Chem. Res. Chinese Universities, 2020, 36(6), 985—991 doi: 10.1007/s40242-020-0289-6

Review

Synthesis of Prebiotic Building Blocks by Photochemistry

LIU Ziwei*

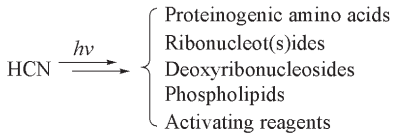
MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Cambridge CB2 0QH, UK

Abstract Ultraviolet(UV) light is a very competent energy source for the synthesis of prebiotic building blocks on early Earth. In aqueous solution, hydrated electron is produced by irradiating ferrocyanide/cuprous cyanide/ hydrosulfide by 254 nm UV light. Hydrated electron is a powerful reducing reagent driving the formation of prebiotic building blocks under prebiotically plausible conditions. Here we summarize the photoredox synthesis of prebiotic related building blocks from hydrogen cyanide(HCN) and other prebiotically related molecules. These results indicate biological related building blocks can be generated on the surface of early Earth.

Keywords Prebiotic chemistry; UV irradiation; System chemistry; Origin of life

1 Introduction

Life needs continuously energy and materials input to keep itself far-from-equilibrium. The light coming from the Sun is a major energy source for the modern life. Because of the lack of ozone layer, young Sun delivered more UV light to Earth before life was existed[1]. Due to the high level of atmospheric carbon dioxide(>10^3 Pa), the far UV light(wavelengths less than 200 nm) is always weakened[2]. A huge amount of chemical reactions are investigated trying to give a clue for the origin of life problem. Suggested by planetary science, a wide range of environments and conditions could exist on early Earth. For example, Miller-Urey experiments[3] indicated the amino acids generated by discharging a reduced atmosphere. Oró *et al*.[4] showed adenine was simply formed by heating ammonium cyanide. The Butlerow synthesis of sugar[5] is a base-catalyzed autocatalytic process. All these reactions have different substrates, different conditions, and the products are complex mixtures with only few percentages of bio-related molecules. Before we go deeply to the geochemical details of the synthesis of prebiotic building blocks, we should glimpse from extant biology down. If a modern cell reduced to a simplest one, by conceptual or experimental way, it still remains complex system. A minimal cell can be separated to three sub-systems: (a) genetic mechanism(*e.g*., DNA or RNA) has the ability to process and transmit heritable information to progeny; (b) metabolic machinery(*e.g*., protein) can capture energy and material source, catalyze chemical reaction in cell; (c) membrane compartment(*e.g*., phospholipid) can keep its components together and distinguish itself from the environment[6]. Nowadays, the origin of life is considered to have occurred through a co-evolutionary process involving different subsystems together rather than through self-organization in a system made of a single biopolymer. In this point of view, herein, I will summarize a systematically prebiotic building blocks synthesis from simple basic molecules under UV irradiation(Scheme 1).



Scheme 1 Photo-synthesis of prebiotic related molecule from hydrogen cyanide

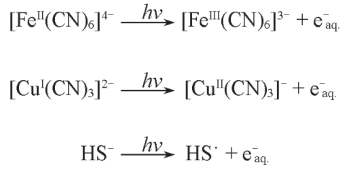
2 Prebiotic Photoredox Catalysts

Since HCN does not have a strong UV absorption, other prebiotic plausible species should be introduced in the system as a photocatalyst. Ferrocyanide, cuprous cyanide, and hydrosulfide are three prebiotically plausible species[2], which are able to absorb photon and release hydrated electron in aqueous solution(Scheme 2), and generate ferricyanide, cupric cyanide, and hydrosulfide radical, respectively.

HCN, a precursor of adenine, is capable to be reduced by hydrated electron or oxidized by ferricyanide, cupric, or hydrosulfide radical. The reduction of HCN results in methanimine, which will be hydrolyzed to formaldehyde, a precursor of sugar. But in the presence of cyanide, glycolonitrile or aminoacetonitrile is the product resulting from a nucleophilic addition of cyanide to formaldehyde or methanimine, respectively. These nitrile groups are capable to be reduced by hydrated electrons. Oxidation products of HCN in these three systems are different. The oxidation product of HCN by ferricyanide and cupric is cyanogen, and it will be hydrolyzed to cyanoformamide and further be decomposed to cyanate and cyanide. Both cyanogen and cyanate are prebiotic phosphate activating reagent resulting the phosphodiester formation[7]. The oxidation product of HCN by hydrosulfide is thiocyanate. In the presence of ammonium, it rearranges to thiourea under geothermal conditions. Thiourea is a precursor of deoxyribonucleoside and cyanamide[8,9]. All products from photo-reduction and photo-oxidation of HCN are prebiotically plausible molecules.

*Corresponding author. Email: zliu@mrc-lmb.cam.ac.uk

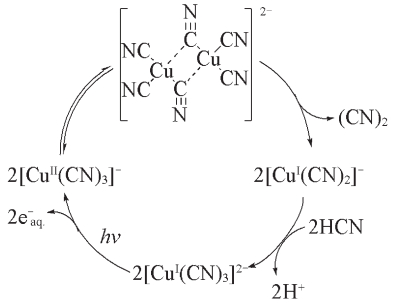
Received September 18, 2020; accepted October 13, 2020.



Scheme 2 Three prebiotically plausible formations of hydrated electron by irradiation at 254 nm UV light

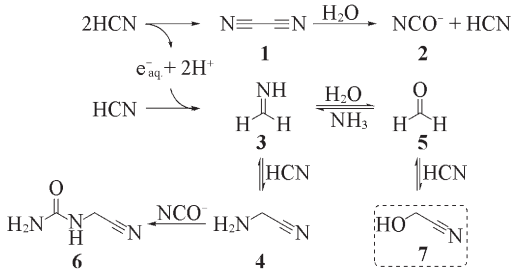
3 Cyanocuprate Photoredox System

Photoredox cycling of cuprous/cupric cyanide complexes in the presence of HCN[10] is summarized in Scheme 3. The cycling started from photo-oxidation of tricyanocuprate(I) to tricyanocuprate(II), and reversible dimerization of the latter compound provides access to hexacyanodicuprate(II). Reductive elimination of cyanogen from hexacyanodicuprate(II) gives dicyanocuprate(I). The last step for the cycling is cyanation of dicyanocuprate(I) regenerating tricyanocuprate(I). The result of each cycle is the oxidation of two molecules of HCN to cyanogen and the production of two protons with two hydrated electrons. Without additional hydrated electron scavengers, nitriles(including HCN) are reduced to imines and further hydrolyzed to aldehydes. Because HCN is in excess, these imines and aldehydes readily react with HCN to generate aminonitriles or cyanohydrins for further photoreduction.



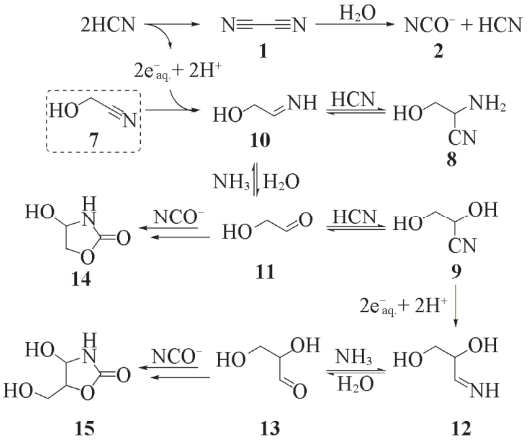
Scheme 3 Photoredox cycling of copper cyanide complexes in the presence of HCN

The first stage of HCN photoredox chemistry in the presence of cyanocuprate cycling is shown in Scheme 4. Some HCN is oxidized by copper(II) and generates cyanogen(**1**), the latter compound hydrolyzes to cyanate(**2**) and cyanide. The hydrated electrons reduce another HCN molecule to methanimine(**3**), which is not a stable compound in aqueous solution and hence either reacts with HCN, giving aminoacetonitrile(**4**) or hydrolyzes to formaldehyde(**5**). Aminoacetonitrile(**4**) is the precursor of glycine, and it is a phosphate activating reagent in the presence of cupric in aqueous solution[7]. In this system, aminoacetonitrile(**4**) readily reacts with cyanate, resulting in carbamoyl aminoacetonitrile(**6**), and hydrolyzes to carbamoyl glycine. Carbamoyl amino acids are initial compounds for prebiotic C-terminal elongation of peptides[11]. Formaldehyde in this mixture reacts with HCN, giving glycolonitrile(**7**), which has a nitrile group that can be further reduced by hydrated electrons.



Scheme 4 The first stage for HCN photoredox chemistry in the presence of cyanocuprate cycling

The second stage of this photoredox chemistry starts from glycolonitrile reduction(Scheme 5). By repeating this reductive homologation, glycolonitrile converts to serine nitrile(**8**) or glyceronitrile(**9**) *via* the formation of 2-iminoethanol(**10**) and glycolaldehyde(**11**). Some glyceronitriles(**9**) undergo the third stage of this reduction and reduces to the imine(**12**), which can be hydrolyzed to glyceraldehyde(**13**). Because of the depletion of HCN, the third stage of reduction is limited. The shortage of HCN results in the increasing of aldehyde. Cyanate, a product of HCN oxidation, accumulates to a certain level, because each turn of photoredox cycling generates one molecule of cyanate. It readily reacts with aldehyde, as the concentration of HCN decreasing, cyanate reacts with aldehydes, following by intramolecular cyclization to the oxazolidinone derivatives **14** and **15**. Until now, there is no evidence indicating the usage of these compounds in prebiotic chemistry field. To avoid the formation of oxazolidinone derivatives, other reductants rather than HCN should be introduced in the system, for example, hydrosulfide.



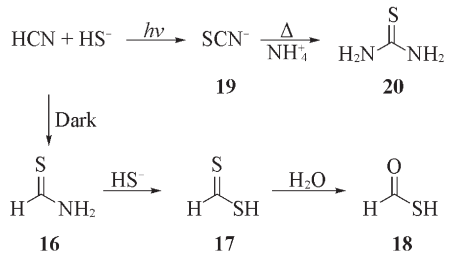
Scheme 5 The second stage and the third stage for HCN photoredox chemistry in the presence of cyanocuprate cycling

4 Cyanosulfidic Chemistry

4.1 HCN Reacts with Hydrosulfide

The cyanocuprate photoredox chemistry indicates sugars and precursors of amino acids can be generated starting from the same substrates and under the same condition, but it is marred by the presence of cyanate, which is the oxidation of HCN. Hydrogen sulfide, one product from volcanoes eruption, is able to reduce cupric to cuprous in aqueous solution[12]. Thus hydrosulfide, which is a conjugate base of hydrogen sulfide, is a reductant in cyanocuprate photoredox chemistry. Before we

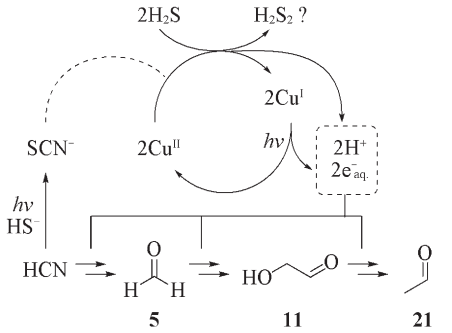
admire the cyanosulfidic chemistry in the presence of cyanocuprate, it is worth to notice the reaction between hydrosulfide and HCN. The nucleophilic addition of hydrosulfide to nitriles group occurs in a dark place[13], but the photoreaction of hydrosulfide and HCN undergoes a different way(Scheme 6). In the dark, hydrosulfide was added to HCN slowly to give thioformamide(**16**) or dithioformic acid(**17**) if hydrosulfide was added twice. The latter compound could be hydrolyzed to thioformic acid(**18**). In the presence of UV irradiation, hydrosulfide oxidizes HCN, generating thiocyanate(**19**)[14]. The latter compound is a catalyst in cyanosulfidic chemistry. If ammonium thiocyanate is heated at 170 °C, it rearranges to thiourea (**20**)[15]. Thiourea(**20**) is a key compound in prebiotic deoxyribonucleoside synthesis and a source of cyanamide, which is a potential prebiotic activating reagent[16] and a precursor of nucleosides, and these parts will be discussed later.



Scheme 6 Reaction between hydrosulfide and HCN in dark place or under UV irradiation

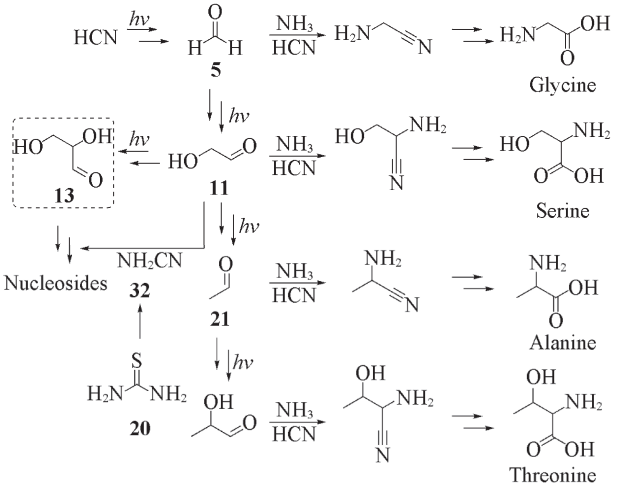
4.2 Cyanocuprate Cycling in the Presence of Hydrosulfide

The photoredox cycling of cyanocuprate in the presence of hydrosulfide is shown in Scheme 7. Some HCNs react with hydrosulfide under UV irradiation, generating thiocyanate(**19**), which has a positive feedback to the cycling[14]. With the help of thiocyanate(**19**), hydrogen sulfide reduces Cu(II) to Cu(I), and releases protons. Under UV irradiation, Cu(I) is oxidized to Cu(II) and generates hydrated electrons. Except a good yield of free glycolaldehyde(**11**) produced in this system, an over-reduced product, acetaldehyde(**21**), was generated as well. It indicated that part of α-hydroxyaldehyde can be reduced to aldehyde without aldehyde reduction. Deoxyribose is formed from ribose by this α-hydroxyl photoreduction as well[17].



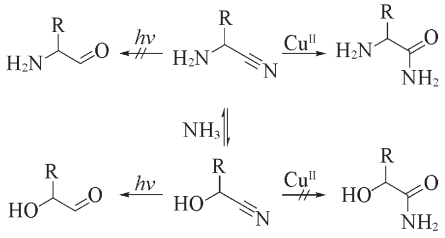
Scheme 7 Proposed mechanism of photoredox cycling of cupric/cuprous in the presence of hydrogen sulfide

Since hydrosulfide was the reductant in this system, cyanide oxidation to cyanate was avoided, but hydrosulfide still reacts with cyanide, giving thiocyanate(**19**). HCN was consumed by reductive homologation or formation of thiocyanate. This was the reason that aldehydes were accumulated in the system. If more HCN was introduced in the system, it would result in the formation of cyanohydrins of all aldehydes present. Beyond the three aldehydes describe in Scheme 7, there have more reductive homologation products that can be generated in this system(Scheme 8). Because Strecker reaction of α-aminonitriles(a precursor of α-amino acids) starts from aldehyde, ammonia, and cyanide, and the first step of Strecker reaction is the imine between aldehyde and ammonia[18], the cyanosulfidic chemistry generates imines directly by nitrile photoreduction. Part of the imines react with cyanide forming α-aminonitriles, and part of them hydrolyse to ammonium and aldehyde that is ready for the further step of reductive homologation or α-hydroxyl reduction. The ammonium in the system will regenerate imine with other aldehyde present. In this respect, four proteinogenic amino acids were produced in this system(Scheme 8).



Scheme 8 Formation of Strecker amino acid precursors in cyanosulfidic chemistry

The products of Strecker synthesis are based on the concentration of ammonium and the pH value of the solution, if ammonium is not enough in the system or in an acidic solution, the equilibrium is favor to cyanohydrins rather than aminonitriles. In system chemistry's view, it will not result in a disaster to the system(Scheme 9). The reasons are as follows. (a) Aminonitriles cannot be photo-reduced under this condition; (b) aminonitriles can be hydrolyzed to amino amides, then to amino acids in the presence of cupric ion; (c) cyanohydrins cannot be hydrolyzed to amides by cupric ion under same condition[7]. That makes the system polarize to two situations: if

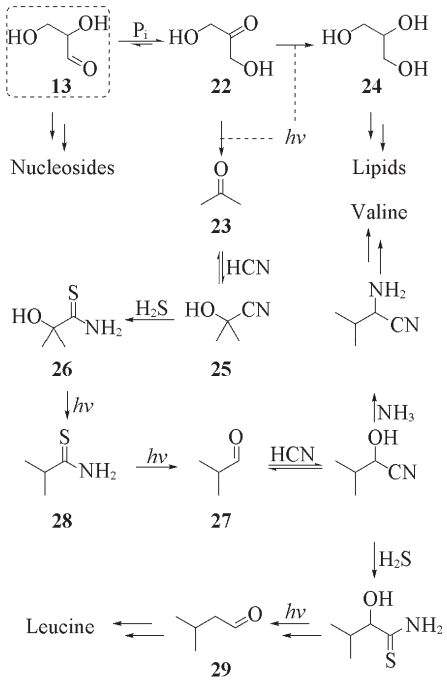


Scheme 9 Equilibrium of cyanohydrins and aminonitriles and the reactivation of them

the medium is more basic with more ammonium, the amino acids are the major products; if the medium is more acidic with less ammonium, sugars are the major products.

4.3 Linkage of Three Subsystems *via* Cyanosulfidic Chemistry

The further photoreduction starting from glyceraldehyde (**13**) generates more prebiotic related stuffs. In aqueous solution with phosphate buffer, dihydroxyacetone(**22**) was formed from glyceraldehyde(**13**) by Lobry de Bruyn-Alberda van Ekenstein reaction[19]. It can be photoreduced to two products, namely acetone(**23**) and glycerol(**24**). The latter compound is the key component of lipid, and the former one reacts with HCN slowly, giving cyanohydrin(**25**, Scheme 10). It cannot be reduced to its α-hydroxyaldehyde by the cyanocuprate cycling, but α-hydroxythioamide(**26**) was formed when left the reaction mixture in the dark. The photoreduction of α-hydroxythioamide(**26**) gave isobutyraldehyde(**27**), which is the precursor of valine *via* thioamide(**28**). The similar reductive homologation pathway generates isovaleraldehyde(**29**) from isobutyraldehyde(**27**), and isovaleraldehyde(**29**) is the precursor of leucine. Hydrosulfide addition following by a photoreduction can efficiently generate aldehyde from cyanohydrin. Thus, six more proteinogenic amino acids(arginine, proline, asparagine, aspartic acid, glutamine, and glutamic acid) can be produced under this cyanosulfidic chemistry as well[19].

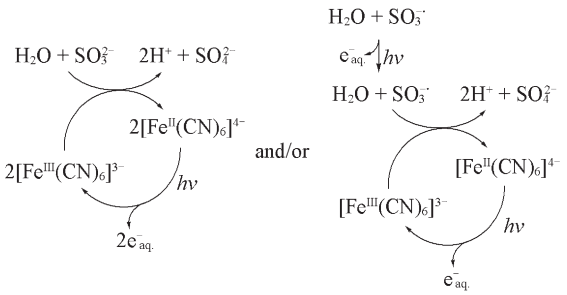


Scheme 10 A linkage between nucleosides, lipids, and amino acids *via* cyanosulfidic chemistry

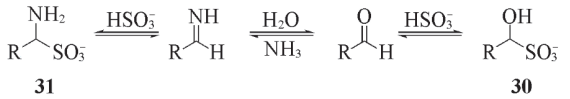
5 Cyanoferrate Photoredox System

5.1 Sulfite as the Reductant

Cyanoferrate(II) or ferrocyanide is prebiotic plausible water soluble repository of HCN delivered from the atmosphere of early Earth[20]. Under UV irradiation, ferrocyanide is photoionized/oxidized to ferricyanide and a hydrated electron[21]. Without other reductant in aqueous phase, HCN is oxidized by ferricyanide to give cyanogen, which will be hydrolyzed to cyanate. Sulfur dioxide, similar to hydrogen sulfide, is one of the volcanic emission components, and the high levels of sulfate in Martian soils suggest that sulfur dioxide and hydrogen sulfide were common on early Mars[22,23]. Since volcanism is still the major source of atmospheric sulfur dioxide and hydrogen sulfide on Earth recently, it is plausible that they were high concentrations on early Earth[24]. Sulfite, hydrate form of sulfur dioxide, is a better reductant(compare to hydrogen sulfide) to reduce ferricyanide back to ferrocyanide in aqueous solution[25]. As shown in Scheme 11, by fueling sulfite to sulfate, hydrated electrons and protons are continuously pumped out from the system. This would lead HCN reductive homologation, and generate sugars and precursors of amino acids as well. Because of the strong nucleophilicity of sulfite, sulfonates(**30** and **31**) are the major byproducts(Scheme 12).



Scheme 11 Proposed mechanism of photoredox cycling of ferricyanide/ferrocyanide in the presence of sulfite

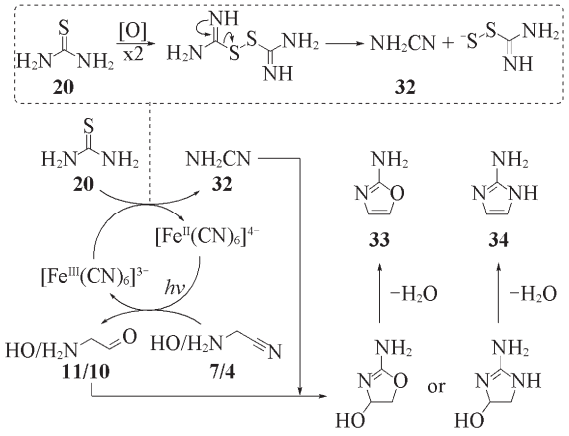


Scheme 12 Equilibrium between aminosulfonates and hydoxysulfonates

5.2 Thiourea as the Reductant

Cyanamide(**32**) is a key reagent for the prebiotic nucleosides synthesis[26]. The source of cyanamide **32** was very inefficient by irradiating cyanide with ammonia[27]. Alternately, calcium ferrocyanide thermally decomposes to cyanamide(**32**)[19], but the formation of calcium ferrocyanide on early Earth has been challenged recently[28]. Thiourea(**20**), which can be generated from irradiation of HCN and hydrosulfide following by a thermal rearrangement, can be oxidized by ferricyanide to give cyanamide[9]. Thus, it is a reductant in the cyanoferrate photoredox cycling. The photoredox cycling of cyanoferrate in the presence of thiourea is shown in Scheme 13. Hydrated electrons were generated from photoionization of ferrocyanide with the formation of cyanamide. Glycolaldehyde(**11**) reacted with cyanamide(**32**) *in situ* to give 2-aminooxazole(**33**), which is another key compound for prebiotic nucleoside synthesis[26]. Furthermore, aminoacetonitrile(**4**), which cannot be photoreduced in cyanocuprate chemistry, was readily reduced here, followed by the addition of cyanamide to give

2-aminoimidazole(**34**). The latter compound is used as a competent activating/leaving group in nucleoside 5'-phosphoro-2-aminoimidazolides mediated non-enzymatic RNA replication chemistry[29,30].



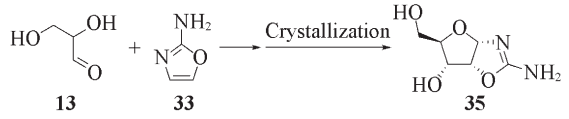
Scheme 13 Proposed mechanism of thiourea oxidation by ferricyanide and the formation of 2-aminooxazole or 2-aminoimidazole by photoredox cycling

6 UV Irradiation and Prebiotic Nucleoside Synthesis

6.1 Pyrimidine Ribonucleoside Synthesis

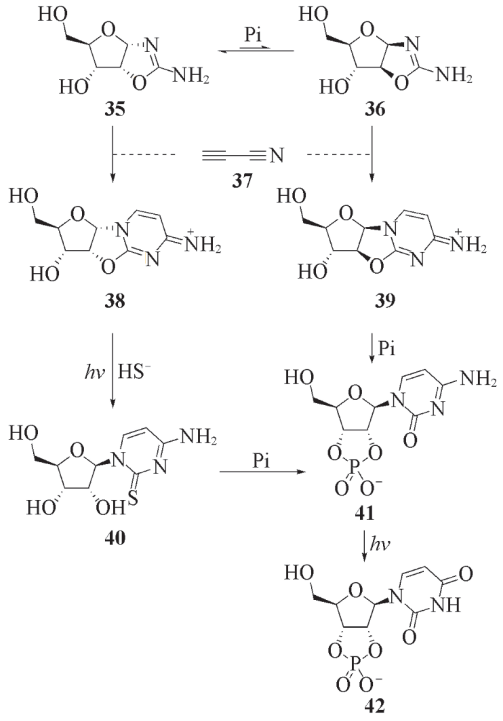
In 2009, breakthrough prebiotic ribonucleotides synthesis by non-classical disconnections was published[26]. This pathway is able to deal with three prebiotic nucleoside synthesis problems: (a) how biology chooses (deoxy)ribose rather than other sugars(which can be formed from formose reaction); (b) how (deoxy)ribose cyclizes as (deoxy)ribofuranose rather than (deoxy)ribopyranose; (c) how nucleobases link to (deoxy)ribose *via* β-glycosidic bond rather than α-glycosidic bond. Even some other pathways were established[31—33], these works left some or all questions untouchable.

Ribose aminooxazoline(RAO, **35**) is the key intermediate in this pathway[26]. It is one of the isomers generated from the reaction between 2-aminooxazole(**33**) and glyceraldehyde(**13**). RAO is able to crystallize from aqueous solution[34]. This step sweeps out other isomers in aqueous solution(Scheme 14).



Scheme 14 Prebiotic synthesis of RAO(35)

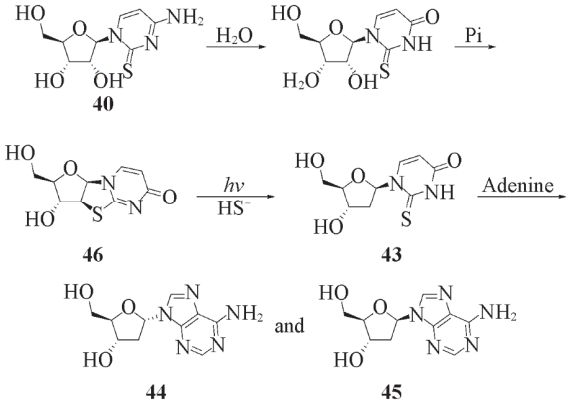
In aqueous solution with phosphate buffer, RAO(**35**) has equilibrium with arabinose aminooxazoline(AAO, **36**). They can react with cyanoacetylene(**37**) to give anhydro-α-cytidine (**38**) or arabino anhydrocytidine(**39**), respectively. The former compound undergoes a photoanomerization under UV irradiation in the presence of hydrosulfide to give 2-thiocytidine (**40**)[35]. Under phosphorylation conditions, both anhydro-α-cytidine(**39**) and 2-thiocytidine(**40**) generate cytidine 2',3'-cyclic monophosphate(**41**), which is a canonical nucleotide in extent biology. Under UV irradiation, cytidine 2',3'-cyclic monophosphate(**41**) can be slowly hydrolyzed to uridine 2',3'-cyclic monophosphate(**42**, Scheme 15)[26].



Scheme 15 Two different pathways to canonical pyrimidine ribonucleotides

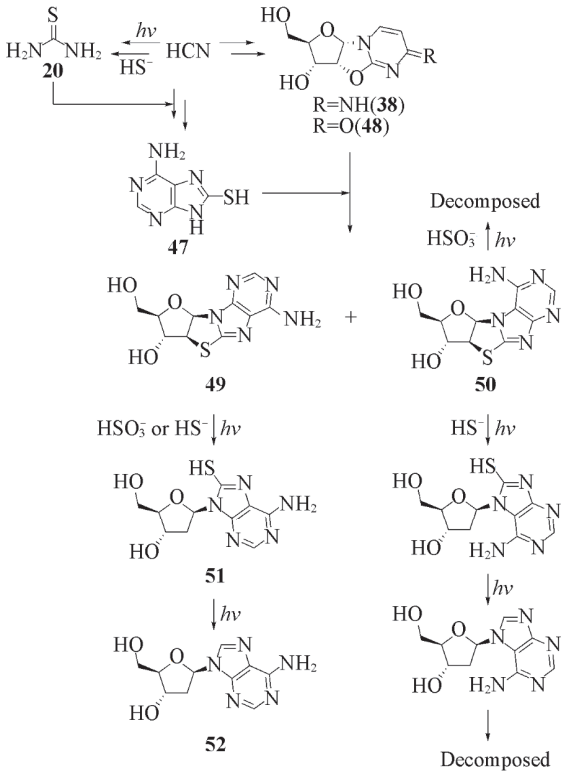
6.2 Purine Deoxyribonucleoside Synthesis

Deoxyribose is reduced from ribose by the hydrosulfide α-hydroxyl photoreduction. Under similar condition, thymine is produced from uracil. But the direct glycosidation process between thymine and deoxyribose has not been established yet[17]. But a transglycosylation reaction between 2-thiouridin-2'-deoxyribonucleoside(**43**) and adenine to give α- and β-adenosine-2'-deoxyribonucleoside(**44** and **45**) was investigated[36]. 2-Thiouridin-2'-deoxyribonucleoside(**43**), the key intermediate in this reaction, was generated from UV irradiation of arabinoanhydrothiouridine(**46**) in the presence of hydrosulfide(Scheme 16). This is the first work indicating that both ribonucleoside and deoxyribonucleoside can be formed from the same prebiotically plausible precursor.



Scheme 16 Formation of deoxyribonucleosides from a ribonucleoside precursor *via* UV irradiation

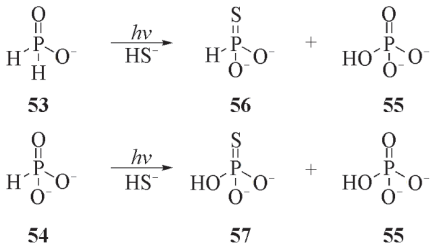
Because glycosidation reaction does not have stereoselectivity, this synthesis doesn't solve all problems discussed before. To deal with the stereochemistry, another pathway was reported by the same group[8]. As shown in Scheme 17, 8-mecaptoadenine(**47**) is a prebiotically plausible compound. It can be formed from thiourea(**20**) and 4,5,6-triaminopyrimidine, which is the product of hydrolysis of adenine under dry state. Under similar condition, 8-mecaptoadenine(**47**) reacts with α-anhydropyrimi-dines(**38** and **48**), undergoing a transglycosylation, giving N^9-8,2'-anhydro-thioadenosine(**49**) and N^7-8,2'-anhydro-thioadenosine(**50**). Interestingly, N^9-8,2'-anhydro-thioadenosine (**49**) can be reduced to 8-mecapto-2'-deoxyadenosine(**51**) under UV irradiation in the presence of bisulfite or sulfide and 2'-deoxyadenosine(**52**) if irradiate for a longer time, but N^7-8,2'-anhydro-thioadenosine **50** will decomposed under similar condition.



Scheme 17 Prebiotically route to deoxyadenosine including photoreaction step

7 Phosphorus Photooxidation

Phosphate is an important component in extend biology, and in prebiotic chemistry as well[37]. The large amount of phosphate in modern Earth would have been meteoritic delivery of mineral schreibersite[$(Fe,Ni)_3P$]. The reduced oxidation state phosphorus oxyacids(hypophosphite or phosphite), which are products of corrosion of schreibersite, have more water solubility of their metal salts[38,39]. While in modern life, phosphorus is in fully oxidized(V) oxidation state. It is difficult to image how phosphorus was oxidized under a reduced environment on early Earth before great oxidation event(GOE) occurred. This is the "phosphate problem" in prebiotic chemistry field[40,41]. Photooxidation is a potential way to oxidize phosphate to the highest oxidation state. As shown in Scheme 18, hypophosphite(**53**) and phosphite(**54**) are able to be oxidized under UV irradiation in the presence of hydrosulfide. Under this condition, not only phosphate(V, **55**) was detected in the system, but also some thiophosphite(**56**) and thiophosphate (**57**) were observed[42]. Thiophosphate(**57**) is a versatile prebiotic reagent[43].



Scheme 18 Prebiotically photooxidation of hypophosphite and phosphite

8 Conclusions

UV irradiation is a prebiotically plausible energy source on early Earth. It can produce hydrate electron as a reductant, and generate more oxidized compounds as oxidant (hydrosulfide radical, ferricyanide or cupric cyanide complex). Some of the essential building blocks for the origin of life like amino acids, (deoxy)nucleoside, phosphate and phospholipid are able to be produced under prebiotically plausible conditions including UV irradiation. All these works support that the UV irradiation condition must be involved in the prebiotic chemistry.

Acknowledgments

The author thanks all John Sutherland's group members for fruitful discussion.

References

[1] Rimmer P. B., Xu J., Thompson S. J., Gillen E., Sutherland J. D., Queloz D., *Science Advances*, **2018**, *4*, eaar3302

[2] Sasselov D. D., Grotzinger J. P., Sutherland J. D., *Science Advances,* **2020**, *6*, eaax3419

[3] Miller S. L., *Science*, **1953**, *117*, 528

[4] Oró J., Kimball A. P., *Archives of Biochemistry and Biophysics*, **1962**, *94*, 217

[5] Butlerow A., *CR Acad. Sci*., **1861**, *53*, 145

[6] Ruiz-Mirazo K., Briones C., de la Escosura A., *Chemical Reviews*, **2014**, *114*, 285

[7] Liu Z., Mariani A., Wu L., Ritson D., Folli A., Murphy D., Sutherland J., *Chemical Science*, **2018**, *9*, 7053

[8] Xu J., Chmela V., Green N. J., Russell D. A., Janicki M. J., Góra R. W., Szabla R., Bond A. D., Sutherland J. D., *Nature*, **2020**, *582*, 60

[9] Liu Z., Wu L. F., Bond A. D., Sutherland J. D., *Chemical Communication*, **2020**, https://doi.org/10.1039/D0CC05752E

[10] Ritson D., Sutherland J. D., *Nature Chemistry*, **2012**, *4*, 895

[11] Abou M. N., Ajram G., Rossi J. C., Boiteau L., Duvernay F., Pascal R., Danger G., *Chemistry: A European Journal*, **2017**, *23*, 7418

[12] Luther G. W., Theberge S. M., Rozan T. F., Rickard D., Rowlands C. C., Oldroyd A., *Environmental Science & Technology*, **2002**, *36*, 394

[13] Wirth T., *Über Thioformamid und Kohlenmonosulfid.*, ETH Zurich,

Zurich, **1910**

[14] Ritson D. J., Sutherland J. D., *Angewandte Chemie International Edition,* **2013**, *52*, 5845

[15] Reynolds J. E., *Journal of the Chemical Society*, **1869**, *22*, 1

[16] Lohrmann R., Orgel L. E., *Science*, **1968**, *161*, 64

[17] Ritson D. J., Sutherland J. D., *Journal of Molecular Evolution*, **2014**, *78*, 245

[18] Strecker A., *Justus Liebigs Annalen der Chemie*, **1854**, *91*, 349

[19] Patel B. H., Percivalle C., Ritson D. J., Duffy C. D., Sutherland J. D., *Nature Chemistry*, **2015**, *7*, 301

[20] Keefe A. D., Miller S. L., *Origins of Life and Evolution of the Biosphere*, **1996**, *26*, 111

[21] Shirom M., Stein G., *The Journal of Chemical Physics*, **1971**, *55*, 3372

[22] Marion G. M., Kargel J. S., Crowley J. K. Catling D. C., *Icarus*, **2013**, *225*, 342

[23] Halevy I., Zuber M. T., Schrag D. P., *Science*, **2007**, *318*, 1903

[24] Kaltenegger L., Sasselov D. D., *The Astrophysical Journal*, **2010**, *708*, 1162

[25] Xu J., Ritson D. J., Ranjan S., Todd Z. R., Sasselov D. D., Sutherland J. D., *Chemical Communications*, **2018**, *54*, 5566

[26] Powner M. W., Gerland B., Sutherland J. D., *Nature*, **2009**, *459*, 239

[27] Steinman G., Lemmon R. M., Calvin M., *Science*, **1965**, *147*, 1574

[28] Toner J. D., Catling D. C., *Geochimica et Cosmochimica Acta*, **2019**, *260*, 124

[29] Li L., Prywes N., Tam C. P., O'Flaherty D. K., Lelyveld V. S., Izgu E. C., Pal A., Szostak J. W., *Journal of the American Chemical Society*, **2017**, *139*, 1810

[30] Walton T., Zhang W., Li L., Tam C. P., Szostak J. W., *Angewandte Chemie International Edition,* **2019**, *131*, 10926

[31] Becker S., Thoma I., Deutsch A., Gehrke T., Mayer P., Zipse H., Carell T., *Science*, **2016**, 352, 833

[32] Kim H. J., Kim J., *Astrobiology*, **2019**, *19*, 669

[33] Becker S., Feldmann J., Wiedemann S., Okamura H., Schneider C., Iwan K., Crisp A., Rossa M., Amatov T., Carell T., *Science*, **2019**, *366*, 76

[34] Hein J. E., Tse E., Blackmond D. G., *Nature Chemistry*, **2011**, *3*, 704

[35] Xu J., Tsanakopoulou M., Magnani C. J., Szabla R., Sponer J. E., Sponer J., Gora R. W., Sutherland J. D., *Nature Chemistry*, **2017**, *9*, 303

[36] Xu J., Green N. J., Gibard C., Krishnamurthy R., Sutherland J. D., *Nature Chemistry*, **2019**, *11*, 457

[37] Liu Z., Rossi J. C., Pascal R., *Life*, **2019**, *9*, 26

[38] Pasek M. A., Lauretta D. S., *Astrobiology*, **2005**, *5*, 515

[39] Bryant D. E., Kee T. P., *Chemcal Communications*, **2006**, *22*, 2344

[40] Gulick A., *American Scientist*, **1955**, *43*, 479

[41] Gulick A., *Annals of the New York Academy of Sciences*, **1957**, *69*, 309

[42] Ritson D. J., Mojzsis S. J., Sutherland J. D., *Nature Geoscience,* **2020**, *13*, 344

[43] Ritson D. J., Xu J., Sutherland J. D., *Synlett.*, **2017**, *28*, 64