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The use of graphene-based nanomaterials is being explored in the context of various biomedical applications. Here, we performed a molecular dynamics simulation of individual amino acids on graphene utilizing an empirical force field potential (Amber03). The accuracy of our force field method was verified by modeling the adsorption of amino acids on graphene in vacuum. These results are in excellent agreement with those calculated using *ab initio* methods. Our study shows that graphene exhibits bioactive properties in spite of the fact that the interaction between graphene and amino acids in a water environment is significantly weaker as compared to that in vacuum. Furthermore, the adsorption characteristics of capped and uncapped amino acids are significantly different from each other due to the desolvation effect. Finally, we conclude that when assessing protein-surface interactions based on adsorption of single amino acids, the minimum requirement is to use capped amino acids as they mimic residues as part of a peptide chain. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4828437]

I. INTRODUCTION

Graphene (GRP), a single layer of graphite, is considered a promising material for various applications in engineering and medicine.[1] GRP is a flexible substrate that can be functionalized with peptides, proteins, and small biomolecules.[2,3] A detailed understanding of protein interaction with GRP may facilitate the development of advanced biological applications such as biosensors for detection of biomolecules[4–12] and living cells,[13,14] drug delivery systems,[15] and cell imaging.[15–18] In particular, an insight into molecular mechanisms of the adsorption of plasma proteins on the biomaterial surfaces may help to understand the reasons for foreign body reactions and implant rejection.[19] This is important knowledge as the properties of implanted biomaterial defines safety of the medical device. In addition, the adsorption capacity of graphene oxide functionalized with RNA can be utilized for self-assembling graphene flakes[20] and purifying contaminated drinking water.[21] Therefore, modeling the interactions between GRP and individual amino acids that constitute biomolecules can advance the development of methods for noncovalent functionalization of GRP and its derivatives as well as provide insight into bioactivity of graphene-based materials.

The very first theoretical studies of the interaction between amino acids and GRP were performed in vacuum using density functional theory (DFT) with local and semi-local exchange correlation functionals.[22–24] These methods under-estimate the adsorption energy by a factor of 2 to 4 in comparison to results obtained using post-Hartree-Fock methods, such as a second-order Møller-Plesset (MP2).[22, 24] The reason for the discrepancy is that MP2 provides a more accurate assessment of the van der Waals interaction.[22, 24] These studies have shown that the MP2 perturbation method is able to quantitatively capture the relevant interactions in GRP-amino acid systems.

One of the most comprehensive force field-based molecular dynamic studies of the adsorption energies for 20 proteinogenic amino acids on a GRP sheet in vacuum and aqueous environment was performed by Pandey *et al.*[25] Their results for adsorption energy in vacuum reproduce *ab initio* data[22, 24] with a 16% average error. According to Pandey *et al.*,[25] the adsorption energy of an amino acid on GRP is minimally affected by the presence of water (the average change of adsorption energy is less than 1%). However, the definition of adsorption energy used in their work accounts only for the adsorbate-substrate interaction and excludes the solvent contribution. In order for the solute to be considered bound to an interface, a solutes association with the surface and surrounding solvent must be more energetically favorable than when the solute remains solvated in the bulk solution.[26, 27] Desolvation effects are a common phenomenon that governs molecular adsorption at all solid-liquid interfaces. For instance, the affinity of oligopeptides for metal surfaces changes from adsorption in the gas phase to desorption under aqueous

conditions.[28] Therefore, neglecting the desolvation effect can lead to a significant error in estimation of binding energies between amino acids and surfaces in general.

Here, we report a detailed theoretical study of the adsorption energies of the 20 proteinogenic amino acids on GRP in vacuum and in explicit water using a force-field molecular dynamics approach. We show that the desolvation effect plays an important role in determining the amino acid–GRP interaction. When desolvation is accounted for, the uncapped amino acids do not adhere to the GRP surface, which is evident from the fact that they all desorb (i.e., drift by more than 10 Å away from the surface) within the simulation time frame (40 ns). However, when a more realistic capped amino acids model is used, they adsorb to the GRP surface even when desolvation effects are incorporated.

II. METHOD

A. Graphene structure

A GRP sheet consisting of 720 carbon atoms was constructed with periodic boundary conditions using experimental C–C distance of 1.418 Å.[29] The structure was minimized in vacuum and then kept fixed (Fig. 1).

B. Amino acid structure

The initial (zwitterionic) structures of the 20 genetically encoded amino acids were imported from the YASARA[30] database. Two different forms of amino acids were considered: capped and uncapped. The uncapped amino acids were used in their zwitterionic form. In the calculations of the capped amino acids, the N-terminal of each amino acid was capped with an acetyl group, and the C-terminal was capped with a N-methyl group (Figs. 2(c) and 2(d)).

C. Molecular dynamics

GRP and each of the 20 proteinogenic amino acids were placed in a simulation cell with dimensions of 44.2 × 42.5 × 50 Å³. The interaction of 20 amino acids and GRP sheet in vacuum was modeled. Following Qin *et al.*,[23] all 20 amino acids were consecutively put on the top of GRP parallel to the surface because this arrangement was found to be energetically more favorable. Molecular dynamics NPT calculations were performed using the Amber03 force field[31] as implemented in the YASARA package. The default cutoff radius of 7.86 Å was used for dispersion interactions. Long-range Coulomb forces were evaluated using a particle-mesh
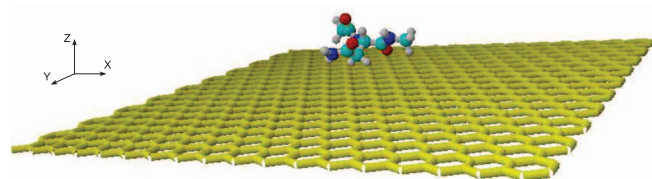

FIG. 1. Structure of optimized GRP sheet and initial position of asparagine before molecular dynamics.
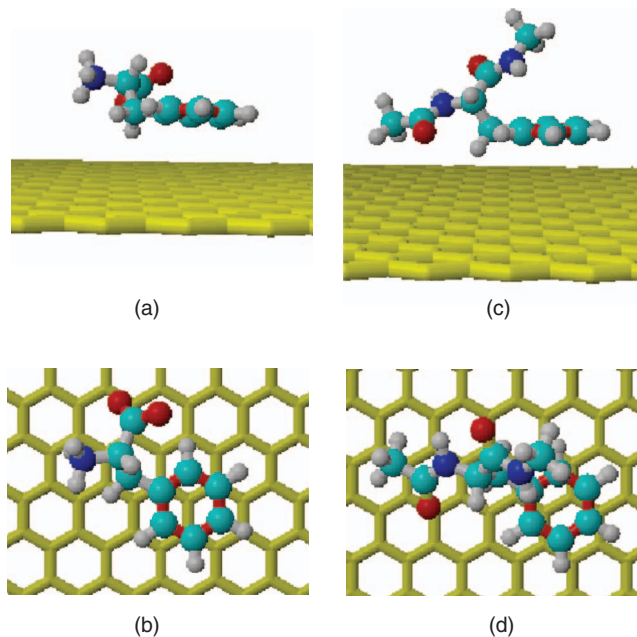

FIG. 2. Optimized structure of phenylalanine on GRP in vacuum: (a) and (b) uncapped, and (c) and (d) capped.

Ewald approach. Periodic boundary conditions were applied in all directions. The simulation time for molecular dynamics was 40 ns, which is sufficiently long to achieve equilibrium as determined based on the stable values of the potential energies of amino-acid–GRP system. The simulations were performed using physiological pH (7.0), one atmosphere pressure, body temperature (310 K), and the density of water 0.993 g/ml that corresponds to the chosen pressure and temperature. TIP3P water model[32] was used, which implies that the water molecules had a rigid geometry, but were allowed to move in the cell. In order to make solvent parameters closer to human blood, 0.9% of NaCl molecules were added to the cell. The simulation cell size was constrained in the x and y directions, but was unconstrained in the z direction in order to enable the constant pressure control.

D. Bound and unbound states

In the calculations that represent the bound state of amino acids to GRP, the carbon-α of the amino acid under consideration was initially placed 3–4 Å above the GRP sheet (Fig. 1) and then allowed to relax freely. The unbound state is represented by the corresponding amino acid and the GRP each simulated individually under the same environment and conditions as their bound state. The adsorption energy was calculated as the difference between the sum of the potential energies of the amino acid and GRP in the bound and unbound states, respectively

$$E_{\text{ads}} = \langle E_{\text{a.a.}} + E_{\text{GRP}} \rangle_{\text{bound}} - \langle E_{\text{a.a.}} \rangle_{\text{unbound}} - \langle E_{\text{GRP}} \rangle_{\text{unbound}}.$$
(1)

Here, the individual energies of amino acid and GRP include their interaction with the surrounding environment (solvent and counterions). The angle brackets $\langle \ldots \rangle$ represent time

averaged values

$$\langle E \rangle = (\tau/\delta t)^{-1} \sum_{i=1}^{\tau/\delta t} E_i \qquad (2)$$

calculated every $\delta t = 10$ ps over the simulation time frame $\tau = 40$ ns. Here, E_i corresponds to a particular energy parameter at the simulation snapshot time $i\delta t$. The average is obtained over 4000 snapshots. The accumulated statistics allows us to determine the adsorption energy with the accuracy of ± 0.007 eV, which is sufficient for the purpose of our study and no further refinement of δt is needed. The equilibration period (approximately 50 ps) was included in the calculation of adsorption energies, which had only minor impact on the final result for the adsorption energy (less than the statistical error of ± 0.007 eV). A negative value of E_{ads} indicates that the solute prefers binding to the surface.

The adsorption energies are slightly sensitive (5% or less) to the chosen initial position of the amino acid with respect to GRP in water. Therefore, two simulations, corresponding to different starting configurations, were performed for each amino acid and the lowest adsorption energy value was selected for further analysis.

III. RESULTS AND DISCUSSION

To validate our method of calculation, adsorption energies of several uncapped amino acids on GRP in vacuum were compared to the *ab initio* data reported by Rajesh *et al.*[22] and Cazorla[24] (Table I). Our results for the adsorption energy of uncapped amino acids are in good agreement (less than 6% deviation) with *ab initio* calculations. Amber03 adsorption energies for capped amino acids are within 28% average deviation from the previous molecular dynamics simulation using Amber ff99SB by Qin *et al.*[23] (selected values are shown in Table I). This deviation is likely due to the differences in dihedral potentials and φ/Ψ back-

TABLE I. Adsorption energy (eV) of amino acids (capped and uncapped) and water molecule on GRP sheet in vacuum calculated using empirical force fields.

Amino acid	Amber ff99SB[a] (capped)	Amber03[b] (uncapped)	Amber03[b] (capped)	MP2 (uncapped)
GLY	−0.34	−0.41	−0.72	−0.38[c]
PHE	−0.78	−0.66	−0.84	−0.62[d]
TRP	−1.01	−0.83	−0.79	−0.84[d]
TYR	−0.87	−0.72	−0.91	−0.76[d]
HIS	−0.73	−0.62	−0.51	−0.55[d]
Water molecule	...		−0.072[e]	−0.103[f]
				−0.174[g]
				−0.250[h]

[a]Reference 25.
[b]This work.
[c]Reference 24.
[d]Reference 22.
[e]The corresponding experimental values are 0.105 ± 0.004 eV (Ref. 34) and 0.097 ± 0.012 eV (Ref. 35).
[f]Reference 36.
[g]Reference 37.
[h]Reference 38.

bone torsions in Amber03 compared to Amber99SB. Dihedral potentials were fit to new quantum mechanical calculations using a low-dielectric continuum model in Amber03,[31] whereas φ/Ψ backbone torsions were fit to *ab initio* calculations of tetrapeptides in Amber99SB.[33]

A. Capped vs. uncapped amino acids on GRP in vacuum

In order to mimic the behavior of amino acids as a part of a peptide chain, the ends of the amino acids were terminated with acetyl and methyl groups. The calculated adsorption energies are presented in Fig. 3. Since the GRP sheet is neutral, the van der Waals interaction is the main contributor to the adsorption energy followed by Coulomb and bonding terms. Our results suggest that the interaction of capped amino acids with GRP is stronger (with only few exceptions) in comparison to uncapped amino acids. This trend can be attributed to a larger number of atoms in the residue that contribute to the dispersion interaction with the GRP substrate.

Adsorption of small biomolecules on artificial surfaces is often studied using electronic structure methods, such as DFT or post Hartree-Fock techniques. Although these studies are very accurate, they require large computational resources. When comparing MP2 and force field total energy calculation for a medium size of the simulation system ($\sim$100 atoms), the difference in central processing unit (CPU) time performance can reach 12 orders of magnitude. Therefore, electronic structure calculations are often performed in a gas phase, i.e., without explicit solvent. Particular examples include studies of the adsorption of amino acids on quartz,[39] nickel,[40] silica,[41] and hydroxyapatite.[42] Attempts to partly account for the solvent contribution by including a limited number of solvent molecules (for instance, 8 water molecules when modeling peptides-hydroxyapatite interaction) are not able to give a realistic description of biomolecule-surface interactions either.[43] Nevertheless, *ab initio* calculations provide an important benchmark for testing the accuracy of empirical potential molecular dynamics. Since the natural environment of plasma proteins is aqueous, it is important to investigate
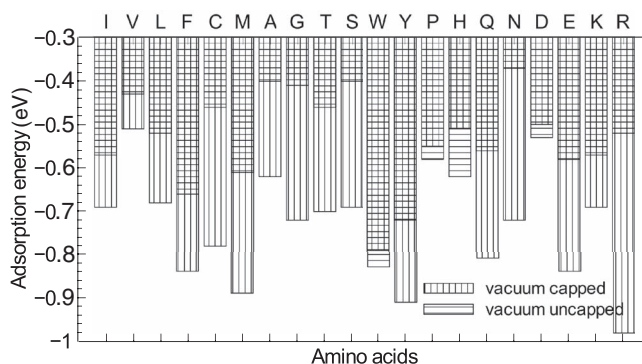

FIG. 3. Adsorption energy of capped and uncapped amino acids to GRP in vacuum. The amino acids are arranged according to their hydrophobicity index (from most hydrophobic to most hydrophilic). In most cases, the adsorption energies for the capped amino acids are higher in comparison to uncapped due to a larger number of atoms in the residue that contribute to the dispersion interaction with the GRP.

how the building blocks of proteins behave on GRP in explicit water.

B. Capped amino acids on GRP in water

The next step is the simulation of capped amino acids on GRP in aqueous conditions. First, we tested the force-field by calculating the interaction between GRP and water. For this purpose, a single water molecule was placed on the top of GRP in vacuum. The obtained adsorption energy of -0.072 eV is in good agreement with both *ab initio* calculations and experimental values (Table I). Figure 4 compares the adsorption energies for single amino acids on GRP in vacuum and in water. The binding affinity of capped amino acids to GRP is reduced in the presence of water on average by a factor of two. The lower values of adsorption energies in aqueous environment can be attributed to a desolvation effect. We anticipate that desolvation effects will also play a profound role in determining the interaction between proteins and GRP substrate as indicated by Camden *et al.*[44]

The analysis of individual contributions to the adsorption energy indicates that in explicit water, the dispersion component of the amino-acid–GRP interactions is partially compensated by the amino-acid–water interaction, which is not present in vacuum. The adsorption energy consists of three main contributions: van der Waals, electrostatic, and bonding terms. The Coulomb component favors solvation of amino acids and amounts to 30% of the dispersion contribution (on average). The bonding terms show an opposite trend with an average magnitude of 15% relative to the dispersion contribution. Therefore, the resultant adsorption energy for capped amino acids in water is mostly governed by the change in the corresponding van der Waals contribution. This contribution correlates with the molecular mass of amino acids as shown in Fig. 5.

Our results are also in good agreement with adsorption energies calculated for glycine tripeptides.[44] The adsorption energies of amino acids (as a part of tripeptides G-X-G) on GRP in water was reported very recently in Camden *et al.*[44] When the peptide was constructed from identical amino acids, such as glycine, the reported binding energy of -0.33 eV per one glycine agrees well with our result of -0.36 eV for the

FIG. 5. The correlation between the amino acid atomic weight and the dispersion (van der Waals) component of the adsorption energy. Results are shown for capped amino acids in water. Larger amino acids exhibit a stronger dispersion interaction with the substrate.

capped amino acids. The good agreement here is likely due to a minimal distortion of the peptide chain since all amino acids are identical. However, the adsorption energy of other amino acids as a part of heterogeneous tripeptides are 2–3 times weaker than our data. For example, the adsorption energy of arginine (as a part of G-R-G peptide) is found to be -0.45 eV compared to our result of -0.73 eV. The reduced adhesion can be attributed to additional distortions of the peptide backbone and need to be taken into account at the coarse-grained molecular dynamics level by parametrized angle potentials.[45]

C. Uncapped amino acids on GRP in water

The molecular dynamics trajectories (Fig. 6) indicate that uncapped amino acids tend to float away from the surface by a distance greater than van der Waals cutoff radius. This behavior is indicative of the weak binding affinity of uncapped amino acids to GRP. For this reason, the potential energy for
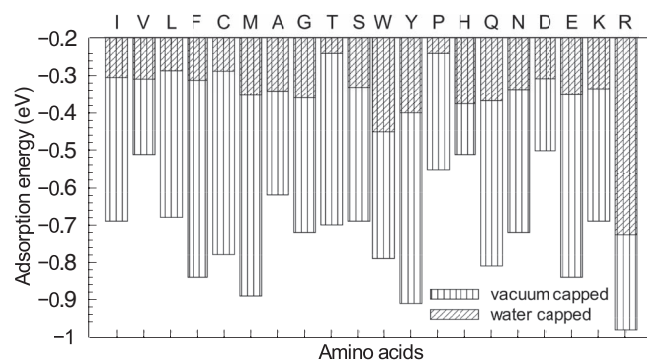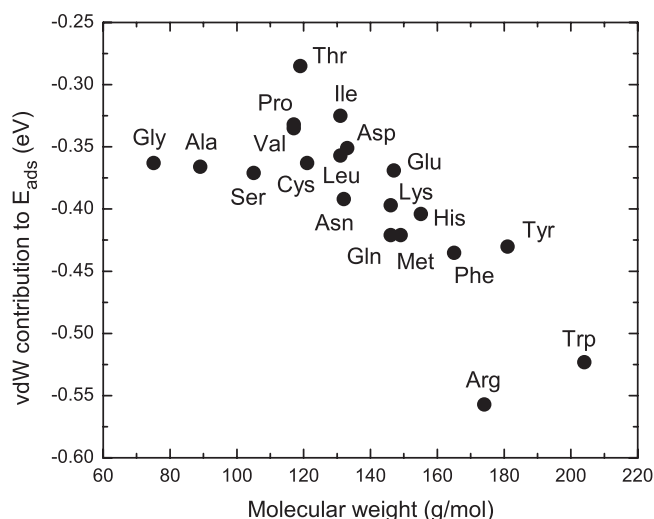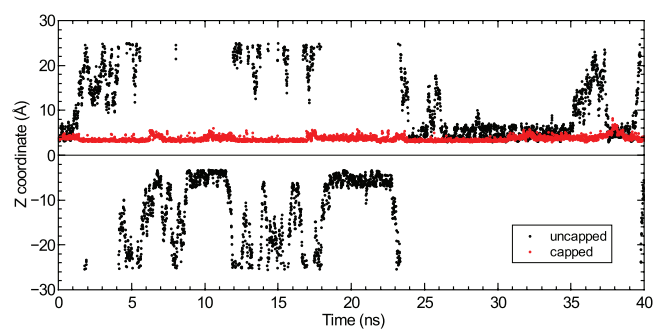

FIG. 4. Adsorption energy of capped amino acids to GRP in water and in vacuum. The adsorption energies for the capped amino acids in water are significantly lower than that in vacuum because of the desolvation effect presented in aqueous environment.

FIG. 6. Position of carbon-α atom in leucine (capped/uncapped structure) on GRP sheet in the simulation cell with water. The z-axis is perpendicular to the GRP layer with the origin assigned to the GRP plane. The graph shows that capped leucine adsorbs to the surface and remains in the bound state during the entire simulation time span. In contrast to that, the uncapped version of leucine frequently desorbs from the surface, which indicates a weaker adhesion to the substrate. This trend was also observed for the remaining 19 amino acids studied here.
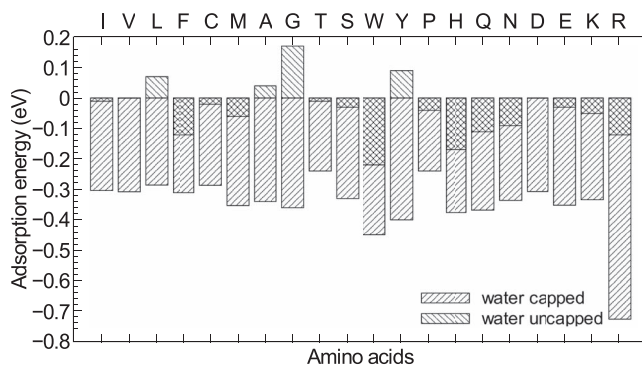
FIG. 7. Adsorption energy of capped and uncapped amino acids to GRP in water. The uncapped amino acids are unable to bind permanently to the surface of GRP because of the stronger interaction (attractive Coulomb and dispersion interaction of the amino acid) with water competing with the amino-acid–GRP interaction.

the bound state of uncapped amino acids was taken as the average energy during the time periods when the amino acid stays at a distance closer than 4 Å from the surface. It is the weak retention of zwitterionic amino acids that justifies a relatively long simulation time of 40 ns used here in order to ensure that enough statistics is accumulated to represent the bound state.

The reason for preferred solvation of the uncapped amino acid is likely their zwitterionic character. The charges at the terminals of the amino acid prefer the polar water environment instead of the neutral surface of GRP. The interaction of uncapped amino acids with water facilitates increasing the solvent accessible surface area of the zwitterionic dipole.[46] In this case, the attractive Coulomb and dispersion interaction of the amino acid with water dominates over the dispersion component of the amino-acid–GRP interaction. Capped amino acids exhibit an opposite trend, i.e., they adhere to the surface during the entire simulation time (Fig. 6). As a result, the adsorption energy for capped amino acids is several times stronger than for uncapped ones (see Fig. 7). No correlation is observed between adsorption energy and hydrophobicity index of amino acids, as indicated in Fig. 7.

Finally, we would like to note that at this level of modeling it is impossible to conclude on the role of π-electrons in the desorption of the uncapped amino acids from GRP. Although force fields employed in molecular dynamics simulations are capable of describing π-π interactions,[47] a quadrupole charge distribution responsible for π-interaction is not explicitly present in the empirical potential model.

IV. CONCLUSIONS

The interaction energy of 20 proteinogenic amino acids and graphene was studied in vacuum and explicit water using the YASARA molecular dynamics package and the Amber03 force field. The proposed method of calculation was justified by comparing the adsorption energies for individual amino acids and single water molecule on graphene with that obtained from first-principle calculations and experiments. Two types of amino acids were modeled: uncapped (zwitterionic form) and capped. The latter form mimics the behavior of

amino acids as a part of a protein and, therefore, provides a more realistic model for describing biomolecular interactions with artificial substrates. Our results suggest that uncapped amino acids do not adsorb to the graphene surface in aqueous environment due to their ionic nature (the average adsorption energy is only −0.04 eV). In contrast, capped amino acids adsorb and remain at the surface of graphene in explicit water. The average adsorption energy of capped amino acids in water is twice lower than that in vacuum. This result can be attributed to a desolvation effect, which is generally expected to reduce the affinity of amino acids to a surface in the presence of solvents. We presume that the desolvation effect will play an important role in protein–graphene interaction studies. The desolvation effect can be further enhanced at the interface between polar solvents and polar surfaces, such as graphene oxide.

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