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Theoretical Insights into the Interaction Mechanism between Protein and SWCNT: Adsorptions of Tripeptides GXG on SWCNT

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Abstract

Adsorptions of nine tripeptides GXG, ranging from negatively (D) and positively (K) charged, to hydrophilic (N and S), and to hydrophobic (G, V, F, W, and Y) residues, on the two cluster models ($C_{54}H_{18}$ and C_{54}) of (10,0) SWCNT are systemically investigated with MPWB1K and MP2 methods. The solvent effects are taken into account with implicit CPCM model. The objective is to provide novel insights into the interaction mechanism between proteins and single-walled carbon nanotube (SWCNT). Results reveal that the adsorption strength of two charged tripeptides is greatly affected by solvent effect and the Hydrogen-saturability of the SWCNT models. In gas phase, on the surface of $C_{54}H_{18}$ GKG has the strongest adsorption (Adsorption energy: -29.3 kcal/mol at MP2 level), whereas the adsorption of the negatively charged GDG is the strongest on C_{54} (AE: -30.4 kcal/mol with MP2). However, because of strong solvation the adsorptions of the *charged* residues (D and K) on both $C_{54}H_{18}$ and C_{54} surfaces in aqueous solution are either rather weak or even unbound. The two neutral *hydrophilic* residues (N and S) exhibit adsorptions on $C_{54}H_{18}$ in gas phase (AE: -3.3 and -4.2 kcal/mol), yet unable to adsorb on SWCNT in aqueous solution (AE: +0.3kcal/mol at MP2 +CPCM). The five *hydrophobic* residues present relatively strong adsorption on SWCNT, especially for the three aromatic residues (GFG, GYG and GWG), regardless of CNT models and in gas phase or solution. These results indicate that in general the aromatic groups of proteins would play very important role on functionalizing CNT, which basically support the relevant experimental observations. In addition, the electron correlation is essential for adsorptions of GXG on pristine SWCNT, and the three aromatic residues have the highest electron correlation effects. The present investigation provides a strong evidence that for the functionalization of CNT via proteins it is most likely that hydrophobic interaction and van der Waals are the dominant driving forces.

1. Introduction

Carbon nanotubes (CNT) have a very low solubility in aqueous solution as well as in organic solvents, which has been a major barrier for a variety of potential biomedical applications. Strategic approaches toward solubilization of CNTs have been developed mainly through their surface functionalization of either covalent or non-covalent attachments to the sidewalls or tips of CNTs.¹⁻⁷ The covalent modification involving chemical reactions between CNTs and molecules somewhat impairs the structural and electronic properties of CNTs. Therefore, noncovalent functionalization of CNT has attracted an increasing attention. Noncovalent functionalization could not only enhance solubility of CNT but also maintain their attractive geometric, electronic and mechanical properties. Among numerous functional species for solubilizing CNTs, biological and bioactive materials are of a special importance. The fundamental components in living system, such as carbohydrates, proteins and nucleic acids, as well as their precursors have been explored to noncovalently functionalize CNTs towards the delivery of therapeutic agents.⁷⁻¹⁰

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Various natural proteins differing in sizes and structures are able to efficiently disperse SWCNT in water due to spontaneous absorbing on sidewalls of CNTs.¹¹ Characterizations by a variety of complementary techniques including UV-Vis spectroscopy, IR and Raman spectroscopy, and AFM confirmed the dispersion at the individual nanotube level. In spite of extensive studies on the non-covalent functionalization of SWCNT with proteins, as briefly discussed below there still exist some controversies in terms of the types of CNTs, net charge of proteins, and in particular the nature of interaction between proteins and CNTs that leads to the protein-CNTs conjugates.⁷

The non-covalent binding of proteins to pristine and acid-oxideized SWCNTs, where sidewalls are partially terminated with carboxyl acidic groups (-COOH), was conventionally attributed to hydrophobic interactions.^{2, 7, 12-14} This attribution has been challenged by a numerous of other findings. For example, Dai et al. used the oxidized SWCNTs to bind three proteins such as streptavidin-protein A (SpA), bovine serum albumin (BSA), and cytochrome c (cyt-c).¹⁵ AFM images showed that the density of proteins on the sidewalls of SWCNT is the highest for cyt-c, followed by SpA and BSA, which follows the order of isoelectric points (pI): 9.2 for cyt-c (positively charged at physiological pH of 7.4), and pI (<7) for SpA and BSA (negatively charged). Thus, it is most likely that electrostatic force, between the negatively charged SWCNTs and the positively charged protein domains, also contributes to the non-specific binding besides hydrophobic interactions. On the other hand, the results indicated that introducing hydrophilicity to SWCNTs by acid-oxidation is insufficient to block protein non-specific binding to SWCNTs. In addition, Shim et al had reported that relatively small proteins such as streptavidin can adsorb readily to the sidewalls of SWCNT, however no adsorption was observed to SWCNTs for a large protein, fibrinogen, despite the well known fact that fibrinogen do strongly adsorb onto hydrophobic surfaces.¹³ This again indicates that hydrophobic interaction is not the sole role for the nonspecific binding of protein to CNTs.

Chen et al. found that all of the proteins (Streptavidin-SA, Avidin, BSA, glucosidase-GCD, staphylococcal protein A) under their investigation caused a decrease in the conductance of semiconducting nanotubes upon introduction of protein solutions, regardless of their net charge.¹⁴ Regarding the effect of net charge, Azamian et al also found that two proteins with opposite charges at physiological pH (7.4), cytochrome c (pI~10.8, positively charged) and ferritin (pI~4.6, negatively charged) have similar strong adsorption on pristine SWCNTs.¹² These examples at least imply that electrostatic force would not be the dominant factor for driving the SWCNT-protein conjugate.

Since there are abundant surface amino groups in proteins, it was suggested that the substantial protein adsorption is at least in part attributed to amino affinity of CNTs. Lin concluded that the amino affinity may be responsible for the strong adsorption for ferritin protein to SWCNTs.⁷ The charge transfer from adsorbed streptavidin protein to CNTs was reported in dry and buffer environments, which was attributed by Bradley et al to the interaction between the -NH₂ groups of the protein and the aromatic surface.¹⁶

The building blocks of protein such as amino acids and peptide could serve as models for CNTs-protein interactions. Wang et al used phage display to identify peptides with selective affinity for carbon nanotubes, and consensus binding sequences showed a motif rich in histidine (H) and tryptophan (W) at specific locations.¹⁷ They suggested that aromatic ring structures in both amino acid residues significantly contributed to the peptide affinity to CNTs via conventional π - π stacking. Zorbas et al reported the importance of aromatic content for peptide and SWCNT interactions.¹⁸ For the α -helical peptide structure, Chiu claimed that π -stacking interaction between the aromatic group of the peptide and the surface of the SCWNT would be dominant.¹⁹ With density function functional theory, the study performed by Roman et al²⁰ on the adsorption of single amino acids, glycine (G), cysteine (C), histidine (H) and

phenylalanine (F), also revealed that the residue F more strongly adsorb on (3,3) SCWNT surface than others.

Proteins consist of numerous active groups such as hydroxyl, amino, thiol, carboxyl acidic and others, which provides sites for further surface functionalization of the SWCNTs. Thus, interactions between proteins and SWCNT surface are most likely to be complicated by involving many types of non-covalent forces such as electrostatic, π - π stacking, hydrophobic, amino affinity via N-H $\cdots\pi$, and entropic in nature related to surface as well as surrounding water molecules. To well understand such nonspecific interactions between SWCNT and proteins requires quality investigations at a molecular level. For example, it is very interesting to get insights into the interaction between charged or neutral amino acids, different amino acid residue compositions as well as different sequences of model proteins, with SWCNT with different electronic structures.

In this paper we will investigate adsorptions of nine tripeptides GXG (X=D, K, G, N, S, V, F, W, and Y) on the (10,0) SWCNT surface with a variety of high level quantum mechanic methods. Various adsorption features of charged, neutral hydrophilic, hydrophobic with aliphatic and aromatic side chain (R) will be addressed, such as the effects of charge, hydrophobic, OH/NH $\cdots\pi$, π - π stacking, as well as bulk solvent effect on adsorption strengths. Systematical investigation on the interactions between these peptides and SWCNT is expected to gain a valuable insight into adsorption mechanism of proteins on SWCNT.

2. Models and Theoretical Calculations

Nine different kinds of amino acid residues (X) were placed between two glycine (G) to form three-residue peptides GXG in α -helix conformations ($\phi=-57^\circ$, $\psi=-47^\circ$, and $\omega=168^\circ$). These tripeptides were constructed using CHARMM software (version c31b1) by applying a 200-step energy minimization with the steepest descent algorithm, and are capped with neutral acetyl and amine groups on the C- and N-termini, respectively. According to properties of the middle amino acid residue in the nine tripeptides, the tripeptides can be classified into three categories:²¹ neutral hydrophobic (aromatic or aliphatic):GFG, GWG, GYG, GGG and GVG; neutral hydrophilic: GNG and GSG; and positively or negatively charged GKG and GDG at pH=7.4. With these model residues, the role of electrostatic force, hydrophobic, van der Waals interactions via π - π stacking, X-H $\cdots\pi$ (X=C, N and O) and solvent effects on the adsorptions of proteins on SWCNT will be addressed. To model the zigzag SWCNT five hexagon layers saturated with hydrogen atoms (C₁₂₀H₂₀) on the two ends were fully optimized at the level of HF/6-31G*. The average C-C bond length and C-C-C angle of the middle hexagon layer are approximately 1.41Å and 119.0°, respectively. Therefore, two fragments of C₅₄H₁₈ and C₅₄ are adapted from the zigzag (10,0) SWCNT and frozen at the C-C distance of 1.41Å and C-C-C angle of 119.0°. The orientations of amino acid residues above the surface of SWCNT are shown in Figure 1. For those tripeptides without aromatic groups such as D, K, G, N, S and V, vertical configurations were intentionally chosen in order to minimize the interactions of the end-group of the peptide with the hydrophobic SWCNT surface, thus enabling the acquired results to primarily reflect the adsorption behavior of the middle residues. The optimal distances are obtained by scanning the vertical distance between the first non-hydrogen atom of the side chain group (R) and the upper most tangent plane of the (10,0) SWCNT surface. For those with aromatic R groups (F, W and Y) their optimal contact distances refer to the ones from the center of the six-member ring to the center of the (10,0) SWCNT surface (marked by pink points in Figure 1), where the six-member ring of R sits right above the central ring of C₅₄ or C₅₄H₁₈, i.e., eclipsed configurations. The potential energy curves were scanned with MPWB1K/cc-pVDZ method in a distance range of 2.5 and 12 Å, a common van der Waals cut off. A couple of typical potential energy curves are shown in Figure 2. As illustrated by the red curve for GWG, the potential energy slightly decreases after approximately 6Å instead of keeping

increase and then converging as the case of GSG (black curve). This may be attributed to the deficiency that DFT is unable to accurately describe electron correlation effects for rather separated systems; however, the minimum predicted with MPWB1K for the bound systems should be reliable.

All of the calculations are performed using the G03 program, revision D.02.²² Accurate description for noncovalent interaction systems like the current π stacked systems or $XH\cdots\pi$ ($X=C, N$ and O) systems is still a challenge for density functional theory (DFT), a promising quantum mechanics method to large systems, although considerable improvements have been achieved over LDA and such conventional hybrid DFT as B3LYP in the recent years.²³ Recently, the novel exchange density functional modified from PW91 exchange functional together with a meta correlation, MPWB1K, provides relatively reasonable results for $\pi\cdots\pi$ stacking systems.²⁴ The MPWB1K/cc-pVDZ method has also been applied to the binding of various DNA bases to SWCNTs via $\pi\cdots\pi$ stacking and $NH/CH\cdots\pi$ interactions, and it is noted that MPWB1K/cc-pVDZ method is able to provide relatively reasonable geometries for further electron correlation treatment with MP2 as compared with the geometries optimized with MP2/cc-pVDZ.^{25, 26} Thus, the MPWB1K/cc-pVDZ method will be employed to optimize the equilibrium distances for the adsorptions of the tripeptides on SWCNTs via various R groups mentioned above, and the binding energies are then corrected with the MP2/A method (Basis set A: 6-31++G(d,p) for the C_6 ring of SWCNT and R group of residue X; 6-31G* for others), in which counterpoise corrections of basis set superposition error (BSSE) are also included.²⁷ To discuss electron transfer induced by the interaction between these different tripeptides and the SWCNT fragments, atomic net charges are calculated using CHELPG schemes.²⁸

In aqueous solution the R groups of the nine tripeptides have a different tendency to dissolve, thereby it is necessary to take into account solvent effects on their adsorption features on SWCNTs. Since the conductor-like polarizable continuum model (CPCM)²⁹ could give more consistent errors on nuclear and electronic total polarization as compared with the dielectric PCM, the bulk solvent effects will be estimated for these interested systems at CPCM-MP2/A//MPWB1K/cc-pVDZ level together with a UAHF radius, which has been verified as the suitable radius for calculating DNA bases-SWCNT.²⁶

The solvation free energies (ΔG^{sol}) at MP2 level are calculated by comparing the results of two separate calculations performed in gas-phase and in solvent,

$$\Delta G^{\text{sol}} = E^{\text{CPCM-MP2}} - E^{\text{MP2}} \quad (1)$$

where $E^{\text{CPCM-MP2}}$ and E^{MP2} represent energies predicted by MP2/A//MPWB1K/cc-pVDZ in gas and in solvent, respectively. The adsorption energies (AE) in gas phase will be calculated by Equation (2).

$$\Delta E_{\text{ads}} = E(\text{AB}, r_c)^{\text{ab}} - E(\text{A}, r_c)^{\text{a}} - E(\text{B}, r_c)^{\text{b}} + \text{BSSE} \quad (2)$$

$$\text{BSSE} = \left[E(\text{A}, r_c)^{\text{a}} - E(\text{A}, r_c)^{\text{ab}} \right] + \left[E(\text{B}, r_c)^{\text{b}} - E(\text{B}, r_c)^{\text{ab}} \right] \quad (3)$$

In Eq. (2) the superscripts *ab*, *a* and *b* indicate that the adsorption complex (AB) at its optimized complex structure and the separate components at their individual equilibrium structures (A

and B) are calculated in the basis sets *ab*, *a* and *b*. The BSSE was estimated by counterpoise method.²⁷ In aqueous solution,

$$\Delta E_{\text{ads}}^{\text{sol}} = \Delta E_{\text{ads}} + \Delta \Delta G^{\text{sol}} \quad (4)$$

$$\Delta \Delta G^{\text{sol}} = \Delta G^{\text{sol}}(AB, r_c) - \Delta G^{\text{sol}}(AB, r=12) \quad (5)$$

In Eq. (5) $\Delta G^{\text{sol}}(AB, r_c)$, $\Delta G^{\text{sol}}(AB, r = 12)$ are solvation free energies predicted by CPCM-MP2 for the optimized adsorption complex and two monomers separated at a distance of 12 Å, respectively.

3. Results and Discussions

3.1 Adsorptions of negatively charged GDG and positively charged GKG on the surface of SWCNT, C₅₄H₁₈

The major characteristics for the adsorption of GXG on C₅₄H₁₈ are summarized in Table 1, including the optimal distance, net ESP charge carried by GXG, and adsorption energy (AE) at MP2/A. Figure 2 shows the potential energy curves for the adsorption of GSG and GWG with the MPWB1K/cc-pVDZ method. It is obvious that the vertical distance from the N of the positively charged GKG to the tangent plane of C₅₄H₁₈ is the shortest (3.00 Å), implying a rather strong interaction between them in gas phase. The significant AE of -21.0 and -29.3 kcal/mol at respective MPWB1K and MP2 level (shown in Table 2), also confirm their strong binding. The corresponding AE for negatively charged GDG are only -7.8 and -2.0 kcal/mol at MPWB1K and MP2, respectively, and the distance from carboxyl carbon to C₅₄H₁₈ is farther than that in GKG (3.25 vs 3.00 Å). Table 1 and 2 also show that the GKG adsorption on C₅₄H₁₈ is the strongest in the gas phase at both MPWB1K and MP2 levels. In spite of not exact parallel in the binding energies, both theoretical methods give a quite similar trend for the investigated GXG. Because of hydrophilicity of ionic groups in the two charged residues, GDG/GKG-(10,0) SWCNT would be greatly affected by the solvent effects. MP2-CPCM results reveal that the adsorption energy of GKG has slumped near to zero (-0.2 kcal/mol), indicating that the adsorption of positively charged residue K on the hydrophobic SWCNT surface is minor in aqueous solution. Similarly, the adsorption of negatively charged GDG also changes significantly from -2.0 kcal/mol in gas phase to 13.9 kcal/mol in aqueous solution. Generally solvation of ions drastically weakens the binding of the charged residues to the pristine SWCNT surface.

3.2 Adsorptions of neutral hydrophilic tripeptides, GNG and GSG on C₅₄H₁₈

For the two neutral tripeptides GNG and GSG with hydrophilic residues (-CH₂C(O)-NH₂, and -CH₂OH), Table 2 shows that in gas phase their adsorption energies are -1.9 and -2.9 kcal/mol at MPWB1K, while -3.3 and -4.2 kcal/mol at MP2 level. The respective vertical distances from N and O to C₅₄H₁₈ are 3.08 and 3.13 Å. Similar distance and adsorption energy indicate that N-H... π interaction in GNG/SWCNT system is primarily comparable to O-H... π interaction in GSG/SWCNT. Such non-covalent interactions induce little charge (~0.13e) transfer from SWCNT to GXG. In gas phase, their adsorptions of a few kcal/mol on C₅₄H₁₈ are remarkably weaker than the charged peptides, GKG and GDG. Because of the hydrophilic property of the residues, in aqueous solution their adsorption strength decreases by a few kcal/mol, for example 4.1 and 4.5 kcal/mol for the N and S residues, respectively. Eventually the two hydrophilic tripeptides (GNG and GSG) may be also unable to adsorb on SWCNT, evidenced by the

positive adsorption energies (0.3 kcal/mol). Although the two hydrophilic tripeptides can be adsorbed on the hydrophobic $C_{54}H_{18}$ surface in gas phase, similar to the case of the two charged peptides they may not bind to hydrophobic SWCNT surface in aqueous solution because of remarkable solvation.

3.3 Adsorptions of hydrophobic peptides: GGG, GVG, GFG, GWG and GYG

For the two neutral aliphatic hydrophobic peptides, GGG and GVG, the adsorption energies (-1.3 and -1.5 kcal/mol) predicted with MPWB1K are negatively less than those of the two neutral hydrophilic tripeptides, GSG and GNG (-1.9 and -2.9 kcal/mol); however, at MP2 level that can better deal with weak noncovalent interaction, the adsorption energies of GGG/GVG are comparable to or slightly more negative than the hydrophilic GNG and GSG (-4.1 and -4.7 vs. -3.3 and -4.2 kcal/mol). These results imply that the two aliphatic hydrophobic groups ($-CH_2$ and $-CH(CH_3)_2$) via $CH\cdots\pi$ have higher electron correlation effects than the two hydrophilic groups ($-NH_2$, $-OH$) via $N/O-H\cdots\pi$. In aqueous solution the adsorptions of the two hydrophobic residues are not so greatly influenced as in the cases of GNG and GSG, especially for the GVG with a larger hydrophobic chain. The adsorption energy of GVG in aqueous solution slightly changes from -4.7 to -4.1 kcal/mol. Although the adsorption energy of GGG remarkably changes to -1.1 kcal/mol, the negative adsorption energy still shows that it may adsorb on the surface of $C_{54}H_{18}$ in aqueous solution. The above results show that the hydrophobic residue has considerable tendency to adsorb on the hydrophobic surface of SWCNT in an aqueous solution.

For the other three tripeptides GFG-, GWG-, and GYG with aromatic rings, it is expected that there will be remarkable $\pi\cdots\pi$ stacking interaction between these aromatic groups and the SWCNT surface, which may play an important role in peptide dispersion of SWNTs.¹⁸⁻²⁰ According to Tables 2 and 3, except for the case of gas-phase GKG tripeptide on $C_{54}H_{18}$ surface, the adsorption of the three tripeptides with aromatic groups are the strongest among the investigated peptides no matter in gas phase or in aqueous solution, and no matter on the surfaces of (10,0) SWCNT with or without H-saturation. In gas phase, the predicted adsorption energies with MP2 method for GFG, GWG and GYG on $C_{54}H_{18}$ surface are -12.0, -12.8 and -11.4 kcal/mol, which agree very well to each other and are also very comparable to the binding energies in the arrange of -11.3 and -14.6 kcal/mol between DNA bases with (10,0) SWCNT.²⁶ Solvent effects also significantly weaken the binding of the three aromatic peptides to SWCNT; however, the adsorption energies in aqueous solution (-6.5, -10.4 and -6.3 kcal/mol) at MP2-CPCM are still higher negative than that of GVG (-4.1 kcal/mol), not to mention those of two charged tripeptides (GDG and GKG) and the hydrophilic ones (GNG and GSG). The higher negative adsorption energy indicates that the SWCNT may easily be dispersed in aqueous solution by the corresponding residue. This result therefore provides a solid theoretical evidence for the importance of aromatic content for peptide/single-walled carbon nanotube interactions.^{18, 19} Tripeptide GWG exhibits the strongest adsorption among the three aromatic tripeptides in both gas and aqueous phase, and on the two surfaces of H-saturated or non-H-saturated SWCNT. This may be attributed to the indole group of tryptophan, where two aromatic rings not only provide the strongest $\pi\cdots\pi$ stacking with SWCNT surface but also have the highest hydrophobic effect.

3.4 Electron Correlation Effects

It is well established that dispersion plays a primary role on the binding of non-covalent systems such as the π - π stacking in GFG, GWG and GYG-SWCNT, amino affinity via $N-H\cdots\pi$ in GNG-SWCNT, noncovalent via $O-H\cdots\pi$ in GSG-SWCNT, and $C-H\cdots\pi$ in GGG and GVG-SWCNT systems. Dispersion is a result of electron correlation effects, therefore to further understand the contribution of electron correlation to adsorptions of tripeptides on SWCNT the binding energies at HF/6-31++G(d,p)//MPWB1K/cc-pVDZ, and electron correlation contributions to

adsorption energies at MP2 level are also listed in Tables 2 and show in Figure 3. Table 2 shows that only for the adsorption of GKG on $C_{54}H_{18}$ can HF method predict a bound state with a significant negative binding energy of -19.2 kcal/mol, which may be attributed to considerable electrostatic attraction in this case. At MP2 level, in gas phase all peptides are turned out to adsorb on SWCNT surface because of incorporation of electron correlation effects. According to Table 2, the contribution of electron correlation effects ranges from -5.0 kcal/mol for GSG to -18.6 kcal/mol for GWG. The high electron correlation contribution again implies that the noncovalent interactions such as π - π stacking, X(N, O and C)-H/ π in deed need high level methods to describe. The significant electron correlation contributions in all of the investigated peptides also show that dispersion, the dominant component of van der Waals interaction, play an essential role on the adsorptions of tripeptides on SWCNT. Without van der Waals force, only the adsorption of positively charged GKG is predicted at HF level and others exhibit unbound on the surface of SWCNT. According to Table 2 and Figure 3, the aromatic rings resulting in π - π stacking have the most significant electron correlation effect (-14.2~-18.6 kcal/mol), followed by the two charged residues (-10.1~-11.0 kcal/mol), and the aliphatic hydrophobic residues with CH- π interactions (-5.1 ~ -8.3 kcal/mol) and hydrophilic residues with O/N-H- π interactions (-5.0 ~ -7.3 kcal/mol) have the lowest electron correlation effect.

Table 2 and Figure 3 also show that MPWB1K/cc-pVDZ predicts bound adsorptions for all of the investigated tripeptides in gas phase; however, the adsorptions are systematically weaker than those predicted by MP2 method except for GDG. This result is similar to other noncovalent systems such as DNA bases-SWCNT systems.²⁶

3.5 Effect of the cluster model on adsorption strength

To elucidate the significant difference of the adsorptions for the two charged peptides, the net atomic ESP charge of $C_{54}H_{18}$ was shown in Figure 5a. The two carbon atoms along the tube axis in the central C_6 ring carry -0.038e, and the other four atoms have +0.019~0.020e. The overall charge of the central C_6 ring is only +0.002e, almost neutral. The 18 atoms in the second successive ring alternatively carry positive or negative charge of 0.02~0.05e, resulting in an overall charge of +0.036e. As peptides approach to the SWCNT surface, the electrostatic binding to the two axial carbon atoms is more important than to the rest of other carbons because of shorter distances. Thus, the electrostatic attraction between positively charged GKG and the electronegative C1 and C2 bring strong adsorption of -19.2 kcal/mol at HF level, while the repulsion between negatively charged GDG and the axial carbons results in an unbound state at HF level (AE: +7.8 kcal/mol). As shown in Figure 5b, when shift to the model C_{54} the axial atoms 1 and 2 carry positive charge of +0.045. The opposite charges to the model $C_{54}H_{18}$ bring about completely different adsorptions for the two charged peptides, i.e., the strong adsorption for the negatively charged GDG and minor adsorption of the positively charged GKG on C_{54} . Thus, the two cluster models of (10,0) SWCNT bring drastic different adsorption energies for the two oppositely charged amino acid residues.

Adsorption strength of the seven neutral peptides change with the cluster models to some extent, yet not as significantly as occurred on the two charged tripeptides. For the two aromatic peptides GFG and GYG, adsorptions on C_{54} are slightly stronger than on $C_{54}H_{18}$ by 1.5 and 1.0 kcal/mol, and for GWG the adsorption on the former cluster become much stronger than on the latter by 3.9 kcal/mol. It seems that this difference can be attributed to the higher electron correlation effects for the former cluster. No consistent difference was observed for the adsorptions of the four aliphatic peptides on the distinct models. Adsorptions of GSG (-4.2 vs. -2.4 kcal/mol) and GVG (-4.7 vs. -3.6 kcal/mol) on the surface of $C_{54}H_{18}$ are stronger than on C_{54} , while those of GNG (-3.3 vs. -5.7 kcal/mol) and GGG (-4.1 vs. -4.9 kcal/mol) on the former are weaker than one the latter surface.

Figure 6 illustrates ESP charge contour for $C_{54}H_{18}$, C_{54} and a few peptide- $C_{54}H_{18}$ systems. According to Figure 6b, the electronegative region in the $C_{54}H_{18}$ model is along the tube axial, whereas for C_{54} in Figure 6a the central area is between electronegative and electropositive. Thus, the adsorption of positively charged GKG on $C_{54}H_{18}$ is rather strong due to the electrostatic attraction, manifested by the adsorption energy of -19.2 kcal/mol at HF level, while the negatively charged GDG exhibits repulsion at HF level (AE: 7.8 kcal/mol). Because of contrary charge distribution in $C_{54}H_{18}$ and C_{54} , the opposite results are obtained for the adsorptions of two charged tripeptides. For all of investigated peptides the adsorptions on $C_{54}H_{18}$ induce electron transfer from SWCNT to peptides in a range of 0.07 for GDG and 0.38e for GKG. The charges carried by peptides are summarized in Table 1, and charge transfer for the adsorptions of GDG, GKG GNG and GWG can also be visualized in b1-b4 of Figure 6. As compared with the H-saturated SWCNT model (b), the central area of the SWCNT becomes slightly more positive because of relatively weak interaction when the negative charged GDG approaches (b1), whereas the strong adsorption of positively charged GKG causes much more positive charge (orange and red) in the central area (b2). For the polar neutral R group carrier, e.g., tripeptide GNG the electron transfer ($\sim 0.13e$) is mild when it is absorbed to the surface of the SWCNT. Obviously, polar interaction plays a role in part and the distribution of charges on the surface of the SWCNT (b3) is between the cases of (b1) and (b2) when the GNG absorbs. As compared with b2 and b3, Figure b4 shows that there is a smaller region of positive charge in the central ring of the nanotube when the aromatic group carriers absorbs, yet a larger electronegative (yellow) region, which would greatly favor the interaction of π electron of the aromatic group. Therefore, the π -stacking interaction on the surface of nanotube is very strong. The contour plot has intuitively revealed the different adsorption strength of the nine tripeptides on two SWCNT models from the view of charge distribution.

4. Conclusions and Remarks

Adsorption of nine tripeptide GXG (X= D, K, G, N, S, V, F, W, and Y, respectively) on the surfaces of hydrogen saturated and non-hydrogen saturated (10,0) SWCNTs are systematically discussed. Since these tripeptides crown major features of 20 kinds of common amino acids, the investigation of their adsorption on the SWCNT surface is expected to offer general sense on the insight into SWCNT functionalization through non-covalent interaction of various peptides and even proteins coating. In Figures 3 and 4, adsorption energies (black lines) predicted by MP2 including solvent effect are clearly divided into three regions: positive AE for charged and hydrophilic residues, and negative AE for hydrophobic residues. The red lines for electron correlation effect reveals the strongest adsorption of aromatic rings accompany the highest electron correlation effects. On the basis of these results it may be concluded that the electrostatic interaction does not play important role for the functionalization of *pristine* SWCNT through protein adsorptions, but it is most likely that the hydrophobic as well as van der Waals interaction resulting from $\pi\cdots\pi$ stacking and $X-H\cdots\pi$ (X=C, H and O) are the major driving force. The detailed remarks are summarized as follows.

As shown in Figure 3, the adsorption energies (MP2+CPCM) are clearly classified into three groups according to the characteristics of GXG. Two tripeptides GDG and GKG with charged R-groups are greatly affected by the solvent effect, and saturability of the SWCNT cluster model. Because of significant electrostatic attraction, the adsorption of GKG on the surface of $C_{54}H_{18}$ is much stronger than that of the GDG and other investigated tripeptides in the gas phase. In aqueous solution, however, because of strong solvation both the charged amino acids will be highly solvated and their adsorptions are significantly weakened on $C_{54}H_{18}$ surface, bringing about binding energies of -0.2 kcal/mol for GKG and 13.9 kcal/mol for GDG. Although on the surface of C_{54} , the adsorption of GDG in gas phase is very strong, solvent effect again disable its adsorption in aqueous solution.

The tripeptides GNG and GSG with a hydrophilic residue exhibit clear adsorptions on $C_{54}H_{18}$ surface in the gas phase (adsorption energy at MP2 level: -3.3 and -4.2 kcal/mol) while their adsorption energies in aqueous solution change to 0.3 kcal/mol, which indicate that the hydrophilic tendency of $-NH_2$ and $-OH$ groups make them difficult to adsorb on the hydrophobic surface of SWCNT.

For GGG and GVG with hydrophobic aliphatic $-CH_2$ and $-C(H)(CH_3)_2$ groups, in gas phase both can be strongly adsorbed on $C_{54}H_{18}$ surface with adsorption energies of -4.2 and -4.7 kcal/mol. Although their adsorptions are also weakened by solvent effects, the negative adsorption energies (-1.1 and -4.1 kcal/mol with MP2+CPCM method) still show that they tend to adsorb on $C_{54}H_{18}$ surface even in aqueous solution. The opposite result to the above tripeptides with charged groups (GDG and GKG) or hydrophilic groups (GNG and GSG) demonstrates that the hydrophobic effects do play very important role on the adsorption of proteins on SWCNT.

It is very interesting to note that the aromatic residues, F, W and Y, have the most favorable adsorption energies on the $C_{54}H_{18}$ surface except for the positively charged residue K in the gas phase. Among the investigated tripeptides, the contribution of electron correlation to the adsorption energies for the three aromatic residues is also the most significant (-17.5, -18.6 and -14.2 kcal/mol). In the aqueous solution these aromatic tripeptides GFG, GWG, and GYG are even more strongly adsorbing than the aliphatic tripeptide GVG by a few kcal/mol, and exhibit significant adsorptions on the $C_{54}H_{18}$ surface with adsorption energies of -6.5, -10.4 and -6.3 kcal/mol, respectively. This result provides a strong evidence for the importance of aromatic content for peptide/SWCNT.^{18, 19}

For a practical nanotube, its enough length leads to its surface state more like that of the H-saturated model employed in the paper. Thus, above results indicate that in the solution phase aromatic R groups of a long peptide chain would be the major ones to absorb on the nanotube surface both from the views of adsorption strength and spatial stretch degree. This is in exactly agreement with the experimental and molecular dynamics simulation results.^{18, 19} According to the adsorption strength, $-CH_2$ (of G) and $-CH(CH_3)_2$ (of V) groups also have the ability to bind to the SWCNT surface, but from their spatial stretch degree in a peptide chain especially in that with aromatic groups, the two groups would hardly approach the surface of nanotube due to the spatial hindrance from surrounding larger groups, such as from the aromatic groups. Due to strong solvation, the charged GDG and GKG, and hydrophilic GNG and GSG have the least opportunity to absorb on the SWCNT surface in aqueous solution, while these charged and hydrophilic groups will interact with the aqueous solution and turn its hydrophobic face to hydrophobic surface of SWCNT.³⁰

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Figure 1. Nine amino acids employed in the GXG tripeptides (X=D, K, G, N, S, V, F, W, and Y in the first row), the fixed positions for scanning the contact distances (pink points), and designed adsorption styles (second row) on the surface of H-saturated CNT, as well as two CNT models employed (third row).

Figure 2.
The potential energy curves for the adsorptions of GSG and GWG on the surface of $C_{54}H_{18}$

Figure 3.
The adsorption energies of tripeptides GXG on the surface of C₅₄H₁₈.

Figure 4.
The adsorption energies of tripeptides GXG on the surface of C₅₄.

Figure 5.
The net ESP atomic charge with MPWB1K/cc-pVDZ: C₅₄H₁₈ (top) and C₅₄ (bottom)

Figure 6.

Contour plots of net ESP charges with MPWB1K/cc-pVDZ for the non-H saturated C_{54} (a), H-saturated $C_{54}H_{18}$ (b) and four typical GXG/ $C_{54}H_{18}$ complexes (b1-b4)

Table 1

The characteristics for the adsorptions of GXG on C₅₄H₁₈: expected major non-covalent interaction, the distance (*d*/Å), net charge carried by GXG (*q*/e) with MPWB1K/cc-pVDZ, and adsorption energies (AE, kcal/mol) with MP2 in the present study

GXG	Group ^a	<i>d</i>	<i>q</i>	AE (MP2)	AE(MP2+CPCM)
GDG	COO ⁻	3.25	-0.93	-2.0	13.9
GKG	NH ₃ ⁺	3.00	+0.62	-29.3	-0.2
GNG	NH ₂	3.08	-0.13	-2.0	2.1
GSG	OH	3.13	-0.13	-4.2	0.3
GGG	CH ₂	3.25	-0.15	-4.1	-1.1
GVG	C(H)(CH ₃) ₂	3.88	-0.15	-4.7	-4.1
GFG	Ar	3.63	-0.14	-12.0	-6.5
GWG	Ar	3.63	-0.11	-12.8	-10.4
GYG	Ar	3.75	-0.14	-11.4	-6.3

^aThe expected major group of side chain R interacting with SWCNT; Ar represents a general aromatic group in residues F, W and Y.

Table 2
Adsorption energies (AE: kcal/mol) of GXG on the C₅₄H₁₈ at different levels

GXG	MPWB1K	HF	Electron correlation	MP2	CPCM	MP2+CPCM
GIDG	-7.8	9.0	-11.0	-2.0	15.9	13.9
GKG	-21.0	-19.2	-10.1	-29.3	29.1	-0.2
GNG	-1.9	4.0	-7.3	-3.3	3.6	0.3
GSG	-2.9	0.8	-5.0	-4.2	4.5	0.3
GGG	-1.3	4.2	-8.3	-4.1	3.0	-1.1
GVG	-1.5	0.4	-5.1	-4.7	0.6	-4.1
GFG	-2.8	5.5	-17.5	-12.0	5.5	-6.5
GWG	-3.7	5.8	-18.6	-12.8	2.4	-10.4
GYG	-4.9	2.8	-14.2	-11.4	5.1	-6.3

Table 3

Adsorption energies (AE: kcal/mol) of GXG on C₅₄ at different levels

	MPWB1K	HF	Electron Correlation	MP2	MP2+CPCM
GDG	-15.2	-18.6	-11.8	-30.4	0.2
GKG	-4.2	3.0	-6.8	-3.9	7.4
GGG	-1.4	1.3	-6.1	-4.9	-0.4
GNG	-2.5	-0.2	-5.4	-5.7	-2.0
GSG	-1.5	2.6	-5.0	-2.4	2.2
GVG	-4.9	1.5	-5.2	-3.6	-3.3
GFG	-3.3	7.5	-21.0	-13.5	-8.6
GWG	-5.1	5.6	-22.3	-16.7	-14.5
GYG	-5.0	2.0	-14.5	-12.4	-8.6