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Direct Prebiotic Pathway to DNA Nucleosides

Jennifer S. Teichert,[a,b] Florian M. Kruse,[a] Oliver Trapp*[a,b]

Abstract: *It is assumed that RNA played a key role in the origin of life. The hypothesis of the RNA world is that the transition to more complex but more stable DNA for continuous information storage and replication requires the development of a ribonucleotide reductase to obtain the deoxyribonucleotides from ribonucleotides. This step, as well as an alternative path from abiotic molecules to DNA-based life, is completely unknown. Here we show that deoxyribonucleosides are formed under relevant prebiotic conditions in water in high regio- and stereoselectivity from all canonical purine and pyrimidine bases by condensation with acetaldehyde and sugar-forming precursors, e.g. formaldehyde, glycolaldehyde and glyceraldehyde. We can explain the origin and selection of deoxyribose versus other deoxysugars during nucleoside formation. Thus, we have found a continuous path to DNA nucleosides, starting from simple, prebiotically available molecules. Furthermore, we identified the deoxyapionucleosides (DApiNA) as a further potential DNA progenitor. Our results allow to conclude that the DNA world evolved much earlier than previously assumed.*

The question of how to create finely balanced living biological systems from a pool of small prebiotic molecules is undoubtedly one of the most fascinating scientific challenges within living memory. It is assumed that complex organic molecules, such as nucleobases **1**, amino acids and sugars, evolved from prebiotic feedstock molecules.[1,2] Today, these molecules can still be detected on extraterrestrial material[3] and they were part of the early Earth.[4,5] The RNA world[6-8] hypothesis postulates that ribonucleosides **2** were initially formed from these molecular building blocks,[9] which are later aggregated to the information-storing RNA polymer. This path, accepted by large parts of the scientific community, combines catalytic function, inherent properties of replication, mutation and selection and is thus able to herald a chemical evolution.[10-14]

Influenced by Emil Fischer's historical approach to nucleosides via glycosidation of nucleobases,[15] accessing RNA nucleosides **2** and nucleotides seems to be easier than the access to the DNA nucleosides **3**, since the former consist of the sugar component D-ribose **4** and the respective nucleobase **1** (Orgel pathway) (Figure 1a).[16-,171819,2021 22] For the purine nucleosides, a modified pathway has recently been proposed by Carell [23,24], based on formamidopyrimidines **5** (FaPys) as purine precursors, which are easier to condense with aldoses (Figure 1a).

While the nucleobases **1** are easily accessible as stable building blocks under prebiotic conditions,[25-29] there is no such simple pathway to D-ribose **4** [30,31] for the formation of ribonucleosides **2**.

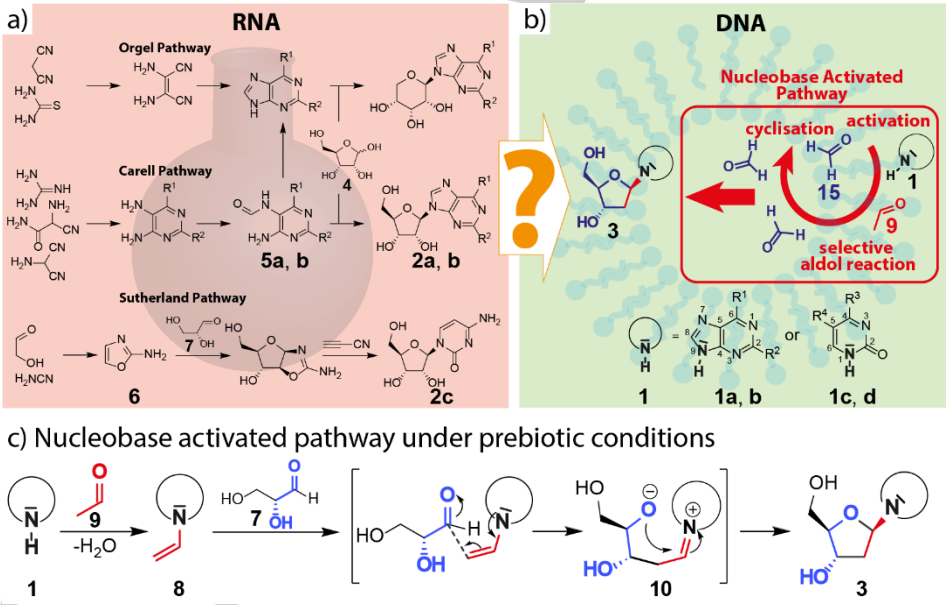

Figure 1. Prebiotic pathways to RNA nucleosides **2** and the so far unknown transition to the DNA nucleosides **3** in comparison to the direct access of DNA nucleosides **3**. a) Orgel and Carell pathways utilizing purines or formamidopyrimidines (FaPys) **5a, b** in a reaction with D-ribose **4**, respectively. The Sutherland pathway via 2-aminooxazole **6** as connecting building block between sugar and pyrimidine base. b) The prebiotic pathway to DNA nucleosides **3** via nucleobase activation of acetaldehyde **9** in combination with sugar forming aldol reactions. c) Stereoselectively controlled mechanism leading to deoxyribonucleosides (dA **3a**, dG **3b**, dC **3c,** dT **3d**) via vinyl nucleobases **8** and reaction with D-glyceraldehyde **7**. a: $R^1 = NH_2$, $R^2 = H$; b: $R^1 = OH$, $R^2 = NH_2$, c: $R^3 = NH_2$, $R^4 = H$; d: $R^3 = OH$, $R^4 = CH_3$.

D-Ribose **4** is subject to rapid decomposition in aqueous solution,[32] however even more crucial, the selectivity of the formose reaction[33] is negligibly low with respect to D-ribose **4**. Sutherland has elegantly solved this challenge for the preparation of pyrimidine ribonucleosides by introducing 2-aminooxazole **6** as the connecting building block between sugar and pyrimidine base.[34] The ribose unit is built up by reaction with D-glyceraldehyde **7**.

The prebiotic access to the DNA building blocks, the deoxyribonucleosides **3**, seems to be even more difficult, since the Fischer-Orgel-Carell strategy would require D-deoxyribose,

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which is not readily accessible under prebiotic conditions.[35] Furthermore, there is no uniform pathway for both purine and pyrimidine nucleosides. The RNA world hypothesis therefore postulates the evolutionary development of a ribonucleotide reductase[36] to create a significantly more stable DNA capable of storing information over a prolonged period of time.[37] A chemical prebiotic pathway via photoreduction has been recently elaborated by Krishnamurthy and Sutherland *et al.*.[38] The possibility that the deoxyribonucleosides **3** could have developed directly from their easily accessible nucleobases and simple prebiotically present aldehydes has not yet been considered. Based on this idea, we performed a retrosynthetic analysis of prebiotic reaction networks and investigated possible reaction pathways activated by in aqueous solution (Figure 1b).

The nucleophilic character of the nucleobases **1** at nitrogen atom *N*-9 in purine **1a** (p*K*a 9.80), **b** (p*K*a 9.21) and *N*-1 in pyrimidine bases **1c** (p*K*a 12.2) , **d** (p*K*a 9.94) (Figure 1b), compared to the primary amino groups, has been neglected so far and has been only recently quantitatively characterized by Mayr *et al.*.[39] In analogy to aminocatalysis,[40,41] the corresponding enamines, the *N*-9-vinylpurine bases **8a**, **b** and *N*-1-vinylpyrimidine bases **8c**, **d**, are obtained with the prebiotically available acetaldehyde[42] **9** (4.0 mmol) and nucleobases **1** (0.1 mmol) in water (1 mL). This reaction mixture is sealed in a glass ampoule, stirred at 50°C for four days and analyzed after opening the ampoule. We verified the formation of the *N*-9-vinylpurine bases **8a**, **b** and *N*-1-vinylpyrimidine bases **8c**, **d**, by HPLC-UV-detection, UHPLC – QTOF MS, coinjection with reference samples (Supplementary Information), and high resolution Orbitrap MS (Figure 2a and b, Supplementary Table S1).It is important to note that the reaction mixture has to be sealed to avoid evaporation of the volatile acetaldehyde. Furthermore the heated ampoule simulates the elevated atmospheric pressure on the early Earth.[43]

The obtained vinyl nucleobases **8a-d** (0.1 mmol) react stereoselectively with D-glyceraldehyde **7** (0.15 mmol) or even with formaldehyde **15** (37 wt. % in water, 4 mL) to the deoxyribonucleosides dA **3a** (0.68%), dG **3b** (0.45%), dC **3c** (2.49%) and dT **3d** (0.33%) (Figure 1b and c, Supplementary Table S2). The reaction mixtures were stirred and heated in a sealed glass ampoule at 50°C for 4 days. We verified the formation of the deoxyribonucleotides **3** by HPLC-UV-detection, UHPLC – QTOF MS, coinjection with reference samples, and high resolution Orbitrap MS (Figure 2c-e).

The nucleophilic attack of the vinyl nucleobase **8** on the carbonyl group of the D-glyceraldehyde **7** is stereoelectronically controlled in an unambiguous manner[44] (Figure 1c). The formed open chained deoxyribose system **10** undergoes kinetically favored *5-exo-trig* cyclization[45] to the furanose form under formation of the β-deoxyribonucleoside **3** in defined stereochemistry (Supplementary Figures S14-S16). In contrast to this, if the reaction takes place at the primary amine group, an easily cleavable iminium ion is formed and therefore it can be considered as a natural protecting group.

The here described deoxyribonucleoside forming reaction proceeds selective and under strictly prebiotic and mild conditions in water between 40 and 70°C with the optimum at 50°C.

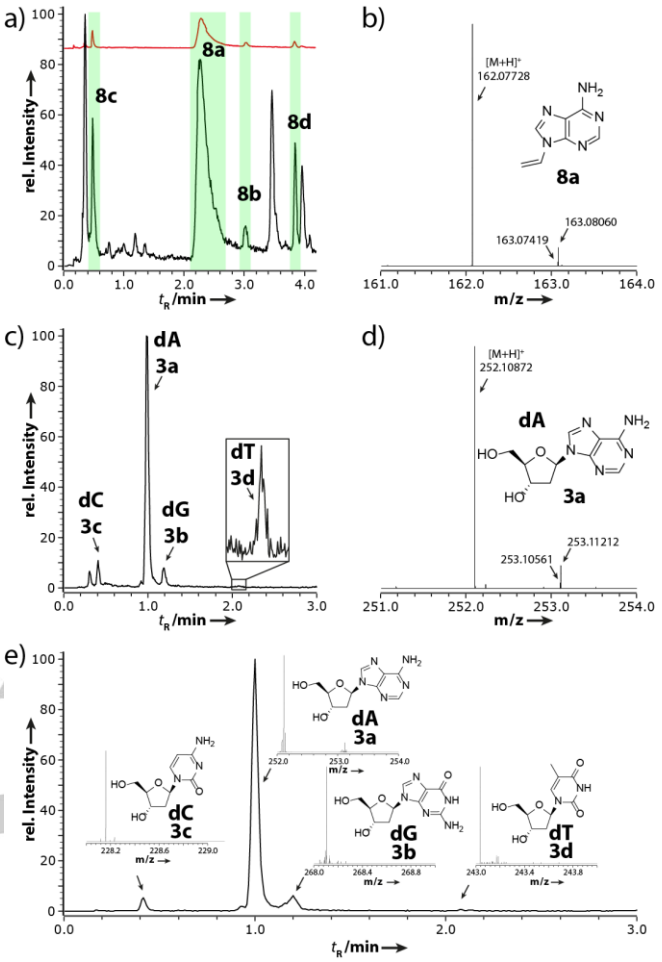

Figure 2. Formation of deoxyribonucleosides **3.** a) Depiction of the vinyl nucleobases **8** obtained by one-pot reaction of all four nucleobases **1** and acetaldehyde **9** in water analyzed by UHPLC-QTOF MS (mass-filter *m/z* 138.064–138.068, 153.063–153.067, 162.075–162.079, 178.070–178.074, black curve) and coinjection of reference compounds (red curve). b) High-resolution Orbitrap mass spectrum of vinyl adenine **8a** (0.1 mmol adenine **1a**, 1 mmol acetaldehyde **9** in 1 mL H_2O for 4 days at 50°C). c) Depiction of the deoxyribonucleosides **3** formed by one-pot reaction of all four nucleobases **1**, acetaldehyde **9** and D-glyceraldehyde **7** in H_2O analyzed by UHPLC-QTOF MS (mass-filter *m/z* 228.095–228.099, 243.095–243.099, 252.107–252.110, 268.102–268.106). d) High-resolution Orbitrap mass spectrum of deoxyriboadenosine **3a** (0.1 mmol adenine **1a**, 1 mmol acetaldehyde **9**, 0.15 mmol D-glyceraldehyde **7** in 1 mL H_2O for 4 days at 50°C). e) Depiction of the deoxyribonucleosides **3** formed by one-pot reaction of all four vinyl nucleobases **8** and formaldehyde **15** in H_2O (0.1 mmol vinyl nucleobase **8** each, 1 mL formaldehyde solution (37 wt. % in H_2O) for 4 days at 50°C) analyzed by UHPLC-QTOF MS (mass-filter *m/z* 228.095–228.099, 243.095–243.099, 252.107–252.110, 268.102–268.106). See Supplementary Information for experimental details of the syntheses and analyses.

Additives, *i.e.* sodium acetate, disodium hydrogen phosphate, are not required, but they enhance the rate of formation (Supplementary Table S7). This reaction is very robust and proceeds in a broad neutral to alkaline pH range. Furthermore, prebiotically difficult explainable modulations of the pH are not necessary.

The excellent selectivity and the slow but continuous formation of deoxyribonucleosides **3** in this way is of great advantage. Usually

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desired rapid reactions with high yields lead from one equilibrium to another, and thus do not favor self-developing reaction networks, which are essential for the formation and maintenance of Life.

The synthesis of single deoxyribonucleosides **3** succeeds not only in a one-pot reaction with the respective nucleobase **1**, but also out of the mixture **1a**-**d**. This underlines the plausibility of the reaction that we have found.

The question arose, which deoxynucleosides are obtained when other sugar precursors and formaldehyde **15** are used in the reaction with the vinyl nucleobases **8**. Therefore, we investigated the reaction of the nucleobases **1** with acetaldehyde **9**, C2 precursor glycolaldehyde **13** and formaldehyde **15**, which yielded deoxythreonucleoside **16** (Figure 3 – red pathway, Supplementary Table S3).

This deoxynucleoside is complementary to Eschenmoser's threonucleosides (TNA) as RNA progenitor.[46] Because the corresponding dTNA nucleoside **16** is unable to polymerize to a polynucleic acid due to the lack of a second hydroxy group, it has to be assumed that this is an evolutionary dead end.

Interestingly, 2*C*-hydroxymethylerythronucleoside **17** (HMENA) can be observed (Figure 3 – red pathway, Supplementary Table S4). This path has to be regarded as an evolutionary dead end as well, due to the formation of eight possible stereoisomers.

A side reaction of vinyl nucleobases **8** and formaldehyde **15** gives two nucleosides derived from 2-hydroxymethyl-1,3-propanediol **19** and pentaerythrol (PentaNA) **20** (Figure 3 – orange pathway, Supplementary Table S5), respectively. The Cannizzaro reaction [47], *i.e.* the reduction by hydride migration from formaldehyde, is the key step in both reactions. Potentially both compounds could form a polynucleic acid, but such a structure would be difficult to replicate due to branching and ambiguous sequencing. In addition, by polymerization the central carbon atom of the sugar type moiety becomes stereogenic leading to enantiomers and diastereomers in the polymer.

In the absence of the Cannizzaro reaction[47] and saturation of the intermediate **18** to the compounds **19**[48] and **20**, the cleavage of the sugar type moiety is favored due to the impossibility of cyclization and the nucleobase **1** is available again as organocatalyst to activate acetaldehyde **9**. It is known that sugars can decompose to formaldehyde **15** by irradiation with UV light,[49] yielding acetaldehyde **9**, and thus both building blocks are available for reaction with nucleobases **1**. Thus, the statistical formation of the reaction products eventually leads to the DNA nucleosides **3**.

The C3-ketose dihydroxyacetone **11** which is isomeric to glyceraldehyde **7** reacts with the vinyl nucleobases **8** to deoxyapionucleosides **12** (Figure 3 – light green pathway, Supplementary Table S6). The unambiguous assignment was made by high resolution Orbitrap mass spectrometry and UHPLC-QTOF-MS. For deoxyapionucleosides **12** two peaks are observed in the HPLC chromatograms due to the formation of the α- and β-deoxyapionucleoside, which results in the formation of diastereoisomers. Remarkably, the carbohydrate apiose occurs in pectins in the cell wall of plants and plays an important role in the glycosylation of secondary metabolites.[50, 51] It is noteworthy that these DApiNA nucleosides **12** are also capable to polymerize to a polynucleic acid and can therefore be regarded as a previously undiscovered DNA progenitor.

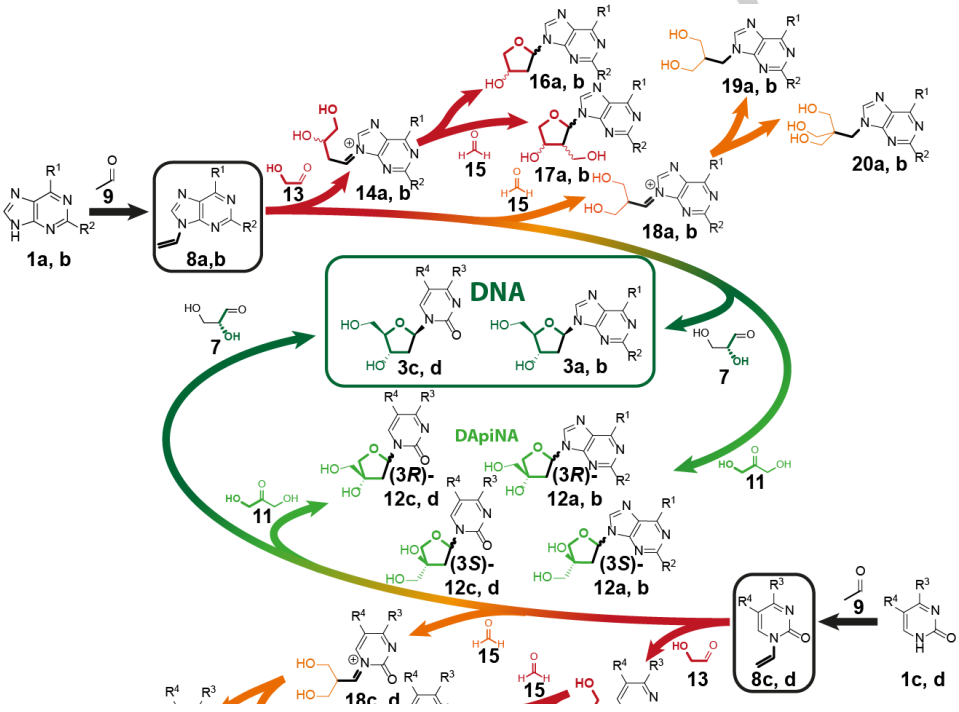

Figure 3. Experimentally verified selective pathways to all deoxysugar nucleosides formed by the nucleobase activated pathway. The initial step is the vinyl nucleobase **8** formation starting from the nucleobase **1** and acetaldehyde **9** (black pathway). Reaction with glycolaldehyde **13** and formaldehyde **15** leads to deoxythreonucleosides **16** (dTNA) and 2*C*-hydroxymethylerythronucleoside **17** (HMENA), which are unable to polymerize in a defined structure (red pathway). In a side reaction under Cannizzaro conditions with formaldehyde **15** two deoxynucleosides are formed derived from 2-hydroxymethyl-1,3-propanediol **19** and pentaerythrol (PentaNA) **20** (orange pathway). Reaction of the vinyl nucleosides **8** with dihydroxyacetone **11** results in the DNA progenitor deoxyapionucleosides **12** (DApiNA nucleosides, light green pathway), and with D-glyceraldehyde **7** the deoxyribonucleosides **3** are obtained (dark green pathway), respectively. **a**: $R^1 = NH_2$, $R^2 = H$; **b**: $R^1 = OH$, $R^2 = NH_2$, **c**: $R^3 = NH_2$, $R^4 = H$; **d**: $R^3 = OH$, $R^4 = CH_3$.

While the D-configured DNA nucleosides **3** result in a defined manner from D-glyceraldehyde **7** (see Figure 1c), two additional configurational isomers of DApiNA

nucleosides **12** are possible, summing up to a total of four epimers.

These results not only prove the highly selective formation of β-deoxynucleosides by activation of acetaldehyde and an *in-situ* sugar-forming cascade (Figure 3), but also in particular the stereochemical course, which has led to the preferred formation of deoxyribose over other deoxysugars. The molecular evolutionary selection principle is clearly the minimization of possible stereoisomers. This corresponds to a minimization of entropy and, by definition, to a shift from equilibrium, which can be understood as a criterion for Life on a molecular basis.

The RNA world hypothesis is the central consensus in the origins of life research, although many questions arising from this hypothesis have not yet been answered. Among these are the transition from RNA to DNA and the pre-eminence of D-ribose in all coding polymers of life. Our results finally provide a rational and provable mechanism for the formation of DNA nucleosides **3**. In a nucleobase activated aldol reaction, a transition from all canonical nucleobases **1a-d**, via the vinyl nucleobase intermediates **8a-d**, to deoxyribonucleosides **3a-d** occurs. The reaction proceeds under constant, ambient conditions, in water, basic mineral additives enhance the reaction. When using glycolaldehyde **13**, formaldehyde **15** or dihydroxyacetone **11**, instead of glyceraldehyde **7**, deoxynucleoside derivatives were also detected. However, these potential DNA nucleoside progenitors are ruled out because of their inability to polymerize or their stereochemical variability. With the DApiNA nucleosides **12**, a potential DNA nucleoside progenitor was found. Likewise, this DApiNA nucleoside **12** could not persist. This proves the ingenuity of Nature to minimize the number of possible stereoisomers (Supplementary Table S8). This work explains why D-deoxyribose is favored over all other sugars and thus opens a non-enzymatic pathway towards DNA nucleosides **3**. We therefore conclude that the DNA world did evolve much earlier than previously proposed.

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Keywords: DNA progenitor • deoxyribonucleoside • deoxyapinonucleoside • origin of Life • prebiotic chemistry

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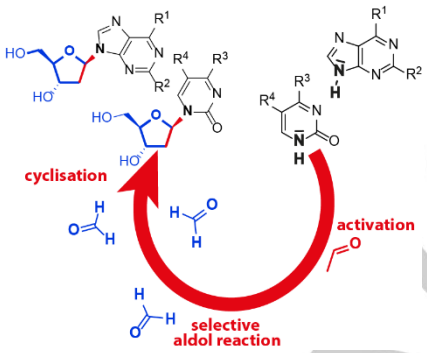

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