PREBIOTIC CHEMISTRY

Unified prebiotically plausible synthesis of pyrimidine and purine RNA ribonucleotides

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Theories about the origin of life require chemical pathways that allow formation of life's key building blocks under prebiotically plausible conditions. Complex molecules like RNA must have originated from small molecules whose reactivity was guided by physico-chemical processes. RNA is constructed from purine and pyrimidine nucleosides, both of which are required for accurate information transfer, and thus Darwinian evolution. Separate pathways to purines and pyrimidines have been reported, but their concurrent syntheses remain a challenge. We report the synthesis of the pyrimidine nucleosides from small molecules and ribose, driven solely by wet-dry cycles. In the presence of phosphate-containing minerals, 5′-mono- and diphosphates also form selectively in one-pot reactions. The pathway is compatible with purine synthesis, allowing the concurrent formation of all Watson-Crick bases.

The discovery of catalytic RNA (*1*) and the development of replicating RNA systems (*2*, *3*) have lent strong support to the concept of an RNA world (*4*). The RNA world hypothesis predicts that life started with RNAs that were able to (self-)recognize and replicate. Through a process of chemical evolution, a complex RNA and later RNA–peptide and protein world supposedly evolved, from which life ultimately emerged (*4*). A prerequisite for the RNA world is the ability to create RNA under prebiotic conditions. This requires as the first elementary step the concurrent formation of pyrimidine and purine nucleosides in the same environment. They must have condensed to form information-carrying polymers able to undergo Darwinian evolution. The question of how the pyrimidine and purine nucleosides could have formed together is an unsolved chemical problem that is under intensive chemical investigation (*5*–*9*). Starting from an early atmosphere mainly composed of N_2 and CO_2 (*10*), the abiotic synthesis of life's building blocks must have occurred on the early Earth in aqueous environments, whose characteristics were determined by the minerals and chemical elements from which the early Earth's crust was made (*11*, *12*). Atmospheric chemistry, impact events, and volcanic activities must have provided the first reactive small molecules. These reacted in surface or deep-sea hydrothermal vents (*13*–*15*), on mineral surfaces (*16*), or in shallow ponds (*17*). Within these environments, volcanic activity, and seasonal or day-night cycles caused fluctuations of pH and temperature. Such fluctuations provided wet-dry conditions allowing precipitation or crystallization of chemicals (*18*). Mixing of microenvironments may have opened up new reaction pathways that led to increasing chemical complexity.

Along these geophysical boundaries, two main reaction pathways have been proposed for the formation of purine and pyrimidine nucleosides. The synthesis of the purines is possible along a continuous pathway based on the reaction of formamidopyrimidine (FaPy) precursors with ribose (*6*, *18*). For the pyrimidines, a reaction sequence involving aminooxazoles has been discovered (*5*). These pathways provide the corresponding nucleosides under very different and partially incompatible conditions, leaving unanswered the question of how purines and pyrimidines could have formed in the same environment. Here, we report a prebiotically plausible pathway to pyrimidine nucleosides that selectively provides the 5′-mono- and 5′-diphosphorylated nucleosides needed for RNA strand formation. By connecting the pathway with the reported purine route (*6*, *18*), we establish a unifying reaction network that allows for the simultaneous formation of both types of nucleosides in the same environment and that is driven by wet-dry cycles.

Results

Prebiotically plausible synthesis of pyrimidine nucleosides

The chemistry leading to pyrimidines starts from cyanoacetylene **1** as the key building block (Fig. 1A). Compound **1** is observed in interstellar clouds and in the atmosphere of Titan (*19*). It has been shown to form in large quantities by electric discharge through a CH_4-N_2 atmosphere (*20*) and is also a product of the Cu(II)-mediated reaction of HCN and acetylene in water (Fig. 1B) (*21*). A recent report suggested that molecules such as **1** are plausible prebiotic starting materials which could have formed in surface hydrothermal vents in significant concentrations (*13*). We found that **1** reacts quickly and cleanly with hydroxylamine **2** or hydroxylurea **3** to give 3-aminoisoxazole **4**. The reaction of **1** with **3** proceeds under slightly basic conditions (pH ~10) with 80 to 90% yield within 2 hours. **3** is formed in almost quantitative yields from the reaction of **2** with cyanate (*22*). Compound **4** formed robustly even if we varied the temperature (10° to 95°C), the reactant concentrations (10 to 100 mM), or added additional compounds, such as urea **5** and/or different metal ions (see below). Reaction of cyanoacetylene **1** with hydroxylamine **2** produced **4** with 17% yield after 2 hours at pH 10.

While hydroxylamine **2** is an accepted building block for prebiotic amino acid syntheses (*23*), its potential formation on the early Earth is unclear. We therefore aimed to demonstrate its prebiotic availability. **2** is ultimately produced by reduction from NO, which is formed in large quantities when lightning passes through moist atmospheres containing N_2 and CO_2 (Fig. 1B) (*10*). NO forms as the main product under these conditions and spontaneously reacts in the presence of water to form nitrite (NO_2^-) and nitrate (NO_3^-), and this leads to the assumption that both anions were quite abundant on the early Earth (*24*–*26*). With Fe(II) as a plausible prebiotic reductant, NO_2^- is converted to NH_3 but not to NH_2OH **2** (*26*). Formation of the latter requires a partial reduction. We found that this can be achieved with HSO_3^-, which forms from volcanic SO_2 and water (*27*). NO_2^- and HSO_3^- react to **2** with up to 85% yield (Fig. 1B and fig. S1) (*28*). We confirmed that this reaction gives first hydroxylamine disulfonate **6** (Fig. 1B), which hydrolyzes to hydroxylamine **2** and HSO_4^-. We found that intermediate **6** reacts with cyanoacetylene **1** as well (88% yield) (Fig. 1B and fig. S2) to give the stable olefin **7**, which upon hydrolysis provides again the key intermediate **4**. The overall yield of **4** via compound **7** is 63% over these two steps. The suggested pyrimidine intermediate **4** is therefore readily available from cyanoacetylene **1** upon reaction with either **2**, **3**, or **6** under prebiotic conditions (Fig. 1B).

When we added urea **5** to a solution of **4**, warming (70° to 95°C) and dry-down resulted in formation of *N*-isoxazolyl-urea **8** (Figs. 1A and 2A) in a spot-to-spot reaction that is catalyzed by Zn^{2+} or Co^{2+}. These metal ions were likely present on the early Earth (*11*, *12*). In the presence of Zn^{2+}, compound **8** is formed in 88% yield after 2 days at 95°C (at 70°C, the same yield is obtained after ~2 to 3 weeks). With Co^{2+}, 68% yield is achieved after 2 days

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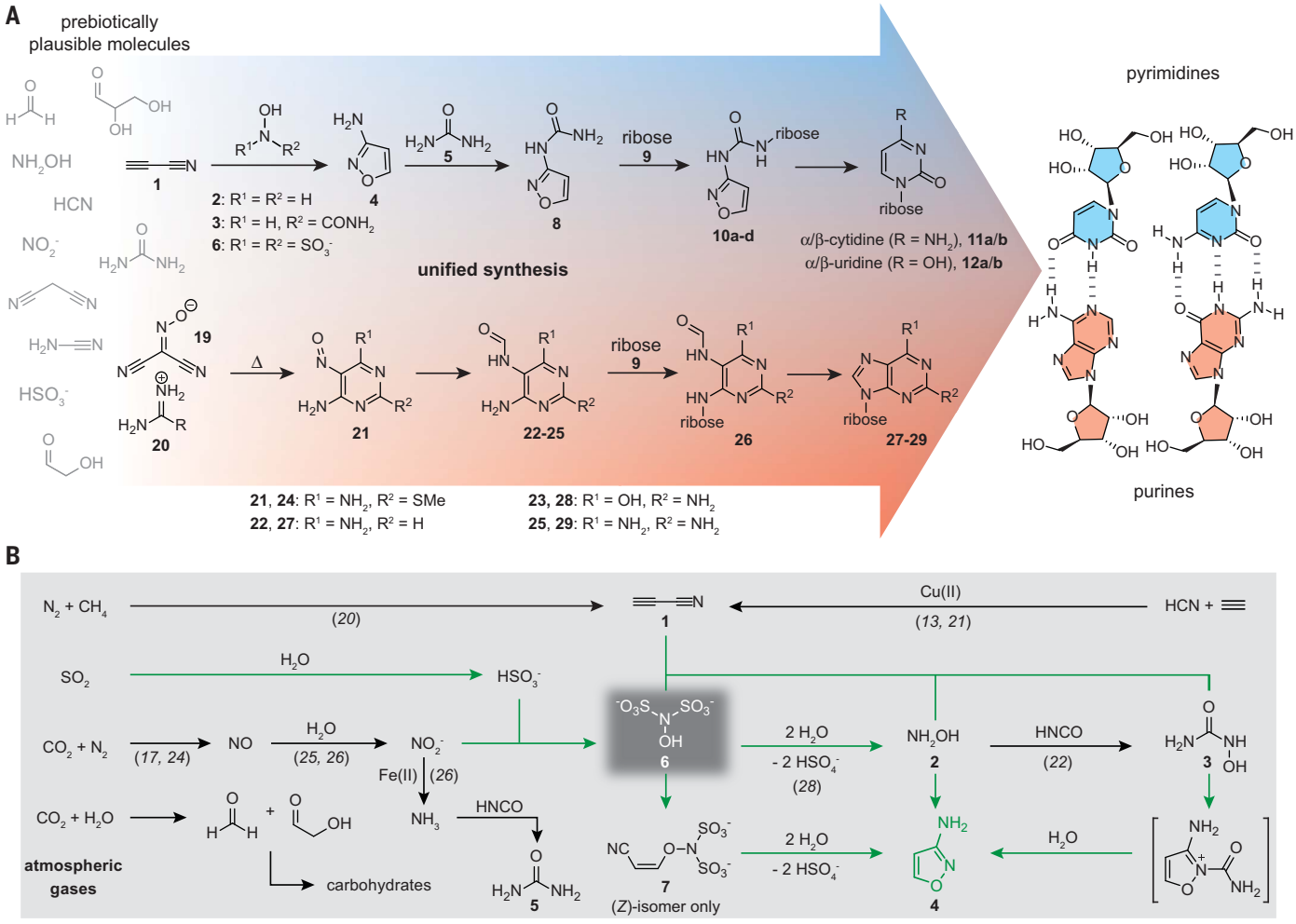

Fig. 1. Unified synthesis of pyrimidine and purine RNA building blocks. (**A**) Starting from plausible prebiotic molecules, the reaction scheme depicts the route toward the pyrimdines via isoxazolylurea **8** (blue background) and the purines via formamidopyrimidines **22** to **25** (red background) (*18*). (**B**) Fundamental chemistry that produces the molecules needed for the pyrimidine pathway. Reactions performed in this work are shown with green arrows, while black arrows represent well-known reactions. Formation of **4** requires reaction of **1** with hydroxylamine **2**, hydroxylurea **3**, or the disulfonate **6** (dark-gray box). **6** is formed from NO_2^- and SO_2/HSO_3^-.

at 95°C. The reaction of **4** to **8** is in all cases a clean process, with the only impurity being unreacted **4** (Fig. 2A). The product **8** can be subsequently physically enriched. Addition of carbonated water to the dried reaction mixture solubilizes **4**, **5**, and **8**, leaving behind the metal ions as hydroxides or carbonates. Subsequent concentration of the supernatant leads to spontaneous crystallization of **8** (55%). This allowed us to obtain a crystal structure of **8** (fig. S3). In order to simulate early Earth chemistry, we performed a one-pot experiment. We mixed **1** with **3**, **5**, and Zn^{2+} or Co^{2+} in a carbonate solution (pH ~10) and obtained compound **4** at 95°C (80 to 90%). Neutralizing the solution to pH ~6 to 7, which may have occurred on the early Earth as a result of acidic rain, followed by dry-down at the same temperature, provided compound **8** with yields between 56% (Zn^{2+}) and 40% (Co^{2+}). The continuous synthesis of the key building block **8** was consequently achieved in a plausible prebiotic setting that could have existed in hydrothermal vents or near volcanic activity, both of which would be able to provide elevated temperatures (fig. S3). The synthesis is also possible at lower temperatures, but with extended reaction times.

For the final step toward nucleosides, we need to assume that, due to flooding or a mixing of environments, **8** came into contact with ribose **9** (Figs. 1A and 2B) or any other sugar unit, such as threose (for TNA) or glyceraldehyde (for GNA), that was able to form a backbone for a pairing system (*29*, *30*). When we mixed **8** with ribose **9** and warmed the mixture to 95°C in the presence of boric acid, we observed a fast and high-yielding reaction that provided the ribosylated products **10a** to **10d** with 95% yield (fig. S4a). Other borate minerals, such as synthetic lüneburgite $\{Mg_3[(PO_4)_2|B_2(OH)_6]\cdot 6H_2O\}$ (*31*) or borax $\{Na_2[B_4O_5(OH)_4]\cdot 10H_2O\}$ (*32*), were also able to catalyze this reaction with high yields (>70%) (fig. S5). The major products were initially the α- and β-pyranosides (**10c** and **10d**), which dominate over the α- and β-furanosides (**10a** and **10b**) (fig. S4a). After heating the mixture under slightly basic conditions at 95°C in the presence of borates, the furanosides (54%; **10a** and **10b**) (Fig. 2B) gradually became the dominant products (fig. S4b). Under these conditions, we also observed hydrolysis of **10a** to **10d** to **8** and **9**. The accumulation of the furanosides **10a** and **10b** is best explained by complexation of their *cis*-diols with borate (*32*).

The final step toward pyrimidine nucleosides requires reductive opening of the isoxazole N-O bond, followed by tautomerization, intramolecular cyclization, and water elimination in a cascade-like fashion (Fig. 2, C and D). We found that this reaction occurred rapidly with Fe^{2+} in the presence of thiols (Fig. 2D) (*33*). Liquid chromatography–mass spectrometry (LC-MS) analysis indicated that cytidine nucleosides **11a** to **11d** formed efficiently under

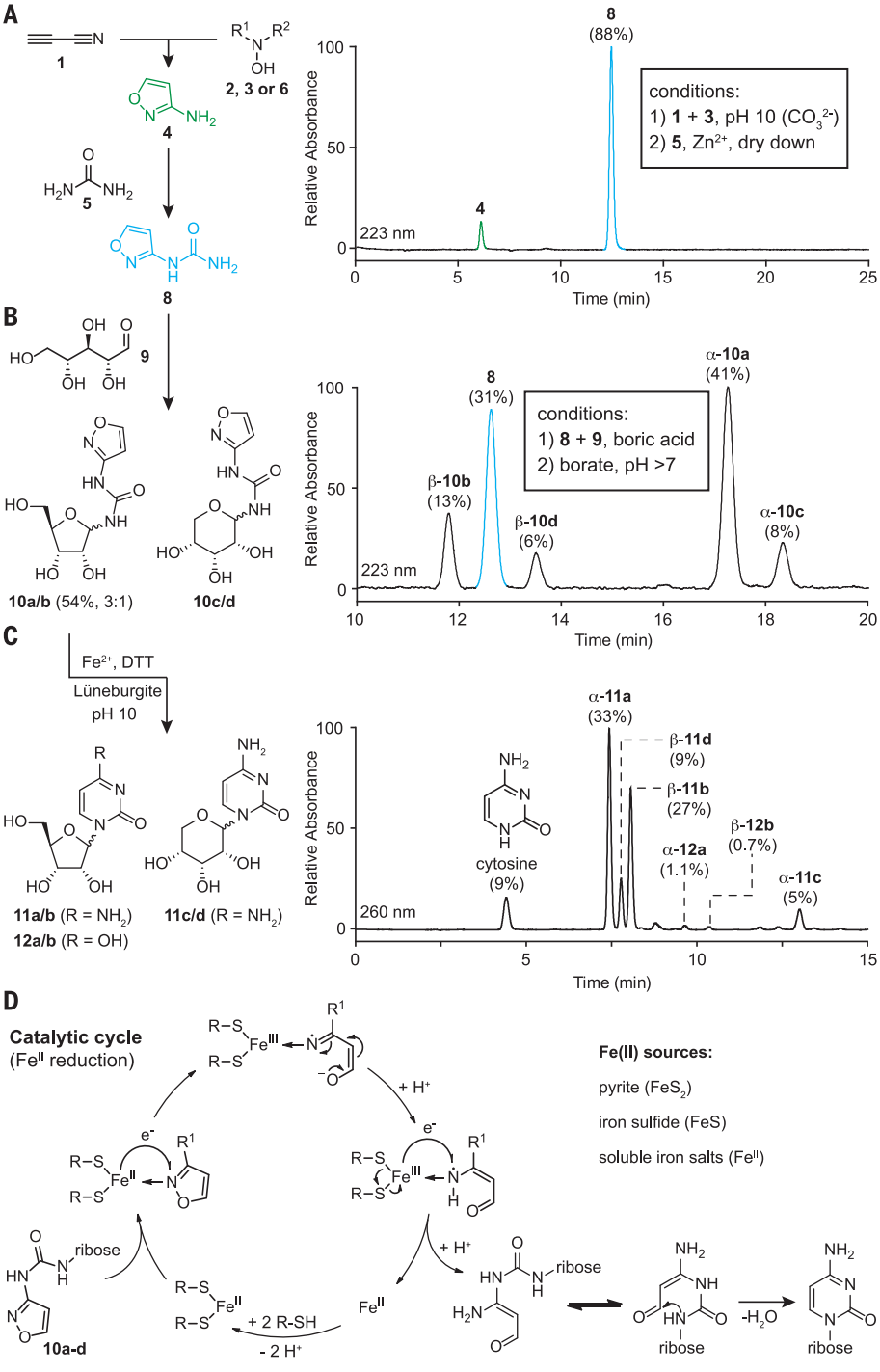

Fig. 2. Formation of pyrimidine nucleosides (11 and 12) from N-isoxazolylurea ribosides 10a and 10b. The different isomers are labeled as follows: **a** = α-furanosyl; **b** = β-furanosyl; **c** = α-pyranosyl; **d** = β-pyranosyl. (**A**) Formation of **4** and its conversion with urea **5** to *N*-isoxazolylurea **8**. (**B**) Ribosylation of **8** with ribose **9** and equilibration of the reaction mixture in the presence of borates gives the furanosidic isomers **10a** and **10b** (54%). (**C**) Pyrimidine nucleoside formation by reductive N-O cleavage from the compound mixture of **10a** and **10b** in the presence of ammonium iron(II) sulfate hexahydrate (0.0005 equiv.). The HPLC results with detection at 260 nm show formation of cytidine (C; **11a** to **11d**) and uridine (U; **12a** and **12b**). (**D**) Proposed catalytic cycle for the Fe^{2+} catalyzed reduction of the N-O bond of the isoxazole moiety.

these conditions, with the furanosidic uridine nucleosides **12a** and **12b** as the corresponding deamination products formed by hydrolysis (Fig. 2C). Reductive pyrimidine formation can be performed with FeS or the mineral pyrite (FeS_2), and both have been discussed in the context of early metabolic pathways (*15*, *34*). Just 0.0001 equiv. of soluble Fe^{2+} in water is sufficient for the reaction. In the absence of Fe^{2+}, pyrimidine formation was not observed. The reduction also appears to be independent of the thiol source, as the products **11a** to **11d** and **12a** and **12b** were obtained regardless of whether we used dithiothreitol (DTT), propanedithiol, mercaptoethanol, or cysteine (fig. S6).

Selective one-pot formation of 5′-nucleoside mono- and diphosphates

The addition of naturally occurring minerals such as hydroxyapatite, colemanite, or (synthetic) lüneburgite to the reductive pyrimidine-forming reaction mixture had a strong influence on the distribution of the four cytidine isomers. Synthetic lüneburgite gave a combined high yield of 85% (Fig. 2C). The natural furanosidic β-cytidine (**11b**) and its α-anomer (**11a**) are formed under these conditions with about the same yields, together with small amounts of α- and β-uridine (**12a** and **12b**). We found only small amounts of the α- and β-cytidine pyranosides (**11c** and **11d**), together with the cytosine base. Because synthetic lüneburgite is known to enable nucleotide formation in the presence of urea (Fig. 3A) (*31*), we simply added urea to the one-pot reaction mixture after pyrimidine formation and allowed the mixture to evaporate to dryness at 85°C over a period of about 20 hours. LC-MS analysis of the reaction mixture showed formation of phosphorylated nucleosides (Fig. 3A) in a substantial 19% yield relative to that for cytidine (Fig. 3B and fig. S7). We assumed that the reaction generated the α- and β-cytidine 5′-monophosphates **13a** and **13b** and the 5′-diphosphorylated cytidines **14a** and **14b**. Owing to hydrolysis, we also expected some α- and β-uridine 5′-monophosphates and 5′-diphosphates **15a** and **15b** and **16a** and **16b**. We isolated the corresponding high-performance LC (HPLC) peaks and removed the phosphate groups enzymatically (Fig. 3, B and C). LC-MS analysis showed the dephosphorylated furanosides **11a** and **11b** and **12a** and **12b** with over 94% in the nucleoside pool, which corresponds to a change of the furanoside/pyranoside ratio from an initial 4:1 to 17:1 (Fig. 3C). The formation of phosphorylated pyranosides **17** are only a minor side reaction. We found no discrimination between α- and β-anomers during the phosphorylation. The furanoside enrichment is best explained by the presence of a primary hydroxyl group in the furanosides which is absent in the pyranosides. The enrichment of 5′-nucleoside monophosphates and diphosphates under these one-pot conditions establishes a further

chemical selection step that favors the furanosides as the components of RNA. We further characterized the structures of the phosphorylated nucleosides and confirmed the formation of the 5′-α- and 5′-β-cytidine mono- and diphosphates (**13a**, **13b**, and **14a**, **14b**; α-/β-CMP and α-/β-CDP) (fig. S8). Additional analysis allowed identification of α,β-UDP **16a** and **16b** (fig. S9). 5′-Pyrophosphates are the dominating species within the diphosphorylated nucleoside mixture (fig. S8a).

Compatible formation of pyrimidine and purine RNA nucleosides

We next investigated if the prebiotically plausible pyrimidine and purine nucleoside pathways are compatible with each other so that they can be connected with the goal to form all Watson-Crick building blocks in the same environment, driven solely by wet-dry cycles. The purine synthesis (*18*) requires as the initial step a reaction of malononitrile **18** with sodium nitrite to give (hydroxyimino)malononitrile **19**. Because malononitrile **18** can be also generated from cyanoacetylene **1**, as shown by Eschenmoser (*35*), pyrimidines and purines can be traced back to the same chemical root (Fig. 4). Compound **19** forms an organic salt with amidines **20** to give nitroso-pyrimidines **21** and, upon reduction and formylation, FaPys (**22** to **25**). The latter can react with ribose **9** to give ribosylated FaPy **26** and then purine nucleosides **27** to **29** (Fig. 1A) (*18*). To investigate how the chemical conditions needed for pyrimidine formation from the urea-isoxazole **8** would affect purine formation, we reacted **8** and the FaPy compounds **22** and **23** with ribose **9** under dry-down conditions. We performed the reaction under identical conditions but in separate reaction vials (Fig. 4). Under these conditions, formation of all four Watson-Crick nucleosides, cytidine **11,** uridine **12**, adenosine **27**, and guanosine **28**, were detected.

We next investigated if pyrimidines and purines can form simultaneously in the same environment (Fig. 5A). For this experiment, we mixed the starting materials cyanoacetylene **1**, hydroxylurea **3**, (hydroxyimino)malononitrile **19**, and amidine **20** under slightly basic conditions (pH ~10). Analysis of the mixture indeed showed formation of **4** with 86% yield, despite the presence of **19** and **20**. It is surprising that the N-OH functionality of compound **19** does not interfere with the formation of **4**. Compound **4** is a liquid that can enrich from a water solution by dry-down, owing to its high boiling point (228°C). Compound **4** can act as a solvent to facilitate the formation of **21** from the reaction of **19** with **20** under milder conditions (50°C to 100°C instead of 126°C), in contrast with results from a previous experiment (*18*). The next step requires reduction and formylation of **21** to the FaPy intermediate, but this step cannot be performed in the presence of the isoxazole. Addition of a water mixture eventually containing urea **5** leads to spontaneous precipitation of **21**. The supernatant containing **4** and **5** can flow away. The water-insoluble **21**, if brought into contact with dilute formic acid and Zn (found in Earth's crust), reacts immediately to form the compounds **22** and **24** with Zn^{2+} as a side product (Fig. 5A and fig. S10a). These reaction products are water-soluble and can potentially recombine with **4** and **5**. The side product Zn^{2+} can then catalyze the reaction of **4** in the presence of **5** to give *N*-isoxazolyl urea **8** in the presence of **22** and **24** (Fig. 5A and fig. S10b). This leads to the formation of the pyrimidine and purine precursors **8**, **22**, and **24**, which can be transformed into the purine and pyrimidine nucleosides. In this scenario, intermediate **4** of the pyrimidine pathway helps formation of the purine precursor **21**, while Zn^{2+} as a side product of the purine pathway mediates formation of the pyrimidine precursor **8** in a mutually synergistic way, driven by wet-dry cycles.

We combined **8** with different FaPy intermediates and investigated if they reacted in a one-pot scenario with ribose **9** to finally give the purine and pyrimidine nucleosides. To examine this, we dissolved a mixture of **8**, **22**, **25**, ribose **9**, and boric acid and warmed the mixture to 95°C for 14 hours, allowing for slow evaporation of water. The solid material was then taken up with a slightly basic solution containing Fe^{2+} (0.0005 equiv.) and DTT (1.5 equiv.), and we allowed the mixture to warm to 95°C. HPLC-MS analysis proved that these conditions simultaneously provided the purine and pyrimidine nucleosides with cytidine (**11a** to **11d**) and adenosine (**27**) as the

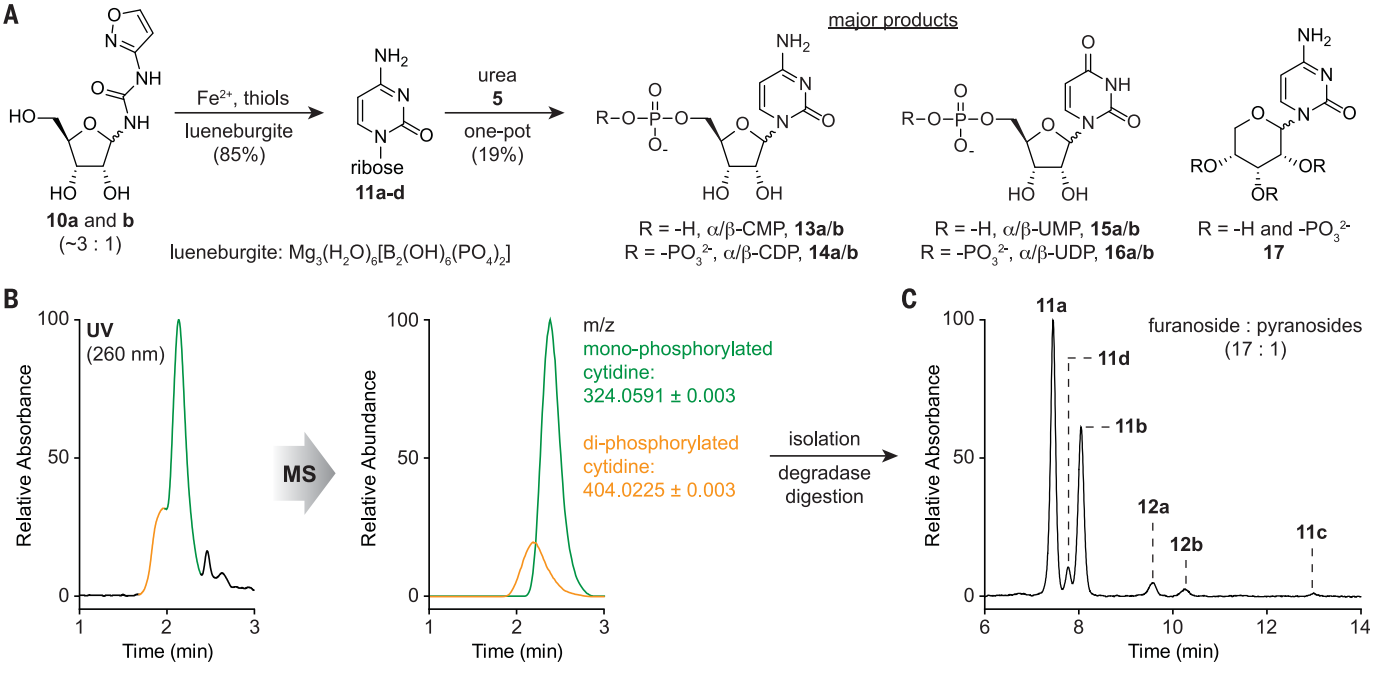

Fig. 3. One-pot nucleotide formation reaction. (**A**) One-pot synthesis of cytidine and uridine 5′-mono- and 5′-diphosphates (**13a** and **13b** to **16a** and **16b**) after urea addition to the reaction mixture and allowing the mixture to dry-down at 85°C for 20 hours. **a/b** represent the α- and β-anomers, respectively. (**B**) LC-MS analysis of the corresponding nucleotide peaks with UV and MS detection and isolation of the formed nucleotides from the prebiotic reaction, followed by an enzymatic removal of the phosphate groups. (**C**) HPLC analysis of the dephosphorylated product mixture showing predominant formation of α- and β-cytidine **11a** and **11b**.

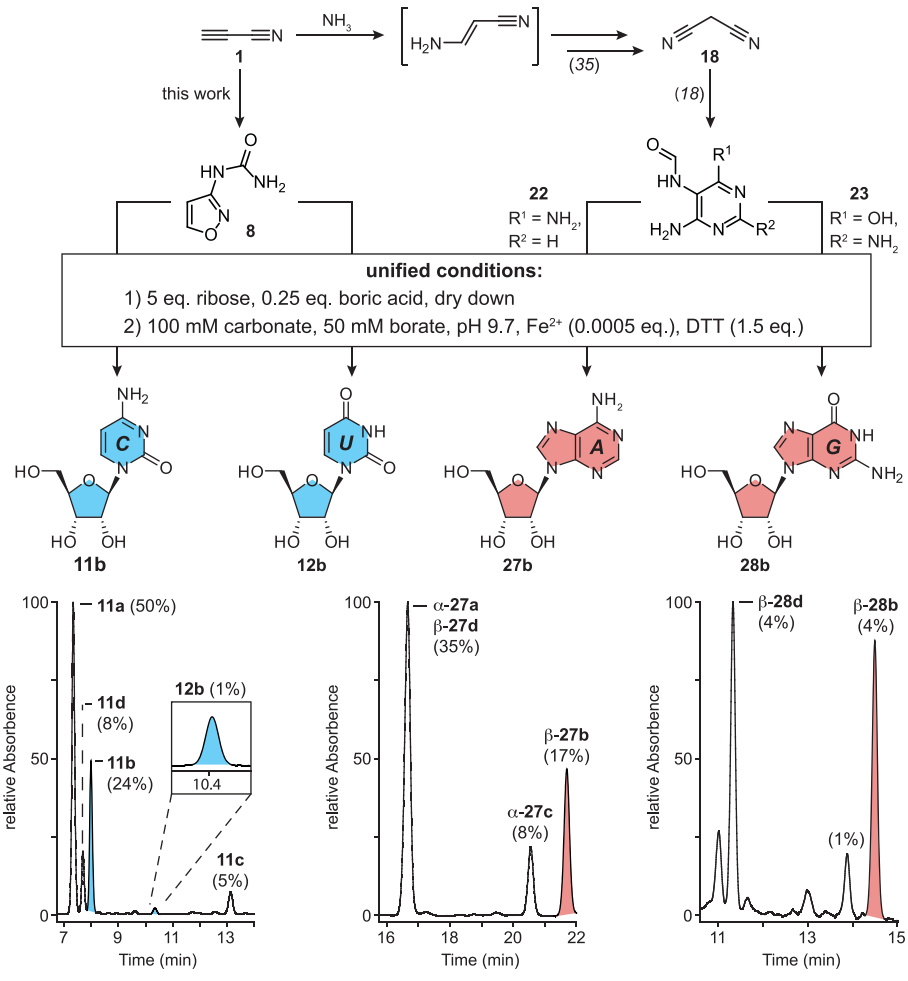

Fig. 4. Formation of all four Watson-Crick RNA building blocks in identical but parallel reactions. C (**11b**), U (**12b**), A (**27b**), and G (**28b**) are formed under the same conditions separately from **8**, **22**, and **23**. HPLC results are shown with a detection at 260 nm. The nucleosides are labeled as follows: **a** = α-furanosyl; **b** = β-furanosyl; **c** = α-pyranosyl; **d** = β-pyranosyl. Canonical pyrimidine and purine RNA building blocks are labeled in blue and red, respectively.

main products. Diaminopurine nucleosides (DA; **29**), which hydrolyze to guanosine **28**, form in this one-pot reaction as well (Fig. 5A, chromatogram). We noted additional formation of double-ribosylated adenine (rib_2-A). Furthermore, the nucleoside **28** was created in this scenario when we used **23** (R^1 = OH, R^2 = NH_2) as the starting material, but the yields were lower.

Discussion

Ribose-based RNA and the four canonical nucleosides, A, G, C, and U, are central to modern life and to prebiotic hypotheses, such as the "RNA world," in which RNA strands replicated and evolved to give increasingly complex chemical systems (*4*). Whether such RNAs were directly assembled from the canonical nucleotides (A, C, G, and U bases) or if they evolved from a simpler proto-RNA system is unclear (*36*).

Here we show that a reaction network toward the purine and pyrimidine RNA building blocks can be established, starting from simple atmospheric or volcanic molecules. Molecular complexity is generated by wet-dry cycles that can drive the chemical transformations. Therefore, any environment that was able to provide wet-dry phases might have been a suitable place for the origin of RNA building blocks. Our geochemical model assumes that chemistry took place in several basins that were needed to locally separate intermediates. We also needed one or two streams of water in our system to allow exchange of soluble molecules (Fig. 5B). Intermediates might precipitate upon fluctuations of physico-chemical parameters, allowing for the separation of soluble and insoluble materials (e.g., **4** and **21**). After further reactions, which reestablish solubility, the compounds can be recombined (Fig. 5B). For our scenario we need to assume that the early Earth provided environmental conditions that fluctuated between slightly acidic (pH 3), potentially caused by acidic rain (SO_2, NO_x), or basic (pH 10) caused by carbonates. Even though most of the chemistry described here was performed at elevated temperatures, the reactions also occur at lower temperatures, but with substantially longer reaction times. We can assume that temperatures fluctuated on the early Earth just like today due to day-night or seasonal cycles. Such fluctuations would certainly have brought about wet-dry cycles, akin to modern droughts and rain. The geophysical requirements needed for the reported chemistry, including elevated temperatures, could have existed in geothermal fields or at surface hydrothermal vents, which are plausible geological environments on early Earth.

Our proposed chemical pathways toward pyrimidines and purines begin with cyanoacetylene **1**, which could have formed in surface hydrothermal vents (*13*). Reaction of **2**, **3**, or **6** with **1** is the starting point for the pyrimidines, but if **1** reacts instead with ammonia, a pathway to malononitrile **18** as the precursor for purine synthesis is possible (Fig. 4) (*35*). Another key molecule for the synthesis of purines and pyrimidines is NO_2^-, which is needed to nitrosate malononitrile **18** to **19** (*18*). NO_2^- is also crucial for the formation of hydroxylamine in the presence of HSO_3^-, which is formed from volcanic SO_2 (*27*). The concentration of NO_2^- that is reachable in a prebiotic setting is under debate, but it is speculated that the most likely place for its accumulation is in shallow ponds, as needed for our scenario (*17*). In general, the limited stability of NO_2^- would not be an issue, provided that it is rapidly captured by HSO_3^- upon its formation. Our model assumes a surface environment, where molecules such as NO_2^-, HSO_3^-, or urea **5** could have been delivered by rain after their formation in the atmosphere (Fig. 5B) (*25*, *37*). Our chemistry shows that robust reaction networks can be established that allow all key intermediates to be generated efficiently from relatively complex mixtures, followed by their physical enrichment or separation on the basis of their solubility in water. Wet-dry cycles govern the formation of purine and pyrimidine RNA building blocks in a scenario depicted in Fig. 5B. Of course, we will be unable to definitively prove that the described scenario indeed took place on early Earth, but the reported chemistry shows that, under plausible prebiotic conditions, mutually synergistic reaction pathways can be established in which the intermediates along one pathway help the chemistry of the other. In such a scenario, we show that the key building blocks of life can be created without the need for sophisticated isolation and purification procedures of reaction intermediates that are common in traditional organic chemistry.

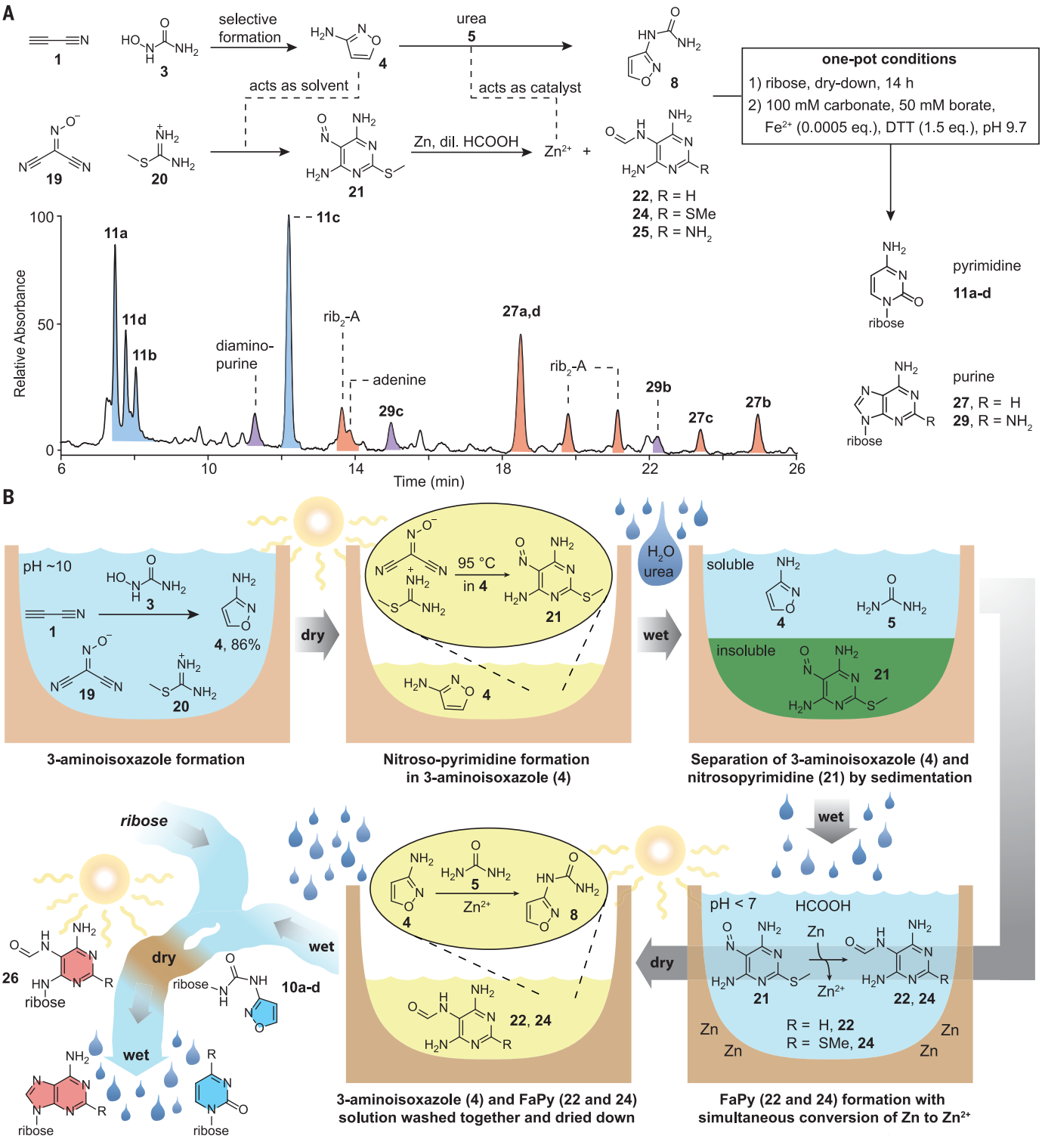

Fig. 5. Unified chemical scenario for the formation of purine and pyrimidine nucleosides. (**A**) Depiction of the connected reaction pathways to pyrimidine and purine nucleosides, together with the HPLC analysis (260 nm) of the final reaction mixtures. Nucleosides are labeled as follows: **a** = α-furanosyl; **b** = β-furanosyl; **c** = α-pyranosyl; **d** = β-pyranosyl. (**B**) Proposed geochemical scenario for the simultaneous synthesis of purine and pyrimidine nucleosides, driven by wet-dry cycles. In yellow, the solvent is 3-aminoisoxazole (**4**), which can be enriched from an aqueous solution due to its high boiling point (228°C). 2-(Methylthio)-5-nitrosopyrimidine-4,6-diamine (**21**) is a general precursor for adenosine and guanosine (*18*). Compounds **8**, **22**, and **24** are accessible in the same pot, and they can react with ribose to the RNA nucleosides in a one-pot reaction.

The concurrent formation of pyrimidine and purine nucleosides in the network can be traced to just a few key starting molecules, such as cyanoacetylene **1**, NH_3, NH_2OH **2** (or the disulfonate **6**), HCN, urea **5**, formic acid, and isocyanate, plus salts such as nitrites, carbonates, and borates. Metals such as Zn or Fe and their ions play an important role in our chemistry, consistent with their proposed involvement in early metabolic cycles (*23*, *38*). In particular, iron-sulfur surfaces needed for pyrimidine formation have been discussed as platforms for early prebiotic chemistry (*15*, *34*, *39*). The 5′-(di)phosphorylation is integrated into our pathway if phosphate minerals such as lüneburgite or struvite (figs. S11 to S13) are present. It remains unclear, however, how ribose or any other carbohydrate, such as glycerol or threose, that is needed to form the backbone of RNA or pre-RNA could have formed selectively (*29*, *40*). Sugars such as ribose can be produced nonselectively in a formose-like reaction, which is possible in a variety of different physico-chemical environments (*32*, *41*–*43*).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
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Unified prebiotically plausible synthesis of pyrimidine and purine RNA ribonucleotides

Sidney Becker, Jonas Feldmann, Stefan Wiedemann, Hidenori Okamura, Christina Schneider, Katharina Iwan, Antony Crisp, Martin Rossa, Tynchtyk Amatov and Thomas Carell

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Conditions right for making nucleosides

In the absence of biological catalysts and metabolism, can atmospheric and geochemical processes provide the substrates and conditions required for production of biological molecules? Becker *et al.* devised an abiotic synthetic scheme that allows for accumulation of both purine and pyrimidine nucleoside mono- and diphosphates (see the Perspective by Hud and Fialho). A key starting material for this chemistry, hydroxylamine and/or hydroxylamine disulfonate, can form under plausible early atmospheric conditions. Cycles between wet and dry conditions provide the environments necessary to complete formation of purine and pyrimidine bases essentially in one pot.

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