Prebiotic Origin of Pre-RNA Building Blocks in a Urea "Warm Little Pond" Scenario

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Urea appears to be a key intermediate of important prebiotic synthetic pathways. Concentrated pools of urea likely existed on the surface of the early Earth, as urea is synthesized in significant quantities from hydrogen cyanide or cyanamide (widely accepted prebiotic molecules), it has extremely high water solubility, and it can concentrate to form eutectics from aqueous solutions. We propose a model for the origin of a variety of canonical and non-canonical nucleobases, including some known to form supramolecular assemblies that contain Watson-Crick-like base pairs.The dual nucleophilic-electrophilic character of urea makes it an ideal precursor for the formation of nitrogenous heterocycles. These reactions involve urea condensation with other prebiotic molecules (e.g., malonic acid) that could be driven by environmental cycles (e.g., freezing/thawing, drying/wetting). The resulting heterocycle assemblies are compatible with the formation of nucleosides and, possibly, the chemical evolution of molecular precursors to RNA. We show that urea eutectics at moderate temperature represent a robust prebiotic source of nitrogenous heterocycles. The simplicity of these pathways, and their independence from specific or rare geological events, support the idea of urea being of fundamental importance to the prebiotic chemistry that gave rise to life on Earth.

The *de novo* prebiotic formation of RNA during the process of life origination is challenging, due to the discussed availability or plausibility of some reagents, and the complexity of the numerous steps required for the synthesis of ribonucleotides and their subsequent polymerization. In recent years, the question of the formation of the canonical components of RNA received intensive research.[1–5] The proposed routes from plausible prebiotic precursors to RNA have been proven to be rife with problems,[6] and have led many scientists to view the RNA World as an intermediate stage in the origins of life, with simpler polymers serving in catalytic and informational roles before the emergence of RNA.[7–10] The possibility of pre-RNA structures and precursors widely opens the evolutionary perspective of the origin of life, as there exist alternative nucleobases that readily form nucleosides with ribose and other sugars,[11,12] and the expanded space of structures is compatible with the view that the evolution of pre-biopolymers resulted in functionally superior RNA and DNA.[8] We propose that concentrated solutions of urea were essential for pre-RNA chemical evolution. This proposal is based upon two primary observations: 1) urea is produced in model prebiotic and astrochemical reactions from one-carbon sources, such as cyanide, cyanamide, methane, or carbon oxides,[13–15] and 2) urea is relatively stable, allowing it to accumulate over time on the surface of the early Earth. Urea forms high-concentration viscous solutions[16] that favor its accumulation in evaporating ponds. The abundance of urea in the presence of other prebiotic components would allow for the creation of large-scale stable eutectic as low-water fluid environments. In these environments, hydration-dehydration (wet-dry) cycles could have concentrated and selected molecules, promoting reactions potentially important for initiating life. The atmospheric formation of reactive species (using methane or acetylene as precursors and UV radiation or spark discharges as energy sources) above a concentrated solution of urea subjected to freeze–thaw cycles has been shown to result in the formation of pyrimidines, triazines, and purines; significant yields being observed for barbituric and cyanuric acid, together with their corresponding aminopyrimidines and aminotriazines.[17,18] Hence, the formation of eutectic urea solutions in a prebiotic environment provides a robust scenario for the origination of nucleobases. This property could be added to the previously reported ability of urea to promote phosphorylation of alcohols, including nucleosides,[16] and its physicochemical properties that are potentially useful for pre-enzyme nucleic acid evolution.[19] Heterocycle synthesis in urea solutions is of renewed interest with the recent discovery of high-yielding model prebiotic reactions for the ribosylation of melamine, 2,4,6-triaminopyrimidine (TAP) and barbituric acid.[11,20] These nucleoside analogs are particularly interesting as they can form supramolecular assemblies as monomers with complementary heterocycles (e.g., TAP with cyanuric acid, melamine with barbituric acid). The C-riboside formed by barbituric acid can be regarded as a prebiotic analog of uridine

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and pseudouridine, which opens the possibility of pre-RNA, informational carrying structures with noncanonical nucleobases that are extremely close to the extant nucleobases.[11] Taken together, these results suggest an early and important role of urea as a precursor of pre-RNA and extant RNA building blocks.[9] We hypothesized that urea enriched ponds could be a source of noncanonical nucleosides, if malonic acid is present in the prebiotic chemical space. In preliminary results[21] we showed that malonic acid, – which could be formed by hydrolysis of malononitrile,[22,23] by irradiation of urea,[13] or by prebiotic proto-metabolic cycles, as the malonate cycle,[24] – could condense efficiently with urea to yield pyrimidines in prebiotic conditions. In this communication we further explore the formation of nucleobases and noncanonical nucleosides of interest for chemical evolution,[8] in a prebiotic urea-rich *„warm little pond"* using malonic acid as precursor.

To explore whether the malonic acid-urea condensation could be a prebiotic reaction for the origin of the barbituric acid family of pyrimidines, we subjected a solution of 2 mmol urea and 0.5 mmol malonic acid to dry-wet cycles: 85 °C for 6 hours in the dry phase, followed by rehydration and heating at 60 °C for 12 hours in the wet phase. After 3 days cycling, barbituric acid crystals had grown. The solution was lyophilized, and the viscous residue was analyzed after trimethylsilyl derivatization (Figure S1A in the Supporting Information). The analysis by gas chromatography-mass spectrometry (GC-MS) showed the formation of barbituric acid with a measured 42% yield with respect to initial malonic acid. Also, 2-amino-4,6-dihydroxypyrimidine and 6-aminouracil were found in low yields, as well as expected 5-carbamoylated products.[25] The dry/wet cycling of the urea-malonic acid solution did not reveal significant production of triazines.

If urea is replaced by biuret in the same reaction conditions, cyanuric acid is formed (Figure S1B). These results are consistent with our previous results on the formation of s-triazines in an ice matrix,[18] in which we postulated that the s-triazine synthesis proceeded through the formation of biuret in an ice matrix containing brines of highly concentrated urea that was under a reducing atmosphere with spark discharge. This reaction is equivalent to the classic cyanuric acid synthesis from urea at high temperature,[26] suggesting that s-triazines could be formed in dehydrating urea solutions through the formation of biuret.

It is unlikely that concentrated urea solutions on the prebiotic Earth were formed with pure urea. Cyanide in a dry/wet scenario in the presence of ammonia in oxidative environments could be an efficient prebiotic source of urea;[14] while the irradiation of an ammonium cyanide solution would lead to a mixture of urea and guanidine. These two prebiotic molecules can support the formation of a viscous solution in heating/dry-wet experiments (Figure S2). Guanidine could represent a prebiotic precursor of 2,4,6-triaminopyrimidine (TAP), a non-canonical nucleobase that readily forms N-glycosides and C-glycosides with ribose and other aldoses.[12] Although TAP was not previously reported in prebiotic model reactions, the condensation of guanidine and malononitrile to produce TAP (and melamine, from self-condensation of guanidine) was observed to happen in high yields under dry conditions at *T*100 °C (Figure S3). Moreover, in the more prebiotically relevant conditions of dry-wet cycles at 85 °C, a mixture of urea and guanidine to which malononitrile has been added yielded TAP, melamine, and related amino-hydroxypyrimidines (Figure S4). Given that malononitrile could be a prebiotic precursor produced from cyanoacetylene,[22] and malonic acid produced by irradiation of urea solutions,[13,21] could malonic acid be a precursor of pyrimidines in the warm little pond prebiotic scenario? Considering that guanidine is a likely prebiotic product along with urea, a solution containing 2 mmol of urea and 1 mmol each of guanidine and malonic acid were subjected to dry-wet cycle under the same conditions previously detailed with urea or biuret alone (Figure S1). After 5 days of wet/dry cycles at 65 °C, a mixture containing pyrimidines was formed (Figure 1) along with crystals whose analysis by GC-MS were reveales to be co-crystals formed by barbituric acid and 2-amino-4,6-dihydroxypyrimidine, consistently with a measured melting point of 240–260 °C (Figure 1B).

This reaction reached a maximum yield of 55% 2-amino-4,6-dihydroxypyrimidine, calculated from chromatographic peak areas and expressed as molar percentage of total malonic acid introduced in the experiment; as accompanying products, significant formation of 2,4,5-triaminopyrimidine, melamine, and a small amount of TAP were observed (Figure 1C). The reaction proceeds optimally in the temperature range of 65–85 °C, losing efficiency at higher temperatures due to the increase of malonic acid decarboxylation to acetic acid and CO_2. In parallel, an experiment performed in the same conditions with urea alone in absence of guanidine, shows barbituric acid as main product, with an increased yield of 6-aminouracil respect to the experiment with guanidine (Figure 1D). We note the absence of cyanuric acid in these reactions, which seems to be formed only when the carbamoylurea (biuret) is present in the reaction (Figure S1).

Hence, these experiment suggest that condensation of malonic acid in the urea/guanidine mixture, subjected to environmental cycles at moderate temperature, could generate trisubstituted pyrimidines in plausible prebiotic conditions. This milieu and environment would be favorable for the capture of sugars incorporated by other processes. One unanticipated product was 2,4,5-triaminopyrimidine (Figure 1), which was identified through electron impact mass fragmentation signatures in GC-MS (Figure S8) and identical retention times with reference samples. This result constitutes a plausible prebiotic synthesis of yet another pyrimidine, that has been proposed as possible building block of pre-RNA[27]

Urea and guanidine are essential in these reactions (Scheme 1), and the two possible urea alteration pathways in solution involve its decomposition into ammonia and carbon dioxide, and its isomerization to ammonium cyanate. The released NH_3 could lead to the formation of monoamidomalonic acid (observed in the experiments with malonic acid, Figure 1), and malonodiamide. The carbamoylation of monoamidomalonic acid by urea-derived isocyanate, followed by cyclization through intramolecular nucleophilic attack of the amino group, could explain the synthesis of the 4-amino-2,6-

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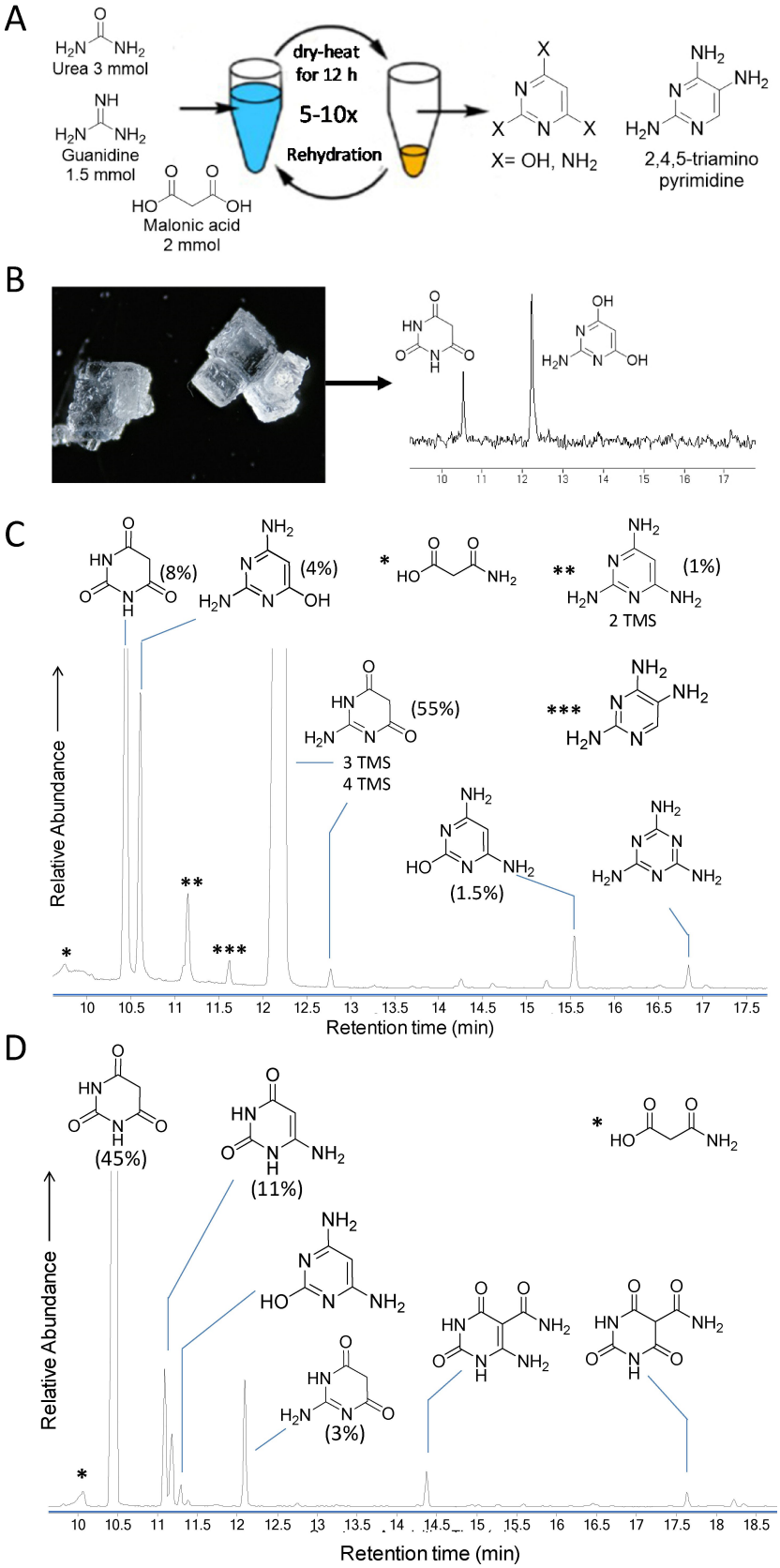

Figure 1. A) Synthesis of 2,4,6-functionalized pyrimidines by condensation of urea/guanidine and malonic acid during environmental cycles under prebiotic conditions. B) Cocrystals of barbituric acid and 2-aminopyrimidine-4,6-diol formed during dry/wet cycles experiment at 65 °C. C) GC-MS chromatogram showing the trimethylsilyl derivatives of the products of condensation of malonic acid in an equimolar urea/guanidine solution subjected to cycles of drying and momentary rewetting. Product yield indicated at each structure. D) GC-MS chromatogram showing the trimethylsilyl derivatives of the products resulting from the condensation of malonic acid and urea in a solution subjected to dry/wet cycles at 65 °C.

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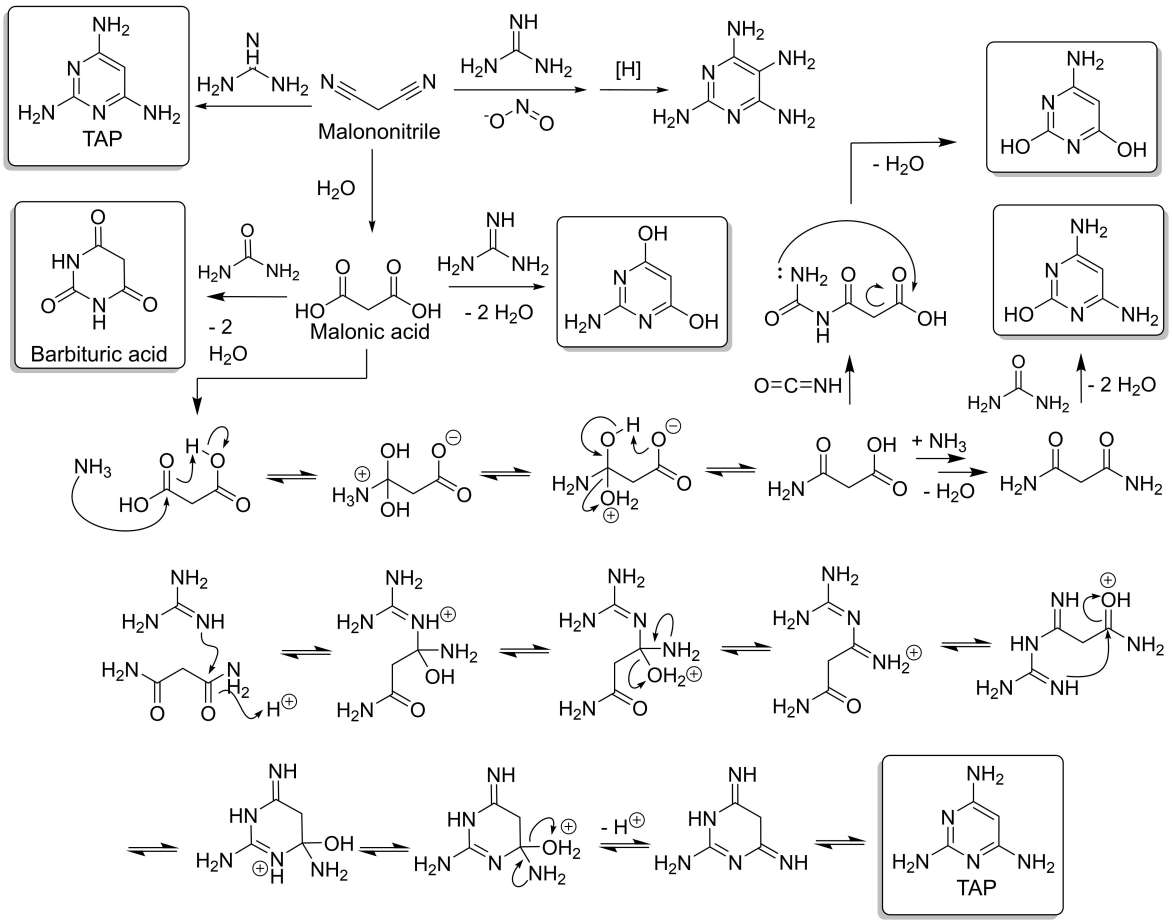

Scheme 1. The versatility of malononitrile. Formation of the barbituric acid family of pyrimidines by urea/guanidine and malonic acid condensation, driven by the decomposition/isomerization of urea in ammonia and isocyanic acid; the condensation of resulting mono and diamides of malonic acid with guanidine or urea lead the corresponding pyrimidines. One possible origin of malonic acid is the hydrolysis of malononitrile, which, in turn, could condense directly with urea/guanidine to yield the 4,6-diaminopyrimidines, or, in presence of atmospheric NO, form 4,5,6-triaminopyrimidines, as observed by Becker et al.[28]

dihydroxypyrimidine. Finally, the condensation of malonodiamide (derived from malonic acid or malononitrile) with urea or guanidine, lead to the formation 2-hydroxy-4,6-diaminopyrimidine and TAP (Scheme 1).

The weaker electrophilicity of an amide carbonyl compared with malonic acid is consistent with the observed yields, and with a preference for 2-amino-4,6-dihydroxypyrimidine formation in presence of guanidine (Figure 1). In support of this proposed reaction pathway, a guanidine solution with malondiamide added showed TAP production by mass spectrometry after 3 days of dry/wet cycles at 85 °C (Figure S5).

These results show that the synthesis of 2,4,6-trisubstituted pyrimidines is possible in mild, prebiotically plausible conditions, by the condensation of malonic acid with urea or guanidine in a simple evaporative setting. This dry-wet warm little pond model, would also promote the prebiotic local concentration of relevant pyrimidines through precipitation/crystallization.

Dilution of the reaction mixture with water after 2 days of dry/wet cycles results in the formation of a flocculent precipitate, which is observed to dissolve in a concentrated urea solution and to re-precipitate upon dilution. The separation of the precipitate and its analysis by Orbitrap mass spectrometry, after dissolution in a methanol/water/ammonia solution, revealed the formation of barbituric acid, melamine, and the acetyl and carbamoyl derivatives of these bases. The fragmentation of *m/z* 170.0560 in positive mode (Figure S6a) suggests it corresponds to barbituric acid acetylated at C5 (expected due to stabilization by its aromatic ring) rather than the acetyl ester. The reaction temperature is an important factor in the process, as the formation of the precipitate and the acetyl and carbamoyl derivatives is favored at of 85 °C, whereas at 65 °C the crystallization of bases is preferred (Figure 2B).

Overall, the composition of products fpr reactions carried out in the range 65–85 °C is similar, but increased temperature favors both the decarboxylation of malonic acid to acetic acid and the formation of isocyanic acid from urea. As a result, the experiments performed at 85 °C shows an increase in acetylated and carbamoylated pyrimidines, as well as in melamine. The formation of 2-amino-4,6-dihydroxy-5-acetyl pyrimidine is preferred relative to the formation of acetyl esters by resonance stabilization. It is interesting to note that the precipitation of

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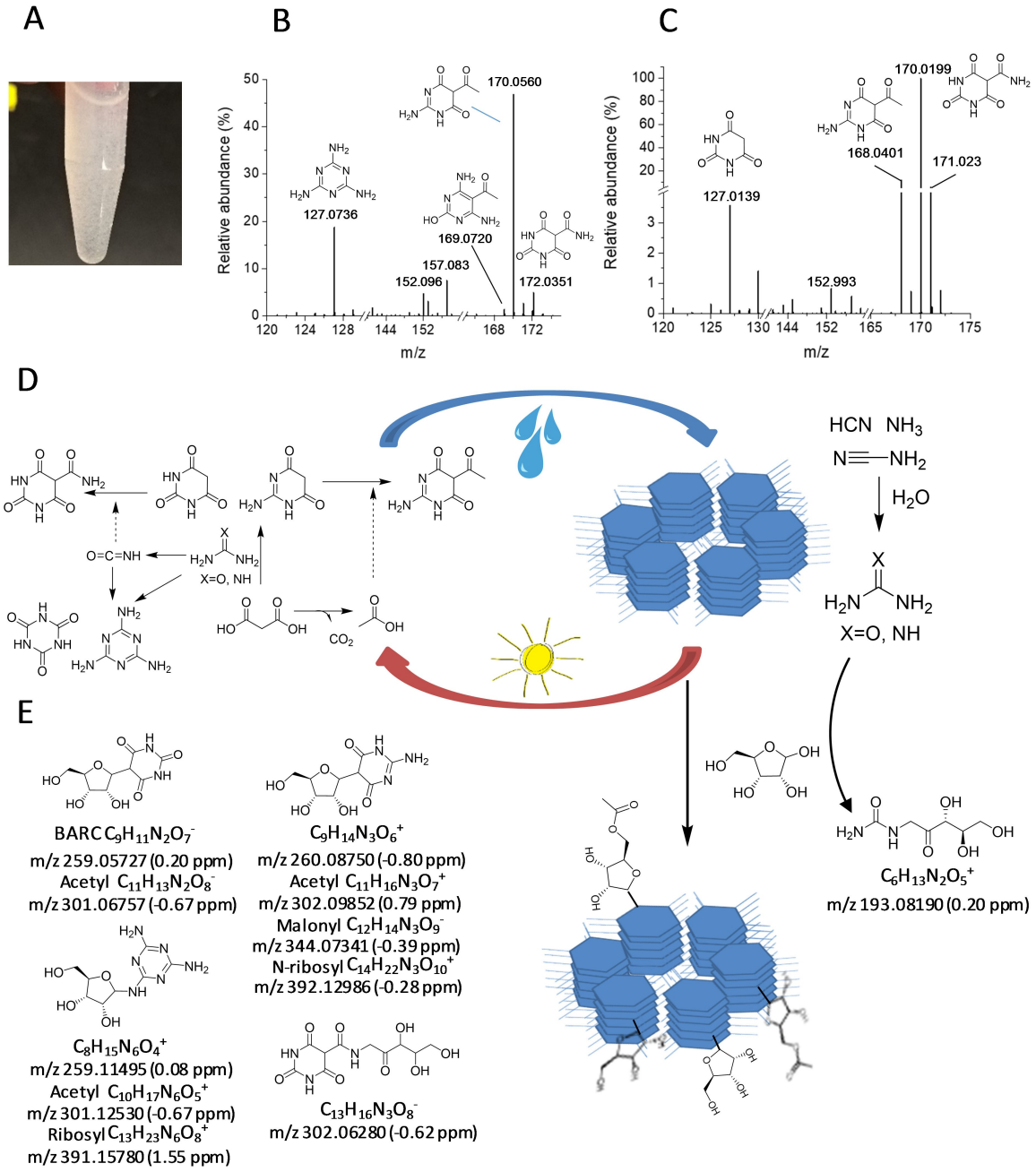

Figure 2. A) Reaction tube showing the formation of a pyrimidine precipitate after dilution with water of the product of wet-dry cycles at 85 °C of a urea/guanidine solution to which malonic acid was added. B) Positive-ion mode-electrospray mass spectrum obtained after dissolution of precipitates in an ammoniacal water-methanol solution. C) Mass spectrum (negative-ion mode) of the precipitate dissolved in ammoniacal water/methanol, showing the exact masses of identified compounds. D) Dry-wet reaction model. Dehydration of the urea-rich solution led to the condensation of urea and malonic acid, forming pyrimidines. This decomposition of urea into isocyanic acid could be the key step in the formation of 5-carbamoylpyrimidines and triazines. In the next phase of rehydration and dilution, previously formed pyrimidines could form by base pairing supramolecular aggregates (blue hexagons) that precipitate. An increase in the concentration of urea, by evaporation or input of urea by hydrolysis of hydrogen cyanide or cyanamide, could dissolve the aggregates totally or partially. Hence, base pairing and dry-wet cycles could be a selection and concentration mechanism of nucleobases formed previously in urea solutions; E) Experimental *m/z*, mass error and possible structures to relevant products found in the reaction between ribose and nucleobase aggregates.

supramolecular aggregates is favored when acetyl and carbamoyl derivatives of pyrimidines are present. Nevertheless, it could be more easily explained by the increase of formation of melamine, whose insoluble aggregate with barbituric acid derivatives precipitates even at very low concentrations. Hence, a urea solution in a wet–dry scenario at moderate temperatures provides a single environment for the synthesis and selection and the selective local concentration of nucleobases through the formation of supramolecular aggregates that contain Watson-Crick-like base-pairs (such as case of barbituric acid

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with melamine, Figure 2), coprecipitation with aggregates, by trapping in the flocculent precipitates, or formation of other low solubility structures (case of barbituric acid-TAP precipitate, for which it has not been demonstrated the formation of hexameric rosettes).

The pyrimidines of the barbituric acid family could have played a key role in chemical evolution through the spontaneous formation of supramolecular aggregates and C-glycosides by reaction with aldoses, preferential at the C5 ring position, even in the presence of amino groups (in the instance of TAP). Considering an input of sugars from external sources, the presence of such pyrimidine bases could harvest the reactive aldoses, resulting in the concentration of these non-canonical nucleosides through the formation of insoluble supramolecular aggregates. The synthesis in the urea-rich scenario is unlikely, due to the reactivity of urea with aldehyde precursors (impairing formose reaction) or glyoxylic acid (inhibiting the glyoxylate scenario) and forming the corresponding urea derivatives. If aldose-reactive nucleobases were accumulated as aggregates as a form of *prebiotic organic mineral*, further input of sugars could lead to the formation of glycosides and their gradual accumulation and preservation in the form of supramolecular aggregates. To test this concept, we collected by centrifugation the precipitates formed by condensation of malonic acid in a viscous urea/guanidine mixture and heated the precipitates with ribose in solution at 70 °C for 6 hours. In a similar experiment, after wet/dry cycles of a urea/guanidine and malonic acid solution, ribose was added during the last wet/dry cycle, with no previous separation of precipitates. The products of both reactions were analyzed by mass spectrometry, showing the exacts masses corresponding to 5-ribosyl-barbituric acid (BARC, confirmed by fragmentation and exact mass, after a control experiment showed in Figure S7), 5-ribosyl-2-aminopyrimidine-4,6-diol, the C-nucleoside of 2,4,6-triaminopyrimidine (TARC), and N-riboside of melamine (Figure 2). It is interesting to note that the formation of monoacetyl-nucleosides is common, as confirmed by observation of the exact *m/z* of monoacetyl derivatives of all identified nucleosides (Table S1). Regarding the formation of malonic acid esters, we only identified the malonyl ester of 5-ribosyl-2-aminopyrimidine-4,6-diol. The formation of dicarboxylic acid esters is predictable, but, in this case, malonic acid is too prone to decarboxylation, leading to the observed acetyl esters. The formation of C-nucleoside of 2-aminopyrimidine-4,6-diol and TARC are demonstrated by the identification of the exact *m/z* of the corresponding di-ribosides. All identified species formed are listed in Table S1. The resulting qualitative composition in both experiments is similar. As expected, the addition of ribose to the urea-rich pond model in one-pot reaction without previous separation of precipitates, lead to ribosyl-urea (Figure 2E) and unidentified species. Hence, the separation and stabilization of non-canonical nucleobases from the urea solution appears to be necessary before glycosylation can happen with ribose or other sugars. The above proposed mechanism for the gradual, local concentrating of heterocycles that form supramolecular aggregates might thefore have also been important for preserving pairing heterocycles in the same location over time, until conditions were favorable for the production of proto-nucleosides as building blocks for a potential pre-RNA molecule.

In summary, we have shown that the condensation of malonic acid and urea or urea/guanidine in a prebiotic scenario, as might have existed on the prebiotic Earth in evaporating warm ponds at moderate temperatures, can lead to a mixture of pyrimidines and triazines. Furthermore, the same molecules can undergo in the spontaneous selection from solution and local partitioning with pairing partners in supramolecular assemblies and glycosylation to produce plausible proto-nucleosides, if a suitable sugar is present. All together, this urea-rich *little warm pond* scenario could provide a prebiotic mechanism for the formation, concentration and selection of pre-RNA building blocks, powered by cycles of synthesis, precipitation, and redissolution, associated to environmental dry/wet cycles in the surface of early Earth.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: nucleosides · origins of life · prebiotic chemistry · pyrimidines · urea

[1] M. W. Powner, J. D. Sutherland, *Philos. Trans. R. Soc. B Biol. Sci.* **2011**, *366*, 2870–2877.
[2] J. D. Sutherland, *Angew. Chem. Int. Ed.* **2016**, *55*, 104–121.
[3] M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242.
[4] H. Okamura, S. Becker, N. Tiede, S. Wiedemann, J. Feldmann, T. Carell, *Chem. Commun.* **2019**, DOI 10.1039/C8CC09435G.
[5] S. Becker, I. Thoma, A. Deutsch, T. Gehrke, P. Mayer, H. Zipse, T. Carell, *Science* **2016**, *352*, 833–836.
[6] H.-J. Kim, S. A. Benner, *Proc. Mont. Acad. Sci.* **2017**, 201710778.
[7] A. E. Engelhart, N. V. Hud, *Cold Spring Harbor Perspect. Biol.* **2010**, *2*, 1–21.
[8] N. V. Hud, B. J. Cafferty, R. Krishnamurthy, L. D. Williams, *Chem. Biol.* **2013**, *20*, 466–474.
[9] B. J. Cafferty, N. V. Hud, *Curr. Opin. Chem. Biol.* **2014**, *22*, 146–157.
[10] N. V. Hud, *Synlett* **2017**, *28*, 36–55.
[11] B. J. Cafferty, D. M. Fialho, J. Khanam, R. Krishnamurthy, N. V. Hud, *Nat. Commun.* **2016**, *7*, 1–8.
[12] D. M. Fialho, K. C. Clarke, M. K. Moore, G. B. Schuster, R. Krishnamurthy, N. V. Hud, *Org. Biomol. Chem.* **2018**, *16*, 1263–1271.
[13] R. Navarro-González, A. Negrón-mendoza, E. Chacón, *Origins Life Evol. Biospheres* **1989**, *19*, 109–118.
[14] R. Lohrmann, *J. Mol. Evol.* **1972**, *1*, 263–269.
[15] L. Stanley Miller, *Science* **1953**, *117*, 528–529.
[16] B. Burcar, M. Pasek, M. Gull, B. J. Cafferty, F. Velasco, N. V. Hud, C. Menor-Salván, *Angew. Chem. Int. Ed.* **2016**, *55*, 13249–13253.
[17] C. Menor-Salván, M. R. Marín-Yaseli, *Chem. Eur. J.* **2013**, *19*, 6488–6497.
[18] C. Menor-Salván, D. M. Ruiz-Bermejo, M. I. Guzmán, S. Osuna-Esteban, S. Veintemillas-Verdaguer, *Chem. Eur. J.* **2009**, *15*, 4411–4418.

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[19] C. He, I. Gállego, B. Laughlin, M. A. Grover, N. V. Hud, *Nat. Chem.* **2017**, *9*, 318–324.
[20] M. C. Chen, B. J. Cafferty, I. Mamajanov, I. Gállego, J. Khanam, R. Krishnamurthy, N. V. Hud, *J. Am. Chem. Soc.* **2014**, *136*, 5640–5646; C.V. Mungi, S.K. Singh, J. Chugh, S. Rajamani, *Physical Chemistry Chemical Physics* **2016**, *18*, 20144-20152.
[21] C. Menor-Salván in *Prebiotic Chemistry and Chemical Evolution of Nucleic Acids* (Ed.: C. Menor-Salvn), Springer International, Basel, **2018**, pp. 85–142.
[22] S. Becker, J. Feldmann, S. Wiedemann, H. Okamura, C. Schneider, K. Iwan, A. Crisp, M. Rossa, T. Amatov, T. Carell, *Science* **2019**, *366*, 76–82.
[23] U. P. Trinks, *Zur Chemie der Aminopyrimidine*, Eidgenössischen Technischen Hochschule Zürich (Switzerland), **1987**.
[24] G. Springsteen, J. R. Yerabolu, J. Nelson, C. J. Rhea, R. Krishnamurthy, *Nat. Commun.* **2018**, *9*, 91.
[25] J. C. Ambelang, T. B. Johnson, *J. Am. Chem. Soc.* **1941**, *63*, 1289–1291.
[26] E. Smolin, L. Rapoport, *The Chemistry of Heterocyclic Compounds*. S-Triazines and Derivatives, Interscience, New York, **1959**.
[27] M. Hernández-Rodríguez, J. Xie, Y. M. Osornio, R. Krishnamurthy, *Chem. Asian J.* **2011**, *6*, 1252–1262.
[28] S. Becker, C. Schneider, H. Okamura, A. Crisp, T. Amatov, M. Dejmek, T. Carell, *Nat. Commun.* **2018**, *9*, 1–9.

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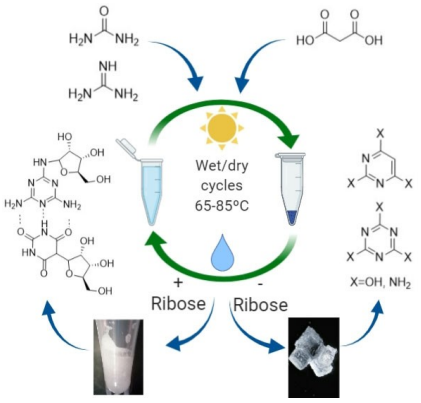
COMMUNICATIONS

Pools of water enriched with urea would have been an efficient source for the formation of noncanonical pyrimidines. In the presence of aldose sugars, bases from these pools could react with the sugars through spontaneous glycosylation, ultimately concentrating de novo nucleosides through aggregation. We demonstrate how such a setting could lead to noncanonical nucleosides on a prebiotic Earth.



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