A computational study of cysteine and glutathione binding to small gold cluster Au$_8$

Nguyen Thanh Si^1, Pham Vu Nhat^2

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ABSTRACT

Introduction: Understanding the binding mechanism between gold nanoparticles and biomolecules is a fundamental step for numerous applications in biosensors and targeted drug delivery. This study aims to clarify the adsorption behaviors of CYS and GSH on the gold surface using a small gold Au$_8$ cluster as a model reactant. **Methods:** Here, we examine in details the molecular interaction between Au$_8$ cluster with cysteine (CYS) and glutathione (GSH) by means of density functional theory (DFT). The PBE functional is employed in combination with the cc-pVTZ basis set for non-metal atoms and the cc-pVTZ-PP basis set for gold. Harmonic vibrational frequencies are also computed to confirm optimized geometries as local minima or transition states on the potential energy surfaces. **Results:** The calculated results show that these molecules prefer to anchor on the gold cluster via the sulfur atom with the adsorption energies of 20.3 and 30.8 kcal/mol for CYS and GSH, respectively, in gas phase. In water, such values are considerably reduced, namely 19.0 kcal/mol for CYS and 26.4 kcal/mol for GSH. If a visible light with a frequency of $\nu = 6 \times 10^{14}$ Hz (500 nm) is applied, the time for the recovery of CYS and GSH from the most stable complexes will be about 1.24 and 6.03x10^7 seconds at 298 K in gas phase. **Conclusion:** The Au$_8$ cluster could be a promising material for designing sensor in CYS and GSH selective detection.

Key words: Au8 cluster, cysteine, density functional theory, glutathione

INTRODUCTION

In the past decades, gold clusters have been the subject of various studies owing to their potential applications in biosensors [1,2], catalysis [3], biomedical diagnostics [4,5], organic synthesis [6,7], environment [4], drug delivery systems [8], analysis [9], electrochemistry [10,11]. Recently, relevant studies have been carried out to elucidate the nature of interactions between biomolecules including amino acids, peptides, DNA constituents and small gold clusters, using both experimental and theoretical techniques.

According to Xie *et al.* [12], the interaction between gold cluster Au$_n$ (n = 3, 4) with cysteine and glycine is stabilized mainly due to Au-NH$_2$ bond *via* the transfer of charge from the amine group to the Au atom. In another investigation on cysteine and larger gold Au$_n$ cluster (n = 8, 10 and 12) [13], the resulting complexes were found to be stabilized due to the strong Au−S bonding. Interactions of proline amino acid with Au$_3$ cluster was also examined by DFT calculations [14]. Accordingly, two factors, i.e. the anchoring N-Au, O-Au bonds and the non-conventional O-H...Au hydrogen bond, dominate the interactions. Other striking finding is that gold clusters prefer to anchor on the terminal amide group [13–15].

In a study of M$_3$ clusters (M = Ag, Au and Cu) binding to histidine in both neutral and anionic states, Javan *et al.* [16] found that the metal clusters tend to oxidize histidine by getting electron from the lone pair orbitals of N, O, S atoms, and form highly stable anchor bonds. Scanning tunneling microscopy was also employed to probe the cysteine deposited on the Au(111) surface [17]. Novel network-like cluster structures of the layers with six and three cystine molecules on the Au surface have been found. A molecular dynamics simulation study of the adsorption mechanism of twenty amino acids and four surfactants on Au(111) in aqueous solution predicted an absorption energy around 3-26 kcal/mol [18]. The adsorption strength were found to correlate well with the degree of coordination of polarizable atoms (O, N, C) and determined by the molecular size/shape.

Cysteine and glutathione are among the most important thiol-containing compounds due to their special role in many biochemical reactions [19]. Cysteine (CYS) has many important cellular functions and its presence in biological fluids such as human plasma and urine is essential for clinical diagnostics of several diseases. The molecule on a solid surface is an important issue for either protein study or differentiating amino acids [19]. Previous study of cysteine adsorption

^{1}*Computational Chemistry Research Group, Ton Duc Thang University, Ho Chi Minh City, Viet Nam*

^{2}*Department of Chemistry, Can Tho University, Viet Nam*

Correspondence

Nguyen Thanh Si, Computational Chemistry Research Group, Ton Duc Thang University, Ho Chi Minh City, Viet Nam

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on Au(100) showed the tendency of flat adsorption geometries due to the thiolate-amino bonds[20].

Glutathione (GSH) or tripeptide γ-L-glutamyl-L-cysteinyl-glycine is well-known for its function in protecting the blood red cells from oxidative damage and maintaining the standard reduced state of the cells. In addition, the molecule is an integral part in the detoxification of the cells, responsible for elimination of harmful organic peroxides and free radicals. Accordingly, it absorbs toxins including pesticides, solvents, and heavy metals, then converting them into forms that are able to be excreted in urine or bile[19]. Moreover, its anionic form exhibits the particularly high tendencies to interact with gold clusters[21]. Recently, Thomas and co-workers[22] introduced a novel approach for selective detection of cysteine and glutathione in many biological systems using gold nanorods.

Despite numerous efforts devoted to the absorption of such thiol-containing compounds on Au_N systems, the interaction mechanism is still not fully understood. Additionally, most of previous studies were performed in vacuum, while the effects of solvents have not been taken accounts. Understanding the interaction mechanism of gold nanoparticles with biomolecules is a fundamental step in designing and development of tiny biosensors.

This theoretical study aims to elucidate the adsorption behaviors of two thiol-containing cysteine and glutathione on the gold surface using small gold Au_8 cluster as a model reactant. Current results could provide us with fundamental insights into the functionalization of gold nanoclusters with biomolecules and envisage their applicability in bio-chemical sensing and detection.

COMPUTIONAL METHODS

All calculations were performed with the aids of the Gaussian 09 program[23]. The geometries were fully optimized, making use of the functional PBE in conjunction with the basis sets cc-pVTZ-PP[24] for gold and cc-pVTZ for non-metals.

Initial structures of the Au_8●CYS and Au_8●GSH complexes for geometry optimizations were created by attaching biomolecules *via* electron-rich centers, i.e. the S, N and O atoms, to the lowest-energy form of Au_8. Harmonic vibrational frequencies were also computed to verify that optimized geometries are true local minima and to estimate the zero-point vibrational energy (ZPE) corrections. Zero-point and thermal enthalpies corrections were then employed to predict free energies *via* the **Equation (1).**

$$\triangle G^o \ (298\ K) \ = \ \triangle E \ + \ \triangle ZPE \ + \ \triangle TCG \qquad (1)$$

where ΔE is the relative electronic energy at 0 K; ΔZPE is the relative vibrational energy at 0 K; ΔTCG is relative changes in Gibbs free energy going from 0 to 298 K. The complextion energy E_c of the interaction between Au_8 cluster and CYS/GSH was computed as the value of energy difference:

$$E_c = E_{Au_8.CYS/GSH} \ - \ (E_{Au_8} + E_{CYS/GSH}) \qquad (2)$$

where E_X is the lowest electronic energy of the X species. Hence, a negative value of E_c indicates a favorable adsorption. The greater the computed value of the complexation energy, the stronger is the affinity of cysteine binding to the gold cluster. The effect of solvent (water) was simulated using the default model IEF-PCM (Integral Equation Formalism-Polarizable Continuum Model)[25] provided by Gaussian.

For deeper insights into the effect of interacting species on each other, the electronic properties such as the HOMO-LUMO energy gap (E_g) and the density of states (DOS) were examined. The E_g is a suitable aspect for defining the kinetic reactivity of materials[26], and its conversion upon the adsorption process reflects the sensitivity of an adsorbent to an adsorbate. The GaussSum program[27] has been used for DOS calculations.

RESULTS - DISCUSSION

Structural optimization

As expected, Au_8 cluster prefers to interact with CYS or GSH species through electron-rich atoms, i.e. S, N and O atoms. These atoms with lone pair are more willing to form bonding with the $5d$ and $6s$ orbitals of the Au atom. At the PBE/cc-pVTZ/cc-PVTZ-PP level of theory, we located four conformations for Au_8×CYS complexes, denoted as **C1-C4** (**Figure 1**), while for Au_8×GSH complexes, eight isomers **G1-G8** (**Figure 2**) have been obtained. Noticeably, the geometries of both CYS, GSH and Au_8 cluster are almost unmodified during the complexation. In addition, these structures have positive harmonic frequencies, indicating that they are local minima on the potential energy surfaces. The calculated complexation energies and bond lengths of the resulting complexes are listed in **Table 1.**

The most stable conformation of Au_8●CYS complex, i.e. **C1** form in Fig. 1, is formed by anchoring the thiol group on the low-coordinated gold atom of the Au_8 ring. This can be understood by the hard-soft acid-base (HSAB) theory[28], as the softer sulfur element is more willing to form strong bonds with soft elements like gold than the harder nitrogen and oxygen elements. In the **C1** complex, the Au-S bond length

Figure 1: **Optimal structures located for the Au$_8$•CYScomplex in gas-phase (C1-C4).** The relative values (kcal/mol) to the lowest-energy C1 conformation are given in brackets
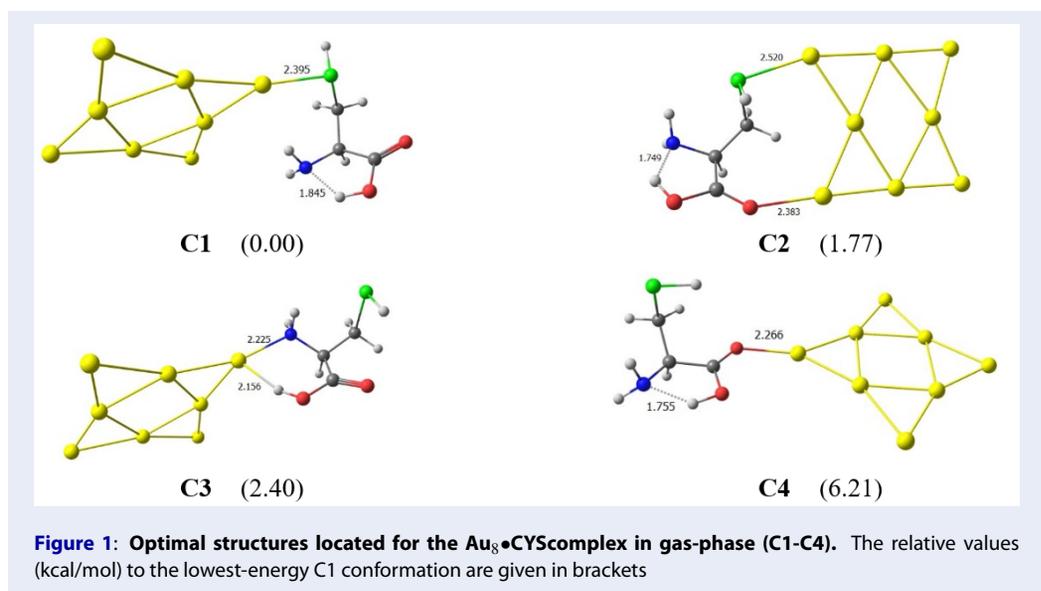
Table 1: **Complexation energy (E$_c$, kcal/mol), Au-Y bond length (r_{Au-Y}, $\overset{o}{A}$) of the Au$_8$.CYS complexes (C1-C4) at the same PBE/cc-pVTZ/cc-pVTZ-PP level of theory**

Conformation	Ec	Bond	
C1	-20.27	Au-	2.395
C2	-18.50	Au-	2.520
		Au-O	2.383
C3	-17.87	Au-	2.225
		Au-H	2.156
C4	-14.06	Au-O	2.266

is 2.395 Å, which is slightly longer than the sum of covalent radii of Au (1.35 Å) and S (1.02 Å) atoms. Previous study also predicted that Au atom exhibits a higher affinity with S atom[29].

The second most stable species **C2**, which is constructed by binding Au$_8$ to the thiol and carbonyl groups of CYS is only about ~2 kcal/mol higher in energy than the **C1** conformation. The Au-S and Au-O distances in **C1** are 2.520 and 2.383 Å, respectively, which are quite larger than the sum of covalent radii of Au-S (2.370 Å) and Au-O (2.080 Å) bonds. The remaining conformations including **C3** and **C4** conformation are the most unstable conformations. In these conformations, they are formed by anchoring Au atom on CYS through N and O atoms, having stronger basicity than S atom. The second element is that their associated lengths are larger than the total of theirs covalent radii are 2.100 and 2.080 Å, respectively.

For the interaction between Au$_8$ cluster and GSH molecules, eight conformations, i.e. **G1**-**G8** in **Figure 2**, have been located. Among these, the most stable structure **G1** is formed by anchoring the Au$_8$ moiety on the S and O atoms of the thiol and carbonyl group. The Au atom has strong affinity with S atom, but the formation of inter-molecular hydrogen bonds (H-bonds) in GSH is also a vital factor that significantly contributes to stabilizing the Au$_8$.GSH complex[21]. In fact, in the **G1** conformer, the calculated result obtain three H-bonds, namely N-H···O=C, S-H···O=C and COOH···NH$_2$ bonds. The H-bonds in **G1** are much shorter than those of other products.

The next isomer **G2** is only about ~3 kcal/mol less stable than the ground-state form **G1**. In **G2**, the Au atom links with cystenyl (Au-S) and glutamyl (Au-O), increasing the internal H-bonds in GSH. The remaining conformations (**G3**-**G8**) are quite unstable, being around 10-19 kcal/mol above the most stable form **G1**. In **G3**-**G8** complexes, the gold cluster bind-

Figure 2: Optimal structures located for the Au$_8$●GSH complex in gas-phase (G1-G8). The relative values(kcal/mol) to the lowest-energy G1 conformation are given in brackets.
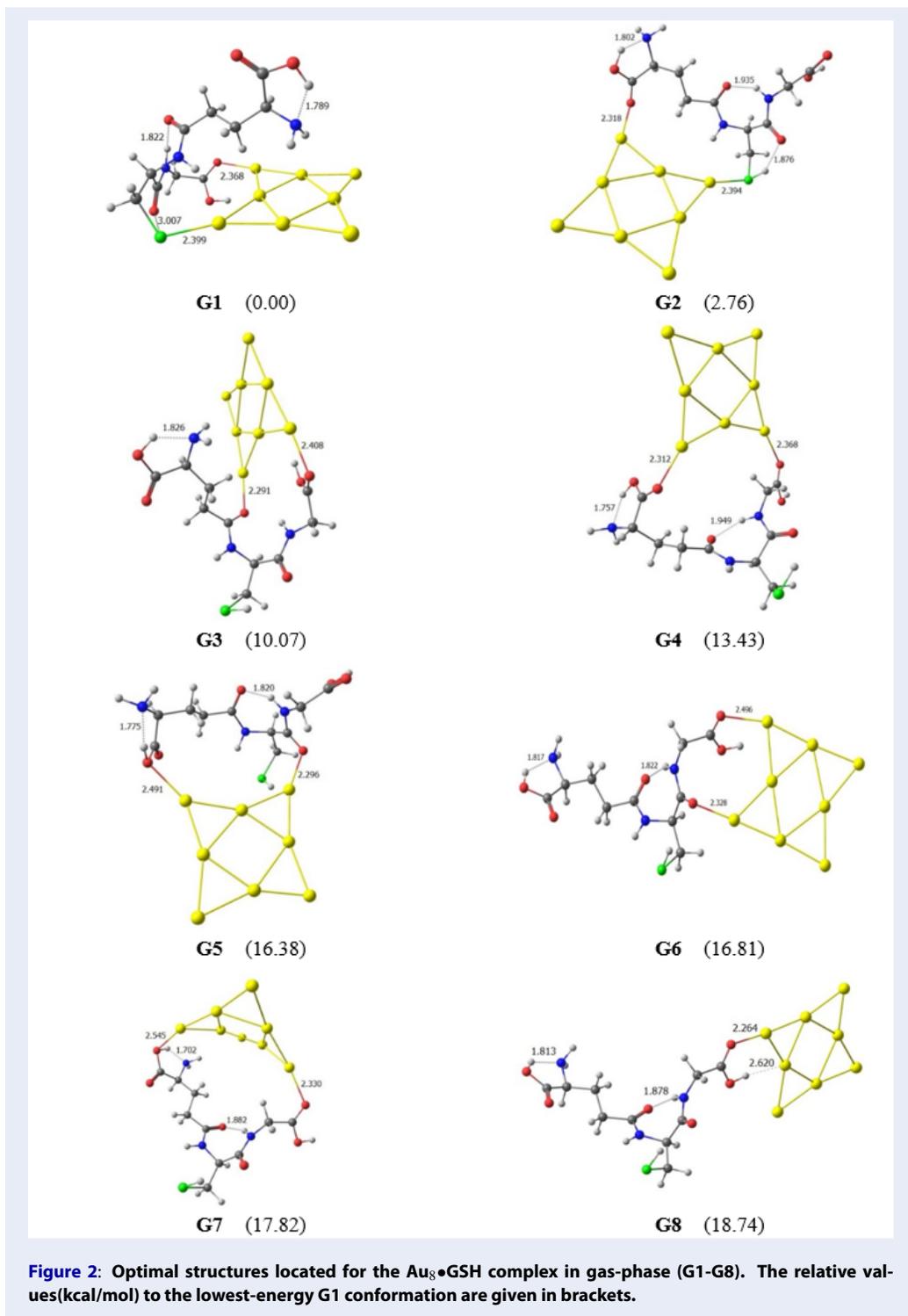
Table 2: Complexation energy (E$_c$, kcal/mol), Au-Y bond length (r_{Au-Y}, Å) of the Au$_8$.GSH complexes (G1 -G8) at the same PBE/cc-pVTZ/cc-pVTZ-PP level of theory

Conformation	Ec	Bond	r_{Au-Y}
G1	-30.75	Au-	2.399
		Au-O	2.368
G2	-27.99	Au-	2.394
		Au-O	2.318
G3	-20.68	Au-O	2.291
		Au-O	2.408
G4	-17.32	Au-O	2.312
		Au-O	2.368
G5	-14.37	Au-O	2.491
		Au-O	2.296
G6	-13.94	Au-O	2.328
		Au-O	2.496
G7	-12.93	Au-O	2.545
		Au-O	2.330
G8	-12.01	Au-O	2.264
		Au-H	2.620

ing to GSH molecule through the O atoms of carbonyl groups.

Chemical re activity

The quantum chemical descriptors of Au$_8$ cluster, CYS and GSH molecules including chemical potential μ, total hardness η and electrophile index ω are also examined to evaluate the chemical reactivity of systems considered. The calculated results at the PBE/cc-pVTZ/cc-pVTZ-PP level of theory are presented in **Table 3**.

As expected, the Au$_8$ has a more negative chemical potential than CYS and GSH molecules. In addition, the cluster exhibits a much larger electrophile index than the biomolecules. This strongly supports for the view that the metals are more willing to act as an electron-acceptor, while both CYS and GSH tend to be an electron-donor. Such a charge transfer from the biomolecules to the gold atoms results in a significant change in the HOMO-LUMO energy gap ($\triangle E_g$), which is reported as follows:

$$\triangle E_g = \frac{\left| E_{g_2} - E_{g_1} \right|}{E_{g_1}} \; x \; 100\% \qquad (3)$$

where E_{g_1} and E_{g_2} are the value of the E_g for the bare Au$_8$ cluster and the Au$_8 \bullet$X (X = CYS, GSH) complexes, respectively. This parameter can also be used to evaluate the sensitivity of the clusters to the presence of biomolecules.

As shown in the plot of DOS (**Figure 3**), the band gap of Au$_8$ in **C1** (1.64 eV) and **G1** (1.69 eV) considerably increase by 17% and 21%, respectively, as compared to that in the free Au$_8$ (1.40 eV). In general, the HOMO energy of Au$_8$ cluster is almost unchanged, while its LUMO energy substantially modified. In fact, due to an electron transfer from biomolecules to cluster, the LUMO of Au$_8$ increased from -4.35 eV in free cluser to -3.92 eV and -3.84 eV in **C1** and **G1** complexes, respectively.

Solvent effect and recovery time

Let us recall that all calculations above are performed in gas phase. In practice, sensors are often used to detect substances in solution, i.e. water environment. Therefore, further calculations have been carried out to examine the effects of water solvent on the interactions, using the IEF-PCM model (Integral Equation Formalism-Polarizable Continuum Model). The computed results are summarized in **Table 4**.

In water, complexation energies, the changes of enthalpy and free energy become less negative, but also exhibit a similar trend as in gas phase. This is due to the fact that hydration energies of products are

Table 3: Quantum chemical descriptors of Au_8 cluster, CYS and GSH at the PBE/cc-pVTZ/cc-pVTZ-PP level of theory

Structures	E_{HOMO}, eV	E_{LUMO}, eV	μ, eV	η, eV	ω, eV	Eg, eV	$\triangle$Eg, %
Au8	-5.75	-4.35	-5.05	0.70	18.22	1.40	-
CYS	-5.99	-1.11	-3.55	2.44	2.58	4.88	-
GSH	-5.79	-1.64	-3.72	2.08	3.33	4.15	-
C1	-5.56	-3.92	-4.74	0.82	13.70	1.64	17.14
G1	-5.53	-3.84	-4.69	0.85	12.94	1.69	20.71
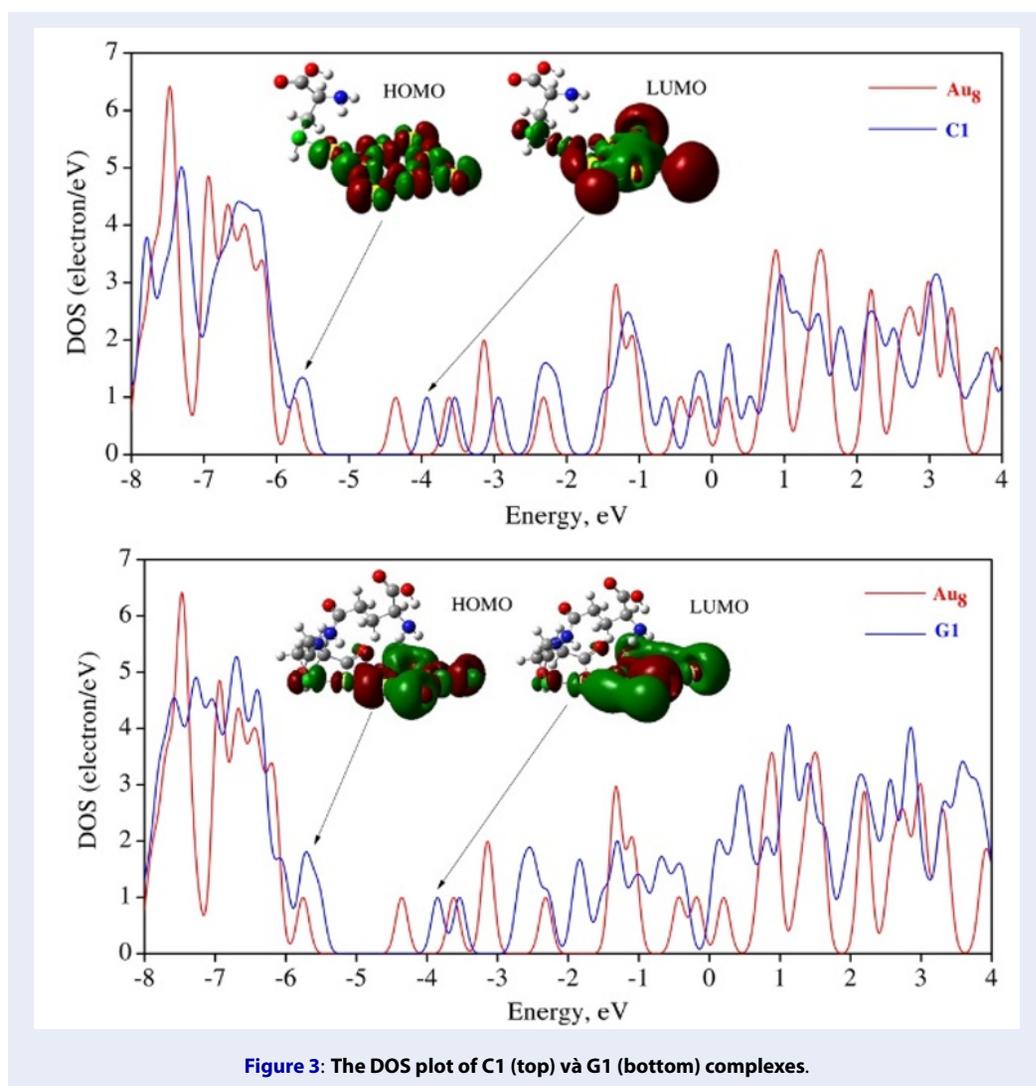
Figure 3: The DOS plot of C1 (top) và G1 (bottom) complexes.

smaller than the sum of hydration energies of reactants. However, the interactions in water are still products favored with negative changes of free energies.

When exposed to the UV-Vis light, the biomolecules can undergo a desorption process. Very strong interactions are not favorable for chemical sensors because the desorption could be difficult and the sensor may suffer from long recovery times. According the transition state theory [30], the recovery time (τ, seconds) exponentially depends on the binding energy E_c as follows:

$$\tau = (v_0)^{-1}.exp(-E_c/\kappa_B T) \qquad (4)$$

where T is the temperature, κ_B is the Boltzmann's constant, v_0 is the attempt frequency and $\kappa_B T$ = 0.059 kcal/mol at 298 K.

For the binding energy of -20.27 kcal/mol in vacuum, the recovery of cysteine molecules from the Au_8 surface at 298 K is in the range of 0.025 to 1.7 seconds (**Table 5**). In water, the recovery of the molecule from the Au_8 surface turns out to be rather faster (3×10^{-2} to 2×10^{-1} s). This indicates that the Au_8 cluster could be a promising candidate for detection of cysteine, even at room temperature. Due to stronger interactions with Au_8, the GSH molecules undergo much longer recovery times, namely from 1.2 x 10^6 to 8.4 x 10^7 s in gas phase and 8.2 x 10^2 to 5.7 x 10^4 s in water. Therefore, the Au_8 cluster can be used to design tiny reusable sensors for selective detection of CYS and GSH molecules.

CONCLUSION

In this work, the structures, energetic properties and effects of water solution on the interaction of cysteine and glutathione molecules with the Au_8 cluster was thoroughly examined by means of DFT calculations. The CYS and GSH moieties prefers to interact with the gold cluster through their thiol group. The nature of interactions is mainly determined by the charge transfer from the non-bonding pair of the sulfur atom to the empty orbitals of the gold cluster. Another noticable finding is that reactions of the gold cluster with these species are facile in nature, i.e. either molecular or dissociative chemisorptions are involved, rather than breaking molecular bonds and making again stronger bonds between the resulting fragments and the metals. The tendency to retain the initial forms of adsorbed molecules makes these clusters of great potential for applications in biochemical sensing and detection. If a visible light with a frequency of v = 6 x 10^{14} Hz (500 nm) is applied, the time for the recovery of CYS and GSH from the most stable

complexes will be about 1.24 and 6.03 x 10^7 seconds at 298 K in gas phase. This indicates that Au_8 cluster can be a promising candidate to develop tiny sensors in CYS and GSH selective detections.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHORS' CONTRIBUTIONS

All the authors contribute equally to the paper including the research idea and written manuscript.

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Table 4: Effect of water solvents on the C1 and G1 conformations

Value	Au8		C1		G1	
	Gas	Water	Gas	Water	Gas	Water
Ec	-	-	-20.27	-18.98	-30.75	-26.43
$\triangle$H	-	-	-19.15	-17.20	-30.77	-25.94
$\triangle$G	-	-	-9.64	-7.99	-16.56	-13.19
HOMO	-5.75	-5.21	-5.56	-5.18	-5.53	-5.16
LUMO	-4.35	-3.63	-3.92	-3.36	-3.84	-3.34
Eg	1.40	1.58	1.64	1.82	1.69	1.82
%$\triangle$Eg	-	-	17.14	15.19	20.71	15.19

Table 5: The time (in seconds) for the recovery of cys and gsh molecules from the Au_8 surface at 298 K

λ, nm	C1		G1	
	Gas	Water	Gas	Water
10	0.025	0.003	1.21x106	8.17x102
200	0.49	0.06	2.41x107	1.63x104
400	0.99	0.11	4.82x107	3.27x104
500	1.24	0.14	6.03x107	4.08x104
700	1.73	0.20	8.44x107	5.72x104

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