

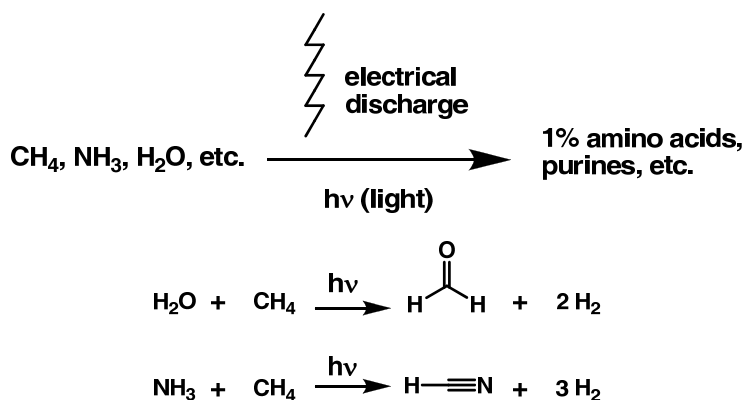
A basic understanding of the mechanistic chemistry of cells, and their evolutionary history, has enabled scientists to delve into questions of the cell's chemical origins. This research seeks to answer questions ranging from how and when cells arose on earth (**origins research**), where to look for them off earth (**astrobiology**) and what types we might find (**exobiology**). All cells on earth that scientists have analyzed employ the same biochemistry; they all store information in DNA, catalyze most reactions with proteins and sequester their contents within membranes. However, no one has come close to synthesizing a cell in the laboratory from basic chemical precursors; cells utilize chemically-rich processes including metabolism and replication, which have been difficult to even vaguely replicate in a flask. Viruses, however, which are composed of simply a nucleic acid associated with a small number of proteins, have been synthesized.

There are two approaches to understanding the origin of cells. One, the **Top-Down** approach, seeks to strip down living cells to their most basic viable form by removing components one piece at a time. The other approach, called **Bottom-Up**, seeks to produce viable cell-like entities starting from small-organic molecules thought to be available on the early earth. The scientific definition of a viable cell-like entity in this context is — a self-replicating, chemical system capable of undergoing Darwinian evolution. Darwinian evolution means that information is encoded, and this information is replicating and mutating.

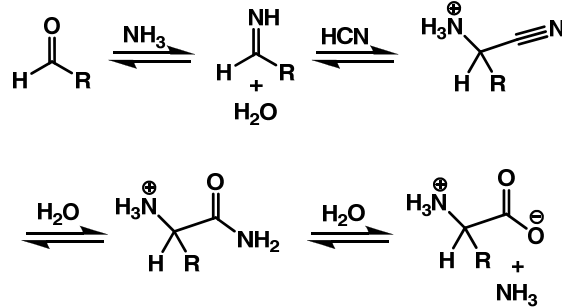
The dual role of RNA, catalytic and informational, has led some to suggest that RNA preceded DNA and proteins in cells. This hypothesis, called the **RNA World Hypothesis**, holds that DNA subsequently evolved from RNA because it better protected genetic information. Proteins evolved because they were more effective catalysts. This hypothesis is supported by observations that RNA is employed in roles that other biomolecules would be better suited for, such as the RNA primers in DNA replication and the RNA ribosomal catalysts in protein synthesis. If it is true that an RNA world preceded our current protein-DNA world, it would not be surprising that RNA remnants are found in these most fundamental biochemical processes. Similarly, that we find RNA in the synthesis of both DNA and proteins is consistent with an RNA first model.

However, we have not recreated the RNA world in the lab. More than 10^{18} (a billion billion) different RNA sequences have been tested in the lab for their ability to self-replicate and evolve in the presence of energy-rich nucleotide triphosphates, and none has succeeded yet. On the other hand, even a small RNA (a 100-mer) has 10^{60} possible sequences, thus only a tiny fraction of potential catalysts have been tested.

Experimental efforts on the Bottom-Up approach began in the 1950's; Stanley Miller, working in Harold Urey's lab, replicated the conditions believed to have been present on Earth billions of years ago. He placed methane, ammonia, and water, all under high pressure and temperature, and subjected them to electrical discharge and ultraviolet light. The result of these experiments was the production of a majority of the twenty natural amino acids and all four bases of RNA.

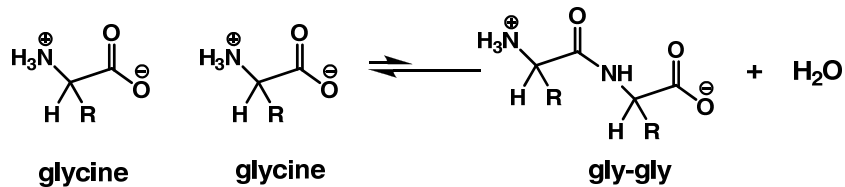


The important steps involve the reaction of methane and water to produce **formaldehyde** (H_2CO), and the reaction of ammonia and methane to form **hydrogen cyanide** (HCN). These two compounds, HCN and H_2CO , along with ammonia and water, then react to produce glycine via the **Strecker Reaction**. These reactions are not limited to the lab or even to earth; amino acids have been found in carbonaceous (carbon-rich) meteorites in similar distributions as in the Miller-Urey experiment. Aldehydes other than formaldehyde generate amino acids with non-hydrogen side chains. Such aldehydes (including aldose sugars such as ribose) are generated by a reaction sequence requiring only formaldehyde, called the **Formose** reaction. This reaction sequence will be covered in class.



Strecker Reaction

Lacking enzymes and energy sources such as ATP, pre-cellular amino acids would have had to consume available chemical energy sources in order to polymerize into peptides. The polymerization reaction is disfavored because of the surrounding aqueous environment (through the actions of a certain French chemist).



Thus, formation of appreciable quantities of polypeptide may have required a coupling reagent (akin to DCC) to facilitate the amidation reaction and make it energetically favorable. One potential compound is **diaminomaleonitrile** (DAMN), a tetramer of hydrogen cyanide. We will cover the mechanism of its formation in lecture. The nucleophilic attack of a glycine carboxylate on DAMN, and subsequent elimination of a cyanide group, results in an activated glycine ester. Subsequent attack by the nitrogen of another glycine would generate a glycine-glycine dipeptide. Repeated iterations could potentially generate longer polymers.

