Highlight Article (Invited)

Understanding how a new Hachimoji nucleobase alters photodynamics of genetic building blocks.

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ABSTRACT

This article is a highlight of the paper by Krul et al. in this issue of *Photochemistry and Photobiology*. It describes the excited state dynamics of 5-aza-7-deazaguanine (^{5N7C}G), which has recently been proposed as an alternative nucleobase. Upon UV absorption to the lowest energy $^1\pi\pi^*$ state, ^{5N7C}G returns to the electronic ground state an order of magnitude more slowly than guanine with a corresponding greater fluorescence quantum yield. These findings are significant because they suggest that ^{5N7C}G is less UV photostable that its canonical nucleobase equivalent, which would have been a selective disadvantage in prebiotic conditions.

COMMENTARY

One way to define life is as a self-replicating system. Replication needs to be faithful but not perfect so the system is be able to evolve. From a chemical perspective then, the origin of life, as we know it, occurred with the formation of the first self-replicating molecules some 4 billion years ago. This could have been RNA or a precursor form, sometimes referred to as proto-RNA (1). It is highly improbable that the chemical inventory of heterocyclic compounds on an early earth – in the so-called primordial soup – would have consisted exclusively of the canonical nucleobases. Many analogs, derivatives, and isomers would have been equally likely (2-4) *(5)*. From among those molecules, several have been proposed as alternative nucleobases that could have been part of “false starts” or of precursor forms of replicating polymers. More profoundly, this variety raises the question: could nature have chosen different sets of building blocks of life? Several alternative genetic alphabets have been proposed and shown to be viable for constructing stable replicating polymers(6-10). A recent such report by Hoshika et al. describes hachimoji DNA and RNA: A genetic system with eight building blocks (hachimoji means “eight letters” in Japanese) (6). As shown in Figure 1, the eight nucleotides form four orthogonal pairs, that meet the structural requirements needed to support Darwinian evolution. Hachimoji DNA was successfully transcribed to give hachimoji RNA in the form of a functioning fluorescent Hachimoji aptamer. These results expand the scope of molecular structures that might support life, including life elsewhere.

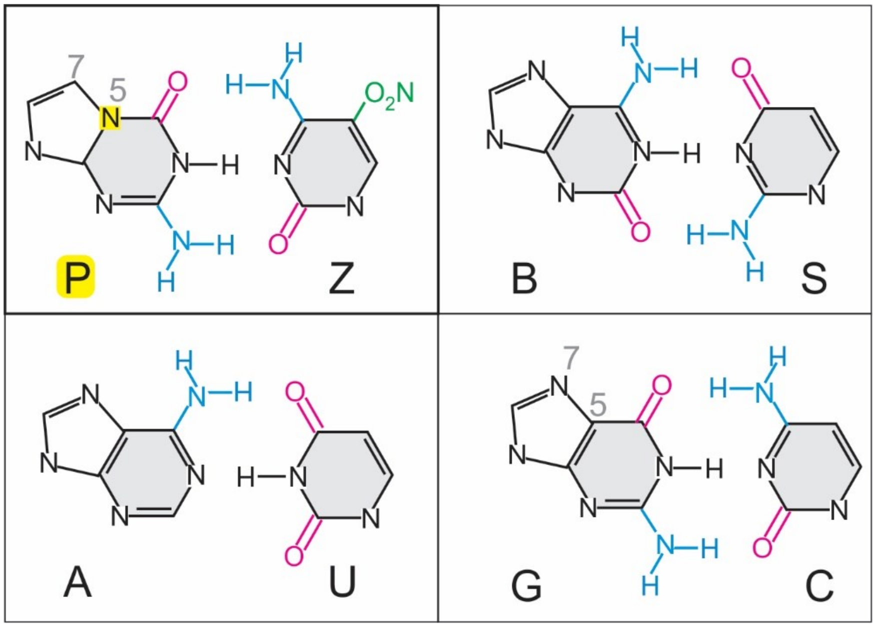

Figure 1: The set of 8 hachimoji bases and the base pairs the form. P is the subject of the study by Crespo-Hernandez at al. in this issue.Compared with G, the nitrogen at N7 is replaced by a carbon atom and the carbon at C5 is replaced by a nitrogen atom.

The fact that biology has selected a very narrow alphabet of RNA and DNA building blocks raises the question why the remaining nucleobase analogs were eliminated as biologically relevant nucleosides during the course of abiogenesis. One possibility that has been raised is that UV radiation played a role in this selection (11) *(12-22)*). For nearly one billion years before the great oxidation event that led to a protective ozone shield, life coped with intense UV surface irradiation (23-26). Models estimate that UV damage rates were three orders of magnitude greater in the Archean oceans of the early Earth than today (27). Following the absorption of a UV photon, many photochemical processes are possible. To be protected from photodamage it is advantageous for a molecule to rapidly return to the electronic ground state, defusing the electronic excitation energy and safely transferring the absorbed energy to the environment (see Figure 2). The canonical bases follow this path in picoseconds or less, leaving the molecule no time for other potentially damaging but slower photochemical processes. By contrast, very closely related derivatives and analogues often lack this property, evidenced by much longer excited state lifetimes (12, 28, 29). Remarkably, the canonical RNA and DNA nucleobase monomers, that now make up life as we know it, have nearly ideal UV resistant properties for organic molecules of their size and complexity in the precise spectral region of intense UV irradiation that characterized the first half of Earth's existence (30). The internal conversion back to the ground state proceeds through conical intersections, which occur at parts of the potential energy surface with nonequilibrium nuclear coordinates (31). In other words, the process involves deformations of the molecular structure, explaining the exquisite dependence of photostability on even small variations between similar molecules (32, 33).

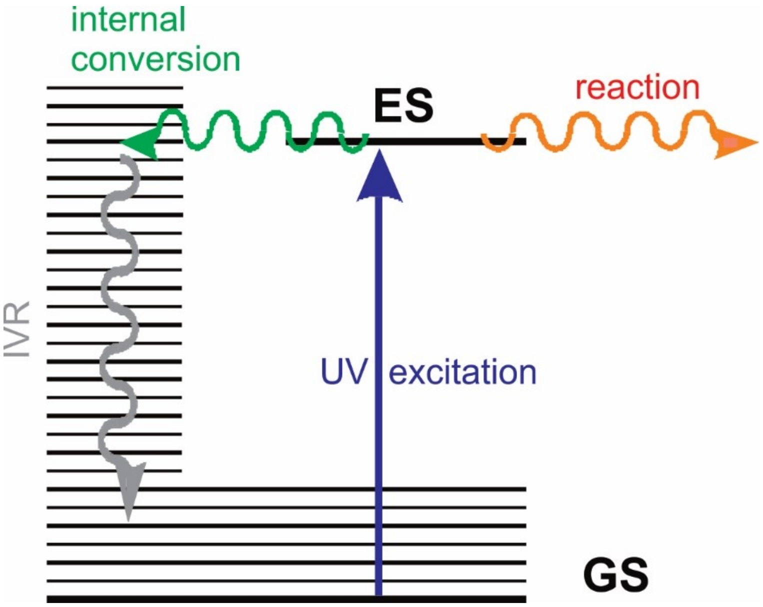

Fig.2 Following absorption from the ground state (GS) to the excited state (ES), reactive pathways (red arrow) compete with safe internal conversion (green arrow) followed by internal vibrational relaxation (IVR, gray arrow).

This issue's paper by Krul et al. examines the excited state dynamics of one of the hajimochi bases, labeled P. With femtosecond transient absorption spectroscopy in different solvents the authors find excited state lifetimes that are 10-30 times longer than those in the closest canonical analog, guanine, and fluorescence quantum yields that are an order of magnitude larger. Supported by high level quantum computational modeling, the authors propose that absorption to S2 is followed by rapid internal conversion through a conical intersection to S1 to reach a local minimum in the S1 state with an extended lifetime. From this relatively long-lived state the molecule will eventually fluoresce or internally convert to S0. The hajimochi P base is characterized by the nitrogen position, N5 and a carbon at C7, compared to guanine with a nitrogen in position N7 and a carbon at C5. This leads to a unique shape for the structure at the conical intersection between the two excited states.

CONCLUSION

The findings of Krul et al. shed new light on the excited state dynamics of heterocyclic compounds. Most importantly, these findings are the first determination of the relative photostability of one of the new hajimochi bases, providing critical data for prebiotic scenarios.

Acknowledgement

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