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A DFT Study of the Mercaptopurine Drug Binding to Gold Clusters

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Abstract:

Density functional theory is employed to examine the adsorption/desorption behaviors of the mercaptopurine (MP) drug on the gold surface using Au_6 and Au_8 species as model reactants. Thermodynamic parameters, electronic structures, bonding characteristics and spectroscopic properties of the resulting complexes are investigated using the B3LYP functional along with correlation consistent basis sets, namely cc-pVDZ-PP for gold and cc-pVTZ for non-metals. Computed results in vacuum show that the drug molecule tends to adsorb on the gold cluster *via* its S atom with adsorption energies of around 26.4 and 29.6 kcal/mol for Au_6 and Au_8, respectively. In water environment, such values are considerably reduced, namely 20.6 kcal/mol for Au_6 and 23.4 kcal/mol for Au_8. As a result, if a visible light with a frequency of $\nu \approx 6 \times 10^{14}$ Hz (500 nm) is applied, the time for the recovery of MP molecules from the most stable complexes will be about 2 – 230 seconds at 298 K. Also, a drug release mechanism is proposed, indicating that in the low pH of the cancer cells the drug is willing to separate from the gold surface. Our findings provide fundamental insights into the functionalization of gold nanoclusters and envisage their applicability for designing of targeted drug delivery systems and biosensors.

I. Introduction

Mercaptopurine (MP), normally sold under the brand name purinethol, is an artificial nucleobase analogue generally used with methotrexate to treat leukemia, Crohn's disease and ulcerative colitis.[1,2] The therapeutic intake of MP may nonetheless cause unwanted side effects including bone marrow suppression, liver toxicity, vomiting, and loss of appetite.[3] In addition, women receiving the drug during the first trimester of pregnancy have a high risk of abortion.[4] Therefore, it is crucial to find an appropriate carrier to deliver the drug where it is needed, enhancing its therapeutic effect. This can allow using a reduced dose of the drug and consequently diminish the side reactions. Designing of a simple and powerful sensor for quick detection of the drug is also of great significance.[5] In this study, a series of DFT calculations are performed to examine the adsorption/desorption behaviors of the MP drug on the gold surface using Au_6 and Au_8 species as model reactants. Current results could provide fundamental insights into the functionalization of gold nanoclusters and envisage their applicability for designing of targeted drug delivery systems and biosensors.

II. Computational methods

All calculations are performed using the Gaussian 09 suite of program.[6] The geometries are fully optimized, without any symmetry or geometry constraints, making use of density functional theory (DFT) with the GGA functional PBE. The basis set cc-pVDZ-PP with an

effective core potential (ECP) is applied for gold, while the all electrons cc-pVTZ basis set is used for non-metals. Initial structures of the cluster-drug complexes for geometry optimizations are generated by attaching the drug molecule *via* electron-rich centers, i.e. the S, O atoms, to the most stable forms of Au_6 and Au_8.[7] The binding energy E_b of the complexes is computed as the absolute value of the energy difference:

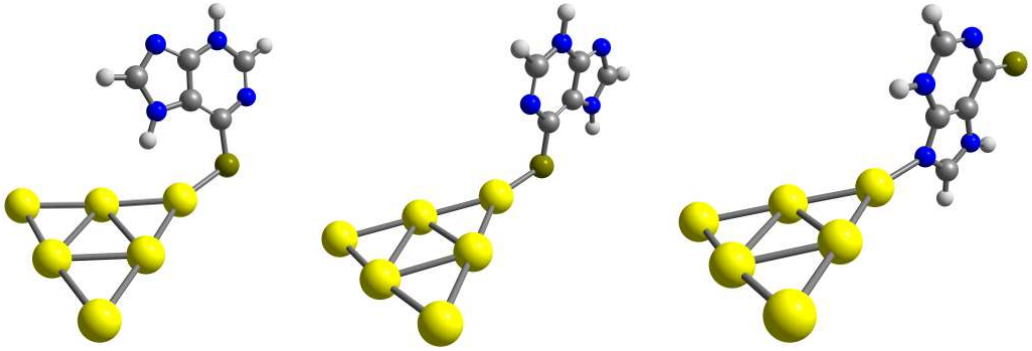
$$E_b = \left(E_{Au_N} + E_{Drug}\right) - E_{Au_N \cdot Drug}$$

where E_X is the lowest electronic energy of the X species. Hence, a positive value of E_b indicates a favorable adsorption. The effect of solvent (aqueous solution) is simulated using the continuum model known as the Integral Equation Formalism-Polarizable Continuum Model (IEF-PCM).[8]

III. Results and discussion

1. Structural optimization

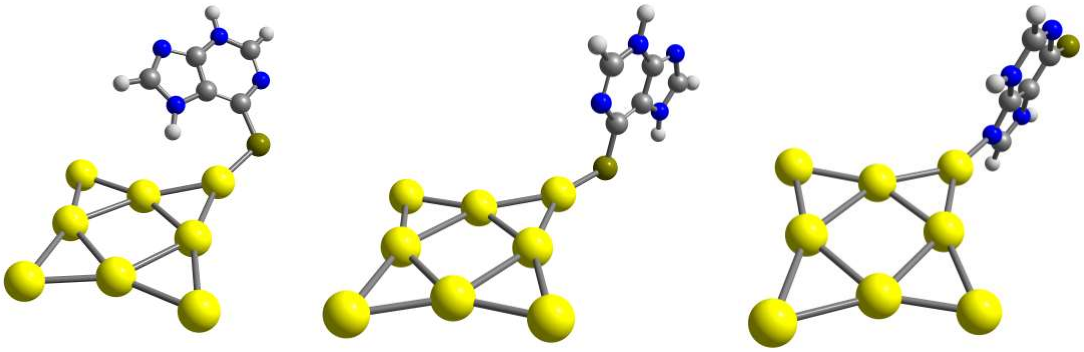
In gas-phase, we located three structures for each Au_N·MP complex in all of which the interaction between the amino acid and gold cluster is mono-dentate.



Au_6·MP_1 (0.00) | Au_6·MP_2 (7.27) | Au_6·MP_3 (15.4)

Figure 1. Plausible structures located for the Au_6·MP complex in gas-phase. The values in brackets are their relative energies (kcal/mol).

Similarly, the most stable conformation of Au_8·MP complex, i.e. **Au_8·MP _1** in Figure 2, is formed by anchoring the sulfur atom on the Au_8 ring.



Au_8·MP_1 (0.00) | **Au_8·MP_2** (7.79) | **Au_8·MP_3** (8.55)

Figure 2. Plausible structures located for the Au_8·MP complex in gas-phase. The values in brackets are their relative energies (kcal/mol).

2. Energetic and electronic properties

The thermodynamic stability of the Au_N·MP complexes is evaluated *via* binding energy, changes of enthalpy and Gibbs energy. The effects of water on the stability of the complexes are also considered.

Table 1. Binding energy E_b, enthalpy ΔH^{298} and Gibbs energy ΔG^{298} (kcal/mol) for the adsorption of mercaptopurine on Au_N clusters and bond lengths Au–X (Å) with X = S, N in the resulting Au_N·MP complexes.

	E_b	ΔH^{298}	ΔG^{298}	r_{Au-X}		E_b	ΔH^{298}	ΔG^{298}	r_{Au-X}
Complex	In vacuum				Complex	In vacuum			
Au_6·MP_1	-34.3	-33.7	-24.0	2.37	**Au_8·MP_1**	-38.5	-38.0	-26.8	2.35
Au_6·MP_2	-27.0	-26.3	-18.9	2.37	**Au_8·MP_2**	-30.7	-30.1	-20.6	2.35
Au_6·MP_3	-18.9	-18.1	-9.52	2.18	**Au_8·MP_3**	-22.2	-21.5	-11.5	2.14
Complex	In water				Complex	In water			
Au_6·MPaq_1	-27.8	-27.2	-16.9	2.37	**Au_8·MPaq_1**	-31.3	-30.7	-21.5	2.35
Au_6·MPaq_2	-25.8	-25.7	-13.6	2.37	**Au_8·MPaq_2**	-29.2	-29.1	-17.0	2.35

In order to uncover the binding mechanisms, the energy levels of frontier orbitals (HOMO and LUMO) for mercaptopurine, Au_N and the resulting complexes are examined. The change of HOMO-LUMO energy gap (ΔE_g) is also calculated.

Table 2. Energy of HOMO, LUMO, HOMO–LUMO gap (E_g) in eV, and the change of E_g upon the mercaptopurine adsorption on Au_N (N = 6, 8) clusters

Species	HOMO	LUMO	E_g	ΔE_g		HOMO	LUMO	E_g	ΔE_g
	In vacuum					In water			
Au_6	-5.94	-3.86	2.09	-	**Au_6**	-5.36	-3.08	2.28	-
Au_8	-5.84	-4.39	1.45	-	**Au_8**	-5.31	-3.68	1.63	-
MP	-4.77	-2.62	2.15	-	**MP**	-5.20	-2.72	2.48	-
Au_6·MP_1	-5.10	-3.66	1.44	31%	**Au_6·MPaq_1**	-4.99	-3.29	1.70	25%
Au_8·MP_1	-5.39	-3.75	1.64	13%	**Au_8·MPaq_1**	-5.19	-3.36	1.83	12%

IV. Conclusion

In this study, the adsorption behavior of MP drug molecule on Au_6 and Au_8 clusters was investigated by means of DFT calculations. Geometrical, energetic properties and the effects of water solution are examined in details on the basis of DFT/TD-DFT approaches and the IEF-PCM model. Current results could provide us with fundamentals for understanding the biomolecules absorption on Au surfaces at the atomic and molecular levels. Computed results have showed that the gold cluster favors to bind with MP *via* the S-atom of the thione group. This is in agreement with the hard – soft acid – base (HSAB) theory, as the softer ═S head group is more willing to establish strong bonds with soft elements like gold than other groups. It is also noticed that unlike Au_8, Au_6 should be a promising candidate for detection of cysteine. This is

due to the fact that the Au_8 suffers from a longer recovery time and a lower sensitivity to MP. On the contrary, Au_6 benefits from a quite shorter recovery time and a larger change of energy gap that could be converted to an electrical signal for biosensors.

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