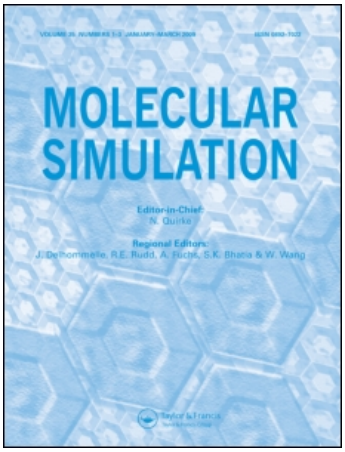

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Molecular dynamics simulations of peptides on calcite surface

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A series of molecular dynamics (MD) simulations has been carried out to investigate the interaction between peptides and a calcite $(1\,0\,\bar{1}\,4)$ surface in water. A 16-amino acid and a 17-amino acid peptide have been built and three different configurations for each peptide are used as starting configurations. The dynamic behaviour of these peptides has been investigated by calculating their radii of gyration and distribution of dihedral angles. For comparison, the simulations of peptides in vacuum and water have also been carried out. The simulations indicate that these peptides generally have strong interactions with the calcite surface and the peptides changed their configuration to favour this interfacial interaction. Continuum electrostatic calculations based on the Poisson–Boltzmann Equation (PBE) have also confirmed strong electrostatic interactions between the peptides and the calcite surface. The results suggest that the peptides can control calcite crystallisation and that the strong electrostatic interactions between the peptides and the calcite surfaces dominate the interfacial interactions.

Keywords: molecular simulation; peptide; biomineralisation; calcite; surface

1. Introduction

Knowledge of the interactions between the proteins and the calcite surfaces is a key to understanding biomineralisation. Progress in experiment has greatly improved our understanding of the role of peptides and proteins in the mechanism of biomineralisation and shows that the structure of these biomolecules is very important in controlling crystal growth. A study on mollusc shell proteins AP7 and AP24 indicates that some structural features of these proteins will greatly influence their kinetic behaviour in mineralisation [1]. Again, the control of crystal growth by proteins is demonstrated in the formation of eggshell. Recently, ovocleidin-17 has been identified as the major protein of calcified eggshell, and the three-dimensional structure of this protein is believed to closely relate to its functionality in the biomineralisation process [2]. Ajikumar and colleagues [3] have used charged peptides to mimic the function of eggshell proteins and the results show that these peptides were able to facilitate the nucleation and growth of polycrystalline calcium carbonate. Metzler and colleagues used X-ray absorption near edge spectroscopy (XANES) to study the electronic structure of crystalline calcium carbonate and peptides at the surface, and hence the mutual effects of calcite on peptides and peptides on calcite during biomineralisation [4]. A study on mollusc shell proteins AP7 and AP24 indicates that some structural features have an important influence in their kinetic behaviour during mineralisation, which suggests that protein structure plays a very important role in controlling biomineralisation [1].

However, current understanding of the interaction between biomolecules and minerals during biomineralisation is far from complete. Here, computer simulations can be an effective tool to explore the mechanism of biomineralisation. Computer simulations can be used to obtain the atomistic details at the interface between biomolecules and mineral surfaces; hence, we can have a better understanding of the mechanisms by which the biomineralisation is controlled.

Potential-based molecular dynamics (MD) simulations are increasingly used in the study of calcite biomineralisation. Normally, a set of potentials is only used for a specific type of molecule models, and potentials used in simulations of macromolecules are usually different from those for crystals. In the case of biomineralisation, potentials for biomolecules, mineral, solutes and their cross terms are needed. The competitive adsorption among organic molecules with different functional groups to the calcite surfaces has been examined with a combination of potentials [5]. Freeman et al. [6] have systematically developed a method to generate a set of potentials for modelling biomineralisation. The potentials have been applied to simulate interaction between polysaccharides and calcite, and facilitate the simulations of biomolecules and inorganic surfaces [7]. Peptides are highly charged molecules, so the electrostatic interactions between

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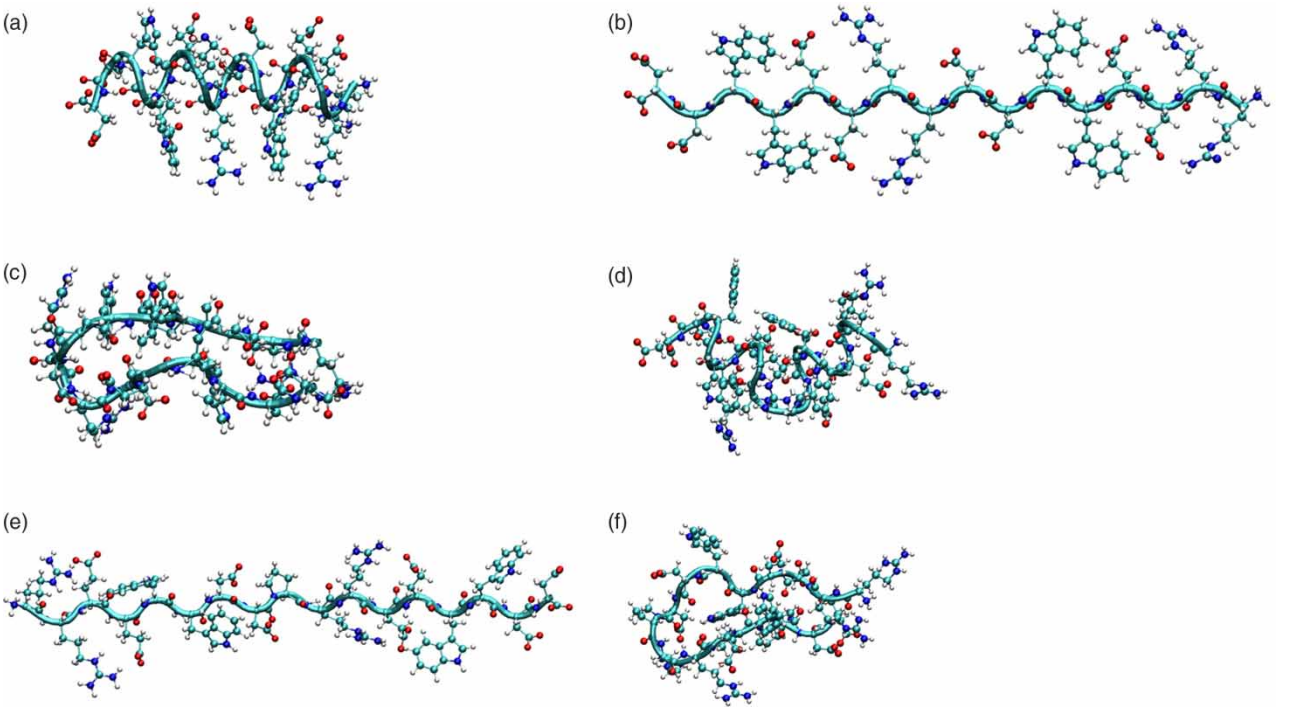

Figure 1. Configurations of $R_2E_2W_2D_2$-16 (PI) and $R_2E_2W_2D_2P$-17 (PII). (a) PI(A), (b) PI(B), (c) PI(C), (d) PII(A), (e) PII(B) and (f) PII(C).

peptides and mineral surfaces dominate the interfacial interactions.

The Poisson–Boltzmann equation (PBE) has been proposed as an effective continuum model to evaluate the electrostatic properties [8]. This model uses implicit solvent and can determine the contribution of electrostatic to the forces and energies of a molecular system.

In this study, we used MD simulations to simulate the dynamical behaviour of peptides on calcite. The adsorption of peptides on calcite $(1\,0\,\overline{1}\,4)$ has been calculated and electrostatic interactions between the peptides and the calcite surface have been examined with PBE continuum electrostatic calculations.

2. Methods

A 16-amino acid peptide (Arg Arg Glu Glu Trp Trp Asp Asp Arg Arg Glu Glu Trp Trp Asp Asp) and a 17-amino acid peptide (Arg Arg Glu Glu Trp Trp Asp Asp Pro Arg Arg Glu Glu Trp Trp Asp Asp) were built with the Amber 9 program [9]. These two peptides have been reported to facilitate the nucleation, growth and aggregation of calcite crystal [3]. A peptide can have a variety of configurations; each configuration may have a different influence on calcite crystal growth. Therefore, for each peptide simulated, we generated three configurations, α-helix, extended and β-turn. The configurations of the two peptides are thus denoted as PI(A), PI(B), PI(C) and PII(A), PII(B), PII(C). The three-dimensional structures are presented in Figure 1.

Calcite has a rhombohedral crystal structure, space group $R\overline{3}c$, where $a = b = 4.988$ Å, $c = 17.061$ Å, $\alpha = \beta = 90°$ and $\gamma = 120°$ [10]. The calcite $(1\,0\,\overline{1}\,4)$ surface shown in Figure 2 was built with Materials Studio 4.0 [11].

In the modelling, we put water and a peptide molecule on a calcite surface as shown in Figure 3. Because all the peptides under study were negatively charged with $-4e$, two calcium ions were added to each peptide in order to neutralise the system. The temperature was 300 K and a three-dimensional periodic boundary was used. All the MD simulations were carried out using the DL_POLY 2.18 code [12] with a set of force fields designed for use at bio-inorganic interfaces [6]. Full details about the force fields between the organic molecule and the mineral are

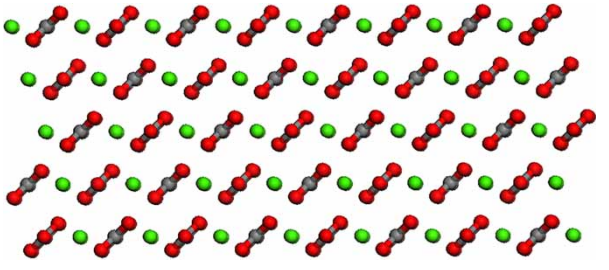

Figure 2. The calcite $(1\,0\,\overline{1}\,4)$ surface.

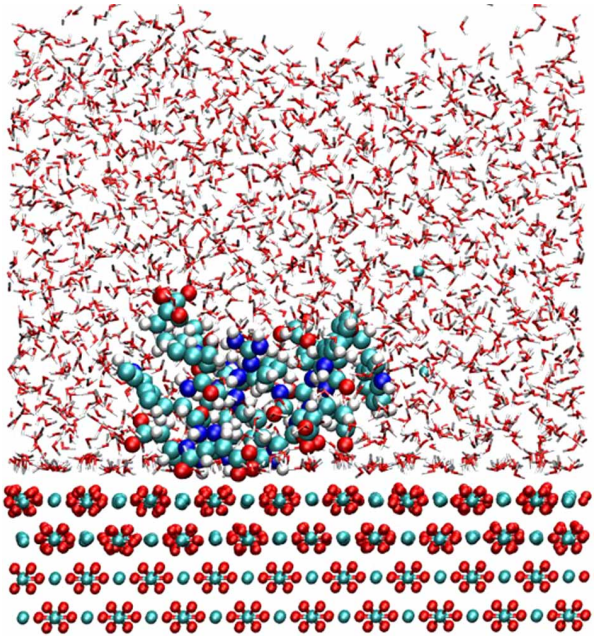

Figure 3. Simulation model of a peptide molecule on the calcite surface.

given in that reference. The interaction potentials used for $CaCO_3$ were those derived by Pavese et al. [13] for modelling a range of properties of calcite and aragonite crystals. The potentials for peptides were obtained from the ff03 force field in AMBER; the flexible TIP3P potential was used for water [14].

The coordinates of both peptides and the calcite surface obtained from the final configuration of MD simulations were used as input for PBE calculations. After taking away all the water molecules, PBE calculations were performed with the APBS program [8]. In the calculation, the solute intramolecular interactions were computed by the usual molecular mechanics methods, while the solute–solvent and the solvent–solvent interactions were computed by a mean-field approximation through the use of PB electrostatic theory. The dielectric constant for water was set to 80.0, and 8.0 for the calcite surface and peptides.

3. Results and discussion

3.1 Peptides in vacuum

The MD simulations of peptides in vacuum were carried out at 300 K for 2 ns. From Figure 4, we can see that after the initial equilibration period, the configurations of the peptides became stable, as characterised by their radii of gyration. The potential energy underwent variance during the simulations. The results show that the potential energy of a peptide in vacuum is closely linked to its specific configuration. Configurations with coiled structure (smaller gyration radius) are energetically favourable since

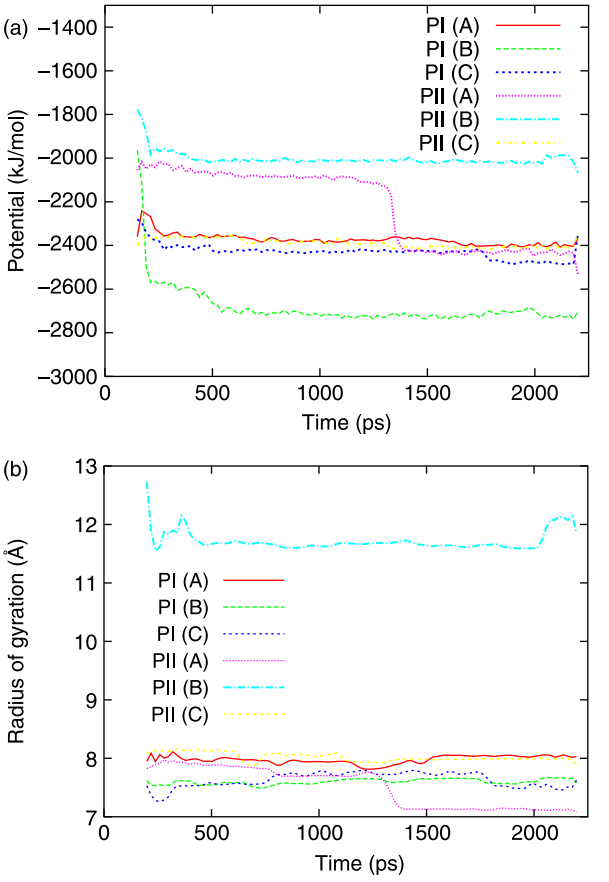

Figure 4. Peptides in vacuum. (a) Potential energy and (b) radius of gyration.

molecules with this kind of configuration are able to interact with themselves, so their potential energy is lowered by these intramolecular interactions. PI(A) and PII(B) have the largest gyration radius in all of the PI and PII configurations during the simulations, and as a result, their potential energies are the largest. The change of peptide configuration as indicated from the gyration radius will induce a change of potential energy of the peptide. For example, the gyration radius of PII(A) decreased sharply (about 10%) at $t = 1300$ ps and accordingly, its potential energy increased from around -2100 to -2400 kJ/mol.

3.2 Peptides in water

The simulations of peptides in water were carried out at 300 K for 2 ns. The potential energy and gyration radius for the peptide molecule were examined for each simulation, and results are shown in Figure 5. The solvation of peptides by water molecules could greatly stabilise peptide molecules. There is no obvious difference in potential energy between the peptides. Their larger gyration radius in water indicates that they tend

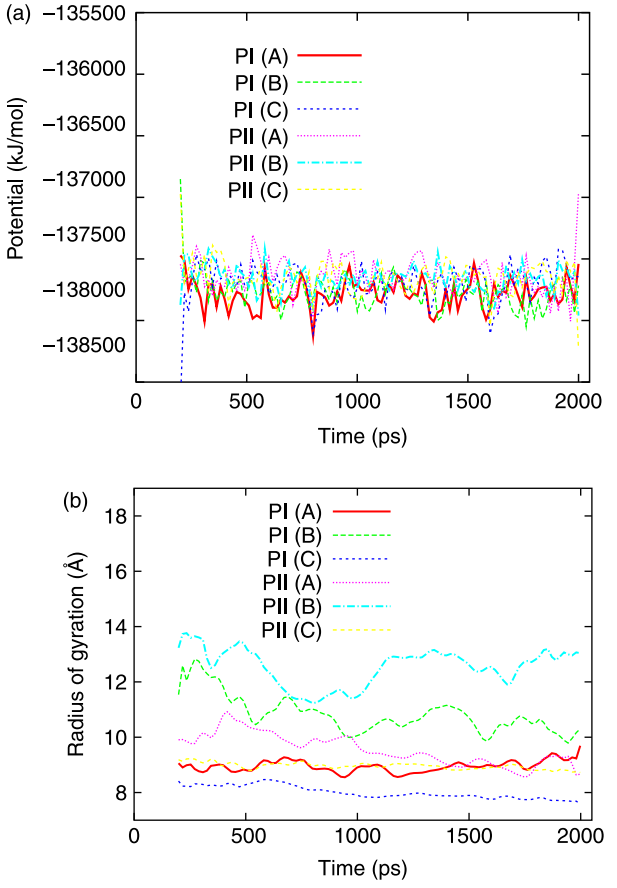

Figure 5. Potential energy and gyration radius of peptides in water. (a) Potential energy and (b) radius of gyration.

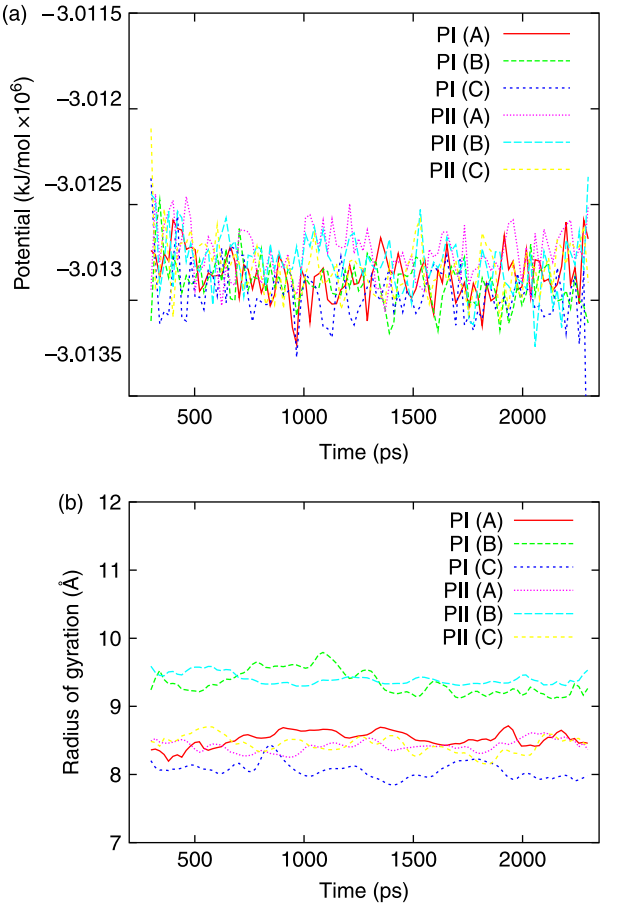

Figure 6. Peptides on calcite in water. (a) Potential energy and (b) radius of gyration.

to maintain an extended structure such as PI(B) and PII(B). The difference in dynamic behaviour of peptides with and without water molecules, as seen from the gyration radius calculations, implies that the presence of water molecules has great influence on the functionality of peptides during biomineralisation.

3.3 Peptides on calcite surfaces in water

These simulations were used to simulate adsorption of peptides on the calcite surface. To make sure that the adsorption of peptides onto the calcite surface is that of a low energy (if possible the equilibrium) configuration, the following procedure was used to build the system. First, the peptide was put about 4 Å away from the surface and the MD simulation ran for 2.5 ns, to allow adsorption to be complete. Second, water molecules were added to the system and a series of stepwise MD simulations were used to relax the system. After the system has equilibrated, the potential energy and the radius of gyration of the peptide could be obtained from the production simulations of 2 ns, and results are shown in Figure 6. The results suggest that although there are differences in the gyration radius, the variability of potential energy among the peptides is insignificant. The adsorption energy could be obtained by comparing the potential energy of the system before and after adsorption using the method described by Yang et al. [7]. The results are shown in Table 1. Low negative adsorption energy means strong adsorption between the peptide and the surface.

The peptides with the β-turn configuration have the strongest adsorption (adsorption energies: -204.4 kJ/mol for PI(C), and -136.8 for PII(C)); those of α-helix configuration have the weakest adsorption, and those of extended configuration have adsorption energies between those of the β-turn and α-helix configurations. The dependence of adsorption energy on peptide configurations indicates

Table 1. Adsorption energies for peptides adsorbed on the calcite $(1\,0\,\bar{1}\,4)$ surface.

	A	B	C
PI (kJ/mol)	6.41	−40.5	−204.4
PII (kJ/mol)	21.4	−48.6	−136.8

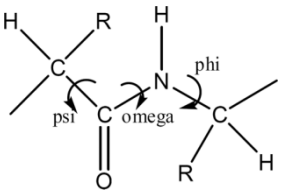

Figure 7. Dihedral angles in a peptide repeating unit.

that the configuration of peptides plays a key role in biomineralisation controlled by peptides or proteins. The results agree well with the experiments, which showed that peptides with specific configurations can facilitate calcite crystal growth [3].

3.4 Changes in dihedral angles of the peptides

The gyration radius of a peptide cannot display all the information about a peptide configuration. Therefore, the dihedral angles of the peptides have been calculated to indicate the change in configuration with more detail. For each residue unit, three dihedral angles can be defined as in Figure 7.

The distribution of each type of dihedral angle could be obtained from the trajectory of the MD simulations. For example, the distributions of all dihedral angles for PI(A) during the former simulations are shown in Figure 8.

During the simulations, the dihedral angle 'omega' hardly changed from around 180°, which agrees with the expected chemical structure. The figures clearly show that the change of peptide configuration can be reflected by the change in the dihedral angles 'phi' and 'psi'. For simulation of PI(A) in water, the distribution of the dihedral angle 'phi' has a major peak around 290°, and a small peak around 230°, while the distribution of the dihedral angle 'psi' has a major peak around 340°, and a small peak around 230°. The distribution of these dihedral angles shows that the peptides can keep their configuration in water without significant changes. From the simulations of the peptides on the calcite surface, we can see some new peaks and slight shifts of previous peaks. The 'phi' type of dihedral angle has two new distribution peaks around 80° and 170°, while 'psi' has peaks around 70° and 160°. The difference in the distribution of dihedral angles shows the alteration of configuration of peptides after they interact with the calcite surface.

3.5 Electrostatic potential isosurfaces

From the MD simulations, we are able to investigate the molecular system in atomistic detail. It is still instructive to plot the potential isosurfaces of the peptide and the calcite with the PBE calculations. The electrostatic potential isosurfaces represent the points of electrostatic potential

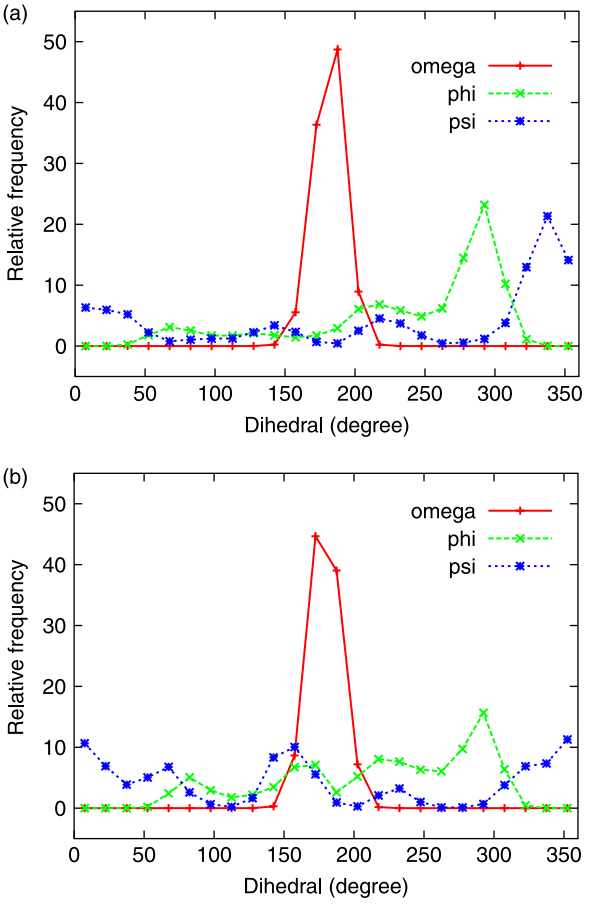

Figure 8. Dihedral angles for peptides. (a) PI(A) in water alone and (b) PI(A) in water on a calcite surface.

within a volume of space. The results from PBE calculations with the APBS program are shown in Figure 9.

From the isosurfaces, we can see that the dominating electrostatic interaction is a key factor in peptide interactions with calcite. Two types of strong binding can be identified: interactions between carbonate groups of the calcite surface and amino groups of the peptides and interactions between calcium ions in calcite and carboxyl groups of peptides.

4. Conclusions

Simulations of two kinds of peptides on the calcite $(1\,0\,\bar{1}\,4)$ surface in water were used to investigate the interaction between the peptides and this calcite surface. The results indicate that the specific configuration of peptides plays an important role in their adsorption. The calculated adsorption energies show that the β-turn configuration peptides have the strongest interaction with the calcite surface, extended configurations have less strong interactions, and α-helix configurations have the least interaction. From the continuum electrostatic calculations with PBE, two types of strong interaction have been

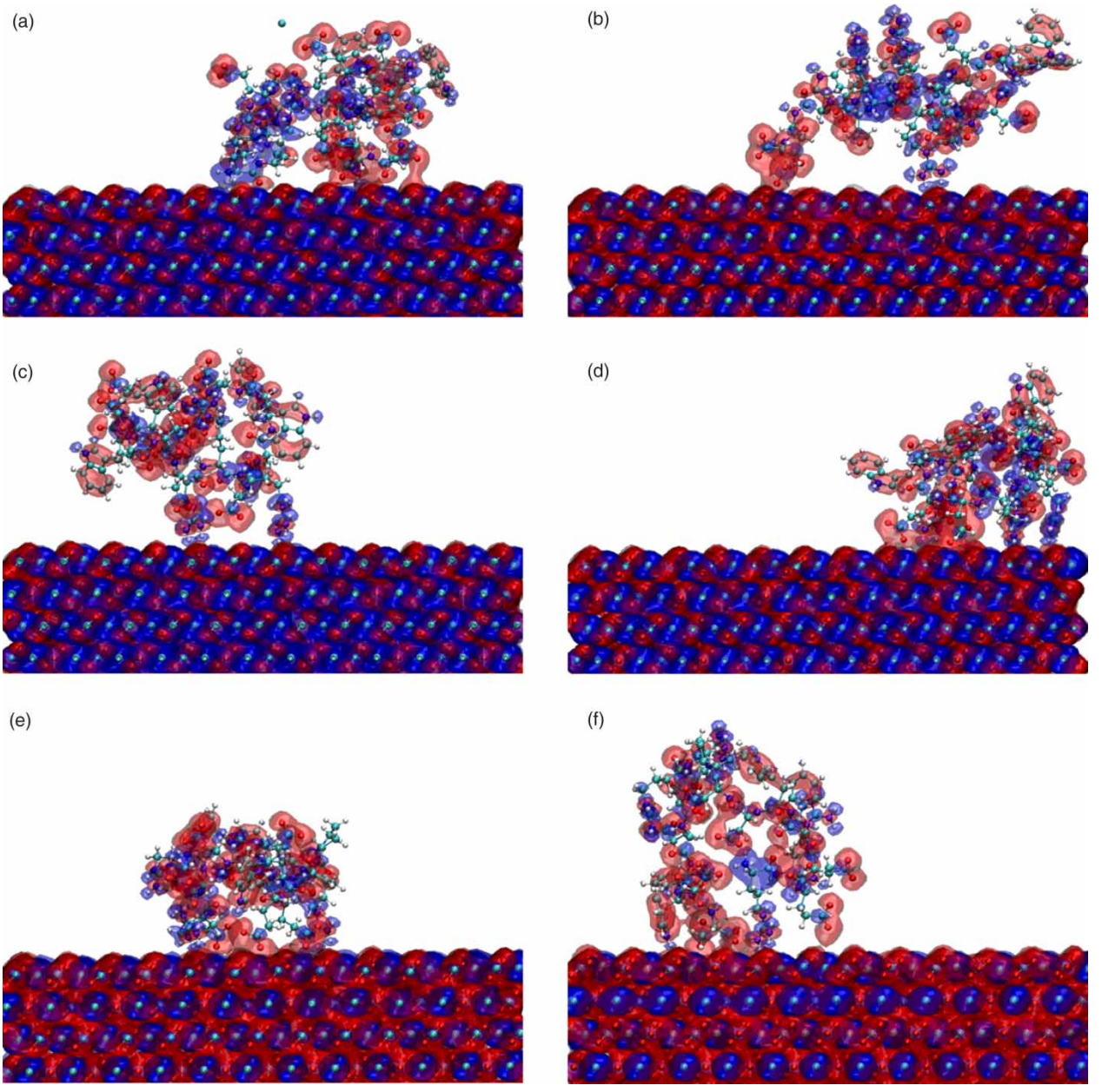

Figure 9. The potential isosurfaces of peptides and a calcite surface. (a) PI(A), (b) PI(B), (c) PI(C), (d) PII(A), (e) PII(B) and (f) PII(C).

identified: interactions between carbonate groups of the calcite surface and amino groups of the peptides and interactions between calcium ions of the calcite surface and carboxyl groups of the peptides. This helps to explain the biological control in biomineralisation.

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