Chemical Physics Letters 598 (2014) 58–64

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Free radical pathways for the prebiotic formation of xanthine and isoguanine from formamide

Yassin A. Jeilani [a,*], Huyen Thi Nguyen [b], Beatriz H. Cardelino [a], Minh Tho Nguyen [b,*]

[a] Department Chemistry and Biochemistry, Spelman College, Atlanta, GA 30314, USA
[b] Department of Chemistry, University of Leuven, B-3001 Leuven, Belgium

ARTICLE INFO

Article history:
Received 24 November 2013
In final form 26 February 2014
Available online 7 March 2014

ABSTRACT

Free radical pathways for the synthesis of xanthine and isoguanine from formamide were studied using density functional theory (B3LYP/6-311G(d,p)). The proposed mechanisms are complex and appropriate for the non-aqueous scenario of prebiotic reactions. Formation of the carbonyl bond in the nucleobases proceeds through enol-keto tautomerization since the direct formation of the C=O bond is a highly endothermic step. The mechanisms show 2-amino-imidazole as a precursor for nucleobases and polyazaporphyrin. The proposed mechanisms contribute to a further understanding of the origin of biomolecules.

1. Introduction

For decades, the origin of biomolecules on the prebiotic Earth has been speculated from various scenarios. The classical Miller experiments showed the first evidence that a mixture of biomolecules can be made in spark-discharge experiments from simple gases (CO_2, NH_3, H_2 and H_2O) [1]. These reactions were suggested to have taken place on the prebiotic Earth. On the other hand, simulation experiments suggested that organic compounds may have originated from an extraterrestrial environment. The presence of a haze layer in Titan's atmosphere has been associated with organic compounds. Likewise, there is evidence for the presence of organic compounds in interstellar clouds, comets, meteorites and other extraterrestrial media [2–5]. New spectral evidence showed that biomolecules such as amino acids are most likely present in the interstellar space. For example, spectral bands for glycine were detected in the hot cores of Sgr B2(N-LMH), Orion KL, and W51 e1/e2 [6]. Detection of organic compounds in meteorites led to the hypothesis that meteoritic impacts on the early Earth may have been the primary source of organic compounds. In fact, the carbon isotope ratio for xanthine and uracil in the Murchison meteorite indicated the extraterrestrial origin of these nucleobases [3]. Also, formation of nucleobases was reported under extraterrestrial conditions including electrical discharge on a mixture of NH_3, CH_4, and H_2O to mimic cold plasma conditions and led to the formation of xanthine and other pyrimidines, and purine bases [7].

It appears that organic compounds may have originated from more than two scenarios. One scenario is that the synthesis took place on prebiotic earth. The second scenario is that some of the early biomolecules may have been reached the earth by meteoritic impacts. The simulation experiments for the formation of biomolecules on prebiotic earth including Miller's experiment have been shown to give complex mixtures of molecules. For nucleobases, both aqueous and non-aqueous syntheses of the nucleobases were considered. The non-aqueous scenario has been preferred because the nucleotides formed in subsequent steps are not stable in aqueous media [8]. Because of this instability, Sponer et al. have recently considered mechanisms for the non-aqueous scenario formation of nucleobases from formamide on Earth [9]. Even more important is the fact that the non-aqueous scenario is consistent with the formation of nucleobases in an extraterrestrial environment.

For the non-aqueous scenario on prebiotic Earth, the formation of the nucleobases was reported from the simultaneous ultraviolet (UV) irradiation and heating of formamide with higher yields observed in the presence of mineral catalysts [10]. Similarly, UV photolysis of formamide led to the formation of xanthine [11]. Formamide has been described as a good source for C, O, and N that is needed for the prebiotic formation of nucleobases. For the formation of nucleobases in an extraterrestrial environment, xanthine together with other nucleobases were found in meteorites [5]. And, these nucleobases may have been formed under extraterrestrial non-aqueous scenario. Therefore, a non-aqueous scenario is needed for the formation of nucleobases terrestrially or extra-terrestrially. Currently, the mechanisms for such formation of nucleobases are not yet well established.

* Corresponding authors.
E-mail addresses: YJeilani@spelman.edu (Y.A. Jeilani), minh.nguyen@chem.kuleuven.be (M.T. Nguyen).

http://dx.doi.org/10.1016/j.cplett.2014.02.053
0009-2614/

Theoretical studies of the mechanisms for the formation of nucleobases are associated with high energy barriers. To lower the energy barriers water has been included along the pathways. For example, Wang et al. have studied by density functional theory (DFT) a potential water-catalyzed pathway for adenine formation starting from formamide [12]. Involvement of water in the reactions was necessary in lowering the energy barriers. Similarly, Roy et al. [13] reported the necessity of including water molecules to lower the activation energies. These studies suggest compelling mechanisms for the formation of one nucleobase. However, they cannot be used to explain the formation of nucleobases from a non-aqueous scenario because water is required to lower the energy barriers.

The prebiotic Earth environment may have restricted the types of reactions that could have been prevalent on Earth. Most probably, the lack of an ozone layer, an oxygen depleted atmosphere, and the high flux of solar UV irradiation had impact on the pathways. Such conditions promote electron-transfer processes inducing free-radical pathways. Recent studies indicated involvement of free radicals in the prebiotic pathways [14,15]. For example, laboratory experiments to simulate high-energy impact events on Earth with an extraterrestrial icy body showed products that were formed from the reaction of free radicals with formamide [15]. Also, formation of organic molecules on Titan's atmosphere has been suggested via free-radical pathways [16–18]. In 1953, Miller stated that he used electric discharge to generate free radicals because an electric discharge scenario may have played a role in the primitive atmosphere [1]. His classic experiment led to the formation of amino acids and other biomolecules from simple gases.

Free-radical pathways constructed by DFT methods were reported for cytosine [18]. There is growing evidence that free radicals were likely involved in prebiotic chemistry [19]. Reactions of the cyano radical (·CN) were also proposed for the synthesis of nucleobases by DFT methods, but the intermediates that were considered did not lead to the targeted nucleobase [17]. Free-radical pathways are consistent with both terrestrial and extraterrestrial prebiotic reactions because radicals can be generated within credible scenarios. Moreover, controlled reactions of formamide with ·CN led to the identification of 2-amino-2-hydroxyl-acetonitrile as a possible precursor for nucleobases [15]. There is an increasing interest in free-radical pathways because theoretical studies demonstrated that these pathways have low energy barriers. We recently reported free-radical pathways for adenine, purine, hypoxanthine, and guanine starting from formamide [20]. These pathways were based on the formation of the imidazole derivative radical (**13**) from formamide (Scheme 1).

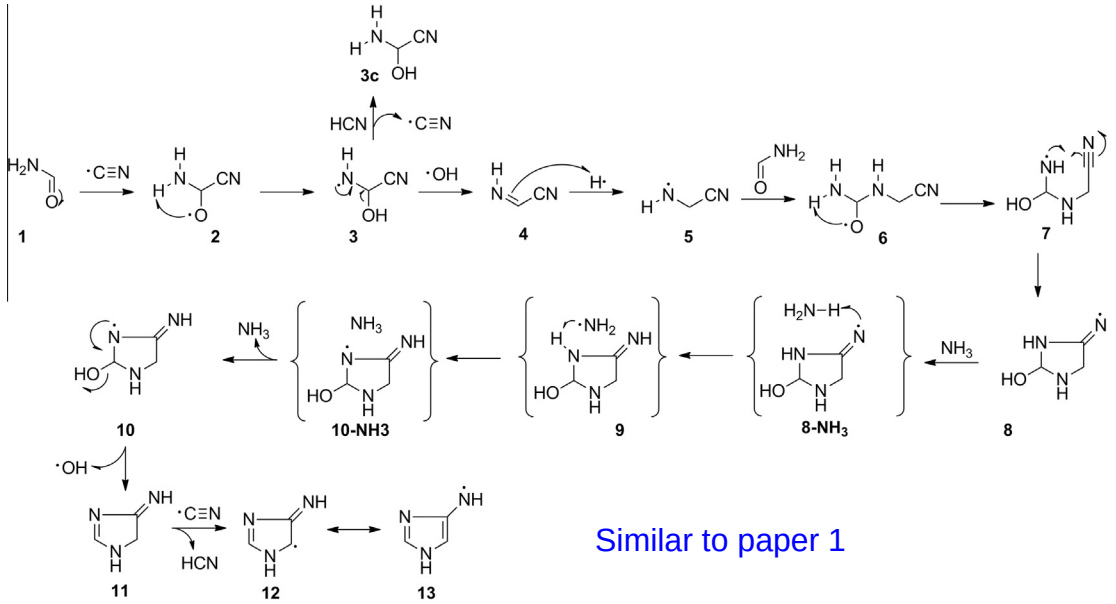
In this context, the free-radical pathways for the formation of xanthine and isoguanine from the reaction of formamide with ·CN were studied by DFT methods. Indeed, the results support that 2-amino-2-hydroxyl-acetonitrile is a precursor for the nucleobases as advanced by Ferus et al. [15]. The proposed mechanisms suggest that both xanthine and isoguanine may be formed under the same microenvironment. These pathways lead to the formation of more than one target molecule further promoting diversity on the primordial Earth. Since water is not included in the proposed pathways, the mechanisms are appropriate for both terrestrial and extraterrestrial microenvironments.

2. Computational methods

All calculations using density functional theory (DFT) were performed with the aid of the Gaussian 09 suite of programs [21]. The popular hybrid B3LYP functional [22,23], in conjunction with the 6-311G(d,p) basis set [24] was used for all calculations. Harmonic vibrational frequency calculations were carried out at the same level in order to confirm the nature of stationary points and to obtain zero-point vibrational energies. Each transition structure was characterized by having one imaginary vibrational frequency for the normal mode corresponding to the correct reaction coordinate. Our recent theoretical studies [12,25] pointed out that the B3LYP functional is suitable for investigating reaction pathways involving formamide. The use of this DFT method, in the unrestricted formalism (UB3LYP), allows us to avoid the severe spin-contamination usually encountered in the UHF and UMP2 computations for open-shell radicals, in particular for the radical ·CN [26–28].

3. Results and discussion

The role of ·CN toward nucleobase synthesis has been considered through diaminomaleonitrile (DAMN) and diaminofumaronitrile (DAFN) [17]. But these intermediates did not lead to the formation of nucleobases. Therefore, the focus of the current



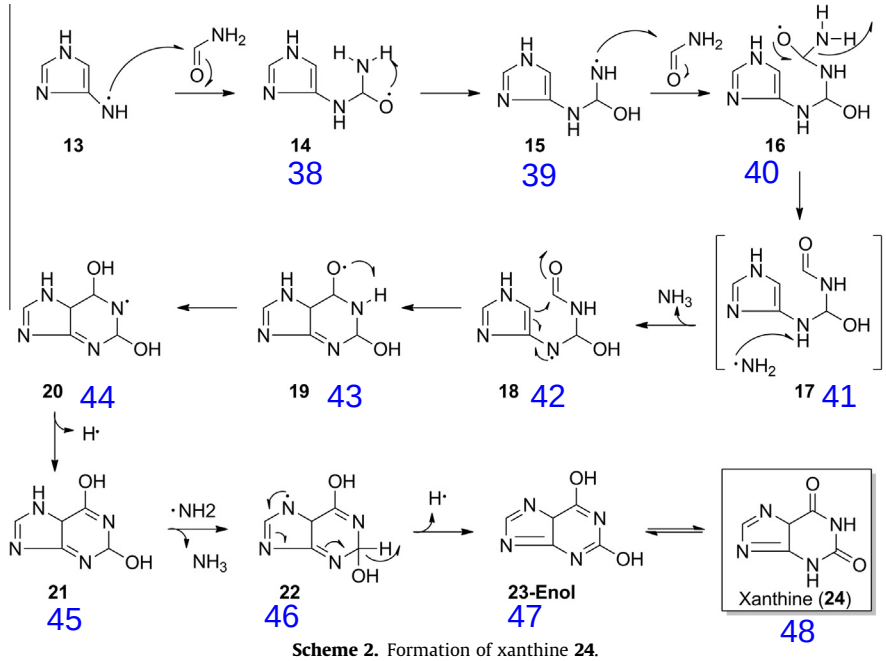
Scheme 1. Production of imidazole precursor **13**.

Letter is on new pathways using ·CN toward the synthesis of xanthine and isoguanine.

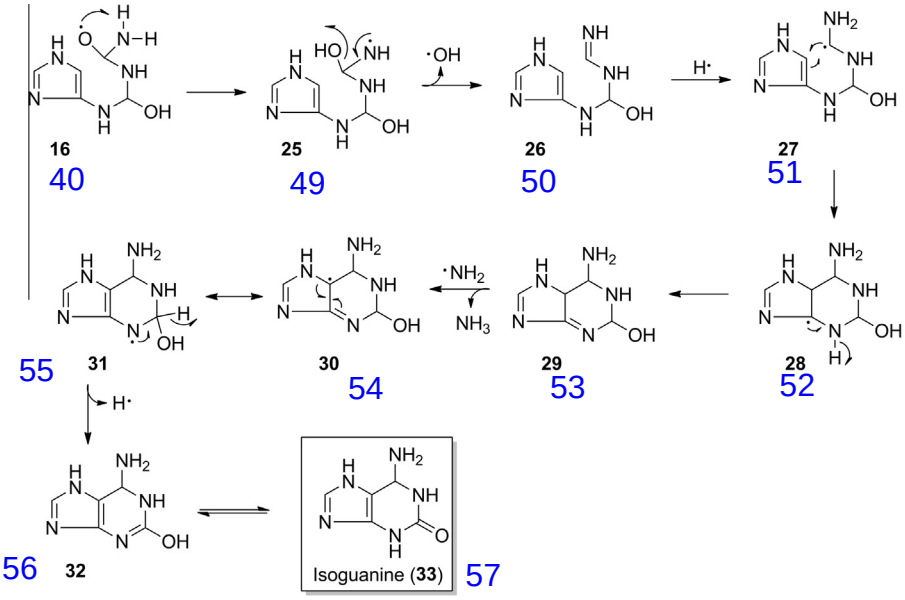
The pathways constructed using B3LYP/6-311G(d,p) computations provide energetic evidence for the non-aqueous prebiotic formation of nucleobases. The pathways suggest formation of a mixture of products. Scheme 1 shows the reaction of formamide with ·CN leading to the formation of **13**. The mechanisms for the formation of xanthine and isoguanine are based on the pre-formation of the imidazole-derivative intermediate (**13**) as a precursor. Schemes 2–4 show the free-radical pathways for xanthine, isoguanine, and polyazaporphyrin. This is the first time that pathways are proposed to address formation of a carbonyl group through enol-keto tautomerization under prebiotic conditions.

3.1. Xanthine pathway mechanism

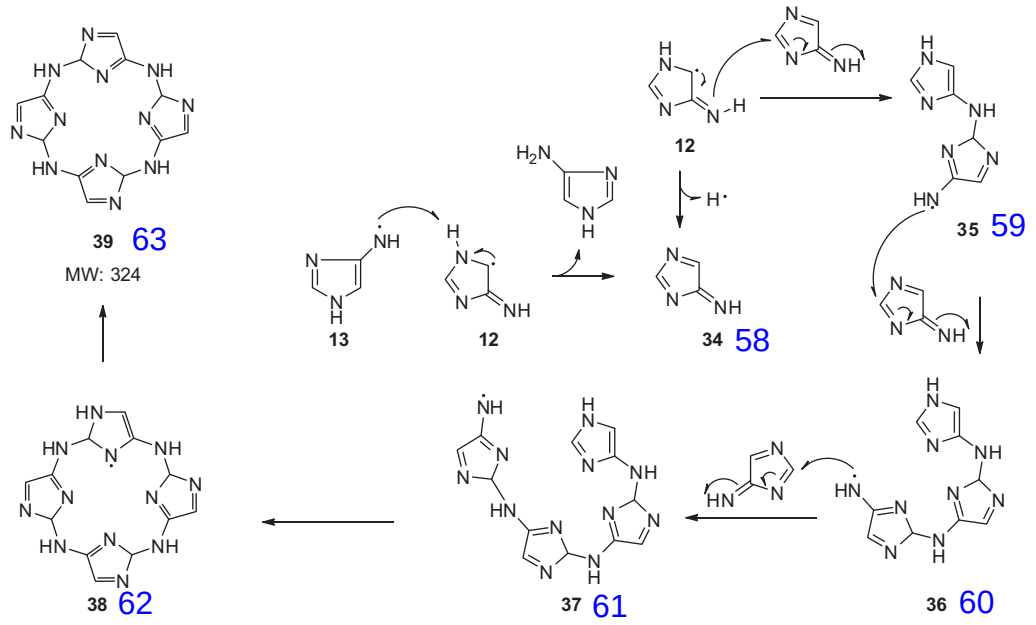
To account for the number of heavy atoms (C, O and N) in xanthine, addition of two molecules of formamide to **13** is required. The first step is a radical addition of **13** to formamide to give **14**, followed by the 1,3-H-rearrangement **14** → **15**. This shift is necessary for N to become part of the heterocycle. Addition of another molecule of formamide to **15** yields **16**, and this completes the number of formamide molecules (a total of four formamide molecules from the beginning of the mechanism) required for the synthesis of xanthine. The calculation of the number of formamide molecules per nucleobase facilitates estimation of theoretical yields for experimental studies. Elimination of a ·NH_2 radical from



Scheme 2. Formation of xanthine **24**.



Scheme 3. Formation of isoguanine **33**.



Scheme 4. Formation of polyzaporphyrin **39**.

16 gives rise to the formation of the radical-molecule complex **17**. Hydrogen abstraction by the $\cdot NH_2$ results in **18** with a small energy barrier of 7.4 kcal/mol (Figure 1).

The cyclization step in nucleobase mechanisms has been previously reported to have the highest activation barrier. Similarly, the radical cyclization of **18** to **19** requires activation energy of 44.3 kcal/mol. The structure of the TS shows a distance of 1.8 Å between the carbonyl carbon and the carbon radical. This is the rate-determining step demanding the largest energy in the present mechanism. However, this value is still less than the activation energy previously proposed for uncatalyzed reactions (including cyclization) [12]. Alternative free-radical cyclization strategies for **18** were considered but the activation energies (data not reported here) were close to that of **18** → **19**. Such a high energy requirement suggests that the use of minerals as catalysts is important for nucleobase synthesis, which is consistent with previous experimental studies. Indeed, the use of minerals was reported to enhance production of nucleobases [10]. Also, **19** is located just 1 kcal/mol below the transition state and the barrier to the next more stable species **20** is 20.7 kcal/mol. Therefore, the barrier is essentially a total of 65 kcal/mol for the two steps **18** → **19** → **20**. This high barrier is for the combined cyclization and H-rearrangement steps. Alternative pathways were considered such as H-abstraction from the OH group of **17**. But this path does not lead to lower energy barrier.

Mechanisms leading to the formation of carbonyl groups are important in prebiotic chemistry due to the fact that a facile formation of carbonyl may lead to the functional group transformations required for the construction of complex molecules. The first route is a H-loss from the H—C—O· group of **19** to give the corresponding —(C=O)—. This reaction is highly endergonic with an energy change of 97.3 kcal/mol for this step, which is quite prohibitive. Therefore, an alternative route involving formation of an enol tautomer is considered and the 1,3-H radical rearrangement from **19** to give **20** is accordingly proposed. The energy barrier for this rearrangement amounts to 20.7 kcal/mol. Loss of a H atom from **20** provides indeed the enol **21**.

Now, sequential loss of two H atoms from **21** forms xanthine. This channel can be achieved through a hydrogen abstraction by $\cdot NH_2$ (or ·CN) followed by a loss of the second atomic hydrogen.

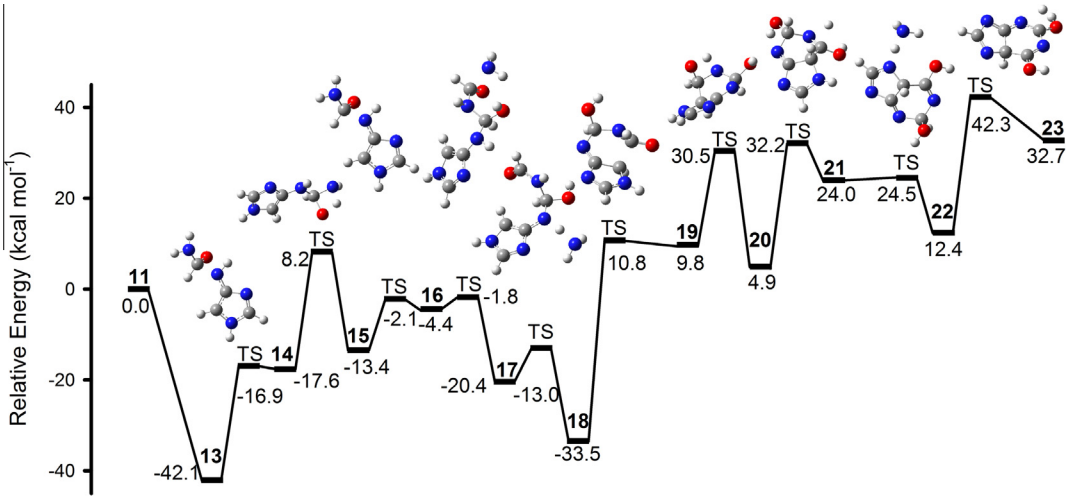


Figure 1. Potential energy profile for formation of enol-form of xanthine **23**.The profile represents the relative potential energies of a sequence of reactions. Values at the B3LYP/6-311G(d,p) + ZPE level.

This loss of two H radicals is equivalent to an oxidation reaction in classical organic chemistry since the oxidation is defined as formation of a double bond by loss of H_2. Therefore, a H abstraction by $\cdot NH_2$ from **21** produces **22**. The H-loss from **22** gives rise to the enol tautomer **23** of xanthine (**24**). The conversion of **21** to **23** is thus equivalent to an oxidation step because there is a net loss of H_2. The conversion of **23** to **24** can again be achieved through keto-enol tautomerization. The latter process is well described in organic chemistry and takes place in the presence of a mineral acid or a base. Since the reactions take place in the gas phase or in the absence of water, the formation of the enol form may be a predominant route in the interstellar medium. Alternatively, enol-keto tautomerization to xanthine (**24**) may have taken place in the presence of a small amount of an acid catalyst or a base in the prebiotic soup.

3.2. Isoguanine pathway mechanism

The abiotic formation of isoguanine is important for the hypothesis of all-purine precursor of nucleic acid. The prebiotic synthesis of isoguanine still needs further studies, since there is still no conclusive evidence about its origin. The synthesis of nucleobases is experimentally challenging because of differences in the stabilities of nucleobases as well as their reactivities under a given set of prebiotic conditions [29]. Isoguanine has been targeted in the analysis of meteorites due to an essential prebiotic role that it may have played. Callahan et al. reported the analysis of meteoritic samples and found purine nucleobases [5], but pyrimidines and isoguanine were not detected in these meteorites. Even though there is no explanation for the absence of these nucleobases in the meteorites analyzed [5]. Analysis of meteoritic samples requires extraction conditions, perhaps the extraction methods need further optimization because solvents have been suggested to change some intrinsic properties of isoguanine tautomers [30]. It should be pointed out that isoguanine has been proposed as the required nucleobase for all-purine nucleic acid [29].

The prebiotic origin of nucleobases is a topic that is evolving, and new studies are needed to better understand the set of conditions that lead to a given set of nucleobases. The mechanism identified here is the first computational evidence to show that an abiotic formation of isoguanine (**33**) is possible. These pathways could be useful in the design of new experimental approaches that target isoguanine. In addition, this prediction supports the all-purine nucleic acids hypothesis that incorporates isoguanine as precursor.

Because of structural similarities, a mechanism leading to xanthine is expected to also generate isoguanine. The latter requires elimination of an $\cdot OH$ from **16** while xanthine requires elimination of $\cdot NH_2$. Therefore, the first step for isoguanine mechanisms is a 1,3-H shift from **16** to **25**. This is consistent with the routes described above (**14** → **15**). Loss of $\cdot OH$ from **25** produces the neutral intermediate **26**.

A two-step radical cyclization reaction can thus be proposed. The first step of the cyclization is the addition of a $\cdot H$ to **26** to give **27**. Cyclization of **27** gives **28** with relatively low energy barrier of 13.8 kcal/mol (Figure 2). This channel shows a relatively lower barrier than the previously reported one for the uncatalyzed cyclization step. However, a H-loss from **28** to form **29** has a relatively high energy barrier of 35.9 kcal/mol.

Similar to the xanthine pathways, loss of two hydrogens from **29** forms the enol of isoguanine. This channel involves $\cdot NH_2$ for the abstraction of a hydrogen from **29** to **30**. A H-loss from **31** yields **32** which is the enol of isoguanine (**33**). The energy barrier for the **31** → **32** step amounts to 30.2 kcal/mol. Again, similar to xanthine, formation of isoguanine (**33**) from the tautomerization of **32** is likely to involve catalysis of an acid or a base.

3.3. Promoting prebiotic diversity with a potential synthesis of polyzaporphyrin from the imidazole precursor 13

Ever since the early studies of prebiotic chemistry, emphasis has been given to the synthesis of biomolecules that may have biological functions. Prebiotic synthesis of porphyrins has been reported based on Fischer–Tropsch type of reactions [31]. Studier et al. suggested that the Murchison meteorite contains compounds similar to those produced from the Fischer–Tropsch reaction [32]. Those studies suggested that porphyrins may have originated from an extraterrestrial environment. In the current Letter, a porphyrin compound is of interest because of the similarities between part of the porphyrin ring and the five-membered ring of nucleobases. Thus, the proposed approach further promotes the fact that free radicals may actually be involved in the synthesis of diverse compounds. Our purpose is to show that a porphyrin can be formed from **13**, an intermediate compound in the synthesis pathways of nucleobases which has structural features of the repeating unit in porphyrin.

Neumer et al. reported a prebiotically feasible synthesis of 2, 5, 7, 10, 12,15, 17, 20-octaaza-21H,23H-porphine (polyazaporphyrin) starting from HCN [33]. This porphyrin was considered as an oligomer of HCN because it has a formula of $(HCN)_{12}$. The study focused on the formation of imidazole-4-nitrenium as the base unit for the synthesis of polyazaporphyrin. Since the structure of the intermediate **13** is the radical analog of imidazole-4-nitrenium ion, a new free-radical mechanism for polyazaporphyrin synthesis can be put

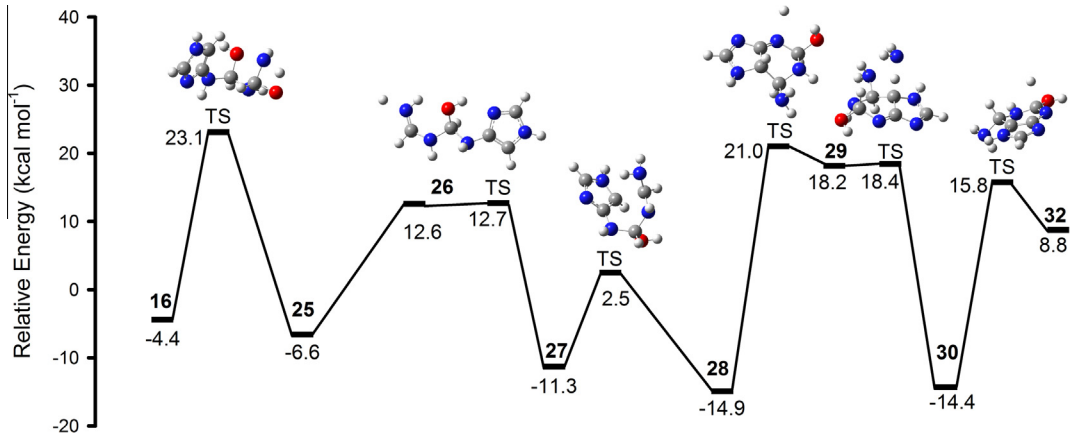


Figure 2. Potential energy profile showing the formation of isoguanine (**32**). The profile represents the relative potential energies of a sequence of reactions. Values at the B3LYP/6-311G(d,p) + ZPE level.

forward. This demonstrates that both nucleobases and porphyrin may arise from the common prebiotic precursor **13**, and therefore strengthens the utility of free radicals as precursors for biomolecules.

Scheme 3 shows a low barrier mechanism for polyazaporphyrin. The bottleneck for the porphyrin mechanism is formation of the monomer repeating unit **34**. Loss of H from **12** yields the neutral intermediate **36** with a high energy barrier of 63 kcal/mol. Such a high energy barrier makes this step unlikely to take place without a catalyst. The formation of the intermediate **34** is critical to the proposed pathway. Alternatively, **34** can be formed by a free-radical disproportionation of **12** (Scheme 4). Note that the final two products of the disproportionation of **12** are both neutral species. However, in spite of extensive attempts, a transition state for this disproportionation reaction could not be found at the B3LYP/6-311G(d,p) level. All subsequent steps for the polyazaporphyrin synthesis have low energy barriers (Scheme 3).

The radical addition of **12** to **34** forms the dimer **35** with an energy barrier of 6.4 kcal/mol (Figure 3). This addition reaction is slightly exergonic (Table 1). Sequential addition of two monomer molecules **34** produces the tetramer **37** through low energy barrier reactions. Cyclization of **37** to form **38** is expected to be a high-energy demanding step but calculations show a small barrier of only 5.6 kcal/mol. Compared to the cyclization barriers in nucleobase synthesis, it appears that the large porphyrin ring is much easier to form than a six-membered ring in nucleobases which proceed with larger barriers. These results also show that the free-radical mechanisms for the cyclization of a porphyrin ring are plausible under prebiotic conditions. A H-loss from the resonance-stabilized **38** gives **39** with a large energy barrier of 44.7 kcal/mol (Figure 3).

The radical **38** is thermodynamically more stable than azaporphyrin **39** (Table 1). This type of radicals has previously been suggested to have an unusual stability. Both radical **38** and neutral **39** species have been observed experimentally [33]. The current mechanisms suggest that **38** is a precursor of **39**.

3.4. Barrierless and highly exergonic free-radical reactions

The use of small basis sets may affect the calculated energy barriers, therefore calculations of the barrierless steps were carried out with a larger basis sets to verify them. The structures optimized at B3LYP/6-311G(d,p) level of theory were thus subjected to reoptimization using the B3LYP/6-311++(3df,2pd) level. Calculations with the larger 6-311++(3df,2pd) basis set gave energies comparable to those obtained using the 6-311G(d,p) basis sets (Supporting Information, Table S1). These results suggest that the transition state energies are not substantially affected by the size of the basis set, and similarly the minimum energy profiles.

Table 1
Relative energies of the prebiotic formation of xanthine, isoguanine, and polyazaporphyrin.

Description	ΔE^a	Description	ΔE^a
13 → 14	24.4	**26 → 27**	−23.8
14 → 15	4.2	**27 → 28**	2.0
15 → 16	9.0	**28 → 29**	38.7
16 → 17	−16.0	**29 → 30**	−32.5
17 → 18	−13.1	**31 → 32**	23.1
18 → 19	43.2	**12 → 34**	−64.2
19 → 20	−4.8	**12 → 35**	−8.2
20 → 21	19.0	**35 → 36**	−18.3
21 → 22	−11.5	**36 → 37**	−20.6
22 → 23	20.3	**37 → 38**	−12.3
16 → 25	−2.2	**38 → 39**	43.0
25 → 26	19.1		

[a] ΔE in kcal/mol.

Recent studies have shown that some steps involving free radicals are exothermic and tend to proceed without or with small energy barriers [16,17]. For example, a barrierless photoisomerization of *cis*-DAMN to *trans*-DAMN was recently reported [34]. These studies are consistent with the current findings that some of the free-radical steps leading to the nucleobases are barrierless. Table 1 shows that the **16 → 17**, **17 → 18**, **19 → 20**, **21 → 22**, **16 → 25**, **26 → 27**, **27 → 28**, **29 → 30**, **12 → 35**, **35 → 36**, **36 → 37**, and **37 → 38** steps are exothermic which is consistent with previous studies on free-radical pathways.

The use of $^{\cdot}NH_2$ as a reasonable agent to activate neutral molecules with low energy barrier is known. Such a strategy is feasible when the product is conjugated as in **30**. The H abstractions steps, **11 → 13**, **17 → 18**, and **29 → 30** proceed with small barriers. Such small energy barriers for H abstraction steps are consistent with recent report of H abstraction from uracil by $^{\cdot}OH$ that proceeds with a low barrier of about 9.5 kcal/mol [35]. Formation of neutral intermediates followed by H abstractions with low energy barriers, may take place over long geological time that fit well with prebiotic scenarios.

3.5. Prebiotic implications of the pathways

The results obtained in the present Letter provide new mechanistic approaches for the prebiotic formation of nucleobases. The

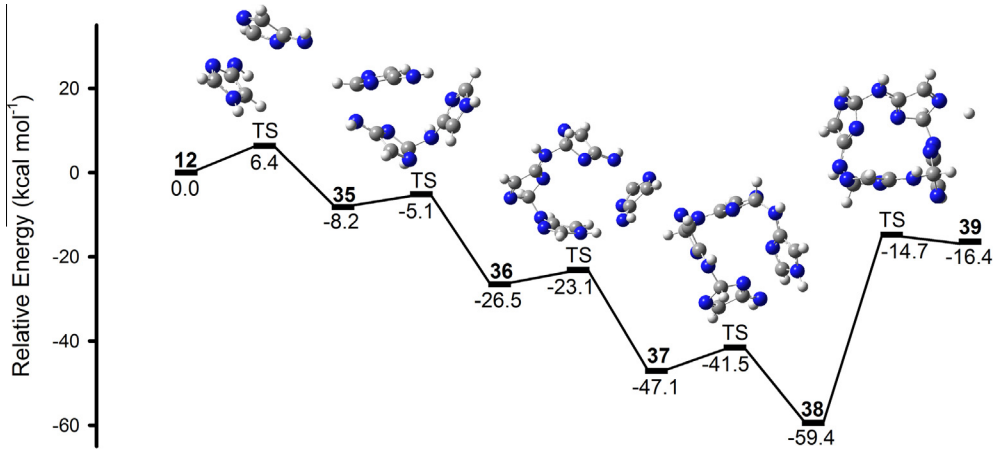


Figure 3. Potential energy profile for formation of polyzaporphyrin (**39**). The profile represents the relative potential energies of a sequence of reactions. Values at the B3LYP/6-311G(d,p) + ZPE level.

aims are to establish some new mechanisms for the formation of xanthine and isoguanine, and to identify routes on the complex PES leading to other biomolecules. The pathways are indeed complex giving rise to a mixture of products. Other pathways on the PES such as the coupling of two radicals should be taken into consideration since they are expected to reduce the yield of nucleobases. Experimentally, low yields of nucleobases have been observed [10]. The proposed mechanisms suggest that the best strategy for the formation of the C=O bond in nucleobases is through the enol form. These results demonstrate the potential role of enolate chemistry in prebiotic reactions. Relatively higher activation energies were calculated for the **18** → **19** cyclization and the **28** → **29** loss of ·**H** steps. These results suggest that mineral catalysis could have played a crucial role in the synthesis of these nucleobases under prebiotic conditions.

On the other hand, a new reasonable mechanism for polyazaporphyrin further expands the diversity of the biomolecules formed in the prebiotic era. The proposed mechanism for polyazaporphyrin is the first theoretical evidence that supports the previously reported detection of porphyrin-like pigments in laboratory simulation experiments. The porphyrin-like pigments were formed in a Fischer–Tropsch type reaction using CO, D_2, and ND_3 with Ni–Fe and Al_2O_3 [31].

Also, porphyrin was detected in the Murchison meteorite albeit the quantity was small and complete characterization was not available [32]. The hypothesis for porphyrin synthesis in the present Letter is based on the fact that free-radical PES is complex and may include pathways to useful compounds. An eventual identification of **13** as a precursor for nucleobases and polyazaporphyrin could further support this hypothesis.

The proposed mechanisms are appropriate for the formation of organic matter observed in the solar system. For example, free radicals may be invoked for reactions taking place in cometary frozen nuclei and aerosols when subjected to high-energy sources. The proposed mechanisms can be used to explain the non-terrestrial origin of xanthine, as previously suggested [3]. Xanthine was found in meteorites by both carbon isotopic ratio methods and formic acid extraction of meteorites samples [3,4]. The formic acid extraction was performed on samples from Murchison, Murray, and Orgueil carbonaceous meteorites and xanthine was detected in all samples [4]. Laboratory simulation experiments of the extraterrestrial conditions are not trivial to setup because of the limited knowledge of the unseen environment. However, there are increasing synthetic and spectral evidences for organic compounds in the organic haze of Titan's atmosphere. Formation of complex molecules under such environments is expected to proceed through free radicals. The pathways for xanthine and isoguanine demonstrated that more compounds may also be expected because there are neutral and stable intermediates in the pathways.

The reactions of HCN are important for both interstellar media and prebiotic Earth. It has been previously speculated that HCN is a precursor for nucleobases and numerous experiments have been reported on HCN chemistry [11]. The results in the present Letter further demonstrate the role of the HCN/·CN pair. Scheme 1 points out that the triple bond in CN facilitates the formation of the five-membered ring (**7** → **8**). The ·CN radical provides a venue for activating neutral intermediates with highly exothermic steps (e. g., **11** → **12**).

The possible formation of isoguanine further advances the all-purine nucleic acid hypothesis because isoguinine is an important nucleobase in this hypothesis. Isoguanine together with the polyazaporphyrin are hypothesized as possible targets that could be formed in the Titan atmosphere as there is no solvent requirement in the mechanisms. Formation of polyazaporphyrin further suggests that future space missions should target complex biomolecules beyond simple amino acids and nucleobases.

Acknowledgments

The computational work was in part performed at the University of Wisconsin-Madison using Phoenix cluster supported by National Science Foundation Grant CHE-0840494. H.T.N. thanks KU Leuven Research Council for a doctoral scholarship via the IDO program on Exoplanets.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cplett. 2014.02. 053.

References

[1] S.L. Miller, Science 117 (1953) 528.
[2] P. Ehrenfreund, S.B. Charnley, Annu. Rev. Astron. Astrophys. 38 (2000) 427.
[3] Z. Martins et al., Earth Planet. Sci. Lett. 270 (2008) 130.
[4] P.G. Stoks, A.W. Schwartz, Geochim. Cosmochim. Acta 45 (1981) 563.
[5] M.P. Callahan et al., PNAS 108 (2011) 13995.
[6] Y.-J. Kuan, S.B. Charnley, H.-C. Huang, W.-L. Tseng, Z. Kisiel, Astrophys. J. 593 (2003) 848.
[7] C. Simionescu, T. Lixandru, V. Gorduza, C. Gorea, Origins Life 8 (1977) 237.
[8] R. Shapiro, Proc. Natl. Acad. Sci. USA 96 (1999) 4396.
[9] J.E. Sponer, A. Mladek, J. Sponer, M. Fuentes-Cabrera, J. Phys. Chem. A 116 (2012) 720.
[10] H.L. Barks, R. Buckley, G.A. Grieves, E. Di Mauro, N.V. Hud, T.M. Orlando, ChemBioChem 11 (2010) 1240.
[11] B. Basile, A. Lazcano, J. Oro, Adv. Space Res. 4 (1984) 125.
[12] J. Wang, J. Gu, M.T. Nguyen, G. Springsteen, J. Leszczynski, J. Phys. Chem. B 117 (2013) 2314.
[13] D. Roy, D. Najafian, P.R. Schleyer, Proc. Natl. Acad. Sci. USA 104 (2007) 17272.
[14] C. Menor-Salván, M.R. Marín-Yaseli, Chem. Eur. J. 19 (2013) 6488.
[15] M. Ferus, S. Civiš, A. Mládek, J. Šponer, L. Juha, J.E. Šponer, J. Am. Chem. Soc. 134 (2012) 20788.
[16] A. Landera, A.M. Mebel, J. Am. Chem. Soc. 135 (2013) 7251.
[17] V.P. Gupta, P. Rawat, R.N. Singh, P. Tandon, Comput. Theor. Chem. 983 (2012) 7.
[18] V.P. Gupta, P. Tandon, P. Mishra, Adv. Space Res. 51 (2013) 797.
[19] J. Xu, N. Nita, Earth Planet. Sci. Lett. 363 (2013) 156.
[20] Y.J. Jeilani, H.T. Nguyen, D. Newallo, J.-M.D. Dimandja, M.T. Nguyen, Phys. Chem. Chem. Phys. 15 (2013) 21084.
[21] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009.
[22] D. Becke, Phys. Rev. A 38 (1988) 3098.
[23] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785.
[24] W.J. Hehre, L. Radom, P.V.R. Schleyer, J.A. Pople, ab Initio Molecular Orbital Theory, Wiley, 1986.
[25] J. Wang, J. Gu, M.T. Nguyen, G. Springsteen, J. Leszczynski, J. Phys. Chem. B 117 (2013) 9333.
[26] G.M. Jensen, D.B. Goodin, S.W. Bunte, J. Phys. Chem. A 100 (1996) 954.
[27] T. Brinck, M. Haeberlein, M. Jonsson, J. Am. Chem. Soc. 119 (1997) 4239.
[28] Y.-W. Huang, V. Srinivasadesikan, W.-H. Chen, S.-L. Lee, Chem. Phys. Lett. 565 (2013) 18.
[29] M. Levy, S.L. Miller, Proc. Natl. Acad. Sci. 95 (1998) 7933.
[30] J.R. Blas, F.J. Luque, M. Orozco, J. Am. Chem. Soc. 126 (2004) 154.
[31] R. Hayatsu, M.H. Studier, S. Matsuoka, E. Anders, Geochim. Cosmochim. Acta 36 (1972) 555.
[32] M.H. Studier, R. Hayatsu, E. Anders, Geochim. Cosmochim. Acta 36 (1972) 189.
[33] J.F. Neumer et al., Orig. Life Evol. Biosph. 28 (1998) 27.
[34] E. Boulanger, A. Anoop, D. Nachtigallova, W. Thiel, M. Barbatti, Angew. Chem. Int. Ed. 52 (2013) 1.
[35] K.P. Prasanthkumar, C.T. Suresh, C.T. Aravindakumar, Radiat. Phys. Chem. 81 (2012) 267.