Prebiotic Photochemistry

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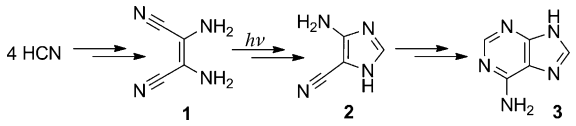
Photochemical Steps in the Prebiotic Synthesis of Purine Precursors from HCN**

*Eliot Boulanger, Anakuthil Anoop, Dana Nachtigallova, Walter Thiel, and Mario Barbatti**

Hydrogen cyanide (HCN) chemistry is believed to be an important part of the abiotic synthesis of organic materials, including nucleobases, amino acids, and oligopeptides.[1] One of the most probable routes for the synthesis of purine nucleobases and nucleotides[2] in the prebiotic world (Scheme 1) involves HCN oligomerization into the tetramer

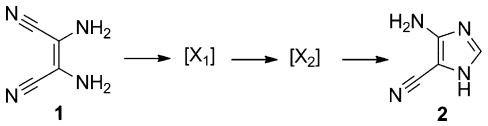


Scheme 1. Conversion of the HCN tetramer *cis*-DAMN (**1**) into AICN (**2**), a key intermediate in the synthesis of purine nucleobases and nucleotides. Adenine (**3**) is shown as one possible product.

cis-2,3-diaminomaleonitrile (*cis*-DAMN, **1**), which may be converted photochemically into an imidazole intermediate (4-amino-1*H*-imidazole-5-carbonitrile, AICN, **2**).[3] Although this reaction has been investigated in detail since its discovery by Ferris and Orgel in 1966,[1,4] the mechanism of the photochemical steps remains unresolved. Herein, we address this issue from a theoretical perspective: by the use of computational chemistry and chemical kinetics we show that among a number of possibilities, including all those previously proposed, there is only one sequence of steps that is thermodynamically and kinetically compatible with the experimental conditions.

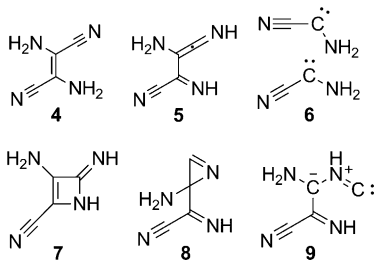
One of the most appealing features of the DAMN→AICN reaction is its robustness.[5] It was observed in a large variety of solvents (polar and nonpolar), with several enaminonitrile derivatives, and at diverse concentrations and temperatures.[6] The imidazole derivative **2** is photostable (5% reduction in absorbance after irradiation at 254 nm for 3 h;[4d] see also Ref. [7] on imidazole photostability) and resistant to hydrolysis (lifetime: 2000 years at pH 8[8]). These characteristics imply that different prebiotic environments, either terrestrial or extraterrestrial, could have been the source of AICN (**2**) in the prebiotic world.[5] The accumulation of AICN, however, requires relatively large HCN concentrations ($>10^{-2}$ M).[9] This requirement sets a first relevant environmental constraint: such high HCN concentrations are only possible in low-temperature environments, such as ice and eutectic water–HCN phases. Therefore, any realistic mechanism cannot count on high thermal energy in addition to the photon energy.

The number of photons and intermediates involved in the photochemical steps is unknown (Scheme 2). The process



Scheme 2. Photochemical steps in the DAMN→AICN reaction.

starts with photoexcitation of *cis*-DAMN (**1**), the first clearly stable HCN oligomer.[10] On the basis of the spectral shifts observed after the irradiation of *cis*-DAMN, Yamada et al.[4e] showed that the first intermediate (X_1) is the *trans*-DAMN isomer **4** (Scheme 3). Irradiation leads to a photostationary



Scheme 3. Previously proposed intermediates.

state with a large predominance of *trans*- (**4**) over *cis*-DAMN (**1**).[4c] Becker et al.[4d] raised the possibility that carbenes, **6**, are the first intermediate, instead of *trans*-DAMN (**4**). However, the absence of cross-products in the experiments of Ferris et al. ruled this hypothesis out.[11]

Little is known about X_2 (Scheme 2), which may represent more than one intermediate. Infrared spectra in a liquid film and a KBr matrix indicated that X_2 may possess a ketenimine group (2000–2020 cm^{-1})[12] and thus indicated a possible

[*] E. Boulanger, Prof. Dr. W. Thiel, Dr. M. Barbatti
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: barbatti@kofo.mpg.de
Homepage: http://www.sgk.mpg.de/private/barbatti
Dr. A. Anoop
Department of Chemistry, Indian Institute of Technology
Kharagpur 721302 (India)
Dr. D. Nachtigallova
Institute of Organic Chemistry and Biochemistry, AS CR
Flemingovo nam. 2, 166 10 Praha 6 (Czech Republic)

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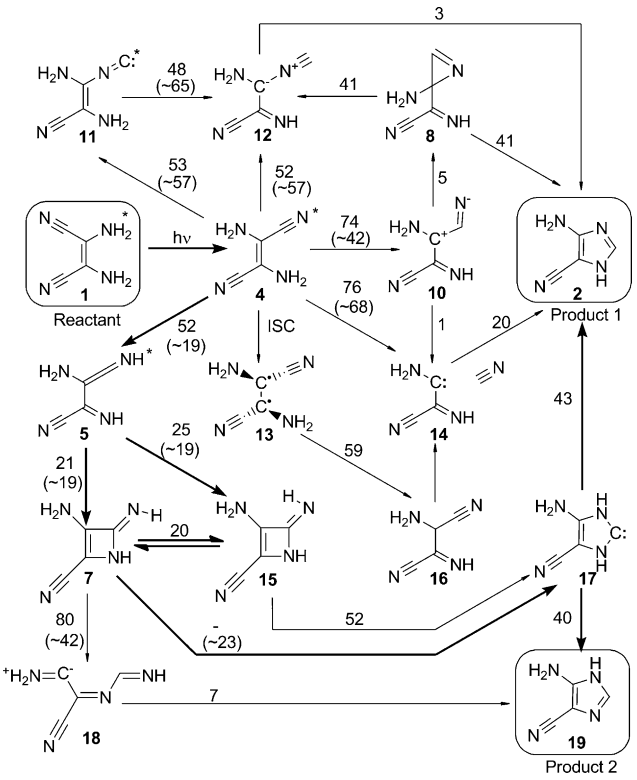
hydrogen-atom transfer from one of the amino groups of **4** to form 2-amino-3-iminoacrylimidoyl cyanide (AIAC, **5**). The subsequent formation of AICN (**2**) requires CN cleavage, for which pathways via the azetene **7**, azirene **8**, and a formal zwitterion **9** have been proposed, without any consensus on which pathway would be predominant.[4a,6]

In this study, we investigated a large number of possible reaction pathways. We examined both thermodynamic and kinetic aspects of the pathways. One first relevant fact revealed by our simulations is that although energy of 4 eV is added to the system by the photoexcitation, most of this energy is quickly dissipated to the environment after relaxation to the ground state. In water, this dissipation happens within about 0.2 ps after internal conversion to the ground state (see the Computational Section). This ultrafast energy dissipation sets up a second important constraint for the reaction: any hot-ground-state reaction should take place in a very short time span. Naturally, the reaction does not need to occur immediately after the first excitation. Indeed, Koch and Rodehorst[4c] showed that the formation of AICN (**2**) from the photostationary state has a quantum yield of only 0.0034, which means that DAMN (**1** or **4**) is excited about 300 times (on average) before cyclization takes place. These two pieces of information together indicate that any statistical reaction in a hot ground state should occur in less than $300 \times 0.2\ \text{ps} = 60\ \text{ps}$, which corresponds to a maximum free-energy barrier of roughly $30\ \text{kcal mol}^{-1}$ (see the Computational Section).

Scheme 4 summarizes our findings. Starting from *cis*-DAMN, photoisomerization to *trans*-DAMN (**4**) occurs without an energy barrier through internal conversion at a twisted conical intersection. From the *trans* isomer, ground-state reactions leading to all relevant intermediates involve barriers of at least $52\ \text{kcal mol}^{-1}$, which is significantly above our kinetic threshold of $30\ \text{kcal mol}^{-1}$. This finding implies that photoexcitation of the *trans* isomer is required for the reaction to proceed. In the excited state of **4**, CN rearrangement (to **11** or **12**), hydrogen transfer from an amino group to the carbon atom of a cyano group (leading to **10**), and HCN dissociation (to **14**) are again not feasible owing to the high energy barriers (see Scheme 4 and the Supporting Information). Intersystem crossing to the triplet ground state, **13**, can be disregarded on the basis of the triplet-sensitizing experiments reported in Ref. [6], which indicated that the photocyclization takes place in the singlet manifold. The only remaining possibility is an excited-state hydrogen-atom transfer in **4** to form AIAC (**5**) with a computed energy barrier of $19\ \text{kcal mol}^{-1}$.

From AIAC (**5**), an azetene intermediate (**7** or **15**) can be readily formed either in the ground or in the excited state. In the ground state, however, there are large barriers to the subsequent rearrangement of the azetene to **17** or **18**, and moreover, azetenes do not absorb in the wavelength region of interest. Therefore, the only option is an excited-state reaction of AIAC (**5**) via an azetene. From the excited-state minimum of AIAC, **18** is not accessible, whereas the N-heterocyclic carbene (NHC) **17** can be formed after a relatively low barrier of $23\ \text{kcal mol}^{-1}$ has been overcome. Finally, the NHC can tautomerize to AICN (product **2** or **19**).



Scheme 4. Possible mechanisms for the reaction *cis*-DAMN (**1**)→AICN (**2** or **19**). The values near the arrows are the computed free energies of activation (ΔG) in kcal mol^{-1} for the ground-state reaction. When an excited-state reaction is relevant, the corresponding energy barrier is given in parenthesis. Species that can be photoexcited near 300 nm are indicated by an asterisk. The final pathway is indicated by bold arrows. See the Computational Section for a description of the computational methods.

The full proposed reaction, which requires the excitation of *cis*-DAMN (**1**), *trans*-DAMN (**4**), and AIAC (**5**), is shown in more detail in Figure 1. The need for these three excitation steps is not a statistical impediment, as we know that the molecule is excited hundreds of times during the process.[4c] After the excitation of *trans*-DAMN, either the *cis* isomer can be repopulated or the molecule can relax to the S_1 minimum. In fact, the existence of this minimum explains the predominance of the *trans* isomer **4** in the photostationary state[4c] (see the Supporting Information). From the S_1 minimum of *trans*-DAMN, AIAC (**5**) can be formed through internal conversion to the ground state at the CI-2 conical intersection. After the photoexcitation of AIAC, it may relax to its S_1 minimum, from which azetene **7** can be formed by excited-state ring closure. Since the S_1 state of the azetene has near-zero oscillator strength, it has time to reach the CI-3 conical intersection. This intersection is characterized by a C–C ring opening, which helps to guide the rearrangement towards the formation of the five-membered ring of NHC **17**.

At the CI-3 conical intersection and even afterwards in the hot ground state (TS-2), some branching is expected. Part of the population will flow back towards the azetene and may return to AIAC (**5**), which may be excited again. Another part will undergo an internal conversion with C–C bond cleavage

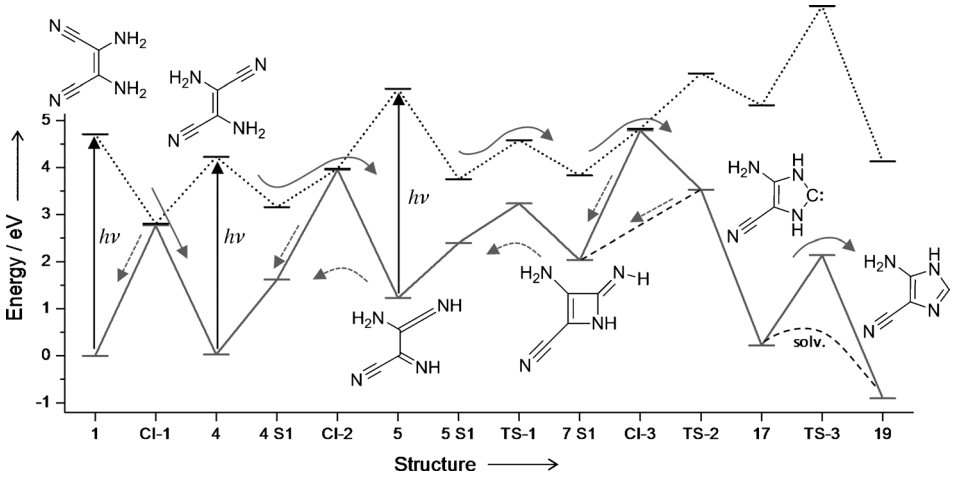


Figure 1. Reaction mechanism for the photoreaction *cis*-DAMN (**1**)→AICN (**19**), including ground (solid lines) and excited states (dotted lines). Dashed arrows indicate back reactions.

in the azetene ring and then directly rearrange to NHC **17**. Such filtering of a reaction at a conical intersection has been observed before for pyrrole, also with the involvement of a ring-opening conical intersection.[13]

From NHC **17**, the final product AICN (**2** or **19**) is obtained by tautomerization. The NHC belongs to the well-studied imidazol-2-ylidene family. Owing to the absence of substituents at the ring nitrogen atoms, it is not stable.[14] In the gas phase, its tautomerization to AICN involves rather high energy barriers, but it should proceed much more readily in polar solvents. Our computations show that the rearrangement to AICN is indeed very facile in solution (see the Supporting Information).

In conclusion, by the use of computational methods, we have identified a multistep mechanism for the DAMN→AICN reaction that is thermodynamically and kinetically compatible with the available experimental data. This mechanism rationalizes the observed ketenimine absorption (at 2020 cm^{-1}) and its disappearance upon heating[12] as well as the preference for the *trans* isomer in the photostationary state. It is consistent with a cold environment, which is required to support a high HCN concentration, and it is also consistent with the lack of luminescence during the reaction.[6] Finally, from a more general perspective, the ultrafast energy dissipation revealed by our simulations provides insight into the time scales that are relevant in photochemical prebiotic reactions.

Computational Section

Energy dissipation: After internal conversion has taken place, the excess electronic energy is transferred to vibrational modes, thus generating a hot ground state. This local hot spot can in principle be the source of energy necessary to overcome a reaction barrier that can normally not be surmounted under standard-temperature conditions. The feasibility of such a process depends on the time during which the molecule is hot enough to undergo the chemical reaction. We employed quantum-mechanical/molecular-mechanical (QM/MM) dynamics simulations to estimate the energy-dissipation time and thus to check whether reactions in the hot ground state may or may not take place in the DAMN→AICN conversion.

We simulated the energy dissipation of a hot *trans*-DAMN ground state into water. Details of the setup for this simulation are specified in the Supporting Information. A QM region composed of DAMN and 9 water molecules was surrounded by a sphere of MM water molecules. The OM2 semiempirical method[15] was used for the QM calculations. MM water was described by the TIP3P model.[16] After equilibration first at MM and then at QM/MM levels, NVE-ensemble simulations were carried out with and without consideration of the hot spot.

To create the hot spot, we kept the direction of the velocities from the initial molecular-dynamics run and only modified their norms to correspond to an excess of 4 eV of photoenergy plus the ground-state zero-point energy, 2.25 eV. Four such trajectories were run, and all of them showed the same tendency. The ratio between the kinetic energy of *trans*-DAMN and the average kinetic energy from the reference simulation (without added energy) is shown in Figure 2a. Evidently,

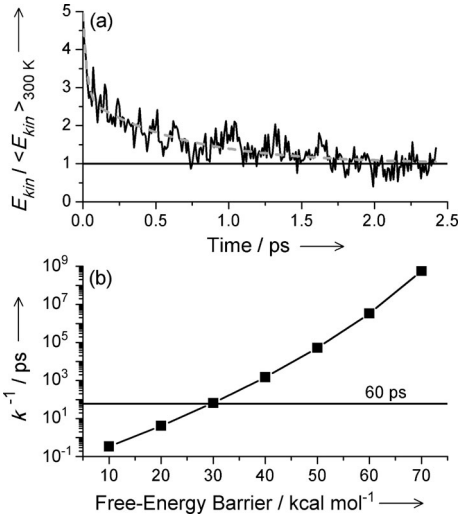


Figure 2. a) Ratio between the kinetic energy of *trans*-DAMN and the average kinetic energy at 300 K as a function of time after creation of the hot spot. The dashed line is a biexponential-decay fitting of the data. b) Inverse of the unimolecular reaction rate as a function of the free-energy barrier.

energy dissipation is extremely fast in water, so that DAMN is already thermalized after about 2 ps. The energy dissipation shows a double-exponential-decay profile, with time constants 0.02 and 0.67 ps. The first dissipation step consists of very fast transfer of about one third of the excess energy to the neighboring water molecules, on the time scale of a couple of N–H stretching oscillations. It is followed by a somewhat slower step, which dissipates the remaining excess energy.

The ultrafast energy-dissipation profile imposes a very short time window for the occurrence of hot-ground-state reactions. For considerations of the reaction rate (see below), we take this window to be

0.2 ps, which corresponds to the time during which the excess energy is reduced to one third of its initial value.

Reaction rate: To estimate the energy barrier that can be overcome within 60 ps given 4 eV of internal energy, we computed unimolecular rates $k(E)$ by using the Rice–Ramsperger–Kassel–Marcus (RRKM) approach.[17] The density and the number of states were estimated with the Beyer–Swinehart direct-count method[18] on the basis of the computed harmonic frequencies for the reactant, *trans*-DAMN (**4**), and the transition state for CN rearrangement, **11**. By solving $k(E)$ for several free-energy-barrier values, we could estimate that the maximum barrier is about 30 kcal mol^{-1} (Figure 2b).

Computational details: Gas-phase minima and transition states in the ground and excited states were determined by density functional theory (DFT) and time-dependent (TD) DFT. The CAM-B3LYP functional[19] with the aug-cc-pVTZ basis set[20] were employed in these calculations. The use of gas-phase model calculations was motivated by the fact that the reaction takes place equally well in a large variety of solvents.[6] Relevant features of the reaction pathways were verified by optimization with the second-order approximate coupled-cluster method (CC2) and the complete-active-space self-consistent-field method (CASSCF) followed by single-point-energy evaluations by second-order perturbation theory (CASPT2). Details of these calculations are described in the Supporting Information. A collection of spectroscopic data obtained at different levels and Cartesian coordinates of all relevant structures are also provided in the Supporting Information. The (TD)DFT and CASPT2 calculations were carried out with the software Gaussian 09[21] and Molcas,[22] respectively.

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