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Theoretical study of adsorption of amino acids on graphene and BN sheet in gas and aqueous phase including empirical DFT Dispersion correction

Preeti Singla, Mohd Riyaz, Sonal Singhal and Neetu Goel*

Department of Chemistry & Centre of Advanced Studies in Chemistry

Panjab University, Chandigarh-160014, India

ABSTRACT

Understanding interactions of biomolecules with nanomaterials at molecular level is crucial to design new materials for practical usage. In the present study, adsorption of three distinct kinds of amino acids namely, valine, arginine and aspartic acid over the surface of structurally analogous but chemically different graphene and BN nanosheet has been explored within the formalism of DFT. The explicit dispersion correction incorporated in the computational methodology improves the accuracy of the results by accounting for long range vander-waal's interactions and are essential for agreement with experimental values. The real biological environment has been mimicked by re-optimizing all the model structures in aqueous medium. The study provides ample evidence in terms of adsorption energy, solvation energy, separation distance and charge analysis to conclude that both the nano-surfaces adsorb the amino acids with release of energy and there are no bonded interactions between the two. The polarity of the BN nanosheet provides it an edge over the graphene surface to have more affinity towards amino acids.

Keywords: Graphene; BN nanosheet; Dispersion corrected DFT; Amino acids; Adsorption.

*corresponding author email neetugoel@pu.ac.in

1. Introduction

The incorporation of biomolecules with inorganic nanomaterial such as nanosheets, nanowires and nanotubes results in bioconjugated nanostructured material with unique features that are derived from the properties of two combining partners[1,2]. Their exclusive physicochemical properties have originated a new era of their application where they act as brilliant candidate for biosensing, drug delivery and medical diagnostics applications[3-5]. The properties of the biohybrid nanomaterial are governed by structure specific binding properties of the interacting components. In order to fully capitalize their potential applications in diverse medical and material related areas, detailed understanding of fundamental interactions between nanomaterials and the biological environment is critically important[6].

Among all the inorganic nanomaterials, graphene has grabbed the great attention of researchers owing to its unique electronic structure that confers its high electron mobility and an inherent ability to interact with other molecules[7-9]. In addition to this, ability of graphene to pass through biological membrane has motivated considerable studies where in its interactions with different biomolecules like amino acids[10,11], nucleobases[12,13] and different organic compounds[14,15] have been analysed. Recent rise of the carbon monoatomic sheet has also brought to the forefront question of suitability of its boron nitride (BN) counterpart for the similar applications. The hexagonal boron nitride (h-BN) is a layered material having graphite like structure with regularly stacked planar networks of BN hexagons. The BN nanosystems have distinct differences/advantages compared to those of C as they exhibit certain polar character[16], have profound chemical and thermal stability[17,18] and at the same time are as mechanical robust[19] as their C counterparts. Such properties of BN nanomaterials have important consequences in their nature of interaction with functional molecules. Different experimental and theoretical studies have focused on the interaction of BN nanotubes/monolayers with a range of biomolecules[20-23]. Among the nanostructured material, graphene and BN nanosheet have been explored as suitable candidates for coupling with biomolecules in the current work. The bio-application opportunities of these two nanomaterials lie in their unique attributes i.e. their nano-scale structure that allows for bio-compatibility. The planar structure allows the attachment of different organic/inorganic molecules that functionalizes them for biological recognition, Though the BN nanomaterials are reported to have better bio-compatibility and lower cytotoxicity than their C counterparts[24-27] still tremendous efforts are underway to evaluate and modulate the cyto-

and bio-compatibility of both the nanosheets[28-31] to further their biological and medical applications.

Incredible progress in speed and accuracy of computer methodologies has made computational chemistry applicable to the problems of broad interest in nearly all areas of chemistry as well as materials science[32,33]. Theoretical reports not only have substantial predictive value of experimental observable but also predict reliably novel materials properties that are especially welcome. Now-a-days first principles quantum chemical studies have been highly focused on investigating the nature and site of interaction between nanomaterials and biomolecules[34]. The literature reports suggest that aromatic molecules[35-37], vitamins[21], nucleobases[12,38,39], amino acids[6,10,40] and drugs[40-42] interact non-covalently with the C/BN nanomaterials. The chemical functionalization of BN nanosheet with different organo-azo derivatives is also reported[43]. In recent years, immobilization of amino acids, peptides, enzymes and proteins has been studied with a view to enhance their application as reusable heterogeneous biocatalysts, purification and for solid-phase chemistry[44,45]. Vovusha et.al[46] have reported that there are π-π type of noncovalent interactions between nucleobases/aromatic amino acids and graphene. Covalent functionalization of CNTs with several amino acids has been carried out using facile, low cost and environmental friendly methods[47]. Hong et.al.[48] have concluded that Au and Pd based nanomaterials have more binding affinity for polar amino acid groups in comparison to non-polar due to charge transfer. Rimola[49] has proposed an intrinsic affinity scale of amino acid analogues towards the BN nanomaterials and revealed that the most stable adduct comprises π-stacking interactions.

As amino acids play a vital role in the living organisms as building blocks of proteins and enzymes; elucidation of their nature of interactions with structurally analogous but widely different graphene and BN nanosheet is the focus of the current study. By combining the unique 2D nanostructures and amino acids, the study provides critical understanding of the interactions between the two that is essential for biomolecule recognition. The present work will provide insightful information to address the fundamental issues like maintaining the chemical and biological activity of amino acids in the course of their delivery to the targeted area that are coming in the way of designing effective amino acid delivery systems.

2. Computational Method

The computational model of graphene consists of 46 carbon atoms in hexagonal arrangement while the BN nanosheet has 36 boron and 36 nitrogen atoms in similar hexagonal pattern (Fig.1). The hexagonal BN nanosheets have been successfully employed as model to understand the adsorption of O_3[50] and to explore them as nanosensor for paracetamol in recent literature[51]. Both the geometries were saturated with desirable number of hydrogen atoms to eliminate the boundary effects and the dimensions of BN nanosheets and graphene are 12 Å x 18 Å and 10 Å x 14 Å respectively. Three major classes i.e. neutral, acidic and basic of amino acids represented by valine ($C_5H_{11}NO_2$), arginine ($C_6H_{14}N_4O_2$) and aspartic acid ($C_4H_7NO_4$,) have been considered in the present work (Fig. 2). It is expected that these amino acids are representative of those amino acids with non-polar, basic and acidic lateral chains respectively and are referred to as Val, Arg and Asp here after. It is to be noted that employed model of both the nanosheets as well as three amino acids considered are neutrally charged. The optimized structures of graphene and BN nanosheet after the adsorption of amino acids are notated as Val/Gra, Arg/Gra, Asp/Gra, Val/BN, Arg/BN and Asp/BN in rest of the paper. A comparative analysis of interactions has been carried out by full structure optimization, natural bond orbital (NBO) analysis and density of states (DOS) plots by performing the computational calculations using Becke, 3-parameter, Lee-Yang-Parr (B3LYP) level of theory[52,53] with 6-31G(d) basis set in DFT formalism as implemented in Gaussian 09 suit of program[54]. It has been emphasized in the literature that precise quantum mechanical description of interaction of molecules with nano-surfaces requires to account for dispersion forces[55,56]. Therefore, it is important to choose the suitable computational method that should consider the correct description of long-range electron correlation. The present study employs Grimme's dispersion corrections[57,58] to incorporate the long distance vander-waal's interactions between the adsorbent and adsorbate. The optimized geometries of amino acid adsorbed nanomaterials were re-optimized by implementing a locally modified version of Gaussian 09. The accuracy and applicability of this procedure has been successfully reported for fullerenes[59]. The precision of the employed level of theory was validated by noting that the calculated lattice constant, HOMO-LUMO energy gap and work function of optimized geometries of graphene and BN nanosheet are in excellent agreement with previously reported theoretical data (Table 1). The adsorption energy (ΔE_{ad}) has been calculated according to the below equation.

$$\Delta E_{ad} = E_{complex} - (E_{adsorbent} + E_{amino\ acid}) + E_{BSSE} \quad (1)$$

where $E_{complex}$ is the total energy of the complex of an adsorbed amino acid over adsorbent, $E_{adsorbent}$ is the total energy of adsorbents i.e. graphene and BN nanosheet while

$E_{amino\ acid}$ is the total energy of amino acids obtained from their fully optimized geometries and E_{BSSE} is the basis set superposition error (BSSE) correction to eliminate the effect of basis set incompleteness by employing counterpoise correction method[60]. According to the definition, $\Delta E_{ad}<0$ indicates the exergonic nature of the adsorption. The effect of solvent on the nature of interactions has been elucidated using integral equation formalism polarized continuum model (IFEPCM)[59,61-63]. Water with dielectric constant 78.4 has been chosen as solvent with a view to understand the interaction of amino acids with the chosen nanosheets in human body. Moreover, the stability of amino acid/nanosheet complexes has been evaluated by calculating the solvation energy using the following equation[64]:

$$\Delta E_{solvation} = E_{sol} - E_{gas} \quad (2)$$

where $\Delta E_{solvation}$ is the solvation energy of the system, E_{sol} and E_{gas} are the total energies of the system in the solvent and gas phase respectively. Additionally, effect of adsorption of amino acids on the electronic properties of both the nanosheets has also been studied by calculating the HOMO-LUMO energy gap, work function and molecular electrostatic potential (MEP) surfaces. According to the classical definition, work function is the minimum amount of energy needed by an electron to overcome the attractive forces of nucleus and move away to an infinite distance. It can be calculated upon the subtraction of fermi energy from the electrostatic potential at infinite distance[65]. The MEP surfaces explain the charge distribution in the system.

3. Results and Discussion

Various orientations of amino acids with respect to the nanosheet were explored by changing their separation distance before concluding about the best optimized geometry (shown in Fig. S1 in supplementary information (SI)). The most favourable orientation has the hetero-atoms of amino acid facing towards graphene (Fig. 3) and BN nanosheet (Fig. 4). To evaluate the suitability of the nanomaterials towards adsorption of amino acids, adsorption energy (ΔE_{ad}) is a major parameter that has been calculated using Eq (1). The adsorption process seems to be either endergonic (Asp, Val) or exergonic (Arg) as depicted from the adsorption energy values (Table 2), but in either case amount of energy required/released is very low. The large nearest atom distances between graphene and amino acids (Fig. 3, Table 3) suggest that the adsorption is physical in nature. Insignificant change in partial charge of the atoms of the nanosheet at the adsorption site augmented the absence of covalent bonding

between the amino acid and the graphene surface. The adsorption of amino acids over the BN nanosheet is endergonic for Arg and Val amino acids while little amount of energy (0.89 kcal/mol) is released during the adsorption of Asp (Table 2 and Fig. 4). The large nearest atom distances (~3.26 Å) eliminate the possibility of any covalent bond formation (Table 3)[68].

In order to provide an avenue for biomedical applications and experimental validity, it is crucial to consider the role of solvent. Therefore, the effect of interaction of amino acids with nanomaterials has also been examined in the solvent phase. Here, water has been taken as solvent media as it mimics the human living system. All the geometries were subjected to re-optimization in the aqueous phase at the same level of theory with incorporating IEFPCM in DFT. The inclusion of solvent does not affect the optimized structures for both the nanomaterials but the impact of the solvent has been greatly imposed over the adsorption energies. For both the nanosheets, the adsorption process is observed to be endergonic in solvent phase (Table 2) except for the adsorption of Asp on BN nanosheet. However, it is important to note that the interactions between the nanosheet and amino acids are physical in nature and though the ΔE_{ad} is positive but with a small magnitude. Thus, it will be premature to decide about the feasibility of the adsorption process without taking the effect of long range interactions into consideration.

Noncovalent interactions are of crucial importance for the binding of small molecules to enzymes and receptors, the folding of proteins and DNA to their three-dimensional structures and the orientation of substrates on surfaces. The main contributions to the noncovalent interactions arise from electrostatics, hydrogen bonding, stacking, and van der Waals interactions. Among these contributions, dispersion interaction, a component of van der-waal's interaction, acts as a major attractive interaction that are reported to guide the interactions of graphene with different hosts (many small molecules, aromatic compounds and nucleobases)[69-71]. Absence of bonded interactions between the amino acids and the nanosheet in the above mentioned results necessitate the implementation of long range dispersion correction to critically elucidate their interactions for realistic compatibility with experimental results. Therefore, long range vander-waal's interactions were taken into account by integrating all the geometries via dispersion correction DFT operations.

The affirmative effect of dispersion correction on the adsorption behaviour of amino acids over the surface of graphene was noticed by large amount of energy released. The

adsorption energy for Val, Arg and Asp adsorption on graphene are -89.76 kcal/mol, -97.00 kcal/mol and -87.66 kcal/mol respectively. The dispersion corrected adsorption energy is negative while that calculated without it was positive (Table 2). This observation emphasizes the role of vander-waal's interactions in the adsorption process. The adsorption energy is maximum for larger sized Arg amino acid; it can be explained on the basis of fundamentals of vander-waal's forces that are directly proportional to the size and mass of the interacting molecules. The distance between closest atoms of amino acid and graphene remained unaltered i.e. ~ 3.14 Å (Table 3). Since the dispersion correction considered here is an empirical add-on term it does not directly alter the wave function or any other molecular property. However, geometry optimizations with dispersion correction led to significantly better stabilized geometries because the applied correction contributed to the forces acting on the atoms.

Similar results were obtained for adsorption of amino acids on the BN nanosheet as dispersion correction profoundly accounted the long distance vander-waal's interactions by stabilizing the amino acid adsorbed complexes as adsorption process is accompanied with release of large amount of energy. The adsorption energy for Val, Arg and Asp on BN nanosheet is -161.32 kcal/mol, -177.44 kcal/mol and -159.27 kcal/mol respectively. The adsorption energy values for the three amino acids are remarkably larger on BN nanosheet in comparison to graphene surface as polar B-N bond enhances the vander-waal's interactions by incorporating the dipole-dipole interactions between polar amino acid molecules and BN nanosheet. These results impress upon the role of dispersion correction while studying adsorption over nano-surfaces and indicate that BN nanosheets have higher affinity towards amino acids in comparison to graphene.

The geometry of BN nanosheet is modified (Fig. 5) so as to facilitate the vander-waal's interactions of amino acid molecules with BN nanosheet by moulding the sheet in a way that enhances the area of contact, BN nanosheet rolled up to get closer to the hetero-atoms of amino acids. These deformations could be an artefact as the nanosheets here are modelled with a cluster approach. Actual periodic systems don't present these deformations. In order to evaluate if these deformations are biasing the calculated interaction energies, the adsorption energy was recalculated by fixing positions of some atoms of the nanosheets as suggested by one of the reviewers. The value of adsorption energy remained unchanged (see Fig. S2 in SI), thus though the structural deformity of the sheet noticed in the current work

may be due to the limited cluster model approach but it does not impact the conclusions drawn in the study.

The effect of solvent was also investigated along with the dispersion correction by re-optimizing the geometries. In the presence of water, adsorption process on the nano-surfaces turned out to be exergonic in contrast to adsorption energy values calculated without employing dispersion correction (Table 2) These results indicate the inclusion of dispersion correction along with solvent effect is crucial for reliable analysis of adsorption studies over the surface of nanomaterials[72,73]. Both the nano-surfaces considered in the present study are seen to be suitable for adsorption of amino acids in aqueous medium, however the BN sheet has an edge over the graphene surface as suggested by the adsorption energy values. The domain of applications of graphene and BN nanosheets in the biomedical applications was expanded by evaluating the stability of their amino acid complexes in the water phase via solvation energy values calculated using equation (2). The solubility and stability of amino acids as well as nanomaterial is significantly enhanced in the aqueous phase after their binding as adsorbate and adsorbent (Table 4). The high solvation energy of amino acid adsorbed BN nanosheets enforced their applicability as nano-carriers in the living system.

The effect of amino acid adsorption on the electronic properties of graphene and BN nanosheet has been inspected by calculating the alteration in the values of HOMO-LUMO energy gap obtained from the DOS plots (provided in SI as Fig. S3 and S4) and it was observed that the HOMO-LUMO energy gap remains unaltered after the adsorption of amino acid in gas and water phase. Moreover, the work function of amino acid adsorbed complexes remains same as of nanomaterial (Table S1 in SI). The MEP surfaces of bare nanosheets, arginine and their adsorbed complexes are demonstrated in Fig 6. The molecular charge distribution remains unperturbed by the interaction between the sheet and the amino acid but the merging of the charge clouds of the adsorbate and the adsorbent is indicative of affinity of the sheet towards the amino acids[74]. These results reinforce the fact that amino acids get physically adsorbed on the nano-surface and this works in favour of the suitability of the nanosheets considered here as it assures reusability of the nanosheet as well as targeted delivery of the amino acid as desorption can be easily achieved. The results indicate that BN sheet is superior candidate than graphene to adsorb amino acids and should be explored to further its biomedical applications.

4. Conclusion

The adsorption behaviour of three different classes of amino acids on the surface of BN nanosheet and graphene has been studied by employing DFT calculations in both gas phase and aqueous phase. The exhaustive search for the genuinely stable minimum energy configuration concluded that amino acid orients itself parallel to the nanosheet with its hetero atoms facing the nano-surface. The adsorption energy values, nearest atom distance and partial charge analysis establish the energetic and physical nature of adsorption on graphene as well as BN nanosheet. The solvation energy and adsorption energy values suggest that BN sheet is more suitable as adsorption surface for amino acids. The electronic changes have been monitored through HOMO-LUMO gap and work function. Negligible changes in their values as well as MEP plots conclude that there is no charge transfer between either of the nano-surface and the amino acid. The study reinforces that dispersion correction is essential for accurate description of adsorption process. The adsorption energy calculated without including dispersion correction deemed the process to be endergonic; it implied that the interaction is not favourable electronically. After the inclusion of explicit dispersion correction term, it became evident that the adsorption is accompanied with release of large amount of energy and is driven by long range interactions. The physical nature of adsorption offers advantages in terms of easy removal and reusability of nanosheet with no structural or electronic change in the adsorbate and adsorbent. The present work emphasizes that graphene and BN sheet are effective substrates to non-covalently bind amino acids. The reliable conclusions drawn in this paper will encourage the experimentalists to explore and use these nanosheets as amino acid carrier and to immobilize the amino acid that can lead to selective peptide linkage.

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Table 1. Comparison of calculated lattice constant, HOMO-LUMO gap and work function with previous theoretical studies and experimental results.

	Current Study	Theoretical Study
Lattice constant (Å)		
Graphene	2.463	2.467[a]
BN	2.509	2.517[a]
HOMO-LUMO gap (eV)		
Graphene	1.89	0.2-3.1[*]
BN	5.75	5.93[b]
Work function (eV)		
Graphene	3.49	4.44[c]
BN	3.33	3.67[a]

[a] Ref 66, [*] HOMO-LUMO gap in the range of 0.2-3.1 of Graphene is dependent on its geometry, [b] Ref 43, [c] Ref 67.

Table 2. Adsorption energies (ΔE_{ad}) values of amino acid adsorbed on nano-surfaces in gaseous and solvent phase.

System	Adsorption Energy (kcal /mol)			
	Without dispersion correction		With dispersion correction	
	Gas phase	Solvent phase	Gas phase	Solvent phase
Val/Gra	-3.65	2.93	-89.76	-81.78
Arg/Gra	0.93	8.57	-97.00	-89.27
Asp/Gra	-0.90	7.06	-87.66	-83.38
Val/BN	0.97	2.09	-161.32	-158.75
Arg/BN	1.55	2.40	-177.44	-172.21
Asp/BN	-0.89	-0.16	-159.27	-156.96

Table 3. The closest atom distances between amino acid and graphene/BN nanosheet.

Systems	Bond distance (Å)	
	Without dispersion correction	With dispersion correction
Val/Gra	3.35	3.07
Arg/Gra	3.49	3.14
Asp/Gra	3.69	3.21
Val/BN	3.26	3.02
Arg/BN	3.32	2.99
Asp/BN	3.19	2.87

Table 4. Solvation energies of amino acid adsorbed graphene/BN nanosheet complex.

Systems	Solvation Energy (kcal/mol)	
	Without dispersion correction	With dispersion correction
Val/Gra	-11.46	-12.24
Arg/Gra	-17.65	-16.89
Asp/Gra	-13.62	-16.05
Val/BN	-13.68	-10.06
Arg/BN	-21.28	-17.64
Asp/BN	-17.62	-17.31

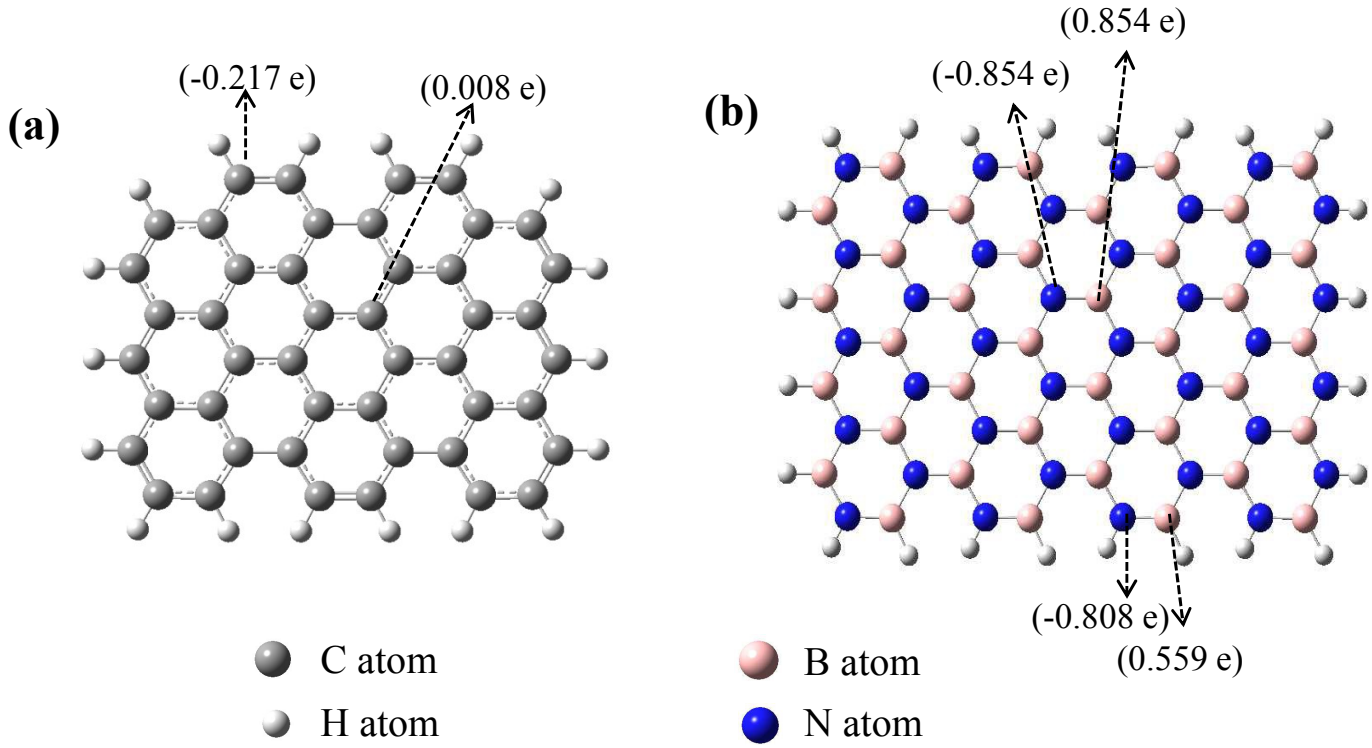

Figure 1. Optimized geometries and partial charges of graphene and BN nanosheet.

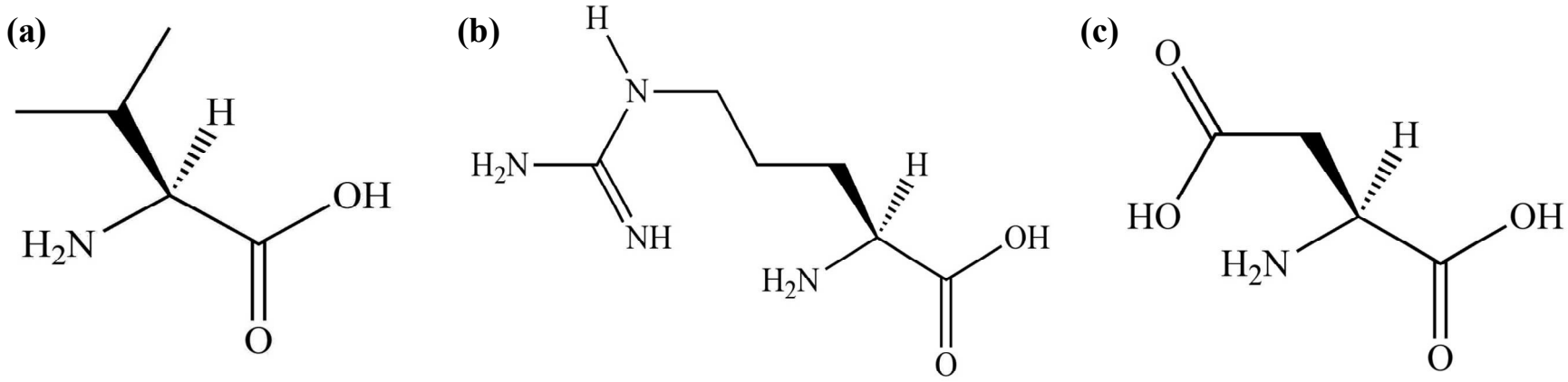

Figure 2. Chemical structures of studied amino acid molecules (a) Val, (b) Arg and (c) Asp.

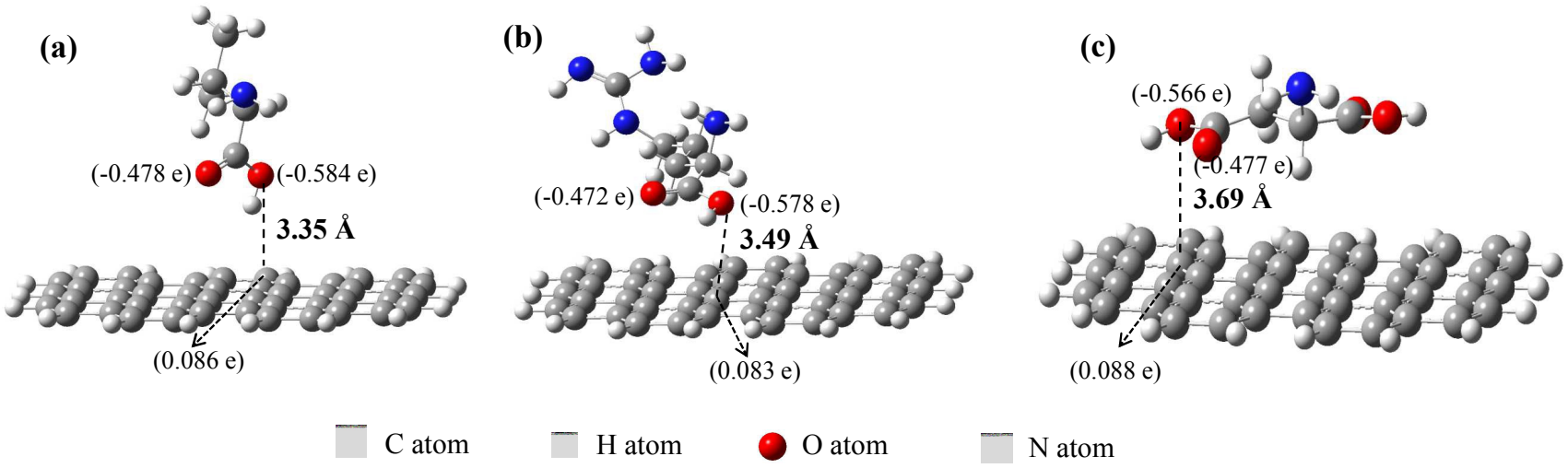

Figure 3. Optimized geometries and partial charges of amino acid molecules (a) Val, (b) Arg and (c) Asp adsorbed graphene complexes.

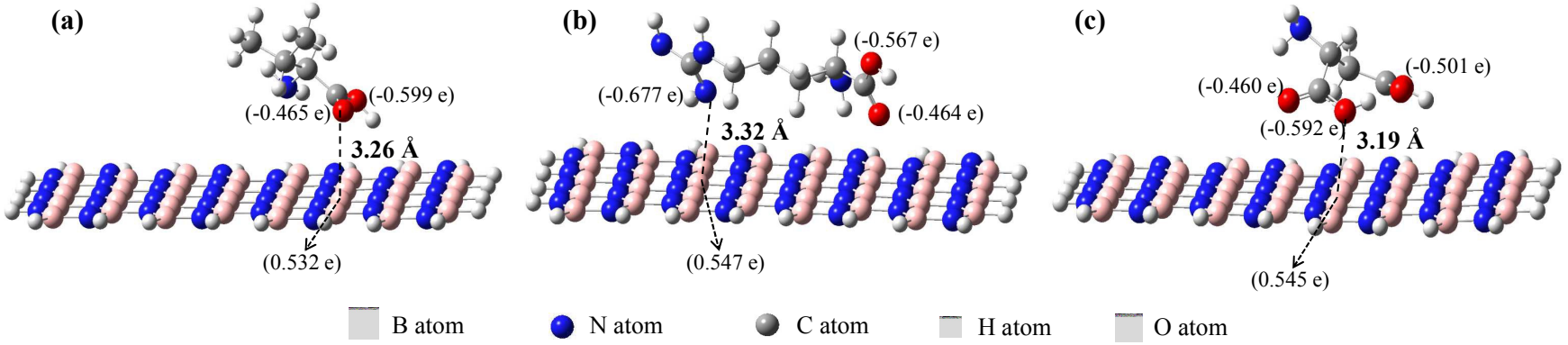

Figure 4. Optimized geometries and partial charges of amino acid molecules (a) Val, (b) Arg and (c) Asp adsorbed BN nanosheet complexes.

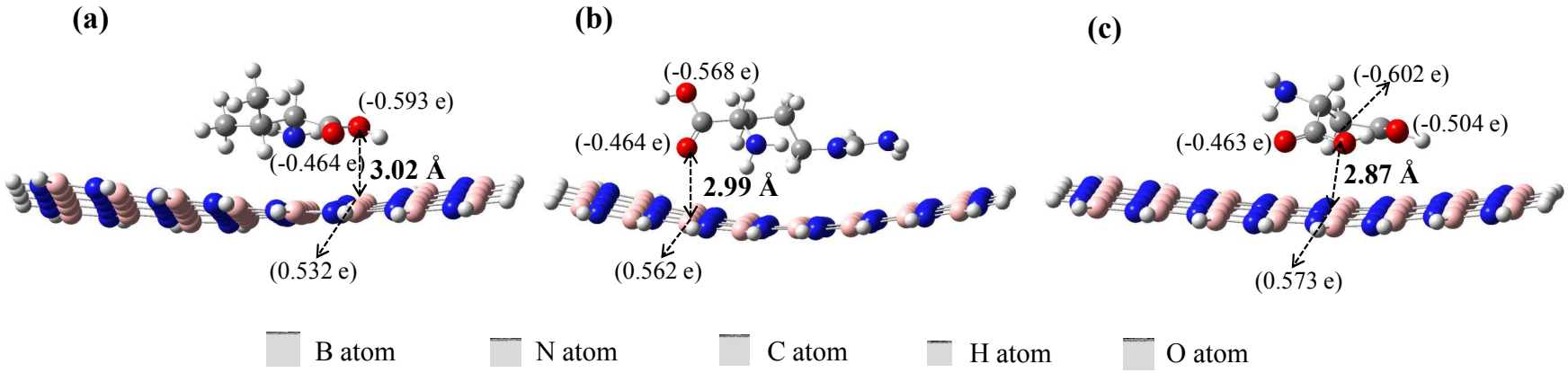

Figure 5. Dispersion corrected optimized geometries and partial charges of amino acid molecules (a) Val, (b) Arg and (c) Asp adsorbed BN nanosheet complexes.

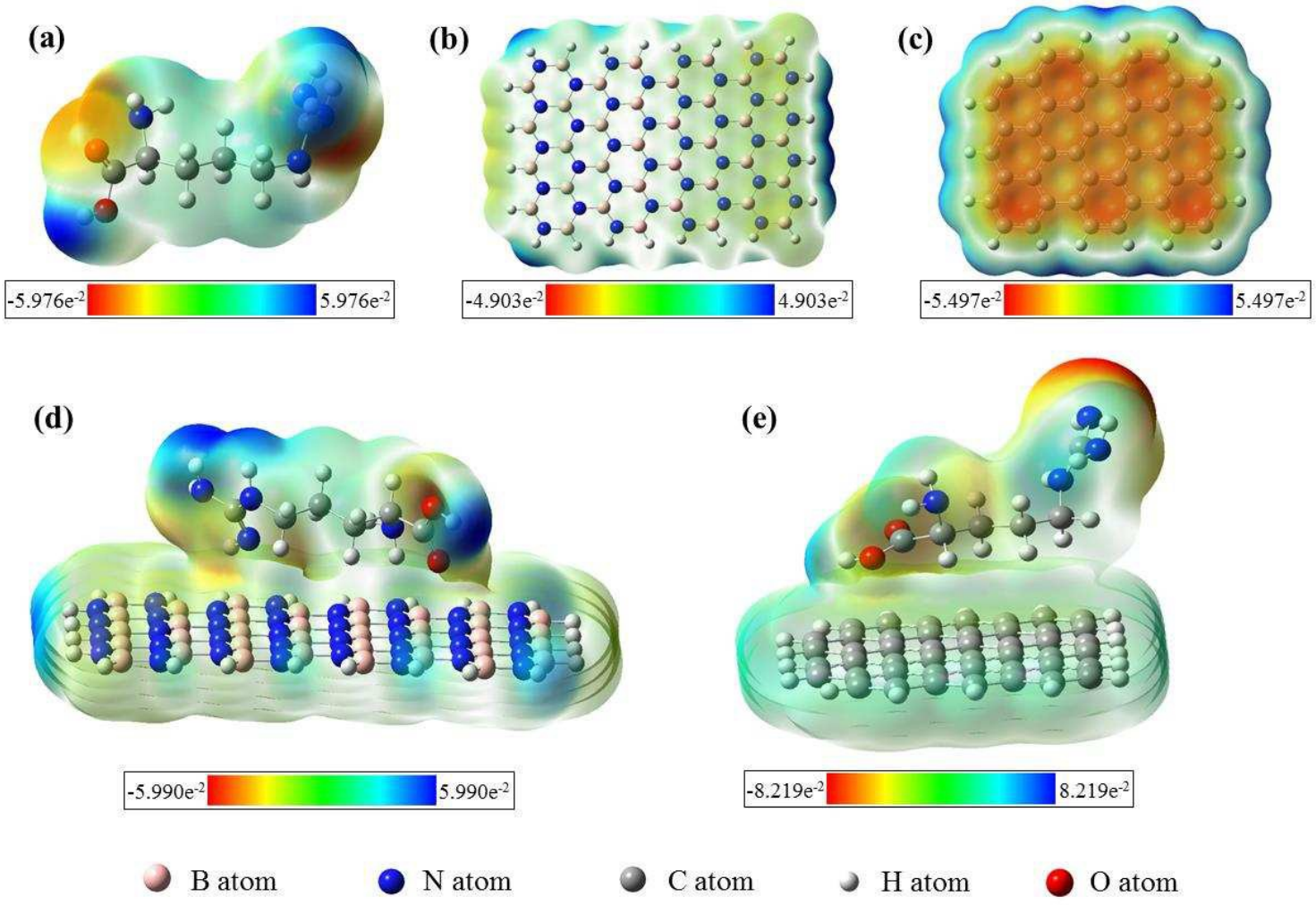

Figure 6. The molecular electrostatic potential surfaces of (a) Arg, (b) pristine BN nanosheet, (c) pristine graphene, (d) Arg adsorbed BN nanosheet and (e) Arg adsorbed graphene complexes.