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Substituent Effects in π -Stacking of Histidine on Functionalized-SWNT and Graphene

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Abstract

Adsorptions of histidine on the functionalized (10,0) single-walled carbon nanotube (SWNT) and graphene were investigated using density function theory methods, M05-2x and DFT-D. The results show that the binding of the histidine ring to the functionalized SWNT is weaker than that to the pristine SWNT for both singlet and triplet complexes, regardless of the electron-donating (-OH, -NH₂) or electron-withdrawing (-COOH) character and their attached sites. The present decreased binding is opposite to the well-known enhanced binding in the substituted benzene dimers. Since the atoms of the histidine are distant from the substituent atoms by over 6 Å, there would be no *direct* interaction between histidine and the substituent as in the case of the substituted benzene systems. The decreased binding can be mainly driven by the aromaticity of the functionalized SWNT. The nucleus-independent chemical shift (NICS) index analysis for the functionalized SWNTs in deed shows that local aromaticity of SWNT is decreased because of the electron redistribution induced by functional groups, and the π - π stacking between the histidine ring and *functionalized*-SWNT is therefore decreased as compared to the pristine SWNT. However, the above trend does not remain for the binding between the histidine and graphene. The binding of the histidine to the functionalized graphene with -OH and -NH₂ is just slightly weaker than that to the pristine graphene, while its binding to COOH-SWNT becomes a little bit stronger.

Keywords

functionalized-SWNTs; π - π stacking interactions; substituent effects; NICS; DFT-D

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Supporting Information Available: Figure S1 displays the optimized adsorption configurations of histidine on the SWNT-OH, and SWNT-NH₂. NICSs scheme for spacer rings were shown in Figure S2 (data were calculated at the B3LYP/6-31G level), NICS(0) values computed at the ring centers were determined by the nonweighted mean of the heavy atoms coordinates and NICS(1) is computed at 1 Å above the molecular plane. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Introduction

Carbon nanotubes (CNTs) have attracted considerable attention since their discovery in the early 1990s due to their unique physicochemical, mechanical and electrical properties as well as their broad range of potential applications.^{1–2} The proposed applications of single-walled carbon nanotubes (SWNTs) in biomedical fields, such as drug or gene delivery and probes for imaging stimulated the extensive exploration for the interaction of biomolecules with SWNTs.^{3–4} Pristine CNTs are insoluble in water and organic solvents, greatly limiting its bio-compatibility. Chemical functionalization of CNTs by introducing molecules and groups is one conventional way to improve this issue. For example, the surface of oxidized nanotubes is mainly covered by carboxylic -COOH groups that make the oxidized nanotubes disperse better in solution than the raw material.^{5,–6} Moreover, chemical modification makes carbon nanotubes more amenable for other various potential applications, such as opening hollow cavities for gas storage or lithium intercalation,⁷ enhancing free radical scavenging,⁵ and mediating the desired bioconjugates for cancer therapy,⁸ etc. The chemical functionalized π systems also play a very important role in molecular assembly and molecular devices.^{9,10,11} Chemical modification by functionalization was usually fulfilled via chemical decoration with organic groups (such as carboxyl and hydroxyl groups),¹² and amidination.^{8,13} The recent theoretical and experimental studies demonstrated that the presence of the functional groups significantly modifies the electron structure and bioactivity of CNTs.^{14,5}

Despite the fact that extensive studies have been carried out on the non-covalent interaction between biomolecules and pristine SWNT,^{15–16} there is little detailed theoretical analysis of the substituent effects on the interactions between biomolecules and *functionalized* SWNTs, which may play major roles in understanding various biological processes. Regarding the substituent effect of the π -stacking systems, since it was defined on the benzene and x -benzene ($x=OH$, CH_3 , F , and CN),¹⁷ the nature and existence have been well investigated on the substituted benzene systems.^{18–19, 20,21,22,23} The substituents enhance the π -stacking regardless of their electron-donating or electron-withdrawing character. It is generally assumed that the major interactions between DNA bases or some amino acids and SWNTs are mediated by the π -electron networks. Whether the π -stacking between the biomolecules and *functionalized*-SWNTs is strengthened or weakened remains unclear. In the present work, we focused on the substituent effects on the interaction between amino acid and functionalized SWNT. Considering that the aromatic rings, nonpolar part of the amino acid, are important contributors in the specific binding to the CNTs,^{24,16} we have restricted our calculations using only the aromatic ring of histidine with the pristine or functionalized (10,0) zigzag SWNT. Here, the electron-donating -OH, and -NH₂, and withdrawing -COOH groups are used to functionalize the SWNT. Because of the importance of the interaction of biomolecules and graphene layer,²⁵ for the sake of comparison with the functionalized SWNT the investigation was also extended to the functionalized graphene.

Results and Discussions

Three repeat units (about 13 Å in length) of zigzag SWNT (10,0) with a diameter of 7.83 Å were used to model a finite CNT. Three different groups, -COOH, -OH and -NH₂, were

attached directly on the sidewall as well as the open end of the SWNT for the aim to explore the substituent effects on the histidine absorption on *functionalized*-SWNT. With respect to the functionalization and adsorption sites, the complexes were noted as types of *S*, *L*, *V*, and *O*, respectively, as shown in Figure 1. The aromatic ring of histidine was initially placed in parallel to the tangent surface of *functionalized*-SWNT at a height of approximately 4.0 Å and allowed to relax freely. Final geometries are shown in Figure 1 for SWNT-COOH, and others in Figure S1 of supporting materials. The optimized average distances, defined as the average from the atoms of pentagonal ring of histidine to the nearest neighbor C atom of *functionalized*-SWNT, are listed in Table 1 with binding energies.

As shown by the top views in Figure 1, the complexes show the displaced AB type of configurations of graphite layer, benzene dimer, DNA bases-SWNT systems,^{17,18,26,27,15} where the pentagon ring of histidine locates above the hexagonal ring of *functionalized*-SWNT with either C or N coordinated with six carbons of *functionalized*-SWNT. Thus the present π - π stacking can be classified into the type of π - π (D) interaction.²³ As expected, the aromatic ring of histidine prefers to almost orient in parallel to the tangent plane of the SWNT with noncovalent signature of weak π - π stacking interaction. However, because of different electronegativity of C and N, the N (H) has the shortest distance to *functionalized*-SWNT at 3.15 ± 0.05 Å, resulting in a slight deviation from parallel configurations. The separation between histidine and pristine SWNT obtained with M05-2x was found to be 3.31 Å, similar to the interplanar distance 3.30 Å between histidine and (5,5) SWNT with the plane-wave GGA in the Vienna *ab initio* simulation package.¹⁶ The separation between histidine and SWNT obtained by the PBE-D is shorter by 0.14 Å than those obtained by the M05-2x, which is attributed to the explicit van der Waals correction included in the PBE-D.

According to Figure 1, it is obvious that functionalization has little influence on the equilibrium geometry of the histidine and *functionalized*-SWNT complexes. The aromatic ring of histidine still orients almost parallel to the *functionalized*-SWNT surface, also bearing the signature of weak π - π stacking interaction. Moreover, compared with the complex of pristine SWNT, the separations between histidine ring and *functionalized*-SWNT remain the same for SWNT-COOH+His (*S*) and SWNT-OH+His (*L*), or decrease slightly by approximately 0.01–0.06 Å except for the increase of 0.1 Å in the complex SWNT-NH₂+His(*L*). For the given functionalization groups, the separations for the end functionalized complexes (*L* and *S*) are slightly higher than those of the sidewall functionalized ones (*O* and *V*).

According to Table 1, the binding energy between aromatic ring of histidine and pristine (10,0) SWNT is approximately –5.24 kcal/mol, in between the binding energy of –3.46 and –9.22 kcal/mol for the histidine and pristine (5,5) SWNT predicted with respective GGA plane-wave and MP2 method.¹⁶ In spite of little influence on the separation between aromatic ring of histidine and *functionalized*-SWNT, it is interesting to find that the binding energies decrease by about 0.6–1.4 kcal/mol for the π - π stacking no matter that the introduced functional groups are electron-withdrawing (–COOH) or electron-donating (–OH, and NH₂) and functional groups are attached directly on the sidewall or the open end of *functionalized*-SWNT. This phenomenon is opposite to the substituent effect in the substituted benzene systems C₆H₅...X,^{18,26} where the binding was enhanced due to the

substituent groups, such as X=F, CH₃, NH₂, OH, etc. The current result supports the previous report that the two N atoms in the histidine ring behave very differently in π interaction from benzene²⁸

Table 1 also shows that, consistent with the smaller separation between histidine ring and *functionalized*-SWNT, the PBE-D predicted binding strength is much stronger than that from the M05-2x. For the pristine SWNT, the binding energy of -10.49 kcal/mol is almost one time higher than that from the M05-2x (E_b =Equation5.23 kcal/mol), yet rather close to that from the MP2 for the histidine with (5,5) SWNT (Equation9.22 kcal/mol).¹⁶ Similar to the trend predicted by the M05-2x, PBE-D results again indicate that functionalization results in less binding of histidine ring to *functionalized*-SWNTs by 2.9–4.6 kcal/mol than to the pristine SWNT.

It is known that a ground state for H-saturated zigzag (n,0) SWNT cluster may be a triplet state, rather than a single state.²⁹ Both the M05-2x and PBE-D calculations confirmed that it is also true for the pristine (10,0) SWNT as well as *functionalized*-SWNT clusters. The triplet complexes of histidine and *functionalized*-SWNT are also more stable than the singlet ones. The binding energies and separations together with the first ionization potentials (IP) and polarizabilities (α) of *functionalized*-SWNT are summarized in Table 2. Comparing Tables 1 and 2, it can be found that separations from histidine ring and *functionalized*-SWNT for the triplet state complexes differ only by $\pm 0.03 \text{ \AA}$ from those of the singlet complexes. For the triplet state complexes, the decrease trend between *functionalized*-SWNT and the histidine ring also remains regardless of the type and location of functional groups. Generally, the stacking *functionalized*-SWNT+His (L) is stronger than *functionalized*-SWNT+His (S). For the functionalization on the sidewall, the complex (V) is only slightly stronger than the complex (O), 0.15kcal/mol for SWNT-COOH, 0.19kcal/mol for SWNT-OH, and 0.45kcal/mol for SWNT-NH₂, which may be attributed to the shorter distance between the histidine and functional groups in the case of *functionalized*-SWNT +His (V) than *functionalized*-SWNT+His (O).

Considering that π -stacking noncovalent interaction is profound importance in molecular biology and other areas, the interaction of aromatic amino acids with SWNT has been studied carefully by previous workers. An excellent correlation was observed between the polarizabilities of the aromatic moieties and their binding strength with the (5,5) SWNT.¹⁶ To get an insight into the substituent effects on the π stacking interactions, the polarizabilities of the *functionalized*-SWNTs are also calculated. However, the correlation between the binding strength and α of *functionalized*-SWNTs was not revealed. This may be explained by the fact that *functionalized*-SWNTs have negligible deformation. It is known that the π - π stacking is stabilized mainly by dispersion effect depending on the surface area of buried as well as on the polarizability and ionization potential (IP) of the moieties. The decrease of binding strength due to the functionlization correlates well with the IP trend shown in Table 2. The primary binding also varies with the types of π interactions.^{23,22}

In another way, the prevailing view of substituent effects in the simplest π - π stacked systems such as benzene dimer is the polar/ π model proposed by Hunter et al.^{30,31} In the polar/ π model, electron-withdrawing substituents will diminish the electron density in the π -

cloud of the benzene ring, which decreases the electrostatic repulsion with the π -system of the interacting ring. As a result, the stacking interaction relative to the unsubstituted dimer will be enhanced. Our theoretical results of the π - π stacking interactions in histidine ring and *functionalized*-SWNT show a different substituent effect from previous results. The π - π stacking between histidine and *functionalized*-SWNT is decreased for both electron-withdrawing (-COOH) and electron-donating (-OH, -NH₂) functional groups, which does not follow the former polar/ π model. As mentioned above, the present results are also opposite to the enhanced binding for the substituted benzene dimers.^{26,19} The enhanced binding for the substituted benzene dimers is most likely due to the direct substituent- π interactions, rather than an indirect modulation of π density.¹⁹ For the current investigated *functionalized*-SWNTs+His complexes, all of atoms in the histidine ring are far from the functional groups beyond 6 Å and there would be no much direct interaction between histidine and the substituent. Thus, it can be speculated that the direct substituent (functional group) and the aromatic ring of the histidine should be minor contribution to the stability of the complexes, and the major interactions come from the π - π density modulation mainly driven by the aromaticity of the functionalized carbon nanotube

To further understand the decrease of binding strength for the histidine ring to *functionalized*-SWNT, nucleus-independent chemical shift (NICS) aromaticity indexes were therefore calculated to assess the electron delocalization in the different interacting hexagonal rings of the *functionalized*-SWNT with histidine ring. The index proposed by Schleyer and co-workers was widely employed as aromaticity or antiaromaticity criterion.^{32,33,34} Significant negative (i.e., magnetically shielded) NICS values in interior positions of rings indicate the presence of induced diatropic ring currents or aromaticity, whereas positive values (i.e., deshielded) at each point denote paratropic ring currents and antiaromaticity. The NICS(0), and NICS(1) indicators of local aromaticity for the interacting rings of the SWNTs are displayed in Figure 2 for pristine and *functionalized*-SWNT (S) and Figure S2 for other functionalized SWNTs (L, O and V), respectively. A comparison of the local aromaticity descriptors indicates that all of three investigated substituents reduce the local aromaticity of the *functionalized*-SWNTs, evidenced by a variation from higher negative NICS for the pristine SWNT to either positive or lower negative NICS of the *functionalized*-SWNT. For the electron withdrawing group -COOH, it was found from Figure 2 that the NICS of SWNT-COOH was indeed increased. The increased chemical shielding indicates the decreased electron density in the π -cloud of the *functionalized*-SWNTs rings interacting with histidine, which decreases the electron overlap of the π -stacking systems and the consequent dispersion. Thus, the stacking interaction between the histidine ring and *functionalized*-SWNT would be decreased as compared to the interaction between histidine and pristine SWNT.

To investigate the substituent effect on the binding between the histidine and graphene (GP), four hydrogen atoms of circumcoronene, C₅₄H₁₈, were replaced with -OH, -COOH and -NH₂ respectively. The complexes between the histidine and graphene were located due to the π - π (D) interaction. As shown in Figure 3, the histidine ring displays from the six member ring of graphene, and the N and N(H) atoms locate over the center of the corresponding rings. According to Table 3, the binding energy of the histidine to the

functionalized graphene only slightly deviates from that to the pristine graphene. For instance, the binding with COOH-GP behaves slightly stronger as compared to the binding with pristine graphene (−9.639 vs −9.496 kcal/mol); however for another two electron donating functional groups (−OH and −NH₂) their bindings get slightly weaker (−9.487 and −0.469 vs. −9.496 kcal/mol), indicating the previous binding decrease trend for SWNT due to functionalization is not remained for functionalized graphene. The binding energy variation for the histidine and functionalized graphene correlates well with IP, rather than their polarizability.

Conclusions

In summary, substituent effects on the absorption of histidine on *functionalized*-SWNTs were investigated using M05-2x and PBE-D methods. The results show that the π -stacking between histidine ring and *functionalized*-SWNT is weakened for both singlet and triplet complexes regardless of the electron-donating (−OH, −NH₂) or electron-withdrawing (−COOH) character and the attached sites of the substituents, which are opposite to the enhanced binding in the substituted benzene dimers. Since the distances between atoms of the histidine and the substituent atoms are over 6 Å, the decreased binding can be mainly attributed to π - π interaction, rather than the direct electrostatic interactions between substituent and the π absorbent as in the case of the substituted benzene systems. The NICS aromaticity index analysis for *functionalized*-SWNTs shows that local aromaticities are decreased, and the π - π stacking between the histidine ring and *functionalized*-SWNT is therefore decreased as compared to the pristine SWNT. However, the above trend was not remained for the binding between the histidine and graphene. The binding of the histidine to the functionalized graphene with −OH and −NH₂ is just slightly weaker than that to the pristine graphene, while its binding to COOH-SWNT becomes a little bit stronger.

Computational Details

The *functionalized*-SWNTs were initially fully optimized at the level of B3LYP/3-21G and the adsorptions of histidine on the constraint *functionalized*-SWNTs were then partially optimized with the hybrid meta-GGA, M05-2x/cc-pVDZ.³⁵ The binding energies (E_b) were calculated for the equilibrium geometries of all of the complexes

$$E_b = E_{\text{SWNT+histidine}} - (E_{\text{SWNT}} + E_{\text{Histidine}})$$

Here, $E(\text{SWNT+Histidine})$, $E(\text{SWNT+FG})$ and $E(\text{Histidine})$ are the total energies of the complexes, of the *functionalized*-SWNT and of the isolated Histidine molecule. The E_b was further corrected by including the basis set superposition error (BSSE) corrections using the Boys-Bernardi counterpoise technique.³⁶

The relevant NMR parameters were determined theoretically for further analysis using B3LYP/6-31G. The NMR isotropic chemical shifts (ICSs, δ) were calculated with the gauge-induced atomic orbital (GIAO) methods. The nucleus-independent chemical shift (NICS) index proposed by Schleyer and co-workers was used,^{32,33,34} as it is an effective and

widely employed aromaticity/antiaromaticity criterion. To match the familiar NMR convention, NICS indices correspond to the negative of the magnetic shielding computed at chosen points in the vicinity of molecules. Significant negative (i.e., magnetically shielded) NICS values in interior positions of rings indicate the presence of induced diatropic ring currents or aromaticity, whereas positive values (i.e., deshielded) at each point denote paratropic ring currents and antiaromaticity. All of the above calculations were performed using the GAUSSIAN-03 package.³⁷

In order to get more accurate prediction of the interaction between the aromatic ring and the substrate, our calculation was also performed with DFT-D method. For an empirical dispersion-corrected density functional theory (DFT-D), Grimme's scheme was adopted,^{38,39} where the van der Waals interaction term is explicitly described by a damped inter-atom potential, accounting for long-range dispersion effects. It was established that DFT-D provides more accurate descriptions for non-covalent interactions, including π -stacking.^{40,41} In this work Perdew-Burke-Ernzerhof (PBE) exchange-correlation functional in the DFT part was employed, and the DFT-D method was therefore referred to as PBE-D. The PBE-D/cc-pVDZ was done with the ORCA suite of program.⁴²

Graphene was modeled as a polycyclic aromatic hydrocarbon cluster C₅₄H₁₈ circumcoronene. Because of smaller size than the above SWNT full optimization was carried out with B97-D/cc-pVDZ implemented in Gaussian 09 for the binding of histidine with pristine as well as the functionalized graphene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The manuscript reports a decreased binding of the histidine to the functionalized single-walled carbon nanotube (f-SWNT), which is opposite to the well known enhanced binding of substituted benzene dimers.
- Supported by geometry and NICS analysis, the decreased binding is mainly due to π - π stacking, rather than the direct substituent- π interactions as in the case of the substituted benzene dimers.

Figure 1. Optimized adsorption configurations of histidine on the pristine and COOH-functionalized (10,0) SWNT.

Figure 2.

NICSs (in ppm) scheme for spacer rings (data were calculated at the B3LYP/6-31G level). NICS(0) values at the ring centers were determined by the nonweighted mean of the heavy atoms coordinates. NICS(1) is computed at 1 Å above the molecular plane; then, out-of-plane molecular orbital contributions are considered. The NICS(1) values should be more indicative of p-electron effects and provide better comparisons with the values found for six-membered rings.

Figure 3.

The binding conformation for the histidine and pristine H-saturated graphene and functionalized graphene with COOH, NH₂ and OH.

The average equilibrium distance of the singlet complexes ($d/\text{\AA}$) and binding energies (E_b , kcal/mol) between the *functionalized* SWNTs and histidine obtained at M052x/cc-pVDZ and PBE-D/cc-pVDZ levels

	M05-2x			PBE-D		
	d	E_b	E_b	d	E_b	E_b
SWNT+His	3.31	-5.23	0	3.17	-10.49	0
SWNT-COOH+His(S)	3.31	-4.17	1.06	3.18	-7.63	2.86
<i>L</i>	3.28	-4.63	0.60	3.22	-5.90	4.59
(V)	3.27	-4.22	1.01	3.19	-6.83	3.66
(O)	3.26	-4.04	1.20	3.20	-6.80	3.69
SWNT-NH ₂ +His(S)	3.29	-4.20	1.04	3.24	-6.66	3.83
(L)	3.40	-3.80	1.43	-	-	-
(V)	3.28	-4.04	1.20	3.06	-6.09	4.40
(O)	3.27	-4.08	1.15	-	-	-
SWNT-OH+His(S)	3.29	-3.90	1.34	3.18	-6.57	3.92
(L)	3.31	-3.85	1.38	3.19	-6.80	3.69
(V)	3.27	-3.94	1.29	3.20	-6.25	4.24
(O)	3.25	-3.92	1.31	3.17	-5.97	4.52

Table 2

Polarizabilities (α /au), the first ionization potentials (IP/eV), and the average equilibrium distance of the triplet complexes ($d/\text{\AA}$) and binding energies (E_b , kcal/mol) between the *functionalized*-SWNTs and histidine with the PBE-D/cc-pVDZ method

	α	IP	d	E_b^*
SWNT+His	1530	4.75	3.18	-22.57
SWNT-COOH+His(S)	3164	4.08	3.19	-9.81
L	2867	4.09	3.22	-10.21
(V)			3.20	-9.10
(O)			3.20	-8.95
SWNT-NH₂+His(S)	3121	3.66	3.23	-11.39
(L)	2687	3.99	3.22	-14.52
(V)			3.20	-13.75
(O)			3.17	-13.30
SWNT-OH+His(S)	2565	2.97	3.21	-9.16
(L)	3140	3.46	3.21	-12.57
(V)			3.19	-9.19
(O)			3.20	-9.00

* BSSE not corrected

Polarizabilities (α /au), the first ionization potentials (IP/eV), and the average equilibrium distance of the singlet complexes ($d/\text{\AA}$) and binding energies (E_b , kcal/mol) between graphene and histidine from B97-D/cc-pVDZ.

	<i>IP</i>	<i>d</i>	<i>E_b</i>	<i>E_b</i>
GP+His	5.893	160.8	3.238	-9.496
GP-COOH+His	6.214	203.9	3.231	-9.639
GP-NH ₂ +His	5.159	177.8	3.252	-9.469
GP-OH+His	5.473	166.8	3.247	-9.487
				0.009