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

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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.

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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–σ* 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-ribopyranosyl)-2′-deoxyadenosine(**1pα/β**), and N^6-(2-deoxy-D-ribofuranosyl)-2′-deoxyadenosine(**1fα/β**) (Fig. 1).[13,24,25] The phosphorylation of adenosine to corresponding nucleotides, including reactive cyclic adenosine monophosphates,[26] was also reported in

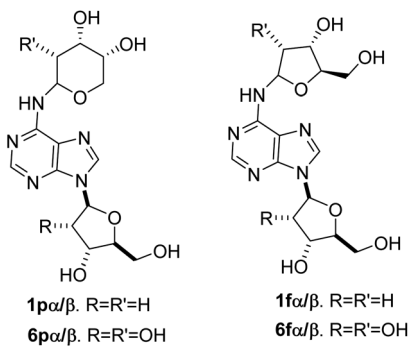

Fig. 1 N^6-(2-Deoxy-D-ribopyranosyl)-2′-deoxyadenosine **1pα/β**, N^6-(2-deoxy-D-ribofuranosyl)-2′-deoxyadenosine **1fα/β**, N^6-(D-ribopyranosyl)-2′-deoxyadenosine **6pα/β**, N^6-(D-ribofuranosyl)-2′-deoxyadenosine **6fα/β**.

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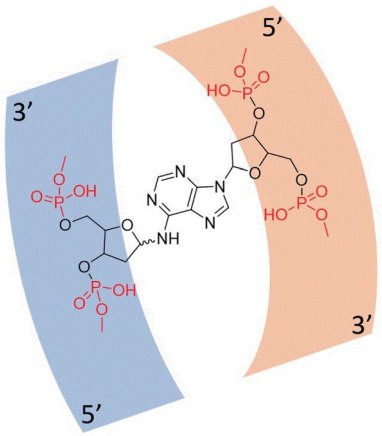


Fig. 2 Structural motif in damaged DNA sites. N^6-(2′-deoxy-D-ribofuranosyl)-2′-deoxyadenosine (black) was selected as a representative case of the four possible isomeric forms of the sugar bonded at the N^6-exocyclic position of the adenosine residue.[29] The sugar-phosphate backbone is reported in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

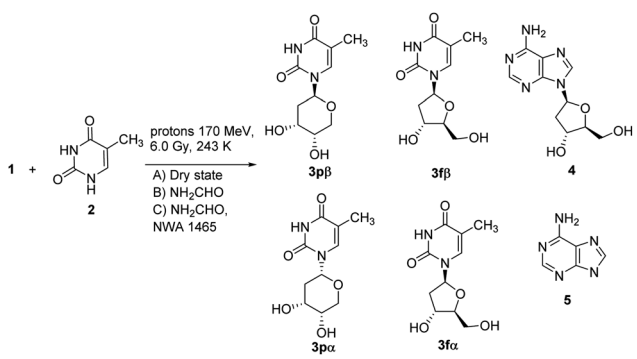
Trans-glycosylation is also relevant in the prebiotic scenario, avoiding independent synthetic for the formation of purine and pyrimidine nucleosides.[36] Chemically-driven *trans*-glycosylation occurs at elevated temperature, or in the presence of heavy metals, usually starting from protected substrates 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 **1pα**, **1pβ**, **1fα**, and **1fβ**, 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 (NH_2CHO, 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 family[38] (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 cm^2 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′-deoxyribopyranosyl)thymine **3pβ**, thymidine **3fβ**, 1-(α-D-2′-deoxyribopyranosyl) thymine **3pα**, and 1-(α-D-2′-deoxyribofuranosyl) thymine **3fα** 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 **3pβ**, **3fβ**, **3pα**, and **3fα** 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**.

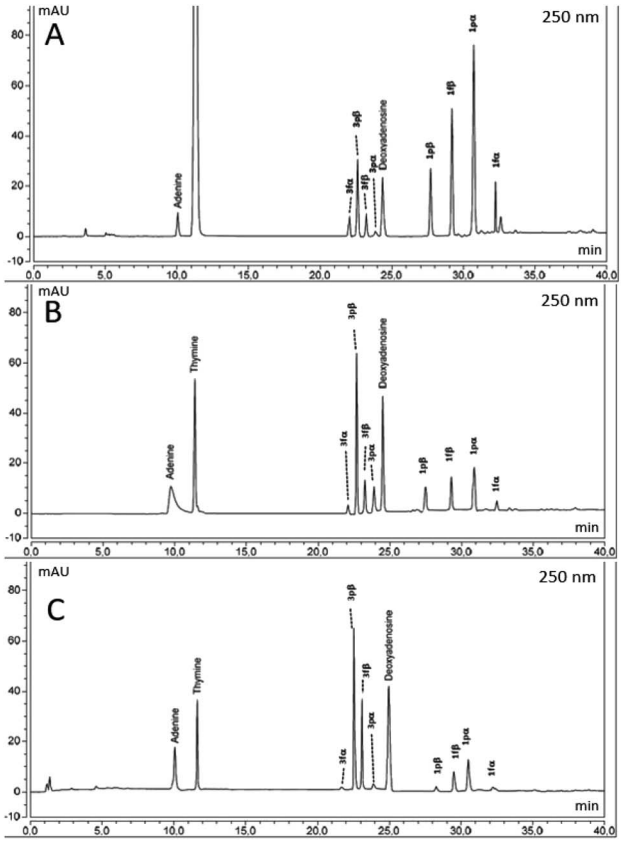


Fig. 3 UHPLC analyses of the reaction between **1** and thymine **2** under different experimental conditions. Panel A: dry-film condition (condition A). Panel B: formamide (condition B). Panel C: formamide + NWA 1465 (condition C). Spectra were recorded at 250 nm.

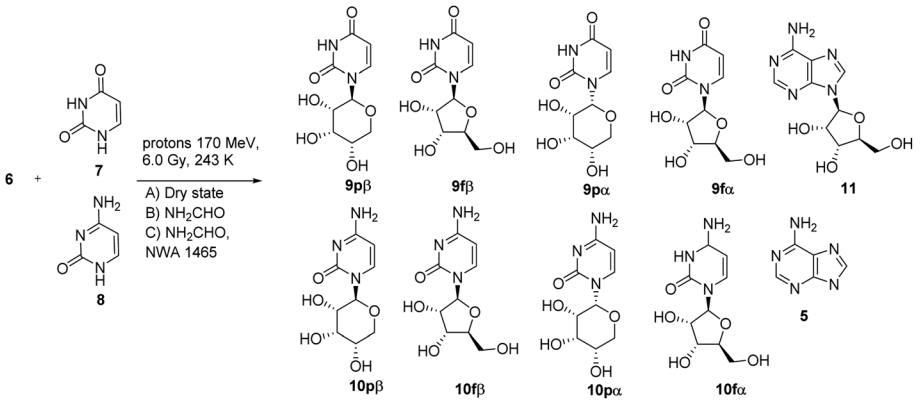
adenosine. The mass to charge (m/z) ratio values and relative MS peak abundances of products are in SI #3,† while the original m/z fragmentation spectra are in SI #4.† Compounds **3pβ** and thymidine were obtained as the major isomers (Table SI-1†), **3pβ** being isolated in the highest yield (the β/α 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*-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 *N*3-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 pathway[15] 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-ribos-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 authentical 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 (H_2O, 0.05% formic acid) and phase B (acetonitrile, CH_3CN). 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 (^{1}H NMR, ^{13}C 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 cm^2 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 ^{1}H–^{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. Phosphorylation[50] and *trans*-phosphorylation processes[51] 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 pathway[11] 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, no-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 sites[56] 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

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