The effect of temperature and ligand structure on the solubility of gold nanoparticles

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Keywords: gold nanoparticles, computational chemistry, solubility, ligand length effect, temperature effect

Abstract
In order to investigate the effect of ligands structure, and temperature on the solubility of the smallest crystallographic gold nanoparticle, Au$_{18}$S$_{14}$, quantum mechanical calculations, and molecular dynamics simulations have been performed. Ligands including 2-dimethyl amino Ethan thiol, 4-mercapto benzoic acid, and 3-mercapto-propionic acid have been used to study the effect of ligand type and temperature, and 4-mercapto butyric acid and 5-sulfanyl pentanoic acid ligands have been used in comparison to the 3-mercapto-propionic acid ligand to study the effect of carbon-chain length differences. Furthermore, three different temperatures: 290, 300, and 310 kelvin have been used to study the effect of temperature. The optimized structures of nanoparticles, electronic band-gap, light absorption, dipole moment values, and hardness were obtained using quantum mechanical methods. Further, hydrogen bond number, root mean squared displacement, the moment of inertia, radial distribution functions, mean square displacement, and solvent accessible surface area parameters were studied by molecular dynamic simulation methods. All quantum mechanics analyses indicated that functionalization improves the nanoparticle's electronic features, solubility, and stability. The studies which have performed with the molecular dynamics simulations indicated that increasing the temperature leads to form more hydrogen bonds between gold nanoparticles and water, making them more soluble. Also, the structures with a longer carbon chain of ligands have stronger interactions with solvent but their mobility in the water can be decreased. From all data of this work, it can be concluded that the 4-mercapto benzoic acid is the ligand that makes more solubility and stability for the mentioned gold nanoparticle.

1. Introduction

Metallic nanoparticles have attracted great interest over the past two decades because of their wide range of applications in medicine, microelectronics, catalysis, biotechnology, optoelectronics, drug delivery, and so on [1–3]. Nanoparticles have high surface-to-volume ratios so their properties are dependent on their size and structure and they have better physical and chemical homogeneity compared to bulk metals [4, 5]. Small metal nanoparticles are catalytically active and have a high tendency to aggregate or interact with the outer environment because of their surface dangling bonds which need to be completed. Such high reactivity and low stability features of nanoparticles diminish their utility [6–10]. Some stabilizers based on polymers, surfactants, and chelating groups can be used on gold nanoparticles, so they usually have a structure including a metallic core and several stabilizer molecules like branches with terminal functional groups which play an important role in increasing their solubility and stability in solvents [11–14]. In addition, some noble metal nanoparticles have the surface plasmon resonance (SPR) feature which can be affected by their size and environment or the type of ligands adding to the surface[15–17]. These nanoparticles can be used in many optical applications and are used often instead of semiconductor (SC) material because they have a good ability to absorb visible light that is
opposed to the SC material’s ability that is limited to absorbing light in the ultraviolet region of spectra [18]. Gold nanoparticles have attracted considerable attention among other metal nanoparticles because they have good properties such as localized SPR, high biocompatibility, high catalytic activity, therapeutic application, and low toxicity that make them useful in a wide range of research fields [19–21]. Bare gold nanoparticles have low solubility so they can’t have good applications in biological fields. The surface of gold nanoparticles is susceptible to many chemical modifications, thus their functionalization with proper molecules can make them more soluble and improve some of their applications such as drug delivery [22–28]. Gold nanoparticles are often protected by self-assembled monolayers (SAM), that most of them are alkanethiols [29]. In many studies, the effect of different densities of ligands on the stability of nanoparticle has been studied and it was found that some ratios of the metal number to ligand numbers can make better stability for them, thus these ratios are called magic numbers, for example, some of these clusters are \( \text{Au}_{10} \text{SR}_{10}, \text{Au}_{15} \text{SR}_{15}, \text{Au}_{18} \text{SR}_{18}, \text{Au}_{23} \text{SR}_{23}, \text{Au}_{25} \text{SR}_{25}, \text{Au}_{33} \text{SR}_{33}, \text{Au}_{39} \text{SR}_{39}, \text{Au}_{46} \text{SR}_{46}, \text{Au}_{55} \text{SR}_{55}, \) and \( \text{Au}_{59} \text{SR}_{59} \) [30–32]. Many other studies have been conducted to investigate the effect of different functional groups on the solubility, SPR, and other features of gold nanoparticles that some of them present here: Susanna Monti et al studied self-assembling, stability, and dynamics of gold nanoparticles that functionalized with cysteine-based peptides using classical molecular dynamics simulations in the solvent phase and found that these biomolecules protect the surface of gold nanoparticles from the action of the solvent and also prevent them from aggregation [33]. Ryo Iida et al investigated the thermo-responsive assembly of gold nanoparticles with three different sizes (diameters of 3, 5, 10 nm) that functionalized with oligo (ethylene glycol) ligands. Their results showed nanoparticles with a diameter of 5 nm being coated with ligands without alkyl head failed to aggregate in the temperature range of 20–70 °C while nanoparticles with ethyl, iso-propyl, and propyl headed ligands assembled at temperatures of 56, 33, and 19 °C. Therefore, it was found that assembly temperature can be affected by the hydrophobicity of ligands alkyl head [34]. Vasumathi Velachi et al examined the structural properties of gold nanoparticles with three different arrangements i.e. random, patchy, and Janus in the presence of some hydrophilic and hydrophobic alkyl thiol ligands using atomistic simulations. They found that the hydration of functionalized gold nanoparticles depends on molecular composition and also on the organization of them [35]. Silvia Barbosa et al evaluated gold nanostructures decorated with an anticancer drug, doxorubicin, and targeting ligand, folic acid, with experimental approaches. Their studies indicated that cellular uptake enhances when targeting ligands are used [36]. Jia-Qi Lin et al performed coarse-grained molecular dynamic simulations to investigate the dynamics of 2.2 nm protected gold nanoparticles in solvents. They studied the effects of ligand length, ligand terminal chemistry, solvents, and temperature on gold nanoparticles and found that with increasing the length of ligands, the aggregation of molecules tends to be more spherical and with increasing the polarity of ligand tail groups, their tendency of aggregation becomes weaker. Furthermore, the increasing temperature can accelerate their aggregation process [37]. Elena Heikkila et al studied 2 nm gold nanoparticles having alkanethiol ligands with carboxyl-terminal groups and they used \( \text{Cl}^-/\text{Na}^+ \) ions to make the positive and negative particles. Their results revealed that ligand on the nanoparticles is significantly flexible and both positive and negative ones have the same solubility [38]. Brian J. Heinz and his group investigated the effect of different functional groups such as \( \text{CH}_3, \text{OH}, \text{NH}_2 \) on the binding energy, density, and solubility of gold nanoparticles. The results showed that with increasing the electronegativity of terminal groups, their solubility becomes better [39]. Antonios G. Kanaras et al studied ligand-stabilized, water-soluble gold nanoparticles of two different sizes (2–4 nm and 5–8 nm) with monohydroxy (1-mercaptopoundec-11-yl) tetraethylene glycol ligand and they found that these nanoparticles are as stable as alkyl thiol-capped structures and they fail to aggregate in solution [40]. Christopher J. Ackerson et al in an experimental study compared the effect of different water-soluble thiolate ligands such as 3-mercaptopropionic acid, 4-mercaptoproic acid, cysteine, 4-mercaptoproic acid, and others on the stability and solubility of gold nanoparticle with 55 atoms (\( \text{Au}_{55} \)) [41, 42]. Many other studies evaluated gold nanoparticle’s different properties in the presence of various ligands on them. The present study aimed to investigate the effect of three different ligands: 2-dimethyl amino ethanethiol, 3-mercaptopropionic acid, and 4-mercaptoproic acid on the solubility of \( \text{Au}_{18}\text{S}_{14} \) nanoparticle, and the effect of temperature on molecules with these mentioned ligands which have the average sizes of >2 nm. Such ligands have been selected because they have a high ability to improve the solubility of nanoparticles and are very common ligands being used for gold NPs in many experimental studies. Then, two other molecules: 4-mercaptoproic acid with the four-carbon chain and 5-sulfanyl pentanoic acid with the five-carbon chain were chosen and their results were compared to the particle with 3-mercaptoproic acid ligands having a chain with three carbon for investigating the effect of ligand length on the stability and solubility of the gold nanoparticle. The general formula of gold core in all particles is \( \text{Au}_{18}\text{S}_{14} \) that is the smallest crystallography thiolated gold nanoparticle being found so far (average size of 1.1 nm) and containing 18 gold atoms connected with 14 sulfur atoms. These 5 atoms make nanoparticles more susceptible to adding above mentioned ligands to make thiolate-protected gold nanoparticles. So in resulted molecules, there are 14 number of each SR groups on the core structure and known as alkanethiols [56–b]. Calculations in this study were performed using quantum mechanical and molecular dynamic simulation.
methods and some parameters have been examined including HOMO-LUMO band-gap, light absorption behavior, dipole moment values, hardness, radial distribution functions (RDF), hydrogen bonds, solvent accessible surface area (SASA) parameter, root mean square deviation (RMSD), root mean square fluctuations (RMSF), the moment of inertia, and mean square displacement (MSD) diagrams.

2. Methods

2.1. Quantum mechanics
Quantum mechanics calculations and structure optimization of all molecules were conducted with Gaussian 03 software [43]. Calculations were performed using the density functional theory (DFT) method for ground states, and the time-dependent density functional theory (TD-DFT) method for excited states (n states = 30) using Lanl2dz basis set [44] and B3LYP hybrid function [45–47]. All computations were performed in the solvent phase using a continuum solvent model (C-PCM) [48, 49].
2.2. Molecular dynamic simulation

Molecular dynamic simulations were performed for all functionalized gold nanoparticles in the box of size $5 \times 5 \times 5$ nm$^3$ using the NVT statistical ensemble with a time step of 2 femtoseconds by GROMACS software [50].

| Compound                                      | E HOMO (eV) | E LUMO (eV) | Band-gap (eV) |
|-----------------------------------------------|-------------|-------------|---------------|
| $\text{Au}_{18} \text{S} \text{I}_{14}$       | $-6.30475$  | $-5.68812$  | $0.61663$     |
| $\text{Au}_{18}(\text{S-2-dimethylamino Ethan thiol})_{14}$ | $-5.21899$  | $-2.56147$  | $2.65752$     |
| $\text{Au}_{18}(4\text{-mercapto benzoic acid})_{14}$ | $-5.3341$   | $-2.66297$  | $2.67113$     |
| $\text{Au}_{18}(3\text{-mercapto propionic acid})_{14}$ | $-5.56458$  | $-2.95087$  | $2.61371$     |
| $\text{Au}_{18}(4\text{-mercapto butyric acid})_{14}$ | $-5.4814$   | $-2.8672$   | $2.6142$      |
| $\text{Au}_{18}(5\text{-sulfanyl pentanoic acid})_{14}$ | $-5.231$    | $-2.6294$   | $2.6016$      |
All systems hydrated with 4000 water molecules using the SPC/E model for them [51]. At first, the position of molecules was restrained and equilibration was conducted at NVT ensemble for 1 ns, and then 50 nanosecond simulations have been performed on them in a production run using the leap-frog integrator [52] with the aid of the UFF force field [53]. Simulations were carried out at temperatures 290, 300, and 310 K. Shake constraint algorithm for h-bonds, Verlet cut-off scheme, V-rescale thermostat [54, 55], periodic boundary conditions (PBC) for all directions (x,y,z), and Van der Waals cut-off distance of 1.0 nanometer have been applied for all calculations. All analyses have been performed in the last 5 ns of simulation.

3. Results

The results of this study are presented in the following two main sections: quantum mechanics and molecular dynamic simulation analysis about the solubility and stability of thiolated gold nanoparticles. In the first section (quantum part) the effect of type and length of ligands on the electronic features and stability of structures, and in the second section (simulation part), the effect of ligand structure and, the temperature on the solubility of molecules are studied:

3.1. Electronic structures and quantum parameters

3.1.1. Optimized geometry, energy level and band-gap of molecules

The correct crystallographic structure of Au$_{18}$SR$_{14}$ nanoparticle was taken from the Cambridge Crystallographic Data Centre [56]. Then, different ligands were substituted on their sulfur atoms, and the final structures were optimized by Gaussian 03 software. All optimized structures are presented in figure 1. The energy of HOMO, LUMO states of molecules, and their band-gap after optimization can be a criterion of their stability. Indeed, the structures with bigger band gaps are more stable and have a lower tendency to interact with the outer environment. Therefore, in this part of the calculations, the values of HOMO, LUMO energies, and band-gap for structures are presented in table 1. Data indicates that the functionalized gold NPs have the wider HOMO-LUMO band-gap rather than the naked one, thus they need more powerful radiations to excite and also are more stable. The structure with 4-mercapto benzoic acid ligands has the most value of band-gap and three molecules with different carbon chain length ligands i.e. the nanoparticles with 3-mercapto propionic acid, 4-mercapto butyric acid, and 5-sulfanyl pentanoic acid ligands have almost the same values as the band-gap. Gold nanoparticles should have the ability to absorb light in the visible or near-infrared region of the light spectrum in biological applications such as hyperthermia, to be safe for biological tissues [57, 58]. Therefore, the next section investigates the absorption spectra of these molecules.

3.1.2. Light Absorption behavior

In this section, the light absorption behavior of gold nanoparticles with 4-mercapto benzoic acid, 2-dimethyl amino Ethan thiol, and 3-mercapto propionic acid ligands is examined by TD-DFT calculations. Data are presented in table 2 and their spectra are given in figure 2. Since the band-gap values of two other particles with 4-mercapto butyric acid and 5-sulfanyl pentanoic acid ligands are quite the same as that for the particle with 3-mercapto propionic acid ligands, thus it was no need to take the absorption spectra of them. As mentioned before, nanoparticles are affected by radiations to killing cancerous cells in some biological applications such as hyperthermia and it is important that the radiated light has low energy and fails to damage the body’s normal cells. The data of this study indicate that all stabilizer ligands being used on gold nanoparticles make the band-gap bigger but their absorption wavelengths are in the visible region (400–700 nm) yet, thus this functionalization cannot have harmful effects and maintain the safety of gold nanoparticles for biological applications. Data also show that despite the small size of functionalized gold NPs, all of them can have local SPR.

3.1.3. Dipole moment values

Dipole moment can be defined as an asymmetry of charge distribution in a molecule and is a criterion of the degree of charge separation. The dipole moment value of a structure can indicate the amount of its solubility.

| Compound | λ$_{max}$ (nm) | Excitation energy (ev) | Oscillator strength (f) |
|----------|----------------|------------------------|-----------------------|
| Au$_{18}$(4-mercapto benzoic acid)$_{14}$ | 575.89 | 2.1529 | 0.2159 |
| Au$_{18}$(S-2-dimethylamino Ethan thiol)$_{14}$ | 562.26 | 2.2051 | 0.2084 |
| Au$_{18}$(3-mercapto propionic acid)$_{14}$ | 558.72 | 2.2191 | 0.2134 |

Table 2. λ$_{max}$, excitation energy, and Oscillator strength values
More polar molecules have more solubility in polar solvents such as water. Naked gold nanoparticles are hydrophobic and make aggregations after introducing to polar solvents and this phenomenon causes them to fail to reach the target cells. Adding water-soluble ligands to these nanoparticles is a method to make them soluble. Measuring the amount of molecules’ dipole moment values is a method to estimate the degree of solubility. In this section, the dipole moment of naked and functionalized gold nanoparticles is calculated (measured) and data are listed in table 3. Based on the achieved data, functionalized gold nanoparticles have higher dipole moment values rather than the naked particle. The structure with 4-mercapto benzoic acid ligands has the highest value of dipole moment among the first four molecules of table 3. Structures with 3-mercapto propionic acid, 4-mercapto butyric acid, and 5-sulfanyl pentanoic acid ligands indicate that the value of dipole moment becomes higher with increasing the ligand length, thus the structure with 5-sulfanyl pentanoic acid ligands has the best solubility among the examined structures but it needs more investigations as will present in next sections.

Table 3. Dipole moment values, electronegativity, chemical potential, and hardness of different molecules.

| Compound                                      | Dipole moment (debye) | IP (ev)  | EA (ev)  | X          | μ           | η          |
|-----------------------------------------------|-----------------------|----------|----------|------------|-------------|------------|
| Bare Au                                       | 3.4405                | 6.304748 | 5.888124 | 5.996436   | −5.99644    | 0.616624   |
| Au$_{18}$(4-mercapto benzoic acid)$_{14}$      | 4.9718                | 5.334096 | 2.662966 | 3.988531   | −3.98833    | 2.67113    |
| Au$_{18}$(S-2-dimethylamino ethanethiol)$_{14}$ | 3.9923                | 5.218898 | 2.561466 | 3.890228   | −3.89023    | 2.657523   |
| Au$_{18}$(3-mercapto propionic acid)$_{14}$    | 4.3652                | 5.564582 | 2.950869 | 4.257726   | −4.25773    | 2.615713   |
| Au$_{18}$(4-mercapto butyric acid)$_{14}$      | 5.129                 | 5.231    | 2.6294   | 3.9302     | −3.9302     | 2.6016     |

Table 4. Intermolecular and intramolecular hydrogen bonds of molecules in different temperatures.

| Compound                                      | Intermolecular hydrogen bonds | Intramolecular hydrogen bonds |
|-----------------------------------------------|--------------------------------|-------------------------------|
|                                              | 290 K  | 300 K  | 310 K  | 290 K  | 300 K  | 310 K  |
| Gold                                         | 0      | 0      | 0      | 0      | 0      | 0      |
| Au$_{18}$(S-2-dimethylamino ethanethiol)$_{14}$ | 2.134293e-01 | 2.303810e-01 | 2.342126e-01 | 0      | 0      | 0      |
| Au$_{18}$(4-mercapto benzoic acid)$_{14}$      | 4.089528e+00 | 4.422862e+00 | 4.524388e+00 | 2.398082e-03 | 3.197442e-03 | 7.993605e-04 |
| Au$_{18}$(3-mercapto propionic acid)$_{14}$    | 4.013589e+00 | 4.245404e+00 | 4.269390e+00 | 1.686651e-01 | 1.366906e-01 | 9.672262e-02 |
| Au$_{18}$(4-mercapto butyric acid)$_{14}$      | —      | 4.352318e+00 | —      | —      | 7.593925e-02 | —      |
| Au$_{18}$(5-sulfanyl pentanoic acid)$_{14}$    | —      | 4.494005e+00 | —      | —      | 6.235012e-02 | —      |

More polar molecules have more solubility in polar solvents such as water. Naked gold nanoparticles are hydrophobic and make aggregations after introducing to polar solvents and this phenomenon causes them to fail to reach the target cells. Adding water-soluble ligands to these nanoparticles is a method to make them soluble. Measuring the amount of molecules’ dipole moment values is a method to estimate the degree of solubility. In this section, the dipole moment of naked and functionalized gold nanoparticles is calculated (measured) and data are listed in table 3. Based on the achieved data, functionalized gold nanoparticles have higher dipole moment values rather than the naked particle. The structure with 4-mercapto benzoic acid ligands has the highest value of dipole moment among the first four molecules of table 3. Structures with 3-mercaptopropionic acid, 4-mercapto butyric acid, and 5-sulfanyl pentanoic acid ligands indicate that the value of dipole moment becomes higher with increasing the ligand length, thus the structure with 5-sulfanyl pentanoic acid ligands has the best solubility among the examined structures but it needs more investigations as will present in next sections.

3.1.4. Ionization potential, electron affinity, hardness and chemical potential

There are other parameters such as hardness (η), electronegativity (X), and chemical potential (μ) which indicate the degree of stability of a molecule in an environment. Such parameters can be calculated by using ionization energy (IP) and electron affinity (EA) based on equations (1) to (5). IP and EA are related to HOMO and LUMO respectively.

\[
IP = -\varepsilon_{\text{HOMO}} \\
EA = -\varepsilon_{\text{LUMO}} \\
X = (IP + EA)/2 \\
\mu = -(IP + EA)/2 \\
\eta = IP - EA
\]

Hardness refers to the resistance of a molecule to charge transfer and reaction with other molecules or with the outer environment. Electronegativity is the ability of a molecule to form a covalent bond and chemical potential is defined as the tendency of a molecule to losing an electron and is the negative sign of electronegativity [39–61]. The results of calculating IP, EA, η, X, and μ are reported in table 3. Data indicate that the amount of hardness for the naked gold nanoparticle is almost zero although functionalized gold nanoparticles have higher amounts of hardness and among them, the molecule with 4-mercapto benzoic acid ligands has the most stability.
3.2. Molecular dynamic simulation analysis

In this section, the effect of ligand type, temperature, and ligand carbon chain length on the solubility and stability of the nanoparticles investigate and the results are presented as follows.

3.2.1. Intermolecular and intramolecular hydrogen bonds

The hydrogen bond is an interaction between a hydrogen atom or a molecular fragment from a structure and an atom or a group of atoms in the same or a different molecule. The acceptor is an electron-rich part such as an atom with a lone pair or a bonded pair. Intramolecular H-bond is a feature of a single molecule whereas the intermolecular H-bond is between two molecules. In some cases, optimized and intramolecular H-bonded atom with a lone pair or a bonded pair. Intramolecular H-bond is a feature of a single molecule whereas the intermolecular H-bond is between two molecules. In some cases, optimized and intramolecular H-bonded structures are not too different [62]. Many molecules such as drug-like molecules contain different numbers of functional groups capable of forming hydrogen bonds that make them soluble. The formation of intramolecular hydrogen bonds prevents water molecules from penetrating the structure, makes more lipophilic molecules, and increases their membrane permeability while open structures which had no intramolecular H-bonds should be more water-soluble [64, 65]. The few numbers of hydrogen bonds are not often a good sign and show the low solubility of a structure. Atoms like nitrogen and oxygen in a molecule can accept hydrogen bonds and increase the solubility of the molecule. In this study, the naked gold nanoparticle has no such acceptor but functionalized ones have nitrogen and oxygen atoms in their terminal groups and can form hydrogen bonds. The calculation of intramolecular and intermolecular hydrogen bond numbers was conducted for three structures in three different temperatures and for structures containing ligands of different carbon chain lengths at the temperature of 300 kelvin and data are listed in table 4. Results show that bare gold nanoparticle has no intermolecular hydrogen bond because there is no hydrogen bond acceptor group on it, and this molecule has no good solubility, but functionalized NPs form some hydrogen bonds with solvent. The number of H-bonds for the molecule with 2-dimethyl amino Ethan thiol ligands is lower than the structures with carboxylic acid functional groups on their ligands. Indeed, the molecules with carboxylic acid functional groups can make more H-bonds with water, and consequently, they are more soluble than amines. Between structures with 3-mercapto propionic acid and 4-mercapto benzoic acid ligands, while both have the same number of carboxylic terminal functions, the number of H-bonds for a molecule with 4-mercapto benzoic acid ligands is more. This phenomenon is due to their structural differences and different ability to form intramolecular H-bonds. Intramolecular H-bonds values show that bare gold nanoparticles and the particle with 2-dimethyl amino Ethan thiol groups have no potential to form intramolecular H-bonds while the molecules with carboxylic acid function have small quantities of this ability. Between two structures with carboxylic acid terminal groups, the molecule with 3-mercapto propionic acid has more internal H-bonds. It is the reason for the lower intermolecular H-bonds of this molecule than the structure with 4-mercapto benzoic acid ligands because there is a competition between forming intramolecular and intermolecular hydrogen bonds, and molecules with more intramolecular H-bonds have a lower number of intermolecular H-bonds and are less soluble. Furthermore, in the structures with aromatic rings, π interactions increase the polarity of molecules, and this can be a factor to increase the H-bond number of them [66, 67]. In addition, increasing temperature leads to increasing intermolecular and decreasing intramolecular H-bonds for all examined structures. This phenomenon is because of increasing the flexibility of the terminal functional group of molecules in higher temperatures that will investigate in the next sections. Three last rows of table 4 that are for molecules with different ligand lengths just for 300 K temperature show the molecules with longer carbon chain ligands have more intermolecular and lower intramolecular hydrogen bonds. Therefore, they can have more solubility in water, but this phenomenon should be more investigated. Data in this part of the study show that gold

| Compound | RMSD 290 K | RMSD 300 K | RMSD 310 K | RMSF 290 K | RMSF 300 K | RMSF 310 K |
|----------|------------|------------|------------|------------|------------|------------|
| Au18(5-2-dimethylamino ethanethiol)14 | 2.104394e-01 | 3.215488e-01 | 3.391088e-01 | 1.085507e-01 | 1.128286e-01 | 1.181714e-01 |
| Au18(4-mercapto benzoic acid)14 | 2.963255e-01 | 3.671764e-01 | 4.862274e-01 | 1.862429e-01 | 1.959429e-01 | 1.975429e-01 |
| Au18(3-mercapto propionic acid)14 | 2.849809e-01 | 3.579263e-01 | 3.948396e-01 | 7.766429e-02 | 8.009643e-02 | 8.197857e-02 |
| Au18(4-mercapto butyric acid)14 | — | 3.649051e-01 | — | 2.215071e-01 | — | — |
| Au18(5-sulfanyl pentanoic acid)14 | — | 5.829245e-01 | — | 2.766464e-01 | — | — |
| Compound                                    | SASA (nm²) | Inertia (nm) |
|--------------------------------------------|------------|--------------|
|                                            | 290 K | 300 K | 310 K | 290 K | 300 K | 310 K |
| Au₁₈(S-2-dimethylamino ethanthiol)₁₄       | 1.572923e+01 | 1.589870e+01 | 1.590774e+01 | 1.029825e+02 | 1.053567e+02 | 1.058324e+02 |
| Au₁₈(4-mercapto benzoic acid)₁₄            | 1.833046e+01 | 1.946806e+01 | 2.018011e+01 | 4.722677e+02 | 4.915784e+02 | 5.159024e+02 |
| Au₁₈(3-mercaptopropionic acid)₁₄           | 1.433770e+01 | 1.448069e+01 | 1.464912e+01 | 2.940387e+02 | 2.94743e+02  | 2.985620e+02 |
| Au₁₈(4-mercaptoproctic acid)₁₄             | —       | 1.770816e+01 | —       | —       | 3.89677e+02  | —       |
| Au₁₈(5-sulfanyl pentanoic acid)₁₄          | —       | 2.089417e+01 | —       | —       | 4.886861e+02 | —       |

Table 6. SASA and moment of inertia values of structures in different temperatures.
nanoparticle with 4-mercaptobenzoic acid ligands has the most number of H-bonds with solvent, thus this molecule has more solubility than others and among structures with linear alkyl carbon chains, the molecule with 5-sulfanyl pentanoic acid ligands has the most number of intermolecular hydrogen bonds that these are in agreement with results of the previous quantum section of the study.

3.2.2. Root-mean-square deviation (RMSD)
The time-dependent root-mean-square deviation is defined as a function of the deviation of the current atomic coordinates from the coordinates of a reference structure with N atoms which can be calculated in simulations according to equation (6). Drugs and many drug-like molecules used in biological fields are smaller than proteins and they are more rigid and have less flexibility. Investigating the RMSD parameter in such studies is better than parameters like gyration radius and can indicate the amount of flexibility of a structure [68, 69]. In this study, RMSD values of functional groups were calculated at different temperatures for three molecules. Then, the calculations were conducted for structures with different ligand lengths according to the previous section. Data are listed in table 5.

\[
RMSD = \sqrt{\frac{1}{N} \sum_{i}^{N} (r_i(t) - r_{i,ref})^2}
\]  

(6)

The data show that the nanoparticle with 4-mercaptobenzoic acid ligands has the most value of RMSD in each temperature, so the flexibility of functional groups of this nanoparticle is more. Further, the data demonstrate that the RMSD values become higher with increasing the temperature because the thermal motions of molecules can be more in higher temperatures, thus it leads to more conformation searches and spontaneously cause lowering of intramolecular hydrogen bonds and more flexibility and consequently more intermolecular H-bonds [69]. All of these results are in accordance with the previous section about the number of intramolecular and intermolecular hydrogen bonds. Data also show that the molecules with longer ligand lengths have more values of RMSD and more flexibility [70]. These results are in agreement with the result of the previous part of the calculations. More analysis is conducted in the next sections to clear the solubility and stability of these structures in water.

3.2.3. Root mean square fluctuations (RMSF)
RMSF is a parameter that shows the local flexibility of molecules. This parameter is similar to RMSD but its difference is that RMSF measures the fluctuation of atoms around their mean position and is calculated using equation (7). Also, its values are generally lower than RMSD. In this part of the study, the amounts of RMSF for terminal functional atoms are calculated at different temperatures for ligands with various lengths. The results are presented in table 5.

\[
RMSF(i) = \sqrt{\frac{1}{t} \sum_{0}^{t} (r_i(t) - \langle r(i) \rangle)^2}
\]  

(7)

Based on the obtained data, increasing the temperature leads to more fluctuation of terminal functional group atoms that is in following RMSD values of the previous part of the study (table 5). In addition, among all structures, the molecule with 4-mercaptobenzoic acid ligands has the most mobility and flexibility of terminal atoms. Nanoparticle with 3-mercaptobut propionic acid functions has the lowest value of RMSF that is because of its internal H-bonds that make the more rigid structure but increase the temperature leads to break some of the intramolecular H-bonds and make a more flexible molecule. RMSF values increase with increasing the ligand length. All of these data are following previous results.

3.2.4. Solvent accessible surface area (SASA)
The solvent-accessible surface area is the surface area of a molecule that is accessible to a solvent. In other words, it can indicate the surface atoms of a molecule to what extent are in contact with solvent and has always been considered as a factor in stability and solubility studies [71, 72]. Bigger molecules have a higher value of SASA [73, 74]. In addition, the molecules with less intramolecular interactions which are more flexible usually indicate a higher amount of SASA parameters that means these structures are more soluble and can affect more by water molecules. Here, SASA values are calculated for structures in different temperatures and with different lengths of ligands, and data are presented in table 6. Such values can help to conclude better about the solubility of structures and is a method for proving before results. As mentioned before, larger structures have higher values of SASA. In this study, the molecule with the 4-mercapto benzoic acid ligands is a little bigger than two other structures with 2-dimethyl amino Ethan thiol and 3-mercapto propionic acid ligands. (average size of optimized nanoparticles: Au18(2-dimethylamino Ethan thiol)14 \( \approx \) 2.14 nm, Au18(4-mercapto benzoic acid)14 \( \approx \) 2.29 nm, and
The data in table 6 show that as expected, the structure with 4-mercapto benzoic acid ligands has the most value of SASA but for two other molecules while having almost the same size, the SASA value is more for a molecule with 2-dimethyl amino Ethan thiol than nanoparticle with 3-mercapto propionic acid ligands. This phenomenon is because of their intramolecular hydrogen bonds. As seen in section 3.2.1 the gold nanoparticle with 2-dimethyl amino Ethan thiol ligands has no internal H-bonds so its structure remains straight in water but the molecule with 3-mercapto propionic acid ligands had the potential to form intramolecular H-bonds. These intramolecular interactions can affect the shape of the molecules and can make them folded to some extent [63]. This effect causes molecule with 3-mercapto propionic acid ligands has a fewer amount of SASA, therefore has less solubility. Furthermore, the values of SASA become higher in higher temperatures because of the increased flexibility of molecules and more stretched structures at higher temperatures due to more interactions with the solvent. For the molecules with longer carbon chain ligands, the value of this parameter is more that is in accordance with the results of the RMSD analyses section.

Figure 3. RDF diagrams for different structures in temperature of (a) 290 K (b) 300 K (c) 310 K.
3.2.5. Moment of Inertia

The moment of inertia ($I$) is another parameter that can be used for determining the flexibility and consequent solubility of molecules in a solvent. This parameter is known as the mass moment of inertia, angular mass, or rotational inertia of a rigid body. The moment of inertia appears in Newton’s laws of motion for a rigid body as a physical parameter that combines its shape and mass. The moment of inertia can be interpreted as SASA and gyration radius parameters, i.e. based on equations (8) and (9), it depends on the bond length and bending angle, thus if the bond length becomes bigger the amount of this parameter increases too and this is like the time that molecules stretch and their SASA or their gyration radius become larger. Further, the moment of inertia depends on the solvent’s degree of association and the rate of formation of solute-solvent hydrogen bonds. Indeed, H-bonds are liberating and show rapid oscillatory motions [75].

$$I_{xx} = (2R^2m_1m_2/M) \cos^2(\theta/2)$$  
$$I_{yy} = 2m_1R^2 \sin^2(\theta/2)$$  
$$I_{zz} = I_{xx} + I_{yy}$$

Where $\theta$ represents a bend of angle and $R$ represents the bond length [76]. Therefore, increasing the bond length leads to an increase in moment of inertia and is a criterion of more stretched structure in liquid and higher values of SASA. Further, the rotation part of the entropy in a system depends on the moment of inertia based on equations (11), (12) which means that some parts of the molecules with a higher moment of inertia have more entropy of rotation:

$$S = S_{trans} + S_{rot} + S_{vib}$$  
$$S_{rot} = R + R \ln \left(8\pi^2IKT/h^2\right)$$  
$$= R + R \ln \left(4\pi^2m_1(r^2)KT/h^2\right)I_{xx}$$  
$$= (2R^2m_1m_2/M) \cos^2(\theta/2)$$

Where $R$ represents the universal gas constant, $k$ represents Boltzmann’s constant, $T$ indicates the temperature, $I$ implies the moment of inertia, $<r^2>$ shows the mean square particle separation, and $h$ indicates the Plank’s constant. The values of the moment of inertia for terminal functional groups of structures in different temperatures and molecules containing various ligand lengths are calculated and their results are presented in table 6. Results show that the gold nanoparticle with 4-mercaptop benzoic acid ligands has the most value of the moment of inertia in all temperatures and is in accordance with SASA, RMSD, and H-bond numbers data investigated before. In addition, the value of the moment of inertia for each structure increase with increasing the temperature and is consistent with previous sections analysis about flexibility and H-bonds. Also, data show that the molecules with longer carbon chain ligands have higher values of the moment of inertia and this is because of their functional group’s flexibility which leads to more H-bonds with water and more SASA values, and consequently more solubility of them in water.
3.2.6. Radial distribution functions (RDF)

The radial distribution function, $g(r)$, in a particulate system, indicates the variation of density as a function of distance from a reference particle [77, 78]. This parameter can be useful for estimating the solubility of a molecule in a solvent. If a molecule has good solubility, it means that this particle can have enough strong interactions with the solvent, then solvent molecules can close it enough. The place and height of RDF diagram peaks indicate the amount of accumulation of solvent molecules around the solute molecule. This study analyzed the RDF diagrams of the oxygen atom of water molecules around the outer layer (functional groups) of the solutes. RDF diagrams of structures in each temperature are shown in figure 3. Then, the radial distribution function diagrams of molecules with various ligand lengths are obtained and presented in figure 4. RDF is a structural parameter that is not dependent on temperature [67]. Therefore, the diagrams for each nanoparticle in different temperatures may overlap with each other and they are not drawn in this part of the study, but small changes can be observed in the height of the first peak of obtained diagrams for different temperatures. Figure 3 indicates that the nanoparticle with 4-mercapto benzoic acid ligands has the sharpest peak than others in all temperatures, which is a sign of more solubility and more powerful interactions of this particle with water. In

![Figure 5. MSD diagrams of different gold nanoparticles in temperatures of (a) 290 K (b) 300 K and (c) 310 K in 2.5 ns after reaching equilibrium.](image-url)
addition, the first peak of the molecules with 3-mercapto propionic acid and 4-mercaptobenzoic-acid ligands are almost near to each other, because both of them have terminal carboxylic acid functional groups which can have good interactions with water. Nevertheless, the structure containing 4-mercapto benzoic acid ligands is more soluble and has more hydrogen bonds and a higher peak for the reasons already mentioned. Diagrams of RDF for molecules with different ligand carbon chain lengths (figure 4) indicate that the molecules with longer ligands have sharper peaks which means that they have stronger interactions with water. All of these results are the following previous results.

3.2.7. Mean square displacement (MSD)

Particle tracking is a method to obtain information about the behavior of a molecule in an environment like in live cells or a solvent. Mean square displacement analysis, showing the Brownian diffusion of a molecule in an anisotropic medium is one of the simplest and widely used approaches [79]. The slope of the linear part of the MSD diagrams shows the lateral diffusion coefficient of that [78]. The diffusion coefficient of a solute show
velocity and flow rate. MSD is a significant parameter for deciding the solubility of a molecule in a solvent. In this study, the MSD diagrams of solute in each temperature, diagrams of each nanoparticle in various temperatures, and diagrams of structures with various ligands lengths are drawn and presented in figures 5–7. In addition, the amounts of the slope of MSD diagrams calculated and data are listed in table 7. The difference of slope of MSD diagrams of a molecule in different temperatures may be small because this parameter such as structural parameters is not highly temperature-dependent while the diagrams of each molecule in different temperatures are drawn because their trends are according to previous parts of work results [67]. The obtained data of MSD diagrams for structures in different temperatures showed that among nanoparticles, the molecule with 4-mercapto benzoic acid ligands has the most mobility and diffusion coefficient, thus this nanoparticle has the best solubility that proved in previous sections. Furthermore, increasing the temperature leads to increasing the slope of diagrams, or the diffusion coefficient of all nanoparticles which is the evidence of more solubility and mobility of molecules in higher temperatures. Figure 7 shows that, despite increasing H-bonds for structures with longer carbon-chain ligands, their mobility could be lower, and this restricts their solubility. In this study, the molecule with 4-mercapto butyric acid ligands has a higher diffusion coefficient than the molecule with 3-mercapto propionic acid ligands but the slope of the MSD diagram for solute contains 5-sulfanyl pentanoic acid decrease that means among these three molecules the molecule with 4-mercapto butyric acid ligands is the best one from the point of view solubility and stability. In general, increasing the chain length of alkanes decreases their solubility in water [70].

4. Discussion

Study the effect of different ligand structures in various environmental situations on the solubility and stability of gold nanoparticles is an important issue because nowadays these particles consider for use in many biological applications such as cancer therapy and they should have enough proper features such as solubility in biological solvents. Therefore this aspect is studied in this work. The results of this study are following existing experimental data that have been reported in [41] by Ackerson et al which studied the stability of gold NPs with
different thiolated ligands such 4-mercapto benzoic acid, 3-mercapto propionic acid, and 4-mercapto butyric acid ligands. Their results indicated that a solution with particles containing 4-mercapto benzoic acid ligands has the most stability than solutions containing two other particles and the stability of solution with molecules containing 4-mercapto butyric acid ligands are more than the solution of gold nanoparticle with 3-mercapto propionic acid ligands.

5. Conclusion

In this study, for the first time, some quantum mechanical calculations and molecular dynamics simulations have been performed to investigate the effect of different ligands structure and temperature on the solubility and stability of Au18S14 nanoparticles as the smallest crystallography gold nanoparticle found until now. ligands including 4-Mercapto benzoic acid, 2-dimethylamino ethanethiol, 3-mercapto propionic acid, 4-mercapto butyric acid, and 5-sulfanyl pentanoic acid used for functionalizing mentioned gold Np. Optimized structures, HOMO-LUMO band–gap, dipole moment values, light absorption behavior, and hardness quantities of gold nanoparticles have been obtained using the quantum mechanics approach, and hydrogen bonds number, RDF, MSD, SASA, RMSD, and RMSF parameters have been calculated by molecular dynamics simulation method. Analysis of energy band–gap and light absorption behavior of nanoparticles showed that although functionalization leads to a wider band–gap of nanoparticles, their absorption wavelength is in the visible region of light spectra, thus using them in biological applications such as hyperthermia is safe. Hardness data showed that naked gold nanoparticles are very unstable while adding ligands makes them more stable because ligands complete dangling bonds of the surface of gold nanoparticles. Dipole moment values indicated that ligands improve the solubility of gold nanoparticles. Results of the analysis of obtained data in the simulation part of the work for different temperatures showed increasing the temperature leads to more solubility of functionalized gold NPs. Also, it was showed that nanoparticles containing ligands with longer carbon chains could form more H-bonds with solvent but their mobility may decrease, so there is a limitation for increasing the length of the ligand to improve the solubility of nanoparticles, and here the molecule with 4-mercapto butyric acid ligands has the best mobility and solubility than two other structures with 3 and 5 carbon chain lengths. From all quantum calculations and molecular dynamics simulation results, it has been concluded that the 4-Mercapto benzoic acid ligand is the best one for improving the solubility of nanoparticles among other functional groups examined here.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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