

A computational study of cysteine and glutathione binding to Au₈ cluster

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Abstract

The interaction between Au₈ cluster with cysteine (CYS) and glutathione (GSH) is investigated by means of density functional theory (DFT) using the PBE functional in conjunction with the cc-pVTZ basis set for non-metal atoms and the cc-pVTZ-PP basis set for gold. Harmonic vibrational frequencies are also calculated to confirm optimized geometries as local minima or transition states on the potential energy surfaces. The computed 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 $\nu = 6 \times 10^{14}$ (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 $\times 10^7$ seconds at 298 K in gas phase. Such values significantly reduce to 0.14 and 4.08 $\times 10^4$ in water. Thus, the Au₈ cluster could be a promising material for designing tiny sensors in CYS and GSH selective detection..

1 Introduction

In the last decades, gold clusters have been the subject of various studies owing to their potential applications in biosensors,¹⁻² catalysis,³ medical 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 elucidated the nature of interactions between biomolecules including amino acids, peptides, DNA constituents and small gold clusters, in terms of both experimental and theoretical aspects.

According to Xie et al.,¹² the interaction between gold cluster Au_n (n = 3, 4) with cysteine và glycine is stabilized due to Au-NH₂ bond via a charge transfer of the amine group to the Au atom. In another investigation on cysteine and larger gold Au_n clusters (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 Au₃ cluster was also examined by DFT calculations.¹⁴ The results show that two factors, i.e the anchoring N-Au, O-Au bonds and the nonconventional O-H---Au hydrogen bond, dominate the interaction. Other striking finding is that gold clusters prefer to anchor on the terminal amide group.¹³⁻¹⁵

In a study of M₃ clusters (M = Au, Ag and Cu) binding to histidine in both neutral and anionic states,¹⁶ Javan et al. 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) is actively involved in a number of important cellular functions and its level in biological fluids such as human plasma and urine is significant for clinical diagnostics of a variety of diseases. Cysteine on a solid surface is an important issue in protein study as well as in differentiating amino acid molecules.¹⁹

Theoretical calculations of cysteine adsorption on Au(100) by Höffling and Ortmann have shown that the flat adsorption geometries are more favored 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 to maintain the normal reduced state of the cells. It also plays an important role in the detoxification of the cells and is responsible for eliminating harmful organic peroxides and free radicals. It binds to toxins, such as heavy metals, solvents, and pesticides, and converts them into a form that can be excreted in urine or bile.¹⁹ Moreover, its anionic form exhibits the particularly high tendencies to interact with gold clusters.²¹ Interestingly, a novel strategy by Thomas et al.²² was developed for the selective detection of cysteine and glutathione using gold nanorods making it useful for sensing biological system.

Although numerous efforts have been 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 nature of interactions between gold nanoparticles and biomolecules is a fundamental step in the development and design of tiny biosensors. This theoretical study aims to elucidate the adsorption/desorption behaviors of two thiolcontaining cysteine and glutathione on the gold surface using Au₈ species 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 biochemical sensing and detection.

2 Computational 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-pVTZPP24 for gold and cc-pVTZ for non-metals.

Initial structures of the Au₈-CYS and Au₈-GSH complexes for geometry optimizations were created by attaching biomolecules via electronrich centers, i.e. the S, N and O atoms, to the lowest-energy form of Au₈. Harmonic vibrational frequencies were also calculated to confirm the character of optimized geometries as 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:

$$\Delta G^{\circ}(298 \text{ K}) = \Delta E + \Delta \text{ZPE} + \Delta \text{TCG} \quad (1)$$

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 complexation energy E_c of the interaction between Au8 cluster and CYS/GSH was computed as the value of energy difference:

$$E_c = E_{\text{Au}_8\cdot\text{CYS/GSH}} - (E_{\text{Au}_8} + E_{\text{CYS/GSH}}) \quad (2)$$

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.

In order to evaluate 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) are examined. The E_g is a useful factor for determining the kinetic reactivity of materials,²⁶ and also its change upon the adsorption process indicates the sensitivity of an adsorbent to an adsorbate. The GaussSum program²⁷ has been used for DOS calculations.

3 Results And Discussion

3.1 Structural Optimization

As expected, Au8 cluster prefers to interact with CYS or GSH species through electron-rich atoms, i.e. S, N and O atoms. These atoms with lone pairs are willing to form bonding with the 5d and 6s orbitals of the Au atom. At the PBE/ccpVTZ/cc-PVTZ-PP level of theory, we located four conformations for Au8□CYS complexes, abbreviated as C1-C4 (Figure 1), while for Au8-GSH complexes, eight configurations G1-G8 (Figure 2) have been obtained. Noticeably, the geometries of both CYS, GSH and Au8 cluster are almost unmodified during the complexation. In addition, all structures located have positive harmonic frequencies, indicating that they are local minimum structures on the potential energy surfaces.

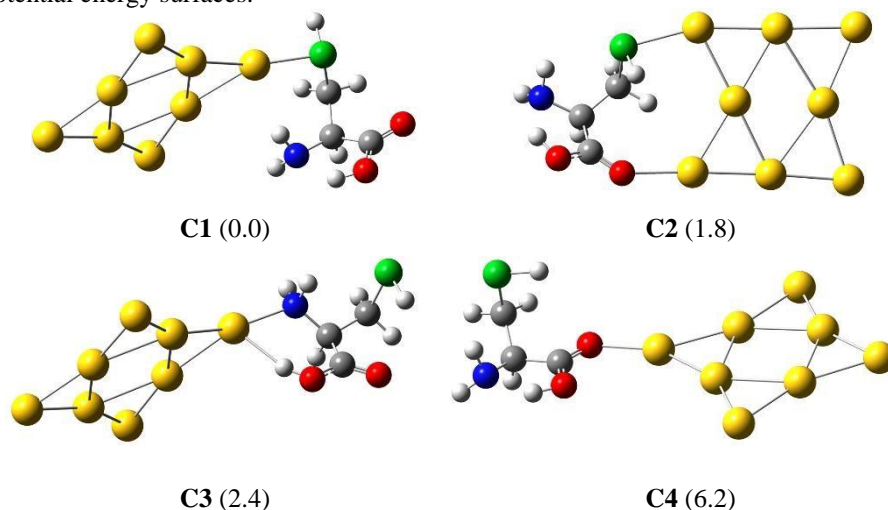


Figure 1: The low-lying structures of Au8□CYS complexes (C1-C4). The relative values (kcal/mol) to the lowest-energy C1 conformation are given in brackets.

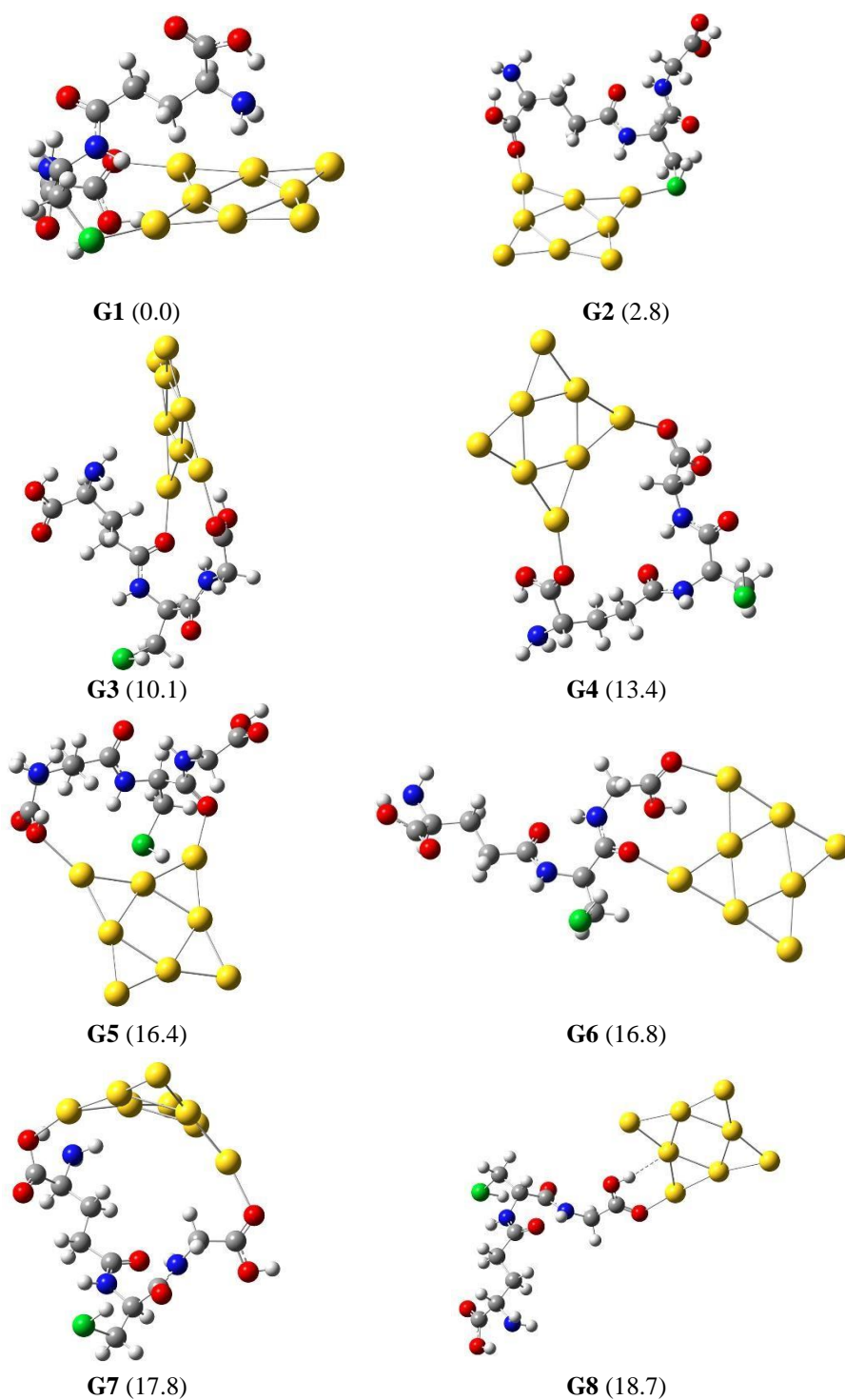


Figure 2: The low-lying structures of Au₈-GSH complexes (G1-G8). The values (kcal/mol) in parenthesis are relative energies as compared to the lowest energy G1 conformation.

In the Au₈-CYS product, CYS is willing to interact with the gold atom via its amine, carboxylic, and thiol groups, forming the Au-N, Au-O and Au-S anchoring bonds. The calculated complexation energy and bond lengths of the resulting complexes are listed in Table 1.

Table 1. Complexation energy (E_c , kcal/mol), Au-Y bond length ($r_{\text{Au-Y}}$, Å) of the Au₈□CYS complexes (C1-C4) at the PBE/cc-pVTZ/ccpVTZ-PP level of theory.

Isomer	E_c	Bond	$r_{\text{Au-Y}}$
C1	□20.3	Au-S	2.395
C2	□18.3	Au-S	2.520
		Au-O	2.383
C3	□17.9	Au-N	2.225
		Au-H	2.156
C4	□14.1	Au-O	2.266

The most stable conformation of Au₈-CYS complex, i.e. C1 form in Figure 1, is formed by anchoring the thiolate group on the lowcoordinated gold atom of Au₈ ring. The interaction between Au and S atoms is quite strong. This can be understood in terms of 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 is 2.395 Å, which is comparable to 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 Au₈ 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 these elements. The remaining conformations C3 and C4 are much less stable. These are formed by anchoring the cluster on CYS through N and O atoms.

Table 2. Complexation energy (E_c , kcal/mol), Au-Y bond length ($r_{\text{Au-Y}}$, Å) of the Au₈-GSH complexes (G1-G8) at the PBE/cc-pVTZ/ccpVTZ-PP level of theory.

Isomer	E_c	Bond	$r_{\text{Au-Y}}$
G1	-30.8	Au-S	2.399
		Au-O	2.368
G2	-28.0	Au-S	2.394
		Au-O	2.318
G3	-20.7	Au-O	2.291
		Au-O	2.408
G4	-17.3	Au-O	2.312
		Au-O	2.368
G5	-14.4	Au-O	2.491
		Au-O	2.296
G6	-13.9	Au-O	2.328
		Au-O	2.496
G7	-12.9	Au-O	2.545
		Au-O	2.330
G8	-12.0	Au-O	2.264
		Au-H	2.620

For the interaction between Au₈ 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 Au₈ moiety on the S and O atoms the thiol and carbonyl groups. The formation of hydrogen bonds (H-bonds) is also an inherent factor that significantly contributes to stabilizing the products.²¹ 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. 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 binding to GSH molecule through the O atoms of carbonyl groups. The calculated complexation energy and bond lengths of the resulting complexes are listed in Table 2.

3.2 Chemical Reactivity

Several quantum chemical descriptors of Au8 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.

As shown in Table 3, Au8 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 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 significantly change in the HOMO-LUMO energy gap (ΔE_g), which is reported as follows:

$$\Delta E_g = \frac{|E_{g2} - E_{g1}|}{E_{g1}} \times 100\%$$

where E_{g1} and E_{g2} are the value of the E_g for the bare Au8 cluster and the Au8·X (X = CYS, GSH) complexes, respectively. This parameter can also be used to evaluate the sensitivity of the clusters to the presence of biomolecules.

The plot of DOS (Figure 3) clearly demonstrate that the band gaps of Au8 in C1 (1.6 eV) and G1 (1.7 eV) considerably increase by 17 % and 21 %, respectively, as compared to that in the free Au8 (1.4 eV). In general, the HOMO energy of Au8 cluster is almost unchanged, while its LUMO energy substantially modified. In fact, due to an electron transfer from biomolecules to cluster, the LUMO energy of Au8 increased from -4.4 eV in free cluster to -3.9 eV and -3.8 eV in C1 and G1 complexes, respectively.

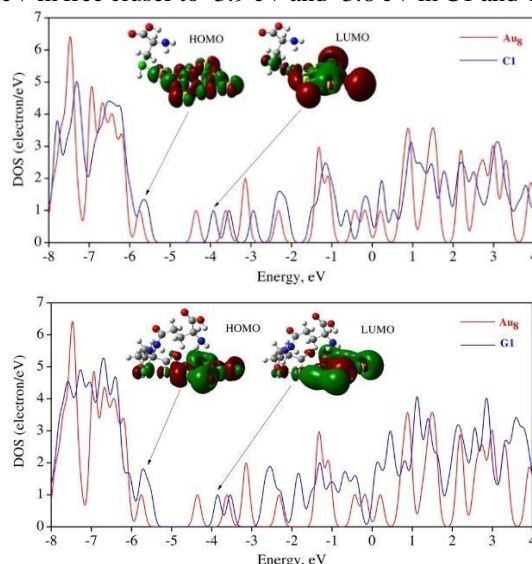


Figure 3: The DOS plot of C1 (above) and G1 (below) complexes.

Table 3. Some quantum chemical descriptors of Au₈ cluster, biomolecules and resulting complexes obtained at the PBE/cc-pVTZ/cc-pVTZ-PP level of theory.

Species	E _{HOMO} , eV	E _{LUMO} , eV	μ , eV	η , eV	ω , eV	E _g , eV	% ΔE_g , %
Au ₈	-5.8	-4.4	-5.1	0.7	18.2	1.4	-
CYS	-6.0	-1.1	-3.6	2.4	2.6	4.9	-
GSH	-5.8	-1.6	-3.2	2.1	3.3	4.2	-
C1	-5.6	-3.9	-4.7	0.8	13.7	1.6	17.1
G1	-5.5	-3.8	-4.7	0.9	12.9	1.7	20.7

3.3 Solvent Effect and Recovery Time

often used to detect substances in solution, i.e.

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

Table 4. Complexation energy, changes of enthalpy and Gibbs energy (kcal/mol), along with HOMO, LUMO energies (eV) obtained for C1, G1 complexes in vacuum and water environment.

Property	Au ₈		C1		G1	
	Gas-phase	Water	Gas-phase	Water	Gas-phase	Water
E _c	-	-	-20.3	-18.9	-30.8	-26.4
ΔH	-	-	-19.2	-17.2	-30.8	-25.9
ΔG	-	-	-9.6	-8.0	-16.6	-13.2
HOMO	-5.8	-5.2	-5.6	-5.2	-5.5	-5.2
LUMO	-4.4	-3.6	-3.9	-3.4	-3.8	-3.3
E _g	1.4	1.6	1.6	1.8	1.7	1.8
% ΔE_g	-	-	17.1	15.2	20.7	15.2

In water, the complexation energies, changes of enthalpy and free energy become less negative, but still exhibit similar trends as in gas phase. This is due to the fact that hydration energies of products are smaller than the sum of hydration energies of reactants. However, the interactions in water are still products favored with negative changes of free energies.

Table 5. The time (in seconds) for the recovery of CYS and GSH molecules from the Au₈ surface at 298 K.

λ (nm)	C1		G1	
	Gas	Water	Gas	Water
10	0.03	0.003	1.21×10^6	8.17×10^2
200	0.49	0.06	2.41×10^7	1.63×10^4
400	0.99	0.11	4.82×10^7	3.27×10^4
500	1.24	0.14	6.03×10^7	4.08×10^4
700	1.73	0.20	8.44×10^7	5.72×10^4

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 to the transition state theory,³⁰ the recovery time (τ , seconds) exponentially depends on the complexation energy E_c as follows

$$\tau = (v_0)^{-1} \exp(-E_c/kBT)$$

where T is the temperature, kB is the Boltzmann's constant, v_0 is the attempt frequency.

For the binding energy of -20.3 kcal/mol in vacuum, the recovery of cysteine molecules from the Au₈ 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 Au₈ surface turns out to be rather faster (3×10^{-2} – 2×10^{-1} s). This indicates that the Au₈ cluster could be a promising candidate for detection of cysteine, even at room temperature. Due to stronger interactions with Au₈, the GSH molecules undergo much longer recovery times, namely from 1.2×10^6 to 8.4×10^7 s in gas phase and 8.2×10^2 to 5.7×10^4 s in water. Therefore, the Au₈ cluster can be used to develop tiny reusable sensors for selective detection of CYS and GSH molecules.

4 Conclusion

In this work, the structures, energetic properties and effects of water solution on the interaction of cysteine and glutathione molecules with the Au₈ cluster was thoroughly examined by means of DFT calculations. Current computed results could provide us with fundamentals for understanding the thiol-containing amino acids or proteins absorption on Au surfaces at the atomic and molecular levels.

In agreement with the HSAB theory,²⁸ CYS and GSH moieties prefer to interact with the gold cluster through their thiol group. In resulting complexes, the Au-S bond length is comparable to the sum of covalent radii of anchoring atoms, while both the Au-N and Au-O anchoring bonds are longer, indicating the more effective interactions of the thiol head.

The nature of interactions is mainly determined by the charge transfer from the non-bonding pairs of the sulfur atom to the empty orbitals of the gold cluster. Another noticeable 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 property to retain the original form of adsorbed molecules makes such clusters of great interest for the use in biochemical sensing and detection. In water solution, GSH molecule suffers from a much longer recovery time (8.2×10^2 to 5.7×10^4 s) than cysteine (3×10^{-2} – 2×10^{-1} s). This indicates that Au₈ cluster can be a promising candidate to develop tiny sensors in CYS and GSH selective detections.

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