MAPPING THE CHEMICAL LANDSCAPE OF PREBIOTIC GENETIC POLYMERS

Reported by Jason Edward Cournoyer Tuesday, 30 March, 2021

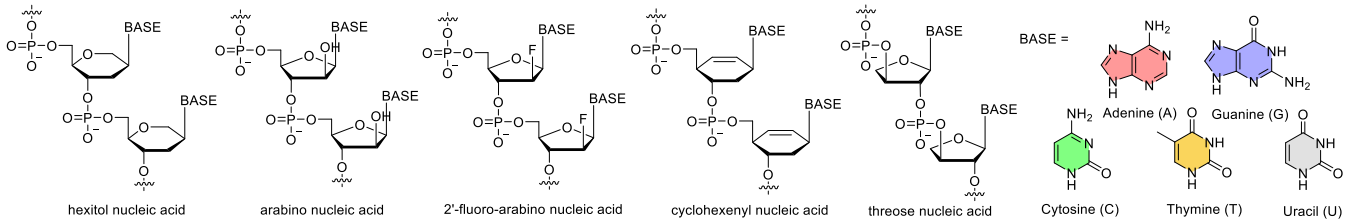
INTRODUCTION

To formulate a molecular basis for the origin of life, intensive studies have explored the emergence of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), the biopolymers which store and transmit genetic information in all organisms. Although it is widely believed that self-replicating RNA proliferated prior to the evolution of DNA and proteins (the "RNA world" hypothesis),[1] the prebiotic conditions which favored the ribofuranosyl sugar-phosphate backbone remain elusive. Hence, chemists have synthesized numerous prebiotically plausible oligomers in search of simpler genetic systems that could have led to the evolution of RNA. These efforts revealed a widespread capability of nucleic acid analogues to form helices and undergo Watson-Crick base pairing with RNA/DNA templates, establishing a robust foundation for engineering the chemical evolution of unnatural polymers.

REPLACING THE β-D-RIBOFURANOSE SUGAR

To identify a plausible antecedent to RNA, Eschenmoser and coworkers systematically evaluated the base pairing capabilities of nucleic acids with prebiotically tractable sugar moieties.[2] The simplest candidate, (L)-α-threofuranosyl-(3',2') nucleic acid (TNA), garnered significant attention as it was shown to form duplexes with RNA, DNA and TNA itself,[2] suggesting a potential route whereby RNA could augment an existing genetic system (Chart 1). Subsequently, TNA and other sugar-modified nucleic acid analogues known as xeno-nucleic acids (XNAs) have been incorporated into replication cycles involving: (1) reverse transcription of XNA into DNA, (2) amplification of DNA *via* polymerase chain reaction, and (3) transcription of DNA into XNA by an engineered polymerase.[3] Although these systems have demonstrated Darwinian evolution in no fewer than five unique XNA polymers,[4] efficient XNA self-replication has not yet been realized. Work is ongoing to develop nonenzymatic XNA-templated XNA polymerization, which may serve as the basis for plausible alternative genetic systems.

Chart 1. Replicable XNA Polymers.



UNNATURAL BACKBONE LINKAGES

Enzyme-catalyzed polymerization has been reported in many backbone-modified nucleic acids, including those linked by phosphonate, phosphorothioate, phosphoroselenoate and boranophosphate groups.[5] Such systems have found promising applications in biotechnology (primarily owing to their

enhanced nuclease resistance) but are not considered likely prebiotic molecules. Szostak and coworkers have shown that nucleic acids linked by (N3',P5') phosphoramidate bonds (3'-NP-DNA) can be prepared through the nonenzymatic polymerization of 3'-amino-2',3'-dideoxyribonucleotides activated at the 5' position with a 2-methyl- or 2-aminoimidazole (2AI) leaving group (Figure 1A).[6] In addition, imidazole-activated ribonucleotides can effect nonenzymatic RNA polymerization through an imidazolium bridged dinucleotide intermediate (Figure 1B).[7] It has been shown that 2AI-bridged dinucleotides can be synthesized under prebiotic conditions which permit nonenzymatic primer extension (Figure 1C),[8] intimating a route towards efficient copying of RNA. Notably, 2AI-activated threonucleotides have been shown to be poor substrates for nonenzymatic RNA polymerization compared to 2AI-activated ribonucleotides, challenging the viability of TNA as a self-replicating system to precede RNA.[9] Further competition experiments may support a model in which self-replicating RNA emerged from a heterogeneous pool of oligonucleotides as a consequence of kinetically favorable nonenzymatic synthesis.

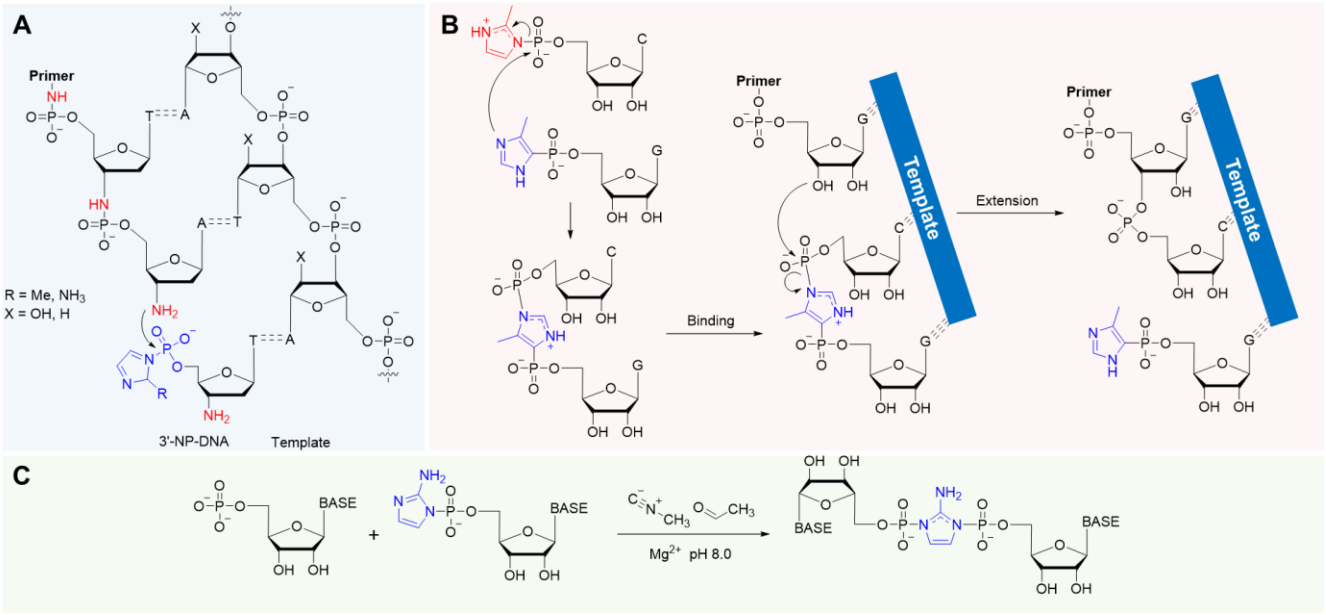


Figure 1. (A) Nonenzymatic polymerization of 3'-NP-DNA. (B) RNA primer extension *via* an imidazolium bridged dinucleotide intermediate. (C) Prebiotic synthesis of 2AI-bridged dinucleotide.

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