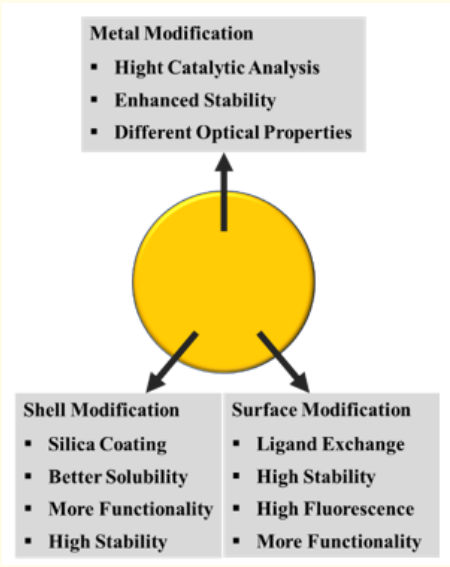

Figure 3: Illustration of the various methods of functionalization and the effects they pose on the properties of a typical core-shell metal nanocluster.

as well as some of their advantages and disadvantages as shown in table 1. As a result, many of these applications rely heavily on optical properties like absorption, luminescence, surface scattering, and surface enhancement. The size and shape of spherical Au nanoparticles (NPs) of 5-100 nm often exhibit a significant absorption peak at 520 nm, which is also known as the surface plasmon resonance (SPR) peak. As a result of light excitation, the SPR peak is generated by the collective excitation of free electrons [22,31].

Enhancing magnetic resonance imaging (MRI)

By collecting and filtering proteins from a mixture, and by providing localized stresses to cells, magnetic nanoclusters can enhance MRI imaging by collecting proteins from a mixture and filtering them from the mixture [27,32,33]. Due to the fact that metal nanocrystals exhibit different levels of absorption energy,

Application	Advantages	Disadvantages	Type of metal	Ref
Imaging	Better resolution	can be affected by magnetic field if they grow too large	Au	[11]
	Easily detected			
	Allows tracing			
	Can be used for detection and separation			
Drug delivery	Non toxic		Au	[33,34]
	Target specific			
	Fast and efficient			
	Does not trigger any immune responses			
	Highly permeable			
Photodynamic therapy	Easily syntheized	Light sensitive	Au, Ag	
	Non toxic			
Photobactericidal activity	Can be activated at low flux levels		Au, Ag	[35,36]
	Efficient			

Table 1: Different applications of nanoclusters.

good photostability, and bright luminescence, they are intriguing candidates for biological research [34]. It is suggested that the advancement of functionalization methods, such as the conjugation of receptor molecules on the NC surface, may make it easier to use functional metal NCs for protein detection in the future. Chang., *et al*. developed a competitive homogeneous fluorescence quenching approach for protein detection by conjugating PDGF AA (platelet-derived growth factor AA) with a fluorescent Au NC. Thiol derivatives-conjugated aptamer-conjugated Au NPs are the donor, while allocated composites are the acceptor. Through resonance energy transfer via the interaction with anti-PDGF AA aptamer and PDGF, Au NPs reduced the fluorescence of Au NCs. However, free PDGF can restore the fluorescence of PDGF-modified NCs via competitive binding. In addition, the same group developed a fluorescent sensor for Concanavalin A (Con A) and Escherichia coli using water-soluble fluorescent Au NCs. Mannose-protected Au NCs were found to be able to detect Con A with extraordinary sensitivity using the aggregation-induced fluorescence quenching technique (LOD 14 75 pM). By contrast, when the probes were incubated with E.coli, the mannose-protected Au NCs adhered to the bacteria, creating brilliantly illuminated clusters of cells. Based on the linear relationship between the fluorescence of the Au NCs and the concentration of E.coli, the LOD was calculated. 7.20 105 cells/mL were counted. These applications require the surface to be functionalized with alkane thiolates in order to bind with the target. According to Love., *et al*. iron platinum nanoparticles (FePt) can be functionalized using thiol chemistry. Separations can be achieved with these [35]. With vancomycin, a thiol derivative, Gram-negative and Gram-positive bacteria were trapped at a concentration of 102 colony-forming units per millilitre (CFU/ml). The level is low, and standard techniques cannot detect it [11]. In addition to biosensing, Au NCs can also be used for bioimaging [36,37].

Drug delivery

Increasingly, alkane thiolate nanoclusters are being used as drug delivery vehicles in a variety of applications [38]. They are characterized by a number of inherent characteristics that make them a very promising means of delivering medicines. We have been able to produce controlled productions of various sized particles (from 1 to 150 nm) that have a minimum size dispersion, such as gold nanoclusters, with a controlled production process [39]. In addition to the monolayers, multifunctional monolayers may also be formed by ligand exchange processes. Because of this structural diversity, particle surfaces can be used to carry a wide variety of targeted agents and chemotherapeutics. Additionally, the gold core is non-toxic, biocompatible, and inert. The release and transport of drugs are essential for the proper functioning of a DDS. It is possible to load pharmaceuticals onto nanocarriers through non-covalent interactions or through covalent conjugation by using a prodrug that is processed by the cell in order to load the drugs onto the carrier [40]. As a result of the functional diversity of their monolayers, AuNPs provide an ideal substrate for DDS design thanks to their functional diversity. Chemotherapeutic drugs are now delivered directly into the bladder through the intravesical method in cancer treatment [41-43]. Intravesical routes can also benefit from nanocarriers that adhere to the mucosal surfaces of the urine bladder. As a result of the nanocarriers' ability to attach to the mucosal epithelia, medications are more likely to be retained in the urine bladder. Through this method, the medicine is able to resist drug wash-out caused by urination. Recently, Bernkop-Schnurch., *et al*. reported that thiolated nanoparticles generated by ionic gelation of thiolated chitosan with tripolyphosphate can be used for intravenous delivery of thiolated drugs [44]. This conjugate of paclitaxel-AuNP is made by combining a linear analogue of paclitaxel with a hydrophilic carboxyl-terminated linker (hexamethylene glycol) that is anchored at the C-7 position of paclitaxel and may be directly interconnected with 4-mercaptoethanol-functionalized Au particles with a diameter of 2 nm. The C7-OH group was selected as the location of attachment because the structure-activity relationships reported for paclitaxel indicate that chemical changes to this site have no significant effect on the ability of the drug to halt cell division processes in cancer cells. On the other hand, when the C2′-OH group is modified, it results in either a significant decrease or completely elimination of biological activity when modified. This differs from the other groups. Similar paclitaxel compounds have been reported to be altered at the C2′-OH group, but these cases rely on enzyme activity that can unmask this hydroxyl group during *in vivo* mechanistic studies [40].

Photodynamic therapy

A novel growing approach that involves the use of light-sensitive medical treatment or therapy to get rid of aberrant cells involves

the use of light as a means of destruction. The photosensitizing chemical ingredient will be combined with molecular oxygen in order to cause the aberrant cells to die as a result [45]. By applying sodium azide to brominated alkanethiol capped gold nanoclusters, they become azide functionalized nanoparticles which can be then photoactivated and conjugated with any molecule containing an alkyne group after they have been treated with sodium azide. The simplicity of the synthesis, the non-toxicity of gold, and the photon absorption cross-sections of gold make it suitable for the study of photodynamics. To label cancer cells with alkanethiol gold nanoclusters *in vivo* and *in vitro*, ligand exchange reactions are needed along with conjugation with a suitable target compound against cancer markers [46-48].

Photobactericidal activity

Today, antibiotic-resistant microbes have become one of the most serious concerns in modern medicine. It is possible to kill specific types of bacteria with the help of bactericidal medicines [49]. In order to be able to achieve photobactericidal activity, a bright white light source or a UV activator is usually required. It has been suggested that a photobactericidal polymer may be used. This polymer is composed of a crystal violate and a thiolated gold nanocluster. It is activated by low flux levels of white light at an average of 312 lux. Nanoclusters of thiolated gold are activated by the presence of bacteria to promote bactericidal activity. In hospitals and other healthcare facilities, Staphylococcus aureus is the most common pathogen and Escherichia coli is the most common pathogen. It is thought that these bacteria cause a wide range of ailments in humans and have developed a resistance to most medications. It is possible to combat both of these infections by encapsulating a thiolated gold nanocluster within a photobactericidal polymer. A significant reduction in the number of live bacteria in the environment has been observed due to the bactericidal activity [46,50-52].

Delivery of DNA plasmids to a cell

Transferrin, a protein used for receptor-mediated gene transport via endocytosis, was attached with thiols. As a result of electrostatic interactions with the amino group of 3-(2-aminoethyl) dithiol propionic acid, the DNA plasmid was located on the NCs segments. Using the NCs technique, DNA plasmids were delivered into the appropriate cells [53]. Other applications include antimicrobial activity [26,54], biosensing[34], tumour targeting [55].

Toxicology

Depending on the type of nanomaterials we use to construct our nanocluster, we will be able to determine the cytotoxicity of the cluster. There are a number of metals that can be used to create clusters, including silver, gold, and iron. There is a rapid advancement in the development and commercialization of nanomaterials. There may be unintended detrimental consequences for the environment and human health as a result of the characteristics that make nanosized structures so attractive. The safe use of nanotechnology will be enhanced if we have a comprehensive understanding of nanoparticle toxicity. A major component of the hazards of AgNP exposure to human health and the environment are the effects of Ag1 ions and Ag nanoparticles [22,56]. Due to the sheer bioavailability of the particles, different routes of exposure may result in different hazards depending on how the particles are absorbed. All of these factors may affect the surface properties of AgNPs, impacting their stability, solubility, and toxicity. A better understanding of sublethal effects will aid in assessing their potential detrimental impact on human health. It is not intended to create lists of genes or proteins that are up- or down-regulated after treatment, but rather to develop adequate prediction models for early detection of potential nanoparticle toxicity. There is a major concern about toxicity. Some reports suggest that nanoclusters can be eliminated from the body through the urinary system [24]. The toxicity of these nanoclusters may become an issue if they are used *in vivo* for treatments and diagnostics. Since AgNCs can break down into Ag(0), they can be tricky [55]. The performance of metal NCs in biological applications is better than that of their nanoparticle counterparts. *In vivo*, metal NPs cannot pass through the renal barrier, causing severe adverse effects in the liver and spleen. However, their ultrafine size allows them to be effectively removed from the body without causing significant harm [26]. AgNPs are widely used in consumer goods, environmental treatments, and biological applications due to their distinctive physical and chemical properties. Humans and other creatures are being exposed to AgNPs at an increasing rate, but there is little knowledge of their potential dangers, both short- and long-term [33,57]. The physical and chemical properties of gold nanoclusters are remarkable. In cancer therapy, gold is easily functionalized, which makes it possible to modify the surface and use it as a drug carrier. In view of the fact that gold nanoclusters are inert and non-toxic, they are considered to be relatively safe [58,59]. There has

been an investigation of the cytotoxicity of gold nanoclusters on leukaemia cell lines. In the study, gold nanoclusters penetrated cells and were not toxic. Other studies, however, indicate that the cytotoxicity of gold nanoclusters depends on their dosage and stabilizer. Cancer cells and human liver cells exhibit varying levels of cytotoxicity [60,61]. While gold particles are non-toxic, they have been widely used in a wide range of biological applications, including cancer treatment [44], pharmaceutical delivery [46], and so on [56]. Silver nanoclusters are often damaging to biological objectives because silver ions infiltrate into cells and eliminate them over a specific level. As a result, they can only be employed for restricted imaging and antimicrobial applications [22,56].

Conclusion

A brief overview of gold-alkane thiolate nanocrystals was provided in this review article, along with recent advances in their functionalization and biomedical applications, which are due to gold-NCs' unique properties, including their attractive physical and chemical properties, as well as their superior biocompatibility [19,21,62]. Despite the fact that this is still novel territory, it is one that needs to be explored. As a result of recent improvements in metal nanocrystal synthesis and surface functionalization, these functionalized nanocrystals are now finding application in biological applications [26]. It is possible to further functionalize the surface functional groups on nanoparticles. Identifying the right ligands and balancing surface charge and hydrophobicity are essential to achieving the desired results [63]. As a result of a reaction with fluorescein maleimide, it was demonstrated that thiolated nanoparticles could be fluorescently identified. There is a possibility that acrylated nanoparticles could be used for post-functionalization of proteins by interacting with proteins containing thiols. Due to the rapid advancement of medical procedures and nanotechnology, alkane thiolate nanoclusters are expected to have additional applications in biomedical applications in the coming years [19,22,55].

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Authors' Contributions

Data collection and manuscript writing were equally shared among all authors.

Data Availability

All data have been included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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