


 Cite this: *RSC Adv.*, 2021, 11, 19258

Meteorite-catalyzed intermolecular *trans*-glycosylation produces nucleosides under proton beam irradiation†

 Bruno Mattia Bizzarri,^{†a} Angelica Fanelli,^a Michail Kapralov,^{bc} Eugene Krasavin^{bc} and Raffaele Saladino^{†a}

Di-glycosylated adenines act as glycosyl donors in the intermolecular *trans*-glycosylation of pyrimidine nucleobases under proton beam irradiation conditions. Formamide and chondrite meteorite NWA 1465 increased the yield and the selectivity of the reaction. The glycosyl transfer process was highly regioselective in yielding canonical *N*¹-pyrimidine nucleosides, the natural β -anomers prevailing in the presence of formamide and NWA 1465. These data highlight the possible role of intermolecular *trans*-glycosylation in the prebiotic formation of purine and pyrimidine nucleosides, avoiding the occurrence of independent synthetic pathways.

Received 25th March 2021

Accepted 14th May 2021

DOI: 10.1039/d1ra02379a

rsc.li/rsc-advances

Introduction

The formation of the glycosyl bond between a sugar and nucleobase is a critical process in the prebiotic origin of nucleosides,¹ since both reagents are thermodynamically stable compounds and no further stabilization occurs upon the linkage, especially in the case of aqueous medium.² In addition, nucleosides lack of the $n-\sigma^*$ hyper-conjugation effect present in the free sugar.³ Multi-steps prebiotic syntheses of nucleosides have been reported,⁴ encompassing the construction of the sugar on the nucleobase, as in the case of the formamido-pyrimidine chemistry^{5–9} or, in alternative, the building of the nucleobase on pre-formed amino-sugar (oxazoline chemistry).^{10–12} These syntheses yield nucleosides in high regio- and stereoselectivity but suffer from the disadvantages of a large number of reaction steps involving protection and de-protection procedures. As an alternative, the one-step synthesis of nucleosides involves the direct formation of the glycosyl bond between the nucleobase and the sugar from pre-formed substrates,^{13,14} and generated *in situ* reagents. Example of this latter procedure is the synthesis of three ribonucleosides (adenosine, uridine and cytidine) and one 2'-deoxy ribonucleoside (thymidine) by proton beam irradiation of formamide and meteorites, mimicking the solar wind conditions.¹⁵ The efficacy

of formamide in the synthesis of biomolecules is evident in a large panel of physical–chemical conditions fueled by mineral catalysis and different energy sources, as reviewed.^{16–21} In addition, formamide is the optimal solvent for the thiolysis step in the oxazoline chemistry,¹² as well as the effective formylating agent in the formamido-pyrimidine procedure.²² The formation of the glycosyl bond under proton beam irradiation occurred by a radical mechanism,²³ the observed β -stereoselectivity being due to the interaction of the sugar with the surface of the mineral.¹² In this latter case, di-glycosylated adenines **1** were detected as a mixture of the corresponding pyranose (**p**) and furanose (**f**) isomers, having β - and α -configuration at the anomeric position, namely *N*⁶-(2-deoxy-D-ribofuranosyl)-2'-deoxyadenosine (**1f α / β**), and *N*⁶-(2-deoxy-D-ribofuranosyl)-2'-deoxyadenosine (**1f α / β**) (Fig. 1).^{13,24,25} The phosphorylation of adenosine to corresponding nucleotides, including reactive cyclic adenosine monophosphates,²⁶ was also reported in

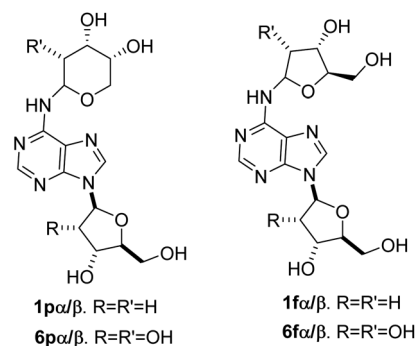


Fig. 1 *N*⁶-(2-Deoxy-D-ribofuranosyl)-2'-deoxyadenosine **1p α / β** , *N*⁶-(2-deoxy-D-ribofuranosyl)-2'-deoxyadenosine **1f α / β** , *N*⁶-(D-ribofuranosyl)-2'-deoxyadenosine **6p α / β** , *N*⁶-(D-ribofuranosyl)-2'-deoxyadenosine **6f α / β** .

^aEcological and Biological Sciences Department (DEB), University of Tuscia, Via S. Camillo de Lellis snc, 01100, Viterbo, Italy. E-mail: bm.bizzarri@unitus.it

^bJoint Institute for Nuclear Research, JINR's Laboratory of Radiation Biology, Dubna, Russia

^cDubna State University, Ulitsa Universitetskaya, 19, Dubna, Moscow Oblast, 141982, Russia

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra02379a



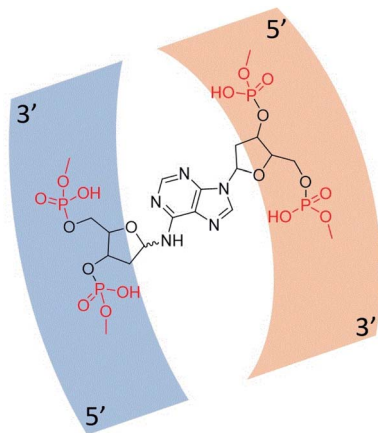


Fig. 2 Structural motif in damaged DNA sites. N^6 -(2'-deoxy-D-ribofuranosyl)-2'-deoxyadenosine (black) was selected as a representative case of the four possible isomeric forms of the sugar bonded at the N^6 -exocyclic position of the adenosine residue.²⁹ The sugar-phosphate backbone is reported in a red code.

similar conditions.²⁷ Remarkably, di-glycosylated adenines have been identified as a “remnant” structural motif in damaged DNA sites (e.g. abasic sites), where the 2'-deoxyadenosine residue of one helix links the opposite site of the double helix (Fig. 2).²⁸

The DNA cross-links are stable at neutral pH and room temperature, but they decompose at relatively high temperature (half-life, 65 days at 37 °C) to yield 2'-deoxyadenosine with release of the N^6 -glycosyl moiety.²⁹ This implies that di-glycosylated adenines are potential reagents for intermolecular *trans*-glycosylation processes,^{30–33} during which the starting nucleoside can perform as the donor of the glycosyl residue when the appropriate nucleobase is provided.³⁴ This process is a valuable entry for the synthesis of a large panel of nucleosides, favoring the easy conversion of purine nucleosides into the pyrimidine counterpart (and *vice versa*).³⁵

Trans-glycosylation is also relevant in the prebiotic scenario, avoiding independent synthetic for the formation of purine and pyrimidine nucleosides.³⁶ Chemically-driven *trans*-glycosylation occurs at elevated temperature, or in the presence of heavy metals, usually starting from protected substrates in multi-step conditions.³⁷ Herein, we report the one-pot glycosylation of un-protected pyrimidine nucleobases by the selective intermolecular transfer of the N^6 -glycosyl moiety from di-glycosylated adenines under proton beam irradiation. The reaction works at low temperature in solid state condition or, in alternative, in formamide and in the presence of the chondrite meteorite Northwest Africa NWA 1465. The complete set of pyrimidine nucleosides in RNA molecules was obtained, the yield and regio- and stereoselectivity of the glycosylation being increased in the presence of formamide and NWA 1465. The reported experimental conditions are similar to those effective during the one-pot synthesis of nucleobases and sugars from a chemical precursor as simple as formamide, furnishing a robust framework for the prebiotic formation of nucleic acid precursors.¹⁶

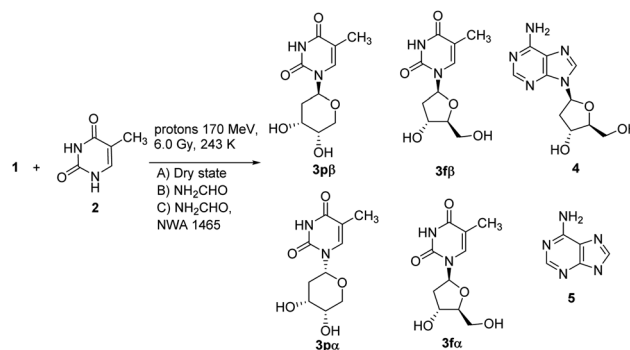
Results and discussion

Di-glycosylated adenines were prepared as previously described.^{28,29} Briefly, 2'-deoxyadenosine **4** (0.57 mmol) and 2-

deoxy-D-ribose (2.62 mmol) were dissolved in glacial acetic acid and methanol (1 : 3 v/v) and the reaction stirred at 40 °C for 72 h to afford **1** in 50% total yield as a mixture of the four corresponding α/β -pyranose and furanose isomers, compounds **1p α** , **1p β** , **1f α** , and **1f β** , respectively. The relative percentage of the four isomers (Table SI-1[†]), their synthesis, NMR data and UHPLC-MS analyses are reported in ESI SI #1.[†] Data were in accordance with those reported in the literature.²⁹

Three types of experiments were performed for the *trans*-glycosylation of thymine **2** with **1** under proton beam irradiation. One of the experiments was performed in dry-film condition starting from a solid layer mixture of **1** (0.1 mmol) and **2** (0.1 mmol) (condition A).

A second was performed in previous experimental conditions in the presence of formamide (NH₂CHO, 1.0 mL) (condition B), while the third experiment was different from the second only for the presence of NWA 1465 (3.6 mg; 10% in weight with respect to **1**) (condition C). NWA 1465 is a meteorite representative of the chondrite family³⁸ (preparation of powdered sample, elemental composition and cosmo-origin data of NWA 1465 are in SI #2[†]) which was previously applied in the synthesis of adenosine derivatives from adenine and sugar in the presence of formamide.¹³ The samples were irradiated with 170 MeV proton beam for 3.0 min at 243 K (the proton field was bounded to 10 × 10 cm² by the collimator system). The averaged linear energy transfer (LET), representing the distribution of the energy in the sample with respect to the track of the proton beam, was kept at 0.57 keV μm^{-1} , while the total radiation absorbed dose was 6.0 Gy (Scheme 1). The UHPLC-MS analyses of the reactions are reported in Fig. 3 (panels A–C). The reactions were purified by semi-preparative HPLC and the reaction products characterized by NMR and MS analyses by comparison with data previously reported.³⁹ The yield of reaction products was calculated as percentage of the isolated nucleoside (mmol) with respect to converted **1**. 1-(β -D-2'-deoxyribofuranosyl)thymine **3p β** , thymidine **3f β** , 1-(α -D-2'-deoxyribofuranosyl) thymine **3p α** , and 1-(α -D-2'-deoxyribofuranosyl) thymine **3f α** were detected in low but appreciable amount (the total yield of **3** is reported in Table 1, entry 1), besides to 2'-deoxyadenosine **4**, adenine **5** and unreacted **1**. The relative percentage of **3p β** , **3f β** , **3p α** , and **3f α** is reported in Table SI-1.[†] Adenine **5** was probably formed by partial degradation of



Scheme 1 Synthesis of nucleoside **3** from **1** and thymine **2**.



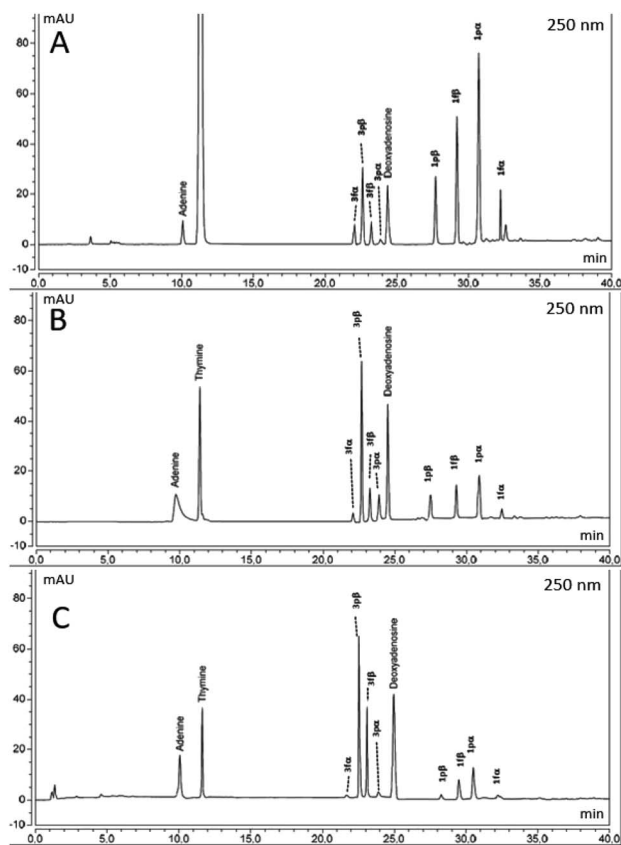


Fig. 3 UHPLC analyses of the reaction between **1** and thymine **2** under different experimental conditions. Panel A: dry-film condition (condition A). Panel B: formamide (condition B). Panel C: formamide + NWA 1465 (condition C). Spectra were recorded at 250 nm.

adenosine. The mass to charge (m/z) ratio values and relative MS peak abundances of products are in SI #3,[†] while the original m/z fragmentation spectra are in SI #4.[†] Compounds **3pβ** and thymidine were obtained as the major isomers (Table SI-1[†]), **3pβ** being isolated in the highest yield (the β/α ratio value of isolated anomers is reported in Table 1). The prevalence of the pyranose form is in accordance with data previously reported

for the glycosylation of pyrimidine nucleobases with unprotected ribose.⁴⁰ The possible role of pyranose nucleosides and of other sugar analogues in the prebiotic origin of nucleic acids has been reported and discussed.⁴¹ The transfer of the glycosyl moiety from **1** to **2** selectively involved the N^6 -glycosyl group as a donor and proceeded with high regioselectivity, the N^1 -glycosylated pyrimidine (thermodynamic product) being the only detected regioisomer. A similar selectivity was reported during the glycosylation of **2** with ribose in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropyl azodicarboxylate (DIAD), and tri-*n*-butylphosphine [$P(n\text{-Bu})_3$],⁴¹ as a consequence of the higher nucleophilicity of the N^1 nitrogen atom in the pyrimidine ring.⁴² In addition, N -glycosylates are thermodynamically stable products with respect to O -glycosylate counterpart during the *trans*-glycosylation of pyrimidine nucleobases.⁴³ The glycosyl transfer from **1** probably occurred through the formation of a sugar open-ring imine intermediate at the N^6 -anomeric position of the donor molecule.²⁹ Note that the regioselectivity was different from that of metal catalyzed conditions, in which case the $N3$ -isomer largely predominate, as a consequence of the formation of the metal σ -complex in the N^1 -position of the heterocycle ring (*e.g.* HgX and SnX_4 complexes).^{44–46} Better results were obtained in condition B, in which case **3** was isolated in 61% total yield with a preferred β -stereochemistry (Table 1, entry 2), **3pβ** and thymidine being again the major isomers (Table SI-1[†]). The increase of the yield of **3** was probably due to the high solubilizing effect of formamide.¹³ Other possible products derived from the formamide condensation pathway¹⁵ were not detected in our experimental conditions since they are expected to be synthesized in a negligible amount (μg scale) with respect to that of nucleosides (mg scale). NWA 1465 (condition C) further improved the yield of **3**, showing the highest stereoselectivity in the synthesis of the β -anomer (Table 1, entry 3; Table SI-1[†]).

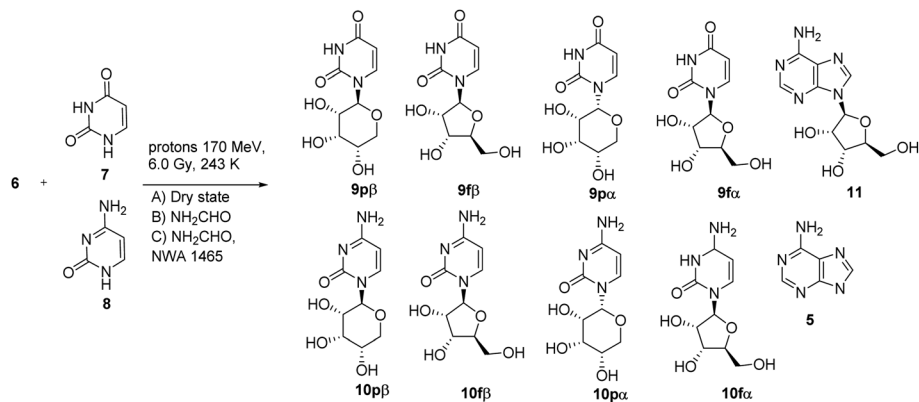
This reaction pattern is in accordance with the preferential attack of the nucleobase from the less hindered side of the sugar once adsorbed on the meteorite surface.⁴⁷ Due to the relevance of ribonucleosides in the “RNA world” hypothesis of the Origin of Life,⁴⁸ we successively evaluated the efficacy of the

Table 1 Intermolecular *trans*-glycosylation of nucleobases **2**, and **7–8** by di-glycosylated adenines **1** and **6** under proton beam irradiation^a

| Entry | Method | Di-glycosylated adenine | Nucleobase | Conv. (%) | Product(s) | β/α ratio ^b | Yield (%) |
|-------|--------|-------------------------|------------|-----------|------------------|-----------------------------------|-------------|
| 1 | A | 1 | 2 | 25 | 3(4)[5] | 68 : 32 | 18(10)[4] |
| 2 | B | | | 71 | 3(4)[5] | 85 : 15 | 61(31)[10] |
| 3 | C | | | 82 | 3(4)[5] | 98 : 2 | 70(39)[14] |
| 4 | A | 6 | 7 | 21 | 9(11)[5] | 70 : 30 | 16 (10)[4] |
| 5 | B | | | 70 | 9(11)[5] | 86 : 14 | 60 (38)[10] |
| 6 | C | | | 78 | 9(11)[5] | 94 : 6 | 65(39)[12] |
| 7 | A | 6 | 8 | 14 | 10(11)[5] | 68 : 32 | 10(5)[2] |
| 8 | B | | | 62 | 10(11)[5] | 82 : 18 | 45(25)[11] |
| 9 | C | | | 70 | 10(11)[5] | 93 : 7 | 49(34)[13] |

^a Reactions were performed in the presence of di-glycosylated adenines **1** and **6** (0.1 mmol) and equimolar amount of the appropriate pyrimidine nucleobase **2**, **7** and **8**. The yield was calculated as percentage (%) of reaction product with respect to converted reagent. The round and square brackets represent the yield of recovered 2'-deoxyadenosine **4** and adenosine **11**, and adenine **5**, respectively. The data are the mean value of three experiments with standard deviation equal to or less than 0.1%. ^b Ratio between the β and α anomers, including both pyranose and furanose forms, was determined by semi-preparative HPLC purification and comparison with standard compounds.





Scheme 2 Synthesis of nucleoside 9–10 from 6 and nucleobase 7–8.

trans-glycosylation procedure in the case of ribose. N^6 -(*D*-ribose-1-yl)-adenosine **6** (Fig. 1) was prepared as a mixture of the four possible isomers by the procedure previously reported for the synthesis of **1**. Adenosine **11** (0.57 mmol) and *D*-ribose (2.62 mmol) were dissolved in glacial acetic acid and methanol (1 : 3 v/v) and the reaction was stirred at 40 °C for 72 h to afford **6** in 25% total yield. Synthesis, NMR data and UHPLC-MS analysis of **6** are in SI #1.† The chromatographic profile of **6** showed four peaks corresponding to the formation of expected isomers **6pα**, **6pβ**, **6fα** and **6fβ** (Table SI-1, SI #1†). The irradiation experiments were repeated in conditions A–C by reaction of **6** with uracil **7** and cytosine **8** as pyrimidine acceptors. The crudes were analyzed by UHPLC-MS analyses (SI #5†) and purified by semi-preparative HPLC to yield pyrimidine nucleosides **9** and **10**, respectively, as a mixture of the corresponding pyranose and furanose isomers (Table SI-1†), besides to unreacted **6**, adenosine **11** and adenine **5** (Scheme 2). The isolated products were analyzed by NMR and MS, and the structural data were in accordance with authentic samples or with data reported in the literature.⁴⁹ The results confirmed the high regioselectivity in the formation of N^1 -pyrimidine isomers, including canonical uridine **9fβ** and cytidine **10fβ**, from low to acceptable yield (Table 1, entries 4–9). Conditions B–C afforded the highest conversion of substrate and yield of nucleoside (Table 1, entry 4 *versus* entries 5–6, and entry 7 *versus* entries 8–9). Irrespective from the experimental conditions, **9pβ** and uridine, and **10pβ** and cytidine, were isolated as the major isomers (Table SI-1†), the β-pyranose derivatives being isolated in the highest yield. In accordance with the Baker's rule (that is the neighboring group participation of the 2'-OH of ribose in the formation of the glycosyl bond), nucleosides **9** and **10** were largely obtained as the corresponding β-anomers, with the only exception of condition A, in which case an appreciable amount of the α-isomer was also detected (Table 1).

Experimental part

General information

All reagents and solvents were purchased from Aldrich and used without further purification. NWA 1465 from Sahara-Naizak was used after previous treatment as described in SI #2.† All

reactions were performed under an inert argon atmosphere. Glassware was dried with a flame under a stream of argon gas and allowed to cool under an inert atmosphere prior to use. Flash chromatography was performed on 230–400 mesh silica gel, and thin-layer chromatography was performed on alumina plates coated with silica gel (Merck 60 F254 plates). TLC plates were performed by UV absorbance at 254 nm or staining with bromo cresol. The analysis of the samples was performed by using the Ultimate 3000 Rapid Resolution UHPLC system (DIONEX, Sunnyvale, USA) equipped with C18 REPROSIL-PUR BASIC column (2.5 μm × 150 mm × 2 mm) or, in alternative, a Phenomenex Gemini AXIA PA C18 reversed-phase semi-preparative column (21 mm × 250 mm, 10 μm). Chromatographic separations were achieved using the following conditions: column temperature 30 °C, flow rate 0.2 mL min⁻¹ or 2 mL min⁻¹, gradient elution with phase A (H₂O, 0.05% formic acid) and phase B (acetonitrile, CH₃CN). The 0–18% linear gradient of phase A to phase B was employed over 50 min, returning to 100% A in 10 min. Products were detected by their absorbance at 250 nm. The UHPLC system was coupled with a mass spectrometer Q-Extractive (Thermo). The instrument was used in positive ionization mode with a full scan program (FS). Nuclear magnetic resonance spectra (¹H NMR, ¹³C NMR) were recorded on Bruker 400 MHz spectrometer.

Synthesis of pyrimidine nucleosides 3, 9 and 10 in dry-film condition (condition A)

Compounds **1** or **6** (0.1 mmol) and the appropriate pyrimidine nucleobase (0.1 mmol) were solubilized in 2.0 mL of water, stirred for 1 min and successive dried under nitrogen and high vacuum until complete solvent evaporation. Thereafter, the mixture was irradiated at 243 K with 170 MeV protons for 3.0 min at the Phasatron accelerator facility of the Joint Institute for Nuclear Research of Dubna (Moscow region, Russia). The uniform proton field was bounded to 10 × 10 cm² by the collimator system. The averaged linear energy transfer (LET) was 0.57 keV μm⁻¹ and the calculated absorbed dose was 6.0 Gy. Thereafter the sample was analyzed by UHPLC-MS detection without any further purification. To unambiguously assign the structures of nucleoside isomers, the reaction mixtures were

purified by semi-preparative HPLC and the isolated products analyzed by ^1H - ^{13}C -NMR and MS (SI #6†). Structures were assigned by comparison with commercially available samples and data in the literature.⁴⁹

Synthesis of pyrimidine nucleosides 3, 9 and 10 in formamide and NWA 1465 (conditions B and C)

Compounds 1 or 6 (0.1 mmol) and the appropriate nucleobase (0.1 mmol) were solubilized in 2.0 mL of formamide (in the case of condition C, 10% w/w of NWA 1465 were added in the mixture), stirred for 1.0 min and irradiated as previously reported. In the case of condition C, the samples were filtered at the end of the irradiation to remove NWA 1465. Thereafter the samples were analyzed as described in condition A.

Equipment

Ultimate 3000 Rapid Resolution UHPLC system (DIONEX, Sunnyvale, USA).

Bruker 400 MHz spectrometer (Bruker Billerica, Massachusetts, USA).

Conclusions

The prebiotic synthesis of nucleosides is a relevant process in the bottom-up model for the origin of pristine nucleic acid molecules. Phosphorylation⁵⁰ and *trans*-phosphorylation processes⁵¹ are available for the successive formation of nucleotides and oligonucleotides, and different mechanisms for the polymerization of these building blocks to larger molecules are reported, encompassing both template and un-template conditions.^{3,18,26} Two different levels of chemical complexity are operative in the synthesis of nucleosides: (i) the correct regioselectivity in the linkage between the nucleobase and the sugar (that is N^1 -position for pyrimidines); and (ii) the control of the β -stereochemistry of the glycosyl bond. Multi-steps procedures solved this hurdle by application of scaffold oriented strategies, including the neighboring assistance as in the amino-oxazoline pathway¹¹ or, in alternative, the controlled addition of the 3-OH group of the sugar on the Re-face of the imine intermediate in the formamido pyrimidine chemistry.⁸ In this latter case, a careful tuning of the pH overcome the regioselectivity problem.⁸ Irrespective from the synthetic strategy, non-convergent procedures are proposed for the contemporary formation of purine and pyrimidine nucleosides.⁵² The occurrence of a *trans*-glycosylation process simplifies this scenario, since the complete set of purine and pyrimidine nucleosides with the correct regio- and stereochemistry can be in principle obtained from only one di-glycosylated derivative, when the appropriate nucleobase is available as glycosyl acceptor. The very fact that di-glycosylated adenine is obtained as a by-product from formamide during the one-pot synthesis of canonical nucleosides and nucleobases, and that they are a “remnant” structural motif in damaged DNA, further suggests that the *trans*-glycosylation can act as a chemiomimetic process^{40,53} in expanding the panel of biologically relevant molecules obtainable from a C-1 chemical precursor as simple as formamide. In

this chemistry, NWA 1465 shows a relevant effect in the control of the stereochemistry of the transformation, expanding the possible role of meteorites as effective prebiotic chemical factories.⁵⁴ Meteorites represent a clear-cut case for the role of catalyst complexity in prebiotic process.⁵⁵ The contemporary presence in meteorites of different minerals and metal oxides in both crystalline and amorphous states furnish a large variety of Lewis acid catalytic sites⁵⁶ to improve the glycosylation process, in accordance with the role played by organometallic species in this kind of reaction.⁵⁷ In particular, titanium silico-aluminate, nickel, and iron derivatives present in NWA 1465 are reported as effective Lewis acid transition metal sites in the glycosylation of carbohydrates.⁵⁸

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is supported by the Italian Space Agency (ASI) BANDO ASI DC-VUM-2017-034 CONTRATTO DI FINANZIAMENTO ASI N. 2019-3-U.0, CUP F86C16000000006 “Vita nello spazio-Origine, presenza, persistenza della vita nello spazio, dalle molecole agli estremofili”.

References

- G. Zubay and T. Mui, Prebiotic Synthesis of Nucleotides, *Origins Life Evol. Biospheres*, 2001, **31**, 87–102.
- J. E. Šponer, J. Šponer and M. Fuentes-Cabrera, Prebiotic Routes to Nucleosides: A Quantum Chemical Insight into the Energetics of the Multistep Reaction Pathways, *Chem.–Eur. J.*, 2011, **17**, 847–854.
- J. E. Šponer, R. Szabla, R. W. Góra, A. M. Saitta, F. Pietrucci, F. Saija, E. Di Mauro, R. Saladino, M. Ferus, S. Civiš and J. Šponer, Prebiotic Synthesis of Nucleic Acids and Their Building Blocks at the Atomic Level-Merging Models and Mechanisms from Advanced Computations and Experiments, *Phys. Chem. Chem. Phys.*, 2016, **18**, 20047–20066.
- R. Saladino, J. E. Šponer, J. Šponer and E. Di Mauro, Rewarming the Primordial Soup: Revisitations and Rediscoveries in Prebiotic Chemistry, *ChemBioChem*, 2018, **19**, 22–25.
- F. Micheel and H. Köchling, Über Die Reaktionen Des D-Glucosamins, V. Die Bildung von Glykosiden Des D-Glucosamins Aus Einem Oxazolin-Derivat, *Chem. Ber.*, 1957, **90**, 1597–1598.
- S. Konstas, I. Photaki and L. Zervas, Überführung von D-Glucosamin in Oxazolone- Und Oxazolinderivate, *Chem. Ber.*, 1959, **92**, 1288–1293.
- R. A. Sanchez and L. E. Orgel, Studies in Prebiotic Synthesis. V. Synthesis and Photoanomerization of Pyrimidine Nucleosides, *J. Mol. Biol.*, 1970, **47**, 531–543.
- S. Becker, I. Thoma, A. Deutsch, T. Gehrke, P. Mayer, Z. Hendrik and T. Carell, A High-Yielding, Strictly



- Regioselective Prebiotic Purine Nucleoside Formation Pathway, *Science*, 2016, **352**, 833–836.
- 9 R. Saladino, E. Mincione, C. Crestini, R. Negri, E. Di Mauro and G. Costanzo, Mechanism of Degradation of Purine Nucleosides by Formamide. Implications for Chemical DNA Sequencing Procedures, *J. Am. Chem. Soc.*, 1996, **118**, 5615–5619.
- 10 M. W. Powner and J. D. Sutherland, Phosphate-Mediated Interconversion of Ribo- and Arabino-Configured Prebiotic Nucleotide Intermediates, *Angew. Chem., Int. Ed.*, 2010, **49**, 4641–4643.
- 11 M. W. Powner, B. Gerland and J. D. Sutherland, Synthesis of Activated Pyrimidine Ribonucleotides in Prebiotically Plausible Conditions, *Nature*, 2009, **459**, 239–242.
- 12 J. Xu, M. Tsanakopoulou, C. J. Magnani, R. Szabla, J. E. Šponer, J. Šponer, R. W. Góra and J. D. Sutherland, Prebiotically Plausible Synthesis of Pyrimidine β -Ribonucleosides and Their Phosphate Derivatives Involving Photoanomerization, *Nat. Chem.*, 2017, **9**, 303–309.
- 13 R. Saladino, B. M. Bizzarri, L. Botta, J. Šponer, J. E. Šponer, T. Georgelin, M. Jaber, B. Rigaud, M. Kapralov, G. N. Timoshenko, A. Rozanov, E. Krasavin, A. M. Timperio and E. Di Mauro, Proton Irradiation: A Key to the Challenge of N-Glycosidic Bond Formation in a Prebiotic Context, *Sci. Rep.*, 2017, **7**, 14709.
- 14 W. D. Fuller, R. A. Sanchez and L. E. Orgel, Studies in Prebiotic Synthesis. VI. Synthesis of Purine Nucleosides, *J. Mol. Biol.*, 1972, **67**, 25–33.
- 15 R. Saladino, E. Carota, G. Botta, M. Kapralov, G. N. Timoshenko, A. Y. Rozanov, E. Krasavin and E. Di Mauro, Meteorite-Catalyzed Syntheses of Nucleosides and of Other Prebiotic Compounds from Formamide under Proton Irradiation, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, E2746–E2755.
- 16 R. Saladino, G. Botta, S. Pino, G. Costanzo and E. Di Mauro, Genetics First or Metabolism First? The Formamide Clue, *Chem. Soc. Rev.*, 2012, **41**, 5526–5565.
- 17 R. Saladino, C. Crestini, S. Pino, G. Costanzo and E. Di Mauro, Formamide and the Origin of Life, *Phys. Life Rev.*, 2012, **9**, 84–104.
- 18 L. Botta, R. Saladino, B. M. Bizzarri, B. Cobucci-Ponzano, R. Iacono, R. Avino, S. Caliro, A. Carandente, F. Lorenzini, A. Tortora, E. Di Mauro and M. Moracci, Formamide-Based Prebiotic Chemistry in the Phlegrean Fields, *Adv. Space Res.*, 2018, **62**, 2372–2379.
- 19 J. E. Šponer, J. Šponer, O. Nováková, V. Brabec, O. Šedo, Z. Zdráhal, G. Costanzo, S. Pino, R. Saladino and E. Di Mauro, Emergence of the First Catalytic Oligonucleotides in a Formamide-Based Origin Scenario, *Chem.–Eur. J.*, 2016, **22**, 3572–3586.
- 20 R. Saladino, C. Crestini, G. Costanzo and E. Dimauero, On the Prebiotic Synthesis of Nucleobases, Nucleotides, Oligonucleotides, Pre-RNA and Pre-DNA Molecules, *Top. Curr. Chem.*, 2005, **259**, 29–68.
- 21 B. M. Bizzarri, L. Botta, M. I. Pérez-Valverde, R. Saladino, E. Di Mauro and J. M. García-Ruiz, Silica Metal Oxide Vesicles Catalyze Comprehensive Prebiotic Chemistry, *Chem.–Eur. J.*, 2018, **24**, 8126–8132.
- 22 L. J. Yu, C. J. Wiederholt, J. N. Patro, K. Haraguchi and M. M. Greenberg, Synthesis of Oligonucleotides Containing Fapy·dG (*N*-6-(2-Deoxy- α , β -D-Erythropentofuranosyl)-2,6-Diamino-4-Hydroxy-5-Formamidopyrimidine) Using a 5'-Dimethoxytrityl Dinucleotide Phosphoramidite, *J. Org. Chem.*, 2005, **70**, 141–149.
- 23 L. Botta, B. M. Bizzarri, D. Piccinino, T. Fornaro, J. Robert Brucato and R. Saladino, Prebiotic Synthesis of Carboxylic Acids, Amino Acids and Nucleic Acid Bases from Formamide under Photochemical Conditions, *Eur. Phys. J. Plus*, 2017, **132**, 317.
- 24 M. Tomasz, R. Lipman, M. S. Lee, G. L. Verdine and K. Nakanishi, Reaction of Acid-Activated Mitomycin C with Calf Thymus DNA and Model Guanines: Elucidation of the Base-Catalyzed Degradation of N7-Alkylguanine Nucleosides, *Biochemistry*, 1987, **26**, 2010–2027.
- 25 M. Berger and J. Cadet, Isolation and Characterization of the Radiation-Induced Degradation Products of 2'-Deoxyguanosine in Oxygen-Free Aqueous Solutions, *Z. Naturforsch. B*, 2015, **40**, 1519–1531.
- 26 G. Costanzo, R. Saladino, G. Botta, A. Giorgi, A. Scipioni, S. Pino and E. Di Mauro, Generation of RNA Molecules by a Base-Catalysed Click-Like Reaction, *ChemBioChem*, 2012, **13**, 999–1008.
- 27 B. M. Bizzarri, J. E. Šponer, J. Šponer, G. Cassone, M. Kapralov, G. N. Timoshenko, E. Krasavin, G. Fanelli, A. M. Timperio, E. Di Mauro and R. Saladino, Meteorite-Assisted Phosphorylation of Adenosine Under Proton Irradiation Conditions, *ChemSystemsChem*, 2020, **1**, e1900039.
- 28 N. E. Price, K. M. Johnson, J. Wang, M. I. Fekry, Y. Wang and K. S. Gates, Interstrand DNA–DNA Cross-Link Formation between Adenine Residues and Abasic Sites in Duplex DNA, *J. Am. Chem. Soc.*, 2014, **136**, 3483–3490.
- 29 N. E. Price, M. J. Catalano, S. Liu, Y. Wang and K. S. Gates, Chemical and Structural Characterization of Interstrand Cross-Links Formed between Abasic Sites and Adenine Residues in Duplex DNA, *Nucleic Acids Res.*, 2015, **43**, 3434–3441.
- 30 B. Shimizu and M. Miyaki, Studies on Nonspecific Adenosine Deaminase from Takadiastase, *J. Biochem.*, 1966, **59**, 265–271.
- 31 B. Shimizu and M. Miyaki, Transglycosylation from pyrimidines to purines, *Tetrahedron Lett.*, 1968, **9**, 855–859.
- 32 B. Shimizu and M. Miyaki, N \rightarrow N Alkyl and Glycosyl Migration of Purines and Pyrimidines. III. N \rightarrow N Alkyl and Glycosyl Migration of Purine Derivatives, *Chem. Pharm. Bull.*, 1970, **18**, 1446–1456.
- 33 M. Miyaki and B. Shimizu, N \rightarrow N Alkyl and Glycosyl Migration of Purines and Pyrimidines. III. (1) N \rightarrow N Alkyl and Glycosyl Migration of Purine Derivatives, *Chem. Pharm. Bull.*, 1970, **18**, 1446–1456.
- 34 J. Boryski, Reactions of Transglycosylation in the Nucleoside Chemistry, *Curr. Org. Chem.*, 2008, **12**, 309–325.
- 35 J. Boryski, Transglycosylation Reactions of Purine Nucleosides. A Review, *Nucleosides and Nucleotides*, 1996, **15**, 771–791.



- 36 N. Kitadai and S. Maruyama, Origins of Building Blocks of Life: A Review, *Geosci. Front.*, 2018, **9**, 1117–1153.
- 37 M. J. McKay and H. M. Nguyen, Recent Advances in Transition Metal-Catalyzed Glycosylation, *ACS Catal.*, 2012, **2**, 1563–1595.
- 38 L. Botta, R. Saladino, B. M. Bizzarri, B. Cobucci-Ponzano, R. Iacono, R. Avino, S. Caliro, A. Carandente, F. Lorenzini, A. Tortora, E. Di Mauro and M. Moracci, Formamide-Based Prebiotic Chemistry in the Phlegrean Fields, *Adv. Space Res.*, 2018, **62**, 2372–2379.
- 39 (a) S. N. Mikhailov and E. V. Efimtseva, Synthesis of enantiomers of 3',4'-seco-2'-desoxythymidine, *Chem. Heterocycl. Compd.*, 1988, **24**, 778–782; (b) Y. M. Ying, W. G. Shan, W. H. Liu and Z. J. Zhan, Alkaloids and Nucleoside Derivatives from a Fungal Endophyte of *Huperzia serrata*, *Chem. Nat. Compd.*, 2013, **49**, 184–186; (c) R. Huang, X. Zhou, Y. Peng, X. Yang, T. Xu and Y. Liu, Nucleosides from the Marine Sponge *Callyspongia* SP, *Chem. Nat. Compd.*, 2011, **46**, 1010–1011.
- 40 A. M. Downey, C. Richter, R. Pohl, R. Mahrwald and M. Hocek, Direct One-Pot Synthesis of Nucleosides from Unprotected or 5-O-Monoprotected D-Ribose, *Org. Lett.*, 2015, **17**, 4604–4607.
- 41 B. Pullmann, Electronic structure, chemical reactivity, and basicity of purines and pyrazolopyrimidines, *J. Chem. Soc.*, 1959, 1621–1623.
- 42 A. Eschenmoser and E. Loewenthal, Chemistry of Potentially Prebiological Natural Products, *Chem. Soc. Rev.*, 1992, **21**, 1–16.
- 43 G. T. Rogers, R. S. Shadbolt and T. L. V. Ulbricht, Nucleosides. Part VII. The Reaction of Metal Salts of Thymine and Uracil with Tetra-Acetyl- α -Glucopyranosyl Bromide, *J. Chem. Soc. C*, 1969, **2**, 203–208.
- 44 H. Vorbrüggen and G. Höfle, Nucleoside Syntheses, XXIII(1) On the Mechanism of Nucleoside Synthesis, *Chem. Ber.*, 1981, **114**, 1256–1268.
- 45 T. Ukita, H. Hayatsu and Y. Tomita, Reinvestigation of the Condensation Reaction of Acetobromoglucose with Chloromercuri-4-Ethoxy-2(1H)-Pyrimidinone to 1-(Tetra-O-Acetyl- β -D-Glucopyranosyl)-4-Ethoxy-2(1H)-Pyrimidinone, *Chem. Pharm. Bull.*, 1963, **11**, 1068–1073.
- 46 H. Vorbrüggen, U. Niedballa, K. Krolkiewicz, B. Bennua and G. Höfle, in *Chemistry and Biology of Nucleosides and Nucleotides*, ed. R. Harmon, R. K. Robins and L. B. Townsend, Academic Press, New York, 1978, pp. 251–265.
- 47 M. Ferus, A. Knížek and S. Civiš, Meteorite-Catalyzed Synthesis of Nucleosides and Other Prebiotic Compounds, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 7109–7110.
- 48 H. S. Bernhardt, The RNA World Hypothesis: The Worst Theory of the Early Evolution of Life (except for All the Others)a, *Biol. Direct*, 2012, **7**, 23.
- 49 (a) U. Kang, S. M. Ryu, D. Lee and E. K. Seo, Chemical Constituents of the Leaves of *Brassica oleracea* Var. Acephala, *Chem. Nat. Compd.*, 2018, **54**, 1023–1026; (b) J. Ren, Y. G. Xie, Y. G. Guo, S. K. Yan and H. Z. Jin, Chemical Constituents of *Liparis viridiflora*, *Chem. Nat. Compd.*, 2019, **55**, 552–554; (c) S. Becker, J. Feldmann, S. Wiedemann, H. Okamura, C. Schneider, K. Iwan, A. Crisp, M. Rossa, T. Amatov and T. Carell, Unified prebiotically plausible synthesis of pyrimidine and purine RNA ribonucleotides, *Science*, 2019, **366**, 76–82.
- 50 (a) Y. Furukawa, H. J. Kim, D. Hutter and S. A. Benner, Abiotic regioselective phosphorylation of adenosine with borate in formamide, *Astrobiology*, 2015, **15**, 1–9; (b) G. Costanzo, R. Saladino, C. Crestini, F. Ciciriello and E. Di Mauro, Nucleoside Phosphorylation by Phosphate Minerals, *J. Biol. Chem.*, 2007, **282**, 16729–16735; (c) B. Burcar, M. Pasek, M. Gull, B. J. Cafferty, F. Velasco, N. V. Hud and C. Menor-Salván, Darwin's Warm Little Pond: A One-Pot Reaction for Prebiotic Phosphorylation and the Mobilization of Phosphate from Minerals in a Urea-Based Solvent, *Angew. Chem., Int. Ed.*, 2016, **55**, 13249–13253; (d) Y. Yamagata, H. Watanabe, M. Saitoh and T. Namba, Volcanic Production of Polyphosphates and Its Relevance to Prebiotic Evolution, *Nature*, 1991, **352**, 516–551.
- 51 (a) L. E. Orgel, Prebiotic Chemistry and the Origin of the RNA World, *Crit. Rev. Biochem. Mol. Biol.*, 2004, **39**, 99–123; (b) J. P. Ferris, Catalysis and Prebiotic RNA Synthesis, *Origins Life Evol. Biospheres*, 1993, **23**, 307–315.
- 52 A. Biscans, Exploring the Emergence of RNA Nucleosides and Nucleotides on the Early Earth, *Life*, 2018, **8**, 57.
- 53 J. Peretó, Out of Fuzzy Chemistry: From Prebiotic Chemistry to Metabolic Networks, *Chem. Soc. Rev.*, 2012, **41**, 5394–5403.
- 54 R. Saladino, L. Botta and E. Di Mauro, The Prevailing Catalytic Role of Meteorites in Formamide Prebiotic Processes, *Life*, 2018, **8**, 6.
- 55 B. M. Bizzarri, P. Manini, V. Lino, M. d'Ischia, M. Kapralov, E. Krasavin, K. Mráziková, J. Šponer, J. E. Šponer, E. Di Mauro and R. Saladino, High-Energy Proton-Beam-Induced Polymerization/Oxygenation of Hydroxynaphthalenes on Meteorites and Nitrogen Transfer from Urea: Modeling Insoluble Organic Matter?, *Chem.–Eur. J.*, 2020, **26**, 14919–14928.
- 56 (a) E. B. Bauer, Transition metal catalyzed glycosylation reaction- an overview, *Org. Biomol. Chem.*, 2020, **18**, 9160–9180; (b) B. M. Bizzarri, R. Saladino, I. Delfino, J. M. García-Ruiz and E. Di Mauro, Prebiotic organic chemistry of formamide and the origin of life in planetary conditions: What we know and what is the future, *Int. J. Mol. Sci.*, 2021, **22**, 917.
- 57 J. Boryski, Transglycosylation Reactions of Purine Nucleosides, 1996 Nucleosides. A Review, *Nucleosides and Nucleotides*, 1996, **15**, 771–791.
- 58 (a) M. Pfaffe and R. Mahrwald, Direct glycosylation of unprotected and unactivated carbohydrates under mild conditions, *Org. Lett.*, 2012, **14**, 792–795; (b) X. Li and J. Zhu, Recent Advances in Transition Metal-Catalyzed O-Glycosylations, *J. Carbohydr. Chem.*, 2012, **31**, 284–324; (c) G. Zhang, Q. Liu, L. Shi and J. Wang, Ferric sulfate hydrate-catalyzed O-glycosylation using glycals with or without microwave irradiation, *Tetrahedron*, 2008, **64**, 339–344.

