Prebiotic Chemistry: Common Origins of Glycerol, Amino Acids, and Pyrimidines, and Cosmic Origin of Nature's Enantiomeric Excess of Amino Acids

Stephen Byrne
Senior Freshman
Science

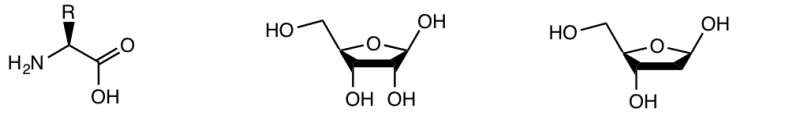
The origin of life on earth remains one of the greatest mysteries in scientific enquiry to date. Recent experiments support a model in which many fundamental biomolecules share a common chemical origin are a recent and major breakthrough in the field of prebiotic chemistry. The results of the experiments could direct researchers in the field to take a more systems chemistry approach. This is where complex mixtures of reactants and products are studied. It is opposed to the approach of assuming biomolecules originated individually from mutually incompatible syntheses. Though the model merely explains the potential origin of precursors and a fraction of amino acids, it does provide clues that could direct researches in the direction of a more encompassing model. Results of various experiments have pointed towards a plausible cosmic origin of the initial enantiomeric excess of amino acids on the prebiotic earth. A proposed cosmic model of the origin of enantiomeric excess of amino acids via the action of circularly-polarised light will be explored. The common origin of biomolecules, and the cosmic origin of enantiomeric excess have minor shortfalls. However, both are major developments in the field of prebiotic chemistry.

Introduction

The earth is approximately 4.55 x 10^9 years old (Patterson, 1956). Life originated nearly 3.8 x 10^9 years ago (Mojzsis *et al.,* 1996). Research into the origin of life seeks to discover what occurred in that first three quarters of a billion years that led to the emergence of cellular life. The physical and chemical conditions that existed on the prebiotic earth pose a dilemma for researchers. Researchers have to work with a multitude of different plausible physical and chemical conditions because the conditions on the early earth are not well understood. This makes it difficult to create a plausible model. A viable model must elucidate how fundamental biological molecules such as lipid bilayers, RNA/DNA, and amino acids originated. Additionally, the chronological order in which these fundamental components arose must be accounted for. Crucially, a successful model must be able to explain the transition from an abiotic world of simple racemic molecules, to the world where complex homochiral organic polymers compose cellular life.

Amino acids are quite easy to synthesise under prebiotically plausible conditions (Miller, 1953; Patel *et al.,* 2015). Ribonucleotides on the other hand are difficult to prepare (Orgel, 2004). The reaction of ribose with nucleobases is either inefficient or non-existent (Fuller *et al.,* 1972; Orgel, 2004). Lipids could have originated from complex metabolic pathways (Ourisson *et al.,* 2005), Lombard *et al.,* 2012). The major problem with all of these proposed chemical origins is that they are different. Patel *et al.,* (2015) have shown that this need not be the case and that these biomolecules may share a common chemical origin. Their findings link ribonucleotides, glycerol, and amino acids to a common chemical origin in what is referred to as a cyanosulfidic protometabolism.

Living things are chiral. Life is composed of polymers, and the monomers that compose those polymers are chiral. These monomers are enantiomerically pure. The origin of this "homochirality" is a mystery, and an important aspect prebiotic chemistry research. Amino acids are only found in the levorotatory form (Figure 1). Ribose and deoxyribose are only found in the dextrorotatory form (Figure 1). How such an asymmetry arose in our universe is perplexing. There are many plausible explanations for this imbalance. One model of the origin of nature's enantiomeric excess (ee) [ee = (R − S)/(R + S), where R and S are the concentrations of both enantiomers] posits a cosmic origin in which "chiral" photons induce an ee of amino acids. A model explaining the origin of a small initial ee has set the stage for models that could explain an enhanced ee via amplification processes analogous to natural selection (Klussmann *et al.,* 2006; Frank, 1953; Breslow *et al.,* 2006).



levorotatory amino acid dextrorotatory ribose dextrorotatory deoxyribose

Figure 1. *Schematic view homochiral biomolecules.*

Common Origin of Activated Pyrimidines, Amino Acids, and Glycerol

Patel *et al.,* (2015) have showed that various biomolecules could share a common chemical origin. This was merely a conceptual possibility, and had not been shown until now. (Miller, 1953), Oró's synthesis of nucelobases (Oró, 1960), and Butlerow's formose reaction (Butlerow, 1861). These syntheses are mutually incompatible. This proves problematic when trying to progress towards nucleotides, and a mix of nucleotides and α-amino acids. Assuming that these syntheses are how biomolecules arose on the prebiotic earth has led to many in the field operating under the assumption that one system preceded another. However, Patel *et al.,* (2015) presented syntheses of these biomolecules that are mutually compatible. They refer to it as a cyanosulfidic protometabolism, where lipid precursors (glycerol-1-phosphate), α-amino acids (e.g. glycine, threonine, valine), and ribonucleotides (β-ribocytidine-2′, 3′-cyclic phosphate, and uridine-2′, 3′-cyclic phosphate) all share a common chemical origin. Figure 2a shows part of the reaction network that relates the origin of the biomolecules mentioned. The chemistry of this network is based upon previous discoveries in the field (Powner *et al.,* 2009; Ritson *et al.,* 2012; Patel *et al.,* 2015). The network is a breakthrough in the field of prebiotic chemistry. It demonstrates the viability and feasibility of the hypothesis that biomonomers arose from mutually compatible syntheses.

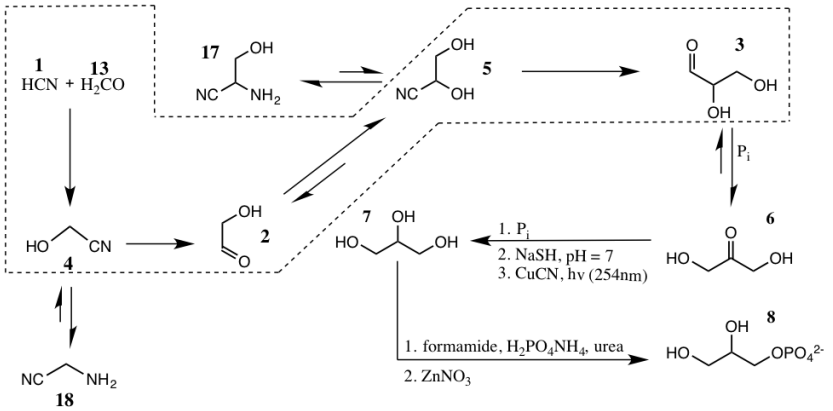


Figure 2a. *Schematic representation of cyanosulfidic protometabolism reaction network. .Pi (NaH2PO4). Source of Cu(I) for pathway in dashed lines: CuCN. Note: solvent is H2O in all reactions. Adapted from Patel et al., (2015)*

Part of the reaction network developed by Patel *et al.,* (2015) is shown in Figure 2a. A central feature of the network depicted in Figure 2a is the synthesis of glyceraldehyde **(3)** from the feedstock molecules **(1)** and **(13)** (dashed lines). **1** is thought to have formed on the early earth via the high temperature impact of carbonaceous meteorites with the earth (Kurosawa *et al.,* 2013). **1** and **3** have been detected on the LEMMON and ISON comets (Cordiner *et al.,* 2014). Analysis of the comet 67P/Churyumov-Gerasimenko via mass spectrometry by the Philae lander revealed the presence of H_2O and **1** (Goesmann *et al.,* 2015) The synthesis of 2-hydroxyaldehyde **(2)** and **3** proceeds by a Fischer-Kiliani-type homologation of **1** via Cu(I)-Cu(II) photochemistry to catalyse the reaction (Ritson *et al.,* 2013; Ritson *et al.,* 2014). The synthesis of **3** is a central feature because intermediates and the product of the pathway feed in to other pathways of the network. For instance, with hydrogen sulfide as a reducing agent 2-hydroxyacetonitrile **(4)** and 2,3-dihydroxypropanenitrile **(5)** are converted to the Strecker precursors of glycine **(18)** and serine **(17)**, respectively (Patel *et al.,* 2015). The Strecker precursors of threonine and alanine are produced as a consequence of the pathway to **3** (Patel *et al.,* 2015). The synthesis of **3** is the starting point for the preparation of glycerol **(7)**: depicted in Figure 2a. **3** interconverts to its more stable isomer dihydroxyacetone **(6)** (59% yield). **6** is then reduced to **7** (34% yield), which reacts with NaH_2PO_4 (Pi) to produce glycerol-1-phosphate **(8)** (31% yield) (Patel *et al.,* 2015). **8** is a lipid precursor. Cell membranes are the primary means of compartmentalization for organisms, and the major components of these cell membranes are esters and ethers of **8** (Lombard *et al.,* 2012). Most notably, intermediates of the synthetic pathway to **3** feed in to a synthetic route towards β-ribocytidine-2′,3′-cyclic

phosphate (9) and β-ribouridine-2′,3′-cyclic phosphate **(10)** (Powner *et al.,* 2009): Illustrated in Figure 2b. This pathway is a strong point of the model. It manages to integrate the prebiotically plausible synthetic pathway to activated pyrimidines developed by Powner *et al.,* (2009) by including **2**, **3**, and Pi (pathway in Figure 2a). **2** undergoes a condensation reaction with **12** to produce oxazol-2-amine **(11)**. **12** is also important because it undergoes hydrolysis to produce urea, which is incorporated into subsequent reactions. The final products are the activated pyrimidines **9** (96% yield), and **10.** UV irradiation of **9** resulted in a solution of an approximately 1:1 ratio of **10:9**. UV irradiation is prebiotically plausible because of the prebiotic earth's lack of O_3 to shield the earth's surface from UV radiation. As can be seen from the synthesis of **6, 7, 8,** and **9**, a major strength of the model is the relatively high yields of biologically relevant molecules, which makes this a kinetically feasible model.

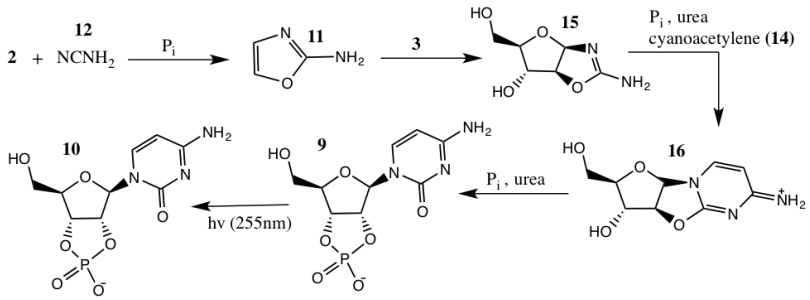


Figure 2b. *Prebiotically plausible synthetic pathway to activated pyrimidines. Adapted from Powner et al., (2009)*

The network requires different conditions for different reactions to progress. Patel *et al.,* (2015) proposed a geochemical model to account for this. It was suggested that different conditions could have existed along a river with tributaries and confluences. UV radiation from the sun could have allowed photochemical reactions to occur. A tributary could have provided isolation, while a confluence could have provided a way of mixing products of different reactions. The model is conceptually simple, but is difficult to recreate. Each synthesis was carried out step-wise with a lot of interference by the researches. Interference with experiments of this nature must be minimized (Bracher, 2015). The prebiotic earth produced life through geochemical processes, and experiments must mimic geochemical scenarios if they are to be successful in elucidating the origin of life. No precautions were taken to carry out the reactions under deoxygenated conditions. In the synthesis of **6** from **3** (50 mM), glycolate and formate were formed due to the presence of athmospheric O_2. These by-products were recognized and dismissed

as by-products that "would not be produced prebiotically because of the lack of oxygen in the atmosphere of the early Earth". These by-products along with O_2 could have influenced the outcome of the experiments. While it may be negligible, it would be good practice to repeat the experiments under deoxygenated conditions. The model is incomplete. It does not incorporate the purines and thymine, and various sulphur and aromatic amino acids e.g. cysteine and phenylalinine. This highlights the need to consider sulfur and aromatic reagents in future research. It is important to note that while a lot of the reaction network presented by Patel *et al.,* (2015) was not explored, the core aspects were emphasized i.e. the integration of various syntheses, the production of fundamental biomolecules, how it fits in to the geochemical and geophysical conditions of the prebiotic earth, and what could be done to improve the model.

Enantiomeric Excess of Amino Acids

Theories concerning the origin of homochirality can be separated into two categories: abiotic and biotic. A biotic origin of homochirality envisions a scenario in which homochirality comes about as a result of selection in early biological evolution. This idea is unlikely, as racemic biopolymers do not perform their function (Joyce *et al.,* 1984). This suggests that an abiotic origin of homochirality in biomolecules is more likely. Chemists have looked at meteorites in order to find a possible abiotic source of the enantiomeric excess (ee) of α-amino acids. Pizzarello *et al.,* (2000) showed that some α-amino acids in meteorites had an ee of (-)-amino acids of 1.0-9.2%. Of the amino acids that were found, valine and alanine were ubiquitous. Interestingly, both of these amino acids are included in the cyanosulfidic protometabolism (Patel *et al.,* 2015). It implies the possibility that the prebiotic earth's source of amino acids came at least in part from meteorites. Additionally, it implies that some sort of amplification process increased the ee, as the observed ee is too distant from homochirality.

A model of the cosmic origin of the ee of amino acids on earth is based on UV-circularly polarized light (UV-cpl). Interestingly, Pizarello *et al.,* (2000) suggest that the origin of the ee of valine and alanine on the Murchison meteorite was due to UV-CPL produced by a neutron star. Circularly polarized light is where the electric field vector describing the electromagnetic wave rotates clockwise (R-CPL) or anticlockwise (L-CPL) as it propagates through space from the perspective of the source. Experimental evidence shows that it is produced in space (Bailey *et al.,* 1998). There are three ways in which UV-cpl could have produced an ee in meteorites: photolysis, isomerization, or synthesis. Isomerization is where (R/L)-UV-cpl favors the conversion of one enantiomer in the racemate to its opposite. This is unlikely as there is little experimental evidence to support it (Inuoe *et al.,* 1996; Inuoe, 1992; Rau, 1983). Synthesis is where (R/L)-UV-cpl favors the production of one enantiomer over another. It has been shown that UV-cpl can induce asymmetry in products that are thought to be prebiotic gases (Takano *et al.,* 2007; Nuevo *et al.,* 2006; Marcellus *et al.,* 2007). The strongest argument rests with photolysis. This is the preferential destruction of one enantiomer induced by UV-

cpl. This was developed through quantum mechanics (Rosenfeld, 1929), which is beyond the scope of this review. Researchers have used this process for years as a way of achieving ee (Balavoine *et al.,* 1974; Nordén, 1977; Flores *et al.,* 1977; Nahon *et al.,* 2004; Meierhenrich *et al.,* 2005; Bailey *et al.,* 1998). Figure 3 depicts the results of an experiment by Flores *et al.,* (1977) that proves an ee of leucine can be produced via photolysis.

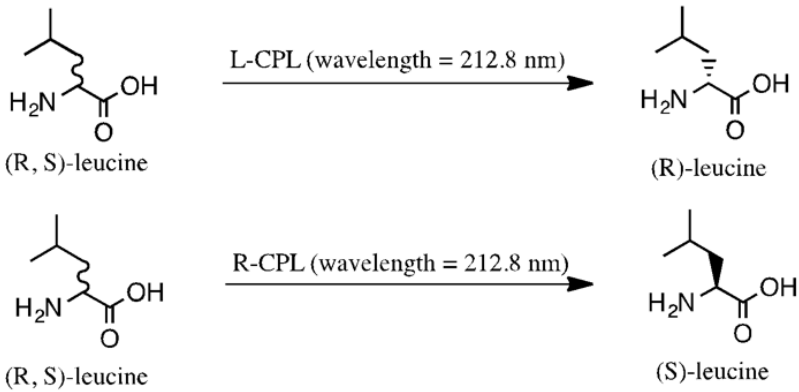


Figure 3. *Two racemates of leucine were treated with ultraviolet CPL (Right (R) or left (L)) When a racemate of leucine was treated with L-CPL an ee of (R)-leucine was produced. When another racemate was treated with R-CPL an ee of (S)-leucine was produced. Adapted from Flores et al., 1977*

The experiments of Pizzarello *et al.,* (2000), Bailey *et al.,* (1998), and Flores *et al.,* (1977) open up the possibility that the meteorites supplied the prebiotic earth with amino acids. One could argue that amino acids either came from meteorites or a synthesis of the sort proposed by Miller *et al.,* (1953) and Patel *et al.,* (2015). It is likely that it was both. Meteorites could have provided an initial ee, which combined with the already abundant amino acids from the synthesis proposed by Patel *et al.,* (2015). If UV-CPL did induce an ee in the prebiotic earth's source of amino acids, then the findings of Pizzarello *et al.,* (2000) suggest that the initial ee was only small. Life exhibits homochirality i.e. 100% ee. In order to explain this, an amplification process analogous to natural selection must be provoked (Klussmann *et al.,* 2006; Frank, 1953; Breslow & Levine 2006). This aspect of the problem is covered in a thorough review by Ruiz-Mirazo *et al.,* (2014). The methodology of Bailey *et al.,* (1998) and Pizzarello *et al.,* (2000) was sound. The only criticism is that the experiment carried out by Flores *et al.,* (1977) was conducted under conditions unlike the conditions present in a meteorite travelling in space.

To conclude that UV-cpl would produce such an ee under the conditions present on a meteorite would not be justified. To reach such a conclusion one would need to carry out the same experiment under conditions comparable to that of a meteorite travelling through the hostile environment of space. Additionally, only leucine was considered. The other amino acids were ignored. All 20 of the common amino acids should be considered in future experiments.

Conclusions

Patel *et al.,* (2015) have shown us that glycerol, various amino acids, and two activated pyrimidines are related through a network involving reagents such as cyanide, phosphate, and hydrogen sulphide. The model is a breakthrough and will likely guide future research. The geochemical scenario is prebiotically plausible. Subsequent research should aim to uncover a prebiotically plausible synthetic route to the purines, thymine, and the amino acids not included by Patel *et al.,* (2015). Future investigations should be carried out under deoxygenated conditions. More geochemical scenarios should be considered, and some effort needs to be made to experimentally justify the geochemical models. Regardless of its minor shortfalls, the cyanosulfidic protometabolism model is an important development in the field of prebiotic chemistry. Its novel syntheses and elaborate geochemical considerations make it a major development in the field. It is very likely to inspire future experiments, and bring us closer to a model of the origin of life on earth.

Pizarello *et al.,* (2000) have shown that ee can arise in abiotic environments. Bailey *et al.,* (1998) have shown a possible cosmic origin of nature's ee. Flores *et al.,* (1977) showed that UV-cpl can induce the enantioenrichment of a racemic leucine. These findings suggest that the earth's initial source of ee in amino acids could have been meteorites. This provides a possible starting point for subsequent research, which should aim to explain how a slight ee can be amplified under prebiotically plausible conditions. The findings of Flores *et al.,* (1977) may not be enough to conclude that UV-cpl produced the initial ee of amino acids supplied by meteorites to the earth. Only leucine was considered, more amino acids must be considered in future photolysis induced enantioenrichment experiments. The findings of Pizarello *et al.,* (2000) and Patel *et al.,* (2015) could lay the foundations for future experiments. These experiments should look to combine a racemic system with a system containing a small ee to produce a homochiral system analogous to life.

Prebiotic chemistry research has evolved a lot since Miller (1953) discovered that biomolecules could be produced under prebiotically plausible conditions. Patel *et al.,* (2015) have linked various biomolecules to a plausible common chemical origin. The discoveries of Pizzarello *et al.,* (2000), Flores *et al.,* (1977), and Bailey *et al.,* (1998) suggest that the earth's initial source ee could be from meteorites.

The links between the various fields of research in prebiotic chemistry are being elucidated as more discoveries are made. Once plausible routes to the synthesis of fundamental biomoleclues and their enantiopurification are uncovered, researchers will be equipped to explain the transition into the "RNA world". This would be a considerable step towards explaining the origin of life on earth.

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