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The Nonenzymatic Copying of RNA Templates

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The copying of short RNA templates without enzymes is likely to have been an important aspect of genetic replication in primitive cells, prior to the evolution of RNA replicase ribozymes. As part of our broader studies of the origins of cellular life, we have therefore been pursuing laboratory studies of nonenzymatic RNA replication. We have recently used both thermodynamic and kinetic studies to demonstrate an important catalytic role for activated downstream nucleotides in the addition of an activated monomer to a primer. We subsequently showed that this catalytic effect was due to the formation of a covalent imidazolium-bridged dinucleotide intermediate in primer-extension. Structural studies suggest that this intermediate binds to the template by Watson-Crick base-pairing, and in the bound state is preorganized for reaction with the primer 3'-hydroxyl. Subsequent mechanistic studies then led to the identification of 2-aminoimidazole as a superior nucleotide activating moiety. Remarkably, our investigations into the potentially prebiotic synthesis of 2-aminoimidazole show that it can be synthesized together with the nucleotide precursor 2-aminooxazole. In addition, we have found that replacing the canonical U monomer with the prebiotically accessible sulfur-substituted nucleotide 2-thio-U allows for faster and more accurate template copying. The combination of 2-thio-U with 2-aminoimidazole activated monomers and activated helper trinucleotides enables the rapid and accurate copying of short mixed sequence templates. Taken together, these advances suggest that the nonenzymatic copying of short RNA templates may have been possible on the early Earth.