Glycosylation of Noncanonical Nucleobases in Water: Implications for the Evolution of Early Genetic Polymers

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The prebiotic formation of nucleosides and nucleotides remains a major challenge to the RNA world hypothesis. While model prebiotic syntheses have been reported for the pyrimidine nucleotides[1] and the purine nucleotides[2], yields are low and/or require spatially separated chemical pathways with specific sequential requirements to produce the canonical Watson-Crick base-pairing units. An alternative hypothesis[3] states that RNA is the product of chemical and biological evolution, and that ancestral genetic polymers may have been composed of recognition units similar to the extant set, but with reactivity profiles more amenable to the prebiotic formation of proto-nucleic acid monomers and polymers. For example, the pyrimidines barbituric acid and 2,4,6-triaminopyrimidine (TAP), along with the triazine melamine, react with sugars (including ribose) in water under prebiotically plausible conditions to form glycosides[3a,4]. Furthermore, these glycosides have the propensity to recognize complementary heterocycles in water at the monomer level in a manner analogous to Watson-Crick base pairing; a property not exhibited by the canonical nucleotides[3a,4]. In particular, TAP was found to react with a large variety of pentoses and hexoses to give either *N*- or *C*-substituted glycosides. These results, together with the observation that prebiotically plausible routes to sugars do not produce ribose selectively or in significant yields[5], suggest that prebiotic nucleoside formation would not have been limited to ribose if ancestral RNA (or proto-RNA) utilized TAP or other proto-nucleobases with similar reactivities.

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