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ABIOTIC SYNTHESIS OF BIOLOGICALLY-RELEVANT
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Richard M. Lemmon

March 1968

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ABIOTIC SYNTHESIS OF BIOLOGICALLY-RELEVANT ORGANIC
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Richard M. Lemmon

INTRODUCTION

The term "chemical evolution" has come to mean the chemical events that took place on the primitive, prebiotic Earth leading to the appearance of the first living cell. In other words, it is the study of the biologically-relevant chemistry that preceded Darwinian evolution.

In this report we shall concentrate on the results of laboratory experiments simulating the presumed environment of the prebiotic Earth. Less attention will be paid to the other planets because (a) we don't know if any of them are (or ever were) a habitat for life and (b) we hardly know more about their present (let alone their past) conditions than we know about the Earth of 4×10^9 years ago. Even less can be said about the possibilities of abiogenic synthesis outside our solar system. Our knowledge of this space is limited entirely to the examination of light reaching us from the stars--locales far too hot for the existence of anything like our terrestrial organic chemistry. It is widely assumed that a small fraction, but a huge number, of these stars have planetary systems comparable to our solar system. However likely this may be, we have only indirect evidence for the existence of planets outside our solar system. Research in chemical evolution has little choice but to focus its attention on planet Earth.

It has been commonplace in the history of science for an area of research to be neglected for many decades, and then suddenly to burst into activity. This is what has happened to chemical evolution. As far back as 1871, the English physicist John Tyndall wrote:

"He [Darwin] placed at the root of life a primordial germ, from which he conceived that the amazing richness and variety of the life now upon the earth's surface might be deduced. If this hypothesis were true, it would not be final. The human imagination would infallibly look behind the germ and, however hopeless the attempt, would enquire into the history of its genesis."¹

For half a century after Tyndall made this statement, chemical evolution was a neglected area of scientific thought, let alone experiment. There were several reasons for this neglect: lack of any clear idea of the chemical environment of the prebiotic Earth, insufficient development of analytical techniques, and a prevailing opinion that such scientific thought and experiment would be an invasion of the precincts of religion. In addition, Pasteur's famous 1864 experiment appeared to have smashed completely the age-old idea of spontaneous generation. Everyone, most scientists included, agreed that "life can come only from life", and thought no more about the subject.

Because of its emphasis on materialistic philosophy, it is not surprising that the U.S.S.R. was the locale of the birth of the studies that we call chemical evolution. In the early 1920s the young Soviet biochemist, A. I. Oparin, expressed the idea that life on Earth must have arisen from a preformed "pool" of organic compounds. In brief,

he was saying that spontaneous generation was indeed the original route to life, although its "spontaneity" had to be stretched to a billion years or more. Oparin's ideas first appeared in print in 1924 in a booklet entitled "The Origin of Life", and he has steadily contributed both ideas and experimental data right up to the present. Oparin's ideas were independently reached by the British biologist, J.B.S. Haldane, who suggested in 1928 that organic compounds must have accumulated on the prebiotic Earth until "the primitive oceans reached the consistency of hot dilute soup".² It was not until after World War II, however, that direct experimental evidence finally put the Oparin-Haldane ideas on firm ground. That experimental work established chemical evolution as a serious scientific study, as we will attempt to show in this chapter.

ABIOTIC SYNTHESIS ON THE PRIMITIVE EARTH

1. Time Scale

There is general agreement that the Earth condensed from a dust cloud $4.5 - 4.8 \times 10^9$ years ago.³ Recent reports of presumed bacterial and algal fossils strongly indicate that life, in the form of unicellular organisms (Protozoa) has been present on the Earth for at least 3.1×10^9 years,^{4,5} and that multicellular organisms (Metazoa) may have been here $2 - 2.5 \times 10^9$ years ago.⁶ A basic concept of chemical evolution is that it declined at the onset of Darwinian evolution; in our present "biological" era, almost any organic compound produced abiotically would be quickly metabolized. The Barghoorn-Schopf 3.1×10^9 year-old algae (which were probably preceded by earlier, anaerobic organisms) seem to leave only about one billion years for the period of chemical evolution--about one-third the time thought available before the Barghoorn and Schopf reports^{4,5} appeared. This has been disturbing to some "chemical evolutionists". But it shouldn't be. There is nothing to indicate that 3.0×10^9 years is enough time, but 1.0×10^9 years isn't.

2. The Primitive Earth's Atmosphere

Any discussion of the chemistry of the primitive Earth must begin with its atmosphere. That atmosphere would, in turn, have controlled the chemistry of the oceans and surface rocks.

There seems little doubt that the primitive planet's atmosphere was a hydrogen-dominated, or reduced, one. The realization that the early atmosphere was quite different than it is today began with the

discovery, in 1929, that hydrogen was by far the solar system's most common element (about 87% of the mass of the sun⁷). It was, therefore, reasonable to suppose that, as the Earth was forming, most of its carbon, nitrogen, and oxygen would be in the form of methane, ammonia, and water. Oparin, in the 1938 edition of his book, "Origin of Life", concluded that "Carbon made its first appearance on the Earth's surface not in the oxidized form of carbon dioxide but, on the contrary, in the reduced state, in the form of hydrocarbons."⁸ Similar conclusions were advanced regarding the chemical nature of the nitrogen and oxygen in the primitive atmosphere.

One problem with respect to this view of the primitive atmosphere is the relatively low percentage of the noble gases in our present atmosphere. Harrison Brown has calculated that neon is present in the Earth's atmosphere today in 10^{-10} of its cosmic abundance;⁹ the other noble gases are similarly conspicuous by their relative absences. At first thought, it seems difficult to imagine the primitive Earth's retaining such low molecular weight molecules as methane, ammonia, and water while losing atoms, such as krypton and xenon, with atomic weights around 80 and 130. However, the carbon may have been initially bound as higher molecular weight hydrocarbons (later converted to methane by thermal cracking), the water retained as hydrates, and the ammonia as ammonium ion.

The potent arguments in favor of a reduced primitive atmosphere may be summarized as follows:

(a) The general geochemical arguments of Oparin⁸ and Urey¹⁰ that, since our solar system and observable universe are so heavily hydrogen-laden, the Earth's primitive atmosphere must have been highly reduced.

This argument also draws attention to the larger and colder planets in our solar system (e.g., Jupiter). The higher gravitational fields and lower temperatures would favor the retention of light molecules and, indeed, the Jovian planets' atmospheres appear to be rich in methane and ammonia.

(b) The meteorites that reach the Earth are, for the most part, reduced. Most of their carbon appears as elementary carbon, carbides, and hydrocarbons. The iron is mostly metallic or ferrous, and the phosphorus appears as phosphides.¹¹

(c) When mixtures of methane, ammonia (or N_2), and water--the principal constituents of the Earth's presumed early atmosphere--are subjected to ultraviolet or ionizing radiation, many biologically important compounds (amino acids, sugars, purines, etc.) are formed. Similar irradiations of samples of the Earth's present atmosphere yield little of biological relevance, e.g., only traces of formic acid and formamide. "As soon as the net [laboratory] conditions become oxidizing, the organic synthesis effectively turns off."¹² It appears that the accumulation, on the primitive Earth, of the necessary "building blocks" for the first living cell required a reduced atmosphere.

(d) Molecular oxygen exerts a deleterious effect on many aspects of cell metabolism--a fact difficult to account for if the first living cells had appeared in an oxygenated environment. Chromosomes appear to operate in an anaerobic medium, and cell division takes place during a temporary period of anaerobiosis.¹³ These facts seem to point to the early evolution of the living cell in a reduced atmosphere.

(e) The work of Rankama, Randohr, and others (as reported by M. G. Ritten¹⁴)--the finding of increased ferrous iron in the oldest Precambrian sediments--indicates that these deposits were laid down under a reduced atmosphere.

The change from the reduced, primitive atmosphere to the present oxidized one is explained by the ultraviolet radiolysis of water in the Earth's upper atmosphere (followed by the preferential escape of hydrogen) and by the development of the process of plant photosynthesis. Along with the change to an oxygenated atmosphere the Earth developed its present "shield" of ozone in the upper atmosphere. Without this shield, which protects our planet from the strong ultraviolet light from the sun, it is difficult to see how the Earth could have become an abode of life.

3. Other Conditions on the Primitive Earth

Other factors on the prebiotic Earth that would have strongly influenced chemical evolution, and that play an important part in the laboratory investigations in this subject, are the energies available, the temperatures, and the oceans and their sediments.

The significant source of energy on our planet, now and in the remote past, is that from the sun. Miller and Urey have summarized this, and other energy sources, as follows:¹¹

Table 1

Present Sources of Energy Averaged over the Earth

<u>Source</u>	<u>Energy cal cm⁻²yr⁻¹</u>
Total radiation from sun	260,000
Ultraviolet light	
$\lambda < 2500 \text{ \AA}$	570
$\lambda < 2000 \text{ \AA}$	85
$\lambda < 1500 \text{ \AA}$	3.5
Electric discharges	4
Radioactivity	0.8*
Volcanoes	0.13
Cosmic rays	0.0015

* 4×10^9 years ago this value was about 2.8

The data of this table show why ultraviolet light is the most desirable laboratory tool for chemical evolution experiments. However, since $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O}$ mixtures show little UV absorption above 2000 \AA , and the region below that wavelength is difficult to employ in the laboratory (e.g., due to UV destruction of the special windows that are needed), researchers have tended to simulate the other primitive Earth-available energies. These include electric sparks and corona discharges (simulating the effects of lightning storms), gamma rays and electron beams (simulating cosmic rays and radioactivity in the rocks), and heat (simulating the thermal effects around volcanoes).

Most laboratory work on the abiogenic synthesis of biologically-relevant compounds has been done at room temperature. Geologists and geochemists are of the general opinion that by the time the Earth

became a solid, cohesive mass it had about the average temperature it has today. The notable exception to ambient-temperature work is that of Professor S. W. Fox and his groups at the Florida State University and the University of Miami; they have emphasized the possible role of local high temperatures, present in areas of volcanic activity, in promoting the initial events of chemical evolution. Using very high temperatures (of the order of 1000°C) they have contributed interesting amino acid-forming experiments; working at much lower temperatures they have shown the formation of peptides from amino acids. We will come back to this work in later sections of this report.

For over a century scientists have regarded the early oceans as the probable birthplace of life on our planet. Darwinian evolution points to this, and chemical evolution seems to point to it too. As was mentioned earlier, J.B.S. Haldane emphasized the role of the primitive oceans and thought that the early abiogenic synthesis would have accumulated in them a considerable concentration of organic compounds. Sagan (Ref. 12, p. 233) calculated, on the basis of (a) average quantum yields for the UV-light conversion of reduced-atmosphere gas mixtures to higher molecular weight compounds and (b) assumed values of the UV photon flux in primitive times, that the abiogenic Earth's oceans could have developed "a one percent solution of organic matter" in 3×10^8 years. For this reason, most chemical evolution experiments have been done in dilute aqueous media. Another consideration that strongly favors the oceans as the principal locale for chemical evolution is that organic compounds, once formed, would be protected against the radiolysis that would be caused by the strong UV flux of

primitive times. The formed amino acids, sugars, etc., would be expected to be adsorbed on mineral particles (muds, clays, etc.), carried down to the bottoms of lakes and seas, and there be protected from the UV light. The ocean would also be an effective medium, or vehicle, for the mixing together of different classes of organic compounds formed at separated points on the Earth's surface as a result of, for example, differing temperatures, cosmic ray fluxes, and available mineral surfaces. The last item brings up the important point of surface catalysis--without doubt, adsorption on mineral surfaces played an important part in chemical evolution; the availability of these surfaces in the transporting and mixing actions of the oceans make the latter even more attractive as promoters of abiogenic syntheses.

SIMULATED PRIMITIVE EARTH EXPERIMENTS--EARLY WORK AND GENERAL GUIDELINES

1. Early Experiments

Studies were made, as far back as 1897, on the effects of high energy sources (electric discharges) on mixtures of carbon dioxide and water.¹⁵ In that experiment, and in subsequent ones throughout the ensuing half-century, claims were made that formaldehyde was a detectable product of such irradiations--other workers, on the basis of their own experiments, denied these claims. The possibilities of formaldehyde as a product of $\text{CO}_2\text{-H}_2\text{O}$ interactions intrigued many scientists as a hint of how green-plant photosynthesis might operate. From 1870 until about 1940 it was widely held that formaldehyde was the first product of CO_2 fixation by green plants, and that the formaldehyde was converted to sugars by the well-known polymerization reaction. Although most of the interest in the possible formaldehyde product was from the standpoint of photosynthesis, some workers additionally suggested that this product could have been involved in the formation of organic compounds on the primitive Earth.¹⁶

In 1950, interest in the possible reduction of CO_2 and its fixation into biologically important compounds through the action of ionizing radiation was rekindled by the experiment of Garrison, Calvin, et al.¹⁷ These workers demonstrated the appearance of formic acid and formaldehyde when $\text{CO}_2\text{-H}_2\text{O-Fe}^{++}$ solutions were irradiated with an alpha-particle beam.

The present era of active research in chemical evolution was put on a firm basis by the tremendously interesting experiments of Miller, first reported in 1953.¹⁸ Having been convinced by the arguments of

Oparin⁸ and Urey¹⁰ that the Earth's primitive atmosphere was reducing, Miller reasoned that the really meaningful chemical evolution experiment would be to subject such an assumed atmosphere (mixture of CH₄, NH₃, H₂O, and H₂) to high energy radiation--in his case, to electrical discharges. In this way, Miller demonstrated the facile appearance of glycine, α -alanine, β -alanine, aspartic acid, and α -aminobutyric acid. This experiment set the pattern for many subsequent ones over the ensuing fourteen years. Many investigators, as will be detailed below, used various energy sources and made many alterations on Miller's original gas (primitive atmosphere) mixture--but this work is all basically the same, namely, studies of the effects of ionizing radiation on reduced gas mixtures of the sort that are presumed to be similar to the early terrestrial atmosphere.

2. General Guidelines

From the foregoing discussions the reader can conclude that there is general agreement as to what may constitute a meaningful "chemical evolution" experiment. The "general agreement" indicates that experiments should be performed at room temperature, in dilute aqueous media, with a mixture of simple molecules (CH₄, NH₃, H₂O, H₂, etc.) of an overall reduced character, and with energy sources that were certainly plentiful on the primitive Earth (preferably UV light and electric discharges). When catalysts are added to such a reaction mixture, they should be of the sort for which there is geological evidence for their existence in the early stages of our planet's development (i.e., around 4×10^9 years ago). Other equally valid experiments involve various treatments (UV light, electric discharges, modest heat, etc.) of simple

compounds (of which the inorganic cyanides are notable examples) that would have formed easily, in primitive times, from the above gas mixtures.

The main disagreement with these guidelines comes, as was mentioned earlier, from those who think that the use of higher temperatures (such as those found in areas of volcanic activity) is also valid. Most researchers, however, feel that the room-temperature, dilute-aqueous media constitute a better model because the primitive oceans were far more widespread and seem, in practically all aspects, to be the logical locale for the appearance of life.

ABIOTIC SYNTHESIS OF BIOMONOMERS

In this section we shall review the progress that had been made, through 1967, in the laboratory synthesis, under the guidelines presented in the previous section, of the biomonomers. By the latter term we refer to the constituent units of the biopolymers (the proteins, nucleic acids, and polysaccharides). To be specific, we shall review the abiotic synthesis of the amino acids, nucleic acid bases, nucleosides, nucleotides, sugars, fats, and porphyrins.

1. Amino Acids

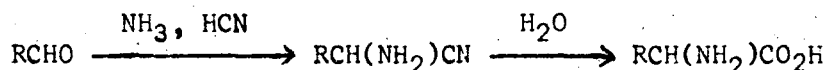
It is the great successes in the abiotic syntheses of the amino acids, beginning with Miller's 1953 experiment, that have made chemical evolution such an attractive area of research. There are several reasons why amino acid syntheses have been so prominent. First, they are the constituent units (monomers) of the proteins, which, with the nucleic acids, are the supremely important biopolymers. Secondly, present data indicates that they form more readily (from CH_4 , NH_3 , H_2O mixtures) than any of the other biomonomers. Finally, very powerful and sensitive techniques exist for amino acid detection and analysis--commercial "Amino Acid Analyzers", paper chromatography, and very sensitive color tests (ninhydrin).

For the present discussion, by "amino acids" we are limiting ourselves to the α -amino acids. All of the 20 common amino acids of the natural proteins have their amino group bonded to the α -carbon, the carbon that is also bonded to the carboxyl group. It is interesting to note that in all chemical evolution experiments where their yields are reported, α -alanine is formed in much higher yield than is β -alanine.¹⁹⁻²²

The characteristic formation of the amino acids seems also reflected in the preferred formation of α -aminonitriles, as reported by Ponnampereuma and Woeller.²³ It seems very likely that, when life got started on Earth, the α -amino acids were the commonest type available for protein construction. Organisms that developed that could metabolize α -amino acids would be the ones most likely to survive.

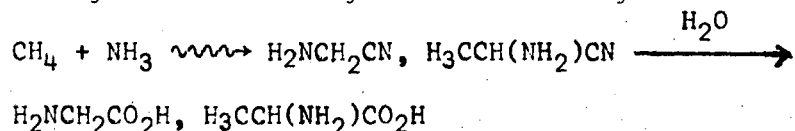
At least four mechanisms, or routes, have been proposed to account for the appearance of amino acids in primitive Earth experiments:

- (a) The cyanohydrin mechanism--invoked by Miller¹⁹ to explain his amino acid products:

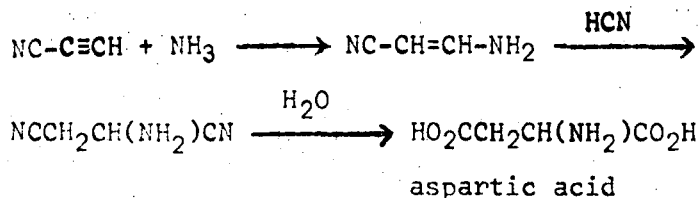


This mechanism is reinforced by the fact that aldehydes and HCN are known products in Miller's system. It also explains the presence of the α -amino acids.

- (b) Since electric discharges in anhydrous methane-ammonia mixtures cause the formation of α -aminonitriles,²³ the intermediate aldehyde formation may not be necessary:



- (c) Sanchez, et al.²⁴ have suggested a possibly important role for cyanoacetylene (a product of $\text{CH}_4\text{-N}_2$ irradiations) in amino acid syntheses. In the presence of NH_3 and HCN, this compound forms considerable aspartic acid--the suggested reactions are:



(d) Abelson,²⁵ Matthews and Moser,^{26,27} and Harada²⁸ have emphasized a possible key role of HCN oligomers. Abelson reports that UV light (2536 Å) speeds HCN polymerization and that, on hydrolysis of such polymers, glycine, alanine, serine, aspartic acid, and glutamic acid are found.

With the data now available, it is impossible to decide whether all, any, or none of the above routes is the true path of amino acid formation in abiogenic syntheses.

Table 2 is a summary of the amino acids whose syntheses have been reported during the past 14 years in "primitive Earth atmosphere" experiments. The table reflects some subjective judgment about what is, or isn't, a "primitive Earth" experiment. The table omits reports where "amino acid products" are indicated merely on the basis of ninhydrin-positive tests, or approximate chromatographic positions of the products. We have included only those experiments in which individual amino acid products were firmly established, taking into account the need for control experiments to eliminate bacterial and other contamination. In general, the experiments recorded in Table 2 were performed on CH₄-NH₃-H₂O-H₂ mixtures; the exceptions are noted. In some cases, the H₂ was omitted; in others, varying amounts of CO, CO₂, or N₂ were added. In all cases the mixture was more reduced than oxidized.

Other relevant primitive Earth experiments in which amino acids were produced, not from the "primitive atmosphere" mixture, but from other compounds that would have accumulated in the primitive oceans, are recorded in Table 3.

Table 2

Production of Amino Acids in Simulated

"Primitive Earth Atmosphere" Experiments (1953-1967)

Amino Acid Formed	Input Energy ^(a)	Product Identification ^(b)	Lit Ref.
Glycine	A	I	19
	A	II	54
	A	II	55 ^(e)
	C	I	33
	A	II	29
	B	II	30 ^(c)
	A	II	40 ^(f)
	A	II	31
	D	II	21
Alanine	A	I	19
	C	I	33
	A	II	54
	B	II	30 ^(c)
	A	II	31
	D	II	21
	A	II	55 ^(e)
	A	II	29
	A	II	40 ^(f)
β-Alanine	A	I	19
	A	II	31
	A	II	54
	A	II	40

Table 2 (continued)

-18-

Cysteic acid	C	I	32 ^(d)
N-methylglycine (sarcosine)	A	I	19
	D	II	21
	A	II	31
	A	II	40 ^(f)
Serine	A	II	29
	D	II	21
Threonine	A	II	29
	D	II	21
α -Aminobutyric acid	A	I	19
	A	II	54
	B	II	40 ^(f)
	D	II	21
	A	II	29
N-methylalanine	A	I	19
Asparagine	A	II	55 ^(e)
Aspartic acid	A	I	19
	C	I	33
	A	II	54
	A	II	55 ^(e)
	A	II	29
	D	II	21

Table 2 (continued)

-19-

Glutamic acid	A	I	19
	A	II	54
	A	II	29
	D	II	21
Valine	D	II	21
Leucine	D	II	21
	D	II	34
	A	II	29
Isoleucine	D	II	21
	D	II	34
	A	II	29
Alloisoleucine	D	II	21
	D	II	34
Lysine	A	II	54
	A	II	29
Phenylalanine	D	II	21
	D	II	34
Tyrosine	D	II	21
	D	II	34

- (a) A = electric discharge (spark or corona)
B = UV radiation
C = ionizing radiation (γ -rays or electrons)
D = heat (about 1000°C)
- (b) I Product identification very secure; for example, absolute chromatographic coincidence between labeled product (from $^{14}\text{CH}_4$) and carrier color or UV absorption, or macro amount of product obtained and physical properties determined.
II Product identification less secure; usually based on chromatographic R_F values, or elution volumes from ion exchange columns.
- (c) Ethane was substituted for methane; with the latter, no amino acid products were detected.
- (d) H_2S was added to the usual $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O}$ mixture.
- (e) Ethane was added to a $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O-H}_2$ mixture.
- (f) Experiments on $\text{CO}_2\text{-N}_2\text{-H}_2\text{-H}_2\text{O}$ mixtures.

The data of Table 2 leave no doubt that amino acids, at least those up to 6 carbons (leucine and lysine) are formed in "reduced atmosphere" experiments. Higher molecular weight amino acids (phenylalanine and tyrosine) have been reported only on heating the $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O-H}_2$ mixtures to about 1000°C . Whether this temperature can be considered "primitive Earth" conditions, and how widespread the locale(s) of such temperatures could have been, has been "warmly" debated--and the reader is referred to the written record of one such debate, following the presentation of a paper at the conference held at Wakulla Springs, Florida, in 1963.³⁵

In addition to the amino acids whose formation from "primitive Earth atmospheres" is recorded in Table 2, there are many reports in the literature of their formation from the sorts of organic compounds known (e.g., HCHO and HCN) or expected (e.g., N-acetylglycine) to accumulate in the primitive atmosphere and oceans (we shall call these "primitive Earth compounds"). Many researchers have studied what could be called the secondary formation of amino acids from these compounds. That work is summarized in Table 3.

Table 3

Formation of Amino Acids from Primitive Earth Compounds (1953-1967)

Reactants	Input Energy	Amino Acids Reported(a)	Lit. Ref.
1. Paraformaldehyde, H ₂ O, NO ₃ ⁻ , Fe ⁺³	Sunlight	gly,ala,asp,val,his,pro,lys,ser,asp,arg	36
2. N-acetylglycine, H ₂ O, NH ₃	γ-rays	gly,asp,thr	37
3. NH ₄ Ac, H ₂ O	e ⁻ beam	gly,asp	38
4. H ₂ NOH, HCHO, CO ₂	UV	gly,ala	39
5. HCHO, NH ₄ Cl, NH ₄ NO ₃	UV	ser,gly,ala,glu,val,ileu,phe	54
6. HCN (at pH 8-9), followed by hydrolysis	UV	gly,ala,ser,asp,glu	25
7. Formamide	Pyrolysis at 250°, followed by hydrolysis of product	gly,ala,asp,ser,thr,val,glu,leu	55
8. Glucose, urea	150-200°, hydrolysis of product	gly	41
9. Malic acid, urea	"	asp	41
10. Hydroxyglutamic acid, NH ₃	"	glu	41
11. HCN, NH ₃ , H ₂ O	90°	asp,thr,ser,glu,gly,ala,ileu,leu,β-ala,abu	42
12. HCHO, H ₂ NOH, H ₂ O	80-100°	gly,ala,β-ala,ser,thr,asp	43

Table 3 (continued)

13.	HCN, NH ₃ , H ₂ O	27-100°	gly,ala,asp	44
14.	HC≡C-CN, NH ₃ , H ₂ O, HCN	100°	asp,aspNH ₂	24
15.	(NH ₄) ₂ CO ₃ (solid)	γ-rays	gly	56
16.	Glycine (on quartz)	260-280°	ala,asp	57

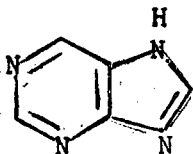
(a) ala = alanine, β-ala = β-alanine, abu = α-aminobutyric acid, asp = aspartic acid, arg = arginine, aspNH₂ = asparagine, gly = glycine, glu = glutamic acid, his = histidine, ileu = isoleucine, leu = leucine, lys = lysine, pro = proline, phe = phenylalanine, ser = serine, thr = threonine, val = valine.

2. Nucleic Acid Constituents

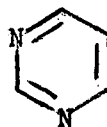
We shall review the progress made in the abiogenic syntheses of the nucleic acid monomers (the nucleotides, which consist, in turn, of three units: base-sugar-phosphate) under the headings of purines and pyrimidines (the organic bases of the nucleic acids), sugars, nucleosides (the base-sugar units), and nucleotides.

Purines and pyrimidines

Compared to the successes in demonstrating amino acid syntheses under primitive-Earth conditions, far less has been achieved in the syntheses of the purines and pyrimidines. The more complex structures of the latter indicate why this should be expected. The two purines



purine



pyrimidine

(adenine and guanine) and the three pyrimidines (cytosine, thymine, and uracil) of the nucleic acids are formed by the attachments of NH_2 , OH , and CH_3 groups to the above basic structures--and the general result is a higher degree of molecular architecture, or specificity, than is exhibited in the amino acid series.

Adenine is the only one of the five nucleic acid bases that has been synthesized in a "primitive-Earth atmosphere" experiment. In 1963, Ponnampereuma, et al. found adenine after irradiating a $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O-H}_2$ mixture with an electron beam.⁴⁵ The yield of adenine from starting methane was very small (0.01%), and none of the other nucleic

acid bases were detected. However, considering the complexities of the adenine molecule and the random, radiolytic processes that led to its formation, one can easily believe that this yield may be highly significant for our understanding of chemical evolution. Of further interest was the fact that the adenine yields increased as the H_2 in the starting gas mixture was decreased--a result that may hint at the absence of significant purine synthesis on the primitive Earth until most of the hydrogen was gone. Also, since the presence of H_2 does not seem to inhibit amino acid production in primitive atmospheres, perhaps we can speculate that protein synthesis preceded nucleic acid synthesis on the prebiotic Earth.

The first "primitive Earth" synthesis of adenine was reported by Oró in 1960;⁴⁶ this work was elaborated in further publications^{44,47} and confirmed by Lowe, et al.²² Adenine, some amino acids, and a variety of other nitrogen-containing compounds are found when aqueous ammonium cyanide solutions are heated at about 90° for several days. Oró and Orgel and their coworkers have studied the mechanism of this most interesting condensation and have presented evidence that it proceeds through aminomalononitrile (an HCN trimer) and diaminomaleonitrile and/or 4-amino-5-cyanoimidazole (both HCN tetramers).^{47,48,98}

Both adenine and the other nucleic-acid purine, guanine, have been synthesized by shining ultraviolet light on dilute solutions of HCN.⁹⁹ These two purines have also been reported as products of the reaction of 4-amino-5-cyanoimidazole (the HCN tetramer mentioned above) with HCN or cyanogen in aqueous solution.^{49,98} There is much reason to believe that HCN played a key role in chemical evolution.⁹⁸

Of the three nucleic-acid pyrimidines, cytosine, uracil, and thymine, the first two have been prepared under more or less abiogenic conditions, but thymine has never been reported as a product of such experiments. Uracil has been prepared by heating (130°) malic acid, urea, and polyphosphoric acid.⁵⁰ This is a doubtful primitive-Earth experiment because of the temperature, the malic acid (which has never been reported as a product of abiogenic synthesis), and the polyphosphoric acid (a compound whose existence in any watery environment would be ~~most~~ transitory). Oró has also recorded the appearance of uracil under conditions he considers relevant to abiogenesis: heating (135°) urea with acrylonitrile (or β -aminopropionitrile, or β -aminopropionamide) in aqueous solution.³⁴

The only reported abiogenetic synthesis of cytosine is that of Sanchez, et al.²⁴ They found this pyrimidine upon heating cyanoacetylene (which they report as a product of the sparking of a mixture of CH_4 and N_2) with an aqueous solution of KCN at 100°. These authors also report that cytosine is obtained in a 1% yield when an aqueous solution of 1.0 M potassium cyanate and 0.1 M cyanoacetylene is allowed to stand at room temperature for 7 days.

Other purines, not normally found in nucleic acids, are also reported to have been synthesized under abiogenic conditions. These include hypoxanthine, diaminopurine, and xanthine.⁴⁹

The abiogenic syntheses of the nucleic-acid purines and pyrimidines are summarized in Table 4.

Table 4

Synthesis of Nucleic-acid Purines and Pyrimidines under
Primitive Earth Conditions

Compound	Experimental Conditions	Lit. Ref.
Adenine	$\text{CH}_4\text{-NH}_3\text{-H}_2\text{O}$; e^- beam	45
"	aq. HCN, UV	99
"	aq. diaminomaleonitrile + HCN, UV, 25°	49
Guanine	aq. HCN, UV	99
"	aq. diaminomaleonitrile + C_2N_2 , UV, 100°	49
Uracil	malic acid, urea, $\text{H}_4\text{P}_2\text{O}_7$, 130°	50
"	acrylonitrile, urea, H_2O , 135°	34
Cytosine	$\text{H}\equiv\text{C-CN}$, NH_4CN , H_2O , 100°	24
Thymine:	No recorded "primitive Earth" synthesis	

Sugars

To some extent, the problem of the abiogenic synthesis of the common hexoses and pentoses was solved long before the present interest in chemical evolution experiments. Over a century ago, the Russian chemist Butlerov showed that dilute aqueous alkali causes formaldehyde to condense to a complex mixture of sugars.⁵¹ Miller's early work produced evidence, not only for the production of formaldehyde on sparking the $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O-H}_2$ mixture, but also ("possibly") for the appearance of sugars.¹¹ Consequently, the abiogenic synthesis of sugars on the primitive Earth is easy to visualize--although no one has yet established a specific sugar as a product of $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O}$ irradiations. Since we are here focusing our attention on the problem of nucleic acid constituents, it is of considerable interest that the sugars (ribose and deoxyribose) of those biopolymers have been found as products of the ultraviolet irradiation of formaldehyde.⁹⁹ Deoxyribose has also been reported as a product of warming (50°) an aqueous solution of formaldehyde in the presence of calcium oxide.⁵² Finally, Gabel and Ponnampereuma have found ribose as a product of the refluxing of aqueous formaldehyde over kaolinite.⁵³

Nucleosides

The only chemical evolution experiments so far reported that relate directly to nucleoside (the base-sugar part of the nucleic acids) formation are those of Ponnampereuma, et al.^{58,59} These workers were able to detect the formation of adenosine when UV light was shown on a dilute (about 10^{-3} M in each reactant) solution of adenine, ribose,

and phosphoric acid (both the UV light and H_3PO_4 were needed).⁵⁸ They also demonstrated the formation of deoxyadenosine under similar conditions.⁵⁹ In the case of the latter nucleoside they showed that cyanide could be substituted for phosphate and that some deoxyadenosine was formed even without the UV irradiation. Curiously enough, substitution of adenine by any one of the other four nucleic-acid bases led to no detectable nucleoside formation.⁶⁰

Nucleotides

In considering the formation of the nucleotides (the base-sugar-phosphate, or monomeric, unit of the nucleic acids) we should first consider the state of the element phosphorus on the primitive Earth. In any watery environment the predominant chemical form of phosphorus is phosphoric acid--Miller and Horowitz have stated (in their excellent review, "Current Theories on the Origin of Life") that "thermodynamic calculations show that all lower oxidation states of phosphorus are unstable under any pressures of hydrogen that are reasonable."⁶¹ Consequently, although there are some problems with respect to the insolubility of the alkaline-earth phosphates, it seems reasonable to envision available phosphate on the primitive Earth for the formation of the extremely important (to life) organic phosphates.

In the work quoted above regarding adenosine formation, the same group found no detectable adenosine phosphate (= the nucleotide; also called adenylic acid) when adenosine was treated with phosphoric acid and ultraviolet light.⁵⁸ They did show that when "polyphosphate ester" (a complex mixture formed by reacting P_2O_5 with ethyl ether⁶²) is substituted for the phosphoric acid, adenylic acid was formed. They also

detected the synthesis of adenosine diphosphate (ADP) and adenosine triphosphate (ATP)--the latter compound is the chief storage depot for energy, and chief supplier of energy, for biological processes. Unfortunately, the "polyphosphate ester" seems a very unlikely primitive-Earth compound (for one thing, it is very quickly hydrolyzed), but arguments have been advanced in favor of its possible existence on the early Earth.⁶²

In subsequent work, Ponnamperuma and Mack heated separately (in the absence of water) the five nucleic-acid nucleosides (adenosine, guanosine, cytidine, uridine, and thymidine) with sodium dihydrogen phosphate (NaH_2PO_4) at 160° for two hours.^{63,100} They demonstrated the formation of the phosphates (nucleotides) of each of the nucleosides, many of the individual monophosphates (2'; 3'; 2'3'-cyclic; and 5'-phosphates), a dinucleoside phosphate (UpU), and a dinucleotide (UpUp). They also showed appreciable yields at temperatures as low as 80° , and that the presence of small amounts of water "is not incompatible with this reaction".

Waehnelde and Fox have recently demonstrated the phosphorylation (on the hydroxyl group of the pentose moiety) of adenosine, cytidine, deoxycytidine, guanosine, uridine, and thymidine.⁶⁴ They employed temperatures from $0-22^\circ$, and their phosphorylating reagent was polyphosphoric acid--the latter compound may well have existed on the primitive Earth since the formation of its principal constituent, pyrophosphoric acid, is formed in dilute aqueous solution by the action of cyanamide (a demonstrated "primitive Earth" compound⁶⁵) on phosphoric acid.⁶⁶ Pyrophosphate has also been prepared by Miller and Parris by

the reaction of potassium cyanate, KCNO , with hydroxyl apatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (this is the Earth's commonest phosphorus-containing mineral).⁶⁷ From the standpoint of chemical evolution, the work of Waehnelde and Fox, with its low temperatures and high yields (25-45%) of nucleoside phosphates, is particularly attractive.

Beck, et al. have recently reported the formation of uridine-5'-phosphate, uridine-2'(3')-phosphate, and some uridine diphosphate on heating (65-85°) uridine with inorganic phosphates for 9 months.⁹⁷ The most effective inorganic phosphates in promoting this reaction were $\text{Ca}(\text{H}_2\text{PO}_4)_2$ and $(\text{NH}_4)_2\text{HPO}_4$. The authors suggest that of the two, the ammonium hydrogen phosphate is the more likely to have played a part in chemical evolution. $\text{Ca}(\text{H}_2\text{PO}_4)_2$ is precipitated only from acid solution, whereas in an ocean containing substantial amounts of ammonia the $(\text{NH}_4)_2\text{HPO}_4$ may have formed on the evaporation of shallow pools.

3. Fats

The fatty (also called aliphatic or carboxylic) acids are another class of compounds whose appearance on the primitive Earth is very easily imagined. Experiments unrelated to the present interest in chemical evolution have demonstrated the formation of a wide variety of hydrocarbons, with molecular weights in the hundreds, on the passage of ionizing radiation through methane.^{68,69} In addition, it has been shown that ionizing radiation effects the direct addition of CO_2 to a hydrocarbon to form the corresponding fatty acid ($\text{RH} + \text{CO}_2 \rightsquigarrow \text{RCO}_2\text{H}$)⁷⁰ and to amines to form amino acids.¹⁰⁴ And it should be remarked here that, even in a predominantly reduced primitive atmosphere, the presence of some CO_2 would be expected.

Allen and Ponnampetuma have recently shown that exposure of methane and water to a semicorona discharge results in the formation of monocarboxylic acids from C_2 to C_{12} .⁷¹ The authors identified acetic, propionic, isobutyric, butyric, isovaleric, valeric, and isocaproic acids, and they presented mass spectrographic evidence that their C_6 - C_{12} acids were predominantly branched-chain.

Since the fats are esters of glycerol, it remains to be remarked that no one has yet reported glycerol as a product of primitive Earth experiments. The compound is not as easily detected as most of the other biologically-relevant compounds that we have been discussing, and this is probably the reason it has not yet been reported. It is a likely product of some future abiogenic synthesis that will be similar to the modern industrial synthetic route, starting with the C_3 hydrocarbon propylene, and proceeding through a series of hydrations and dehydrations.

4. Porphyryns

Another biologically very important class of compounds that need be considered are the porphyryns. Chlorophyll and heme (of hemoglobin are, respectively, magnesium and iron complexes (or "chelates") of substituted porphyryns. The porphyryns (or similar visible-light absorbing pigments) had to pre-exist the first alga. The established biosynthetic route to the porphyryns utilizes glycine and succinic acid (both known primitive-Earth compounds) and proceeds through a C_5 compound, δ -aminolevulinic acid.⁷² The latter has been sought, but not found, as a product of CH_4 - NH_3 - H_2O irradiations; it has been found as a product of the irradiation of dilute aqueous solutions of glycine and

succinic acid.⁷³ However, a very recent report asserts that porphyrins are detectable (no yields are given) after the passage of electric discharges through $\text{CH}_4\text{-NH}_3\text{-H}_2\text{O}$ mixtures.¹⁰¹) In the biosynthetic pathway two molecules of δ -aminolevulinic acid are condensed to form a pyrrole, four of which, in turn, condense to form a porphyrin. Szutka has demonstrated the appearance of pyrrolic compounds on the UV irradiation of aqueous solutions of δ -aminolevulinic acid.⁷⁴ One class of pyrrolic compounds, the porphyrinogens, are known to condense easily to porphyrins--however, enzymes are required for this condensation.⁷⁵ In the prebiotic Earth other catalysts, or long times, may have been effective.

It has been pointed out that during the Earth's transition from a reduced to an oxidized atmosphere, the presence of the porphyrins may have been critical for the further progress of chemical evolution. The gradual building up of O_2 (brought about, before the appearance of plant photosynthesis, by the radiolysis of water in the Earth's upper atmosphere) would have led to the appearance of hydrogen peroxide--the latter, in turn, would have produced widespread oxidation (i.e., destruction) of organic compounds. However, Calvin has pointed out that the incorporation of ferric ion into the porphyrin chelate heme increases, by a factor of one thousand, the catalytic effectiveness of the iron's ability to destroy peroxide.⁷⁶

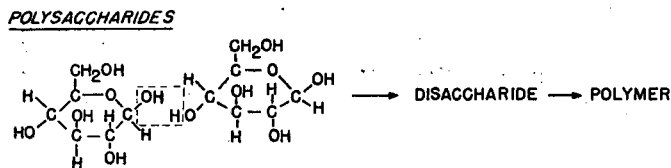
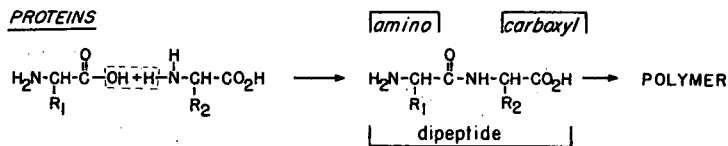
This section on the abiogenic synthesis of the biomonomers should not close without a comment on the limited number of these compounds that are so basic to our biochemistry. To quote George Wald, concerning what he calls the "alphabet of biochemistry":

"It turns out that about 29 organic molecules are enough to introduce the bare essentials [of biochemistry]. They include glucose, the major product of photosynthesis and major source of metabolic energy and hydrogen; fats as a principal storage form of metabolic energy; phosphatides as a means of circulating lipids in aqueous media and for their remarkable structure-forming proclivities; then the 20 amino acids from which all proteins, including all enzymes, are derived. Five nitrogenous bases (adenine, guanine, cytosine, uracil, thymine), together with ribose or its simple derivative deoxyribose and phosphoric acid, form all the nucleic acids, both RNA and DNA. These 29 molecules give students a first entry into the structures of proteins and nucleic acids, the coding of genetic information, the structure of enzymes, the composition and general properties of cell structures, and bring them to a point from which they can begin to explore the complexities of energy metabolism. That this is not the whole of biochemistry goes without saying; the extraordinary thing is that it makes so good a start. Yet this alphabet of biochemistry is hardly longer than our verbal alphabet."⁷⁷

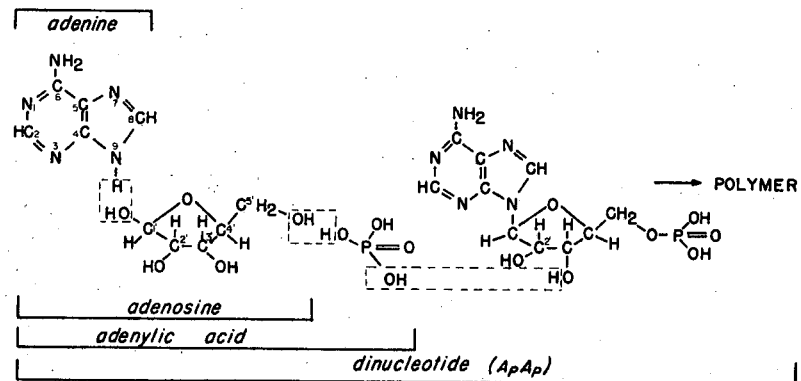
In view of the above statement it may not be amiss to feel that the "chemical evolutionists" have put together a satisfactory picture of the accumulation of the biologically important monomers on the primitive Earth.

ABIOTIC SYNTHESIS OF BIOPOLYMERS

Granted a primitive ocean with a lot of biomonomers in solution, one next comes upon the problem of how these compounds may have gotten condensed to form the biopolymers. In all cases the monomers are attached to each other with a concomitant elimination of water (dehydration condensation). These attachments are shown below for the three major classes of biopolymers: proteins, nucleic acids, and polysaccharides. In all cases the elimination of water is indicated by the dotted rectangles.



NUCLEIC ACIDS (3 STAGES) RNA SHOWN - DNA LACKS OH ON 2' POSITION



The chemical evolutionists have used two methods, both with some success, in trying to accomplish these condensations under assumed primitive Earth conditions. The first is to use the high-temperature, relatively anhydrous conditions (the volcanic-areas rationale). The second is to search for simple primitive-Earth compounds whose free energy, and selectivity of hydration, is such that they could promote the dehydration condensations--even in dilute aqueous solution. We shall review the progress toward a picture of the abiogenic synthesis of the biopolymers by separately considering the proteins and the nucleic acids. As yet, there is very little to report on polysaccharide abiogenic synthesis.

1. Proteins

As was mentioned earlier under "Other Conditions on the Primitive Earth," S. L. Fox and his coworkers have emphasized the possible role of high temperatures (around volcanoes) in promoting chemical evolution. They have done considerable research which has shown that dry mixtures of amino acids are condensed to protein-like material ("proteinoids") by simple heating to temperatures of 150-200°C; in the presence of polyphosphoric acid temperatures below 100° are still effective.⁷⁸⁻⁸⁰ The dicarboxyl amino acids, glutamic acid and aspartic acid, are peculiarly effective in promoting these condensations. When they are in excess in mixtures containing essentially all the natural-protein amino acids, the resultant copolymer is found to incorporate all the starting amino acids. This incorporation is not completely random--the incorporation of, for example, glycine, alanine, lysine, and methionine being slightly favored.⁷⁸ The amino acids lose their optical activity during the process of being built into the "protenoid".

Fox and coworkers call their products protein-like because (a) their infrared spectra show the typical bands of peptide (amino acid-amino acid) bonds, (b) they give positive biuret reactions (color tests for peptide bonds), (c) they can be hydrolyzed to amino acids, (d) they are susceptible to attack by proteolytic enzymes, and (e) they show some weak catalytic activity. Also intriguing, but somewhat outside the scope of this report, is the behavior of this "protenoid" material when it is dissolved in warm water, and the solution allowed to cool. When the solution (suspension) is viewed under the microscope, it is seen to contain a great number of small globules, or "microspheres".^{79,81} These globules have some properties that have led Fox and coworkers to call them proto- or pre-cellular. They are about 2 microns in diameter (in the size range of many living cells), they are not broken up by centrifugation at 3000 rpm, they can be sectioned and stained, they have pronounced outer membranes, and they show ATP-splitting (hydrolyzing) ability. Fox's work has led him to suggest that, on the primitive Earth, there was "a spontaneous synthesis of protein-like material sufficiently similar to yield a protocell," and that "one might thus visualize a natural evolution to cells and subsequently to cellular synthesis of macromolecules."⁸¹ A vast quantity of successful research will be necessary before such a vision will be based on solid fact--but chemical evolutionists are notoriously optimistic.

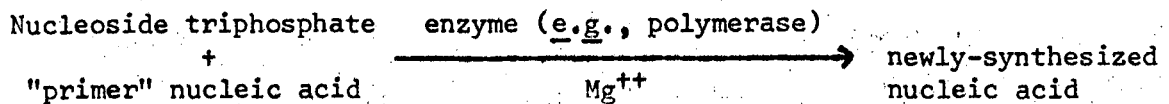
Peptides (two or more amino acids condensed together) have been reported as products from heating glycine in aqueous NH_4OH ,¹⁰² products of the γ -irradiation of N-acetylglycine,³⁷ and indicated as products of the thermal (90°) treatment of ammonium cyanide solutions.⁴²

Matthews and Moser found peptide-like material upon hydrolysis of the products obtained from (a) sparking $\text{CH}_4\text{-NH}_3$ mixtures²⁶ and (b) heating HCN-NH_3 mixtures²⁷--these experiments the authors advance as support for the idea that polypeptides may have resulted on the primitive Earth from hydrolysis of HCN polymers.⁸² Others have suggested a key role for hydrolyzed aminoacetonitrile polymers in the chemical evolution of the polypeptides (proteins), and this reaction has been used successfully to produce di- and tri-glycine.⁸³⁻⁸⁵

Some successes have been reported in forming peptides in dilute aqueous solutions at room temperature. This has been done by using simple analogs of the carbodiimides ($\text{RN=C=NR}'$), reagents that the synthetic organic chemist has been using for over a decade to effect dehydration condensations (in non-aqueous media). Cyanamide, $\text{H}_2\text{N-C}\equiv\text{N}$, a known "primitive-Earth" compound⁶⁵ and a tautomer of the parent (and unknown) member of the carbodiimide series (HC=C=NH), has been used to prepare simple peptides (glycylleucine, leucylglycine, and alanyl-alanine.^{86,87,66} A closely related compound, dicyanamide (NC-NH-CN) has also been used, again in dilute aqueous solution at room temperature, to convert up to 30% of starting glycine into diglycine.⁸⁸

2. Nucleic Acids

Just as some modest progress has been recorded in chemical evolution experiments in producing peptides (on the road towards the proteins), so also has progress been made in producing polynucleotides (on the way to the nucleic acids). Of great interest here is the work of Ochoa, and Kornberg, et al.,^{89,103} who showed the in vitro synthesis of nucleic acids as follows:



If the "primer" is left out of the reaction mixture, nucleic acid synthesis still occurs--only at a slower rate. The nucleoside phosphates, we have already seen, are synthesized under more or less primitive Earth conditions (see section headed "Nucleotides"), and there has always been plenty of magnesium ion available. The above reaction will not take place in the absence of the enzyme, and that, of course, cannot be present in an abiogenic experiment. However, to quote Shklovskii and Sagan (Ref. 12, p. 237, in referring to the above reaction):

"What is the function of the enzyme? These enzymes are catalysts which increase the rate, but not the direction, of a chemical reaction. This means that in the absence of DNA polymerase, appropriate nucleoside triphosphates will spontaneously join together, or polymerize, but on a much longer timescale than occurs in the presence of the enzyme. We do not now know what the rate of spontaneous polymerization of nucleoside triphosphates is, in the absence of the appropriate enzyme. Suppose it takes 1000 years. Clearly, such an experiment is not practicable to perform in the laboratory without the enzyme. In fact, the enzyme provides us with the laboratory tool we need. We can trade the enzyme for geological time."

In a more typical chemical evolution experiment it has been shown that cytidine phosphate (cytidylic acid) can be condensed to oligonucleotides (average number of monomers per chain = 5.6), at 65°, by the action of polyphosphoric acid.⁹⁰ The oligonucleotide was found to contain the 3'-5' phosphate linkages (to the ribose) that are characteristic of the natural nucleic acids. The difficulty with this work, is of course, the use of the polyphosphoric acid. However, Fox and others have suggested the possibility of localized concentrations of acid on the primitive Earth.^{88,91} Such concentrations, plus volcanic heat, might have made it possible for polyphosphoric acid to play a role in chemical evolution. The formation of oligonucleotides has also been reported on the heating (160°) of uridine phosphate and uridine.⁹²

It was mentioned earlier (under "Nucleotides") that Schramm, et al. have prepared a "polyphosphate ester" that has been used in dehydration condensation work.⁶² The same authors also reported that the preparation of polynucleotides (from nucleotides) with this reagent and have claimed some chemical-evolutionary relevance for their results.⁶² However, the existence of their reagent on the primitive Earth would have required a very unlikely set of circumstances.

Although they did not investigate nucleotide condensations, Steinman, et al. found that the previously mentioned cyanamide compounds did form (from glucose and H₃PO₄, in dilute aqueous solution), via dehydration condensation, the sugar-phosphate ester bond characteristic of the nucleic acids.⁶⁶

CONCLUDING REMARKS

Outside the scope of this report, as they are not really matters of "synthesis", are such subjects as Oparin's model of precellular organization,⁹³ current theories on the origin of optical activity,⁹⁴ the way in which the biopolymers, once formed, would organize themselves into the particular shapes (conformations) in which they exhibit biological activity,⁹⁵ and molecular self-duplication.⁹⁶ (The references are to excellent discussions of these particular topics.)

The new research "area" of chemical evolution is extremely broad and has excited the imaginations of all sorts of scientists, from astronomers to physiologists. Its steady progress, and resultant enrichment of human knowledge, is assured.

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