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Why nature chose α-amino acids*

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Abstract: The autocatalytic system, N-phospho-α-amino acids, could not only self-assemble into oligo-peptides but also act as the phosphorylation reagents to phosphorylate the nucleosides into nucleotides and oligo-nucleotides, in aqueous medium. While, the β-amino acids did not have such properties.

NATURE SELECTION

Protein of all species, from bacteria to humans, is made of the same set of 20 standard amino acids. Nineteen of them are α-amino acids with a primary amino group and a carboxylic group attached to a central carbon atom. One exception is proline, which has a secondary amino group. Why nature chose α-amino acids for the protein backbone? To answer this question, one should analyze the key character for the structure of protein. It is obvious that the repeating amides bonds are the major compositions. But amide bonds could be derived from any compound contained both amino and carboxyl functional groups. (Scheme 1), no matter what kinds of linkage between them. How could nature selects only one of them, namely, α-amino acids?

$$NH_2--(X)---COOH$$

$$NH_2-\underset{R'}{CH}-COOH \quad \alpha\text{-amino acid.}$$

Scheme 1 Structure of amino acid.

Is there any connection between the natural selection and the chemical selectivity among all different amino acids? When the amino group of the amino acids were protected by acetyl-, sulfonyl-, there will be no reaction happened on the amino group. However, the N-(O,O-dialkyl-phosphoryl) α-amino acids with a phosphoryl amino protecting group had interested chemical reactivities [1]. For example, N-(O,O-diisopropyl)-phosphoryl-α-alanine, **1**, proceeded the mono-and di-esters exchange if the reaction medium contained the hydroxyl compounds. But under the same conditions, the β-alanine derivative, **2**, a chemical inert species, did not react with any hydroxyl compounds.

PENTA-COORDINATE PHOSPHORUS TRANSITION STATE

Since, the difference between the α-alanine and β-alanine was one CH_2-unite, it might be the variation of transition state. The isomers, **1** and **2**, could form the intramolecular phosphoric-carboxylic mixed anhydride, **a** and **b**, as the transition states, which have the approximate geometry of trigonal bipyramid (TBP) [2]. Base on the empirical observation, the TBP oxyphosphorane structure embodies some general rules, such as, five membered ring occupies apical-equatorial positions, while the six membered ring

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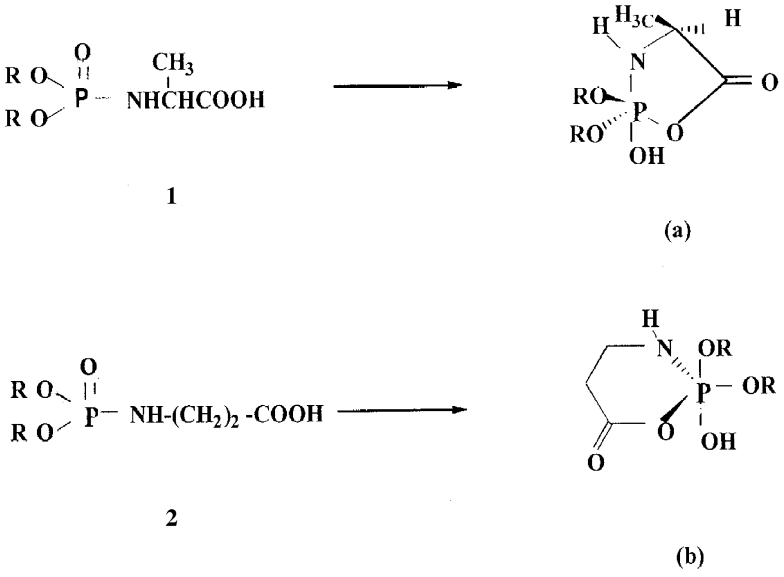
occupies preferentially the di-equatorial positions. Scheme 2 showed that in the intermediate (a)[3], the axial bond has much more d-character than the equatorial bond, which has mostly the sp^2 character therefore the axial bond is much longer and much weaker than the equatorial bond, Consequently, the nucleophile entering into the axial position and the leaving group will departure from the axial position.



Scheme 2 The reaction intermediates for N-DIPP-Ala(a) and N-DIPP-β-Ala(b).

One the other hand, the intermediate (b) derived from the β-amino acids, with the presence of two stronger equatorial bonds was not able to proceed the substitution reactions.

BIS-NUCLEOPHILIC REACTION

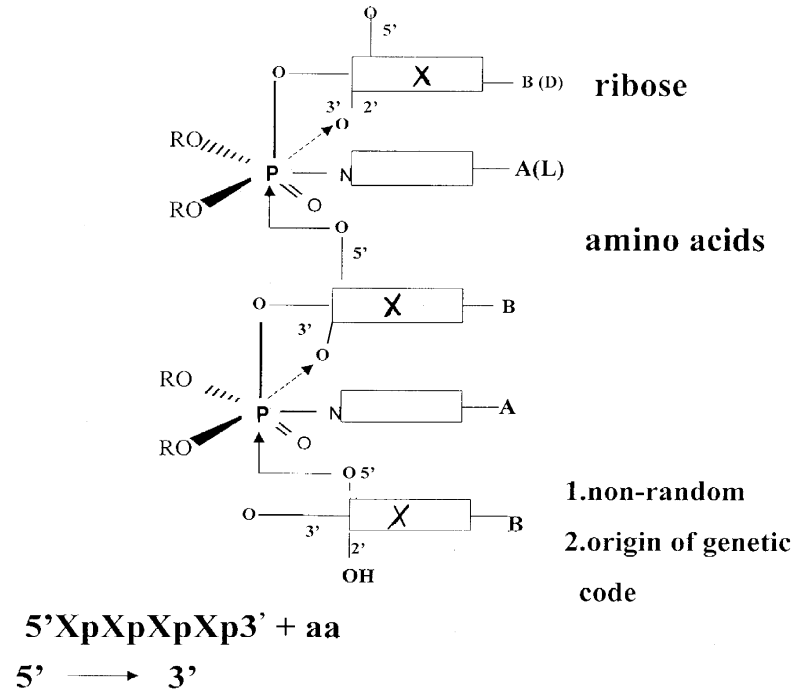
Indeed, the intermediate **a** had been trapped [3], while the proposed transition state **b** had never been observed yet. In intermediate **a**, carboxyl group is activated by the phosphoryl group, simultaneously, the phosphoryl group is activated by the carboxyl group. As a result, both phosphorus and carbonyl are electrophilic centers. Hence, both phosphoryl and carbonyl centers are chemically reactive. Nucleophilc attacking on carboxyl group by amino acid will result into the peptide bond formation [4,5].

PHOSPHORYLATION OF THE NUCLEOSIDES

The most important reaction is the nucleophilic substitution on the phosphorus by the *cis*-diol of the nucleoside to give the nucleotide. It was found that the penta-coordinate phosphorus compound, oxyphosphorane reacted with *cis*-diol much faster than with the primary alcohol [6] by a factor of 20. No wonder, the *cis*-2′,3′-diol were exchanged with the di-alkoxyl groups compound **1** easily to produce a cyclic-phospho-amidate, which in turn was ring-opened by the next nucleoside 5′-hydroxyl group. The result is the yield of di-nucleotide. And the repeating of the described steps, the oligo-nucleotides were obtained (Scheme 3), It is worthwhile to note that the direction for the synthesis of the oligo-nucleotides by N-phospho-α-amino acids is from 5′ to 3′, which is parallel to the bio-synthesis.

In addition, the sequential polymerization, showed that the α-amino acid is sandwiched between two nucleosides, which results into the direct stereo-interactions between the bases and amino acid, namely, acid–base ionic contact, nucleoside base X_1-side chain of amino acid-nucleoside base X_2 double sandwich stacking, and the microenvironment surrounding the phosphorus center. Totaling these interactions might give a clue to the genetic code origin (Scheme 3).

However, from the reaction of N-phospho-β-amino acids, neither the peptide nor the nucleotide was detected. These chemical selectivities might provide the clues for why nature chose α-amino acids as the protein building blocks.



Scheme 3 Assembly of nucleoside by phospho-amino acids.

CONCLUSION

In the literature, Fox [7] also had showed that by treatment with polyphosphoric acid at 273 K the nucleosides but not the deoxynucleosides could be converted into the nucleotides. Schwartz isolated the 2′, 3′ and 5′-AMP by mixing the adenosine with linear polyphosphoric acid [8]. These nucleoside synthesis were independent on the peptide synthesis. In our laboratory, it was found that N-phospho-α-amino acids not only could self-assemble into oligopeptides, but also could phosphorylate the nucleosides or the deoxynucleosides to give mononucleotide, dinuleotides and their aminoacyl-conjugate. the P31-NMR HPLC, FAB-MS, CE (Capillary Electrophoresis), CE-MS were used for multiple checks on the products. Hence, the N-phospho-α-amino acid and the coevolution of protein and nucleic acids was proposed [9–11]. On the contrary, the other types of amino acids, although were capable of polymerization chemically, was not selected by the nature for the protein backbone. What is the standard for the selection? It seems that the phosphorylation-dephosphorylation selectivity is a very important credit, since most enzymes' activities are regulated by the phosphorylation and dephosphorylation mechanism. This paper has described that both α- and β-alanine were N-phosphorylated, however, only the N-phospho-α-amino acids could be dephosphorylated by peptides formation and oligonucleotides formation reactions. The chemical selectivity and the nature selection were matched plausibly.

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