Prebiotic Systems Chemistry

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Synthesis of Aldehydic Ribonucleotide and Amino Acid Precursors by Photoredox Chemistry**

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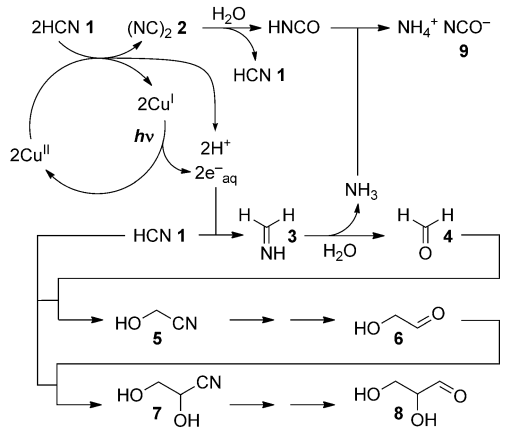
In continuing studies aimed at understanding the prebiotic origin of RNA, we recently demonstrated a Kiliani–Fischer-type synthesis of simple sugars from hydrogen cyanide **1** using photoredox cycling of cyanocuprates (Scheme 1).[1]



Scheme 1. Photoredox systems chemistry of hydrogen cyanide **1**, with **1** also acting as the ultimate reductant.

The photoredox cycle oxidizes **1** to cyanogen **2** and generates associated reducing power in the form of protons and hydrated electrons, which reduce further **1** to formaldehyde imine **3**. Hydrolysis of **3** to formaldehyde **4** is then followed by addition of **1** to give glycolonitrile **5**. Iteration of this process results in the sequential production of glycolaldehyde **6**, its cyanohydrin **7**, and glyceraldehyde **8**. Sugars **6** and **8** are required by our recent synthesis of pyrimidine ribonucleotides as starting materials,[2] but there is a catch. The concurrent hydrolysis of cyanogen **2** produces cyanate **9**, which irreversibly traps the sugars **6** and **8** as cyclic adducts. We wondered if the free sugars could be obtained by a variant of the process in which something other than **1** served as the ultimate reductant in the system, and report herein our findings with hydrogen sulfide (H_2S, **10**) fulfilling that role.

Although our previous Kiliani–Fischer-type synthesis started with hydrogen cyanide **1** and proceeded through glycolonitrile **5**, compound **5** itself is probably a more plausible starting point for the synthesis. This is because **1** produced in the atmosphere, (for example through impact shock[3]), would have been rained into bodies of ground water along with formaldehyde **4** (produced in the upper atmosphere by photoreduction of CO_2[4]) with which it would have reacted to give **5**. Accordingly, in this work we initially explored the copper-catalyzed photoreduction of **5** with **10** in aqueous solution (containing 10% D_2O to allow direct analysis by NMR spectroscopy). As phosphate is a reagent in a later stage of our ribonucleotide synthesis,[2] we incorporated it into the system from the outset wherein it functioned as a pH buffer. Mixing of this solution with solid copper(I) cyanide (10 mol% with respect to **5**) resulted in the formation of a fine black powdery precipitate, and a stirred suspension of this powder in the solution was irradiated at 254 nm in a quartz cuvette. Samples were withdrawn over time and analyzed by ^{1}H NMR (with HOD suppression), or, if [$^{13}C_2$]-labeled **5** was used, ^{13}C NMR spectroscopy. After 2 h of irradiation, NMR analysis (Figure 1 and Supporting Information) showed that efficient reductive conversion of glycolonitrile **5** to glycolaldehyde **6** had taken place (with **6** being detected as its hydrate **6**(h) in 42% yield in solution). However, other reduction products, namely acetonitrile **11** and acetaldehyde **12**,[5] were also present (as confirmed by sample spiking) that we had not observed in our earlier work. Furthermore, some cyanide had been abstracted from **5** and converted into thiocyanate **13**,[6] leaving formaldehyde **4** present in the form of its hydrate **4**(h) and hydrogen sulfide addition product **14**. The most obvious pathway to acetaldehyde **12** appeared to be deoxygenation[7] of glycolaldehyde **6** (Scheme 2), and to investigate this we irradiated a system comprising copper(I) cyanide and a solution of **6**, sodium phosphate, and **10**. Conversion into **12** occurred, but was inefficient unless we additionally included thiocyanate **13** in the system. This suggests that **13** in some way enables more efficient redox cycling, and we note in this regard that copper(I) thiocyanate is a p-type semiconductor.[8]

Although the formation of glycolaldehyde **6** is important in the context of ribonucleotide abiogenesis, the formation of acetaldehyde **12** alongside **6** and formaldehyde **4** is particularly noteworthy in the context of amino acid abiogenesis as these aldehydes are the Strecker precursors of alanine, serine, and glycine.[9] Thus hints of a linked origin of ribonucleotides and amino acids began to emerge.

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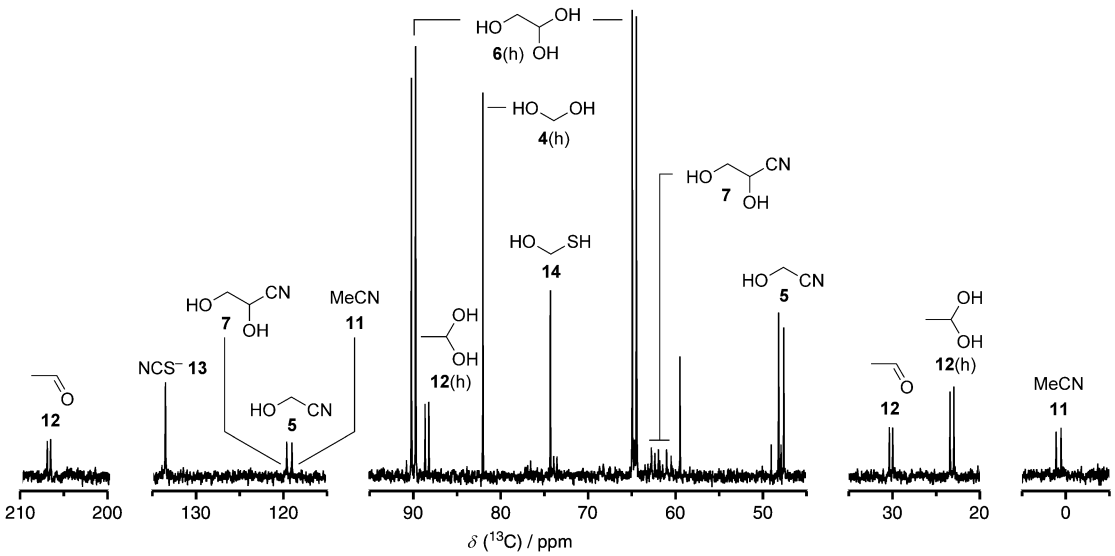
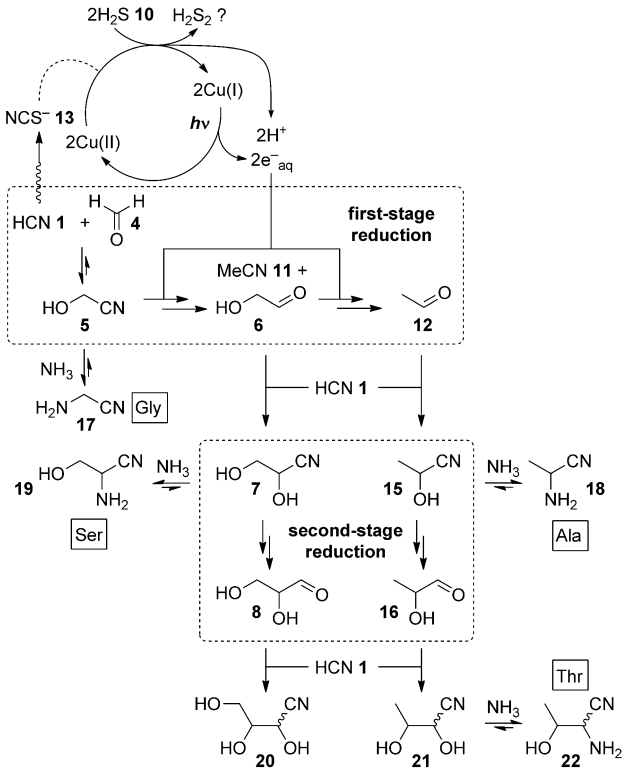


Figure 1. ^{13}C NMR spectrum of the products of irradiation (2 h, pH 7) of a system made by mixing a solution of [$^{13}C_2$]-labeled glycolonitrile **5** (10 mM), hydrogen sulfide **10** (30 mM), and sodium phosphate (33 mM) with solid copper(I) cyanide (10 mol% with respect to **5**).



Scheme 2. Photoredox systems chemistry of glycolonitrile **5**, with hydrogen sulfide **10** as the ultimate reductant.

Addition of hydrogen cyanide **1** and ammonia to such a system would convert the aldehydes into the corresponding cyanohydrins and aminonitrile Strecker intermediates. Among other things, the ratio of cyanohydrin to aminonitrile would depend on the parent aldehyde and the amount of added ammonia. Although we are ultimately most interested in mixed systems, we have first explored simpler variants in which ammonia is either absent, or in excess.

In the absence of added ammonia, cyanohydrins **7** and **15** produced by rain-in of hydrogen cyanide **1** into the system have the potential to be further reduced in a second stage of photoredox chemistry (Scheme 2).

We had considered the formation of **7** in this way, and envisaged its subsequent reduction as a way of producing glyceraldehyde **8** in the same system as glycolaldehyde **6**, but at a later juncture. However, we had not previously considered the formation and reduction of acetaldehyde cyanohydrin **15**. We thus prepared separate samples of **7** and **15** from the parent aldehydes and hydrogen cyanide **1**, and subjected them to the photoreduction conditions (Supporting Information). After 2 h of irradiation of a system containing glycolaldehyde cyanohydrin **7**, glyceraldehyde **8** was obtained in 17% yield. The corresponding system based on acetaldehyde cyanohydrin **15** furnished lactaldehyde **16**, which is the Strecker precursor of (*allo*-)threonine, in 19% yield.

In the presence of added ammonia, the cyanohydrins produced by rain-in of hydrogen cyanide **1** would be expected to undergo slow conversion to aminonitriles. Addition of **1** and excess ammonia to the system after 4 h of first-stage reduction resulted in the smooth conversion of the aldehydes **4**, **12**, and **6** into the corresponding aminonitriles **17**, **18**, and **19** over a period of days to weeks (Supporting Information). A second rain-in of hydrogen cyanide **1** after the second-stage reduction would convert some of the glyceraldehyde **8** and lactaldehyde **16** into the cyanohydrins **20** and **21** and thence to aminonitriles if sufficient ammonia were still in the system, or if more was added. In support of this, when we added **1** and ammonia to the (second-stage) photoreduction products of acetaldehyde cyanohydrin **15**, lactaldehyde **16** was smoothly converted via cyanohydrin **21** to (*allo*-)threonine Strecker intermediate aminonitrile **22** (Supporting Information).

If the first-stage reduction were to proceed to completion, all of the glycolaldehyde **6** needed to make ribonucleotides and serine (via **7** and **19**) would instead be converted into acetaldehyde **12**. We found that **12** was the major product

after 6 h irradiation thus 2–4 h would seem to be synthetically most productive from a systems perspective. Not knowing the UV light intensity on the early earth means that we cannot convert our experimental irradiation times into real time spans, but diurnal cycling and/or weather effects mean that illumination periods corresponding to 2–4 of our hours are plausible. Addition of hydrogen cyanide **1** is needed to make cyanohydrins for the second-stage reduction as well as for aminonitrile synthesis. If the rain-in of **1** occurred during a dark period and was accompanied by the addition of cyanamide, with which glycolaldehyde **6** also reacts (to make a key ribonucleotide intermediate), then second-stage reduction of the cyanohydrins **7** and **15** giving **8** and **16** should leave this ribonucleotide intermediate and any aminonitriles unchanged (the nitrile carbon atoms of aminonitriles endure less electron-withdrawal than those of cyanohydrins, and are thus considerably less susceptible to reduction). Subsequent addition of **1** and ammonia (or equilibration with that reversibly contained in other aminonitriles) would then additionally generate the aminonitrile **22**.

Thus the abiogenesis of the simple sugars required to make RNA appears to be closely related to the abiogenesis of at least four of the proteinogenic amino acids of extant biology. This relationship suggests that the systems described herein have a real etiological relevance, and this has prompted us to consider geochemical scenarios that could provide appropriate conditions and starting materials.

As well as being concentrated by trapping through reaction with formaldehyde **4**, cyanide can also be concentrated through complexation to ferrous ions giving ferrocyanide.[10] Thermal decomposition of ferrocyanide gives different products depending on the counter cation.[11,12] Sodium and potassium ferrocyanide give the corresponding alkali metal cyanide salts MCN,[11] magnesium ferrocyanide gives magnesium nitride Mg_3N_2,[12] and calcium ferrocyanide gives calcium cyanamide $CaCN_2$.[12] Rehydration of the residue remaining after strong heating of mixed ferrocyanide salts can thus give solutions containing cyanide, ammonia, and cyanamide, which are all needed for the chemistry described herein or for later stages of ribonucleotide synthesis.[2] The reductant hydrogen sulfide **10** and the copper(I) cyanide based catalyst could be produced by dissolution of a copper sulfide mineral in cyanide solution,[13] additional **10** being produced by similar dissolution of ferrous sulfide.[14] At this stage we do not attempt to describe a more detailed scenario other than to point out that the RNA and amino acid syntheses could take place in one mixed system or in several closely related systems which then become mixed. Finally, we note that the chemistry we describe, utilizing the reducing power of hydrogen sulfide **10** to generate multiple (proto)-biomolecules ultimately from C_1 feedstock(s), is reminiscent of the general scenario put forward by Wächtershäuser.[15]

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[5] After 6 h irradiation, the system had simplified, and acetaldehyde **12** and formaldehyde **4** were the predominant products. The apparent yield of **12** at this point was 15% (as measured by ^{1}H NMR integration relative to an added standard of pentaerythritol) based on starting glycolonitrile **5**. The production of **4** also consumes **5** but the amount of **4** could not be quantitated by integration owing to overlap with the HOD signal. We did not quantitate products by another method because the system generates multiple biomolecule precursors, so the yield of any particular product has less significance than it does in conventional synthetic chemistry, it being unclear what the ideal product distribution should be: the compositional ratio of **5**/**6**/**11**/**12** changes from 14:41:8:37 after 2 h to 0:15:10:75 after 4 h, and 0:0:12:88 after 6 h.
[6] In our previous work using hydrogen cyanide **1** as substrate and reductant, cyanate was formed by hydrolysis of cyanogen.[1] By analogy therefore, it is possible that in this work, thiocyanate **13** is formed by (copper-catalyzed) thiolysis of cyanogen. Alternatively, **13** could result from the nucleophilic attack of cyanide ion on the terminal sulfur atom of an oligosulfide formed by oxidation of H_2S **10**.
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