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Stability of Unnatural Hachimoji Nucleosides in Natural Hydrothermal Fluids

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The selection of canonical nucleosides in RNA and DNA systems remains a central theme in origin-of-life research, with differences in their thermal and hydrolytic stabilities often cited as a key selection pressure during early nucleic acid evolution [1,2]. To explore this for an unnatural genetic alphabet, we measured the high-PT UV-vis spectra of artificial Hachimoji-type nucleic acid systems to assess their kinetic stability under simulated prebiotic hydrothermal conditions. UV-vis spectra of aqueous Hachimoji-type nucleosides (isoguanosine and isocytidine) and nucleobases (isoguanine and isocytosine) were measured in a custom-built high-PT spectroscopic cell at 90-180°C and 7.5 MPa. The cell interior was electroplated with a 5 µm Au layer to minimize catalytic alloy wall interactions; sapphire windows were sealed with 50 µm Au disks and Au-coated caps. The cell optical path was coupled to a custom-modified Varian Cary 50 spectrophotometer via high-temperature-resistant fibre optics mounted to the sapphire windows of the high-PT cell. Experiments involved loading the preheated cell with degassed Hachimoji nucleoside and nucleobase solutions in 0.1 mol/kg NaH_2PO_4/Na_2HPO_4 buffers (~pH 6.5) followed by stopped-flow acquisition of time-dependent uv-vis spectra at constant PT; time-dependent spectra were obtained at 24-60 nm/min scan rates every 2-5 min and analyzed by global spectral-kinetic fitting, decomposing full wavelength-time datasets into reactant and product contributions using consecutive-reaction models, that were constrained by reference high-PT anchor spectra. As a preliminary benchmark, isoguanosine decomposition at pH 6.5 and 120°C yields a first-order rate constant $k=9.4x10^{-6}$ s^{-1} or a half-life $t_{1/2}$ = 20.5 hr. In contrast, the acid-catalyzed isoguanosine glycosidic cleavage at 120°C at pH=3.0 proceeds ~3000-fold faster with $t_{1/2}$ =24 s [1]. For comparison, the neutral hydrolysis rate constant for canonical guanosine at 120°C is $k=2.5x10^{-6}$ s^{-1} ($t_{1/2}$ =77.1 hr), indicating that isoguanosine exhibits a moderately reduced hydrolytic stability relative to guanosine under neutral hydrothermal conditions. We are currently expanding these experiments to a broad range of temperature and pH conditions and will report a full set of Arrhenius parameters for Hachimoji nucleosides in hydrothermal fluids. [1] Rios *et al* (2015) *J.Phys.Org.Chem.,* **28**, 173-180; [2] Balodis *et al* (2010) *Geochim. Cosmochim. Acta*, **74**, 6374-6386