Top Curr Chem (2014)
DOI: 10.1007/128_2013_499

Photosynthesis and Photo-Stability of Nucleic Acids in Prebiotic Extraterrestrial Environments

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Abstract Laboratory experiments have shown that the UV photo-irradiation of low-temperature ices of astrophysical interest leads to the formation of organic molecules, including molecules important for biology such as amino acids, quinones, and amphiphiles. When pyrimidine is introduced into these ices, the products of irradiation include the nucleobases uracil, cytosine, and thymine, the informational sub-units of DNA and RNA, as well as some of their isomers. The formation of these compounds, which has been studied both experimentally and theoretically, requires a succession of additions of OH, NH_2, and CH_3 groups to pyrimidine. Results show that H_2O ice plays key roles in the formation of the nucleobases, as an oxidant, as a matrix in which reactions can take place, and as a catalyst that assists proton abstraction from intermediate compounds. As H_2O is also the most abundant icy component in most cold astrophysical environments, it probably plays the same roles in space in the formation of biologically relevant compounds. Results also show that although the formation of uracil and cytosine from pyrimidine in ices is fairly straightforward, the formation of thymine is not.

Chapter 14 for the book *PHOTOINDUCED PHENOMENA IN NUCLEIC ACIDS* – Mario Barbatti, Antonio C. Borin, Susanne Ullrich (eds.)

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This is mostly due to the fact that methylation is a limiting step for its formation, particularly in H_2O-rich ices, where methylation must compete with oxidation. The relative inefficiency of the abiotic formation of thymine to that of uracil and cytosine, together with the fact that thymine has not been detected in meteorites, are not inconsistent with the RNA world hypothesis. Indeed, a lack of abiotically produced thymine delivered to the early Earth may have forced the choice for an RNA world, in which only uracil and cytosine are needed, but not thymine.

Keywords Astrochemistry · Extraterrestrial abiotic nucleobase synthesis · Ice irradiation · Nucleobases · UV irradiation

Contents

1 Introduction

The processes by which life on Earth originated are not well understood and have been the subject of considerable speculation. While numerous pathways for the emergence of life have been suggested, it was presumably preceded by some sort of prebiotic chemical evolution that set the stage. In this chapter we will concentrate on only one aspect of this potential prebiotic chemistry, namely, the synthesis of nucleobases in extraterrestrial environments.

1.1 Prebiotic Synthesis of the Building Blocks of Life

It is generally assumed that, before life emerged on the primitive Earth, there must have been a period of time during which its basic "building blocks" were synthesized and confined in an environment where they could be protected and interact with each other. There is a priori no requirement for all the building blocks to be synthesized in the same environment, so it cannot be excluded that the individual components in the mixture of materials that led to the emergence of life could have been formed in different locations and at different times. Indeed, individual classes of components, such as amino acids, could have been made and provided from multiple prebiotic environments. Presumably newly forming life had no concern about the different origins of these compounds and instead used whatever was available in the surrounding environment.

1.1.1 Abiotic Chemistry and the Origin of Life

The chemical steps that progressively led to life are still unknown, but they were probably driven by the inventory of molecules that were present on the primitive Earth and/or the astrophysical environment where they took place. All of these ingredients, together with the principles of thermodynamics, may have played an important role in the processes changing non-living molecules into living entities.

The origin of the building blocks of life has been extensively debated since the 1950s, at which time Miller produced small quantities of amino acids and other organic molecules of prebiotic interest in his famous experiment, from the spark-induced chemistry of a gas mixture that was assumed to simulate the primitive atmosphere of the Earth [1]. However, more recent studies suggest that this was probably not the most relevant model because the actual primitive atmosphere was not as reducing as the gas mixture used by Miller [2]. The discovery in the 1960s and 1970s of a rich variety of organic molecules such as amino acids, carboxylic acids, hydrocarbons, sugar-related compounds, as well as puric and pyrimidic bases in carbonaceous meteorites like Murchison (e.g., [3–8]) supported an extraterrestrial delivery of the building blocks of life rather than an indigenous production of these molecules on the primitive Earth. In particular, the amino acids and nucleobases found in the Murchison meteorite were shown to be of extraterrestrial origin, as they display enrichments in ^{13}C relative to standard terrestrial values [9–11]. This scenario of an extraterrestrial delivery of the building blocks of life to the primitive Earth via meteorites, originating from comets and asteroids, is strengthened by the fact that meteoritic bombardment was significantly heavier during the first hundreds of millions of years of the Earth's history [12–17].

A few chemical mechanisms were proposed for the formation of prebiotic molecules under abiotic conditions. For example, amino acids are usually thought to have formed via the Strecker synthesis in the meteorites' parent bodies during phases of aqueous alteration or in a primitive ocean. This synthesis involves an aldehyde that reacts with hydrogen cyanide (HCN) and ammonia (NH_3) to form an aminonitrile that can be hydrolyzed into the corresponding amino acid [18, 19]. Other chemical pathways to the formation of amino acids involve the formation of *N*-carboylamino acids as intermediate species via the Bücherer–Bergs reaction from an aldehyde, HCN, NH_3, and CO_2, also leading to amino acids via subsequent hydrolysis [19, 20]. The polymerization and/or oligomerization of HCN in H_2O is another potential pathway to the formation of both amino acids and nucleobases, as HCN is abundant in comets [21–28] and can also be found in interstellar ices [29–34]. However, while this chemical route has been extensively studied both in the laboratory [35–39] and more recently from a theoretical point of view [40], it has also been strongly debated. A similar mechanism involving cyanoacetylene (HC_3N) reacting with either the cyanide anion (OCN^-) or water in the presence of urea (NH_2CONH_2) may also lead to the formation of the nucleobases cytosine and uracil [41], which are of great interest in this chapter. Finally, sugars, in particular glucose, ribose, and deoxiribose, as well as their derivatives, could be formed via the formose reaction, i.e., a polymerization of formaldehyde (H_2CO) [42–46].

The final step from a collection of non-living molecules to those capable of self-replication and evolution is probably the least understood of all. Indeed, even if the primitive Earth contained an abundance of all the molecules required for life, constituting the so-called "primordial soup" [12, 13], it was also probably supplied with an abundance of compounds that did not have the right properties for self-replication and evolution that may have inhibited the emergence of life. The reactions that led to self-replication and evolution are believed to have occurred in a solvent, most probably H_2O, to allow molecules to meet and react under favorable thermodynamic conditions [47]. In addition, H_2O probably played an important role in the formation of prebiotic membranes, as shown by some experiments in which organic molecules produced from the UV irradiation of simple ices spontaneously led to the formation of vesicles, a phenomenon also observed with organic extracts of the Murchison meteorite [48]. Membranes provide considerable advantages for chemical evolution, as they can protect molecules inside the vesicles from external lethal radiation, and because enclosed molecules can evolve under specific chemical conditions (solvent, temperature, pH) that can be different from the outside medium. Reactions inside a membrane-enclosed vesicle can occur under conditions of non-thermodynamic equilibrium, which, when coupled to prebiotic reactions and exchange of entropy with the external medium, can lead to complex reactions including polymerization of amino acids and sugars. Finally, exothermic reactions between organic compounds, in particular polymerizations, may also have occurred on the surface of minerals [49–53], which can play the role of a third body capable of absorbing the excess reaction energy and preventing the dissociation of newly formed products. Clays, in particular montmorillonite, are often cited as one of the minerals likely to have played such a role because of their chemical and physical properties [54, 55].

1.1.2 Potential Environments for Prebiotic Synthesis

While numerous environments for prebiotic chemistry have been suggested, most fall into one of two main categories, namely, extraterrestrial environments and environments found on the early Earth. We briefly comment on both of these environments below, although the bulk of the discussion in this chapter will be devoted to prebiotic chemistry that occurred prior to incorporation of the material into the Earth. Within this category, we will comment on the abiotic synthesis of a

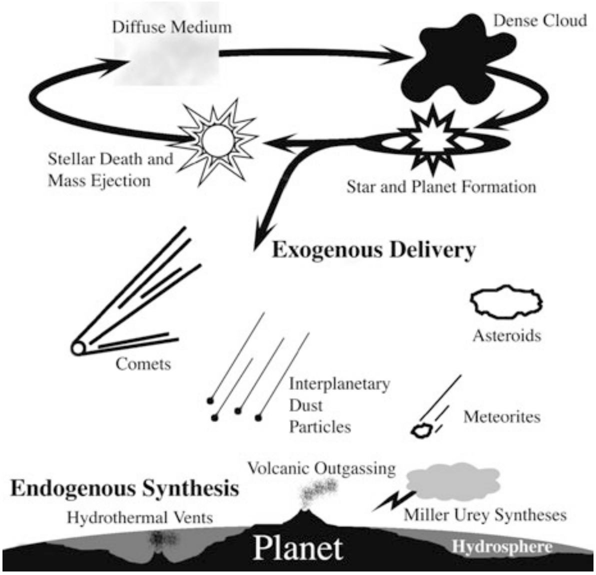


Fig. 1 The life cycle of matter in galaxies. New atoms and molecules formed in stars are ejected into the diffuse interstellar medium (ISM). Some of these materials can subsequently be gathered into dense molecular clouds, the formation sites of new stars and planets. During the formation of new stellar systems these materials can be modified, and new materials made, as they are incorporated into small objects such as asteroids, comets, and planetesimals. Organic matter contained in asteroids and comets can then be delivered to telluric planets such as the Earth via meteorites and interplanetary dust particles (IDPs). Those organic compounds may constitute an inventory of prebiotic molecules that subsequently play a role in the emergence of life if favorable chemical and physical conditions are available (from [48])

number of classes of compounds of astrobiological interest, but will specifically concentrate on the prebiotic extraterrestrial synthesis of the nucleobases.

Extraterrestrial Environments: ISM Dense Clouds, Protosolar Nebula, Comets, and Asteroids

Prior to the middle of the last century it was generally assumed that the conditions found in space were hostile to molecules, that chemistry could not proceed efficiently in space, and that most of the material in space would exist as either atoms or amorphous dust grains. The advent of radio and infrared telescopes, detectors, and spectrometers ultimately showed this to be untrue. We now know that much of the material in circumstellar and interstellar space is in molecular form, and that a variety of chemical processes occur as these materials cycle through a range of astrophysical environments (Fig. 1). In the paragraphs below we describe several environments in which chemistry is observed to occur in space.

Many stars, late in their life cycles, undergo phases in which they lose significant portions of their mass through either gradual (stellar winds) or explosive (nova and supernova) processes. Where the outflow conditions allow, these materials can form molecules and dust grains. Depending on the local C/O ratios in the ejectae, the main products can be minerals (O-rich ejecta) or carbonaceous molecules and grains (C-rich ejecta) [56, 57].

Much of the material ejected from stars is subsequently destroyed or modified in the diffuse interstellar medium (ISM) where it is subjected to shock waves from supernova, sputtering, photo-destruction, etc. However, there are several lines of evidence that some of these materials survive transit through the diffuse ISM. Indeed, astronomical observations clearly indicate that the diffuse ISM contains silicate grains and solid organic materials that contain both aromatic and aliphatic components [56, 58–60]. Most individual molecules are unable to survive in the gas phase in the diffuse ISM, with the notable exception of polycyclic aromatic hydrocarbons (PAHs) and related species. These molecules are seen in the outflows of dying stars and are sufficiently robust to resist complete photolytic destruction in the diffuse ISM. As a result, they are the dominant form of molecular carbon found in many astrophysical environments [61–64].

Perhaps the most compelling and interesting proof that at least some material survives the trip from stellar synthesis through the diffuse ISM is the existence of presolar grains in meteorites. Presolar grains having a number of different compositions (aluminum oxides, silicates, SiC, graphite, etc.) have been identified and their circumstellar formation is demonstrated by the presence of non-solar isotopic ratios that indicate formation in a variety of nucleosynthetic environments.

However, from the perspective of prebiotic chemistry and astrobiology, the most interesting type of extraterrestrial environment is that of dense interstellar molecular clouds. Such clouds contain enough material to be optically thick so that they screen out much of the stellar radiation that destroys most molecules in the diffuse ISM. The large optical depths of these clouds allow their interiors to cool to temperatures as low as 10–15 K. At these temperatures, most gas phase species other than H, H_2, He, and Ne will condense out onto dust grains in the form of ice mantles (Fig. 2). Little "normal" chemistry of the sorts we are familiar with on Earth can take place under such conditions, but chemical reactions occur nonetheless.

Some chemistry occurs via gas–grain reactions in which individual gas-phase atoms like H, C, N, and O collide with grains, react with resident surface species on the grains, and form new compounds [65]. None of the species made in this manner are particularly complex. In dense cloud environments where $H > H_2$, these reactions simply tend to create hydrides like CH_4, CH_3OH, NH_3, and H_2O, and this process is thought to be the principle source of interstellar H_2 via reactions between two H atoms on the surface of cold dust grains. When $H < H_2$, reactions involving heteroatoms become important and species like N_2 and O_2 predominate.

More complex species can be created when ionizing radiation is present (Fig. 2). The large optical depth of dense clouds screens out most stellar radiation, but cosmic rays and the energetic photons they create when colliding with interstellar matter produce some ionization, even in the densest clouds [66]. Newly forming stars within dense interstellar clouds can also irradiate nearby materials. Ionizing radiation produces ions and radicals that are able to react even at the low

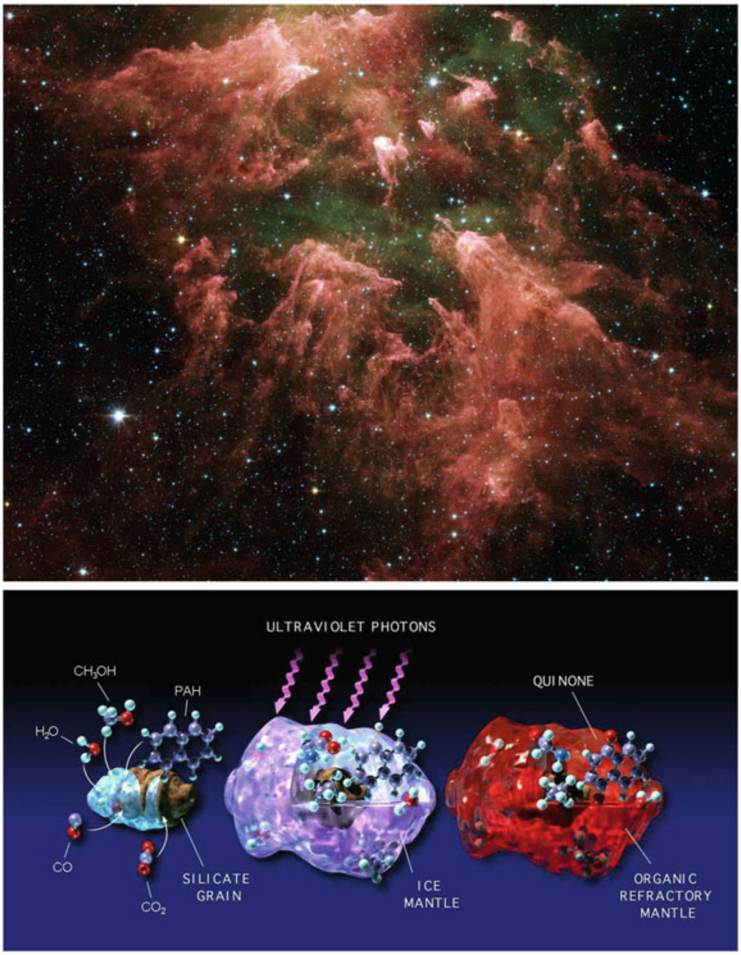


Fig. 2 *Top:* Spitzer telescope image of the Eta Carinae molecular cloud. *Bottom:* Schematic of a cold interstellar dust grain. Volatiles such as H_2O, CO, CO_2, CH_3OH, and larger molecules such as polycyclic aromatic hydrocarbons (PAHs) can condense on the surface of cold dust grains in interstellar clouds. Such ice mantles can be processed by ionizing radiation, including UV photons, leading to the formation of more complex, refractory molecules (adapted from [197])

temperatures common in these clouds. Ions created in the gas phase can react in an extensive chain of ion-molecule reactions that can lead to numerous gas-phase species [67, 68]. To date more than 175 specific molecules have been identified in the gas phase in such clouds [69], although most are relatively small (<7–8 atoms). However, the majority of the material other than H and He in dense clouds is trapped in the dust grains and their icy mantles, and it is in these ices that ionizing radiation likely produces the most complex molecular species [65, 70–72]. Such a radiation process will be the subject of much of the discussion in this chapter, particularly in the context of the abiotic formation of the nucleobases.

Because of their biological significance, astronomers have sought to confirm the presence of small *N*-heterocycles, including pyrimidine, purine, and their derivatives, in the gas phase of the ISM. To date, none of these compounds have been detected [73–77]. Nonetheless, PAHs are known to be ubiquitous in galactic and extragalactic interstellar/circumstellar environments, and polycyclic aromatic nitrogen heterocycles (PANHs) are expected to be present as well [61–64]. It is therefore reasonable to assume that *N*-heterocycles, including pyrimidine-based species, may be present in space where they can condense on the surfaces of cold, icy grains, such as those found in dense molecular clouds [78, 79]. These materials are therefore expected to participate in the types of ice irradiation process mentioned above.

Delivery of Extraterrestrial Organics to the Early Earth

Of course, the creation of organics in extraterrestrial environments is somewhat inconsequential, at least with regards to the origin of life, if these materials are unable to survive incorporation into planetary environments. Organics incorporated into the early Earth during its initial molten accretion were presumably destroyed – arriving organics would do little beyond contributing part of the inventory of important elements like C, N, O, and H. The actual delivery and survival of astrobiologically important compounds would have had to wait for the surface of the Earth to become a more hospitable place. It is therefore likely that the majority of complex organics delivered intact to the surface of the early Earth were first incorporated into small bodies like comets and asteroids and only delivered to the Earth at a later stage [80].

The efficiency of successful delivery of extraterrestrial organics to the surfaces of planets depends critically on the nature of the body that delivers them [17]. While comets and asteroids can contain large amounts of organics, as whole bodies they are not a very efficient way to deliver organics intact to planetary surfaces. The enormous energy releases that occur during hypervelocity impact of such large objects is likely to destroy or modify much of their organic molecule content, not to mention mediating the destruction, alteration, and creation of compounds on the planet. However, over the course of their orbital evolution, bodies like asteroids can shed material in the form of smaller meteoroids or dust particles generated by impacts with other asteroidal bodies. Comets can also shed rocks and dust through collisions as well as lose dust during outgassing that occurs when cometary volatiles sublime during warming.

These smaller meteoroids and cosmic dust particles can deliver organics much more efficiently than their cometary and asteroidal parent bodies. When smaller bodies like meteorites and cosmic dust collide with the Earth, they are slowed to terminal velocity high in the atmosphere and can deliver organics to the surface of the planet with far less degradation [81, 82]. For example, while the exterior of a meteoroid suffers serious heating and ablation during atmospheric entry, the interiors of meteorites experience little or no changes in temperatures during the entire infall process because ablation removes their surface faster than heat can thermally conduct into the interior of the meteorite. For a typical meteorite that makes it to the surface of the Earth, atmospheric entry only affects the outer few millimeters of the surviving material. Meteorites typically land on the surface of the Earth with their interior temperatures largely unchanged from what they were in space and can therefore preserve and deliver their initial organic contents (e.g., [3–8]).

The Early, Prebiotic Earth

Since the focus of this chapter is on the possible extraterrestrial abiotic formation of nucleobases, we will not go into great detail regarding the possible synthesis of these compounds in terrestrial environments. Nonetheless, the origin of life would almost certainly have occurred in an environment in which compounds of both extraterrestrial and terrestrial origin could have been present. While the issue of terrestrial synthesis is not central to the subject of this chapter, the possible importance of extraterrestrial delivery of nucleobases (as well as many other molecules of biological importance, for that matter) should be assessed in context with terrestrial sources. There are a number of excellent papers that address prebiotic chemistry on the early Earth, including extensive discussions of the nucleobases, and the reader is invited to examine them for informative reviews (e.g., [83–86] and references therein).

Note that we are not concerned here with the formation of RNA and DNA in their macromolecular forms. While it is the ultimate formation of RNA and DNA that motivates much of the interest in the abiotic formation of nucleobases, it is likely that this advance in chemical complexity occurred in a planetary environment, which falls outside the purview of our discussion here. Indeed, it has even been suggested that the formation of RNA and DNA need not have required the preexistence of nucleobases [87].

1.2 Abiotic Extraterrestrial Chemistry and the Origin of Life

There are several lines of evidence that suggest abiotic extraterrestrial chemistry may have resulted in the delivery of numerous compounds of biological importance to the early Earth. Some of this evidence comes from astronomical observations of dense clouds and forming planetary systems, but the main lines of evidence come from laboratory simulation experiments and the detection of biologically important species in the organic materials found in primitive meteorites.

1.2.1 Evidence from Astronomical Observations and Laboratory Simulations

Astronomical spectral observations of the ISM at infrared and longer wavelengths have demonstrated that the molecular composition of interstellar dense clouds is dominated by simple species. For example, absorption spectra taken along lines of sight towards embedded and background stars show that the ices in most dense clouds are dominated by H_2O along with varying amounts of other simple molecules like CH_3OH, CO, CO_2, CH_4, NH_3, HCN, etc. [59, 88–93]. These ices are exposed to doses of ionizing radiation in the form of cosmic rays and high-energy photons that can create ions and radicals in the ices that can ultimately react to form more complex molecules (Fig. 2). Evidence that interstellar ices are truly processed by ionizing radiation in this manner comes from the observation of a broad absorption feature near 4.62 μm (2165 cm^{-1}) in the infrared spectra of the ices in many clouds [59, 88, 89, 91, 94, 95]. This feature is reliably reproduced in virtually all laboratory experiments involving the irradiation of ices containing sources of O, C, N, and H, and is due to the C≡N stretching mode in what is most likely OCN^- [96–98].

Numerous laboratory studies have demonstrated that irradiation of astrophysically relevant ices dominated by simple molecules like those listed above results in the production of numerous ions and radicals within the ices that can then combine as the ice warms to form a wide variety of new molecular species that are considerably more complex than those seen in the gas phase in dense clouds [72]. Many of these species are of astrobiological interest and include amino acids [99–102], amphiphiles [48], urea, glycerol, glyceric acid, hydantoin [103, 104], and, if aromatic species are present in the ices, quinones, ethers [105–109], and nucleobases [110–112].

This chemistry appears to be very "robust" in the sense that the types of organic materials that are produced are relatively insensitive to many of the experimental parameters of the irradiation. For example, the temperature of the ice during irradiation is relatively unimportant; all that is required is that the ice be cold enough that the starting materials remain condensed during irradiation. Since H_2O is the dominant species in many astrophysical ices, this means that ice irradiation processes yield similar products over the entire 10–150 K temperature range [71]. This processing is similarly insensitive to the source of the ionization: identical ices will yield very similar products independent of whether they are irradiated by energetic protons or UV photons [108, 113–115]. Indeed, the basic suite of products is even relatively insensitive to the composition of the ices themselves provided they contain fragmentable sources of C, H, O, and N. For instance, ices containing widely different relative abundances of the same starting molecules will produce much the same set of products, although their relative and total abundances may vary. Similarly, laboratory experiments performed with ices in which the initial sources of C, H, O, and N are different will still often yield similar products. For example, irradiation of ices yields amino acids independent of whether the initial carrier of C in the ices is CH_3OH, CH_4, or CO_2 [99–102], and whether the initial carrier of N is NH_3 or HCN [116].

Of particular interest is the radiation processing of ices that contain aromatic molecules like PAHs and related aromatic species that contain heterocycles. In dense molecular clouds, they should be largely condensed out onto grains [78, 79]. As previously stated, these molecules are relatively robust against photo-destruction in the gas phase in the ISM, but they can also participate in a rich chemistry when irradiated in mixed molecular ices. One of the chief outcomes of the irradiation of PAHs in ices is the addition of side groups to the aromatic rings of the PAHs. Since most interstellar ices are dominated by H_2O, this largely results in O and H addition reactions that make aromatic ketones, alcohols, ethers [105–109], and hydrogenated PAHs (H_n-PAHs [117]); however, additional side groups like $–NH_2$, $–CH_3$, $–OCH_3$, $–C{\equiv}N$, etc. can be added if other molecules are present in the starting ice [105, 107]. As we will see, this process is likely to play an important role in the abiotic production of nucleobases in astrophysical environments.

1.2.2 Evidence from Meteorites

Meteorites that fall on the Earth are divided into a wide variety of classes having different compositions and evolutionary histories [118, 119]. Among these classes, carbonaceous chondrites are of the most interest for studies of extraterrestrial organics. These meteorites typically contain a few weight percent carbon [120]. Much of the carbon is in the form of insoluble organic matter (IOM), a material that consists of small aromatic moieties interlinked by a complex variety of bridging units [121, 123]. Meteoritic IOM has a number of interesting properties, for example, it is the carrier of components having large D/H and $^{15}N/^{14}N$ isotopic anomalies [122, 123]. However, other than being a major carrier of carbon in meteorites, it is of limited interest in astrobiology because it is chemically intractable.

Of more interest in astrobiology are the soluble carbonaceous components of these meteorites. A wide variety of soluble compounds are found in carbonaceous meteorites, including aliphatic and aromatic hydrocarbons, carboxylic and dicarboxylic acids, amines, and amides [120]. These individual classes of compounds are typically present at concentration falling in the range from a few ppm to a few hundred ppm.

A number of compounds are of clear astrobiological interest, including amino acids [4, 10, 124–127], amphiphiles [48], and *N*-heterocycles [11, 128–135], which are the building blocks of proteins, membranes, and nucleic acids, respectively. There is ample evidence that many of these materials are truly extraterrestrial, and not terrestrial contamination. For example, the extraterrestrial nature of the many amino acids detected in meteorites is supported by the presence of (1) amino acids not used by biological systems on Earth, (2) amino acids that are largely (but not entirely) racemic, and (3) amino acids having non-terrestrial isotopic ratios [9, 10, 124, 136–140].

Of particular relevance to the discussion in this chapter are *N*-heterocyles. To date, a series of pyrimidines, quinolines, isoquinolines, benzoquinolines, and several of their methyl isomers have been identified in meteorites ([120] and references therein). Purine- and pyrimidine-based compounds have so far been detected in the carbonaceous chondrites Orgueil, Murchison, Murray, and Lonewolf Nunataks 94102 [128–135, 143]. The extraterrestrial origin of these compounds has been confirmed in many cases by isotopic analysis [11], lending further credence to their extraterrestrial formation via at least one astrophysical, non-biological process.

Uracil is, to date, the only pyrimidine-based nucleobase that has been unequivocally identified in meteorites [11, 132]. The extraterrestrial nature of uracil in the Murchison meteorite is supported by $\delta^{13}C$ measurements by Martins et al. [11], although it has been suggested that coeluting compounds could be confusing the issue [134]. The lack of detection of cytosine in meteorites might be explained by its conversion into uracil via hydrolysis when the organics are extracted from the meteorite, as cytosine was shown to be easily hydrolyzed in the laboratory [141, 142]. Thus, the presence of cytosine in meteorites cannot currently be ruled out.

So far, studies of the Allende, Orgueil, Murchison, and Murray have only managed to establish upper limits on the presence of thymine in these meteorites, but these upper limits are an order of magnitude *lower* than those for uracil [132]. The non-detection of thymine cannot be explained by the same conversion process that may be limiting the detection of meteoritic cytosine. This suggests that there must be another reason for its lower abundance in meteorites relative to uracil. We will return to this point later in this chapter.

Several purines have been identified in meteorites, including xanthine, hypoxanthine, and the nucleobases guanine and adenine [128–135, 143]. The presence of pre-terrestrial pyrimidine and purine-based compounds in meteorites clearly indicates that some extraterrestrial abiotic processes are capable of making at least some of the nucleobases in space. In the sections that follow we will discuss some of the extraterrestrial environment in which these processes may occur.

2 The Synthesis/Stability of Nucleobases in Extraterrestrial Environments

The primary environments of interest for chemistry in the interstellar medium are dominated by materials in the gas phase and, in dense clouds and protostellar disks, in solids and ices. Chemistry in the liquid phase is largely restricted to planetary environments and, for brief periods in the early history of the Solar System, to some asteroids, and is therefore not considered in any detail here. In the sections that follow we will thus concentrate on gas- and solid-phase photochemistry.

2.1 Synthesis/Stability in the Gas Phase

A few mechanisms for the formation of both pyrimidine- and purine-based nucleobases have been proposed and tested experimentally and theoretically. Among them, the most popular is probably the formation of purine-based compounds from the polymerization or oligomerization of HCN in the gas phase. HCN is a common component of astrophysical ices; in particular it is found in comets [21–28], but also in interstellar and circumstellar sources [29–34]. In the 1960s, Matthews noticed that adenine, one of the purine-based biological nucleobases found in DNA and RNA, was a pentamer of HCN, i.e., that it could be obtained from the combination of five molecules of HCN. This mechanism was tested experimentally by his team and independently by Ferris' and Toupance's teams, but none of them could find a pathway that could lead to an efficient production yield of adenine [35–39]. However, the probability for five molecules of HCN to encounter one another in low-density astrophysical gas phase environments is small, so such a process would not be very efficient in space. The formation of adenine from the pentamerization of HCN in the gas phase has also been studied theoretically via density functional theory (DFT) and singles and doubles coupled-cluster with perturbational triples [CCSD(T)] computations, which showed that such a process is energetically favored [40, 144], and thus that adenine could be formed abiotically. Similarly, ab initio CCSD(T) quantum chemical computations indicate that pyrimidine could be formed in the gas phase via an ion–molecule mechanism through a structural isomer of vinyl cyanide ion [145].

Another mechanism, involving the reaction between cyanoacetylene (HC_3N) and the cyanate anion (OCN^-), could lead to the formation of the pyrimidine-based nucleobases uracil and cytosine [146]. HC_3N is abundant in comets [147–149], circumstellar disks [150–153], as well as in the atmosphere of Titan [154–157], the largest satellite of Saturn, known to house a very complex chemistry that may be in some points similar to what existed on the primitive Earth several billions of years ago [158–162]. OCN^- has been observed in the solid phase (ice) in several astrophysical sources [59, 88, 89, 91, 94, 95], and is often considered to be the proof that photo-induced chemical reactions do occur at the surface of icy cold grains, since it can be formed from the irradiation of H_2O, CO, CO_2, and NH_3 [96, 97]. However, to date, OCN^- has not yet been observed in the gas phase. Alternatively, HC_3N could also react with H_2O to form an intermediate species, cyanoacetaldehyde ($N{\equiv}CCH_2CHO$), which, by reacting with urea (NH_2CONH_2), could lead to the formation of uracil and cytosine [146, 163].

In dense environments, such as molecular clouds or Titan's atmosphere, *N*-heterocycles such as pyridine and pyrimidine may be formed in the gas phase via copolymerization of HCN and acetylene (C_2H_2), believed to be one of the precursors of PAHs in space [164, 165]. Acetylene and ethylene could also react with protonated hydrogen cyanide ($HCNH^+$), considered to be a major ion in Titan's ionosphere due to its high concentration, that could lead to synthesis of cyclic molecules involving nitrogen, and possible precursors of nucleobases [166]. $HCNH^+$ is also known to exist in the gas phase in interstellar clouds, where it plays a role in the conversion of HCN to HNC [167]. Once formed, *N*-heterocycles and PAHs could condense on small, cold grains in the ISM [78, 79] and be photo-processed together with other ices present, such as H_2O, CH_3OH, CO, CO_2, CH_4, and NH_3 [59, 88–93], to form subsequently complex molecules of prebiotic and biological interest such as quinones [105, 107] and nucleobases [110–112].

Once formed in astrophysical environments, nucleobases, like other gas-phase and ice components, will be subjected to strong ionizing radiation. While radiation can affect the chemical composition of a medium by breaking bonds, creating ions and radicals, and drive the formation of new, more complex products after recombination, it can also destroy these same compounds. Because of this, studying the photo-stabilities of compounds of interest is also important. Peeters et al. [168] studied the photo-stability of pyridine, pyrimidine, and triazine in an argon matrix under astrophysically relevant conditions. Their results show that these molecules, if isolated in the gas phase and subjected to UV radiation, would have half-lives of 2–20 years in the optically thin diffuse ISM, and up to 2 Myr in the dense ISM, which is mostly opaque to UV photons but subjected to cosmic-ray radiation and their secondary electrons as well as UV photons produced from the interaction between cosmic rays and grains [168]. Because of higher UV fluxes, these numbers drop to 4–30 min in the Solar System. All these values are smaller than those expected for small PAHs irradiated in astrophysical environments [61, 169–171], probably due to the smaller bond energies and the polarization of the C–N bonds in heterocyclic compounds. The stability of nucleobases under UV irradiation, and the processes of radical and ion formation on them, were also studied both experimentally [172, 173] and theoretically [174].

2.2 Synthesis of Pyrimidine-Based Nucleobases in Extraterrestrial Ices

Laboratory and theoretical work has been done on the ice-phase photochemistry of pyrimidine, leading to the synthesis of all three pyrimidine-based nucleobases. In the sections that follow, we summarize the results of this work separately for uracil, cytosine, and thymine (Fig. 3). We use the discussion of uracil to provide a general overview of the approaches that have been used for this kind of work. The subsequent discussions about cytosine and thymine are largely restricted to details unique to these individual molecules.

2.2.1 Synthesis of Uracil

Uracil (2,4-dihydroxypyrimidine) is a doubly oxidized pyrimidine derivative. It is one of the five biologically relevant nucleobases, and is found only in RNA. The "RNA world" hypothesis proposes that RNA served as the original genetic material and as biological catalysts [175–177]. Under this paradigm, understanding the abiotic formation of uracil is of great importance.

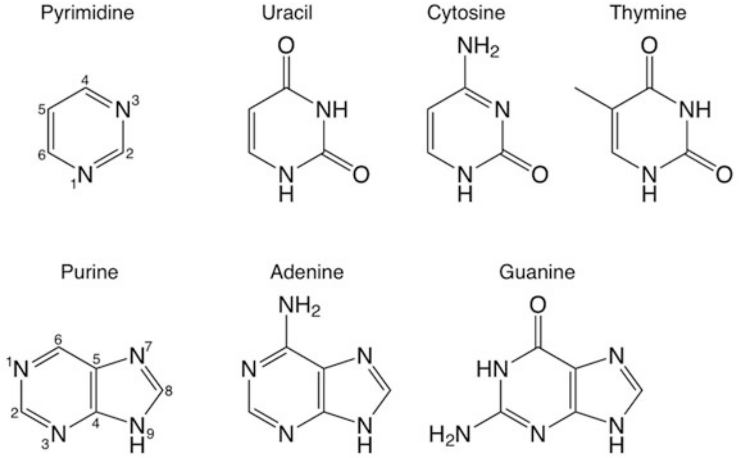


Fig. 3 The molecular structures of pyrimidine, purine, and the five biological nucleobases whose backbones are based on these compounds: uracil (2,4-dihydroxypyrimdine), cytosine (4-amino-2-hydroxypyrimidine), and thymine (2,4-dihydroxy-5-methylpyrimidine) for pyrimidine, and adenine (6-aminopurine) and guanine (2-amino-6-hydroxypurine) for purine

As mentioned earlier, the detection of pyrimidine- and purine-based nucleobases in meteorites suggests that such molecules may be present on the surfaces of cold grains in astrophysical environments and mixed into ices. If this is so, then biologically relevant molecules such as nucleobases might be formed via photo-processing of pyrimidine in ices, the same way other organic compounds such as amino acids are probably formed in similar environments [99–102].

The formation of uracil via the photo-irradiation of pyrimidine mixed with simple ices requires an oxygen source. Among the catalog of compounds present in interstellar ices, H_2O is by far the most abundant [90–93], and can be a strong oxidant. Consequently, H_2O:pyrimidine ices subjected to UV photon irradiation are simple, relevant models to simulate the oxidation of pyrimidine under astrophysical conditions in the laboratory.

Laboratory Synthesis of Uracil

In these laboratory experiments, H_2O:pyrimidine mixtures prepared in the gas phase are deposited in a controlled fashion onto a substrate cooled to temperatures as low as 15–20 K inside a cryogenic vacuum chamber evacuated to a pressure of a few 10^{-8} mbar. During deposition, the growing ice films are simultaneously irradiated with UV photons emitted by a microwave-powered H_2 discharge lamp. Such a lamp provides UV photons mainly at 121.6 nm (Lyman-α) and a continuum

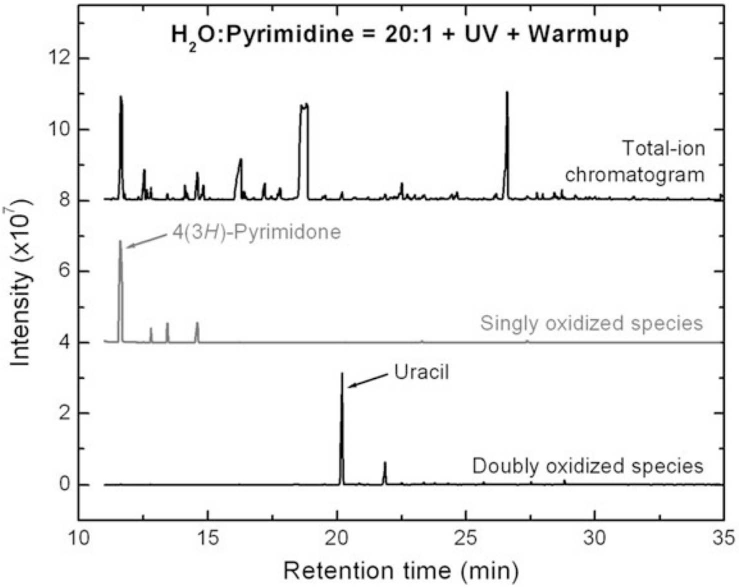


Fig. 4 Total-ion chromatogram (*top trace*) of a residue produced from the UV photo-irradiation of an H_2O:pyrimidine = 20:1 ice mixture at low temperature followed by a subsequent warmup to room temperature. The *middle* and *bottom* traces show the single-ion chromatograms of the same residue corresponding to the masses for the singly and doubly oxidized pyrimidine derivatives, respectively, and show the identification of 4(3*H*)-pyrimidone and uracil in this sample (from [110])

centered around 160 nm, with a flux of about 2×10^{15} photons cm^{-2} s^{-1} [178] that simulates the UV radiation field observed in many astrophysical environments [66, 179, 180].

Following the simultaneous deposition and radiation process, each ice sample is warmed to 220 K to allow the original ice components to sublime away, at which temperature the resulting refractory residue material is extracted from the vacuum chamber for further analysis with high-performance liquid chromatography (HPLC) and gas chromatography coupled with mass spectrometry (GC-MS).

Two of the major compounds successfully identified in these residues include 4(3*H*)-pyrimidone (or 4-hydroxypyrimidine), a singly oxidized pyrimidine derivative and precursor of uracil, and uracil itself (Fig. 4; [110]). It should be noted that 2-hydroxypyrimidine, another singly oxidized variant of pyrimidine and a uracil precursor, is only detected in very small quantities in this series of experiments, indicating that oxygen addition to pyrimidine occurs in a regioselective manner [110, 111]. These experiments also show that UV photons can break the pyrimidine ring, leading to the formation of small aliphatic molecules such as urea and the amino acid glycine in measurable quantities [111]. As previously observed in other simple ice mixtures, for example ices in which amino acids are formed [99–102], the list of products formed is relatively insensitive to the ratios of the starting H_2O and pyrimidine, though their relative abundances vary.

Since data regarding the composition of the residues are obtained ex post facto, it is difficult to know at which point during the irradiation and/or subsequent warm-up products the likes of 4(3*H*)-pyrimidone, uracil, and their isomers are actually formed. However, it is known that the formation of uracil does not occur as a result of exposure to the aqueous phase while awaiting analysis, since its presence is confirmed in samples that were kept free of exposure to liquid water [110]. While this does not answer the question of when uracil is produced, it shows that such compounds can form in the absence of liquid water.

There are limited experimental data related to the reaction mechanisms for the formation of oxidized pyrimidines and their derivatives. Such issues can be addressed with theoretical computations and are discussed in the next section. Nevertheless, experiments reveal that the formation of these compounds is relatively insensitive to temperature and wavelength, which suggests a radical and/or ion chemistry driven by the photo-decomposition of H_2O. Given this hypothesis, the unstable radicals and/or ions engage in a chemistry of opportunity that is not bound by thermodynamic favorability.

Theory of Uracil Synthesis in the Condensed Phase

Detailed quantum mechanical theoretical computations have been conducted to understand the process of photo-oxidation of pyrimidine in a pure H_2O ice matrix [181]. B3LYP DFT, which contains Becke's three-parameter exchange functional (B3) [182], and the correlation functional of Lee, Yang, and Parr (LYP) [183], were used in conjunction with Pople's 6-31G(d,p) split valence basis set [184]. Structures were optimized to obtain the lowest energy minima on the potential energy surfaces of the reactants, intermediates, and products, and were confirmed by a subsequent harmonic frequency calculation. Energy differences were then obtained using second-order Møller-Plesset (MP2) perturbation theory for closed shell species and second-order Z-averaged perturbation theory (ZAPT2) [185, 186] for the open shell species, in conjunction with Dunning's correlation consistent polarized valence triple zeta basis set (cc-pVTZ) [187]. The Q-Chem 3.1 and 3.2 suites of ab initio and DFT quantum mechanical codes were used for all computations [188].

H_2O possesses a large photo-dissociation cross-section in the UV wavelength range [189]. Hydroxyl ($^{\bullet}OH$) radicals are therefore readily produced in the ices by the following process:

$$H_2O + h\nu \rightarrow H^{\bullet} + {}^{\bullet}OH$$

It is therefore reasonable to assume that the chemistry in these ices is dominated by reactions of $^{\bullet}OH$ radicals with pyrimidine and its derivatives. Other radicals and ions can also be generated from the pyrimidine itself via the following processes:

$$\mathrm{Py} + \mathrm{h}\nu \rightarrow [\mathrm{Py}]^{+\bullet} + \mathrm{e}^{-}$$
$$\mathrm{Py} + \mathrm{h}\nu \rightarrow [\mathrm{Py}/\mathrm{H}]^{\bullet} + \mathrm{H}^{\bullet}$$

where $[\mathrm{Py}_{/\mathrm{H}}]^{\bullet}$ designates a radical formed from the cleavage of a C–H bond on the pyrimidine ring. $^{\bullet}$OH radicals can react with either neutral pyrimidine molecules or pyrimidine cations to form cations and radicals of oxidized pyrimidines.

An important step in these mechanisms is the loss of either a proton or a hydrogen atom from the intermediates to form the final products. Reactions involving a pyrimidine cation and an $^{\bullet}$OH radical (first oxidation step) are presented in Fig. 5a. Oxidation products of pyrimidine can be further oxidized by $^{\bullet}$OH radicals, and produce doubly oxidized products:

$$[\mathrm{Py-OH}]^{+\bullet} + {}^{\bullet}\mathrm{OH} \rightarrow \left[\mathrm{Py}(-\mathrm{OH})_2\right]^{+}$$
$$\mathrm{Py-OH} \;\; + {}^{\bullet}\mathrm{OH} \rightarrow \left[\mathrm{Py}(-\mathrm{OH})_2\right]^{\bullet}$$

The above reactions are ion–molecule or radical–molecule type in nature, and are typically barrierless and fast. Neutral–neutral reactions between H_2O and pyrimidine can also occur but, because of their high activation barriers, should be several orders of magnitude slower than reactions involving radicals or cations, particularly in cold ices.

Computations show that an ionic mechanism in which a pyrimidine cation reacts with an $^{\bullet}$OH radical is energetically favorable and can lead to the formation of intermediate species followed by the subsequent loss of a proton to form the final products [181]. Among all possible products, 4-hydroxypyrimidine and its tautomer 4(3*H*)-pyrimidone are the most favored singly oxidized products, followed by 2-hydroxypyrimidine and its tautomer 2(1*H*)-pyrimidone (Fig. 5b). This result is important since any of these singly oxidized compounds can be further oxidized, leading to the formation of uracil. Additionally, computations show that a purely gas-phase proton loss from the ionic intermediate species is unfavorable, as illustrated in the energy diagram (Fig. 5b). The presence of several H_2O molecules in the ice matrix, acting as proton acceptors, allows this reaction to become favorable towards the formation of the products. In other words, a condensed-phase environment is critically important for these mechanisms to be viable. Oxidation of neutral pyrimidine via a reaction with an $^{\bullet}$OH radical is also shown to be energetically favorable and leads to the expected products, although this mechanism is not as energetically favorable as that of an ionic mechanism according to the ab initio MP2/ZAPT2 calculations.

As illustrated in Fig. 6a, Bera et al. [181] showed that oxidation of 4(3*H*)-pyrimidone (and its tautomer 4-hydroxypyrimidine) via an ionic mechanism follows a similar path as that described for the first oxidation step via an ionic mechanism. That is, the initial hydroxylation step is highly exothermic and should be barrierless, and the subsequent proton loss is energetically favorable in the presence of the surrounding H_2O molecules (i.e., a condensed-phase environment

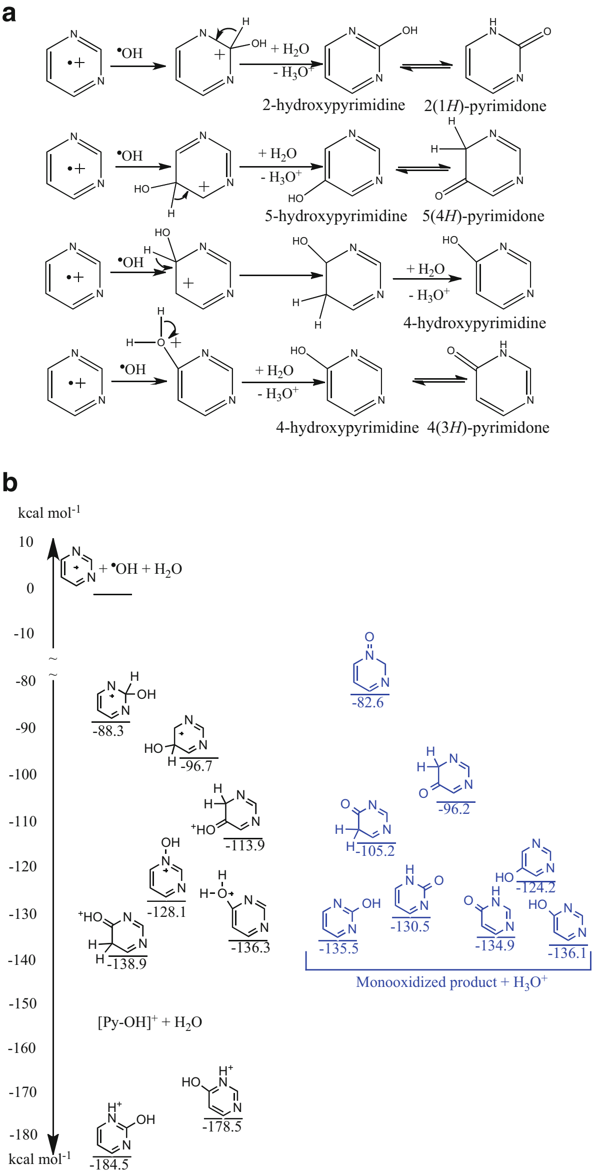


Fig. 5 (**a**) Mechanistic routes of pyrimidine cation reaction with hydroxyl radicals. The first step is a nucleophilic attack of a hydroxyl radical to pyrimidine cation. The second step is the loss of a proton assisted by H_2O. The third step is a tautomerization. (**b**) Energy diagram of the first oxidation step (energies are in kcal mol^{-1}). On the left hand side are the energies of intermediates + H_2O, and on the right hand side are the energies of singly oxidized products + H_3O^+ (see [181])

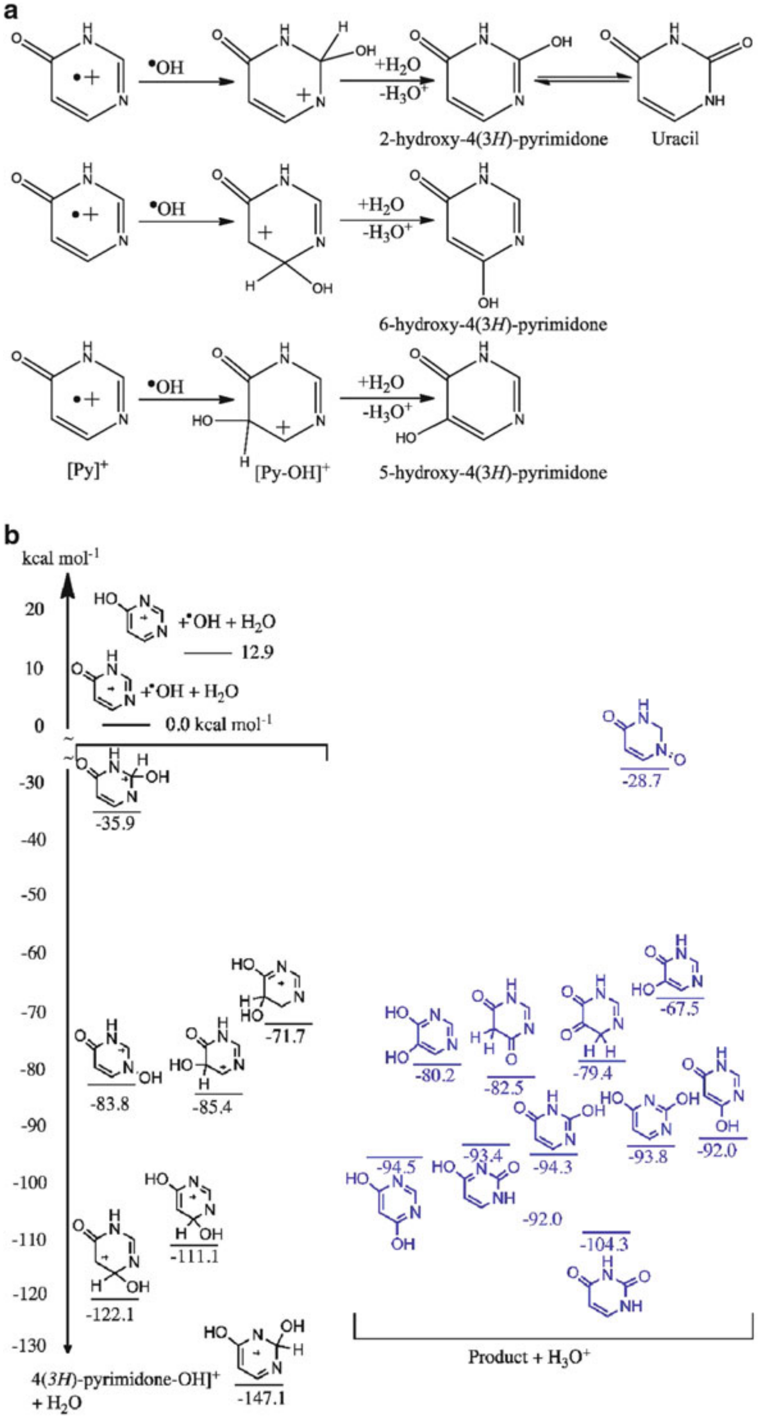


Fig. 6 (**a**) Mechanistic routes of hydroxyl radical attacking the 4(3*H*)-pyrimidone cation. The first step is a nucleophilic attack of a hydroxyl radical to pyrimidine cation. The second step is the

is again required for the deprotonation step). From the energetic order of the formed intermediate species and products (Fig. 6b), it is evident that the formation of *uracil* is favored over that of other doubly oxidized products. Additionally, the reaction between an $^{\bullet}$OH radical and a neutral 4-hydroxypyrimidine molecule, which requires a neutral–radical intermediate species, is also a viable route for the formation of uracil and other doubly oxidized pyrimidine derivatives.

Another route for the formation of uracil is via the oxidation of 2-hydroxypyrimidine or its tautomer 2(1*H*)-pyrimidone. The reaction schemes for an ionic mechanism reaction are shown in Fig. 7a, and the associated energies are shown in Fig. 7b. It is interesting to note that 2,4-dihydroxypyrimidine, the dienol tautomer of uracil, is found to be the most stable doubly oxidized product. Again, the presence of H_2O molecules to abstract a proton from the intermediate is essential for the oxidation reaction to proceed via an ionic mechanism. A similar result was found for a neutral–radical oxidation mechanism, which showed that the formation of uracil is still favored over that of other products.

Therefore, theoretical computations are in agreement with laboratory studies of the UV photo-irradiation of H_2O:pyrimidine ice mixtures at low temperature [110], in which 4(3*H*)-pyrimidone was found to be the most abundant singly oxidized pyrimidine. The detection of only small quantities of 2-hydroxypyrimidine in laboratory samples favor a route for the formation of uracil in which 4(3*H*)-pyrimidone is its main precursor, though computations show that the oxidation of 2-hydroxypyrimidine towards the formation of uracil is also energetically favored in an H_2O ice matrix [181]. Similarly, uracil was found to be the most abundant doubly oxidized pyrimidine in laboratory samples [110], as well as the most favorable product in the ab initio quantum calculations, regardless of its singly oxidized precursors, i.e., 4-hydroxypyrimidine, 2-hydroxypyrimidine, or their tautomers. Finally, both experimental and theoretical results show a clear regioselectivity for the oxidation of pyrimidine, favoring position 4 of the ring over position 2 for the first oxidation, and the formation of uracil as the most stable doubly oxidized product.

Perhaps the single most important conclusion from these quantum mechanical computations is that the oxidation of pyrimidine is not expected to be energetically favorable in the gas phase, whereas it is feasible in an ice matrix. The presence of several H_2O molecules surrounding the reactants in the condensed phase is absolutely necessary to assist the proton abstractions leading to the formation of the final products for both oxidation steps of pyrimidine and its derivatives. This important result indicates that the formation of uracil, as well as other pyrimidine derivatives, via the oxidation of pyrimidine under astrophysical conditions is likely to be viable

◀

Fig. 6 (continued) loss of a proton. (**b**) Energy diagram of the second oxidation step starting from 4(3*H*)-pyrimidone (energies are in kcal mol^{-1}). On the *left hand side* are the energies of intermediates + H_2O, and on the *right hand side* are the energies of singly oxidized products + H_3O^+ (see [181])

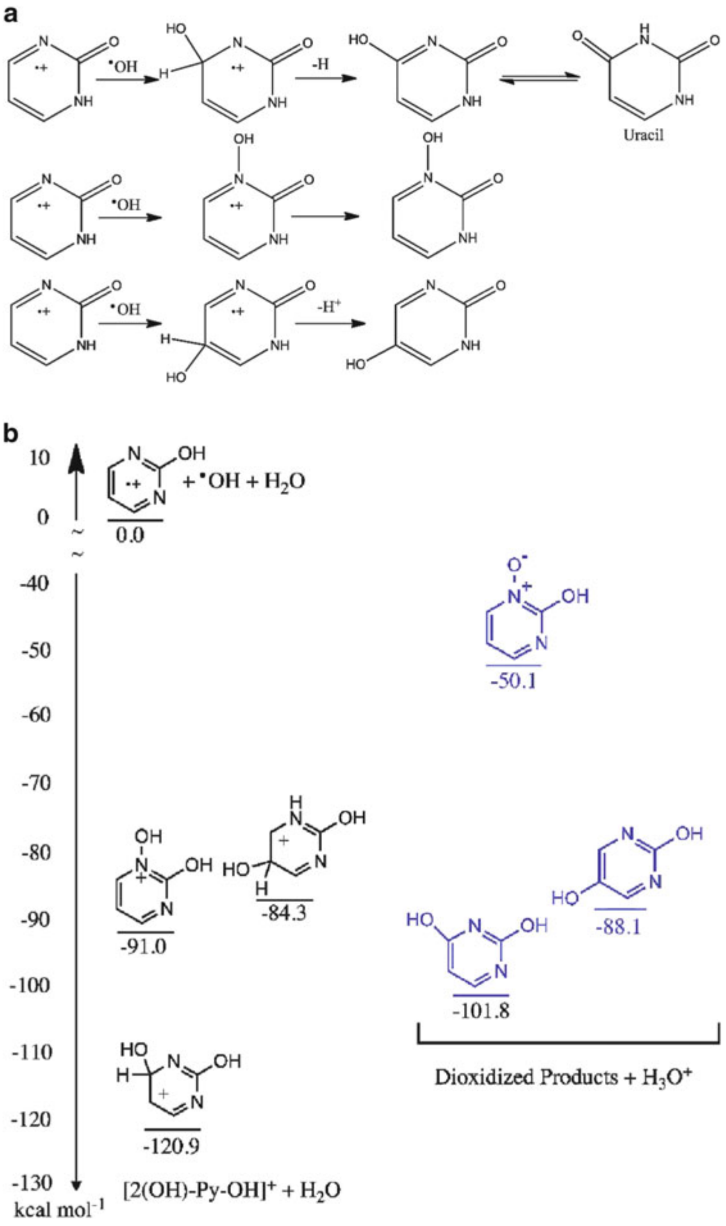


Fig. 7 (**a**) Mechanistic routes for the oxidation of starting from 2(1*H*)-pyrimidone towards the formation of uracil and its isomers. The first step is a nucleophilic attack of a hydroxyl radical to the 2(1*H*)-pyrimidone cation. The second step is the loss of a proton. (**b**) Energy diagram of 2(1*H*)-pyrimidone cation and hydroxyl radical (energies are in kcal mol^{-1}). On the *left hand side* are the energies of intermediates + H_2O, and on the *right hand side* are the energies of doubly oxidized products + H_3O^+ (see [181])

only in icy mantles, such as those observed at the surface of cold grains in the ISM, and in the presence of ionizing radiation [181].

2.2.2 Synthesis of Cytosine

Cytosine (4-amino-2-hydroxypyrimidine) is another biologically relevant pyrimidine-based nucleobase, which is found in both DNA and RNA. Like uracil, this compound is a doubly substituted pyrimidine derivative, but has an amino (NH_2) group replacing the OH group on position 4 (Fig. 3). Therefore, the abiotic production of cytosine from the irradiation of pyrimidine requires the addition of both one OH group to position 2 of the pyrimidine ring and one NH_2 group to position 4. $^{\bullet}OH$ and $^{\bullet}NH_2$ radicals are nucleophilic species that are readily formed from the photo-dissociation of H_2O and NH_3, respectively, both in laboratory ices and cold astrophysical environments such as diffuse clouds, protostellar disks, circumstellar sources, and comets [90–93]. Because of the low NH_2–H and HO–H dissociation energies of 4.60 eV [190] and 5.10 eV [191], respectively, both $^{\bullet}OH$ and $^{\bullet}NH_2$ radicals are expected to react with pyrimidine in a similar way under these experimental conditions.

Laboratory Synthesis of Cytosine

The irradiation of pyrimidine mixed with H_2O and NH_3 ices in the laboratory is thus expected to lead to the formation of cytosine, uracil, and a suite of other oxidized and/or aminated pyrimidine derivatives. Experiments in which H_2O:NH_3:pyrimidine ice mixtures with different relative proportions are irradiated following the same protocol as for the formation of uracil show that cytosine can be formed efficiently under similar conditions, and with a comparable yield to uracil [111]. As was observed for the oxidation of pyrimidine, the addition of amino groups is regioselective and favors the amination of position 4 of the ring over the other positions to form 4-aminopyrimidine (one of cytosine's precursors), though small quantities of other isomers such as 2-aminopyrimidine are also formed.

However, even if 4-aminopyrimidine is a logical precursor of cytosine, its formation in H_2O+NH_3 is in competition with the formation of 4(3*H*)-pyrimidone via oxidation of pyrimidine ([110, 111]; Sect. 2.2.1). The amination of 4(3*H*)-pyrimidone leads to the formation of isocytosine (2-amino-4-hydroxypyrimidine), an isomer of cytosine that has been detected in most of the residues produced from the UV photo-irradiation of H_2O:NH_3:pyrimidine ice mixtures [111].

Finally, it is interesting to note that, although both OH and NH_2 groups have similar nucleophilic properties and are expected to react with pyrimidine in a similar manner, these experiments indicate that the presence of H_2O in the starting ice mixtures enhances the addition of NH_2 groups, in particular to increase the formation yield of products such as 2-aminopyrimidine, whose formation in an H_2O-poor ice matrix is not favored for regioselective reasons [111].

Theory of Cytosine Synthesis in the Condensed Phase

Investigating reaction mechanisms in mixed ices such as H_2O+NH_3 is more complicated than in separate pure H_2O or pure NH_3 ices. In order to perform theoretical computations aimed at understanding such processes, one needs to identify the most probable sequence of reactions in these ices. Since $^{\bullet}OH$ and $^{\bullet}NH_2$ radicals are known to be readily formed from the photo-degradation of H_2O and NH_3, respectively, it appears logical that the two main types of reactions that will affect pyrimidine in these systems are oxidation (i.e., hydroxyl group addition) and amination (i.e., amino group addition).

Following what is known about the oxidation of pyrimidine from both the experimental and theoretical studies of uracil formation, it is reasonable to assume that functional group additions on pyrimidine (neutral, cation, or radical) take place one after the other rather than simultaneously. Because $^{\bullet}OH$ and $^{\bullet}NH_2$ radicals have a reasonably similar probability to react with pyrimidine, the most important factor concerning which groups is most likely to be added first will largely depend on the relative abundance of their respective parent molecules (H_2O and NH_3) in the ices. For most astrophysical ices and the studies described here, where H_2O is generally the dominant ice component, oxidation will be favored over amination.

When oxidation takes place first, it favors the formation of 4(3*H*)-pyrimidone over that of 2-hydroxypyrimidine for regioselective reasons ([110, 181]; Sect. 2.2.1). The subsequent amino group addition, if it occurs at position 2 of the pyrimidine ring, will lead to the formation of isocytosine (2-amino-4-hydroxypyrimidine), an isomer of the nucleobase cytosine. Of course, 4(3*H*)-pyrimidone and its isomers can also undergo further oxidation, towards the formation of uracil and its isomers, as shown for pyrimidine in a pure H_2O ice ([110, 181]; Sect. 2.2.1).

In the case where amination takes place first, the most favored product may be 4-aminopyrimidine, similar to the oxidation step, which may then be either aminated to form doubly aminated pyrimidine derivatives or oxidized to form cytosine and its isomers. Similar to what happens for the oxidation of 4(3*H*)-pyrimidone, the oxidation of 4-aminopyrimidine may favor the 2 position on the ring, resulting in the formation of cytosine. The formation of other isomers will likely also be exothermic, although they may be less abundant than cytosine if the formation of cytosine follows that of uracil.

The detailed ab initio quantum chemical calculations describing these reactions for three types of mechanisms, namely, ionic, neutral–radical, and radical–radical, are currently in progress [192].

2.2.3 Synthesis of Thymine

Thymine (2,4-dihydroxy-5-methylpyrimidine) is the third and last biologically relevant pyrimidine-based nucleobase. Thymine is found only in DNA and thus is not necessary for the emergence of an RNA world [175–178]. The formation of this tri-substituted pyrimidine derivative requires a double oxidation in the same positions on the ring as uracil, and the addition of a methyl (CH_3) group to position 5. Therefore, the abiotic production of thymine from pyrimidine requires both a source of oxygen and a source of methyl groups.

Since H_2O is by far the most abundant component of interstellar ices, its presence in any starting ice mixtures to be studied is essential. On the other hand, possible sources of methyl groups in interstellar ices could include both methanol and methane, as both are widely observed in cold astrophysical environments, although methanol is usually observed with abundances that are an order of magnitude larger than those of methane [90–93]. Thus, H_2O:CH_3OH:pyrimidine and H_2O:CH_4:pyrimidine mixtures appear to be the simplest relevant ice analogs to be studied both experimentally and theoretically for the formation of thymine through photo-irradiation. Experiments in which H_2O-free ice mixtures (CH_3OH:pyrimidine and CH_4:pyrimidine) are irradiated have also been performed in order to evaluate better the methylation efficiency of CH_3OH and CH_4, as well as the role of H_2O in these experiments.

Laboratory Synthesis of Thymine

Experimental protocol and analysis techniques employed in the study of the formation of thymine are similar to those previously employed for studying the formation of uracil and cytosine [112]. One notable exception, however, is that laboratory experiments on thymine formation also included experiments that employed higher UV photon doses than needed for the formation of uracil and cytosine.

Experimental results indicate that ice mixtures containing CH_3OH as a methyl group source do not yield measurable quantities of pure methylpyrimidines, although they may still produce small quantities of thymine. The lack of methylpyrimidines may be partially explained by the fact that the photo-dissociation of pure CH_3OH is known to lead to branching ratios from which only 1 in 7 photolytic reactions will result in the production of a CH_3 group [193].

In contrast, methane is a much better source of CH_3 groups than methanol. Experiments on the irradiation of CH_4:pyrimidine ice mixtures do lead to the production of 4-methylpyrimidine, although no other methylpyrimidine isomers were detected [112]. It is interesting to note that similar HPLC analysis of residues produced from experiments involving quinoline rather than pyrimidine yielded similar results for the non-detection and detection of methyl addition in CH_3OH- and CH_4-containing ices, respectively [194]. The addition of H_2O to CH_4:pyrimidine mixtures results in the production of both 4- and 5-methylpyrimidine, once again highlighting the role H_2O can play as a catalyst for the formation of other less abundant methylpyrimidine isomers such as 5-methylpyrimidine, as is also observed for the formation of aminopyrimidines from H_2O:NH_3:pyrimidine ice mixtures [111].

While the production of thymine has been observed in these experiments, its overall abundance is relatively low in comparison to uracil or cytosine in similar previous experiments. One likely cause for this difference is the fact that thymine formation requires three substitutions, while both uracil and cytosine only require two each. This means that more photons are required, and this puts further constraints on the makeup of the surrounding ice to ensure that the proper radicals and/or ions are available. Additionally, since the formation of thymine via UV processing of pyrimidine in ices requires more photons than would be required for either uracil or cytosine, there are more opportunities to derail its formation with an alternative substitution or through further modification of the final product or its precursors.

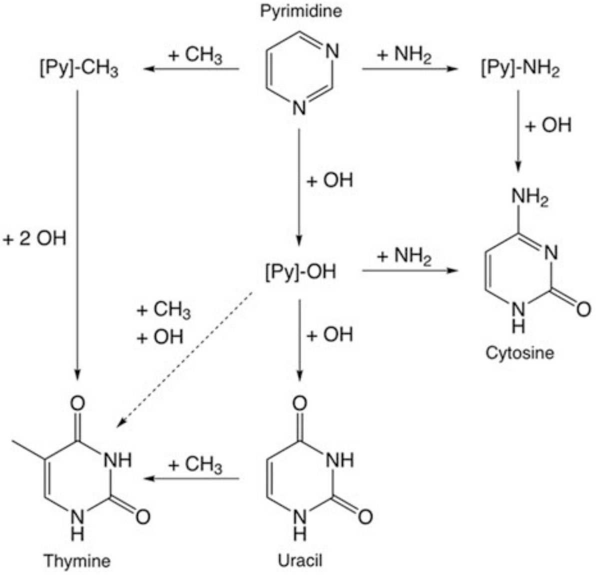
Theory of Thymine Synthesis in the Condensed Phase

Detailed quantum chemical methods have been used to study the formation of thymine in a system where pyrimidine is surrounded by H_2O molecules, OH radicals, and $^{\bullet}CH_3$ radicals, using the same computational methods as described in Sect. 2.2.1 for uracil [195]. As mentioned earlier, the formation of thymine from pyrimidine requires the addition of three groups, two OH groups (positions 2 and 4 on the ring) and one CH_3 group (position 5).

As in the case of cytosine, investigating the reaction mechanisms of thymine formation is complicated because the process occurs in mixed ices in which the addition of different groups can be carried out in several different orders (Fig. 8). The two main types of reactions in these systems are oxidation and methylation. Three different routes have been explored: (1) the double oxidation of pyrimidine followed by a methylation, (2) the methylation of pyrimidine followed by a double oxidation, and (3) the oxidation of pyrimidine, followed by a methylation, followed by a second oxidation. As in the case of uracil, Bera et al. [195] studied each of these routes for three types of mechanisms, namely, ionic, neutral–radical, and radical–radical.

In the first case, reactions will lead to the formation of uracil via the same route as described for pyrimidine in pure H_2O ice ([110, 181]; Sect. 2.2.1). The subsequent reaction is the methylation of uracil, which can lead to thymine as well as to its isomers. Computations show no clear preference for the product of methylation of uracil, indicating that thymine has the same, or a smaller, probability to be formed relative to its isomer 6-methyluracil. In the second case, pyrimidine is first methylated and then oxidized to form thymine and its isomers. Interestingly, 5-methylpyrimidine, which is the methylated pyrimidine precursor of thymine, is not the most energetically favored product among all possible methylpyrimidine isomers. The oxidation steps have much more favorable reaction energies compared to the methylation steps, which is the key reason why oxidation is overwhelmingly favored. Moreover, although the addition of methyl groups to pyrimidine is energetically favorable, in an H_2O-rich ice methylation will compete unfavorably against oxidation for two main reasons: (1) because $^{\bullet}OH$ radicals

Fig. 8 Pathways leading to the formation of the three nucleobases uracil, cytosine, and thymine from the UV photo-irradiation of pyrimidine in H_2O, NH_3, CH_3OH, and/or CH_4 ices, via the successive addition of OH, NH_2, and CH_3 groups



outnumber $^{\bullet}CH_3$ radicals in these ice mixtures, and (2) because calculations show that the oxidation step is significantly more exothermic and thus favored. It was also shown experimentally that 5-methylpyrimidine deposited in an H_2O ice and UV irradiated can lose its CH_3 group to form pyrimidine, which can then be oxidized to form 4(3*H*)-pyrimidone ([112]). All these results are in agreement with what was seen experimentally, namely, methylation is the limiting step in the formation of thymine.

The theoretical investigations of Bera et al. [195] also revealed two very interesting points. First, following the reactions of a hydroxyl radical with the pyrimidine cation and its derivatives, their results show that, as is the case for uracil, the formation of thymine is not energetically favorable in the gas phase, and only becomes feasible in the condensed phase, where the H_2O ice matrix plays two roles, both as an oxidant and as a solvent for proton abstraction in both oxidation and methylation steps. Second, computations confirm that the oxidation of pyrimidine is significantly favored over its methylation. By combining all these results, it appears that the most probable pathway for the formation of thymine from pyrimidine is via the formation of 4(3*H*)-pyrimidone as a first step, then the formation of uracil after a second oxidation, and finally the methylation of uracil [195]. The fact that methyl addition is the limiting step in this process, and that the formation of thymine in this route is not particularly favored over those of its isomers, could explain the very low quantities of thymine detected in laboratory samples [112] compared to what is seen for uracil and cytosine [110, 111].

The Interesting Difference of Thymine

Experiments showed that thymine is not efficiently produced from the UV photo-irradiation of pyrimidine in ices containing H_2O and a methyl source such as the interstellar icy components CH_3OH and CH_4. This result may be attributed to the fact that the formation of thymine requires three substitutions, and thus higher doses of photons compared with the formation of uracil and cytosine, and to the fact that in an H_2O-rich ice mixture, as is the case in the ISM, methylation becomes the limiting step to forming thymine. From a theoretical point of view, quantum chemical computations do not show any clear thermodynamic preference for the formation of thymine over other competing products; indeed, the methylation of uracil actually slightly favors the formation of 6-methyluracil over that of thymine (5-methyluracil). In an environment where methylation competes with oxidation, oxidation is expected to dominate by virtue of its significantly larger reaction energies compared to methylation. Even if methylation takes place before oxidation in the process leading to the formation of thymine, experiments starting with 5-methylpyrimidine in H_2O ice clearly showed that the CH_3 groups can be easily cleaved off to form pyrimidine, which subsequently will most probably be oxidized to uracil.

The fact that thymine is not formed as easily as the other two pyrimidine-based nucleobases under astrophysical conditions, as demonstrated by both experimental and theoretical studies, and the fact that thymine has not been detected in carbonaceous meteorites, raise an interesting question about its role in the origins of life. If we assume that photo-processing of icy grains plays an important role in the formation of nucleobases in astrophysical environments (Fig. 2), we can imagine a scenario in which the pyrimidine-based nucleobases are formed in space, preserved in small objects such as asteroids and comets during the formation of the Solar System, and subsequently delivered to the early Earth and other telluric planets [12, 13, 17]. However, since (1) methylation is an important step in the formation of thymine, (2) this reaction appears inefficient in CH_3OH-rich ices like those seen in many interstellar dense clouds, and (3) the formation of thymine requires at least three substitutions as opposed to two for uracil and cytosine, it is possible that thymine was not formed in the ISM as efficiently as the other pyrimidine-based nucleobases.

Therefore, the abundance of thymine in the comets and asteroids which seeded the primitive Earth may have been significantly smaller than those of uracil and cytosine. It is interesting to consider these results and assumptions in light of the fact that terrestrial thymine is only found in DNA, but not in RNA. Indeed, several scenarios for the emergence of life involve a period of time during which RNA was the molecule dominating biological reactions as a catalyst and storage for a primitive genetic information [175–177]. It should be mentioned, however, that the RNA world hypothesis is still debated and alternative mechanisms involving small organic molecules which interact with each other via catalyzed reaction cycles driven by a flow of available free energy have also been proposed [196].

Nonetheless, in the hypothesis that such an RNA world did lead to the origin of life, a paucity of thymine among the building blocks that were delivered to Earth could potentially have forced the emergence of replicable systems involving uracil rather than thymine, such as RNA. In such a scenario, the emergence of DNA, and thus the use of thymine, as a more stable, robust molecule to store genetic information, may have appeared at a later stage in the complexity of life, in part because it was not effectively delivered to the early Earth.

2.3 *Synthesis of Purine-Based Nucleobases in Extraterrestrial Ices*

Although the formation of pyrimidine-based nucleobases under extraterrestrial abiotic conditions has been extensively studied, the same cannot be said about the formation of purine-based nucleobases and their derivatives. Purine is the backbone of the two other biological nucleobases that constitute the genetic material of DNA and RNA, namely, adenine and guanine. There are also a wide variety of biological and non-biological molecules based on the backbone of purine, such as xanthine, hypoxanthine, and caffeine. Most of these compounds have been detected in meteorites [11, 128–135], and it appears that meteoritic purine based compounds are always more abundant than pyrimidine-based compounds.

Therefore, the study of the formation and photo-stability of purine-based compounds is important from both astrochemical and astrobiological points of view. Unfortunately, to date there have been no experimental or theoretical studies of the photolytic formation of such purine-based compounds in ices under astrophysically relevant conditions. However, numerous experimental results have been obtained for radiation-induced functional group addition to small polycyclic aromatic hydrocarbons (PAHs; [99, 105–109]) and small PANHs [194], including pyrimidine-based compounds [110–112], and these allow us to comment on what might be expected for purine.

Given the fact that purine-based species are more stable to UV radiation than are pyrimidine-based species, it is reasonable to predict that experiments in which purine is mixed in ices of astrophysical interest containing compounds like H_2O, NH_3, CH_3OH, and CH_4 will lead to the formation of mostly purine-based compounds, including adenine and guanine, as opposed to pyrimidine, whose ring can be broken by UV radiation to form smaller, aliphatic compounds [111]. Indeed, the abiotic formation of adenine from the UV irradiation of purine in ices would only require the addition of a single NH_2 group, while that of guanine would require the addition of only one OH group and one NH_2 group (Fig. 9). Since previous irradiation studies of small PAHs and pyrimidine have shown that the addition of OH and NH_2 groups to aromatic cyclic molecules is an efficient process, the formation of adenine and guanine from purine ought to be straightforward. Furthermore, since the needed functional group additions involve only OH and NH_2,

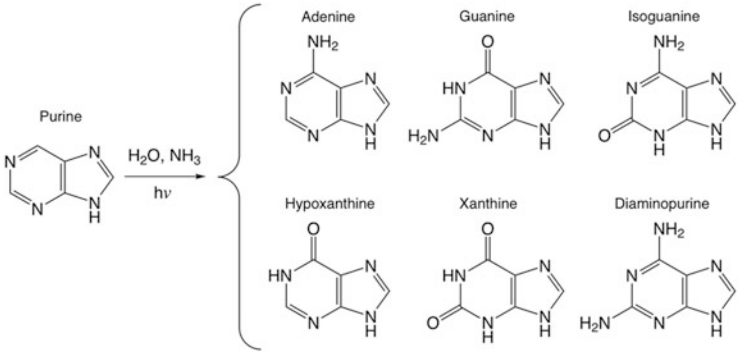


Fig. 9 Schematic showing how the UV photo-irradiation of purine in simple ices consisting of H_2O and/or NH_3 can be expected to lead to the formation of the biological nucleobases adenine and guanine, as well as several other derived compounds of astrobiological interest such as xanthine (2,6-dihydroxypurine) and hypoxanthine (6-hydroxypurine)

and not CH_3, one might expect production yields comparable or higher to those for uracil and cytosine under similar conditions, rather than the lower yields seen for thymine.

Finally, since astrophysical ices contain not only H_2O and NH_3 but also a variety of carbon sources such as CO, CO_2, CH_3OH, or CH_4, it will be interesting to (1) understand the effect of these compounds on the formation of adenine, guanine, and other purine-based nucleobases such as xantine and hypoxantine, (2) verify whether the inclusion of carbonaceous species leads to the methylation of purine, known to be the limiting reaction for the formation of methylated pyrimidine derivatives when formed in an H_2O-rich ice matrix, and (3) verify whether carbon sources have any inhibiting effects on the addition of OH and/or NH_2 groups.

2.4 *Photo-Stability of the Nucleobases in Ices*

Although there is no extensive body of research examining the photo-stability of pyrimidine-based nucleobases in ices, we can make some general observations. Little work has been done to quantify the effect, but it is clear from the synthesis work that products are not simply made and left alone, but are continuously susceptible to further photolytic reactions, i.e., the abundance of any given species in the ices is the result of the competition between “creation” and “destruction”, where this latter term can include complete disruption of the molecule or alteration of the functional groups to form other pyrimidine-based molecules. It is not currently established what radiation exposures are needed to bring the competing creation–destruction processes into quasi-equilibrium, but true equilibrium is never likely to be attained since irradiation will steadily drive H from the ices [198].

In most experimental mixtures, much of the original pyrimidine survives and is detected in HPLC chromatograms of the resulting residues [111, 112], with the exception of H_2O:pyrimidine ice mixtures in which pyrimidine is nearly fully consumed by either photo-destruction or the formation of new products [110]. Having said that, these experiments show that the pyrimidine ring is susceptible to photolytic destruction and rearrangement in ices, and photo-products that could not have been produced from any other source have been detected. For example, in experiments examining the formation of uracil, cytosine, and thymine, acyclic compounds including urea, glycine, *N*-formylglycine, and alanine are also detected [110–112]. Experiments starting with only H_2O, CH_3OH/CH_4, and pyrimidine, where the only source of available nitrogen is from the destruction of pyrimidine itself, also show the presence of aminopyrimidines [112]. Hydantoin, an oxidized carbon and nitrogen heterocyclic molecule with a five-membered ring, is also detected in many of these experiments. It is therefore clear that photolytic destruction of the pyrimidine ring occurs in these ices.

In addition to the destruction of the ring itself, we know that side groups can be cleaved from pyrimidine rings. A good example to demonstrate this is a series of experiments starting with H_2O:5-methylpyrimidine ice mixtures that were designed to test the efficiency of the conversion of the latter into thymine in the presence of H_2O. In these experiments, oxidized pyrimidines, such as 4(3*H*)-pyrimidone, that lacked any methyl group, are found among the products. The formation of these oxidized pyrimidines lacking any methyl side group requires that the initial CH_3 group in 5-methylpyrimidine is cleaved from the ring [112]. Though in this case 5-methylpyrimidine is one of the initial ice components, we can expect to observe the same effect in molecules formed during the UV photolysis, further demonstrating the interaction of creation and destruction processes.

We are currently unaware of any data regarding the photolytic stability of purines in these types of ices. On the basis of irradiation experiments of normal PAHs and pyrimidine in similar ices [99, 106, 107, 109], we would expect that substitutions or rearrangement of side groups should occur. The degree to which the purine ring system is susceptible to photolytic destruction is less clear. In the case of PAHs, ring destruction is greatly diminished with an increasing number of rings. The extent to which this trend can be extended from pyrimidine to purine is unknown because of the heterocyclic nature of the rings.

3 Conclusions

Numerous studies have demonstrated that the radiation processing of astrophysically relevant ices can lead to the production of a host of organic molecules of astrobiological interest, including amino acids, quinones, and amphiphiles. Recent experimental and theoretical work has demonstrated that the presence of pyrimidine in such ices is expected to lead to the formation of the three pyrimidine-based nucleobases uracil, cytosine, and thymine, along with a number of their isomers.

Formation of the pyrimidine-based nucleobases requires various combinations of oxidation, amination, and methylation, all of which are observed experimentally. However, theoretical work makes it clear that the presence of condensed phase H_2O in the ice matrices plays a key role in formation of the nucleobases. Its most obvious role is as a source of oxygen for the oxidation reactions needed to make all of the pyrimidine-based nucleobases. However, it also plays a key role in the addition of hydroxyl, amino, and methyl groups by mediating the abstraction of either a proton or a hydrogen atom from intermediaries to form the final products. Since H_2O is the most abundant component observed in most astrophysical ices, this critical compound is likely to be available to play these roles in most cold astrophysical environments.

The relative abundances of uracil, cytosine, and thymine produced during ice photolysis depend on both the composition of the ices and on the photon dose. In general, larger photon doses will lead to greater degrees of ice processing, but do not necessarily lead to greater yields of any particular photo-product. This is because the abundance of any given photo-product is the result of competing creation and destruction reactions, where "destruction" includes both the rupture of the pyrimidine ring and the replacement of a previously added functional group with a different group. Thymine represents a good example of this issue. While experiments show that photolysis of pyrimidine in CH_4-rich ices can lead to methylation of the pyrimidine, and that thymine can be made in H_2O:CH_4:pyrimidine ices, thymine is generally seen to be produced in far lower abundances than uracil, presumably because relevant astrophysical ices are dominated by H_2O, not CH_4, methylation is less energetically favorable, and the formation of thymine requires the addition of three functional groups instead of the two required for uracil or cytosine. Understanding the true range of relative production efficiencies of uracil, cytosine, and thymine will require the completion of studies of pyrimidine photolysis in more complex, realistic astrophysical ice analogs.

It is interesting to note that the lower production efficiency of thymine relative to uracil is consistent with what is seen in the organics in meteorites. A paucity of abiotically produced thymine delivered to, and available on, the early Earth is also of interest because it is consistent with the idea that modern DNA-based life may have been preceded by an earlier "RNA world" that did not involve any thymine.

While a growing body of work exists for the photoprocessing of pyrimidine in ices, little comparable work has been done for purine in ices. As a result, it is not known whether similar ice photolysis processes can produce the two purine-based nucleobases adenine and guanine. However, based on the earlier work on pyrimidine, as well as ice photolysis experiments on PAHs and other aromatic heterocycles, it is anticipated that such processing should create both adenine and guanine. Since the only reactions needed to make these two nucleobases involve the addition of a few hydroxyl and amino groups, and no methyl groups, these two nucleobases are expected to be formed with efficiencies similar to those seen for uracil, rather than the lower efficiencies associated with the production of thymine.

Acknowledgements The authors are grateful for support from the NASA Origins of Solar Systems, Exobiology, and Astrophysics Research and Analysis, and Astrobiology Programs. Much of the work reported in this chapter also benefited from support of postdoctoral researchers under the NASA Postdoctoral Program. PPB and TJL would like to acknowledge financial support from NASA to investigate the formation and evolution of carbon-based material in the universe. This manuscript benefited from the helpful comments of an anonymous reviewer.

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