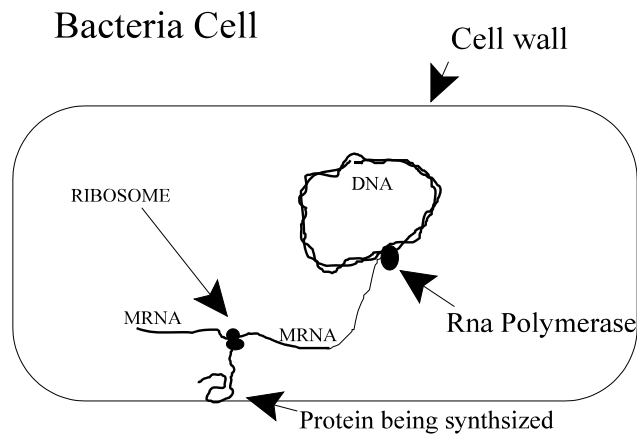


Chapter 9: Prebiotic Synthesis of RNA, DNA and Peptides

Naturalistic theories concerning life's origin began to take shape in 1953. Watson and Crick unraveled the structure of DNA, and Stanley Miller performed an experiment showing that amino acids can be produced in a spark chamber. Most scientists of the day assumed that the mystery of life's origin would be solved in a few years.

The early pioneers in this field realized that a complete living organism, like the bacteria in figure 9.1, could not spontaneously appear in a spark chamber or in any other environment governed by purely naturalistic laws. The pioneers needed the first form of life to be simpler than any living thing that is present on earth today.

Figure 9.1: Information Transfer in a Bacteria Cell



Initial theories hypothesized that the first living thing was a protein. These theories seemed reasonable at the time because many of the building blocks of proteins, amino acids, are easily synthesized under plausible prebiotic conditions. Because proteins regulate and control almost all of the activities necessary for life, the living protein theory quickly gained widespread acceptance, but soon scientists realized that there was a major flaw with the protein theory.

Proteins cannot self replicate, so the first living protein would not be able to reproduce itself, and without replication there can be no natural selection; therefore, the first living protein would have no way to evolve.

This issue led to the demise of the protein theory. In its place, emerged the RNA theory. This theory gained substantial momentum when it was found that just like proteins some RNA molecules can catalyze chemical reactions. Recently this theory has also fallen out of favor because it has its own set of problems which will be discussed later. Today the most popular theory involves a self replicating pre-RNA molecule.

Self replicating molecules are probably not the best theory to pursue, because such molecules cannot reproduce for any length of time without running into serious problems with the second law. Nevertheless, many researchers in the origins field are absolutely sure that the first living thing was a self replicating chemical, and their point of view is understandable. There is simply no chance that a complete bacterium spontaneously formed from the chemicals in a puddle four billion years ago. In many ways, a self replicating molecule that violates the second law is a better choice.

Nevertheless, the second law should not be casually dismissed because its existence explains why investigators have not been able to create a self replicating molecule in the lab. Unless a self replicator has the knowledge and ability to harness the power of sunlight (or some other abundant energy source) and use this energy to drive its own replication, then its lifetime will be short lived and its existence forbidden by the laws of physics.

The origin of self replication requires a solution to five problems:

- Chemical evolution must create a protein, an RNA molecule or an RNA like molecule.
- This molecule must possess the molecular knowledge that enables self replication.
- It must also be able to implement this knowledge.
- The molecule must be able to harness an energy source to do useful work.
- The first self replicator must be able to synthesize any chemicals lacking from its surroundings that it needs to self replicate.

Experiments investigating the origin of life have for the most part ignored the last two issues. This is understandable because until a molecule that can at least replicate itself for a little while can be found, there is no need to try to find one that can replicate itself indefinitely. This chapter will investigate the prebiotic synthesis of RNA and proteins. The next chapter will investigate self replication. The pioneers in chemical evolution expected to show that the primordial ocean was full of biological molecules. These researchers suggested that the early atmosphere contained no free oxygen, and that under these conditions, the required biological precursors should be plentiful. The remainder of this chapter will evaluate the validity of this hypothesis.

It is extremely difficult to synthesize biological molecules under plausible prebiotic conditions, and today this difficulty has led most to conclude that the primitive ocean contained a very limited supply of biological precursors. This finding does not mean that the primordial soup did not exist. It does mean that the primitive ocean was not the primordial soup because any relevant molecules in it would be too dilute.^{4,11,18}

It is possible to imagine environments that will concentrate biological precursors, but this leads to further problems. It limits the soup in such a way that the conditions necessary for its existence rarely exist and leads to the perhaps alarming conclusion that even given 5 billion years the soup may not have existed.

Zero Tries

The goal of this chapter and the next is to show that given 5 billion years and an almost unlimited source of energy, the probability of creating a protein or an RNA molecule is vanishingly small. Furthermore, the probability that the molecule so created contains the knowledge needed to self replicate is also vanishingly small. The chance of success is given by multiplying these two vanishingly small numbers. The trapped scientist in figures 9.2 and 9.3 helps illustrate this concept. With zero tries, even a short combination eludes the scientist (figure 9.2), and unfortunately, the required combination for self replication whether protein or RNA is quite long (figure 9.3).

Figure 9.2: Zero Tries

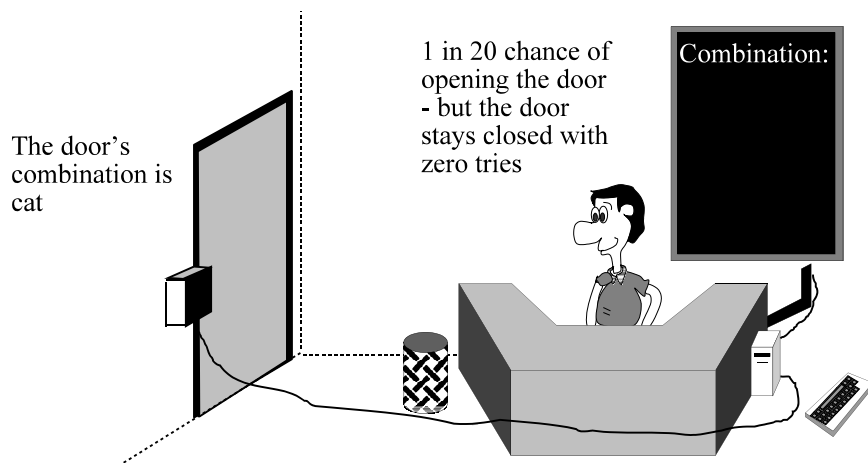
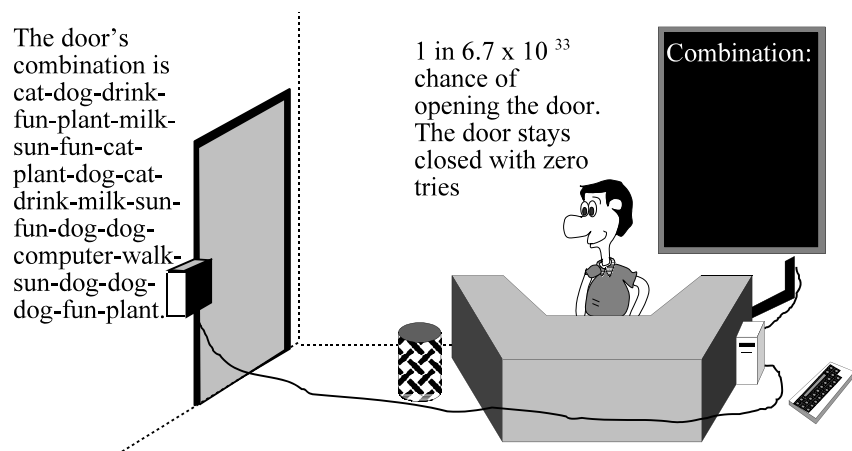


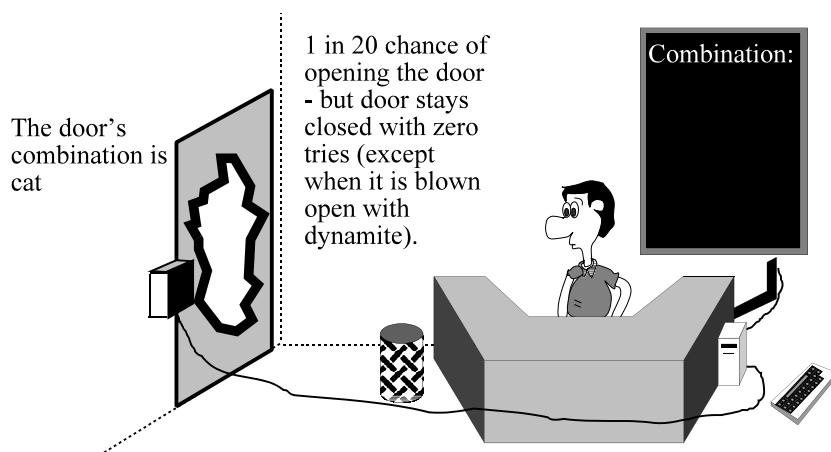
Figure 9.3: Zero Tries with Long Combination



Investigator Interference

In figure 9.2, the scientist is not cooperating. He refuses to play the game. He enters no words into the computer, so he accumulates no tries. The researchers are very unhappy with these results. So they blast the door with dynamite. This of course opens the door (figure 9.4). The researchers then conclude that given 5 billion years the door will open. Figure 9.4 is an obvious example of investigator interference.

Figure 9.4: Investigator Interference



The concept of investigator interference was first introduced by Thaxton et al. in [The Mystery of life's Origin: Reassessing Current Theories](#). In this book, the authors suggest that some interference is warranted. Scientists cannot conduct experiments that last for one billion years. So interference is useful in that it speeds up the process of evolution, and to be fair, the interference is a great learning tool because it allows scientists to rule out extremely unlikely scenarios. Thaxton also concludes that in many cases the interference is excessive.

While interference is a good idea because it helps scientists learn, it can also be very misleading. The scientist did not open the door in figure 9.4. The dynamite opened the door. Any conclusion that given time, the scientist will open the door is completely unfounded. This chapter will introduce many examples of interference. Readers should use their own judgement as to whether the degree of interference is acceptable or excessive using the following criteria: if the artificial conditions generated in the lab might happen in nature given 5 billion years, then the interference is acceptable. Otherwise, it is excessive. Proteins will be considered first followed by RNA.

Protein Synthesis

Synthesizing proteins under prebiotic conditions is not as straight forward as many would have predicted. Ten (maybe 12) of the amino acids are relatively easy to create. Both L and D isomers are created, and two amino acids alanine and glycine almost always dominate the mixture. Despite these issues, creating amino acids is not that difficult. It is forcing the amino acids to form peptide bonds that is difficult.

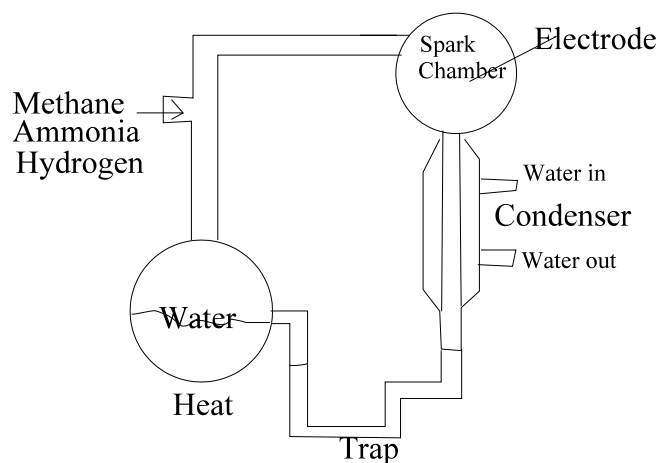
Miller's Experiment

Figure 9.5 illustrates the Miller spark chamber. The water in the flask is boiling. The atmosphere above the water and in the spark chamber is controlled. In this example, hydrogen, methane and ammonia are introduced. The electrode is charged to a very high voltage, and it creates an electric spark. This spark is an energy source. It allows the chemicals in the chamber to react and form new chemicals. The condenser removes the chemicals from the spark chamber, and they accumulate in the trap. Life uses 20 amino acids. Miller's chamber can create between 0 and 10 of the 20 (the number created depends on the gases used in the atmosphere).

The chamber also creates many other chemicals. Other scientists have repeated this experiment with alternative energy sources like UV light and heat. These experiments demonstrate that many amino acids are easy to create. Miller's chamber is a non-equilibrium system cleverly designed and optimized to create nonvolatile organic compounds like amino acids.

Whether or not this experiment is representative of the conditions on the early earth is questionable. Many scientists today do not believe that ammonia, hydrogen and methane were present in the earth's early atmosphere, and without at least one of these, no amino acids are produced by the spark chamber.

Figure 9.5: Miller's Chamber



Thermal Proteins or Protenoids

Since water inhibits the formation of peptide bonds, the first step to create a peptide often involves removing water. Fox successfully created chains of amino acids by heating a purified concentration of amino acids to 150 degrees Celsius for about 14 hours. At this temperature, water and other volatile compounds vaporize. This is important because when a peptide bond forms, a single water molecule is also produced. The heat drives this molecule off forcing the reaction forward because without water it cannot go backwards.

Fox obtained very long chains when he included high concentrations of the amino acids, glutamate, aspartic acid and lysine. Fox called the amino acid chains formed by heating, protenoids. They are also called thermal proteins. They are different from normal proteins in two important ways. Thermal proteins contain both D and L isomers, and the peptide bonds that form are very unusual. The side chains associated with lysine, glutamate and aspartate form over $\frac{1}{2}$ of the peptide bonds.¹ This second feature has led most origin of life researchers to drop protenoids as a viable candidate for the first living protein. Stanley Miller in particular has criticized thermal proteins as unlikely candidates because the conditions necessary to form them probably rarely exist. The temperature has to fall within a narrow range (150-180 deg C), and if the heating lasts too long (more than a day), then the thermal proteins are destroyed.² Furthermore, given that amino acids will not form thermal proteins without a very high concentration of aspartate, glutamate, or lysine leads to another question. How do proteins with reasonable concentrations of these 3 amino acids form in the soup?

Protenoids do have several significant advantages over all the other processes that will be considered in this chapter. The temperature of the reaction is high enough to prevent many cross reactions.

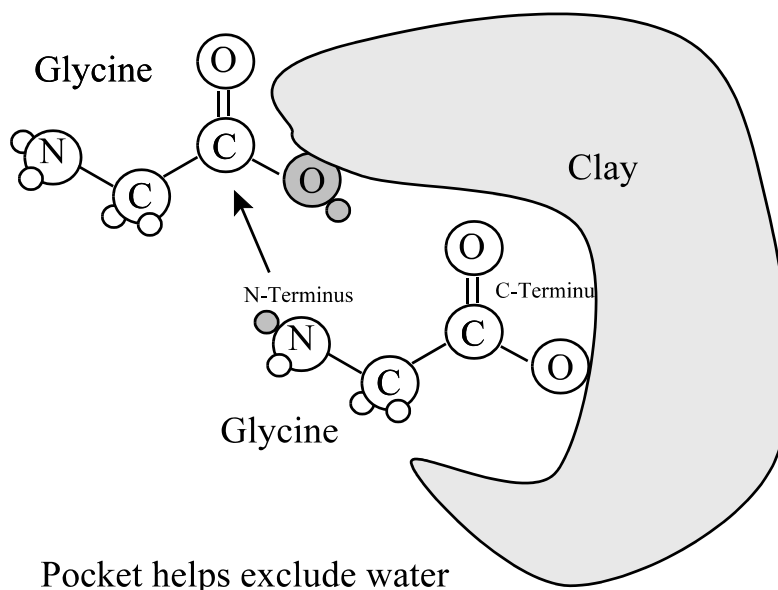
Formic acid and formaldehyde are always chemicals found in the Miller water trap. Formaldehyde is so reactive that it probably combines with the amino acids and drops out of the solution. Formic acid can react with amino acids to form an amide bond. Because formic acid only has a C-terminus (no N-terminus), this reaction is a chain terminator. Once it happens, the chain cannot grow by adding another amino acid to formic acid. Since formic acid and formaldehyde boil at very low temperatures, Fox's approach vaporizes both.

Given 5 billion years, a few thermal proteins may have had a chance to form. In this respect, thermal proteins are unique. While they are not biological precursors (due to the unconventional peptide bonds), they do at least have a chance of existing.

Short Peptides Chains in Water

Short peptide chains have been produced in water. Usually a catalyst like clay or some other mineral like pyrite is required. The minerals interact with the C-terminus of one amino acid making it more vulnerable to attack by the N-terminus of another. Clay in particular can form pockets that may help exclude water. These techniques are interesting, but peptides composed of 6 to 10 amino acids are not proteins. It is not clear how such a process can explain the origin of a 150 amino acid protein. Figure 9.6 shows how a mineral may help peptide bond formation. The C-terminus of each glycine molecule interacts with the clay substrate. The arrow shows how the N-terminus of one glycine attacks the C-terminus of the other. This forms a peptide bond. The resulting peptide will contain two glycines.

Figure 9.6: Clay and Peptide Bond Formation

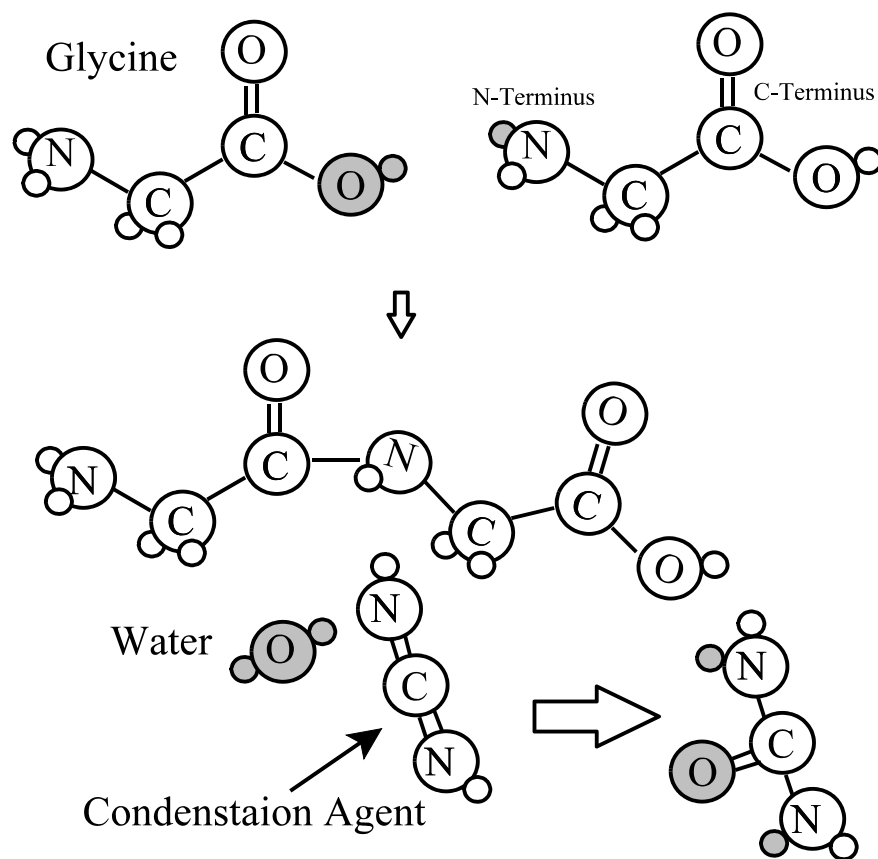


Long Peptide Chains in Water

The last class of experiments will consider extreme investigator interference. In these experiments, a chemical that is either not found in the Miller type spark chamber or is very rare is added to the solution in high concentrations. The chemical is almost always a condensation agent. These chemicals contain double bonds that can absorb water. The reaction is sometimes carried out in a set of sequential steps specifically designed to elongate the peptide chain. Figure 9.7 shows how this process works. The condensation agents must be used in high concentrations because they are not stable in the presence of water. Condensation agents do not have the ability to differentiate between the water molecule released when two amino acids combine and the water already present in the soup. Thus, finding a condensation agent in the primordial soup is like finding a dry sponge in the ocean.

Many authors have claimed that experiments that use condensation agents are relevant to the origin of life. Nevertheless, the justification for adding a condensation agent (that is absent from Miller type experiments) to the mixture is questionable, and adding it in the excessive quantities required for peptide chain growth is certainly not justified. The sequential washing steps which are controlled by the investigator add to the already excessive interference. The results of these experiments are not relevant to the origin of life.

Figure 9.7: Peptide Bonds With Condensation Agents



RNA Synthesis

When researchers moved from the living protein theory to the living RNA theory, they unknowingly took a giant step backwards. The decision to switch was made for two reasons: 1) conceptually RNA should be able to replicate itself much more easily than a protein and 2) RNA can under special circumstances regulate a few chemical reactions. This second finding solidified RNA as the natural choice for the first living organism. The hope was that it might be able to regulate its own synthesis and thus be a very effective self replicating molecule. Nevertheless, the living RNA theory has created a whole new set of problems that need a solution. Many are much more difficult than the problems created by the living protein theory.

1) The building blocks for RNA are harder to synthesize under plausible prebiotic conditions than amino acids. In fact, cytosine has never been synthesized. Cytosine is also absent from meteorites.

2) Unlike amino acids, two of the building blocks required for RNA (cytosine and ribose) are not stable and have very short lifetimes. It is unlikely that these molecules existed in the soup.

3) Just like proteins, the building blocks for RNA do not form RNA molecules unless water is excluded. Given the short lifetimes of many of the RNA subunits, the high temperatures required to drive off water just accelerate decomposition.

RNA Building Block Synthesis

Creating several amino acids is easy. The hard part is coercing the amino acids to link together in a chain to form a protein. RNA proves much more difficult because even the building blocks are hard to synthesize. Furthermore, once they are created, they do not last long. This makes it difficult to understand how the necessary building blocks achieved a suitable concentration for further reactions. Several key building blocks will now be considered.

Adenine and Cytosine

Adenine has been synthesized in the lab from concentrated solutions of hydrogen cyanide and ammonia. While this process works in the lab, it is not clear how the necessary conditions to create adenine would arise in nature.

To synthesize significant quantities of adenine, a concentrated solution of hydrogen cyanide and ammonia is required. Concentrating hydrogen cyanide and ammonia under plausible conditions is problematic. Hydrogen cyanide is a very reactive chemical. In low concentrations, it reacts with water to form many products that are not adenine. These side reactions use up the hydrogen cyanide and lower its concentration. To make the process more difficult, one of the most abundant chemicals produced in the early atmosphere was undoubtedly formaldehyde and “Formaldehyde reacts spontaneously with hydrogen cyanide to form cyanohydrin, a well known reaction that has vexed workers in the field of prebiotic chemistry relying on the unencumbered availability of HCN in high concentration to form a plethora of evolved molecules.”²¹ Ammonia is equally problematic because it decays rapidly when exposed to sunlight,¹⁵ and it boils at sub-freezing temperatures. So while some adenine might be formed under plausible conditions, very little is produced. The high concentration of ammonia and hydrogen cyanide required to make adenine does not represent plausible prebiotic conditions.³

Because adenine has been found in meteorites, there is evidence that it is produced by nature in space.³ Nevertheless, based on the above discussion, adenine was certainly a very rare chemical 4 billion years ago.

Cytosine is much more problematic than adenine. It has never been produced under any plausible prebiotic conditions, even in minute quantities. It is not found in meteorites, so it is not easily synthesized in space. Cytosine is not stable in water. Its lifetime depends on the temperature. At 100 degrees Celsius, cytosine decomposes in 19 days. At room temperature, the decomposition is 340 years. These observations have led Miller and several other researchers to suggest that Cytosine was not found in the first self replicating molecule.^{5,6}

Ribose

Ribose is the most troublesome subunit. It can only be synthesized in small quantities under plausible prebiotic conditions, and its lifetime in water is extremely short (73 minutes at 100 degrees Celsius, and 44 years at 0 degrees Celsius). Given that it is hard to synthesize in large quantities and that it decays rapidly once it is produced, it is difficult to see how a reasonable concentration of ribose ever existed in the soup. Many scientists including Miller have suggested that the first RNA molecules probably did not include ribose (thus the term pre-RNA).⁷

Ribose presents another difficulty. Just like amino acids, sugars have isomers (mirror images). It has been found experimentally^{8,9} that these isomers interfere with self replication. The interference is severe because it terminates the growing chain. So when the first living prebiotic RNA tries to replicate, it must do so in an environment enriched in one isomer of ribose. No mechanism for such an enrichment has been proposed by researchers.

Many scientists have decided that the problems with ribose are so severe that the molecule should be excluded as a possible building block. Since ribose is just the glue that holds RNA together, other chemicals should be able to take its place.⁸

Finally, ribose is a reducing sugar. This means that it will react very quickly with amino acids, and the resulting polymer will fall out of solution. Any ribose in the soup will quickly be eliminated by reactions with the amino acids in the soup.

A Pre-RNA World?

The most recent origin of life theory involves a pre-RNA living molecule. This molecule probably lacked cytosine and ribose. Because such a molecule no longer exists in life, it is hard to address all the possible candidates. How can one possibly test an hypothesis phrased as follows: We believe that some chemical (but we don't know what it was) at one time lived on earth, and this chemical was capable of self replication. We are confident that one day we will find it, and prove our hypothesis correct.

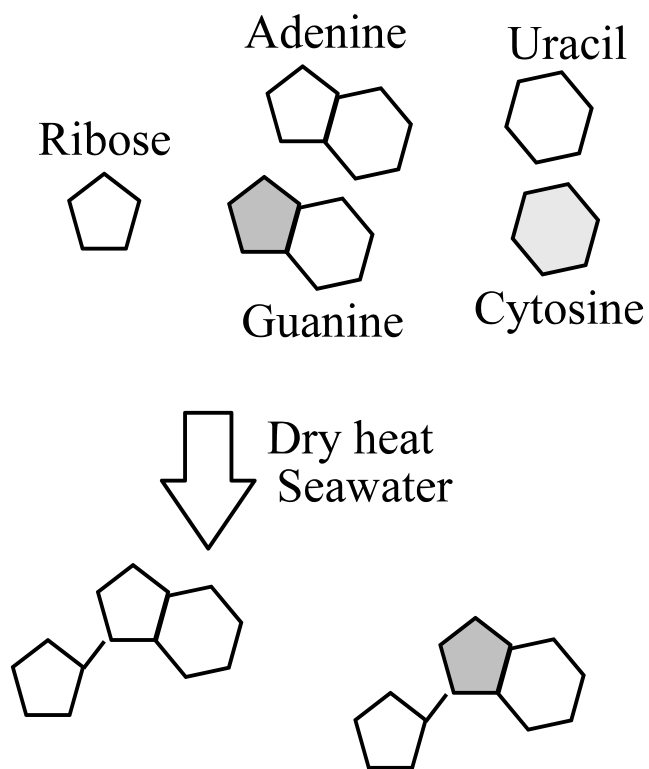
Assembling the Building Blocks

The building blocks for RNA are called nucleotides. A nucleotide consists of 1 phosphate group attached to a ribose which in turn is attached to one of the four bases, uracil, cytosine, adenine or guanine.

In the case of proteins, the amino acid is the smallest building block. No condensation reactions are required to create amino acids. In contrast, two condensation reactions are required to create a nucleotide. One to attach the phosphate to ribose and one to attach one of the bases (adenine, guanine, uracil, and cytosine) to the ribose (figure 8.10).

Under optimal conditions, adenine and guanine can be attached to ribose in the lab. The procedure involves dry heat and sea water. Nucleotides that use cytosine and uracil have no plausible mechanisms to attach the base to ribose.¹⁰

Figure 9.8: Condensation Reaction (Subunits of RNA)

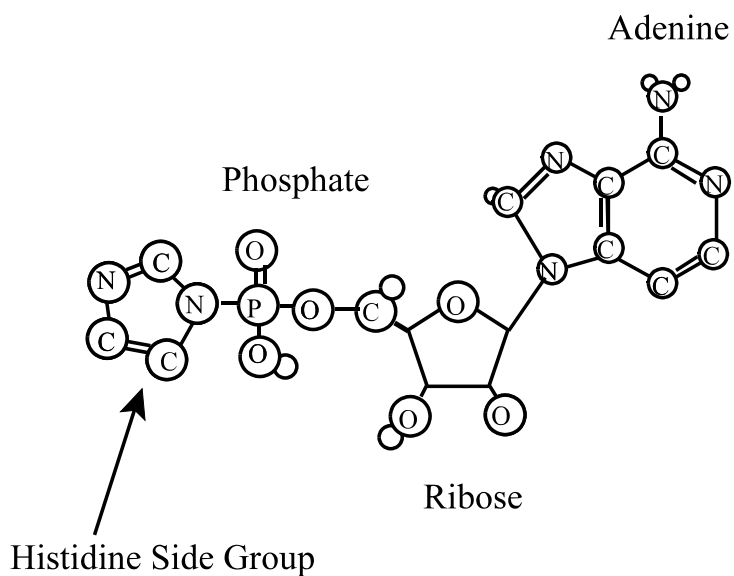


Uracil and Cytosine do not participate.

Activated Monomers

Condensing agents are popular for peptide synthesis. They are also effective for RNA synthesis, but in the case of RNA, the nucleotides are usually directly activated before being added to the mixture. In the presence of clay, such activated monomers have been shown to form chains greater than 50 nucleotides long.¹⁶ The most popular activation agent is impA and is shown in figure 9.9. To form impG, impC, and impU replace the adenine with the appropriate base. The source of these activated molecules is unknown. They would have not been present in the soup, so when researchers add them to test tubes in high concentration and then claim that their experiment models the origin of the life, their claim is without merit.

Figure 9.9: ImpA



Review of Investigator Interference

Investigator interference will now be summarized. As mentioned earlier, investigators do not have 5 billion years to observe experiments, so some interference is necessary.

Interference Strategy #1: Eliminate the Undesirable Chemicals

If chemical A and chemical B react to form chemical P, then this chemical reaction can be written as $A+B \rightarrow P$. Suppose that Miller's water trap contains 3 chemicals, A, B and C. The possible reactions involving the chemicals are as follows: $A + B \rightarrow P$ and $A + C \rightarrow D$.

Unfortunately, the second reaction is favored. So after a few days all of the chemicals in the flask are D, but the researcher desires chemical P. So instead of using the contents of the flask to create P, he orders A and B from his chemical supplier. He mixes these two chemicals while applying heat, and the product is P. This process is how organic chemists make chemicals. They control the chemicals that they start with, and this influences the products that they get. Applying this technique to origin of life scenarios is questionable because it is not clear how nature can exclude the undesirable chemicals.

In chapter 7, figure 7.1 shows that one of the functions that enzymes perform is to eliminate undesired reactions. They accomplish this by speeding up the desired reactions. When investigators manipulate the chemicals in their system to create a desired product, they are mimicking this particular mode of enzyme action. They are using their knowledge of chemistry because the required molecular knowledge is not present in the system.

Examples of cross reaction elimination:

- Fox's thermal proteins. He did not include carboxylic acids or other organic components (like aldehydes) that might terminate a growing protein chain.

- The most extreme examples of cross reaction elimination involve RNA. The reason is that ribose is included freely, but no amino acids are included. This is not a plausible condition. Amino acids react very quickly with sugars like ribose to create very long chain polymers. Anyone who has baked cookies or toasted a piece of bread is familiar with this reaction. Browning is caused when amino acids (especially lysine) react with sugar. This reaction would make any sugar present in the primordial soup unavailable for RNA formation.^{11,12}

Interference Strategy #2: Concentrating Volatile Chemicals

Concentrated formaldehyde is critical for the synthesis of ribose. Concentrated hydrogen cyanide and ammonia are critical for the synthesis of adenine. It is not clear how these chemicals could ever be present in high concentrations on the early earth.¹³ How does one concentrate a chemical that boils at sub-freezing temperatures in a small puddle? This is a difficult problem.

Interference Strategy #3: The Use of Condensation Agents or Activated Monomers

Condensation agents help form many of the bonds that are necessary in biological precursors, whether RNA or protein. Condensation agents remove water and by doing so promote the formation of large biological molecules. Condensation agents were discussed for proteins, but they have also been used to successfully join RNA nucleotides into short chains. RNA synthesis usually just skips this step, and instead researchers usually just add an activated monomer like impA, impG, impC, or impU.

There are no plausible synthesis mechanisms for the condensation agents or the activated monomers. If they are created in Miller's spark experiment or if they exist in meteorites, then the amount present is minuscule. How some investigators can add these chemicals to reactions in massive quantities, and still think that they are modeling plausible prebiotic conditions is certainly an unsolved mystery.

Nevertheless, the motivation for using these techniques is clear. Without these techniques, the biological precursors are limited to a size that is too small to be biologically active.¹⁶ Given that condensation agents and activated monomers are often coupled with carefully timed washes designed to grow the protein or RNA molecule, the analogy to blowing up the door in figure 9.4 definitely applies.

Interference Strategy #4: Controlling the Energy Sources

In most experiments, destructive energy sources are eliminated by the investigator. For example, if the trap in Miller's spark chamber is illuminated with UV light, many of the products will be destroyed.⁴

Interference Strategy #5: Substituting Human Knowledge

This is the most subtle form of interference, and the most common. In systems that lack the required molecular knowledge, it is very easy for researchers to unintentionally add knowledge to the system through the design of their experiment.

The carefully controlled sequential washes that accompany many RNA and protein chain elongation experiments are a perfect example. Often a growing RNA or protein molecule is attached to a stationary substrate, activated nucleotides or amino acids are added, and a rinse is applied after the desired chemical bond forms. This form of interference is present in most prebiotic experiments, and sometimes it goes unnoticed.

Conclusion:

The goal of this chapter was to show that the precursors to life whether RNA or proteins are extremely difficult to create. Maybe one or two such molecules are expected given optimal conditions and 5 billion years. The design inference based on this conclusion alone is very strong. The inference will be strengthened in the next chapter. The next chapter will show that the knowledge required for self replication is very large. If the entire ocean is packed tight with either proteins or RNA, then the odds that one of the molecules can self replicate is still zero. Several thousand bits of knowledge are required, and zero tries (or almost zero) will never allow chance to find a solution.

Many investigators researching the origin of life are disappointed with their progress, and this shows in the scientific literature. Today, it is acceptable to publish an article that is critical of the origin of life paradigm as such articles do get published.

Any publication suggesting the possibility of design is either rejected or starts a witch hunt in which the editor who approves the article is the target. The first step in any scientific revolution is to realize that there is a problem with the current theory, and for many scientists this realization has already taken place. Joyce and Orgel summarize the situation as follows:

“In our initial discussion of the RNA World we will accept The Molecular Biologist’s Dream: “Once upon a time there was a prebiotic pool of Beta-D-nucleotides We will now consider what would have to happen to make the dream come true. This discussion triggers the Prebiotic Chemist’s Nightmare: how to make any kind of self replication system from the intractable mixtures that are formed in the experiments designed to simulate the chemistry of the primitive earth.”²⁰

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Readers who wish to read more about chemical evolution and its problems should try to find Thaxton's book, The Mystery of Life's Origin: Reassessing Current Theories, in their local university library. Unfortunately, the book is out of print. His book was the primary reference for this chapter. The two papers by Shapiro, reference 3 and 6, are also excellent resources.

<http://www.theory-of-evolution.net>