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First principle study of cysteine molecule on intrinsic and Au-doped graphene surface as a chemosensor device

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Abstract To search for a high sensitivity sensor for cysteine, we investigated the adsorption of cysteine on intrinsic and Au-doped graphene sheets using density functional theory calculations. Binding energy is primarily determined by the type of atom which is closer to the adsorbed sheet. Compared with intrinsic graphene, Au-doped graphene system has higher binding energy value and shorter connecting distance, in which strong Au-S, Au-N and Au-O chemical bond interaction play the key role for stability. Furthermore, the density of states results show orbital hybridization between cysteine and Au-doped graphene sheet, but slight hybridization between the cysteine molecule and intrinsic graphene sheet. Large charge transfers exist in Au-doped graphene-cysteine system. The results of DOS and charge transfer calculations suppose that the electronic properties of graphene can be tuned by the adsorption site of cysteine. Therefore, graphene and Au-doped graphene system both possess sensing ability, except that Au-doped graphene is a better sensor for cysteine than intrinsic graphene.

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Introduction

The good sensor properties of carbon nanotubes have already been known for some time [1], but recently, the possibility to use graphene as a highly sensitive sensor was also reported [2]. Graphene is a novel material recently proposed as one of the main alternatives to overcome the performance limitations of materials such as silicon and carbon nanotubes. Alwarappan and co-workers found that graphene electrodes exhibit superior biosensing performance over CNTs toward dopamine detection in the presence of common interfering agents such as ascorbic acid and serotonin [3]. Liu and co-workers found that the functionalized nanographene sheets are biocompatible and applicable for drug delivery [4]. Despite technological and biological interest, the intrinsic feature of interaction between biological molecules and graphene remains obscure, which limits the biological and biomedical applications of graphene. A number of theoretical studies were performed to fully exploit the possibilities of graphene sensors. For example, using first principle calculations, Leenaerts et al. investigated the adsorption of NH_3, NO_2, NO, CO and H_2O on graphene sheet [5]. The operational principle of graphene devices is based on changes in their electrical conductivity induced by the adsorption of gas molecules on graphene's surface acting as donors or acceptors, similar to that for other solid state sensors [6–8].

Cysteine ($HS-CH_2-CH$ $(NH_2)-COOH$), an amino acid with a thiol end group, widely presents in proteins, and plays crucial roles in molecular biology, medicine, and biochemistry, especially in the interaction of biomolecules with the inorganic world. Particular examples include the

attachment of proteins and antibodies to metal (and functionalized insulator) surfaces [9, 10]. Cysteine–metal coupling is related to the activity of this amino acid as a chemosensor for metal ions. For such an application, cysteine can either polymerize through amino and carboxyl groups and interact with metal ions through thiol group [11], or bind to metal electrodes through thiol group and use other end groups to capture foreign ions.

Fig. 1 Optimized structures of a cysteine molecule adsorbed on the intrinsic and Au-doped graphene (left and right panels show the total and local schematic diagram of Isomers, respectively)-the adsorbed systems are labeled by a, a′, b, b′ and c, c′. Orange, yellow, white, blue, red, and gray spheres represent Au, S, H, N, O, and C atoms, respectively
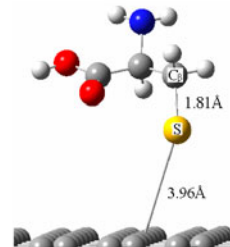
Adsorbate
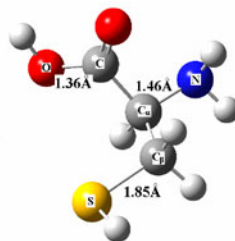
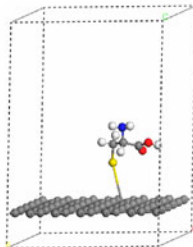cysteine

System substrate
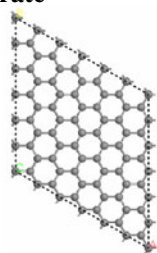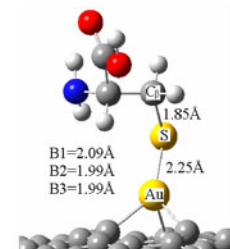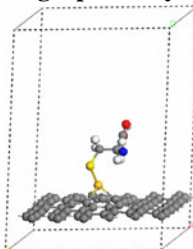

Graphene

Au-doped graphene

a graphene-cysteine with the SH group close to the substrate

a' Au-doped graphene-cysteine with the SH group close to the substrate

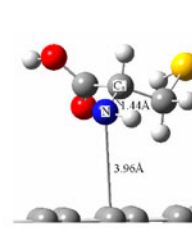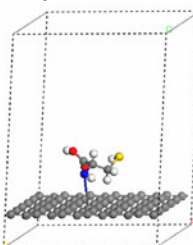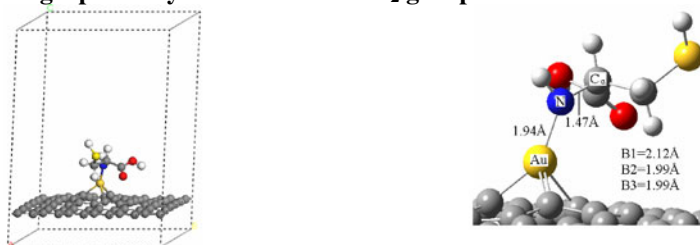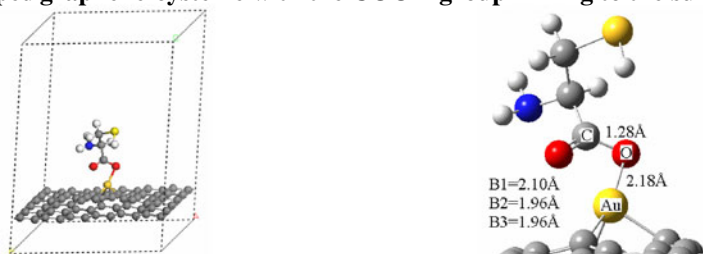**b** graphene-cysteine with the NH2 group attached to the surface

Fig. 1 (continued)

b'   Au-doped graphene-cysteine with the NH₂ group attached to the surface

c   graphene-cysteine with the COOH group linking to the surface

c'   Au-doped graphene-cysteine with the COOH group linking to the surface

The ultimate aim of any detection method is to achieve such a level of sensitivity that individual quanta of a measured entity can be resolved. In the case of chemical sensors, the quantum is one atom or molecule. However, such resolution has so far been beyond the reach of any detection technique, even the solid state gas sensors hailed for their exceptional sensitivity [12]. Thus, considerable experimental and theoretical work has focused on improving the sensing performance of graphene for various molecules by doping or functionalizing the graphene. In this article, we report from our density functional theory (DFT) calculation that the sensitivity of graphene system to cysteine could be enhanced to a higher level through gold doping. We hope our result may provide new insight into the detection of protein. These preliminary discussions have been inspired by research efforts of other groups who attempt to amplify the interaction of graphene in biological systems.

Theoretical methodology

All DFT calculations on the interactions between cysteine and graphene sheet were performed using DMol^3 code [13,

14]. Full geometry optimizations of cysteine-graphene systems were carried out by means of DFT calculations using the PBE exchange–correlation functional [15]. Different from local density approximation (LDA), the generalized gradient corrected (GGA) functional does not lead to a strong bonding of molecules. To take into account relativistic effects in treating Au atom, we chose the all-electron scalar relativistic method utilizing the Douglas–Kroll–Hess (DKH) Hamiltonian [16], which is the most accurate approach available in DMol^3 package. To ensure that the results of the calculations are comparable, identical conditions were employed for isolated cysteine molecule, graphene sheet and also adsorbed graphene system. Self-consistent field procedure was carried out with a convergence criterion of 10^{-6} a.u. on the energy and electron density, and geometry optimizations were performed with a convergence criterion of 10^{-3} a.u. on gradient, 10^{-3} a.u. on displacement and 10^{-5} a.u. on energy.

In the present calculations, periodic boundary condition was taken with the supercells. A vacuum width of 20 Å above was constructed, which ensures that the z-axis of the periodic supercell (perpendicular to the graphene layer) is large enough to eliminate interaction between graphene sheets of adjacent supercells. Optimized structural model

containing 72 carbon atoms of the 6×6 intrinsic graphene is shown in Fig. 1, which ensures a lateral distance between cysteine molecules of at least 10 Å to eliminate interaction between cysteine molecules in neighboring supercells. By substituting a Au atom for the center carbon atom, the Au-doped system configuration can be obtained. The most stable optimized geometries, their geometrical parameters and the binding energies and charge transfers of cysteine adsorption on each support are given in Fig. 1 and Table 1.

Results and discussion

Structure

Cysteine is usually responsible for the bond at the bioinorganic interface. Its functional groups (SH, NH_2, COOH) are stimulated by a delocalized metallic environment. From the previous finding that all of the thiolate, phosphino, and amino groups are able to bind to gold surfaces [17, 18], it is expected that the three functional groups, thiol (SH), amino (NH_2), and carboxyl (COOH), of cysteine molecule can induce complex adsorption modes on graphene. We start by considering the optimized geometries of intrinsic and Au-doped graphene which serve as the sensing platforms toward cysteine as adsorbed radical. The selected systems, illustrated in Fig. 1, are: (i) a, a thiolate cysteine in which the SH headgroup is close to the substrate lattice, and the NH_2 and COOH groups away from the substrate toward the vacuum; (ii) b, the NH_2 headgroup is

attached to the surface, and the other two functional groups away from the surface; and (iii) c, the COOH headgroup is close to graphene and the OH group oriented toward the surface with the O atom directly above a C or Au atom of the outermost layer. In Isomer a, b and c, the substrate is intrinsic graphene surface. Isomer a′, b′ and c′ are the corresponding isomers with Au-doped graphene surface as the substrate. Different adsorption sites were examined in order to find out the most stable configuration.

All structures were optimized without any constrain. The calculated geometrical parameters, as reported in Fig. 1 and Table 1, also include the equilibrium bond distances and angles for cysteine, which are compared with X-ray data (in parentheses) for a monoclinic crystal with two cysteine molecules per unit cell [19]. The agreement of our results with the X-ray data as well as with the results of quantum chemistry calculations is quite good [20]: the bond lengths and angles have an average deviation of 3%, with the only notable exceptions being the C-OH distance (4%) and the C_α–C–O angle (5%). These larger deviations are most likely related to the fact that in the crystal the protons of carboxylic groups are largely transferred to neighboring amino groups through intermolecular O···H−N hydrogen bonds.

As shown in Table 1, for cysteine, the internal conformation of the adsorbed radical is slightly affected by the adsorption process, with the only exception being the torsion angles involving the carboxyl and amino groups for the adsorption. The large variation of the torsion angles, with respect to the free molecule, is attributed to the steric attractive interactions between the molecule and the substrate.

Table 1 Structure, binding energy (E_b) and charge transfers (Q) for cysteine molecule and the adsorbed cysteine on graphene. The values in parenthesis correspond to experimental X-ray data [19].) Bond distance is in Å

Structural parameters	cysteine	Isomers					
		a	a′	b	b′	c	c′
N−C_α	1.46 (1.47)	1.47	1.45	1.44	1.47	1.41	1.47
C-O	1.22 (1.25)	1.22	1.22	1.22	1.22	1.23	1.29
C-OH	1.36 (1.31)	1.36	1.36	1.36	1.36	1.24	1.28
C_β-S	1.85 (1.82)	1.81	1.85	1.84	1.84	1.85	1.84
C–C_α–N	106.6 (109.9)	109.3	108.4	107.3	111.0	109.8	107.3
C_α–C–O	123.9 (118.0)	126.0	124.9	125.2	125.6	110.9	119.9
C_α–C–OH	112.6 (116.7)	111.3	111.7	111.4	111.0	109.7	122.1
C_α–C_β–S	110.7 (115.1)	114.4	113.1	114.6	113.1	111.1	115.5
C_β–C_α–C–OH	67.3	7.4	82.2	25.0	11.6	69.6	67.6
S–C_β–C_α–N	6.7	1.6	58.3	4.0	13.4	6.2	7.0
N–C_α–C–O	56.3	50.2	31.2	98.8	66.3	51.4	58.2
N–C_α–C–OH	56.4	52.0	28.8	79.3	65.9	51.5	57.4
C_{gra}-L[b]	-	3.96	-	3.96	-	3.28	-
Au-L[c]	-	-	2.25	-	1.94	-	2.18
Au-C[d]	-	-	2.02	-	2.03	-	2.00
E_{bin} (kcal/mol)	-	7.16	-45.85	23.38	-23.89	7.94	-37.30
Q	-	0.005	-0.073	0.007	-0.143	-0.047	-0.263

[a] Experimental data [19] are reported in parentheses.

[b] C_{gra}-L refers to the lengths for linking between cysteine and intrinsic graphene surfaces in Isomer a, b and c.

[c] Au-L refers to the lengths for Au and the atom L which is closer to the adsorbed sheet in Isomer a′, b′ and c′.

[d] Au-C is the average bond length value for B1, B2 and B3.

To evaluate the interaction between cysteine molecule and graphene sheet, the binding energy (E_b) of adsorbed systems was calculated, which is defined as:

$$E_b = E_{total} + 1/2\, E_{H2} - \left(E_{sheet} + E_{cys}\right),$$

where the E_{total}, $1/2\, E_{H2}$, E_{sheet} and E_{cys} denote the total energy of intrinsic or Au-doped graphene adsorbed system, one half of the hydrogen molecule, intrinsic or Au-doped graphene and a cysteine molecule, respectively. A negative E_b corresponds to a stable adsorption structure.

It can be seen that the cysteine molecule is merely weakly adsorbed on the intrinsic graphene with positive E_b (7.16 — 23.38 kcal mol^{-1}) and a long distance linking between cysteine and intrinsic graphene surface. The geometries of graphene and cysteine molecule are nearly undisturbed. In our three intrinsic graphene-cysteine models, the graphene-cysteine distance varies from 3.28 to 3.96 Å after cysteine binding, which is larger than standard C-S, C-N, and C-O bond length, indicating the weak binding between graphene and cysteine. The C_β-S, C_α-N and C-O distances contract by 0.04, 0.02 and 0.12 Å, respectively, as shown in Fig. 1a, b and c. A larger change for C-O distance is due to large charge transfer between cysteine and graphene (Table 1). For Isomer a, b and c, the bond lengths and angles of cysteine radical remain basically unchanged. Larger differences for C_β–C_α–C–OH and N–C_α–C–O torsion angles are due to the rearrangement of the functional groups to adjust to the substrate.

In contrast to intrinsic graphene, Au-doped graphene shows a significantly stronger graphene-cysteine interaction (-23.89 — -45.85 kcal mol^{-1}) because in three cases, Au-S, Au-N and Au-O chemical bonds play the key role for stability. Doping of large Au atom (Fig. 1 Au-doped graphene) causes deformation of nearby hexagonal rings in the doping region. The Au–C distances (B1, B2 and B3 in Fig. 1) between Au and C_1, C_2, and C_3 atoms are all 1.98 Å. The C_β-S and C_α-N bonds are kept unchanged in Isomer a′ and b′. In Isomer c′, C-O bond reduces to 1.28 from 1.36 Å for free cysteine molecule. In Au-doped graphene-cysteine model, the B1, B2 and B3 distances increase a little from 1.98 Å to 2.00 Å after cysteine binding, indicating that the strong binding of cysteine comes at the expense of destabilized Au-doped graphene. For Isomer a′, adsorption of cysteine does not result in any significant structural distortion in graphene, and the B1, B2 and B3 bonds increase from 1.98 Å to 2.10 Å. The S atom is coordinated to the Au atom with a S–Au bond length of 2.26 Å, longer than typical value of thiol-Au bond. The data reported in Table 1 shows that the bond lengths of cysteine radical remain almost unaltered with respect to the free molecule values. The bond angles do not change significantly, except for the SH (C_α–C_β–S) and NH$_2$ (C–

C_α–N) orientations with respect to the backbone, which show changes up to 6%. All the dihedral angles are instead affected with respect to these in free molecule. In particular, those between SH and the NH$_2$ (S–C_β–C_α–N), and between NH$_2$ and COOH (N– C_α–C–OH), show a change up to 89%. The largest change of the torsion angles occurs when cysteine is adsorbed on the facet with so large an area. The NH$_2$ and COOH groups remain away from the facet, free for reaction with other macromolecules like peptide chains [9]. For Isomer b′ and c′, similar results are also obtained.

The calculation results show that E_b is primarily determined by the type of atom which is closer to the adsorbed sheet. The strongest adsorptions take place with atomic sulfur linking the intrinsic and Au-doped graphene surface, as shown in Fig. 1a and a′. The calculated E_b of Isomer a, b and c are 7.16, 23.38 and 7.94 kcal mol^{-1}. So small E_b reflects that cysteine undergoes weak interactions on the intrinsic graphene. These weak interactions mean that intrinsic graphene is inappropriate sensing platforms for cysteine detection.
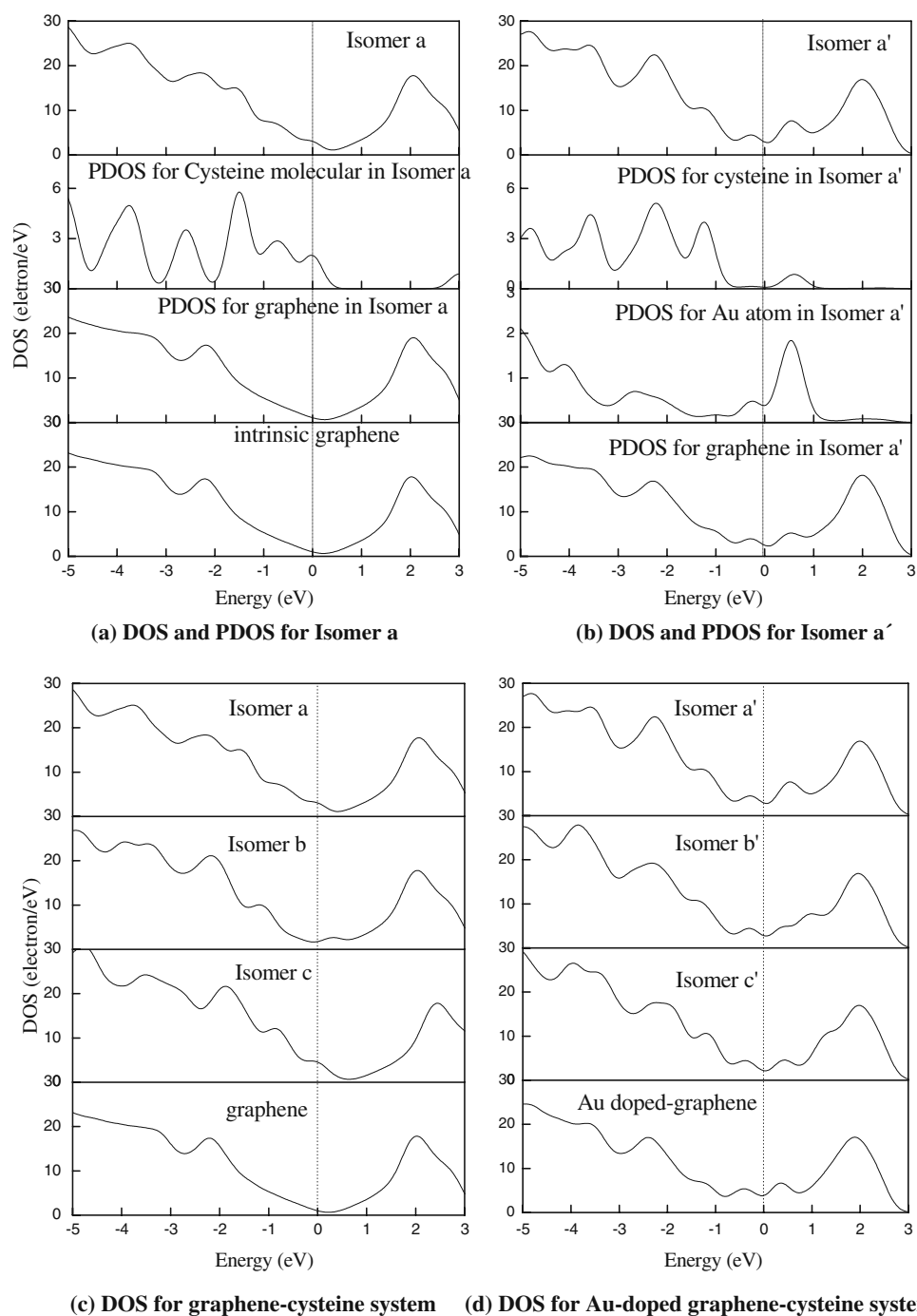
Cysteine, like other thiols, becomes strongly bound to gold atom *via* dehydrogenation of its SH group [21], resulting in the formation of a fairly strong covalent S-Au bond. The adsorption energy of Isomer a′ is -45.85 kcal mol^{-1}, indicating the strong interaction of cysteine with Au-doped graphene. The binding of Au-doped graphene to cysteine *via* its nitrogen atom (Isomer b′) or oxygen atom (Isomer c′) is 21.96 or 8.55 kcal mol^{-1} less stable, respectively, than the binding in Isomer a′. The stability of the Isomer c′ complex is similar to that of Isomer a′, which is attributed to the strong binding between Au and O atoms.

The electronic structure of intrinsic graphene and Au-doped graphene-cysteine molecule systems was analyzed in order to estimate the sensing susceptibility. The partial and total density of states (PDOS and DOS) and net charge transfers from a Mulliken population analysis were calculated.

The densities of states

The relevant sensing mechanisms are attributed to the conductance change caused by charge transfer between graphene and adsorbed molecules [22, 23]. Figure 2 plots the total electronic DOS for intrinsic and Au-doped graphene-cysteine molecule systems, with a dotted line showing the Fermi level. The DOS of the energetically most favorable Isomer a and a′ are plotted in Fig. 2a and b, together with the DOS of intrinsic graphene and the PDOS of Au, cysteine and graphene in Isomer a and a′, separately. Compared with intrinsic graphene, Isomer a shows some changes in DOS near the Fermi level (Row I and Row III in Fig. 2a), which would lead to a conductance change of graphene upon adsorption of cysteine molecules; there is weak hybridization between cysteine molecule and intrinsic

Fig. 2 The electronic density of state (DOS) and partial density of state (PDOS). A dotted line indicates the Fermi level

(a) DOS and PDOS for Isomer a

(b) DOS and PDOS for Isomer a´

(c) DOS for graphene-cysteine system

(d) DOS for Au-doped graphene-cysteine system

graphene sheet at -2.2, -1.5 and -0.74 eV relative to E_f, as shown in Fig. 2a. For Isomer a′, the band gaps near the Fermi level disappear after adsorption of cysteine molecule, indicating that the graphene becomes conductive. Cysteine molecule hybridizes with Au atom and carbon atoms of graphene sheet at -4, -2.2, -1.4 and 0.52 eV, as shown in Fig. 2b.

The DOS of intrinsic and Au-doped graphene-cysteine molecule systems was summarized in Fig 2c and d. In Fig 2c, the DOS curve indicates hybridization in the Isomer

b and c. There is hybridization at -1.18 eV and the Fermi level for Isomer b (Row II in Fig. 2c); while for Isomer c, hybridization exists at -2.36 eV, -0.83 eV and the Fermi level. It is worth mentioning that there is obvious conductance change near the Fermi level of Isomer c, because Isomer c has the largest electron transfers among three isomers, as shown in Table 1. The DOS of Isomer b′ and c′ also shows hybridization upon adsorption of cysteine (Row II and III in Fig. 2d). So, the hybridization is independent of the way of cysteine adsorption on the surface of the sheet.

The charge transfer

The fundamental sensing mechanism for sensors is the modulation of the conductivity of the base as a result of the charge transfer between base and adsorbate. Mulliken charge analyses were performed to reveal electron transfers (Q) from graphene sheet to cysteine molecule as shown in Table 1. Owing to weak interactions, Isomer a, b and c exhibit insignificant charge transfers of 0.005 to -0.047e. Large charge transfers are found in Au-doped graphene-cysteine, with values of -0.073, -0.143 and -0.263e for Isomer a′, b′ and c′, respectively. It is noticeable that Isomer c′ has the largest electron transfers to cysteine as a result of the strongest Au-O bond among Au-S, Au-N and Au-O. For cysteine adsorption, Au-doped graphene shows larger electron transfers to graphene, supporting the notion that Au doping influences the electronic properties of graphene substantially. Generally, Au-doped graphene-cysteine adequately satisfies the basic sensitivity requirements.

The results of DOS and charge transfer calculations suppose that, the electronic properties of graphene can be tuned by the site of cysteine adsorption. Despite the different binding energy, each isomer has electron transfer and hybridization between cysteine molecule and graphene base.

From the viewpoint of electronics, the interaction of Au-doped graphene with cysteine molecule results in a large charge transfer from cysteine molecule to Au-doped graphene, which dramatically changes the conductance of graphene. It is obvious that Au-doped graphene shows stronger changes in conductance than intrinsic graphene after adsorption of cysteine molecule. The results in Table 1 clearly show that E$_b$ increases with Au doping, indicating that graphene would become more sensitive to cysteine with Au doping. Thus, relative to intrinsic graphene, Au-doped graphene would be a better and more promising candidate for effective sensors to detect cysteine molecules.

Conclusions

First principle calculations were used to study the adsorption geometry and binding properties of cysteine on intrinsic and Au-doped graphene surface as a chemosensor device. Cysteine was found to be only weakly adsorbed on the graphene plane while it interacts strongly with the Au atom embedded in graphene.

The results of DOS and charge transfer calculations suppose that, the electronic properties of graphene can be tuned by the site of cysteine adsorption. Adsorption of cysteine on Au-doped graphene surface causes larger charge transfer between graphene and cysteine. Charge transfer leads to dramatic changes in the electrical conductance of graphene, which can serve as the basis for highly sensitive graphene-based molecular sensors.

Both graphene and Au-doped graphene possess sensing ability, while Au-doped graphene is a better sensor for cysteine than intrinsic graphene. In other words, Au doping improves graphene's sensing ability.

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