Amino Acids (2014) 46:911–920
DOI 10.1007/s00726-013-1642-6

ORIGINAL ARTICLE

Comparison of amino acids interaction with gold nanoparticle

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Received: 8 July 2013 / Accepted: 9 December 2013 / Published online: 31 December 2013

Abstract The study of nanomaterial/biomolecule interface is an important emerging field in bionanoscience, and additionally in many biological processes such as hard-tissue growth and cell-surface adhesion. To have a deeper understanding of the amino acids/gold nanoparticle assemblies, the adsorption of these amino acids on the gold nanoparticles (GNPs) has been investigated via molecular dynamics simulation. In these simulations, all the constituent atoms of the nanoparticles were considered to be dynamic. The geometries of amino acids, when adsorbed on the nanoparticle, were studied and their flexibilities were compared with one another. The interaction of each of 20 amino acids was considered with 3 and 8 nm gold GNPs.

Keywords Gold nanoparticle · Amino acid · Molecular dynamic · OPLSAA

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Introduction

In the past two decades, there has been an exponential growth in the number of commercially available therapeutic products based on nanoparticles (NPs). More than 150 companies are developing nanoscale therapeutics and 24 nanotechnology-based clinical products have received approval for utilization (Zhang et al. 2008; Salata 2004). While new applications of NPs in biology are rapidly growing, the largest challenge in the use of NPs is their interface with biomolecules. Proteins can be adsorbed non-specifically on the surface of NPs, changing the biomolecular structure and function, which consequently create adverse biological effects (Kishore 2013; Mandal and Murali 2005; Andre et al. 2009; Eugene et al. 2012).

In many applications like self-assembly, sensing, imaging, therapy, bio-catalysis, and in several biological process such as hard-tissue growth and cell-surface adhesion, NPs are conjugated to biological systems (Kishore 2013; Agnieszka et al. 2011; Dykman and Khlebtsov 2010).

Among polymeric and metal NPs, GNP has attracted enormous scientific and technological interest due to their ease of synthesis, stability and inertness (Alkilany and Murphy 2010).

GNPs, present fascinating aspects such as optical (quantum size effect), size-related electronic, magnetic as well as applications to catalysis and biology. GNP has a range of biomedical applications including its use in sensitive diagnostic assays (Pingarron et al. 2008; Liu et al. 2010; Goodman et al. 2004; Saleh et al. 2011; Tang and Hewlett 2010; Neng et al. 2010; Javier et al. 2008; Duncan et al. 2010; Xu et al. 2007), thermal ablation and radiotherapy improvement (Rahman et al. 2009; Huang et al. 2008; Geoffrey et al. 2009; Finkelstein et al. 1976;

Leonaviciene et al. 2012), antitumor activities (Shanei et al. 2012; Yang et al. 2010), implants (Shuoqi et al. 2013), drug and gene delivery (Xu et al. 2007; Dakrong et al. 2011; Nikunj et al. 2012; Valerio et al. 2012; Ghosh et al. 2008).

Despite these extensive applications of GNP, a design-oriented approach for protein/GNP adsorption remains restricted since we do not know the details of protein/GNP affinity (Verde et al. 2009). With growing applications of GNPs in biology and medicine, its conjugation to the biomolecules is increasingly attracting attention (Lee and Ytreberg 2012; Chen et al. 2007). Therefore, not only is the exploiting of properties of the GNPs extremely necessary, but also their interface with biomolecules is crucial for more effective applications in biology (Kishore 2013; Mandal and Murali 2005).

To enable a design-oriented approach, we need a theoretical framework that explains experimental observations and provides tips for showing features of protein/GNP interface. Necessary for this framework is a molecular description of peptide adsorption that identifies and isolates contributing factors such as amino acid identity, associated characteristics (charge and polarity), flexibility, and structural stability in solution (Sobczak-kupiec 2011; Zhang et al. 2009).

As finding actual experimental data for describing and visualizing protein/GNP conjugates is difficult, computer simulation could be a very valuable resolution (Lee and Ytreberg 2012). Computational methods provide direct access to the structural properties of interacting elements (Hoefling et al. 2010).

In 2003, the adsorption of the Cys amino acid on the Au (111) surface of gold was studied by means of periodic density functional calculations. Results for various adsorption sites and molecular configurations showed that chemisorption involving S (thiolate)–Au bonds on Au (111) was favored by starting with either cysteine or cystine (Felice 2003).

In 2005, Podstawka et al. worked on Surface-Enhanced Raman Scattering (SERS) of amino acids deposited onto colloidal gold surface. The orientation of amino acids as well as specific and competitive interactions of their functional groups with the gold surface were predicted by detailed spectral analysis of the obtained SERS spectra (Podstawka et al. 2005).

In 2010, Martin et al. explored the conformations of amino acids on gold metal surface by GOLP force filed in which the gold atoms were considered constant (Hoefling et al. 2010). In addition, in 2011, using this force field, they showed the interaction of β-sheet polypeptides with a gold surface and found that adsorption occurs in a stepwise mechanism (Hoefling et al. 2011).

In 2012, using MD simulation, Kuo Hao Lee et al. found that GNP conjugation effect on peptide dynamics and structure depends on the amino acids sequence of the peptide (Lee and ytreberg 2012).

With the help of MD simulation and COMPASS force field, Zhen et al. showed histidine and histidine-containing peptide adsorption behavior on gold surface, which gold atoms were considered constant during the simulation (Zhen et al. 2011).

In 2012, Sandhya et al. studied the interaction of proline with gold cluster by theoretical methods and using DFT. They found that higher tendency for interaction with Au cluster is through amine terminal (Rai et al. 2012).

Amino acids are the building blocks of proteins which can be found free in the blood, and once encountered with GNPs, they are attracted to them (Miyagi et al. 2011; Stanford and william 1954). Thus, evaluating how each of them interacts with the surface of the gold nanoparticles is very crucial.

In the present research, we performed molecular dynamics (MD) studies of adsorption of each of the 20 amino acids on the GNP by OPLSAA force field, where gold atoms were dynamic (Fig. 1). The molecular structure of adsorbed amino acids on the GNP, their flexibility and stability and the effect of nanoparticle size was studied.

Computational method

In these simulations, it was expected that the adsorption geometry of L-amino acids on GNPs could be obtained from the molecular level. Meanwhile, the priorities of the adsorption of all amino acids on GNP, which is not easily understandable in experiments, could be determined. MD was used to simulate amino acids/GNP interaction in explicit solvent in a cubic simulation box of volume 50 $Å^3$. In the solvated box, Na and Cl ions were added to obtain physiological conditions of 150 mM and an overall neutral box. All simulation was performed in natural biologic condition (normal saline: containing ions Na^+ and Cl^-, pH = 7.4, Temperature = 27 °C) that was fixed during the simulation. During the simulation, periodic boundary conditions were applied in all three dimensions. $3 \times 3 \times 3$ nm^3 cubic shape GNP was constructed with 2,048 atoms and $8 \times 8 \times 8$ nm^3 GNPs from 32,000 atoms.

All simulations were performed using Gromacs 4.5.5 software package (Spoel et al. 2005) with the TIP4P model of water (Mark and Nilsson 2001; Guillot 2002) and the OPLSAA force field (Kahn and Bruice 2002; Jorgensen and Tirado-Rives 1988). Visual Molecular Dynamics 1.9 (VMD) (Humphrey et al. 1996) was used for preparation of snapshots. The parameters describing the interactions for Au atoms were taken from Hendrik Heinz et al. (2008) where $r_0 = 2.951$ Å and $\varepsilon_0 = 5.29$ kcal/mol. These new Lennard–Jones (LJ) parameters can be implemented in the

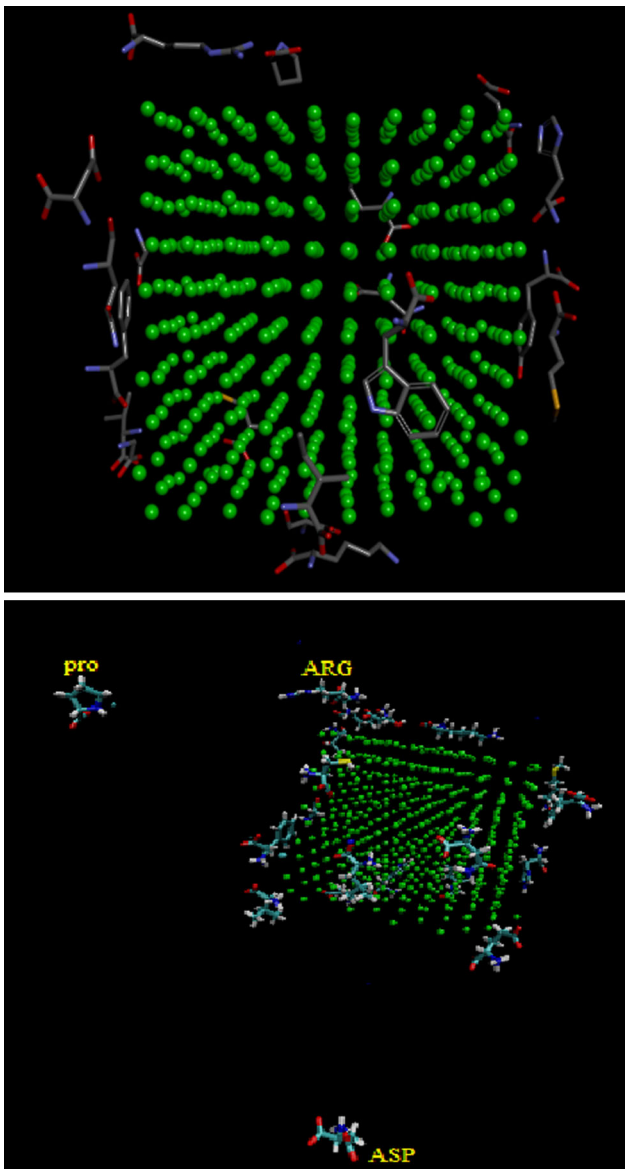

Fig. 1 Figure shows (*up*) all 20 amino acids interaction with gold nanoparticle. (*down*) Amino acids adsorption on GNP are competitive and when the number of amino acids are high, some of them such as PRO, ASP and ARG are not adsorbed on the surface

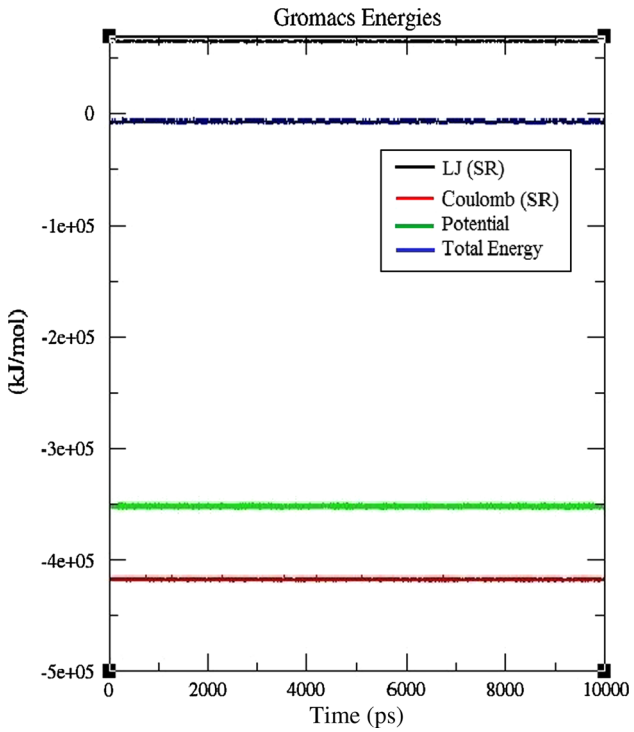

Fig. 2 Energies graph show energies are stable throughout the simulation

OPLSAA force field and applied to the simulation of GNPs and their interfaces with water, biopolymers, organic molecules, and inorganic components. Using these parameters, we can consider all atoms of gold in a dynamic mode (Heinz et al. 2008).

For our simulations, charges for the gold atoms were set to zero and the atoms were dynamic during the simulation. Minimization was performed for 2 ns in the NPT ensembles to remove potential overlaps between water and amino acids, followed by 10.0 ns of dynamic simulation in the NVT ensembles at $T = 300$ °K. During the minimization and simulation process, a Nose'-Hoover thermostat was utilized (Hunenberger 2005) to enforce the desired temperatures. The LINKS algorithm was implemented to allow 8×10^{-4} ps time step (Hess et al. 1997). The long-range electrostatic interactions were accounted for using the Ewald method with a real-space cutoff of 12 Å. Van der Waals interactions were cut off at 12 Å with a switching function between 10 and 12 Å. For analyzing the result of simulation, the root mean square deviation (RMSD) (Eq. 1) (Yang and Zhao 2007) is as follows:

$$\mathrm{RMSD}(t1,t2) = \left[\frac{1}{N}\sum_{i=1}^{N} m_i ||r_i(t1) - r_i(t2)||^2\right]^{\frac{1}{2}} \quad (1)$$

where N is the number of target molecules and $r_i(t)$ is the position of molecule i at time t.

Root mean square fluctuations (standard deviation) of atomic positions in the trajectory after (optionally) fitting to a reference frame were calculated. RMSF of the Cα quantifies the peptide dynamics.

Amino acids adsorption rate was found by measuring diffusion coefficients. Diffusion coefficient calculation was done by directly measuring the mean square displacements (MSD) of the center of mass of amino acids from the MD trajectory. Diffusion coefficients (D) can be obtained from the slope of the mean square deviation versus time curve, using the Einstein relation Eq. (2) (Zhen et al. 2011):

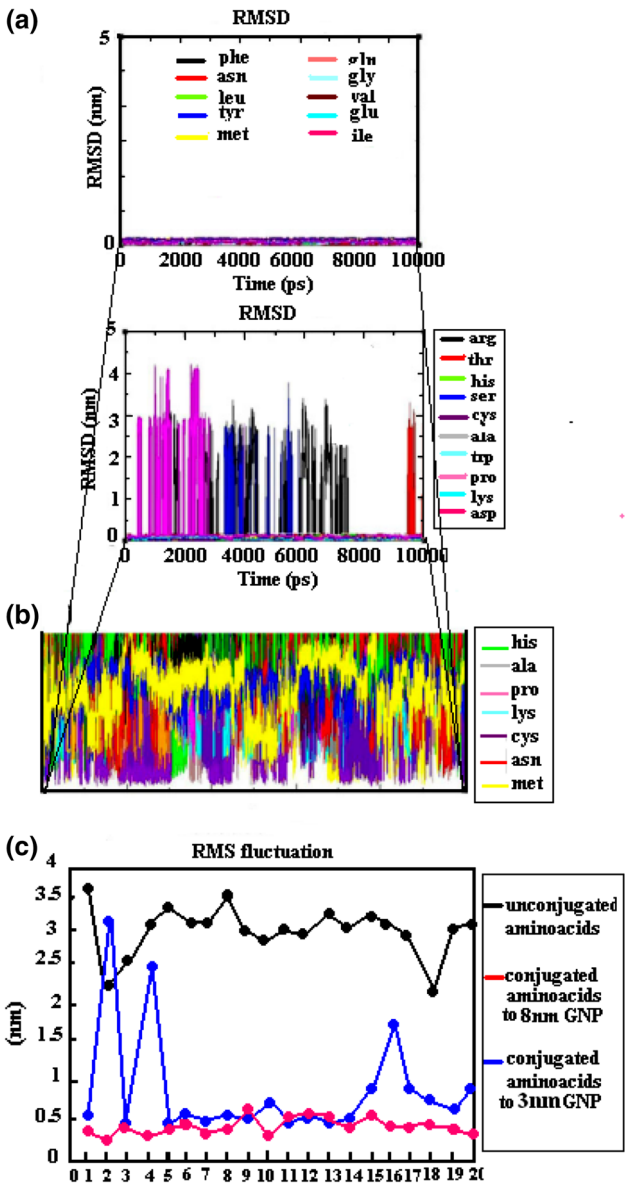

Fig. 3 These figures show RMSD and RMSF between unconjugated and conjugated structure of amino acids during the adsorption on the GNP surface. **a** Figure show some of the amino acids after adsorption on the GNP continue to fluctuate on the surface of gold. **b** Figure shows Pro, Cys, and Met that after adsorption on the GNP surface stay in nearest distance from the surface that confirms their entropy decrease more than the other amino acids. **c** Figure shows RMSF of unconjugated (*black*) and conjugated amino acids to 3 nm (*blue*) and 8 nm (*red*) GNP. Residue names from 1 to 20 are: Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val (color figure online)

$$D_\alpha = \frac{1}{6N_\alpha} \lim_{t\to\infty} \frac{d}{dt} \sum_{i=1}^{N\alpha} \left\langle \left[r_i(t) - r_i(0)^2 \right] \right\rangle \quad (2)$$

d = dimensionality of system, $r_i(t)$ = center-of-mass coordinates of the ith amino acids at time t, $r_i(0)$ = center-of-mass coordinates of the ith amino acids at $t = 0$.

Table 1 Self-diffusion coefficients of amino acids during the adsorption on the GNP

Amino acid	D (amino acid)/10^{-6} cm^2 s^{-1}
Ala	0.19
Arg	0.009
Asn	0.01
Asp	0.44
Cys	0.02
Gln	0.1
Glu	0.03
Gly	0.02
His	0.1
Ile	0.15
Leu	0.04
Lys	0.02
Met	0.09
Phe	0.04
Pro	0.1
Ser	0.001
Thr	0.27
Trp	0.17
Tyr	0.02
val	0.07

The simulation of 8 nm GNP was also done under the same conditions. The minimum distance of amino acids from the surface for both nanoparticle sizes was measured, too. To have a rough measure for the compactness of a structure, the radius of gyration was calculated as follows (Eq. 3):

$$Rg = \frac{\left(\sum i||r_i||^2 m_i\right)^{\frac{1}{2}}}{\sum i \;\; m_i} \quad (3)$$

where m_i is the mass of atom i and r_i is the position of atom i with respect to the center of mass of the molecule.

Results

We demonstrated the effect of GNP on the structure of each of the 20 amino acids. All simulations were performed for 10 ns. The analysis of the energy graphs during the simulation of amino acids adsorption on GNP depicted that energies were stable throughout the run (Fig. 2). This indicated that the system remained stable during the course of the MD run after the adsorption of amino acids on GNP surface.

Flexibility and stability of amino acids after adsorption on GNP

Protein flexibility and stability in solution are related characteristics. Stability refers to the ability of the protein

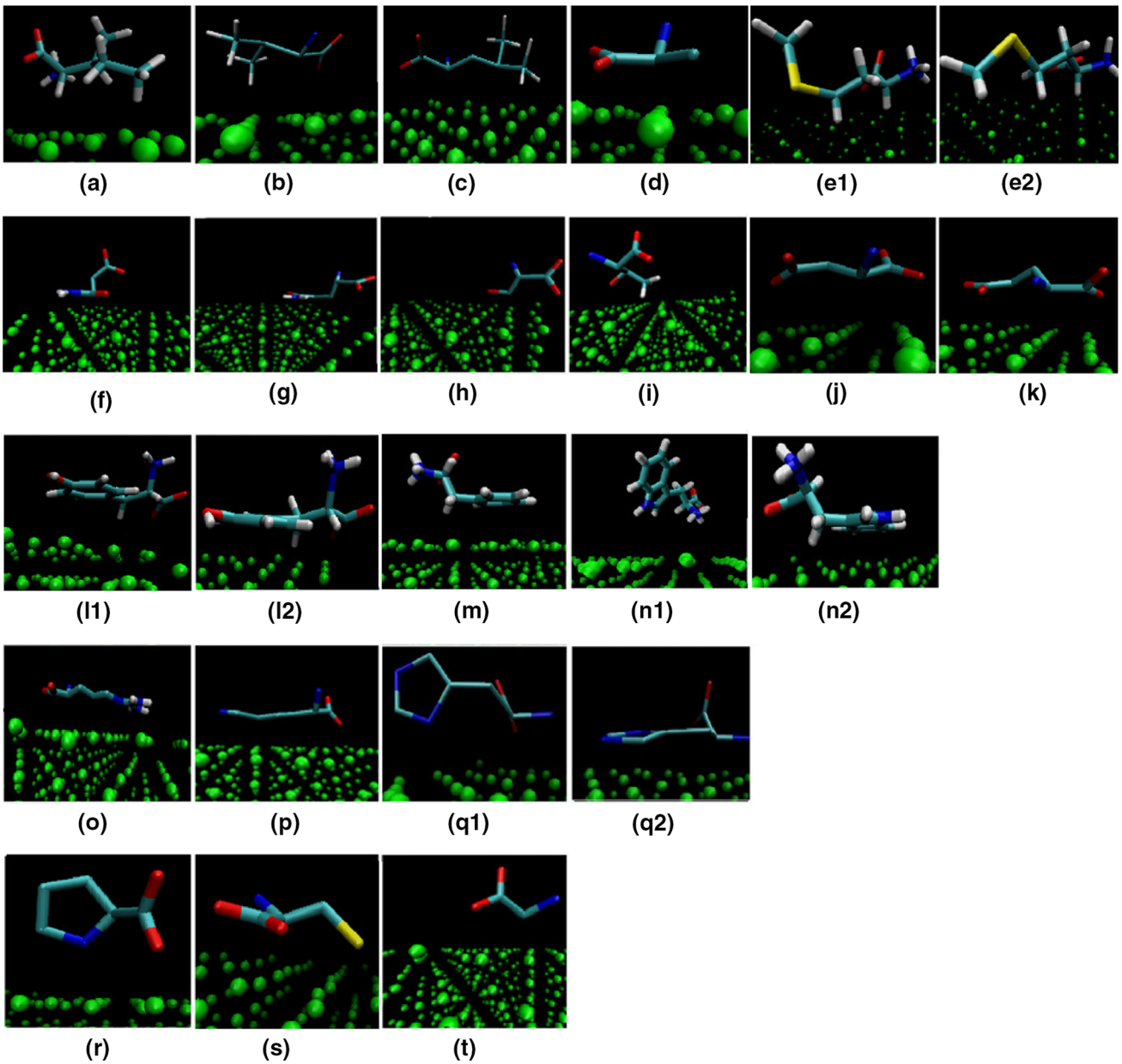

Fig. 4 This figure shows the snapshots of the final configuration of adsorbed amino acids on GNP. *Blue* rods are carboxylic group and red rods are amine group. *Yellow* rod shows S atoms. **a** Ile, **b** Val, **c** Leu, **d** Ala, **e1**, **e2** Met, **f** Asn, **g** Gln, **h** Ser, **i** Thr, **j** Asp, **k** Glu, **l1**, **l2** Tyr, **m** Phe, **n1**, **n2** Trp, **o** Arg, **p** Lys, **q1**, **q2** His, **r** Pro, **s** Cis, **t** Gly (color figure online)

to maintain its overall conformation, whereas protein flexibility deals with oscillations about this overall conformation (Verde et al. 2009).

The analysis of RMSDs give insight into how the flexibility of each amino acid changes when conjugated to the GNP (Fig. 3a, b). The fluctuations of Pro, Cys, and Met on surface are the lowest, meaning that these three amino acids are the most stable species on the gold nanoparticle.

RMSF results on the 3 nm GNP (Fig. 3c) show that the fluctuations of Arg, Asp, Pro, Ser, Thr and Val are more than those of other amino acids, and once the flexibility of most amino acids decreases on the gold surface rather than in the absence of GNP, the flexibility of Thr may still increase when conjugated.

Adsorption rate of amino acids on GNP

We obtained the diffusion coefficients of the amino acids using Einstein relation (Eq. 2). Based on the calculated values in Table 1, we can conclude that the adsorption rates of Asp, Met and Lys on the GNP are the highest.

Adsorption geometry

To clearly display the adsorption geometry of the amino acids on GNP surface, we took the snapshot of the final configuration of amino acids adsorbed on GNPs.

Aliphatic amino acids have linear hydrophobic side groups. In Fig. 4, their interaction with GNP is illustrated. The amino acids that have methyl group in their side chain such as Ile (Fig. 4a), Val (Fig. 4b), Leu (Fig. 4c) and Ala (Fig. 4d) are adsorbed through methyl group. In addition, in these amino acids, carboxylic head assists them to interact with GNP.

Met adsorption on the nanoparticles is mediated by S–CH3 group. In Fig. 4e1, e2, it is observed that Met is adsorbed on the nanoparticle surface in two various forms whose difference is how the S–CH_3 groups approach the GNP surface.

Asn (Fig. 4f) and Gln (Fig. 4g) adsorptions on the surface of the GNP take place through the amino group in side chain.

Ser (Fig. 4h) and Thr (Fig. 4i) have a hydroxyl group in their side chain, and their uptake on the surface of GNP occurs via this OH through Au–O interaction.

The interaction of GNPs with the negatively charged amino acids is considered in Fig. 4j and k. Asp and Glu, side chains contain a carboxyl group. The carboxylic groups of these amino acids, when placed on the surface of GNPs, oscillate along the z direction on the surface, and keep amino acids close to the surface.

Phe, Tyr and Trp are generally hydrophobic (Dennis 2007). According to our results, these amino acids, with aromatic rings, were adsorbed with a similar pattern so that the aromatic ring was in parallel orientation to the gold surface (Fig. 4l, m, n). Hydroxyl group in the phenyl of tyrosine was oriented toward the gold surface (Fig. 4l1, l2).

Three amino acids—His, Arg and Lys—have NH_2 functional group with positive charge. Figure 4o, p, q show how each of them interacts with GNPs. These amino acids are adsorbed from the amine group on the surface of GNPs by Au–N interaction.

Cys has a sulfur atom that can bond to the GNP covalently. Cys stays near the surface through sulfur atom (Fig. 4s). Sulfur atom distance from the surface is 2.6 Å, which matches very well with the S–Au distance reported for the DFT Study of Cys Adsorption on GNP (111) (Felice 2003).

Gly was adsorbed on the surface through COOH (Fig. 4t) which was in accordance with the experimental result (Podstawka et al. 2005).

Pro interacts through the amine (Au–N) and carboxylic group (Au–O and Au–H–O); the corresponding complexes with gold cluster are referred to Fig. 4r.

Our simulation results about adsorption structure on the GNP for Met, Cys, Gly, Leu, Phe and Pro, are fully matched with the experimental results of Podstawka et al. that were obtained by SERS (Podstawka et al. 2005). They showed the aromatic ring of Phe, taking part in the adsorption on the GNP surface. Regarding our results, all amino acids with aromatic rings had a similar adsorption pattern on GNP surface through the π–metal interaction. π–Metal interactions play a major role in making organometallic components (Podstawka et al. 2005; Miessler and Tarr 2010). Trp and Tyr, which have nitrogen and hydroxyl in their aromatic rings, respectively, do not stay completely parallel to the surface and may fluctuate. Both Cys and Met adsorb on the GNP through the sulfur atom. However, the side chain of Met has more fluctuation. All amino acids containing hydroxyl group in the side chain such as Tyr, Thr and Ser are adsorbed on the surface through the Au–OH interactions. Even in Tyr, in which there is π–metal interaction, hydroxyl group has a tendency toward the surface. Ala, Val, Ile and Leu, with linear side chain, adsorb on the GNP surface by the methyl group. His, Arg, Lys adsorption on the GNP surface is through amino group which is presented in their side chain. Our simulation results on lysine confirm the experimental work by Ossi Horovoitz who used lysine as a connector among gold atoms, and showed that the amine group of lysine is linked to the GNP (Horovitz et al. 2007). The geometry of the His obtained from our simulations is in agreement with the model for adsorption of His on Au surface based on the experiments of Feyer et al. (2010).

Comparison of amino acids adsorption behavior on 3 and 8 nm GNPs

The main purpose of this study was to investigate how each of the 20 amino acids interacts with gold nanoparticle. To show whether the size increase in the GNP has any effect on aminoacids interaction or not, simulation of 8 nm nanoparticles interaction with amino acids was performed.

There was no difference between the structure of proteins adsorption on the 3 and 8 nm GNPs, and the functional groups involved. The results of minimum distance of amino acids from the surface were almost the same in both cases (Fig. 5).

According to the results of our simulation (Fig. 6), changes in nanoparticle size had no significant effect on the compactness of the amino acids. By comparing the RMSF of both systems, we can understand the effect of nanoparticle size increases on the flexibility of the amino acids. According to Fig. 3c, in 8 nm GNP, the flexibility of amino acids was further reduced.

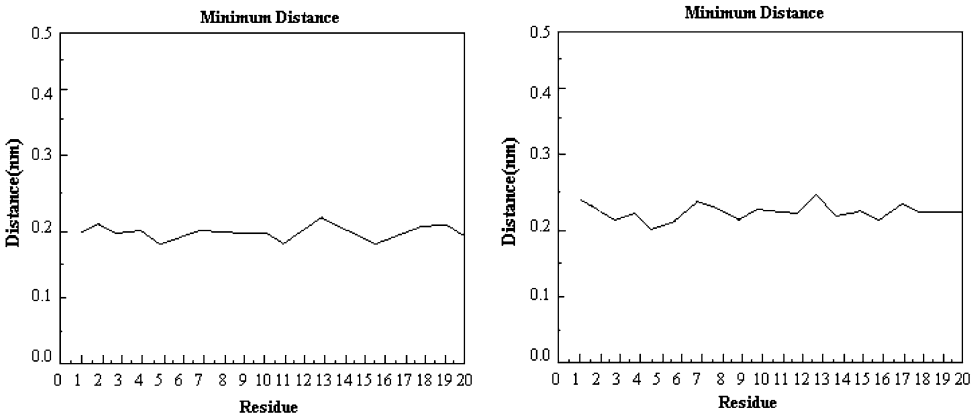

Fig. 5 Residue minimum distance from the 3 (*left* hand) and 8 nm GNP (*right* hand) are shown. As can be seen, amino acids are located in the same distance from both GNP. Residue names from 1 to 20 are: Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val

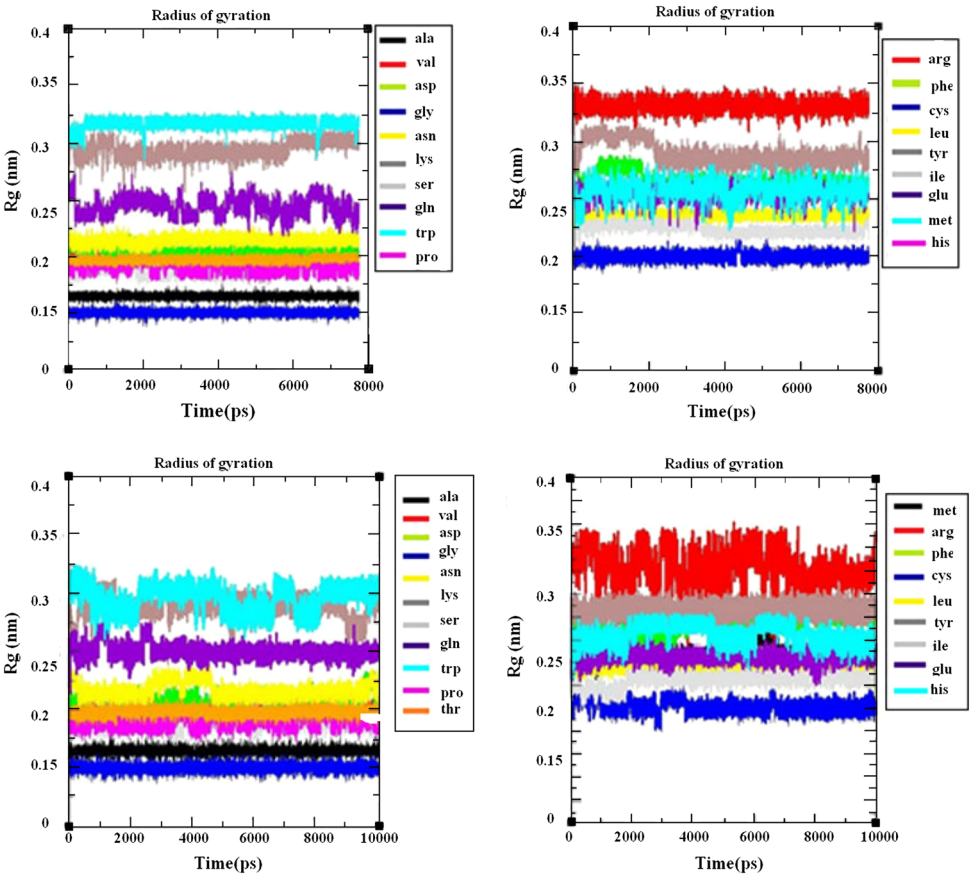

Fig. 6 Gyration of amino acids on 8 nm (*up*) and 3 nm (*down*) GNP. It is clear that amino acid compactness do not change by nanoparticle size

Conclusion

GNPs are one of the most widely used nano products. We are able to conjugate GNPs with peptides, drugs, and other molecules to gain desirable effects (Logothetidis 2006; Surendiran et al. 2009; Dykman and Khlebtsov 2011; Rippel and Seifalian 2011). MD simulation is still proved to be a valuable tool to study the adsorption of proteins on the organic metals, mainly due to the high degree of consistency between the MD results and the experimental conclusions (Zhen et al. 2011). Our findings in this paper are the result of a computational calculation that was compared with the experimental results. For validation of our model, we compared our simulation results for six amino acids including Cys, Phe, Met, Gly, Leu and Proline with Podstawka et al.'s experimental results, Lys with Ossi Horovoitz experimental result and His with Feyer et al.'s experimental result that were in good agreement. Despite the growing applications of amino acids conjugated to gold nanoparticle, there is not

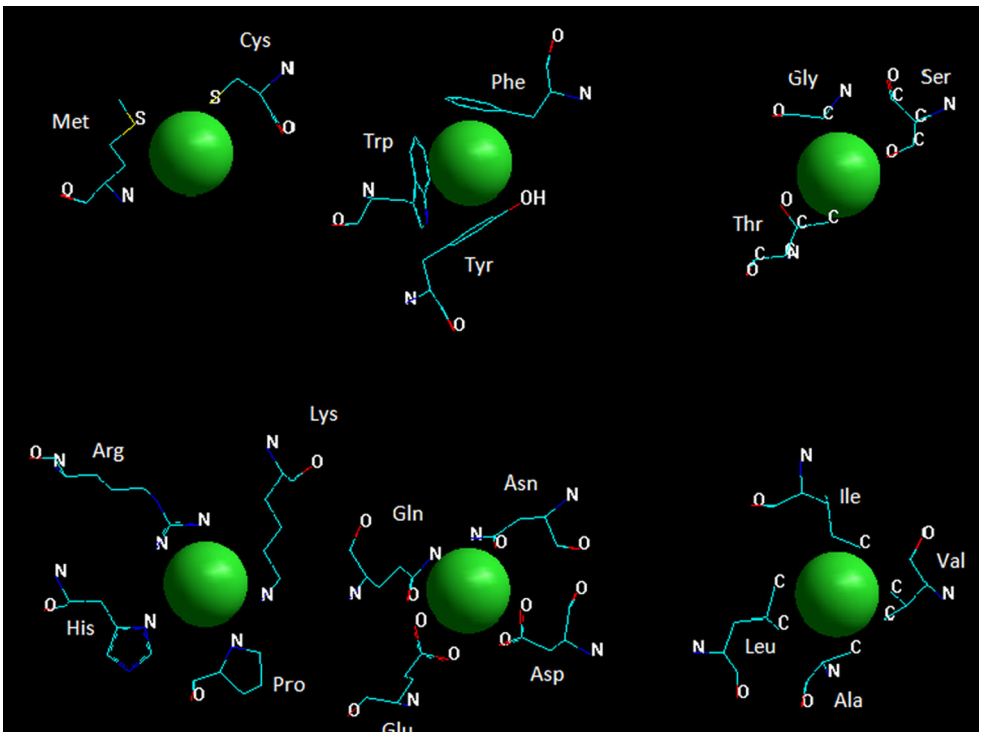

Fig. 7 Schematic representation of the amino acids adsorption on the gold atom

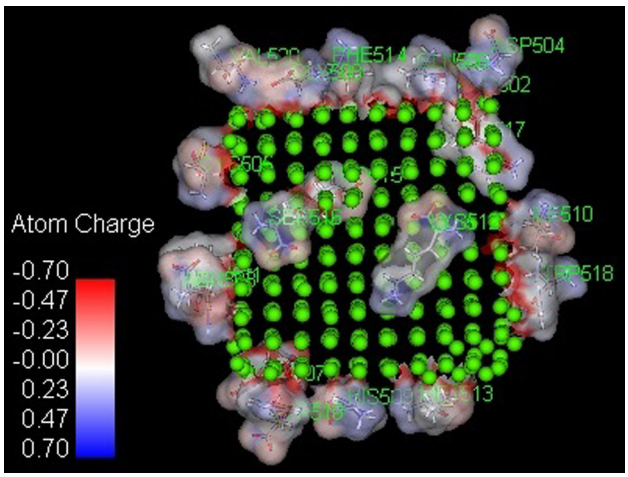

Fig. 8 Charge distribution of amino acids adsorbed on gold nanoparticles

much experimental work that describes the molecular level of interaction and this was one of our purposes for this study. The demonstration of the composition of amino acids with high affinity for GNP surface reveals the fact that the 20 natural amino acids are not equal (Chen et al. 2007). We described preferred orientations of the amino acids on the GNP (Fig. 7). The adsorption rate of Asp on the GNP surface is faster than that of others, while the flexibility of ASP plus Ser, Arg and Thr on the GNP is more than that of other amino acids. Pro, Cys, and Met are more stable on the GNP surface. Therefore, we suggest that wherever we need protein connected tightly to the nanoparticle, we can establish a connection through one of these amino acids.

The data described herein show that the stability of the nanoparticles depends on the concentration of amino acids, and it is competitive.

All the 20 amino acids compete for adsorption on the 3 nm GNP, the stability of amino acids such as Arg, Asp and Pro is less than that of the others. But when these amino acids were exposed to 3 nm GNP individually, they remained quite stable and did not get separated from the nanoparticle surface during the simulation. On the basis of the previous finding, we can conclude that since 8 nm nanoparticle has a greater surface area, the density of amino acids is lower on it.

When the stability of amino acids on the 3 and 8 nm GNPs was compared, it was found that on the 8 nm GNP, amino acids reached more stability. In many papers, it is reported that smaller gold nanoparticles are more toxic than larger ones (Coradeghini et al. 2013; Mironava et al. 2010). We suggest that, the cause of it could be the more flexibility of amino acids on the smaller GNP. As a consequence, it can be said that when larger GNPs are inserted into the body, amino acids bind more tightly to them, and cover them. Therefore, they are not known as foreign agent, in the body. However, once smaller GNPs are inserted into the body, it reacts to them as foreign agents.

By detecting the charges of atoms in the system, we found that negatively charged atoms, shown red in Fig. 8, play a significant role in adsorption of amino acids on the GNP.

The simulation of amino acids is a crucial initial step in describing the interactions of more complex bio-molecular systems with nanoparticles. We hope our basic level study reveal an important insight into future effective design of GNP-binding polypeptides.

Acknowledgments This paper is part of a PhD thesis in nanomedicine by Fatemeh Ramezani. Financial support was provided by Tehran University of Medical Sciences.

Conflict of interest The authors report no declaration of interest.

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