Ring Stacking and Hydrogen Bonds are Correlated with Aggregation and Structure of a Propose Precursor of Modern Nucleotides

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Abstract

- Pathway from prebiotic chemistry to modern DNA-protein machinery currently unknown
- Evidence for this pathway not well preserved in the geologic record, and not yet found active anywhere else in the solar system
- A primitive polymer that could spontaneously form from available precursors may have preceded DNA as the first genetic molecule
- 5-Hydroxymethylated Pyrimidines (HMPs) have been identified as potential nucleic acid precursors because research has shown they can spontaneously form oligomers up to eight monomers in length in aqueous conditions, and they contain uracil and cytosine (Smith, K., et al. Orig Life Evol Biosph. 2016, 47, 3 – 11)
- There is an association between ring stacking interactions in HMPs and monomer aggregation.
- There is an association between increased intramolecular hydrogen bonding and greater compactness in HMP oligomers, and contributes to their structure.

Background

How do we progress spontaneously from a primordial soup of biochemical precursors to replicating DNA?

Molecular Dynamics (MD) Simulation

Determining Hydrogen Bonding

- Defined by software as present if the angle between heavy atoms is within constraints and the distance between hydrogen and heavy atom acceptor is less than cut off.
- Can be discriminated as between water and oligomer, intermolecular oligomer, or intramolecular hydrogen bonds.

Molecular Dynamics (MD) Simulation

Determining Ring Stacking Interactions

- Define a plane for each ring and calculate the angle between planes
- Ring stacking interactions occur when Cos (θ) approaches 0 or 1

Summary of Findings & Further Research

- Ring stacking occurring between monomers is associated with increased monomer aggregation.
- Feature A, long range ring stacking interactions occurs with increased frequency in systems with HMC present compared to systems with only HMU present. This suggests HMC plays an important role in further aggregation, leading to a higher frequency of formation of covalent bonds between monomers.
- As the number of intramolecular hydrogen bonds increases there is an association with a decreased radius of gyration. This suggests intramolecular hydrogen bonding increases secondary structure, a finding analogous to modern biomolecular secondary structure.
- By analyzing the dihedral angle of the backbone covalent bonds of oligomers it may be possible to associate certain angles with hydrogen bonding, radius of gyration, and modern analogues.

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Findings of Hydrogen Bond to Radius of Gyration Analysis

- A measure of compactness of a molecule
- A more compact molecule is associated with having higher order structure.

Ring Stacking Interaction & Monomer Aggregation

Findings of Ring Stacking Analysis

Homogenous Mixture of HMC Monomers

Inc. # of Monomers

- Feature A represents long range ring stacking interactions
- Feature B represents monomers approaching alignment
- Feature C represents short range ring stacking interactions

Intermolecular H Bonds

- No association is observed between hydrogen bonds formed with water and radius of gyration
- A negative association is observed between hydrogen bonds formed intermolecularly between oligomers and radius of gyration
- A positive association is observed between hydrogen bonds formed intramolecularly within an oligomer and decreased radius of gyration

Molecular Dynamics Simulation

How do we determine if this molecule is plausible as a genetic precursor?

HMC octamer solvated in H$_2$O

HMC octamer H$_2$O removed for clarity