CHEMICAL AND CATALYTICAL PROPERTIES
OF THERMAL POLYMERS OF AMINO ACIDS (PROTEINOIDS)

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Abstract. The significance of thermal polyamino acids (proteinoids) as abiotic predecessors of proteins is reviewed on the basis of new experimental results. Most proteinoids yield only 50 to 80 % amino acid upon acid hydrolysis. They contain 40 to 60 % less peptide links than typical proteins, whereas their average nitrogen content is like that of proteins. The arrangement of amino acid residues is nonrandom. The degree of nonrandomness is difficult to determine because unusual crosslinks disturb most of the sequencing methods typically applied in protein chemistry. The products obtained in a polymerization experiment are heterogeneous. They can be separated into a limited number of related fractions by chromatography or electrophoresis and other separation methods applied in protein chemistry. Their molecular weights are typically between 4000 and 10000. The number of free NH₂-groups is usually smaller than in comparable proteins. A significant fraction of NH₂-groups yields imidazole-type bases during the thermal polymerization. Optically active amino acids racemize during the same process. So far no helicity could be detected. Proteinoids are thus clearly distinct from proteins. However, many of them exhibit weak catalytic activities and tend to undergo self-assembly into microstructures. Their properties of which only a few have been mentioned still support their role as possible candidates for ancestors of first proteins.

The ‘central dogma’ of molecular biology as postulated by Watson and Crick in 1953 (Watson and Crick, 1953) and by Crick in 1958 (Crick, 1958) allows for the transfer of genetic information from nucleic acid to protein, but neither from protein to nucleic acid nor from protein to protein. Lipmann and his associates (Gevers et al., 1969; Lipmann et al., 1971), however, have demonstrated that information can flow from proteins to polypeptides in some contemporary systems.

If we project molecular evolution backwards in order to trace the primary origins of biologically significant macromolecules, we finally face the question of what came first.

The three possible alternatives (proteins came before nucleic acids, nucleic acids came before proteins and both came simultaneously) have been discussed in detail (Lacey and Mullins, 1972; Kaplan, 1971; Calvin, 1969; Eigen, 1977). Experiments designed to simulate the abiotic synthesis of pre-nucleic acids and pre-proteins in the laboratory have been carried out by a large number of investigators (Fox and Dose, 1972a). So far, however, no evidence has been presented indicating a successful a priori synthesis of polynucleotides which exhibit the structural and biological properties of contemporary nucleic acids. The polymerization of amino acids under simulated prebiotic conditions on the other hand has yielded materials which resemble in many aspects polypeptides and proteins such as found in contemporary organisms.

The essential reaction of condensation and its energetics (Borsook, 1953) is depicted

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by the equation:

$$\text{H}_3\text{N}--\text{CHR}--\text{COO}^- + \text{H}_3\text{N}--\text{CHR'}--\text{COO}^- \approx$$

$$\text{H}_3\text{N}--\text{CHR}--\text{CO}--\text{NH}--\text{CHR'}--\text{COO}^- + \text{H}_2\text{O} \quad \Delta G^o = 2-4 \text{ Kcal}$$

In aqueous solution the hydrolysis of the peptide is favored. The reaction proceeds from left to right only if the water is removed from the system. Theoretically, this can be achieved by consuming the water in a secondary reaction (use of a condensing agent) or by evaporation. Removal of water by evaporation is operationally very simple inasmuch as the reactant mixture of amino acids has just to be heated above the boiling point of water. The energy of activation for peptide formation is relatively high. If the starting material is an unhydrated mixture of amino acids, the temperature must usually be raised to 180°C for several hours to initiate the condensation. At such a high temperature amino acids begin to decompose. Thus side reactions compete with the condensation reaction. Some of the difficulties brought about by side reactions were initially overcome by the inclusion of a relatively high proportion of aspartic acid, glutamic acid or lysine (Fox, 1969; Fox, 1956). Other authors have tried to circumvent the barrier between the free amino acids and the peptides by other methods. The use of clays to provide hypohydrous conditions, as suggested by Bernal, has been advanced by the use of montmorillonite with aminoacyl adenylates (Paecht-Horowitz and Katchalsky, 1967; Paecht-Horowitz et al., 1970). Another mode is the conduct of the reaction in the presence of anhydrizing agents such as polyphosphoric acid and other polyphosphates (Harada and Fox, 1965), or cyanamide (Ponnamperuma and Peterson, 1965) or dicyanamide (Steinman et al., 1964; Steinman, 1967). Akabori and his colleagues (Akabori and Yamamoto, 1972) have proposed that the 'fore-protein' (pre-protein) could have been formed by the polymerization of amino-acetonitrile followed by hydrolysis to polyglycine and then by the introduction of various side chains onto the methylene group of polyglycine.

Experiments which circumvent the thermodynamic barrier of amino acid condensation have either yielded only extremely small amounts of polymeric materials or – if large amounts could be produced – have lacked widely accepted geological relevance (e.g., experiments with polyphosphoric acid).

Of all methods to produce biologically significant macromolecules under geochemically relevant conditions only the polymerization of amino acids at elevated temperatures has so far yielded products which show a narrow relationship to the corresponding contemporary types, the proteins. I shall now review a number of criteria which support the idea that thermal polymers of amino acids may be regarded as prebiotic foreproteins.

1. Quantitative Composition

Except for serine, threonine, and cystine, the relative composition of almost any contemporary protein has been simulated quite closely by the thermal condensation product in earlier experiments, particularly by Fox and his associates (Fox, 1968;