# Computational Investigation of Adsorption Behaviors of Human Fibrinopeptide Segment at Different Polymer Material Surfaces

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**Abstract**: Since the adsorption behaviors of the peptides at material surfaces play an important role in many research fields and simulation studies can provide deep insights into more interaction details of the adsorption behaviors. A molecular simulation is performed using Materials Studio 4.4(MS 4.4) software package to investigate the physical adsorption behavior of the fibrinopeptide segment(HFG) separated from fibrinopeptide, which is the most important protein in the processes of hemeostasis and thrombosis, at three different kinds of polymeric biomaterials— polytetrafluoroethylene(PTFE), polyvinyl chloride(PVC), and Silicone Rubber(SR). The results suggest that the adsorption of HFG is weaker and weaker with the hydrophobicity increasing of the materials surfaces. The hydrophobic PTFE polymer materials show the best behavior to prevent the adsorption while the significant adsorption of HFG on the Silicon Rubber surface occur. Moreover, water also plays a promoting role to the interaction properties between the HFG and the polymer materials. The existence of water is strongly tend to take the peptide molecule away form the adsorption surface.

**Key words**: anticoagulative polymer material, fibrinopeptide segment, physical adsorption, molecular simulation
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# 人血纤肽片段分子在高分子材料表面吸附行为的分子模拟研究

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[**摘要**] 吸附是生物材料与血液接触后最先发生的重要现象, 是研究抗凝血材料的重要环节. 本文以在凝血过程中起着重要作用的人血纤肽片段分子-Asp-Ser-Glu-Asp-Glu-(HFG)为研究对象, 采用 Materials Studio4.4 软件包, 在真空和水溶液环境中, 我们分析了 HFG 分子在聚合物表面上的最短距离、吸附能和氢键作用, 同时也得到了 HFG 分子不同的构型变化. 分析结果显示: 亲水性表面更有利于吸附的进行; 随着疏水性的增强, 吸附能逐渐减小, 预示着疏水性聚合物材料有利于抗凝血性能的提高; 水介作用导致纤维蛋白原在表面上的排斥力增大, 对提高材料的抗凝血性能有积极作用.

[**关键词**] 抗凝血聚合物材料, 人血纤肽片段分子, 物理吸附, 分子模拟

The adsorption behaviors of small peptides or proteins at material surfaces play an important role in many research fields, such as the biocompatibility of biomedical implant devices, the thrombosis caused by contacting with

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the blood stream, the preparation of the biosensor, and the molecular designing of the other valuable biologically active substances in terms of producing antithrombogenicity. When a biomaterial is implanted into living tissue and then contact with blood, inevitably a cascade of host reactions occur at the material surface and therefore affect its biological functions and the hemolysis or coagulation processes[1,2]. Of them the physical adsorption is the first step and becomes a key issue needed to be understood of biomaterials[3-6], which is significantly important for the blood coagulation and biocompatibility.

**Table 1 The water droplet contact angles obtained by experiment**

| | water contact angles |
|---|---|
| PTFE | 118° |
| PVC | (85±3)° |
| SR | 65° |

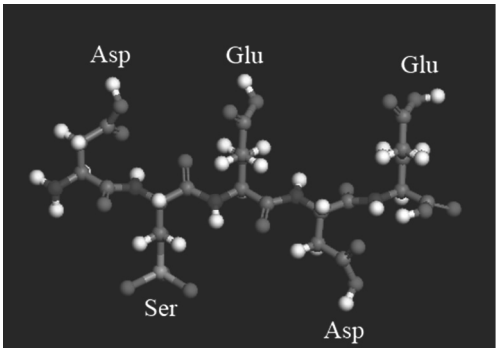



**Fig. 1 The optimal conformation of HFG**

Biomolecule and material surface are the two protagonists in the physical adsorption. At present, many polymer materials as important biomaterial have been successfully applied in the medical field because of their similar chemical structures and physical properties to those of natural polymers of human organs and tissues[3,4]. For instance, polytetrafluoroethylene (PTFE), polypropylene (PP), polyurethane (PUR), silicone rubber, polyvinyl chloride (PVC), polysulfone (PSU) and so on[7,8]. Herein we chose three kinds of polymeric biomaterials—PTFE, PVC and Silicone Rubber (SR) with different hydrophilic or hydrophobic properties as the research materials. Table 1 shows the water droplet contact angles on these surfaces obtained by experiments[9-11]. The other protagonist we chose is the fibrinopeptide segment (Asp-Ser-Glu-Asp-Glu, abbreviation HFG) separated from fibrinopeptide with the similar negative charge as the active parts of plasma fibrinogen, which is the most important protein in the processes of hemeostasis and thrombosis[12-14]. The optimal structure of HFG is shown in Fig. 1.

Although many experimental studies on the biomolecule-surface interaction have been carried out, little information about the interactions at the molecular and atomic level could be gained. One of the facts that is significantly important is the atomic-level interaction characterastics between the chemical groups of the biomolecules and the complementary reactive groups of the different surfaces[15-19], which is still not well understood. Computational studies are an attractive alternative to provide deep insights into more molecular and atomic interaction details. An adsorption simulation is performed to investigate the physical adsorption behavior of HFG at three different kinds of self-assembled minelayer (SAM)—PTFE, PVC and SR detailed above.

# 1 Method

All simulations were performed using Materials Studio 4.4 (MS 4.4) software package (Accelrys, USA)[20]. The Compass force field (distributed by Accelrys) was used throughout this study[21]. All the minimizations were carried out by the Forcite Module using the steepest descent method (until the derivative reaches 1 000 kcal/mol Å) and followed by the conjugate gradient method (until the derivative convergences to 0.01 kcal/mol Å).

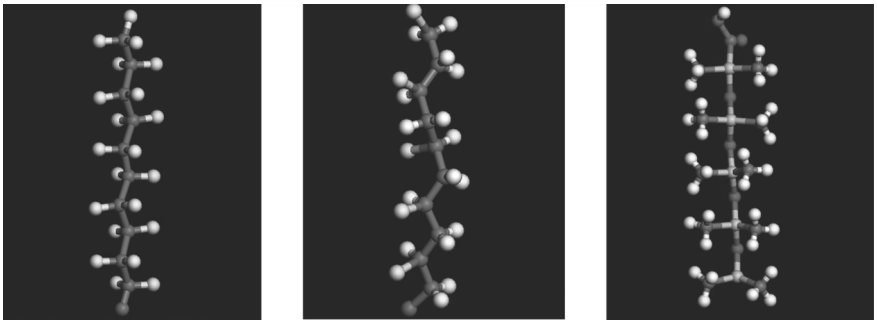
## 1.1 Self-assembled monolayer (SAM)

The entire process requires an understanding of the interactions that occur between a solid material surface and the biological environment. Thus, the construction of surfaces becomes very important with bio-specific binding properties and minimized back ground interferences. Self-assembled monolayers recently attract considerable attention for the creation of the surfaces due to their intriguing physicochemical surface properties and ease of processing[22-24]. Self-assembled monolayers, also known as SAMs, are surfaces made from a thin molecular film of biological or chemical moieties and have been applied to the molecule simulation widely, due to their flexibility of

processing, molecular order, versatility, and simplicity[25]. Therefore, we built three kinds of SAM surfaces according to the structural characteristics of polymer for adsorption simulation.

### 1.2 Single Polymer Chain

The initial structure of a PTFE(PVC and SR) chain was constructed out of the tetrafluoroethylene(polyvinyl chloride and dimethylsiloxane) pentamer. Among them, because of different kinds of constructions of Silicone Rubber, a simple monomer was built containing the structural characteristics. Carboxyl group(−COOH) was used as the headgroup, which could reinforce the hydrophilicity of Silicone Rubber surface. Then, the monomers were subjected to geometry minimization. The optimal polymer material monomers were shown in Fig. 2.



(a)　(b)　(c)

**Fig. 2　The monomer of PTFE (a) PVC (b) and SR (c)**

### 1.3 Self-assembled monolayer surface

The optimized polymer monomer was attached to the surface on Au(111), forming a lattice structure with a chain-chain distance of 4 Å. A(15×15) supercell with the SAM surface dimensions of 60 Å×60 Å in the *xy*-plane was used. The polymer chains were aligned parallel to each other on the surface to minimize their dipole components. Then, a large vacuum gap(larger than the Coulombic cut off length of 12.0 Å) was introduced on the top in the *z*-direction to mimic the three-dimensional periodic system. Finally, the polymer surface was also subjected to geometry minimization respectively. The atom-based method with a 15.5 Å cut off was used to compute the non-bonded interactions.

### 1.4 Adsorption simulation

Adsorption Locator simulates a substrate loaded with an adsorbate, allowing you to find low energy adsorption sites on the substrates. Adsorption Locator implements simulated annealing using the Metropolis Monte Carlo method[26-28], and it has been used to investigate the adsorption of a small molecule to various surfaces[29-33]. Therefore, we chose this method to obtain the optimal configuration of fibrinogen adsorption based on this theory for the first time.

The adsorption simulation was performed in vacuum and aqueous conditions respectively. The aqueous system in the simulation is composed of 1 500 water molecules. HFG and water molecules were confined in the box with the size of 60.0 Å×60.0 Å×30.0 Å. In this study, the automated temperature control was employed, and 100 temperature cycles were used for each run. For each surface, the structures within 10 kcal/mol of the minimum were reported(total of 10 structures). The entire system was subjected to five cycles and each cycle included 50 000 steps. Electrostatic and Van der Waals interactions were calculated using the Ewald and atom-based algorithms, respectively.

## 2 Results and Discussions

The surface wettability of polymer materials is the focus of the adsorption of HFG because they are mostly used in the aqueous environment[34-37]. Three types of interface from hydrophobicity to hydrophilicity were considered in this adsorption simulation study, and the effects on adsorption modes and conformational changes of HFG by the surface wettability were investigated. In order to analyze the importance of water molecules, the ad-

sorption simulation was performed in vacuum and aqueous solution, respectively. So we can compare the adsorption differences considering the existence of water. The optimal conformations of HFG on the different polymer material surfaces and the distances between them are depicted in Fig. 3 in the simulations. A collective view of the entire figure suggests that HFG molecule behaves remarkably different structural preferences at different interfaces depending on the interfacial chemistry.

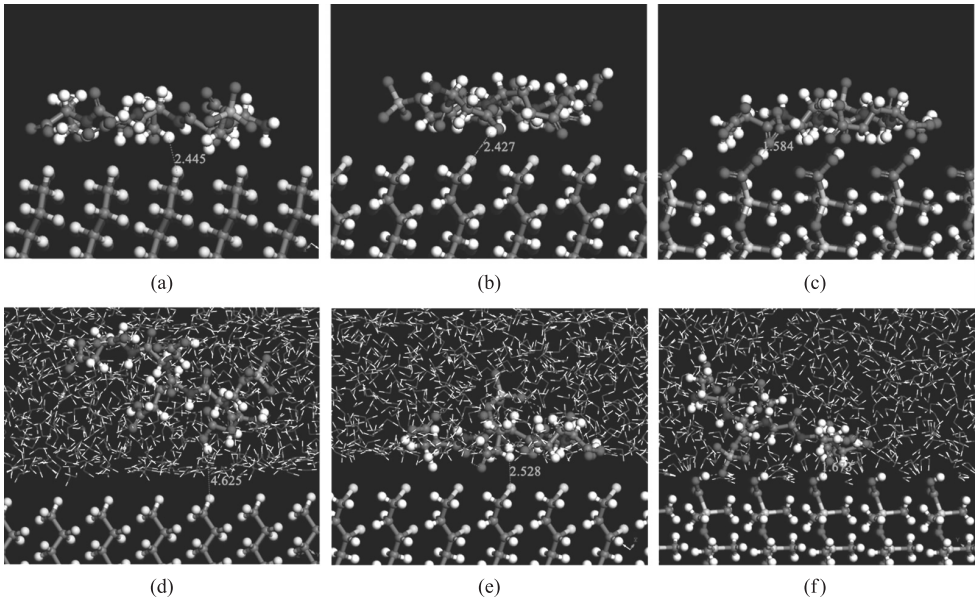



**Fig. 3 Representative conformations of HFG at PTFE(a), PVC(b) and SR (c) interfaces in vacuum. Representative conformations of HFG at PTFE(d), PVC(e), and SR (f) interfaces in aqueous solution. The polymer surface and HFG are shown using a ball and sticks representation. Water molecules are shown using a line representation.**

## 2.1 Shortest distances between HFG and the surface

In order to compare the strength of adsorption intuitively, we calculated the shortest distances from HFG to the polymer interfaces in vacuum and aqueous solution and listed in Table 2. The results reveal that adsorption is strongly favored at the Silicon Rubber surface as indicated by the minimum distance 1.548 Å and 1.673 Å in vacuum and aqueous solution, respectively (Fig. 3 c, f). The distance becomes much longer at PVC and PTFE surface (Fig. 3 a, b, d, e), especially when they are in aqueous solution the fibrinopeptide segment HFG is far away from the PTFE surface and the shortest distance has reached 4.265 Å (Fig. 3 d), nearly two times than that of PVC and three times than that of SR. Obviously, water and the hydrophobic properties can greatly affect the small molecule HFG adsorption behaviors onto the polymer material surface. They tend to repel HFG away from the surface effectively and show the weak interaction with the fibrinopeptide segment while the hydrophilic surface tends to strongly adsorb the HFG molecule according to the calculations results.

**Table 2 The shortest distances between HFG and the polymer interfaces in vacuum and aqueous solution**

| | In vacuum/Å | In aqueous solution/Å |
|---|---|---|
| PTFE | 2.445 | 4.265 |
| PVC | 2.427 | 2.528 |
| Silicon Rubber | 1.584 | 1.673 |

## 2.2 Adsorption energy between HFG and the surface

The adsorption energy between HFG and the surface were calculated as a direct description of surface adsorption capacity. In the following discussion, the adsorption energy of the simulated systems was calculated according to:

In vacuum

$$E_{\text{Adsorption}} = E_{\text{Total}} - (E_{\text{HFG}} - E_{\text{Surface}}), \quad (1)$$

In aqueous solution

$$E_{\text{Adsorption}} = E_{\text{Total}} - (E_{\text{HFG}} + E_{\text{Surface}} + E_{\text{Water}}), \quad (2)$$

where $E_{Adsorption}$ is the adsorption energy between HFG and polymer surface; $E_{Total}$ is the total energy of the entire system; $E_{Surface}$, $E_{Water}$ and $E_{HFG}$ are the energies of the isolated polymer surface, water molecules and HFG, respectively.

The adsorption energies of HFG onto various surfaces were also calculated using Forcite module of Materials Studio 4.4 and the results were listed in Table 3. From which, we know that the adsorption energy decreases obviously with the hydrophobicity increasing, indicating the adsorption ability of HFG on the hydrophobic polymer materials is weaker than that of the hydrophilic ones and the strong hydrophilicity is favor of the adsorption of HFG to a polymer material surface. Moreover, the water effects on the adsorption energy are surprising. The adsorption energies in aqueous solution are about 20－30 times that of vacuum for PTFE, PVC and SR. The adsorption energy is −2 371.87 kcal/mol at Silicone Rubber surface and is much bigger than that of the other materials. HFG is repelled by the hydrophobic PTFE surface more easily, which is in good agreement with the shortest distances discussed above.

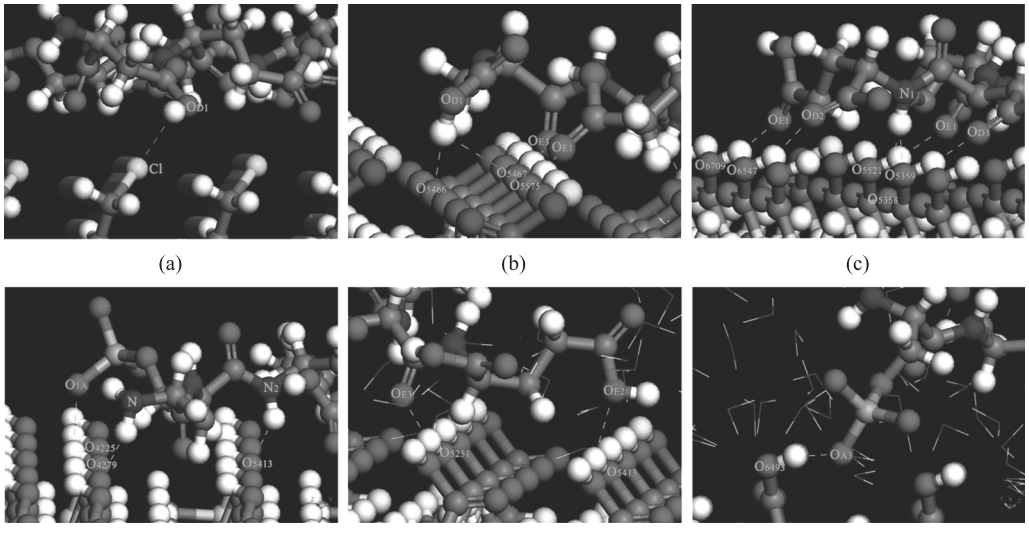
**Table 3　The adsorption energy(kcal/mol) between HFG and various surfaces**
**(up: in vacuum, down: in aqueous solution for every polymer material.)**

| | $E_{Total}$ | $E_{Surface}$ | $E_{Water}$ | $E_{HFG}$ | $E_{Adsorption}$ |
|---|---|---|---|---|---|
| PTFE | 30 207.35 | 30 323.43 | / | −85.75 | −33.33 |
| | 13 228.95 | 30 323.43 | −16 204.16 | −61.80 | −858.52 |
| PVC | 12 634.40 | 12 759.85 | / | −79.37 | −46.08 |
| SR | −4 471.63 | 12 759.85 | −16 245.83 | −61.31 | −924.34 |
| | −23 614.23 | −23 456.78 | / | −72.11 | −85.34 |
| | −40 543.35 | −23 456.78 | −14 650.94 | −63.76 | −2371.87 |

## 2.3　Hydrogen bonds between HFG and the surface

The hydrogen bond is one of the strong intermolecular interactions and usually can make great contributions to the improvement of molecular stability and the determination of molecular orientation. Therefore, the hydrogen bonds are employed to further understand the adsorption ability of polymer materials. The characteristics of a hydrogen bonds can be evaluated according to the distance between the donor(D) and acceptor(A) (usually is shorter than 2.5 Å) and the angle D—H···A(usually ranges from 90° to 180°). Generally, hydrogen bonds with distance between H and A less than 2 Å are considered to be very strong[38].

The hydrogen bonds around HFG molecule on the different surfaces are depicted in Fig. 4(a-f) and the parameters are listed in Table 4. There is no any hydrogen bond at the PTFE surface in vacuum and aqueous solu-




(a)　(b)　(c)

(d)　(e)　(f)

**Fig. 4　The hydrogen bonds formed by the amino acid residues of HFG and the atoms at PVC surface(a) and Silicon Rubber surface(b, c and d) in vacuum and aqueous solution(e, f). The hydrogen bonds are represented by dashed lines.**

tion because the non-polarized PTFE has no proton donor and acceptor and so it is very difficult that the hydrogen bond forms on its surface. A weak O-H···Cl hydrogen bond forms between the O atom of the hydroxyl group of the amino acid residue ASP and the chlorine atom of PVC surface in vacuum(Fig. 4 a). But in aqueous solution this unique hydrogen bond disappears and weakens the HFG adsorption at the PVC surface.

**Table 4 Length and angle of hydrogen bonds formed by HFG molecule in vacuum and aqueous solution**

| | | D-H···A | $d_{(D-H)}$/Å | $d_{(H\cdots A)}$/Å | $d_{(D\cdots A)}$/Å | ∠DHA/(°) |
|---|---|---|---|---|---|---|
| In vacuum | PTFE | / | / | / | / | / |
| | PVC | $ASP:O_{D1}-H\cdots Cl$ | 0.96 | 2.43 | 3.18 | 135.0 |
| | SR | $ASP:O_{D1}-H\cdots O_{5466}$ | 0.97 | 1.72 | 2.68 | 168.7 |
| | | $ASP:O_{D1}-H\cdots O_{5467}$ | 0.97 | 2.42 | 2.89 | 109.4 |
| | | $O_{4279}-H\cdots N_2:ASP$ | 1.00 | 2.29 | 3.16 | 143.1 |
| | | $O_{5467}-H\cdots O_{E3}:ASP$ | 1.00 | 1.58 | 2.58 | 171.2 |
| | | $O_{5575}-H\cdots O_{E1}:GLU$ | 1.00 | 1.65 | 2.65 | 171.2 |
| | | $GLU:N_2-H\cdots O_{5413}$ | 1.01 | 2.19 | 2.84 | 120.8 |
| | | $O_{5521}-H\cdots O_{E2}:GLU$ | 1.00 | 1.73 | 2.72 | 166.5 |
| | | $O_{4225}-H\cdots O_{A1}:SER$ | 1.00 | 2.21 | 2.72 | 109.9 |
| | | $GLU:_{N1}-H\cdots O_{5358}$ | 1.01 | 2.46 | 3.47 | 179.4 |
| | | $GLU:_{N1}-H\cdots O_{5359}$ | 1.01 | 2.09 | 2.75 | 120.7 |
| | | $O_{5359}-H\cdots O_{D3}:ASP$ | 1.01 | 1.68 | 2.67 | 167.7 |
| | | $O_{6547}-H\cdots O_{D2}:GLU$ | 1.00 | 1.84 | 2.70 | 141.5 |
| | | $O_{6709}-H\cdots O_{E1}:GLU$ | 1.00 | 1.76 | 2.58 | 135.9 |
| In aqueous solution | PTFE | / | / | / | / | / |
| | PVC | / | / | / | / | / |
| | SR | $O_{5251}-H\cdots O_{E3}:ASP$ | 1.00 | 1.67 | 2.55 | 143.0 |
| | | $O_{6493}-H\cdots O_{A3}:SER$ | 1.00 | 1.73 | 2.71 | 163.5 |
| | | $O_{5413}-H\cdots O_{E2}:GLU$ | 0.99 | 2.26 | 2.90 | 120.3 |

On the contrary, the Silicon Rubber surface is very different from them and the hydrogen bond interactions between HFG and SR surface are very strong. It is covered by carboxyl groups including the proton donor-hydroxyl group and the proton acceptor-carbonyl group while the HFG is compose of amino group, carboxyl group and phosphate radical, all of which are suitable radicals for forming hydrogen bonds. Thus, the space and chemical matching produce the rich hydrogen bonds between the SR surface and the HFG molecule. There are thirteen O-H···O hydrogen bonds via the O atom of carbonyl, phosphate, carboxyl group and the H atom of the hydroxyl and amino group between the Silicon Rubber and the amino acid residue SER, ASP and GLU of HFG in vacuum, respectively(Fig. 4 b, c, d). Among them, seven hydrogen bonds are strong and six are relatively weak. We can see that the HFG molecule is adsorbed closely to the SR surface and has the nearest distance comparing to the PTFE and PVC, which can be attributed to the strong hydrogen bond interaction.

On the other hand, water can greatly affect the hydrogen bond interactions between HFG and SR surface. Most of them disappear and only three hydrogen bonds formed in aqueous solution. Two fairly strong hydrogen bonds are linked via the oxygen atom of the carbonyl and phosphate groups of amino acid residue ASP and SER with the hydrogen atoms of the hydroxyl groups of the SR surface, $O_{5251}-H\cdots O_{E3}:ASP$ and $O_{6493}-H\cdots O_{A3}:SER$, respectively(Fig. 4). These results demonstrate that the water medium and the hydrophobic surface are highly favorable to weak adsorption of fibrinopeptide segment HFG.

## 2.4 Structure characterization of HFG

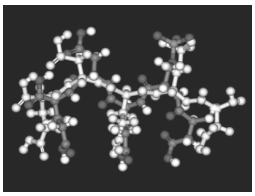
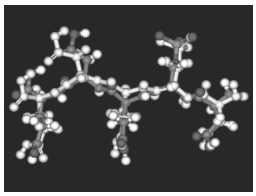
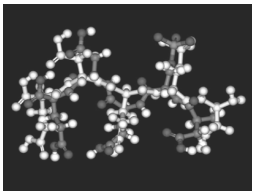
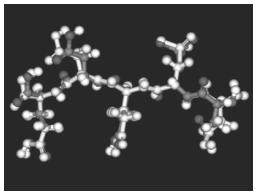
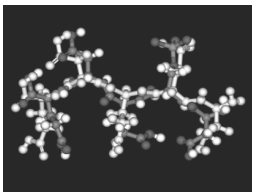
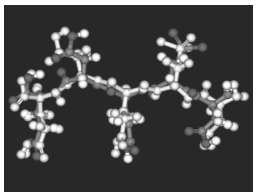
The structure differences of HFG can also illustrate the changes of adsorption strength in different environments. The structure of HFG in aqueous solution is obviously different from that in vacuum. fibrinopeptide segment molecule adopts quasi-2D flat, pancake-like conformations once it is firmly adsorbed on the polymer surfaces in vacuum(Figure 3a, b and c). In aqueous solution, HFG samples a broad range of roughly 2D conforma-

tions with no preference for any one in particular at different SAM interfaces(Figure 3d,e and f). But,we find that the conformation of HFG has not "laid on" the surface any more,whereas tends to leave the surface. Especially,HFG molecule is actually repelled at the strong hydrophobic PTFE surface and has left the surface to get into the bulk water phase.

In order to analyze the conformational changes of HFG molecule at different surfaces we calculated the RMSD values compared with the original structure of HFG and are shown in Table 5. Meanwhile,the structures of HFG at different surfaces and environments are superimposed on the original ones,which are also depicted in Table 5,the structure of original HFG is in ball and stick representation. From table 5 we can see that the RMSD value increases with the hydrophobicity increasing and the conformation change of HFG is the largest at the PTFE surface leading to the largest RMSD value in vacuum. However,HFG has the smallest change on the Silicon Rubber surface(Figure 4b,c and d)although the carboxyl(−COOH),phosphate($-PO_4^{3-}$),amino($-NH_2$)and amid(−CO−NH−)groups forms many strong hydrogen bonds. Moreover,RMSD values in aqueous solution are all smaller than those in vacuum. These results demonstrate the water and the hydrophilic material surface are beneficial to weakening the physical adsorption onto the material surfaces,the HFG molecular structure maintenance and therefore the possible anticoagulation and biocompatibility.

**Table 5　RMSD values and overlapping structures of HFG at the different surfaces**

**(the structure of original HFG is in ball and stick representation.)**

| | Surface | RMSD/Å | Structure Overlay | | Surface | RMSD/Å | Structure Overlay |
|---|---|---|---|---|---|---|---|
| In vacuum | PTFE | 1.82 |  | In aqueous solution | PTFE | 0.93 |  |
| | PVC | 1.65 |  | | PVC | 0.76 |  |
| | Silicone Rubber | 1.42 |  | | Silicone Rubber | 0.90 |  |

Since the fibrinopeptide segment is negatively charged its physical adsorption onto the surfaces of the polymer materials,as well as their hydrophilicity/hydrophobicity,should be closely related to the electronic properties of the material surfaces[39-41]. Fig. 5 shows the electronic characteristics of the different surfaces taken from negative to positive charged in vacuum(Fig. 5 top)and aqueous solution(Fig. 5 bottom)using a solid surface representation. We find that their surface electrical properties are remarkably different,the PTFE、PVC and SR surfaces behave negative electricity,weak negative electricity and positive charged,respectively. It is easy to understand that the negative charged HFG can be easily kept away by the positively charged PTFE and PVC surfaces and strongly adsorbed by the positively charged SR,which is in good agreement with the above analysis results.

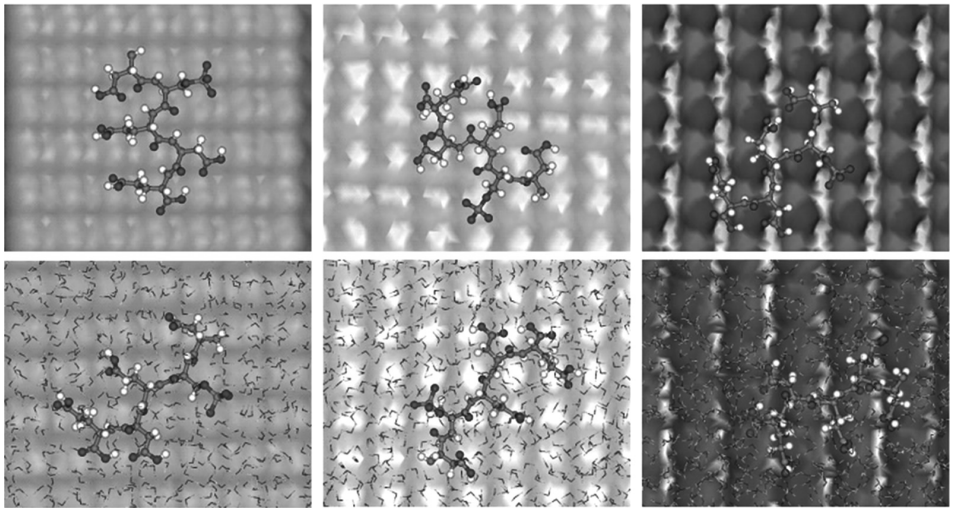



**Fig. 5 The distributions of partial charges on the atoms to the surfaces in vacuum and aqueous solution. The polymer surfaces are shown using a solid surface representation. Surface charge was taken from −0.1 to +0.1. HFG is shown using a ball and sticks representation. Water molecules are shown using a line representation.**

## 2.5 Water effect on adsorption

It is widely believed that water is the first molecule to contact biomaterials in any clinical application[37]. Once entering into the system, liquid-water molecules will be interconnected in a hydrogen-bond network of three or four nearest neighbors and then a compact "protective umbrella" water layer is formed on the surface of polymer materials (depicted in Fig. 6) and therefore play a very important role in effectively preventing the adsorption of HFG molecule on the surface. As can be seen from the calculation results above that the water-mediated interactions lead to effective repulsion and prevent the adsorption of HFG on the material surfaces, which can significantly influence or even dominate adsorption phenomena such as the structure characterization of HFG, adsorption energy, distance and the interaction between HFG and the surface. The HFG molecule is surrounded by a condensed high-density water phase by the strong hydrogen-bond forces with the adjacent water molecules in aqueous solution (Fig. 7). Therefore, water is not only just a carrier system for biochemical processes but also is an active participant in biology, which simply could not and would not work the way it does without the special mediating properties of water.

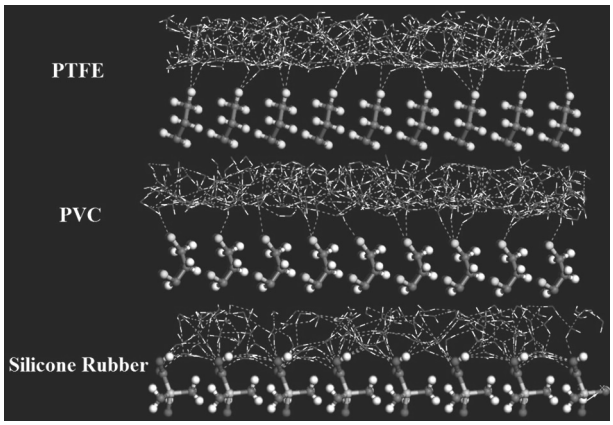



**Fig. 6 The partial graph of water layer on the different polymer material surfaces. The polymer surfaces are shown using a ball and sticks representation. Water molecules are shown using a line representation. The hydrogen bonds are represented by dashed lines.**

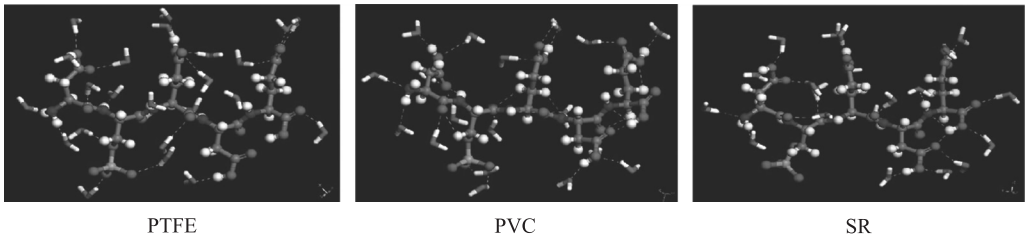



**Fig. 7 Hydrogen bond networks formed between HFG and the adjacent water molecules on the different polymer material surfaces. HFG is shown using a ball and sticks representation. Water molecules are shown using a stick representation.**

## 3 Conclusion

The physical adsorption mechanism of the active fibrinopeptide segment separated from the most important protein fibrinopeptide in the processes of hemeostasis and thrombosis on the surfaces of different three kinds of polymer materials—PTFE, PVC and SR had been theoretically investigated in this study. The characteristics of the material surfaces and the water layer can significantly influence or even dominate the adsorption phenomenas. We analyzed the shortest distance, the adsorption energy, the hydrogen bonds and conformational characteristic of HFG and the surface charges at these polymer interfaces from hydrophilic to hydrophobic in vacuum and aqueous solution. The results suggested that the adsorption of HFG was weaker and weaker with the hydrophobicity increasing of the materials surfaces. The hydrophobic PTFE polymer materials showed the best behavior to prevent the adsorption while the significant adsorption of HFG on the Silicon Rubber surface occurred in all cases of the molecular simulations. Moreover, water also played a promoting role to the interaction properties between the HFG and the polymer materials. The existence of water is strongly tend to take the peptide molecule away form the adsorption surface. The present work can be considered to be an interesting research on the deep insights into interaction details between the adsorbed biomolecule and the valuable biologically active substances at the molecule and atom microscopic level by means of molecular simulations.

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