A theoretical study on interaction of proline with gold cluster

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Abstract. Interaction of proline with gold cluster was studied using density functional theory (DFT). Two types of mixed basis sets UB3LYP/6-311++G ∪ LANL2MB and UB3LYP/6-311++G ∪ LANL2DZ were used for optimization of complex structures. Proline interacts with gold cluster either through one anchor bond, N–Au or an anchor bond O–Au associated with a non-conventional O–H...Au hydrogen bond. Among these interactions, higher tendency for interaction is seen with Au cluster through amide terminal. Natural bond orbital analysis (NBO) is used to substantiate the results.

Keywords. Proline; gold nanoparticles; interaction energy; DFT; NBO.

1. Introduction

Gold nanoparticles have attracted much attention in material science due to their biocompatibility and ability to conjugate with organic and biomolecular systems (Shafai *et al* 2007; Shukla *et al* 2008) which make them suitable for use in biochemical sensing and detection (Storhoff *et al* 1998; Riboh *et al* 2003; Shafer-Peltier *et al* 2003). Several experimental and theoretical investigations are focused on the interaction of gold with amino acids and DNA. Small clusters formed by metals such as Cu, Ag and Au have been studied experimentally (Bucher *et al* 1988; Cheeseman and Eyler 1992; Lian *et al* 1993; Lee and Ervin 1994) using resonant two-photon ionization, photoelectron spectroscopy and Raman spectroscopy. Theoretical studies on neutral (Balasubramanian and Liao 1991, 1992; Lee *et al* 2003; Zheng *et al* 2003; Soule de Bas *et al* 2004; Xiao and Wang 2004; Walker 2005; Yuan *et al* 2005; Xiao *et al* 2006), anionic (Furche *et al* 2002; Hakkinen *et al* 2002; Kim *et al* 2003; Lee *et al* 2003; Niemietz *et al* 2003; Agrawal *et al* 2004; Remacle and Kryachko 2005) and cationic clusters (Gilb *et al* 2002; Weis *et al* 2004; Fielicke *et al* 2005; Remacle and Kryachko 2005; Walker 2005) formed by Au and Ag were mostly devoted to provide geometry, binding energy and spectroscopic details.

Detection of α-amino acids is an important area of research in proteomics (Pakiari and Jamshidi 2007). Major difficulty associated with the detection of α-amino acids in proteins using chemosensors is their structural similarity (Ait-Haddou *et al* 2001). Thomas *et al* reported selective detection of micromolar concentrations of cysteine/glutathione by exploiting the interplasmon coupling of Au nanorods (Sudeep *et al* 2005). Further theoretical studies such as adsorption of the cysteine on the Au(111) surface (Felice *et al* 2003), interaction of glycine and cysteine with Au$_3$ (Pakiari and Jamshidi 2007) and interaction of

small gold clusters with xDNA base pairs (Sharma *et al* 2009) have motivated us to carry out a theoretical study on interaction of proline with gold nanoparticles. Proline is unique among the natural amino acids as its side chain is cyclized to the backbone, which gives exceptional conformational rigidity to the proteins. It is commonly found as first residue of an alpha helix, beta sheets and turns (Moradi *et al* 2009).

In the present work, we have attempted to study the nature of interaction of small gold cluster composed of three gold atoms with neutral amino acid, proline, in order to locate preferable binding sites of gold atoms. The cluster size of Au$_3$ is considered for the following reason: A recent Car–Parinello *ab initio* molecular dynamics study demonstrated that the optimal size of gold cluster to mimic conjugation of gold nanowires with organic molecules is composed of three to four bonded gold atoms (Krűger *et al* 2002). We have carried out density functional theory (DFT) (Kohn *et al* 1996) based quantum chemical analysis of the interactions.

2. Methodology

GAUSSIAN03 (Frisch *et al* 2003) suite of quantum chemical programs was used for carrying out all electronic and structural calculations. Initial geometries of proline complexed with Au$_3$ cluster were generated by placing the cluster atoms near amide and carboxylic groups of proline. This was done by using GaussView (Dennington *et al* 2003) software. The geometries were optimized using density functional theory with UB3LYP functional in gas phase. Hybrid B3LYP exchange-correlation functional was used in recent computational studies on gold clusters tagged with natural amino acids, glycine and cysteine (Pakiari and Jamshidi 2007) and natural DNA bases and base pairs (Kryachko and Remacle 2005a, b; Kumar *et al* 2006) and its use is justified in the present context. It should be noted that for larger

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systems where stacking may be possible, dispersion interactions should be accounted for carefully and the level of calculations as presented here may not suffice. For our systems mostly stabilized by hydrogen bonding, the missing dispersion component and missing BSSE correction approximately compensate each other (Černý and Hobza 2007). Basis set 6–311++G was used for atoms of the amino acid and two different basis sets, LANL2MB (Hehre *et al* 1969) and LANL2DZ were applied for the gold atoms. The LANL2MB and LANL2DZ basis sets use 11-valence electron pseudopotential for Au atoms and interaction of $[Xe]4f$ inner electrons are considered as relativistic effective core potential (RECP) (Pakiari and Jamshidi 2007; Sharma *et al* 2009). These basis sets differ in treating outer $5d^{10}6s^1$ valence orbitals (11 valence electrons) of Au, where LANL2DZ uses a double-ζ basis set and LANL2MB employs a minimal basis set (Sharma *et al* 2009).

Vibrational analysis was carried out on optimized geometries of the complexes and real frequencies were obtained in all cases. Interaction energy, E_{int}, was corrected for zero point vibrational energy (ZPVE). It was calculated using the following equation:

$$E_{int} = E_{complex} - \left(E_{proline} + E_{Au_3} \right), \qquad (1)$$

where $E_{complex}$, $E_{proline}$ and E_{Au_3} are zero point corrected electronic energies of proline complexed with the gold cluster, proline and gold cluster, Au_3, respectively.

Natural bond orbital (Read *et al* 1985) (NBO) analysis was employed to calculate charge transfer interactions in the complexes.

3. Results and discussion

The basis sets, UB3LYP/6-311++G ∪ LANL2MB and UB3LYP/6-311++G ∪ LANL2DZ used for the optimization of the structures are referred to as **1** and **2**, respectively in the subsequent text. Figures and tables labeled '*n*' are in the main text and '*Sn*' are in the supporting information. Optimized geometries of the proline tagged with gold cluster, obtained using the basis sets **1** and **2**, are shown in figures 1 and 2, respectively. Coordinates of optimized species are given in tables S1–S7. Nitrogen of amide and oxygen of carboxylic groups can donate their lone pair electrons to gold atoms. Gold can also act as proton acceptor and forms nonconventional H-bonds with amide and hydroxyl groups of the amino acid. Interaction of the amino acid with gold may be either monodentate or bidentate. The bidentate interaction involves a non-conventional H-bonding interaction.

3.1 *Structure and energetic aspects of complex*

Proline interacts through the amide group (Au–N) and carboxylic group (Au–O and Au…H–O); the corresponding complexes with gold cluster are referred to as Pro-Au$_3$ **(a)**
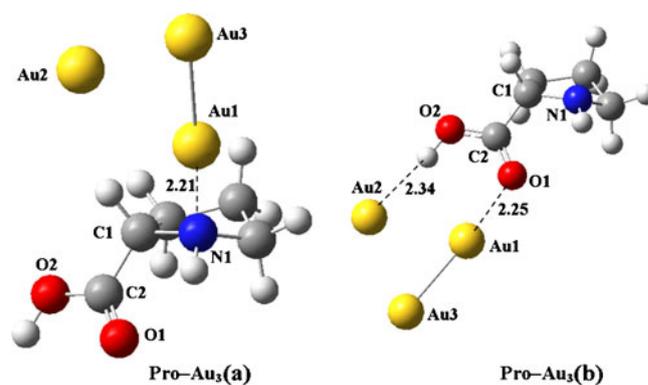

Figure 1. Geometries of proline tagged with Au$_3$ at its amide terminal, Pro-Au$_3$ **(a)**, and at carboxylic terminal, pro-Au$_3$ **(b)**, optimized at UB3LYP/6-311++G ∪ LANL2MB level of theory. Bond lengths are given in angstrom. Atom numbering scheme for atoms at active sites is shown.

Figure 2. Geometries of proline tagged with Au$_3$ at its amide terminal, Pro-Au$_3$ **(a)**, and at carboxylic terminal, pro-Au$_3$ **(b)**, optimized at UB3LYP/6-311++G ∪ LANL2DZ level of theory. Bond lengths are given in angstrom. Atom numbering scheme for atoms at active site is shown.
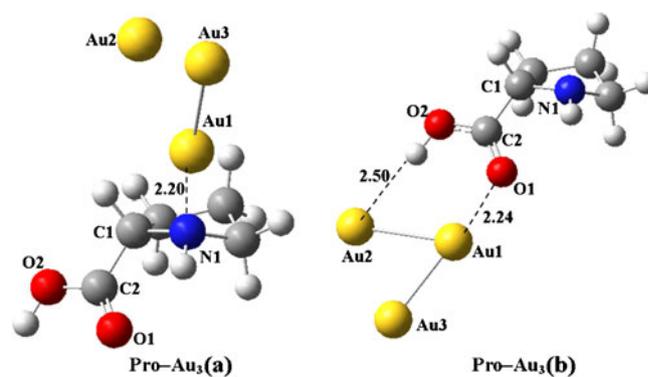
and Pro-Au$_3$ **(b)**, respectively in the subsequent text. Magnitudes of various bond lengths and interaction energies are shown in table 1. Additional structural details and absolute energies of the geometries are shown in table S8.

The structure of Pro-Au$_3$ **(a)** has a monodentate interaction through Au1–N1 with gold cluster. As expected, the Au1–N1 bond length (2·20–2·21Å) does not change much as the basis set is varied, but the interaction energy changes from −36·45 to −28·80 kcal/mol when the gold atoms are treated with LANL2DZ as compared to the case with LANL2MB basis set. This can be attributed to use of higher level of basis set. The enhanced basis set considers inner Au electrons as RECP and uses a double zeta basis set to treat valence electrons.

Significant change is observed in the dihedral angle O1–H–N1–C1 (referred to as ϕ) in isolated proline and Pro-Au$_3$ **(a)**. In isolated proline the angle ϕ is 20·6°, in Pro-Au$_3$ **(a)** optimized at the level of basis sets **1** and **2**, it is 13·9° and 15·0°, respectively (table S8). The reduction in the angle

Table 1. Geometric and energetic features of proline complexed with Au_3 clusters.

Basis set	Molecule	R(X–Au) (Å)	ΔR(X–A) (Å)	$\angle$X − A...B (degrees)	$\Delta \nu$ (X–A) (cm^{-1})	E_{int}(kcal/mol)
1	Pro–Au$_3$ (a)	N1–Au1(2·21)	N1–H(0·01)	N1–H...O1 (110·6°)	N1–H($-112·95$)	$-36·45$
	Pro–Au$_3$ (b)	O1–Au1(2·25)	C2=O1(0·03)		C2=O1($-116·85$)	$-24·66$
		O2H...Au2(2·34)	O2–H(0·01)	O2–H...Au2 (174·1°)	O2–H($-616·30$)	
2	Pro–Au$_3$ (a)	N1–Au$_1$(2·20)	N1–H(0·01)	N1–H...O1 (110·9°)	N1–H($-117·46$)	$-28·80$
	Pro–Au$_3$ (b)	O1–Au1(2·24)	C2=O1(0·03)		C2=O1($-111·31$)	$-17·19$
		O2H...Au2(2·50)	O2–H(0·01)	O2–H...Au2 (177·2°)	O2–H($-477·00$)	

R(X–Au) = length of anchoring bond or non-conventional hydrogen bonds (X = O, N and H); ΔR(X–A) = difference between bond lengths of N–C, O–C and N–H in complexed and isolated fragments; $\angle$X − A...B= H-bond angle (conventional or non-conventional); $\Delta \nu$ (X–A) = difference between frequency of N–C, C–O, N–H and O–H bonds in complexed and isolated fragments; E_{int} = interaction energy; Magnitude of all parameters except interaction energy is given in parenthesis; Basis sets **1** and **2** refer to UB3LYP/6-311++G ∪ LANL2MB and UB3LYP/6-311++G ∪ LANL2DZ, respectively (see text).

Table 2. NBO analysis of donor acceptor interactions in proline tagged with gold cluster, optimized using basis sets **1** and **2** in gas phase.

Molecule	Charge transfer interaction	$E(2)$ (kcal/mol) In complex optimized with basis set **1**	In complex optimized with basis set **2**
Pro-Au$_3$ (a)	$n_{O1} \rightarrow \sigma^*_{N1-H}$	0·55	0·54
	$n_{Au1} \rightarrow \sigma^*_{N1-H}$	0·34	0·39
	$n_{Au3} \rightarrow \sigma^*_{N1-Au1}$	74·12	60·96
Pro-Au$_3$ (b)	$n_{O1} \rightarrow \sigma^*_{Au1-Au3}$	5·35	5·61
	$n_{O1} \rightarrow \sigma^*_{Au1-Au2}$	5·31	-
	$n_{Au2} \rightarrow \sigma^*_{O2-H}$	1·87	1·63
	$n_{O1} \rightarrow n^*_{Au1}$	8·42	8·09

increases proximity of hydrogen of amide with carbonyl oxygen (distance O...H is reduced by 0·22Å). Angle O1...H–N1 in Pro-Au$_3$ (a) optimized at **1** and **2** levels of basis set is 110·6° and 110·9°, respectively, i. e. angle is increased by about 9·0° (tables 1 and S8). This data confirm existence of a weak H-bonding interaction N1–H...O1. This interaction is further substantiated by red shift in the stretching mode of N1–H bond vibration. The frequency of N1–H bond in the complex structure optimized at **1** and **2** levels of basis set is red shifted as compared to isolated fragment, proline, i. e. $\Delta \nu$, which is $-112·95$ and $-117·46$ cm^{-1}, respectively. Overall the results indicate that proline exhibits a favourable interaction with the Au$_3$ cluster through its amide end. This favourable binding induces an intramolecular H-bonding interaction in proline.

The other structure Pro-Au$_3$ (b) has a bidentate interaction through Au1–O1 and Au2...H–O2 bonds with gold cluster. In this case, the magnitude of Au1–O1 bond length (2·24–2·25 Å) does not change much but the Au2...H distances in Au2...H–O2 (2·34 and 2·50 Å, respectively) are significantly different for structures optimized at **1** and **2** levels of basis set, respectively. Interaction energy in the two cases, $-24·66$ and $-17·19$ kcal/mol, respectively differ significantly. The C2=O1 and O2–H bond distances increased by 0·03 and 0·01 Å, respectively after interaction with gold for both choices of basis sets. The stretching mode

of C2=O1 bond in Pro-Au$_3$ (b) undergoes a red shift, i.e. $\Delta \nu = -116·85$ cm^{-1} with respect to isolated proline when the complex structure is treated with basis set **1**. The magnitude of $\Delta \nu$ decreased to $-111·31$ cm^{-1} when basis set **2** is used for the molecule. On the other hand, when optimized with basis set **1**, stretching mode of O2–H shows a large red shift of 616·30 cm^{-1} due to the non-conventional H-bonding interaction, O2–H...Au2. The magnitude of $\Delta \nu$ is reduced to $-477·00$ cm^{-1} when basis set **2** is used for optimization of the molecule. This value is close to the values reported for same kind of interaction seen in glycine and cysteine tagged with Au$_3$ (Pakiari and Jamshidi 2007).

A comparison of interaction energies of the complexes Pro-Au$_3$ (a) and Pro-Au$_3$ (b) indicates that Pro-Au$_3$ (a) possesses highest affinity to the gold cluster. Significantly, both the basis sets **1** and **2** confirmed the trend. This is in agreement with the earlier results of Pakiari and Jamshidi (2007) on glycine-Au$_3$ and Cysteine-Au$_3$ linkages which concluded that amine end of the amino acids has more affinity to the gold cluster.

3.2 *Natural bond orbital analysis*

Natural bond orbital (NBO) analysis has been performed on the geometries in order to quantify noncovalent donor–acceptor interactions between gold cluster and the amino

acid. Such interactions result in transfer of occupancy from the localized bonding orbital to empty non-Lewis orbitals. The study provides additional insights into interaction of the amino acid with gold cluster. Results of second order perturbation theory analysis of the Fock matrix for donor and acceptor delocalization interactions observed in the complex structures optimized using basis sets **1** and **2** are given in table 2. The discussion mainly refers to geometries optimized with basis set **2**.

Stabilization energy, $E^{(2)}$, of charge transfer interaction, $n_{Au3} \rightarrow \sigma^*_{N1-Au1}$ in Pro-Au$_3$ **(a)** is significant as the magnitude is 60·96 kcal/mol. Charge transfer from lone pair of Au1 to antibonding orbital of N–H is low, as the value of $E^{(2)}$ for the interactions is 0·39 kcal/mole in the geometry. This is an obvious result since hydrogen of amide does not lie between Au1 and N1. Additionally it forms a hydrogen bond interaction with carbonyl oxygen of proline, the energy, $E^{(2)}$, of which is 0·54 kcal/mol.

NBO analysis of interactions in other complex structure Pro-Au$_3$ **(b)** confirms existence of stabilizing interactions. Energy of non-conventional O2–H. . . Au2 hydrogen bonding interaction is 1·63 kcal/mol, indicating a smaller amount of charge transfer from lone pair of Au2 to σ^*_{O2-H}.

A comparison of magnitudes of $E^{(2)}$ shown by the molecules optimized at basis sets **1** and **2** indicates that interactions in the geometries optimized at basis set **1** are larger when compared to those seen with basis set **2**. This result agrees with greater amount of interaction energies, E_{int}, determined at basis set **1** (table 1). Similarly, comparison of the values obtained for Pro-Au$_3$ **(a)** and **(b)** indicates that magnitudes of sum of all charge transfer interaction in Pro-Au$_3$ **(a)** is greater than that in Pro-Au$_3$ **(b)**. This result also agrees with our earlier conclusion that amide end of proline shows higher affinity to gold cluster.

4. Conclusions

Interaction of proline with Au$_3$ has been described using energetic, geometrical and spectroscopic aspects. The metal interacts with proline through anchoring bonds, N–Au, O–Au and a non-conventional O–H. . . Au hydrogen bond. Basis set dependence of interaction energies is noticed. Though trend of results provided by both the basis sets is the same, magnitudes of interaction energies obtained from basis set **2** are more reliable. Amide terminal of proline shows highest affinity to the cluster. Bond lengths of N–H, C=O and O–H in the amino acid are increased after complexation. The stretching mode of vibrations of these bonds undergoes red shift with respect to isolated proline structure. Interaction of cluster through amide end of proline induces a weak intramolecular H-bonding interaction, N1–H. . . O1. NBO analysis of the noncovalent interactions substantiates favourable interaction of proline with the cluster through its amide terminal.

Further study on interaction of gold with a proline associated with a secondary structure and a comparison with the present study is in progress.

Electronic supplementary material

Supplementary material pertaining to this article is available on the Bulletin of Materials Science Website (www.ias.ac.in/matersci).

References

Agrawal B K, Agrawal S, Srivastava P and Singh S 2004 *J. Nanopart. Res.* **6** 363

Ait-Haddou H, Wiskur S L, Lynch V M and Anslyn E V 2001 *J. Am. Chem. Soc.* **123** 11296

Balasubramanian K and Liao D 1991 *J. Chem. Phys.* **94** 5233

Balasubramanian K and Liao D 1992 *J. Chem. Phys.* **97** 2548

Bucher S W, Gold J R and Freiser B S 1988 *J. Chem. Phys.* **88** 3678

Černý J and Hobza P 2007 *Phys. Chem. Chem. Phys.* **9** 5291

Cheeseman M A and Eyler J R 1992 *J. Phys. Chem.* **96** 1082

Dennington R II, Todd K, Millam J, Eppinnett K, Lee Hovell W and Ray G 2003 *GaussView3.09* (Shawnee Mission, KS: Semichem, Inc.)

Felice R D, Selloni A and Molinari E 2003 *J. Phys. Chem.* **B107** 1151

Fielicke A, von Helden G, Meijer G, Pedersen D B, Simard B and Rayner D M 2005 *J. Am. Chem. Soc.* **127** 8416

Frisch M J *et al* 2003 *Gaussian03* (Pittsburg, PA: Gaussian, Inc.) revision B.05

Furche F, Ahlrichs R, Weis P, Jacob C, Gilb S, Bierweiler T and Kappes M M 2002 *J. Chem. Phys.* **117** 6982

Gilb S, Weis P, Furche F, Ahlrichs R and Kappes M M 2002 *J. Chem. Phys.* **116** 4094

Hakkinen H, Moseler M and Landman U 2002 *Phys. Rev. Lett.* **89** 03340

Hehre W J, Stewart R F and Pople J A 1969 *J. Chem. Phys.* **51** 2657

Kim Y D, Fischer M and Gantefor G 2003 *Chem. Phys. Lett.* **377** 170

Kohn W, Becke A D and Parr R G 1996 *J. Phys. Chem.* **100** 12974

Krűger D, Fuchs H, Rousseau R, Marx D and Parrinello M 2002 *Phys. Rev. Lett.* **89** 186402

Kryachko E S and Remacle F 2005a *Nano Lett.* **5** 735

Kryachko E S and Remacle F 2005b *J. Phys. Chem.* **B109** 22746

Kumar A, Mishra P C and Suhai S 2006 *J. Phys. Chem.* **A110** 7719

Lee H M, Ge M, Sahu B R, Tarakeshwar P and Kim K S 2003 *J. Phys. Chem.* **B107** 9994

Lee T H and Ervin K M 1994 *J. Phys. Chem.* **98** 10023

Lian L, Hackett P A and Rayner D M 1993 *J. Chem. Phys.* **99** 2583

Moradi M, Babin V, Roland C, Darden T A and Sagui C 2009 *Proc. Nat. Acad. Sci. USA* **106** 20746

Niemietz M, Gerhardt P, Gantefor G and Kim Y D 2003 *Chem. Phys. Lett.* **380** 99

Pakiari A H and Jamshidi Z 2007 *J. Phys. Chem.* **A111** 4391

Read A E, Weinstock R B and Weinhold F 1985 *J. Chem. Phys.* **83** 735

Remacle F and Kryachko E S 2005 *J. Chem. Phys.* **122** 044304

Riboh J C, Haes A J, McFarland A D, Ranjit C and Van Duyne R P 2003 *J. Phys. Chem.* **B107** 1772

Shafai G S, Shetty S, Krishnamurty S, Shah V and Kanhere D G 2007 *J. Chem. Phys.* **126** 014704

Shafer-Peltier K E, Haynes C L, Glucksberg M R and Van Duyne R P 2003 *J. Am. Chem. Soc.* **125** 588

Sharma P, Sharma S, Mitra A and Singh H 2009 *J. Biomol. Struct. Dyn.* **27** 65

Shukla M K, Dubey M and Leszcynski 2008 *ACS Nano* **2** 227

Soule de Bas B, Ford M J and Cortie M B 2004 *J. Mol. Struct.: Theochem.* **686** 193

Storhoff J J, Elghanian R, Mucic R C, Mirkin C A and Letsinger R L 1998 *J. Am. Chem. Soc.* **120** 1959

Sudeep P K, Joseph S T S and Thomas K G 2005 *J. Am. Chem. Soc.* **127** 6516

Walker A V 2005 *J. Chem. Phys.* **122** 094310

Weis P, Welz O, Vollmer E and Kappes M M 2004 *J. Chem. Phys.* **120** 677

Xiao L and Wang L 2004 *Chem. Phys. Lett.* **392** 452

Xiao L, Tollberg B, Hu X and Wang L 2006 *J. Chem. Phys.* **124** 114309

Yuan D W, Wang Y and Zeng Z 2005 *J. Chem. Phys.* **122** 114310

Zheng J, Petty J T and Dickson R M 2003 *J. Am. Chem. Soc.* **125** 7780