Cerium Phosphate-Assisted Formation of Nucleosides and Nucleotides from Formamide in a One-Pot (Photo)catalytic Reaction

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ABSTRACT:

The abiotic formation of nucleotides from small, simple molecules is of large interest in the context of elucidating the origin of life scenario. In what follows it is shown that nucleosides and nucleotides can be formed from formamide in a one-pot reaction utilizing the mineral Cerium Phosphate ($CePO_4$) as both a photocatalyst, a catalyst and a reactant that supplies the necessary phosphate groups. While the most abundant RNA / DNA building blocks were thymidine and thymidine monophosphate, considerable yield of other building blocks such as cytidine, cytidine monophosphate and adenosine cyclic monophosphate were found. Comparing the yield of nucleosides and nucleotides under light conditions to that in the dark suggests that in the presence of cerium phosphate, light promotes the formation of nucleobases, whereas the formation of nucleotides from nucleosides from nucleobases can take place even in the absence of light.

INTRODUCTION

The RNA world hypothesis postulates that the first step towards the appearance of living entities involves the formation of RNA, since this molecule may not only self-replicate[1] but also may act as a catalyst[2,3]. The hypothesis leans on the concept that under the conditions of the primitive atmosphere of the primordial earth, prebiotic chemistry played a role by increasing the complexity of simple organic molecules to eventually form biological compounds such as RNA chains. Such a process is likely to comprise of the following sequence: formation of sub-building blocks (most likely, but not necessarily, nucleobases and ribose) that produce, together with phosphate, building blocks (nucleotides). This is followed by spontaneous polymerization, yielding oligomers of short RNA that may function as non-enzymatic catalysts[2].

Formamide, a simple molecule containing the four essential elements (nitrogen, oxygen, hydrogen, and carbon) has been considered as a good candidate for forming life-building blocks[4]. It is also known to be prevalent in abiotic environments, such as on comets and in outer space, increasing the likelihood of its involvement in the creation of life[5–7]. Indeed, many studies have indeed shown the formation of amino acids[8], nucleobases[9–11], sugars[12,13] and nucleosides[14] from primitive molecules (such as formamide and formaldehyde), in some cases in the presence of different catalysts, and under diverse conditions. Furthermore, formamide can also be utilized as a medium for the synthesis of prebiotic substances such as amino acid derivatives[15].

Previous works have shown the formation of nucleotides from existing nucleosides, through the addition of a phosphate group[16,17]. However, none have so far managed to demonstrate the formation of a complete nucleotide from primitive precursors in an abiotic one-pot reaction under constant conditions. So, while a certain level of

understanding has been obtained about how the different steps in the process may have taken place, science has not yet managed to unfold the whole process[18,19].

This final step, grafting a phosphate group onto a nucleoside, requires an available source of phosphates. Accordingly, this step may be reliant on the presence of phosphate minerals, which may serve as a reservoir of these functional groups. An appropriate candidate as a phosphate-donating mineral for prebiotic synthesis is cerium phosphate ($CePO_4$). This common mineral[20] not only contains a phosphate group, which presumably could be donated during the reaction to form nucleotides, but also acts as a low-activity photocatalyst that promotes the formation of electron-hole pairs under UV irradiation, which can be further involved in redox reactions[21–23]. For this reason, a scenario in which $CePO_4$ plays an essential role in a one-pot reaction leading to formation of nucleotides from the simple molecules seems plausible. Its low photocatalytic activity[22] may potentially even be of benefit, allowing for more delicate reactions to occur without the rapid formation of reactive oxygen species such as hydroxyl radicals, ozone, and atomic oxygen. These species, if formed, could cause the complete oxidation of formed products, since oxidation reactions, being competing downhill reactions, are known to be a major limitation in artificial photosynthesis[24]. Nevertheless, despite the potential advantages of utilizing cerium phosphate as a photocatalyst for synthesizing biomolecules from simple compounds, we are not aware of any work demonstrating its operation in this context.

Another important obstacle in the abiotic formation of biological building blocks, which still puzzles scientists around the world, is the water paradox, manifested by the fact that water is crucial for life, yet its presence is deleterious for the formation of biomolecules[25,26]. One way to resolve this paradox is by considering a multi-functional catalyst, which functions as a reaction promoter, photocatalyst, phosphate donor, and

an adsorption site for life-building sub-blocks formed in the process, thus increasing their stability and promoting high concentrations of both nucleobases and sugars in close proximity. This facilitates the formation of more complex compounds, such as nucleotides and eventually strands of RNA.

In what follows, the formation of RNA-building blocks such as nucleobases, nucleosides, and nucleotides (Figure 1) by heterogeneous photoreactions is demonstrated, thus supporting the notion that these (or similar) processes were at the core of the formation of the first biological molecules. To the best of our knowledge, this is the first ever manuscript detailing the successful formation of complete nucleotides, including a phosphate backbone, in a one-pot reaction, from primitive organic molecules, and without the presence of biological catalysts. The results shown herein may not only help our understanding of how life on earth could have started but may also be of use in learning how to better implement photocatalytic reactions, typically applied for the aggressive degradation of organic compounds, towards the highly delicate synthesis of fine chemicals.

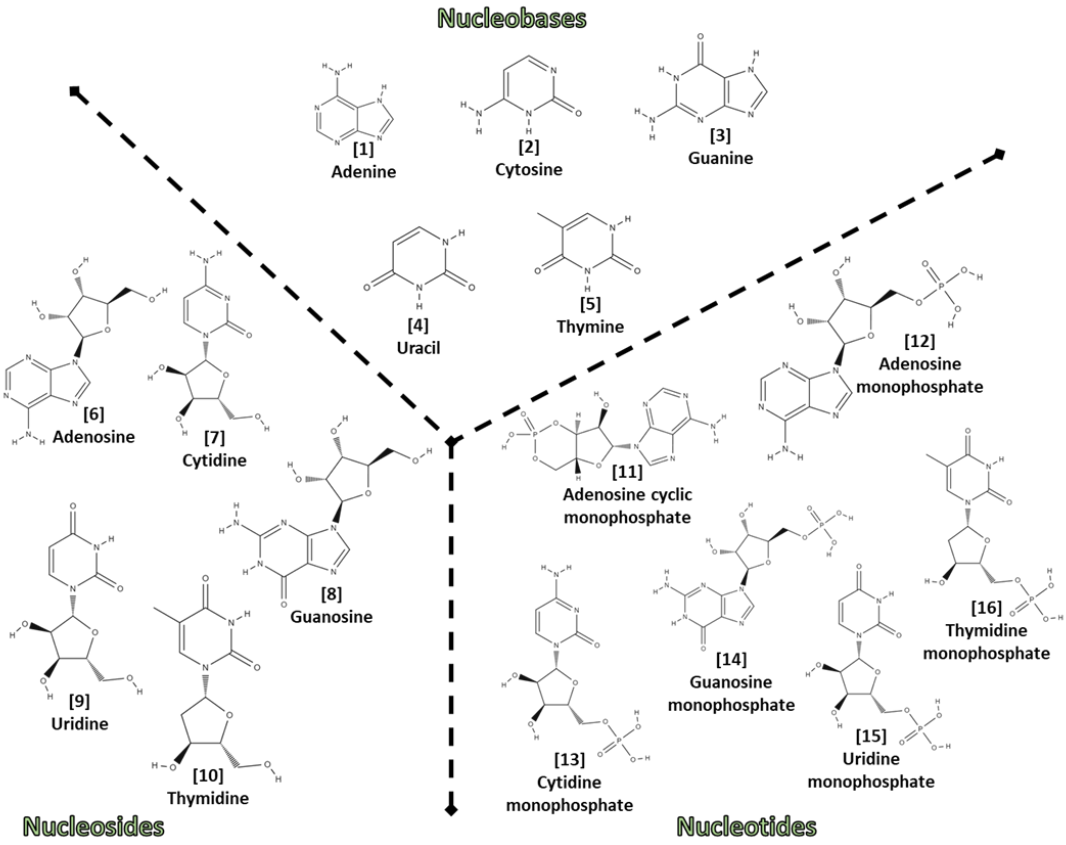

Figure 1. The various RNA-building blocks discussed in this manuscript.

EXPERIMENTAL METHODS

Chemicals. $CePO_4$ (CAS:13454-71-2) was purchased from Alfa-Aesar and was characterized by XRD (crystallite size of 14.8 nm by the Scherrer equation) and BET adsorption isotherms (46.4 m2/gram). Formamide (CAS:75-12-7) was purchased from Merck. All standards used for LCMS (adenine, thymine, cytosine, uracil, adenosine, uridine, thymidine, guanosine, cytidine, AMP, CMP, TMP, UMP, GMP) were purchased from Sigma- Aldrich. The cyclic nucleotide cAMP was purchased from TCI company. HPLC-grade water was purchased from Macron LTD.

Reactions. Prior to any reaction, all reaction vessels were cleaned using a piranha solution (Caution!). 10 ml of formamide and 0.264 gr of $CePO_4$ were introduced to each reaction vessel. The tubes were then heated to 170°C under stirring and remained at that temperature for 48 hrs. Nitrogen gas flowed into the reaction vessel continuously at a volumetric flow of 0.2 l/min. Half of the samples were irradiated by a UV 365nm LED (18.6 mW/cm^2, irradiated area: 1.45 cm^2), while the other half of the samples were kept in the dark. Following a reaction time of 48 hours, the liquid was separated from the catalyst by centrifugation at 14,000 rpm for 10 min. Then, 0.1 ml of the liquid phase was introduced into a rotary evaporator (90°C, 2 hours, under vacuum). Once the solvent had been fully evaporated, a brown crude product was obtained. This crude product was dissolved in 0.5 ml of HPLC-grade water and measured by high-resolution LC-MS.

Identification of products. Identification and quantification of formed DNA- and RNA-building blocks were performed by LC-MS Maxis impact Bruker with a positive ESI (Electron Spray Ionization) MS method, in two configurations: High Resolution direct MS (HRMS) and LCMS. For the LCMS measurements, two mobile phases were used A: acetonitrile, B: 0.1%w/w formic acid in HPLC-grade water. The separation sequence started with 100% of B for 5 minutes at a flow rate of 0.3 ml/min (for all samples). Then, 1 minute of a mixture comprising of 99% B and 1% A, 1 minute of 95% B and 5% A, 2.5 minutes of 100% A and at last 5.5 minutes of 100% B, based on a previously published procedure[27]. A C18 Luna 5µ column (Phenomenex) was used. In each measurement a volume of 5µL was injected into the column. The ESI detector conditions were: capillary 4500V, nebulizer 3.0 bar, source 180°C and dry gas flow of 8L/min. Quantification was made by comparing the integrated signals of the samples at a specific m/z and retention time to that of calibration curves of commercial standards.

The High-resolution direct MS measurements served for preliminary identification of the building blocks, as well as for analyzing control experiments used for verifying the lack of contaminants in the formamide and the $CePO_4$. Here, a Xevo G2 QTOF (Waters Ltd.), with a positive ESI detector was used. The mobile phase comprised of 30% water and 70% acetonitrile at a flow rate of 0.5ml/min, and a sample volume of 40µL. For the $CePO_4$ measurements, the catalyst particles were added into a tube containing HPLC-grade water and heated for one hour to 90°C. Then, the liquid was separated from the catalyst by centrifugation at 14,000 rpm for 10 min and measured by HRMS (see support information).

The identification of the main constituents in the crude mixture of products was performed by GC-MS using a HP 6890N (Agilent), equipped with a HP5-MS capillary column and a Mass Selective Detector (MSD). Here, a volume of 1µL of each sample was injected into the GC column that was maintained at 100°C (for 2 minutes). The temperature was then raised to 280°C at 10°C/min and maintained at this temperature for 20 minutes. The temperatures of the injector and the detector were set to 280°C and 300°C, respectively. Helium (1 ml/min) was used as the carrier gas. Identification was based on a comparison of the mass spectra with selected commercial compounds (adenine, cytosine, thymine, and uracil – all in formamide). No comparison with guanine was performed as it does not dissolve well in formamide. Alternatively, a comparison with a MS library data (NIST mass spectral library V. 2.0) was performed.

Adsorption experiments.

3.7mM solutions of each one of the compounds (adenine, adenosine, AMP, or cAMP) in formamide were prepared under stirring. A volume of 4ml solution was added into a tube together with 105.2 mg CePO4, (2% by weight). The tubes were held in the dark, under stirring and nitrogen flow (0.2 l/m), half of which at a temperature of 300° K and the other half at 333°K. Samples (70µL) were taken at 0, 10, 30, 60, 90, and 120 minutes from the beginning of the process. The samples were centrifuged (10,000 rpm, 10 min.) to separate the liquid from the particulate matter. 25µL of the liquid phase were placed in a clean Eppendorf together with 15µL of formamide, and 1.96 ml of HPLC-grade water. The water was added to stabilize the absorption curve of adenine, whose UV-vis absorption spectrum is known to depend on its charge[28]. The UV-vis absorption of said solution was measured using a Shimadzu UV-2600 spectrophotometer to determine the concentration of the species of interest in the solution.

Accordingly, all calibration curves were prepared with the same water: formamide ratio (1.96 ml water + 0.04 ml formamide).

RESULTS AND DISCUSSION

A brown viscous mixture of products, termed hereby as "crude", (13±3 % of the initial formamide mass) was obtained following 48 hours of illumination in the presence of the $CePO_4$ particles. The obtained crude was measured by GCMS (Figure 2A). As shown in the figure, the main constituents of the crude were N,N'-Methylene-bis-formamide and 9H-purine.

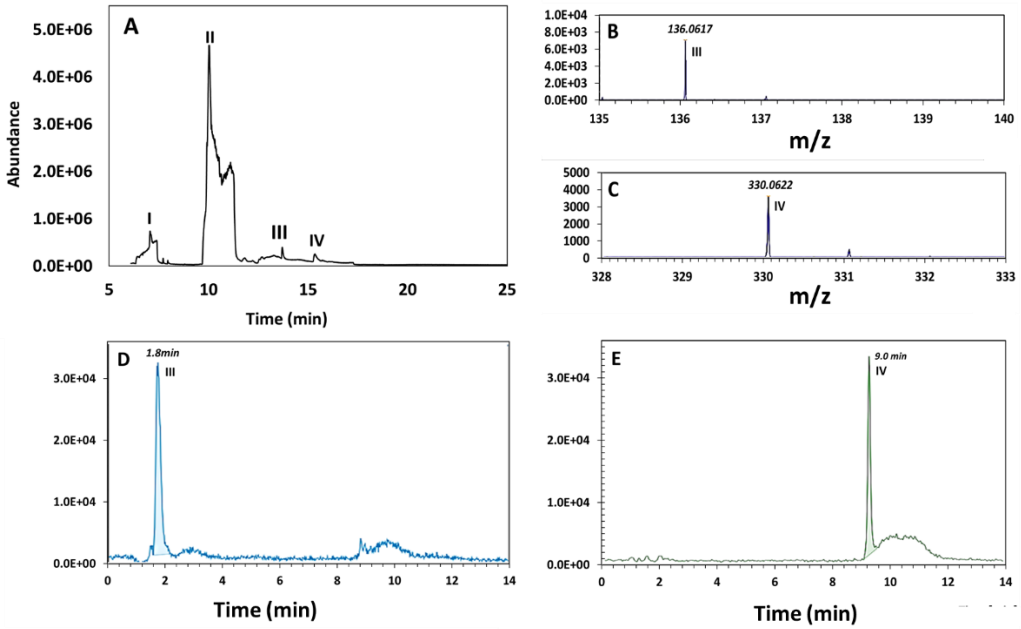

Figure 2. (A) GCMS data of the brown crude product: I - N,N'-Methylenebis (formamide) II - 9H-purine, III – Adenine, IV – Adenosine cyclic monophosphate(cAMP) (B),(C) HR direct MS revealing adenine and cAMP, respectively (D),(E) Extract-mass LC-MS result of adenine and cAMP, respectively.

High resolution direct MS and LCMS measurements (Figure 2B-2E and supporting information), performed on the products, revealed that the crude also contained considerable amounts of other compounds, identified as nucleobases, nucleosides and even nucleotides. The yield of these species, in terms of mg of product per gram of crude products (averaged over 8 repetitions) is given in Figure 3. As shown in the figure, the main RNA building blocks that were obtained were the nucleoside and the nucleotide of thymine (1.5 mg / g crude). Apart from these compounds, the nucleobase and the cyclic nucleotide of adenine, as well as the nucleoside and nucleotide of cytosine were found at a yield of 0.1-0.3 mg/ g crude. In addition, traces of uridine, guanosine monophosphate, cytosine and thymine, at concentrations below accurate quantification limit, were found. It should be noted that these building blocks were attained at a considerable yield in a one-pot reaction, without altering the conditions during its progression, and without optimizing the reaction time, a parameter which was not investigated in the presented work and is currently under study.

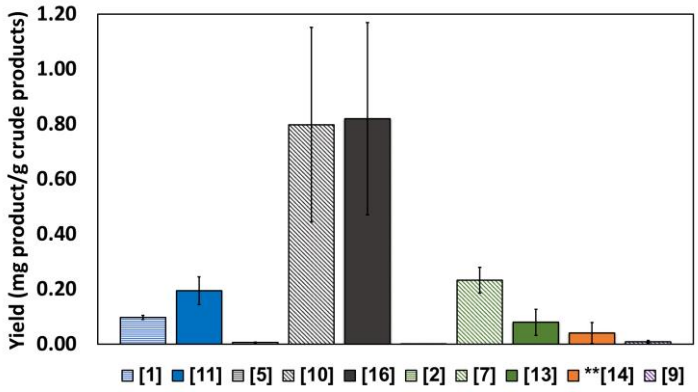

Figure 3 - The formation of nucleobases, nucleosides, and nucleotides from formamide in the presence of $CePO_4$ and under UV-irradiation. Adenine species are shown in blue, thymine in gray, cytosine in green, guanine in orange, and uridine in purple. Nucleobases are presented by horizontal lines, nucleosides by diagonal lines and nucleotides by filled color bars. The numbers in the legend correspond to the molecules listed in Figure 1. ([1]=adenine, [11]=adenosine cyclic monophosphate, [5]=thymine, [10]=thymidine, [16]=thymidine monophosphate, [2]= cytosine, [7]=cytidine, [13]=cytidine monophosphate, [14]=guanosine monophosphate **- large standard deviation [9]=uridine).

A set of measurements was performed to negate the possibility of artefacts. The formamide used for the reaction was measured prior to the photocatalytic reaction by MS. None of the above-mentioned compounds was found. In addition, the $CePO_4$ catalyst was added to HPLC-grade water and heated to 90°C for 1 hour. Then, the liquid phase was separated from the catalyst by centrifugation and measured by MS. Here, again, no RNA building blocks were detected [see supporting information].

Another set of experiments served to resolve the contribution of each parameter (catalyst and light) on the formation of the RNA building blocks. Figure 4 depicts the distribution of RNA building-block products upon performing the same procedure in the absence of UV light. It was found that the average weight of the obtained crude was not altered significantly with respect to the previous case, (14± 3 mg per 0.1 ml of liquid), suggesting that the UV-light was not the main reason for the formation of N,N'-Methylene-bis-formamide and 9H-purine. Nevertheless, when it comes to the formation of RNA building blocks, significant differences between the two cases were noticed. First, under dark conditions, the overall yield of RNA building blocks was significantly (20-40%) lower than the yield obtained under light. Second, cytidine mono phosphate (CMP), found under light, was not observed in this case. Third, cytosine, thymine, and guanosine monophosphate, found at sub-quantification concentration under light, could not be observed when the reaction took place in the dark. Hence, it can be concluded that UV light played an important role in increasing the yield and the diversity of the RNA building blocks formed during the one-pot reaction.

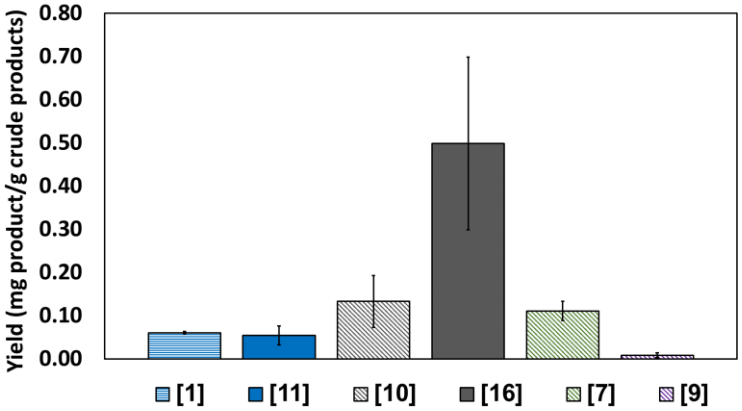

Figure 4. The synthetic yields of life-building blocks from formamide in the presence of $CePO_4$ in the dark. Adenine species are shown in blue, thymine in gray, cytosine in green, guanine in orange, and uridine in purple. Nucleobases are presented as horizontal lines, nucleosides as diagonal lines and nucleotides as full color bars. The numbers in the legend correspond to the molecules listed in Figure 1 ([1]=adenine, [11]=adenosine cyclic monophosphate, [10]=thymidine, [16]= thymidine, [7]=cytidine, [9]=uridine).

The reaction was run under the same conditions but without the presence of a catalyst. Under dark conditions, the only RNA-building blocks to be formed were adenine and the nucleoside cytidine (Figure 5), both at yields considerably lower than the yield in the presence of cerium phosphate under illumination. In the absence of cerium phosphate and under illumination, the only product of interest was adenine, at a concentration that was slightly smaller than that obtained in the absence of cerium phosphate under dark conditions.

Previous works have shown that formamide may be converted into formaldehyde[29], which acts as a precursor for the formation of sugars, including ribose, by the Butlerov reaction[30,31]. This may explain the formation of the ribose-containing cytidine even without the presence of a catalyst. The similar yields of adenine under dark and under UV-irradiation conditions suggest that in the absence of a catalyst and under the experimental conditions, light hardly plays any role in the formation of adenine from formamide. In parallel, lack of cytidine upon performing the reaction under light suggests that in the absence of a catalyst, UV-light seems to hinder the appearance of cytidine, either by interfering with the formation of ribose or by degrading any formed cytidine.

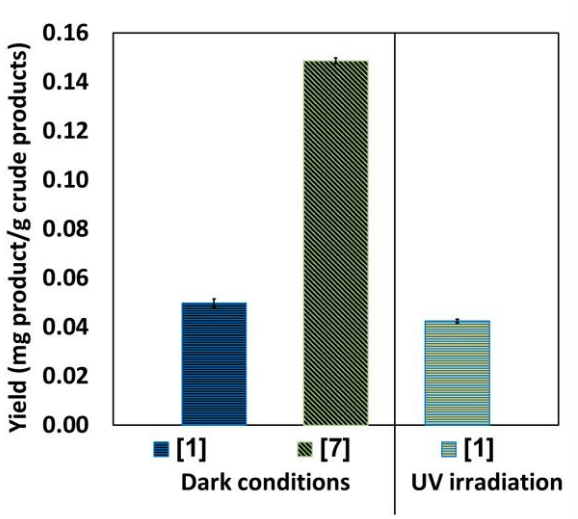

Figure 5. Products formed upon performing the reaction in the absence of a catalyst, under dark conditions (left) and upon exposing to UV light (right) ([1]=adenine, [7]=cytidine).

An assessment of the role that cerium phosphate plays in the reaction of formamide can be obtained by summing up the yield of all nucleobases and comparing it to the yield of nucleosides and nucleotides (Figure 6A). Such a comparison clearly shows that $CePO_4$ acts not only as a reactant, supplying phosphate to form nucleotides, but also as a (photo)catalyst, catalyzing the formation of ribose, which eventually reacts with nucleobases to form nucleosides. It is further noted that the formation of the more advanced species, nucleosides and nucleotides, did not come at the expense of the formation of nucleobases. On the contrary: the yield of nucleobases in the presence of cerium phosphate was higher than in the absence of $CePO_4$, regardless whether the reaction occurred in the dark or under exposure to light.

Figure 6B presents the total yield of each of the nucleobases formed in the presence of cerium phosphate (under light and in the dark), as well as the overall yield in the absence of cerium phosphate. Here, the total yield of each base was calculated by summing up the contribution of nucleobases, nucleosides, and nucleotides. The figure makes it clear that while the contribution of $CePO_4$ to the formation of adenine is relatively mild, the effect of cerium phosphate on the formation of the oxygen-containing nucleobases, in particular the di-ketone thymine, is dramatic. Thus, our results suggest that $CePO_4$, and probably similar phosphate-containing compounds, are essential for the formation of the variety of nucleobases, necessary for obtaining nucleotides and eventually RNA and DNA. Comparing the yield of nucleosides and nucleotides under light conditions to that in the dark suggests that in the presence of cerium phosphate, light has larger effect on the relative increase in the nucleosides' yield than on the relative increase in the nucleotides' yield.

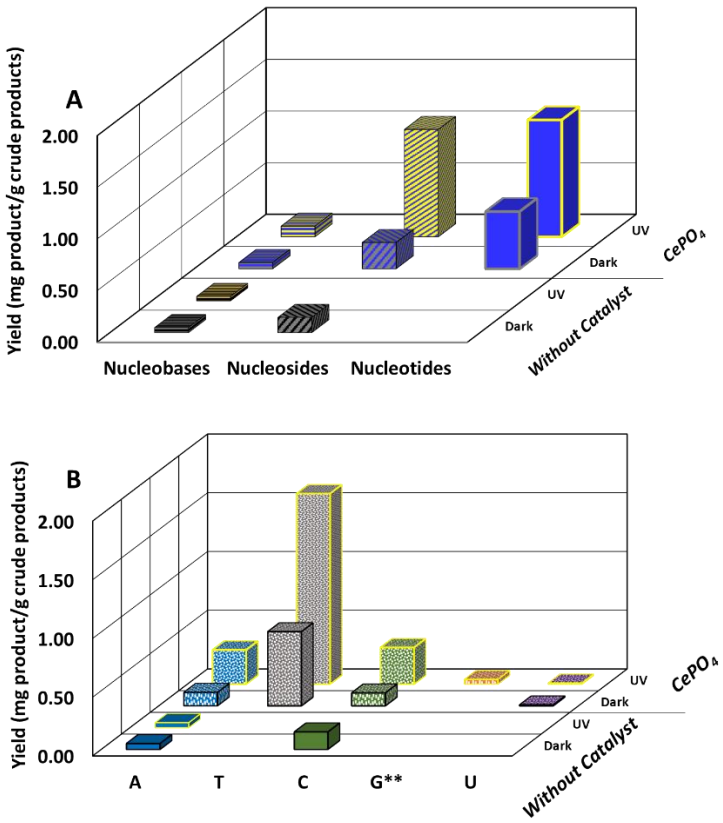

Figure 6. (A) The total yield of different forms of the RNA building-blocks, categorized according to nucleobases, nucleosides and nucleotides, as obtained after 48 hours with and without $CePO_4$. (B) The total yield of RNA building blocks (nucleobases+ nucleosides+ nucleotides) categorized according to the type of nucleobases, as obtained after 48 hours with and without $CePO_4$.

The brown-colored crude mixture of products containing mostly N,N'-Methylene-bis-formamide and 9H-purine could affect the photocatalytic production of RNA-building blocks by blocking the 365 nm light used for exciting the $CePO_4$. Therefore, the change in the absorption at 365 nm was measured along the progression of the reaction. The results are given in Figure 7. The figure clearly shows that the formation of the UV-blocking crude is induced by the high temperature of the formamide and not by the presence of cerium phosphate, or by light. In fact, exposure to UV light seems to slow down the formation of the crude mixture. No matter whether $CePO_4$ was present or not, and whether UV light was introduced or not, within 24 hours the contents in the reactor absorb practically almost all impinging photons, so that for the results presented herein the photocatalytic contribution to the formation of the RNA-building blocks was limited to the first 10 hours. Combining the data depicted in figures 6 and 7 suggests, alas not proves, a scenario in which formation of nucleobases and sugars took place predominantly by photocatalysis during the first ten hours or so. The process continues in the dark by the growth of nucleosides and eventually by the formation of nucleotides while partially consuming the phosphate groups of the photocatalyst.

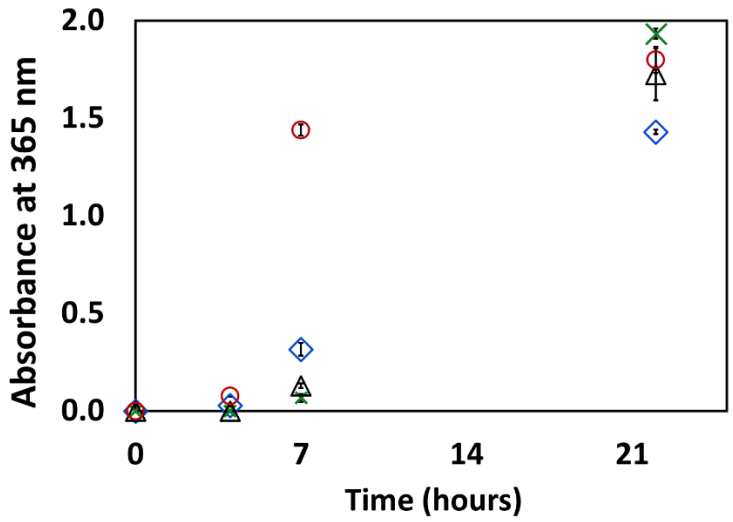

Figure 7. The change in the absorption of the solution at 365nm during the propagation of the reaction. Red circles: formamide under dark conditions, black triangles: formamide under UV-light, green crosses: formamide in the presence of $CePO_4$ under dark conditions, blue diamonds: formamide in the presence of $CePO_4$ under UV-irradiation.

One of the main disadvantages of the homogeneous scenario for the origin of life is the inherent difficulty of maintaining high concentration of the sub-building blocks (most likely nucleobases, sugars, phosphate) in close proximity, to enable the formation of nucleotides and eventually also their polymerization. This drawback is resolved, at least partially, if the formation of the nucleotides from their building blocks occurs in a heterogeneous manner, and if the involved species adsorb weakly on the surface. To verify that cerium phosphate is adequate also from that aspect we have measured the adsorption of adenine, adenosine, adenine-monophosphate (AMP) and cyclic adenine-monophosphate (CAMP) on cerium phosphate under a formamide environment, mimicking the conditions during the preparation of these compounds (alas at lower temperatures, due to technical reasons). The measurement time was limited to two hours to prevent any reactions.

As expected, the adsorptivity increased with the size of the specie in the order adenine < adenosine < adenosine monophosphate, i.e. with the molecular mass of the specie. The only exception was cyclic adenosine monophosphate, whose adsorptivity was found to be very low. The adsorbed amounts, in the order of 10^{-7} – 10^{-8} moles per m^2 of catalyst, are quite considerable and correspond, under conservative assumptions, to a coverage of 0.5-48% percents of the surface area of the catalyst at 300°K and 0-29% at 333°K under the experimental conditions. While these values were obtained in the absence of any competition by other species on the adsorptive sites, they are still of importance as they indicate that the adsorption of sub-building blocks, en-route for formation of nucleotides (and eventually their polymerization), cannot be ruled out.

Conclusion

The one-pot formation of nucleobases, nucleosides and even nucleotides from formamide at elevated temperatures and under exposure to UV light was found to be feasible in the presence of cerium phosphate. The role of the cerium phosphate can be described, at large, by acting as a weak photocatalyst during the first hours of the reaction to form nucleobases. At a later stage it acts mainly as a catalyst for forming nucleosides and eventually contributes phosphate groups for the formation of nucleotides. One of the most intriguing findings is the formation of large variety of RNA / DNA building blocks, beyond the easy-to-form adenine. It was shown that heterogeneous (photo)catalysis (or cerium phosphate or on other minerals) may provide adequate conditions for nucleotides' formation and eventually for polymerization, by virtue of adsorption, leading to the high local concentrations required for RNA / DNA formation.

ASSOCIATED CONTENT

Supporting Information .

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Author Contributions

S. Gilboa: reactions, measurements, writing

L. Fanz: LC-MS measurements.

N. Arbell: discussions, writing.

Y. Paz: Initiating, discussion, writing.

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ABBREVIATIONS

$CePO_4$, Cerium Phosphate; cAMP, Adenosine cyclic monophosphate; AMP, Adenosine monophosphate; TMP, Thymidine monophosphate; CMP, Cytidine monophosphate; GMP, Guanosine monophosphate; UMP, Uridine monophosphate ;

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