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MACROMOLECULAR RECOGNITION: STRUCTURAL ASPECTS OF THE ORIGIN OF THE GENETIC SYSTEM

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Theoretical simulation of prebiotic chemical processes is an invaluable tool for probing the phenomenon of evolution of life. Using computational and modeling techniques and guided by analogies from present day systems we seek to understand the emergence of the genetic apparatus, enzymatic catalysis and protein synthesis under prebiotic conditions.

Modeling of the ancestral aminoacyl-tRNA-synthetases (aRS) may provide important clues to the emergence of the genetic code and the protein synthetic machinery. Assuming that the catalytic function evolved before the elements of specific recognition for a particular amino acid, we are exploring the minimal structural requirements for the catalysis of tRNA aminoacylation. The first step reaction, a formation of an aminoacyl adenylate was studied in the framework of *ab initio* MO theory. Based on the available inhibitor-TyrRS complex, the role of individual residues in the vicinity of the TyrRS active site was examined. The effect of all possible amino acids substitutions near the active site was studied by estimating differential stabilization of the corresponding transition complex. Results indicated prominent catalytic role of His45, His48, Lys225, Lys230 and Lys233. Subsequent sequence analysis indicated that the pattern of these positively charged residues is conserved among different aRSs. This led us to propose a hypothesis that the three dimensional orientation of these positively charged residues may confer the essential catalytic role of the ancestral aRS. The second reaction, a formation of aminoacyl tRNA was studied by the molecular modeling system SYBYL with the high resolution crystallographic structures of the present day tRNA, aRSs complexes. The trinucleotide CCA of the 3'-end of tRNA is placed into the active site pocket of TyrRS, based upon the interaction scheme between tRNA^{Gln} and GlnRS, and upon the assumed stereochemistry of the TyrRS:tRNA:Tyr-AMP transition state.

In another possible scenario, RNA enzymatic reactions play a key role in the emergence of the self-replicating system offering a clue to the onset of enzymatic catalysis prior to the existence of the protein biosynthetic machinery. Our ultimate goal is to propose a simple RNA segment that is small enough to be built in the primordial chemical environment but maintains the specificity and catalytic activity of the contemporary RNA enzyme. To understand the mechanism of ribozyme catalyzed reactions, *ab initio* and semi-empirical (ZINDO) programs were used to investigate the reaction path of transphosphorylation. A special emphasis was placed on the possible catalytic and structural roles played by the coordinated magnesium cation. Both the inline and adjacent mechanisms of transphosphorylation have been studied. The structural characteristics of the target helices, particularly a possible role for the G•T pair, is also studied by molecular dynamics (MD) simulation technique.