

Mechanism of promoted dipeptide formation on hydroxyapatite crystal surfaces

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The formation of dipeptides from amino acids can be driven by hydroxyapatite at a relatively low temperature in air. For example, the formation of (Ala)₂ from Ala is induced on hydroxyapatite at 110°C with considerable yield. Typically, condensing agents, high temperatures (>250°C) or high pressures (>25 MPa) are required to drive the condensation of amino acids. Similar effects are observed in the condensation of Gly, Glu and Asp. Experiments demonstrate that hydroxyapatite is an effective inorganic catalytic agent, reducing the activation barrier for the formation of dipeptides by more than 50%. HAP promotes condensation by adsorbing amino acid monomers in an organized manner, which decreases the distance between amino and carboxyl groups on neighboring molecules and extends the contact time of the reaction groups. This work provides a chemical understanding of the primitive condensation of amino acids and reveals a mechanism for enhancement of mineral catalysts. It is important that the conditions used for hydroxyapatite-assisted dipeptide formation are not harsh and can be readily achieved, revealing a possible mechanism for the chemical evolution of biomolecules over geologic ages.

condensation reaction, dipeptide, hydroxyapatite, amino acid, catalysis

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The initiation of polymerization of amino acids is a vital step in the primitive formation of proteins and this procedure is irreplaceable in the chemical evolution of life precursors [1–4]. However, the condensation reaction involving the elimination of H₂O molecules between amino acids to link them together is not favored energetically or dynamically [5,6]. It is generally believed that inorganic minerals have an important role in the primitive evolution of biomolecules because they were present in large amounts in the prebiotic earth crust after the formation of the hydrosphere [7]. It has been suggested that clays such as montmorillonite and kaolin facilitate the synthesis of organic molecules [8–11]. These clays can enhance the conversion of amino acid amides into polypeptides; however, the mechanism is still unknown. Polycondensation of amino acids has also

been observed on silica and alumina surfaces but its efficiency is poor [12]. It should be noted that condensing agents (e.g. carbonyl diimidazole [13]), high temperature (>250°C) and high pressure (>25 MPa) are still frequently used to promote amide formation [13,14]. However, these models cannot provide a better understanding of the primitive formation of dipeptides because they require harsh conditions. It has been noted that calcium phosphate minerals are widely distributed on our planet. Among them, hydroxyapatite (HAP, Ca₁₀(PO₄)₆(OH)₂) is the most thermodynamically stable [15,16]. Unlike other inorganic compounds, HAP is also an important biomineral with specific affinity for amino acids, peptides and proteins [17–22]. Therefore, it is reasonable to suggest that HAP may accumulate biomolecules to promote their chemical evolution. Here, we show that amino acids can be linked on an HAP surface at a relatively low temperature (110°C) in air. The

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catalytic effect originates from the organized adsorption of amino acid monomers on the HAP surface, which significantly reduces the distance between intermolecular amino and carboxyl groups as well as increasing their contact time. From the viewpoint of cybernetic chemistry [23], these features can greatly reduce the activation barrier to facilitate the polymerization of amino acids. This study provides physicochemical insight into the mechanism of mineral-based catalysis in the primitive evolution of biomolecules under relatively mild conditions in air.

The hydration-dehydration process in the hydrothermal conversion of amino acid amides into polypeptides in a marine environment is widely accepted as an important pathway in the formation of life precursors [14,24–26]. Evaporation of a solution of amino acids to dryness and subsequent heating of the dried molecules has often been used as an experimental model in laboratories [27–29]. In the current study, a mixture of amino acid solution and HAP crystals was thermally treated to simulate this natural process.

1 Experiments and methods

1.1 Materials

The four typical amino acids used in this study, *L*- α -alanine (Ala), glycine (Gly), glutamic acid (Glu) and aspartic acid (Asp) were purchased from Sinopharm Chemical Reagent Co., Ltd. Dialanine (Ala)₂ and diglycine (Gly)₂ were purchased from Sigma. Diketopiperazine (DKP) was purchased from Acros Organics. HAP crystals were synthesized as follows. Distilled water (500 mL) and CaCl₂ (0.5 mol/L, 250 mL) were mixed in a reaction vessel and the pH was adjusted to 9.5 using ammonia. A solution of (NH₄)₂HPO₄ (0.3 mol/L, 250 mL) was then added drop-wise. The pH was maintained at 9.5 by slowly adding ammonia. The precipitated HAP solids were collected by centrifugation at 5000 r/min, and then washed extensively with distilled water.

1.2 Condensation and characterization

Condensation of monomeric amino acids on HAP was performed by heating a mixture of HAP (400 mg) and a solution of amino acids (2 mL, 1 mol/L) in a glass beaker at 110–190°C in air for 10 h. In the control experiment, only a solution of amino acids was added to the beaker. After the thermal treatment, distilled water (10 mL) was added into the beaker and then left for 24 h to dissolve the adsorbed compounds from HAP. After centrifugation at 12000 r/min and filtration through a 0.22- μ m Millipore membrane, the composition of filtrate was examined by high-performance liquid chromatography (HPLC, Agilent 1100, Agilent Technologies, Paulo Alto, CA, USA) with a reverse-phase column (Zorbax Eclipse XDB-C18, Hewlett-Packard, Newport, DE, USA). The mobile phase consisted of KH₂PO₄

(50 mmol/L) and C₆H₁₃SO₃Na (7.2 mmol/L), with the pH adjusted to 2.5 by H₃PO₄. The flow rate of the mobile phase was 1 mL/min. The compounds were analyzed at 195 nm with a UV detector. The reaction yields were determined as the percentage of reactant converted to the reaction product. The products were identified by liquid chromatography/mass spectrometry LC-MS (Agilent 1100 LC/MSD SL, Agilent Technologies, Paulo Alto, CA, USA).

1.3 Computer simulation

The Hauptmann apatite model [30] was used for the simulation, and the experimental crystal parameters and infrared spectra of HAP were accurately reproduced by the simulation. An HAP (010) interface was created by splitting the crystal structure and inserting a layer of water with a thickness of 3 nm and a density of 1000 kg/m³ between the separated crystal surfaces. Simple point charge (SPC) force fields, which are widely used in the modeling of large aqueous biological systems, were applied for water. Optimized potentials for liquid simulations for all atom (OPLSAA) force fields, which are commonly used in biological systems, were applied for the amino acids. Molecular dynamic (MD) simulations were performed using Gromacs 3.3 [31,32] software. Periodic boundary conditions were applied in all directions. Particle mesh Ewald (PME) summation was applied for the treatment of the long-range Coulombic interactions, with a cutoff distance of 1.3 nm. Simulations were performed using the NpT ensemble [33]. Anisotropic Berendsen pressure coupling was applied allowing cell shape variation so as not to impose artificial symmetry restrictions. A time step of 2 fs was found to be appropriate. Initial velocities according to the Maxwell distribution at the desired temperature were used as the starting configuration. To ensure thermodynamic equilibrium, the data from the first 1 ns of the NpT run was abandoned, and the remaining data was used for radial distribution function analysis.

2 Results and discussion

The specimens after thermal treatment were characterized by comparing the HPLC retention times of the products, which were identified by LC-MS, with those of standard reagents (Figure 1(a)). In the control experiments, the condensation of Ala did not occur in the temperature range between 110 and 190°C, indicating an inert nature of Ala in spontaneous condensation. However, when HAP solids were added, the amide reaction of Ala could be initiated. Some new peaks were found in the HPLC profiles of the reaction products when the temperature was above 110°C (Figure 1(b)). It was confirmed by LC-MS that DKP (143.1 [M+H]⁺, 158.9 [M+NH₄]⁺, 165.1 [M+Na]⁺) and (Ala)₂

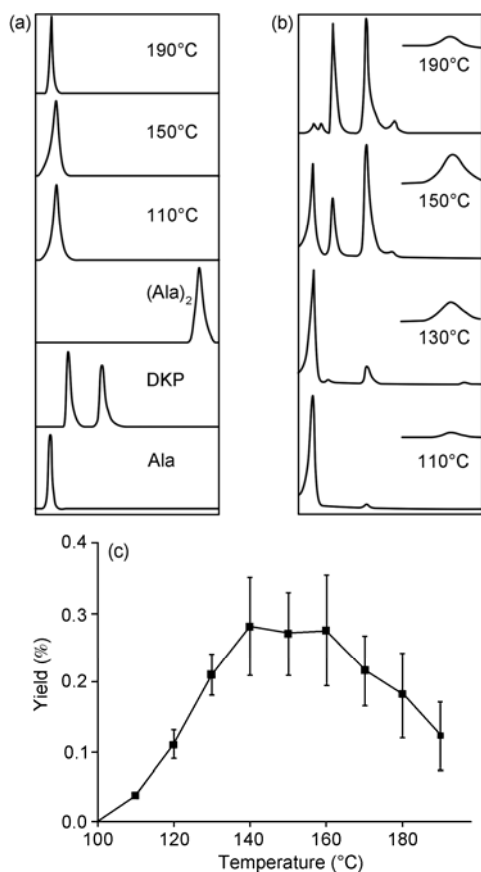


Figure 1 (a) HPLC of authentic reagent (Ala) and products ($(\text{Ala})_2$ and DKP) in the absence of HAP. (b) HPLC of the products in the presence of HAP; the $(\text{Ala})_2$ peaks have been enlarged. (c) Yields of $(\text{Ala})_2$ from 10-hour cycles at different temperatures.

(161.1 $[\text{M}+\text{H}]^+$, 183.1 $[\text{M}+\text{Na}]^+$) were produced. At a temperature of 110°C, the estimated yield of $(\text{Ala})_2$ was ~0.03% after 10 h. The reaction yield increased with temperature and the highest yield, ~0.28%, was achieved at 140–190°C (Figure 1(c)). It should be emphasized that only a 10-h cycle was applied in this experiment; the yield reached 6%–10% when the reaction time was extended to 1 month compared with the small yield without HAP. Clearly, HAP readily catalyzed the formation of $(\text{Ala})_2$. The experimental conditions used were not harsh, so it is realistic that they could be provided by the earth.

It should be noted that the formation of DKP frequently dominated the condensation reaction. This phenomenon can be attributed to the intramolecular condensation of Ala [34], which proceeded readily because of the short distance between the amino and carboxyl groups of a single Ala molecule. Besides, the stereochemical feasibility of Ala made the intramolecular condensation much more readily [35,36]. It has been reported that the activation energy for the conversion of $(\text{Ala})_2$ to DKP is significantly lower than that for the formation of $(\text{Ala})_2$ from two Ala molecules, and the formation of DKP is preferred in most condensation reactions

especially at relatively high temperature [37]. Accordingly, in our experiments the yield of $(\text{Ala})_2$ decreased remarkably when temperature was >150°C. This result also reveals the importance of a lower temperature in the generation of dipeptides under thermal conditions.

Similar results were obtained for the condensation of Gly (Figure 2). In the absence of HAP, the formation of diglycine was not detected even when the reaction temperature was increased to 130°C. However, a signal consistent with $(\text{Gly})_2$ was found in the HPLC profiles of products when the temperature was only 100°C in the presence of HAP. The yield of $(\text{Gly})_2$ increased significantly as the temperature increases. The intramolecular condensation side reaction was not significant when temperature was lower than 130°C. However, performing the reaction at a higher temperature led to significant amounts of intramolecular condensation.

The effect of HAP in promoting dipeptide formation was further confirmed using other amino acids such as Glu and Asp (Figure 3). In the control experiments performed without HAP, there was no product signal in the HPLC profiles when the reaction temperature was 130°C. However, the formation of $(\text{Glu})_2$ and $(\text{Asp})_2$ with estimated yields of around 0.06% and 0.1%, respectively, were observed at 130°C when HAP was added to the reaction mixture. The results clearly show that HAP promotes the thermal condensation of Glu and Asp. It is expected that the general trend found for the above-mentioned amino acids will also hold for the formation of other dipeptides.

It was noticed that the yield of $(\text{Ala})_2$ was negligible at a low temperature (<110°C) and that the formation of DKP dominated the reaction at a high temperature (>150°C).

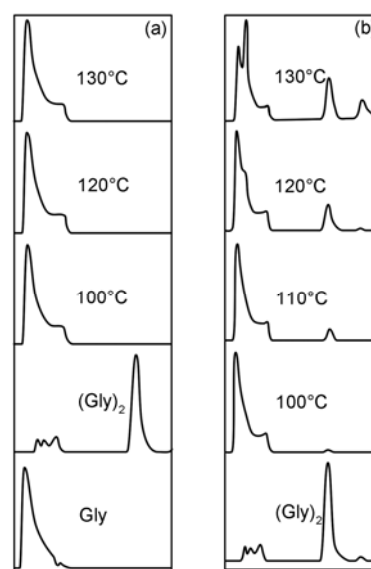


Figure 2 (a) HPLC of the products from condensation of Gly in the absence of HAP. (b) HPLC of the products from condensation of Gly in the presence of HAP.

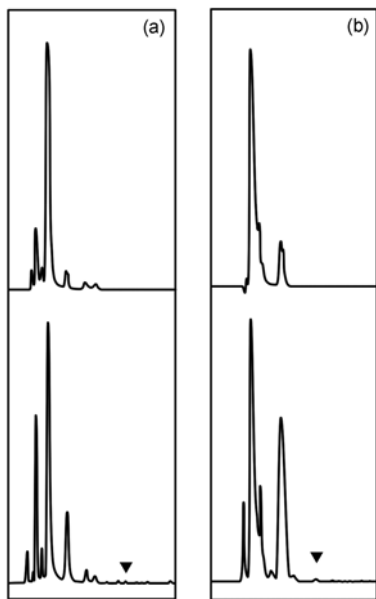


Figure 3 (a) Condensation of Glu; (b) condensation of Asp. The upper and lower curves show the products from reaction at 130°C in the absence and presence of HAP, respectively. The dipeptide signals are indicated by an arrow.

Therefore, a suitable temperature range was essential for the formation of (Ala)₂ in air. Because of the relatively fast generation of (Ala)₂ on the HAP surface, a 10-h reaction time was sufficient for the analysis. In kinetic studies, approximately linear relationships between the (Ala)₂ concentration and reaction time, *t*, were found between temperatures of 110 and 140°C (Figure 4(a)), indicating a pseudo-zero order reaction. HPLC analysis showed that the change in the amount of Ala during the reaction was not remarkable (less than 5%) after 10 h, even at 140°C. Thus, the reaction rate could be estimated directly from the slope of the plot of the concentration of (Ala)₂ against *t*. At 110°C, (Ala)₂ was generated at a rate of 3.7×10^{-8} mol/h, which is defined as a relative rate constant, *k*, of 1. The *k* values at 120, 130 and 140°C were about 3.0, 5.8 and 7.5, respectively. A plot of $\ln k$

against $1/T$ (*T* is the absolute temperature) gave a straight line (Figure 4(b)) and the behavior of the data was expressed mathematically by the Arrhenius equation,

$$\ln k = \ln A - \frac{E_a}{RT}, \quad (1)$$

where *A* and *R* are the frequency factor and gas constant, respectively. The activation energy, *E*_a, was obtained from the slope of the line, $-E_a/R$. It was calculated that the *E*_a for (Ala)₂ formation on HAP was just ~89 kJ/mol. The kinetic behavior of (Gly)₂ generation on the HAP mineral surface was also examined. Analogous to that in the Ala system, a pseudo-zero order reaction was obtained for a reaction time of 10 h. At 100°C, (Gly)₂ was produced at a rate of 1.27×10^{-7} mol/h, which was defined as a relative rate constant, *k*, of 1. The *k* values at 110, 120 and 130°C were about 2.91, 4.74 and 7.09, respectively (Figure 5). Thus, a value of *E*_a of 80 kJ/mol for (Gly)₂ formation on HAP, was also estimated using the Arrhenius equation. Previous studies have reported that Gly is the amino acid with the greatest propensity to form dipeptides [38]. The reported the *E*_a for amide bond formation between Gly molecules was 209 kJ/mol [39], which was more than 2.5 times larger than that found in the presence of HAP. Furthermore, the role of silica has been already highlighted in previous studies on mineral-assisted condensation. In comparison, it was reported that the adsorption of Gly on silica reduced the *E*_a by only 10% [40]. In our experiment, HAP decreased the *E*_a of Gly condensation by more than 60%. The *E*_a for the dimerization of Ala is greater than that of Gly. Even under harsh hydrothermal conditions (temperature >120°C and pressure of 2 MPa), the reported *E*_a for the formation of (Ala)₂ was 114 kJ/mol [37]. In contrast HAP reduced the *E*_a to ~89 kJ/mol. Clearly, the catalytic effect of HAP on the condensation of amino acids is significant. Our results suggest that it is the most effective inorganic catalytic agent for the formation of dipeptides found to date.

The mechanism for how HAP crystals promote the formation of (Ala)₂ is not yet understood. Although the en

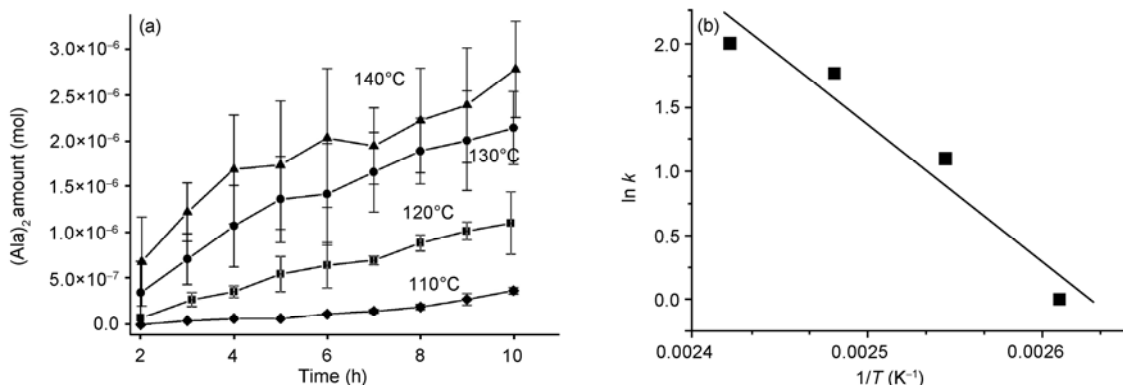


Figure 4 (a) Formation of (Ala)₂ as a function of experimental time. (b) Plot of $\ln k$ against $1/T$.

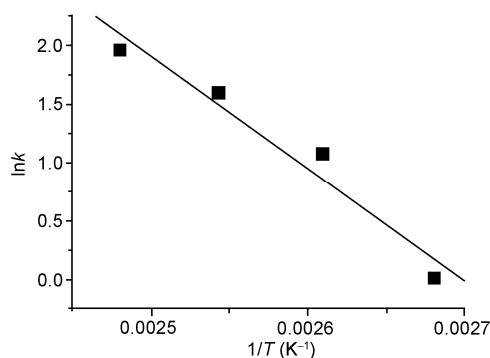


Figure 5 Plot of $\ln k$ against $1/T$ for generation of $(\text{Gly})_2$ on HAP.

hancement induced by various inorganic minerals on the formation of dipeptides and polypeptides have been well reported, the mechanism for this effect is still unclear. It is important to understand the behavior of amino acid molecules on the mineral surface. Sophisticated computer simulation can provide a powerful tool to investigate this behavior. The adsorption of different amino acids on HAP {100} facets (the largest habit surfaces in HAP crystals) were studied at the atomic level. Unlike on other minerals, the adsorption of Ala on HAP was strong and well-organized [23]. The simulation results showed that each Ala molecule had a certain adsorption site (Figure 6(a)). The distance between an H atom of the amino group in an Ala and an O atom of the carboxyl group from the neighbouring Ala

molecule was 0.169 nm (Figure 6(b)). The radial distribution function (Rdf) confirmed that the maximum distribution of an H atom in the amino group was 0.169 nm away from an O atom in the carboxyl group of the neighbouring molecule (Figure 6(c)). Thus, the formation of a hydrogen bond was induced. The intermolecular distance between N and C was fixed at around 0.330–0.370 nm on the HAP surface (Figure 6(d)). The same result was obtained at the Gly-HAP adsorption interface (Figure 7). The distance between an H atom of the amino group in a Gly molecule and an O atom in the carboxyl group of the neighbouring Gly was 0.172 nm, and the intermolecular distance between N and C was fixed at 0.365 nm on the HAP surface. Because adsorption restricts the movement of Ala and Gly molecules on HAP, the contact time between the two reaction groups was extended. In our computer simulation, the configurations of the neighbouring amino acid monomers remained unchanged over the whole simulation period (>2 ns) after adsorption. The extended contact time is another important factor in increasing the reaction between amino acids.

3 Conclusions

In this study, it was shown that the condensation of amino acids to dipeptides is greatly promoted by mineral HAP. Amino acid molecules are adsorbed into an organized pattern on HAP, which places neighbouring molecules in closer proximity for condensation. Using HAP to catalyze the

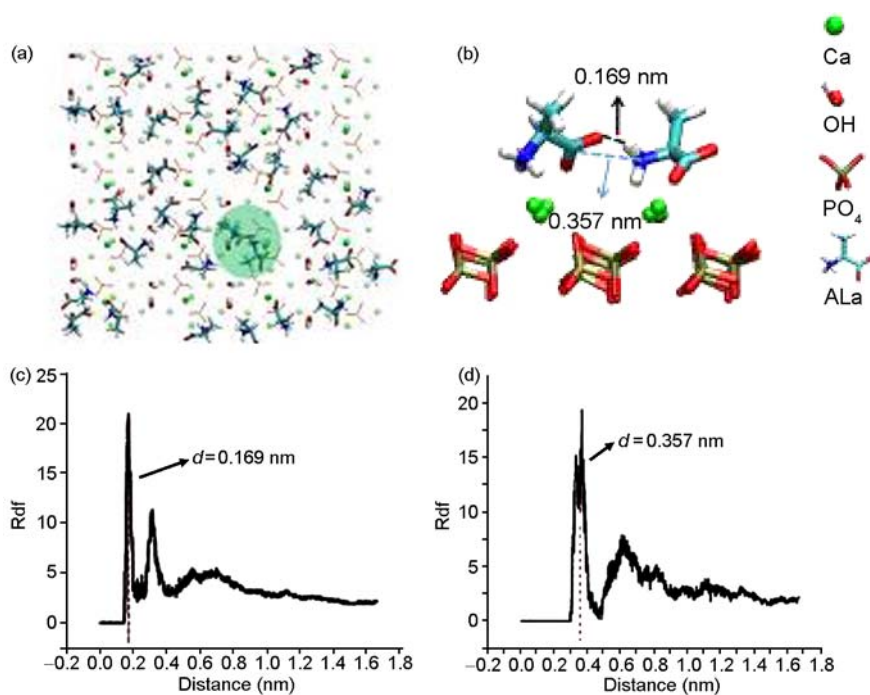


Figure 6 (a) Overhead view of the adsorption pattern of Ala on HAP {100} facets. (b) Image at higher magnification revealing the interaction between neighboring Ala molecules marked by the green oval in (a). (c) Rdf of an H atom in an amino group around an O atom in the carboxyl group on the neighboring molecule. (d) Rdf of the N atom in an amino group around the C atom in the carboxyl group on the neighboring molecule.

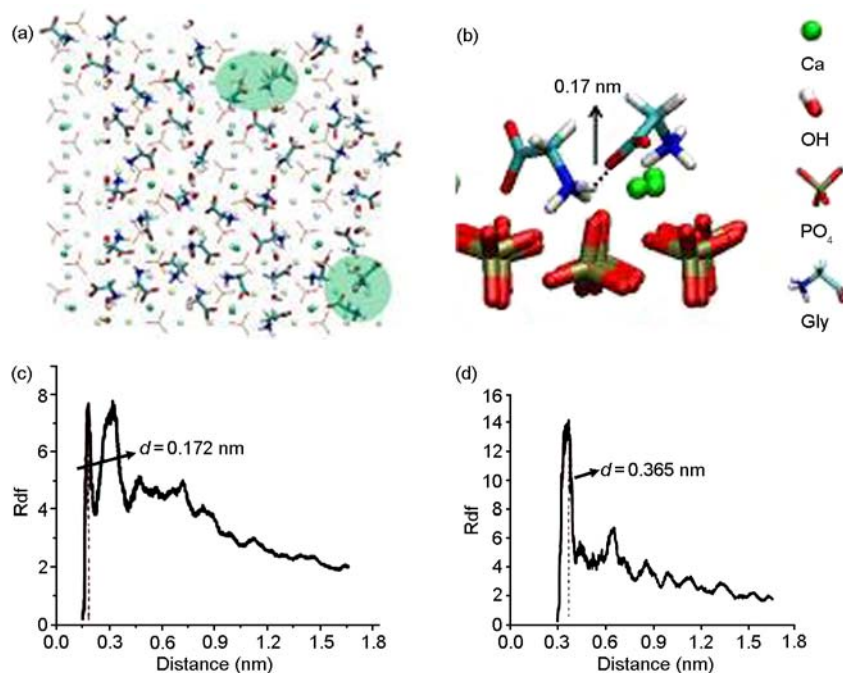


Figure 7 (a) Overhead view of Gly adsorption pattern on HAP {100} facets. (b) Magnified views showing interactions between neighboring Gly molecules that are marked by green shadows in (a). (c) Rdf of an H atom in the amino groups around an O atom in the carboxyl group on the neighboring molecule. (d) Rdf of the N atom in an amino group around the C in the carboxyl group on the neighboring Gly molecule.

formation of dipetides does not require the harsh reaction conditions such as high temperature or high pressure that were essential for the continued chemical evolution of biomolecules over the long geological ages.

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