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LETTER TO THE EDITOR

A New Perspective on the Maillard Reaction and the Origin of Life

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Abstract

The Maillard reaction, a spontaneous 'one pot' reaction between amino acids and reducing sugars that occurs at low reactant concentrations and low temperatures, is a good candidate for having played a role in the origin of life on the Earth. In view of the probability that RNA and DNA were preceded by an evolutionary forerunner with a more straightforward prebiotic synthesis, it is a testament to the prescience of Oró and colleagues that, in 1975, they drew attention to the Maillard reaction, in particular evidence that melanoidin polymers (the end-product of the reaction) contain '…heterocyclic nitrogen compounds similar to the nitrogenous bases' (Nissenbaum in J Mol Evol 6:253–270, 1975). Indeed, reports of the Maillard reaction product, 2-Acetyl-6-(Hydroxymethyl)-5,6-Dihydro-4H-Pyridinone (AHDP), with a structure reminiscent of the pyrimidine nucleobase uracil, suggest the Maillard reaction might have played a key role in the synthesis of components of a proto-RNA polymer, with AHDP and two structurally related products predicted to be similar to uracil in the latter's ability to form non-standard base pair interactions. It is possible that the primary function of these interactions was to allow molecules such as AHDP to separate out of the prebiotic chemical clutter. If this were the case, catalysis, and coding—made possible by the polymerization of proto-nucleoside monomers into linear sequence strings—would have been evolving properties.

Keywords Origin of life · Maillard reaction · Pyridinone · Pyridone · Uracil · Uridine · RNA

The Maillard reaction, which occurs between amino acids and reducing sugars, comprises a 'complex network of chemical reaction[s]', with the reaction between glycine and ribose alone producing more than 300 products, the majority of which have not been structurally characterised (Hemmler et al. 2017). Oró and colleagues suggested a prebiotic role for this reaction(s), proposing that melanoidin polymers (the end-product of the Maillard reaction) exhibited coenzyme-like activity, due to their ability to concentrate redox-active metal ions, and their containing stable free radicals and '…heterocyclic nitrogen compounds similar to the nitrogenous bases' (Nissenbaum et al. 1975). Further, they suggested that melanoidin polymers might contain nucleoside- and nucleotide-like structures. While the authors acknowledged this was extremely speculative, their idea may prove remarkably prescient. Here, we draw attention to a small heterocyclic molecule discovered in a model Maillard reaction between glycine and xylose (Ames et al. 1999), which has a similar structure to the RNA pyrimidine nucleobase uracil. It is proposed to have been a proto-nucleobase within an evolutionary forerunner to RNA and DNA.

The Maillard reaction appears plausibly prebiotic, being a spontaneous 'one-pot' reaction which occurs at temperatures as low as – 20 °C and even at very low reactant concentrations (Nissenbaum et al. 1975; and references therein). The reactants have likely prebiotic syntheses: amino acids through Miller-Urey atmospheric synthesis (Cleaves et al. 2008) and reducing sugars through a permutation of the formose reaction (Yadav et al. 2020) or possibly synthesis from glyoxylate (Sagi et al 2012). Eschenmoser has done extensive research into the base pairing abilities of alternative

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The authors dedicate this paper to the late Emeritus Professor George Petersen, the father of DNA in New Zealand, who not only inspired their careers, but influenced many other biochemistry and molecular biology students.

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RNAs with backbones containing sugars other than ribose (Eschenmoser 2011). Kruse et al (2020) and Yadav et al (2020) have recently extensively reviewed potential prebiotic syntheses of nucleosides/nucleotides. Impressive recent successes have been reported in the chemical synthesis of RNA and DNA from a variety of small molecule precursors (Powner et al. 2009; Islam and Powner 2017; Stairs et al. 2017; Kim et al. 2021; Kim and Benner 2017; Patel et al. 2015; Sutherland 2015; Xu et al. 2017, 2020; Becker et al. 2016, 2019; Okamura et al. 2019; Teichert et al. 2019). While in the laboratory they often have required stepwise addition of reagents these still have potential for taking place in the prebiotic environment.

The difficulty of finding a plausible prebiotic synthesis of RNA and DNA has given weight to the idea that they were preceded in early evolution by an alternative polymer with a more straightforward synthesis, with a recent review concluding that 'many noncanonical nucleotides and related glycosides are formed more easily than the canonical nucleotides' (Fialho et al. 2020). We have previously proposed that the purine nucleobases were preceded by simpler versions of these molecules (similar to the intermediates of the contemporary de novo purine biosynthetic pathway), which were able to form progressively stronger and more stable base-pairing interactions (Bernhardt and Sandwick 2014). This hypothesis did not, however, address the origin of the pyrimidines, or pyrimidine-like nucleobases. In this letter we propose that the pyrimidine nucleobase uracil might have been preceded in early evolution by a molecule(s) produced in prebiotic Maillard reaction(s), amidst a potpourri of other small molecules in what is termed the prebiotic chemical 'clutter' (Krishnamurthy 2017).

Reported by Ames and colleagues, 2-Acetyl-6-(Hydroxymethyl)-5,6-Dihydro-4H-Pyridinone (AHDP) (Fig. 1A) is a yellow solid produced in small quantities from the Maillard reaction of xylose and glycine after 2 h at 100 °C and pH 5 (Ames et al. 1999). Two other compounds with closely related structures to AHDP—most likely azepinones with seven-membered rings—were isolated from the reaction of glycine and glucose under the same conditions. In a later paper, the same authors report that AHDP is also produced from the Maillard reaction between xylose and lysine (Bailey et al. 2000). While the mechanism of formation of AHDP-like compounds is unclear (Ames et al. 1999), the evidence that it proceeds from the reaction of different amino acids with a variety of sugars, supports the generality of this reaction-type. However, whether AHDP-like compounds are produced from prebiotically reasonable mixtures of amino acids and sugars (including formose reaction mixtures), remains to be shown. In addition, as noted by Ames et al. (1999), AHDP and the two related heterocycles 'possess several reactive groups and may be expected to participate in further reactions in Maillard systems'. While some of these reactions might abolish their ability to function as proto-nucleobases, glycosylation with unreacted sugar(s), to produce AHDP (and related) nucleosides also appears possible. An alternative AHDP nucleoside formation is demonstrated by the interesting recent synthesis of the DNA nucleosides in Teichert et al (2019). The assembly of 2-deoxyribose here on a nucleobase scaffold suggests the potential for components of the formose reaction to participate in such reactions. Phosphate is strongly enhancing in the Maillard reaction either free in solution or when covalently attached to the sugar (Sandwick et al. 2005), and the potential role of phosphate in AHDP formation also needs investigation.

Figure 1 compares the structure of (A) AHDP and (B) uracil. The two most important similarities are: (i) AHDP, like uracil, contains an unsubstituted ring nitrogen (N1-H), potentially enabling glycosylation and formation of an

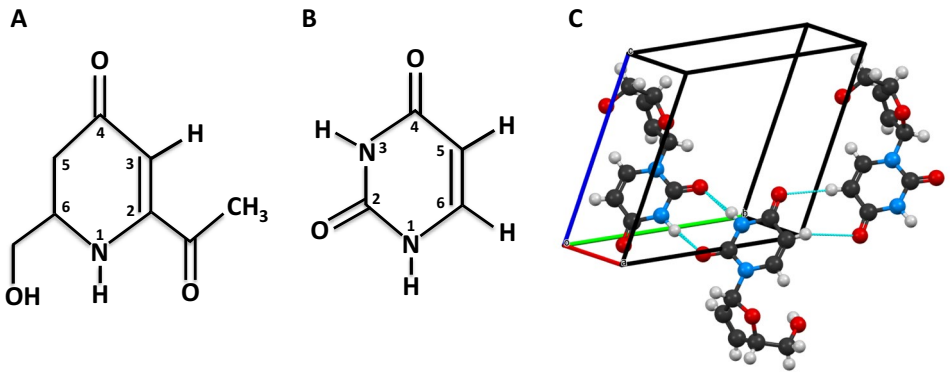

Fig. 1 Structural comparison of **A** AHDP and **B** uracil. **C** CH—X H-bonding interactions (right-hand side of image) in the asymmetric unit plus neighbouring unit cell of the 2',3'-didehydro-2',3'-dideoxyuridine crystal structure (Van Roey et al. 1993). Here X=O. The geometry of the two CH–O bonds is: 1. D…A length 3.46 Å, D–H…A angle 162°. 2. D…A length 3.58 Å, D–H…A angle 134° (D=H-bond donor; A=H-bond acceptor). Figure created with Microsoft PowerPoint and Mercury 2020.3.0 (Build 298224) (Macrae et al. 2020)

AHDP nucleoside. (ii) The O4 and C3-H face of AHDP is identical to the O4 and C5-H face of uracil, and therefore AHDP should in theory be able to form base-pair interactions similar to those formed by the Hoogsteen edge of uridine. Importantly, the O4 and C3-H groups of AHDP are planar, due to the conjugated pi-bonding system (and delocalized pi electrons) that extends from the O4 keto group to the acetyl carbonyl group, and also includes the ring nitrogen N1. The two closely related compounds discovered by Ames et al. (1999) also possess these same features and should be capable of forming similar base pairing-type interactions.

The standard A–U base pair between adenosine and uridine utililizes uridine's Watson–Crick edge (N3-H and O4). However, uridine is also able to utilize the opposite (Hoogsteen) edge (O4 and C5-H) to form nonstandard base-pair interactions with adenosine, cytidine, guanosine and uridine, for example the U–U 'Calcutta' base pair (Wahl et al. 1996; Wahl and Sundaralingam 1997). Uridine Hoogsteen interactions also occur as part of RNA base triples, which play a critical role in the tertiary structure and function of tRNA and rRNA (Almakarem et al. 2012; Leontis et al. 2002). Similarly, several uridine derivatives form base pair-type interactions in their crystal structures utilizing this same edge. As shown in Fig. 1C, 2',3'-didehydro-2',3'-dideoxyuridine forms a creased ribbon conformation in the crystal structure, in which reciprocal O4/C5-H H-bond interactions alternate with reciprocal N3-H/O4 H-bond interactions (Van Roey et al. 1993; Cabaj and Dominiak 2020).

Base pairing involving uridine's Hoogsteen edge includes a CH—X H-bond, in which carbon is the H-bond donor (Brandl et al. 1999; Taylor and Kennard 1982). C–H H-bonds are typically somewhat weaker than those involving N and O atoms exclusively (Desiraju 1991, 1996). However, as described above, it is likely strong enough to have enabled the first base pairing-type interactions. It is possible that the primary function of these interactions was in allowing molecules such as AHDP to separate out of the prebiotic chemical clutter. If this were the case, catalysis, and coding—made possible by the polymerization of proto-nucleoside monomers into linear sequence strings—would have been evolving properties.

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Declarations

Conflict of interest The authors declare they have no conflicts of interest.

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