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Unified Reaction Pathways for the Prebiotic Formation of RNA and DNA Nucleobases

Yassin Aweis Jeilani,[a,*] Phoenix N. Williams,[a] Sofia Walton,[a] and Minh Tho Nguyen[b,*]

[a] *Department Chemistry and Biochemistry, Spelman College, Spelman Lane S.W., Box 1134, Atlanta, GA 30314, USA*

[b] *Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium*

Abstract

The reaction pathways for the prebiotic formation of nucleobases are complex and lead to the formation of mixture of products. In the past 50 years, there has been a concerted effort in identifying a unified mechanism for the abiotic origin of the biomolecules but with little success. In the present theoretical study, we identified two prominent precursors for the building up of RNA and DNA nucleobases under prebiotic conditions: (a) 1,2-diaminomaleonitrile (DAMN), which is a tetramer of hydrogen cyanide (HCN), and (b) formamide, a hydrolysis product of HCN; it is important to emphasize that HCN is the source of both precursors. We find that free radical pathways are potentially appropriate for accounting the origin of nucleobases from HCN. The current study unites the formamide pathways with the DAMN pathways. The mechanisms for the formation of the RNA and DNA nucleobases (uracil, adenine, purine, cytosine) were studied by quantum chemical computations using density functional theory at the B3LYP/6-311G(d,p) level. All the routes involved proceed with relatively low energy barriers (within the error margin of DFT methods). We showed that the radical mechanisms for formation of

nucleobases can be unified through common precursors. The results demonstrated that the 4-aminoimidazole-5-carbonitrile (AICN), which is a known precursor for nucleobases, is a product of DAMN. The overall mechanisms are internally consistent with the abiotic formation of the nucleobases, namely (a) under meteoritic impact scenario on the Early Earth's surface that generated high internal energy, and/or (b) in the (gas phase) interstellar regions without the presence of catalysts.

KEYWORDS: Prebiotic formation of nucleobases, free radicals, reaction mechanisms, DAMN, HCN.

*) E-mails: yjeilani@spelman.edu and minh.nguyen@chem.kuleuven.be

1. Introduction

The origin of primitive RNA and DNA nucleobases from the interstellar space has often been investigated because the nucleobases, together with other small biomolecules, were identified in meteorite samples.[1,2] These detections suggested that there are diverse sets of reactions taking place in extraterrestrial environments. As expected, such chemical transformations are extremely complex, and the primary origin of biomolecules either in the Early Earth or in interstellar media still remains an open question.[3] For example, adenine was detected in simulation experiments of Titan's aerosol (including N_2, CH_4, CO_2 and H_2O) using X-ray irradiation.[4] These experiments using mixture of gases give tholins (a complex mixture of compounds) including nucleobases. Hydrogen cyanide (HCN) polymers have long been proposed as constituents of the Titan's tholins.[5] HCN has also been detected in Titan atmosphere,[6,7] cometary ices,[8] nebulae,[9] and molecular clouds.[10] HCN is a primary source for the three main elements required for the formation of DNA nucleobases in the interstellar regions.

Diaminomaleonitrile (DAMN), a stable tetramer of HCN, has long been renowned as a precursor for the formation of nucleobases. DAMN which can be formed directly from HCN through the more reactive aminomalononitrile (trimer),[11] yields 4-aminoimidazole-5-carbonitrile (AICN) in photochemical reactions.[12] These studies suggested the following sequence of steps: HCN → DAMN → AICN → adenine (Scheme 1).[13] The emphasis is on the use of HCN as a precursor for the nucleobases because this is relevant for the extraterrestrial formation of the nucleobases. Boulanger *et al.*[14] reported on the mechanism for the conversion of DAMN → AICN portion of the energy surface involving the carbenes and diradicals with relatively high energy barriers.[14] Also, previous studies on proton-catalyzed mechanisms for the formation of adenine from HCN identified entrance channels with high energy barriers.[15]

Formamide (FM) which is the hydrolysis product of HCN, has been proposed as a prebiotic precursor of nucleobases because of its stability and high boiling point, and in particular the equilibrium between HCN/H_2O and FM (Scheme 1).[16] FM has thus been detected in the dense molecular clouds of the interstellar star forming regions.[17] Formamide yields adenine directly following heating, or, by the reaction of its formamidine isomer with AICN.[12] Formation of DAMN from FM has been previously suggested,[18] an alternative pathways for nucleobases generation from both FM and DAMN have been also investigated.[16,19] Accordingly, there is enough evidence that the channels to nucleobases from HCN and FM are interconnected.

Alternative to their extraterrestrial origin, small biomolecules can also be formed under meteoritic impacts on the early Earth's surface.[20] These scenarios have been demonstrated in laboratory simulation studies. Experiments on extraterrestrial-body impact simulations showed that nucleobases can be formed from simple prebiotic molecules.[21,22] High-power laser was used in these experiments to induce the formation of nucleobases from both DAMN and FM.[23] Formation of adenine, cytosine, uracil, and guanine from DAMN was reported. The experimental conditions for these reactions suggested free radical pathways. Also, DAMN is formed in significant quantities when formamide is heated.[22] They proposed the formation of HCN followed by the formation of HCN-dimer, trimer, and then DAMN is formed. An alternative pathway for the formation of DAMN was also reported from FM through 2-amino-2-hydroxy-acetonitrile and 2-amino-2-hydroxy-malononitrile intermediates.[24] These two intermediates were identified by infrared spectra. Recently, Ferus *et al*.[23] reported a combined experimental and theoretical study on the formation of nucleobases from FM and DAMN. A mechanistic model for the simultaneous formation of pyrimidine and purine bases was suggested.[23] The pathway for the conversion of trisubstitued pyrimidinyl radical to 2,4-diaminopyrimidine (2,4-

DAP) was reported at B3LYP/6-311++G(2d,2p) level. The resulting 2,4-DAP was suggested as a precursor for the pyrimidine bases. They showed that the pathway is highly exothermic. Formation of both cytosine and uracil requires a source of oxygen. The authors proposed •OH as the source of oxygen for the formation of the pyrimidines (Scheme 1).

We recently reported the free radical pathways for the nucleobases production from small molecules such as FM.[25–29] All these pathways proceed through relatively low-energy barriers. The radical pathways starting from HCN are not known yet. Therefore we set out in the present study to investigate the HCN pathways yielding first the DAMN, and then the adenine, purine, cytosine, and uracil. The strategy of the proposed mechanisms is to identify known and unknown intermediates that are relevant in the DAMN pathways. We find that not only does a unified mechanism emerge from the formation of RNA and DNA nucleobases but the pathways reveal a number of precursors pertinent to HCN transformations. The results reported in this paper suggest that free radical mechanisms are feasible in these transformations. Scheme 1 shows the distinct pathways for FM and DAMN toward the nucleobases production. In particular, we focus on the DAMN channels as well as the feasibility of identifying the interconnections with the FM pathways as displayed in Scheme 1.

2. Computational Methods

All standard electronic structure calculations using density functional theory (DFT) are carried out with the aid of the Gaussian 09 suite of programs.[30] The popular hybrid B3LYP functional,[31,32] in conjunction with the 6-311G(d,p) basis set, is used for all calculations.[33] Harmonic vibrational frequency calculations are carried out at the same level in order to confirm the nature of stationary points located, and to obtain zero-point vibrational energies. Each

transition structure (TS) is characterized by having one imaginary vibrational frequency for the normal mode corresponding to the appropriate reaction coordinate. Intrinsic reaction coordinate (IRC) calculations at the same B3LYP/6-311G(d,p) level are performed for representative transition states to confirm the connections between each first-order saddle point and the two respective energy minima.[34,35] Geometrical parameters of the relevant stationary points are listed in the Supplementary Information file (ESI). Let us mention that the B3LYP functional has been employed in several previous studies to explore the production of purine nucleobases in both neutral and free radical states under prebiotic conditions.[25,27,36,37] A uniform scaling factor of 0.967 was used for the ZPE values when calculating the relative energies of the structures considered. Computational resources (XSEDE)[38] available at the Gridchem website (http://www.gridchem.org) are used to perform DFT calculations.[39,40]

3. Results and Discussion

The RNA and DNA bases adenine, cytosine, and uracil were found to be formed when DAMN was irradiated with high-power laser leading to very high temperatures conditions.[19] Free radicals such as •NH_2 and •CN are formed under these conditions. These small radicals are used to initiate the reactions and are also regenerated along the pathways. The free radical mechanisms for the formation of the nucleobases are proposed for reactions taking place under high temperature conditions, though there are alternative pathways leading to related products. Herein, DFT data is presented suggesting a common pathway for the formation of both purines and pyrimidines from DAMN. The first part of the discussion focuses on the formation of known precursors. These precursors have been previously proposed for the formation of the nucleobases

from either DAMN or formamide. Table 1 shows the calculated energies and free energies for the pathways.

3.1. Formation of AICN and Imidazole-derivative (11)

AICN, denoted for 4-aminoimidazole-5-carbonitrile, turns out to be an important intermediate that has been observed in experiments performed under prebiotic conditions. DAMN has often been postulated as a precursor for AICN. Our DFT results point out that the formation of AICN from DAMN proceeds through an energetically feasible free radical pathway (Figure 1). As DAMN has two equivalent NH_2 groups, therefore either NH_2 group can participate in a hydrogen abstraction step. The first step is in fact a hydrogen abstraction from the NH_2 group of DAMN by an amino radical $\bullet NH_2$ (Scheme 2). A radical-molecule complex (DAMN-NH_2) is formed first followed by an exothermic hydrogen abstraction and the release of NH_3. The energy barrier for this step is 5.1 kcal/mol (Figure 1). A new C–N is formed by the radical attack of **2** on the triple bond of a neutral HCN molecule to give **3**. The structure of **3** has all atoms needed for the formation of the imidazole ring of AICN. An exothermic cyclization of **3** leads to **4** with an energy barrier of 20.3 kcal/mol.

The next step for the formation of AICN involves the loss of one •CN radical. The carbon radical in **4** is at a β-position with respect to the CN group (NH_2–C–CN). A TS for this •CN-loss from **4** to give AICN directly could not be found at both B3LYP/6-311G(d,p) and B3LYP/6-311++G(d,p) levels. We find an alternative route based on a direct addition of •H to the CN triple bond group followed by the elimination of HCN, being step **6** → 7, instead of a direct •CN elimination. To accomplish this elimination, a hydrogen abstraction (**4** → **5-NH_2**) is followed by a regeneration of $\bullet NH_2$ to give **5**. This step **4** → **5-NH_2** includes the formation of a C–H bond,

and proceeds through an energy barrier of 26.2 kcal/mol (Figure 1). Addition of •H to the triple bond of the CN group **5** → **6** proceeds with the exothermic release of -30.3 kcal/mol with a rather small energy barrier of 5.1 kcal/mol. The neutral elimination of HCN, **6** → **7** is again exothermic with a small energy barrier of 6.6 kcal/mol. This demonstrates that the overall strategy of the sequential •H addition to the CN group, followed by HCN elimination is energetically feasible, taking even the expected error margins of the DFT methods into account, being ± 5 kcal/mol on relative energetic values. Indeed, these are the key mechanistic steps used in the subsequent steps for the elimination of HCN. Loss of •H from 7 leads to AICN with an energy barrier of 20.5 kcal/mol.

Scheme 1 shows the imidazole-derivative radical precursor **1** formed from FM to give purines. Formation of this derivative from DAMN will provide with an important route that unifies the pathways from DAMN to the pathways from FM (Scheme 1). The structure of **7** has a carbon framework that is needed for the generation of this amino-imidazole derivative. We therefore explore the possibility of forming the imidazole derivative **11** from DAMN (Scheme 2).

The hydrogen abstraction process **7** → **8** proceeds with an energy barrier of 27.6 kcal/mol (Figure 2). Again, the HCN elimination in initiated by the addition of a H radical to the triple bond CN group **8** → **9**, followed by a HCN elimination **9** → **10**. Both steps proceed again through relatively small energy barriers (Figure 2). Elimination of •H from **10** leads to the amino-imidazole derivative **11**. By a simple hydrogen abstraction, **11** gives rise to the amino-imidazole radical **1** shown in Scheme 1. We have recently reported on the formation of purines from this amino-imidazole radical **1**,[25,27] and will therefore not further comment on. By unifying the DAMN mechanisms with the FM mechanism, it implies that the formation of purines from

FM should be enhanced in the presence of DAMN. Indeed, Barks *et al.*[18] reported an increase in the yield of purines in FM reactions when DAMN is added at the beginning of the reaction.[18] For convenience, the pathways depicted in Scheme 1 involving DAMN are named as the HCN pathways because DAMN is a tetramer of HCN.

3.2. Formation of Adenine and Purine

Since 1960s, DAMN has consistently been proposed to give adenine through AICN.[12] However, recently reported mechanisms for formation of purines from AICN proceed through high energy barriers.[36,37,41] We report in the present paper the free radical pathways from DAMN → AICN → purines that actually proceed through relatively low energy barriers (Figure 3). The overall pathways are exergonic with a net release of 36.7 and 30.8 kcal/mol associated with the formation of adenine and purine, respectively. The mechanism starts with the addition of one HCN molecule to AICN followed by •H abstraction/addition steps. This pathway is strictly HCN pathway.

The first step of this route is the formation of a six-membered ring of purine. This is accomplished by the addition of HCN to AICN followed by a cyclization step. The NH_2 group of the AICN makes it easy for a hydrogen abstraction step leading to **12**; this step proceeds through a radical-molecule complex **AICN-NH$_2$**. The HCN addition to **12** gives **13** with a modest energy barrier of 14.6 kcal/mol (Figure 3). Again, the cyclization **13** → **14** to form the six- membered ring is slightly exothermic with an energy barrier of 14.0 kcal/mol. Two successive hydrogen abstractions, namely **14** → **15** → **16-NH$_2$**, lead to formation of adenine **17** with the regeneration of •NH_2 used in the first step **8** → **8-NH$_2$** of this sequence. As expected, formation of purine from adenine **17** takes place is two steps. Addition of •H, **17** → **18**, is followed by a •NH_2

elimination **18** → **19**. These proposed routes are advantageous in that these reactions can proceed without the need of a catalyst. These free radical pathways for the formation of purine bases involve small molecules such as HCN and NH and can take place in an extraterrestrial environment.

3.3. Formation of Cytosine 36

In this section, we report on the pathways yielding the pyrimidine bases, cytosine and uracil, from DAMN. Again, these mechanisms, as shown in Scheme 4, require the addition of one HCN molecule at an early step of the mechanism **22** → **23**, which is regenerated in a subsequent step **30** → **31**. In other words, these mechanisms fall again strictly in the HCN pathway. The source for the oxygen in the pyrimidines comes from the radical •OH as previously suggested.[19] In our initial attempts, we notice that it is rather easy to introduce an •OH before the cyclization step. Therefore, this OH group of the pyrimidine is added to the carbon framework at an early entrance channel.

The first entrance channel of the mechanism is a highly endothermic addition of •H to DAMN (Figure 4) with a net release of 38.7 kcal/mol (Figure 4). The addition DAMN → **20** is however followed by the radical-induced elimination of •NH_2 (**20** → **21**) with an energy barrier of 27.8 kcal/mol. This is the highest energy barrier along this reacting route (Figure 4). The energy released in the first step of this sequence is available to overcome this energy barrier. Hydrogen abstraction from the NH_2 group of **21** leads to **22** through the radical molecule complex **21-NH_2**. The radical attack **22** → **23** at the triple bond of HCN proceeds with an energy barrier of 15.3 kcal/mol. Hydrogen abstraction from NH_3 leads to **24** (Scheme 4) in two steps.

The addition of •OH to the C=NH bond takes place in a radical molecule complex **24-OH** with an energy barrier of 6.4 kcal/mol (Table 1). Again, the cyclization to form the pyrimidine ring is associated with a small energy barrier (Figure 4). This is followed a hydrogen abstraction to give the neutral species **27**. This step thus completes the formation of the pyrimidine ring for both cytosine and uracil bases.

The neutral species **27** has all the elements needed for cytosine. As a consequence, the remaining steps mainly involve hydrogen additions and abstractions with the regeneration of one HCN molecule that was used at the early stage of this sequence of steps (Scheme 5). The first steps **27** → **28** → **29** induce formation of the NH_2 group of the cytosine. Next, it is necessary to eliminate a CN group from **29**. As stated earlier, the strategy adapted for this elimination is an •H addition followed by a neutral elimination of HCN occurred in two steps. Both the •H addition **29** → **30** and HCN elimination **30** → **31** turn out to be exothermic (Figure 5). The next hydrogen abstraction **31** → **32** is characterized by the highest energy barrier of 29.6 kcal/mol along this route. The final steps are thus formation of the unsaturation sites of cytosine. This is mainly accomplished by •H addition and hydrogen abstraction/elimination. Figure 5 illustrates that these steps are characterized by relatively low energy barriers, being from 6 to 11 kcal/mol, that completes the formation of cytosine.

3.4. Formation of Uracil 41

The RNA base uracil is formed from the same HCN pathway as cytosine. The radical **35** exhibits two possible eliminations, namely an elimination of •H leads to cytosine (Scheme 5), and another elimination of •NH_2 **35** → **37** leads to uracil (Scheme 6). Either elimination proceeds with a low energy barrier (cf. Figures 5-6). Again, the addition of •OH within the radical

molecule complex **37OH** yielding **38** is associated with low energy barrier that is comparable to the step **24OH** → **25**. The next step is the formation of the second carbonyl group of uracil, which is actually accomplished by two consecutive hydrogen abstractions **38** → **39** → **40**, followed by a •H elimination **40** → **41**. The steps in this sequence are characterized by low energy barriers (Figure 6) and complete the formation of uracil **41**.

3.5. Formation of DAMN from HCN

If the equilibrium between formamide and HCN/H_2O (Scheme 1) takes place then the mechanisms from HCN to DAMN is needed to complete the pathways. The mechanisms for the formation of DAMN from HCN are also essential for the extraterrestrial formation of the nucleobases from HCN. Scheme 7 shows the pathways for the formation of DAMN from HCN through the dimer (**43a**) and the trimer (**45**) of the CN radicals. The formation of DAMN is a highly exothermic reaction with the release of 110.5 kcal/mol (Figure 7).

The addition of •CN to HCN gives **42** (Scheme 7) without an energy barrier at B3LYP/6-311G(d,p) level of theory. This type of barrierless addition of ethynyl radicals to the triple bond of acetylene has been reported without energy barrier;[42] The radical product **42** from the •CN addition to HCN can either eliminate an •H to form **43a** or abstract hydrogen to form **43b**. Either pathway leads to **45** (Scheme 7). The energy barrier for the hydrogen abstraction (**42** → **43a**) proceeds through the radical molecule complex **43a-NH_2** with an energy barrier of 13.3 kcal/mol. This is followed by the addition of •CN to form **44a**. Note the steps involving addition of •CN to -C≡N (HCN → **42** and **43a** → **44a**) are highly exothermic with low energy barriers with the release of 43.1 kcal/mol and 38.9 kcal/mol (Figure 7), respectively. Loss of •H from **44a** leads to **45**. The energy barrier for this loss is 32.5 kcal/mol.

Scheme 7 shows a second path to **45** through **43b**. This path was evaluated because it predicts the formation of NC-CN (**43b**, dimer of CN) in two steps; the formation of this dimer has been previously proposed.[43] Also, the structure of this dimer has been studied by DFT.[44] The first step is the addition of •CN to HCN that is followed by the elimination of •H. The energy released from the first step (ΔE = -43.1 kcal/mol, Figure 7) is available to overcome the energy barrier ($\Delta E^{\pm}$ = 34.8 kcal/mol) for the loss of the •H in the second step (Figure 8). The addition of •CN step **43b** → **44b** is exothermic and proceeds with a small energy barrier of 5.0 kcal/mol. Hydrogen abstraction by **44b** leads to **45** through the radical molecule complex **45-NH$_2$**. It appears that the formation of **45** can proceed through either **43a** or **43b** because both pathways are energetically feasible.

The next step toward the formation of DAMN is another exothermic addition of •CN to **45**. Again, this step **45** → **46** proceeds with a small barrier of 1.8 kcal/mol (Figure 7). This addition completes the number of C and N atoms needed for the formation of DAMN. The remaining steps lead to the formation of the symmetric **47** that requires the addition of two •H to complete the abiotic synthesis of DAMN. The first addition of •H to **47** is highly exothermic with the release of 66.0 kcal/mol (Figure 7). The final step is hydrogen abstraction followed by loss of NH_2 group **48** → DAMN-NH_2 → DAMN. This leads to the formation of DAMN with an overall release of 110.5 kcal/mol.

3.6. Prebiotic Implications and Conclusions

In summary, we have described the pathways for the formation of the nucleobases from HCN through DAMN. The proposed HCN pathways illustrated in Scheme 1 are based on the formation of both purines (adenine and purine) and pyrimidines (cytosine and uracil) from

reaction of HCN and NH_3 as neutral species, and •H, •CN, and •OH as radical species. NH_3 is directly involved along the pathways (**7** → **8**, **14** → **15**, and **16** → **17**) which is consistent with the use of ammonia for reactions of HCN leading to adenine.[45,46] The reactions of these small chemical species, together with the reactive radicals, can take place in a meteoritic impact scenario on the Early Earth as well as in an extraterrestrial environment. These reactional routes represent realistic pathways for the formation of the RNA and DNA nucleobases: (1) under high energy conditions of the meteoritic impact scenario, or (2) in the presence of mineral catalysts taking place with ultraviolet light irradiation. Also, the pathways could be relevant for catalytic reactions taking place in aqueous media.[47] Water is known to lower the products yields. These reactions lead to the formation of mixture of products that is consistent with the multichannel free radical pathways. Free radical reactions are not selective, and imply the formation of mixture of different products. The mechanisms proposed in the present study take advantage of the availability of these nonselective multichannel routes in free radical reactions to demonstrate that multiple nucleobases can be formed from the same simple reactants. This is consistent with HCN transformations that usually give complex mixture of compounds (tholins) that have been often proposed as part of the brown haze in the Titan's atmosphere.

AICN can be formed through the HCN pathways. Its detection in reaction mixtures implies that the HCN pathway is taking place. Previous studies that showed formation of AICN from FM suggested that the HCN pathways could take place as FM first dissociates into HCN and H_2O (cf. Scheme 1). This hypothesis implies that both HCN and FM pathways are distinct, but interconnected under appropriate reaction conditions through a dehydration/hydration reaction equilibrium.

Barks *et al.* demonstrated that the mechanisms for the formation of nucleobases from formamide are directly linked to the DAMN-pathways.[18] This is consistent with the proposed mechanisms. With respect to the formamide pathway (Scheme 1), the amino-imidazole precursor **1** is a precursor for the nucleobases that is now accessible via DAMN (Schemes 1 and 2). This route demonstrates that other nucleobases are also accessible through the HCN pathways (Scheme 1). We refer the reader to our previous reports for the pathways starting from the amino-imidazole precursor **1** towards the formation of the nucleobases;[25,27,29] the emphasis here is that the pathways (HCN and formamide) are unified, and the pathways depend on the reaction conditions as well as the starting material.

The present mechanisms also take advantage of the C≡N bond in HCN that allows the formation of C–N bonds with low energy barriers, such as in the steps **2** → **3**, **12** → **13**, and **22** → **23**. The HCN chemistry is known to be quite complex and the sequence of steps are important. A new route consisting of a CN group elimination by a sequential addition of •H radical to the CN group followed by elimination of HCN is demonstrated in the following steps: **5** → **6** → **7**, **8** → **9** → **10**, and 2**9** → **30** → **31**. In many cases, the HCN needed for the nucleobases production can be regenerated at a following stage of the synthesis. In this sense, like water molecules, HCN can also be regarded as a co-reactant and a catalyst.

Finally, the focus of this study has been on pathways that may take place under meteoritic impact events that generate high temperature. As expected, the hydrogen abstractions have $\Delta \boldsymbol{G}^{\mp}$ relatively higher than $\Delta \boldsymbol{E}^{\mp}$ (Table 1) such as **4** → **5-NH$_2$**, **7** → **8, 14** → **15-NH$_2$**, **16** → **17-NH$_2$**, **23** → **24-NH$_2$**, and **31** → **32-NH$_2$**; this is due to loss of entropy as NH_2 radicals are formed from NH_3. Similarly, there is a loss of entropy in radical addition to the triple bond of HCN (**2** → **3**, **12** → **13**, and **22** → **23**). It is important to note that some of the steps along the pathways are

highly exothermic (**DAMN → 20**, **27 → 28, HCN → 42, 43a → 44a, 45 → 46, 47 → 48, 43b → 44b**). The energy released in these steps is available to overcome the energy demanding steps.

The proposed pathways are relevant to conditions that promote the generation of free radicals such as the ultraviolet light irradiation that reached the surface of the Early Earth or photochemical reactions in the haze of Titan's stratosphere. Some of the steps have relatively high energy barriers (**4 → 5-NH$_2$**, **7 → 8**, and **31 → 32-NH$_2$**) and suggest that mineral catalysts and dust particles may have played important role to lower these energy barriers.

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References

(1) Martins, Z.; Botta, O.; Fogel, M. L.; Sephton, M. A.; Glavin, D. P.; Watson, J. S.; Dworkin, J. P.; Schwartz, A. W.; Ehrenfreund, P. *Earth Planet. Sci. Lett.* **2008**, *270*, 130–136.
(2) Callahan, M. P.; Burton, A. S.; Elsila, J. E.; Baker, E. M.; Smith, K. E.; Glavin, D. P.; Dworkin, J. P. *Meteorit. & Planet. Sci.* **2013**, *48*, 786–795.
(3) Carota, E.; Botta, G.; Rotelli, L.; Di Mauro, E.; Saladino, R. *Curr. Org. Chem.* **2015**, *19*, 1963–1979.
(4) Pilling, S.; Andrade, D. P.; Neto, A. C.; Rittner, R.; Naves de Brito, A. *J. Phys. Chem.* **2009**, *113*, 11161–11166.
(5) Vuitton, V.; Bonnet, J.-Y.; Frisari, M.; Thissen, R.; Quirico, E.; Dutuit, O.; Schmitt, B.; Le Roy, L.; Fray, N.; Cottin, H. *Faraday Discuss.* **2010**, *147*, 495–508.
(6) Marten, A.; Hidayat, T.; Biraud, Y.; Moreno, R. *Icarus* **2002**, *158*, 532–544.
(7) Vuitton, V.; Yelle, R. V.; Anicich, V. G. *Astrophys. J. Lett.* **2006**, *647*.
(8) Woodney, L. M.; A'Hearn, M. F.; Schleicher, D. G.; Farnham, T. L.; McMullin, J. P.; Wright, M. C. H.; Veal, J. M.; Snyder, L. E.; de Pater, I.; Forster, J. R. *Icarus* **2002**, *157*,

193–204.
(9) Thorwirth, S.; Wyrowski, F.; Schilke, P.; Menten, K. M.; Brünken, S.; Müller, H. S. P.; Winnewisser, G. *Astrophys. J.* **2003**, *586*.
(10) Goldsmith, P. F.; Langer, W. D.; Ellder, J.; Kollberg, E.; Irvine, W. *Astrophys. J.* **1981**, *249*, 524–531.
(11) Sanchez, R. A.; Ferbis, J. P.; Orgel, L. E. *J. Mol. Biol.* **1967**, *30*, 223–253.
(12) Ferris, J. P.; Orgel, L. E. *J. Am. Chem. Soc.* **1966**, *88*, 1074–1074.
(13) Burton, A. S.; Stern, J. C.; Elsila, J. E.; Glavin, D. P.; Dworkin, J. P. *Chem. Soc. Rev.* **2012**, *41*, 5459–5472.
(14) Boulanger, E.; Anoop, A.; Nachtigallova, D.; Thiel, W.; Barbatti, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 8000–8003.
(15) Jung, S. H.; Choe, J. C. *Astrobiology* **2013**, *13*, 465–475.
(16) Hudson, J. S.; Eberle, J. F.; Vachhani, R. H.; Rogers, L. C.; Wade, J. H.; Krishnamurthy, R.; Springsteen, G. *Angew. Chem.* **2012**, *124*, 5224–5227.
(17) Adande, G. R.; Woolf, N. J.; Ziurys, L. M. *Astrobiology* **2013**, *13*, 439–453.
(18) Barks, H. L.; Buckley, R.; Grieves, G. A.; Di Mauro, E.; Hud, N. V.; Orlando, T. M. *ChemBioChem* **2010**, *11*, 1240–1243.
(19) Ferus, M.; Nesvorný, D.; Šponer, J.; Kubelík, P.; Michalčíková, R.; Shestivská, V.; Šponer, J. E.; Civiš, S. *Proc. Natl. Acad. Sci.* **2015**, *112*, 657–662.
(20) Furukawa, Y.; Sekine, T.; Oba, M.; Kakegawa, T.; Nakazawa, H. *Nat. Geosci.* **2009**, *2*, 62–66.
(21) Furukawa, Y.; Nakazawa, H.; Sekine, T.; Kobayashi, T.; Kakegawa, T. *Earth Planet. Sci. Lett.* **2015**, *429*, 216–222.
(22) Ferus, M.; Michalčíková, R.; Shestivská, V.; Šponer, J.; Šponer, J. E.; Civiš, S. *J. Phys. Chem. A* **2014**, *118*, 719–736.
(23) Ferus, M.; Civiš, S.; Mládek, A.; Šponer, J.; Juha, L.; Šponer, J. E. *J. Am. Chem. Soc.* **2012**, *134*, 20788–20796.
(24) Ferus, M.; Nesvorný, D.; Šponer, J.; Kubelík, P.; Michalčíková, R.; Shestivská, V.; Šponer, J. E.; Civiš, S. *Proc. Natl. Acad. Sci.* **2014**, 201412072.
(25) Jeilani, Y. A.; Nguyen, H. T.; Cardelino, B. H.; Nguyen, M. T. *Chem. Phys. Lett.* **2014**, *598*.
(26) Jeilani, Y. A.; Orlando, T. M.; Pope, A.; Pirim, C.; Nguyen, M. T. *RSC Adv.* **2014**, *4*, 32375–32382.
(27) Jeilani, Y. A.; Nguyen, H. T.; Newallo, D.; Dimandja, J.-M. D.; Nguyen, M. T. *Phys. Chem. Chem. Phys.* **2013**, *15*, 21084–21093.
(28) Jeilani, Y. A.; Fearce, C.; Nguyen, M. T. *Phys. Chem. Chem. Phys.* **2015**.
(29) Nguyen, H. T.; Jeilani, Y. A.; Hung, H. M.; Nguyen, M. T. *J. Phys. Chem.* **2015**, *119*, 8871–8883.
(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. *Gaussian Inc., Wallingford* **2009**.
(31) Becke, A. D. *Phys. Rev.* **1988**, *38*.
(32) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*.
(33) Hehre, W. J.; Radom, L.; Schleyer, P. von R.; Pople, J. A. *Ab initio molecular orbital theory*; Wiley New York et al., 1986; Vol. 67.
(34) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Phys.* **2004**, *120*, 9918–9924.

(35) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Theory Comput.* **2005**, *1*, 61–69.
(36) Roy, D.; Najafian, K.; von Ragué Schleyer, P. *Proc. Natl. Acad. Sci.* **2007**, *104*, 17272–17277.
(37) Wang, J.; Gu, J.; Nguyen, M. T.; Springsteen, G.; Leszczynski, J. *J. Phys. Chem. B* **2013**, *117*, 9333–9342.
(38) Towns, J.; Cockerill, T.; Dahan, M.; Foster, I.; Gaither, K.; Grimshaw, A.; Hazlewood, V.; Lathrop, S.; Lifka, D.; Peterson, G. D. *Comput. Sci. & Eng.* **2014**, *16*, 62–74.
(39) Shen, N.; Fan, Y.; Pamidighantam, S. *J. Comput. Sci.* **2014**, *5*, 576–589.
(40) Dooley, R.; Milfeld, K.; Guiang, C.; Pamidighantam, S.; Allen, G. *J. Grid Comput.* **2006**, *4*, 195–208.
(41) Wang, J.; Gu, J.; Nguyen, M. T.; Springsteen, G.; Leszczynski, J. *J. Phys. Chem. B* **2013**, *117*, 14039–14045.
(42) Stahl, F.; Schleyer, P. V. R.; Schaefer Iii, H. F.; Kaiser, R. I. *Planet. Space Sci.* **2002**, *50*, 685–692.
(43) Kliss, R. M.; Matthews, C. N. *Proc. Natl. Acad. Sci. United States Am.* **1962**, *48*.
(44) Bickelhaupt, F. M.; Nibbering, N. M.; Van Wezenbeek, E. M.; Baerends, E. J. *J. Phys. Chem.* **1992**, *96*, 4864–4873.
(45) Oró, J. *Nature* **1961**, *191*, 1193–1194.
(46) Oró, J. *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407–412.

Scheme and Figure Legends

Table 1. Energies and free energies of the pathways in kcal/mol

Scheme 1. Unified prebiotic pathways

Scheme 2. Formation of AICN and amino-imidazole deriviative **1**

Scheme 3. Formation of adenine (**17**) and purine (**19**)

Scheme 4. Formation of cytosine precursor **27**

Scheme 5. Formation of cytosine (**36**)

Scheme 6. Formation of Uracil (**41**)

Scheme 7. Formation of DAMN from HCN

Figure 1. Potential energy diagram for the formation of AICN

Figure 2. Potential energy diagram for the formation of amino-imidazole derivative **11**

Figure 3. Potential energy diagram for the formation of adenine (**19**)

Figure 4. Potential energy diagram for the formation of pyrimidine ring

Figure 5. Potential energy diagram for the formation of cytosine (**36**)

Figure 6. Potential energy diagram for the formation of uracil(**41**)

Figure 7. Potential energy diagram for the formation of DAMN

Figure 8. Potential energy diagram for the formation of DAMN precursor (**45**)

List of Tables

Table 1

Description	$\Delta E^{\mp}$	ΔE_{rxn}	$\Delta G^{\mp}$	ΔG_{rxn}
1 → 1-NH_2	N/A	-7.4	N/A	-0.4
1-NH_2 → 2	5.1	-13.9	6.4	-21.4
2 → 3	14.4	1.5	24.4	12.2
3 → 4	20.3	-10.3	20.8	-9.8
4 → 5-NH_2	26.2	22.2	35.4	30.2
5-NH_2 → 5	N/A	5.7	N/A	-2.1
5 → 6	5.1	-30.3	12.1	-23.1
6 → 7	6.7	-7.6	6.6	-17.8
7 → AICN	23.2	20.5	23.4	13.4
7 → 8	27.6	26.6	36.1	26.9
8 → 9	4.7	-25.0	11.8	-17.7
9 → 10	9.9	3.6	9.5	-6.6
10 → 11	24.6	18.6	24.7	11.3
AICN → AICN-NH_2	N/A	-7.2	N/A	0.6
AICN-NH_2 → 12	6.6	-9.2	7.4	-17.1
12 → 13	14.6	-2.4	24.1	7.4
13 → 14	14.0	-6.1	15.3	-4.4
14 → 15-NH_2	6.4	-1.7	15.5	6.9
15-NH_2 → 16	4.2	-6.3	4.4	-14.8
16 → 17-NH_2	1.4	-2.4	10.9	5.8
17-NH_2 → 17	N/A	8.0	N/A	-0.1
17 → 18	10.2	-9.3	17.4	-2.3
18 → 19	12.1	5.9	12.0	-3.6
DAMN → 20	2.4	-38.7	2.7	-38.3
20 → 21	27.8	23.1	27.4	13.1
21 → 21-NH_2	N/A	-8.1	N/A	-0.8
21-NH_2 → 22	7.6	-4.4	9.0	-11.7
22 →23	15.3	2.1	25.1	12.3
23 → 24-NH_2	9.2	4.3	17.9	12.2
24-NH_2 → 24	N/A	5.0	N/A	-2.7
24 → 24-OH	N/A	-7.8	N/A	-.1
24-OH → 25	6.4	-15.2	7.4	-14.1
25 → 26	11.4	-12.9	12.5	-11.1
26 → 27-NH_2	7.3	6.2	16.6	14.1
27-NH_2 → 27	N/A	3.1	N/A	-4.7
27 → 28	4.9	-27.2	12.2	-19.9
28 → 29	16.5	5.9	25.4	20.5
29 → 30	18.6	-11.9	11.6	-18.8
30 → 31	3.0	-8.2	2.8	-17.3
31 → 32-NH_2	29.6	25.5	37.3	32.7
32-NH_2 → 33	5.8	-0.5	6.4	-8.6
33 → 34	8.1	-6.6	7.5	-14.7
34 → 3 5	5.7	3.9	14.8	3.6

35 → 36	10.6	-1.5	11.0	-8.3
35 → 37	7.5	0.4	7.7	-9.0
37 → 37-OH	N/A	-11.9	N/A	-3.6
37-OH → 38	6.8	-10.6	7.1	-10.3
38 → 39-NH_2	22.4	10.4	31.4	19.6
39-NH_2 → 40	8.8	7.1	8.6	-1.6
40 → Uracil	9.1	-1.5	8.9	-9.4
HCN → 42	-.07	-43.1	5.4	-35.1
42 → 43a-NH_2	13.3	8.1	21.9	15.5
43a-NH_2 → 43a	N/A	5.7	N/A	-1.6
43a → 44a	1.0	-38.9	9/0	-29.3
44a → 45	32.6	26.2	32.5	19.0
45 → 46	2.1	-40.6	9.7	-31.1
46 → 47-NH_2	7.4	0.9	16.1	9.1
47NH_2 → 47	N/A	7.6	N/A	0.0
47 → 48	0.2	-66.0	6.5	-58.5
48 → DAMN-NH_2	28.3	22.1	36.8	29.7
DAMN-NH_2 → DAMN	N/A	7.4	N/A	-0.9
42 → 43b	34.8	28.5	34.6	25.8
43b → 44b	5.0	-37.2	8.6	-32.2
44b → 45-NH_2	8.3	2.2	16.8	9.9
45-NH_2 → 45	N/A	7.5	N/A	0.0