CHEMICAL EVOLUTION

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I. Introduction

The term "chemical evolution" has come to mean the chemical events that took place on the primitive, prebiotic Earth (about 4.5–3.5 billion years ago) 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 review the results and implications of chemical evolution experiments performed over the past two decades. 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 do not 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.

There are several reasons for the recent rise of research in chemical evolution. (1) One method of studying the detailed chemistry of the living cell is to try to reconstruct the chemistry of the prebiotic Earth that led to the appearance of life. (2) Laboratory work has shown that the exposure to high energies of samples of the primitive Earth's presumed atmosphere leads to the appearance of many biologically important organic molecules. (3) The immediacy of lunar and planetary exploration has made it important to know what compounds and conditions to seek in determining whether a given locale is now, ever was, or might be in the future an abode of life. (4) Chemical evolution is "interdisciplinary" in the widest and best sense. It is a field of research that promotes the active collaboration of (to name a few) astronomers, geologists, organic chemists, radiation chemists, and biologists.

In the latter half of the 19th century Darwin and Tyndall recognized that the backward extension in time of biological evolution led to a kind of chemical evolution. However, for the most part, this 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 little about the chemical events that must have preceded the appearance of life.

The USSR was the locale of the birth of the studies that we call chemical evolution. In the early 1920's 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," [1] 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 large amounts of organic compounds must have accumulated on the prebiotic Earth, particularly in the oceans.[2] It was not until after World War II, however, that direct experimental evi-

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(1) A. I. Oparin, "Proiskhozhdenie zhizni," Izd. Moskovskii Rabochii, Moscow, 1924.

(2) J. B. S. Haldane, "Rationalist Annual," 1929; "Science and Human Life," Harper Bros., New York and London, 1933, p 149.

dence finally put the Oparin–Haldane ideas on firm ground and established chemical evolution as a serious scientific study.

II. Abiogenic Synthesis on the Primitive Earth

A. TIME SCALE

There is general agreement that the Earth condensed from a dust cloud 4.5–4.8 × 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,[4–6] and that multicellular organisms (Metazoa) may have been here 2–2.5 × 10^9 years ago.[7] 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 abiogenetically 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 is not.

B. 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 is now general agreement 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 sun[8]). 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 most of the carbon present on the early Earth was in the form of hydrocarbons.[9] 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 the fraction of neon present in the Earth's atmosphere today is only 10^{-10} of its cosmic abundance;[10] the other noble gases are similarly conspicuous by their relative absences. At first thought, it seems difficult to imagine the primitive Earth 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 carbides (from whence methane and other hydrocarbons may have come by reaction with water), the water retained as hydrates, and the ammonia as ammonium ion. A similar view is that the Earth's first atmosphere was lost by diffusion, and was replaced by a secondary one (also reduced) that resulted from outgassing from the Earth's interior.[11] Such a secondary atmosphere may have been kept in the reduced form for as long as 10^9 years by the presence of metallic iron in the Earth's upper mantle and crust.[12]

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

(a) The general geochemical arguments of Oparin[9] and Urey[13] 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.[13]

(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.[14]

(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. 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.[15] 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 Rutten[16])—the finding, for example, of increased ferrous iron in the oldest Precambrian sediments—indicates that these deposits were laid down under a reduced atmosphere.

It should be noted that this view of a reduced early atmosphere is not without its detractors. Abelson[17] and Cloud[18] have asserted, mostly because "carbon is not a conspicuous

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(3) G. R. Tilton and R. H. Steiger, *Science*, **150**, 1805 (1965).

(4) E. S. Barghoorn and J. W. Schopf, *ibid.*, **152**, 758 (1966).

(5) J. W. Schopf and E. S. Barghoorn, *ibid.*, **156**, 508 (1967).

(6) A. E. J. Engel, *et al.*, *ibid.*, **161**, 1005 (1968).

(7) H. J. Hofman, *ibid.*, **156**, 500 (1967).

(8) H. N. Russell, *Astrophys. J.*, **70**, 11 (1929).

(9) A. I. Oparin, "Origin of Life," 2nd English ed, 1953, Dover Publications, Inc., New York, N. Y., p 101.

(10) H. Brown, "The Atmospheres of the Earth and Planets," University of Chicago Press, Chicago, Ill., 1952, p 258.

(11) H. D. Holland in "Petrologic Studies: a Volume in Honor of A. F. Buddington," A. E. J. Engel, H. L. James, and B. F. Leonard, Ed., Geological Society of America, New York, N. Y., 1962, p 447.

(12) S. I. Rasool and W. E. McGovern, *Nature*, **212**, 1225 (1966).

(13) H. C. Urey, "The Planets: Their Origin and Development," Yale University Press, New Haven, Conn., 1952.

(14) S. L. Miller and H. C. Urey, *Science*, **130**, 245 (1959).

(15) H. Stern, *ibid.*, **121**, 144 (1955).

(16) M. G. Rutten, "The Geological Aspects of the Origin of Life on Earth," Elsevier Publishing Co., Amsterdam, 1962, p 106.

(17) P. H. Abelson, *Proc. Natl. Acad. Sci. U. S.*, **55**, 1365 (1966).

(18) P. E. Cloud, Jr., *Science*, **160**, 729 (1968).

component of the oldest sediments," that there was little methane in the primitive atmosphere. However, we have no samples of rocks reliably known to an age greater than about 3.5 billion years. It may be that, by that time, the carbon in the Earth's atmosphere had shifted from predominantly CH_4 to predominantly CO_2. The era of chemical evolution that we are considering may be considered as taking place during the first billion years of the Earth's history—at a time when, it is very probable, the atmosphere was reduced.

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.

C. 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. Table I is a compilation of data supplied from several different sources.[14,19,20]

Table I

Main Present Sources of Energy at Earth's Surface

Energy source	*Energy, cal/year* $\times 10^{-19}$
Total radiation from sun	132,000
Ultraviolet light	
$\lambda < 2500$ Å	300
$\lambda < 2000$ Å	45
$\lambda < 1500$ Å	1.8
Electric discharges	2.1
Radioactivity	0.4[a]
Volcanoes	0.07
Cosmic rays	0.0008

[a] 4×10^9 years ago this value was about 1.4×10^{19} cal/year.[19]

Since methane, ammonia, and water all absorb very little at wavelengths longer than 2000 Å, only shorter wavelengths can be considered as having been effective on the Earth's primitive atmosphere. Since, however, the region below 2000 Å 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), γ 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 ambient 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°) 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, 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 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 1% solution of organic matter in 3×10^8 years.[21] 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 photolysis by 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.

III. Simulated Primitive-Earth Experiments. Early Work and Usual Experimental Conditions

A. 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.[22] In that experiment, and in subsequent ones throughout the ensuing half-century, claims were made

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(19) E. Bullard in "The Earth as a Planet," G. P. Kuiper, Ed., University of Chicago Press, Chicago, Ill., 1964, p 110.

(20) A. J. Swallow, "Radiation Chemistry of Organic Compounds," Pergamon Press, New York, N. Y., 1960, p 244.

(21) I. S. Shklovskii and C. Sagan, "Intelligent Life in the Universe," Holden-Day, Inc., San Francisco, Calif., 1966, p 233.

(22) S. M. Losanitsch and M. Z. Jowitschitsch, *Ber.*, **30**, 135 (1897).

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 CO_2–H_2O 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.[23]

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.*[24] These workers demonstrated the appearance of formic acid and formaldehyde when CO_2–H_2O–Fe^{2+} solutions were irradiated with an α-particle beam. A far greater interest was engendered by the experiments of Miller, first reported in 1953.[25] Having been convinced by the arguments of Oparin[9] and Urey[13] 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 CH_4, NH_3, H_2O, and H_2) 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 16 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.

B. EXPERIMENTAL CONDITIONS

From the foregoing discussions, the reader can conclude that there is general agreement as to what may constitute a meaningful "chemical evolution" experiment. In order to determine what biologically relevant chemistry may have occurred in the Earth's early atmosphere, one employs a mixture of simple molecules (CH_4, NH_3, H_2O, N_2, CO, H_2, etc.) of an overall reduced character, and with energy sources that were certainly plentiful on the primitive Earth (preferably uv light and electric discharges). If one is interested in the chemistry of the primitive oceans, it is desirable to work at ambient temperature, in dilute ($\sim$1%) solution, and with reactants that (a) appear as products of the early-atmosphere processes and (b) are reasonably stable toward hydrolysis; the same energy sources are employed. 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).

The main disagreement with these experimental conditions 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. When one considers the problem of the formation of the biopolymers in dilute aqueous solution, one realizes that high temperatures and/or nonaqueous environments may indeed have played important, perhaps indispensable, roles in chemical evolution. However, the dilute solution (ocean) model is preferred because the oceans would have provided a wealth of catalytic surfaces, transportation and mixing of intermediate products, and protection from ultraviolet light. Additional considerations are that the oceans cover such a large fraction of the Earth's surface and that they are the almost certain locale for the emergence of life.

IV. Abiogenic Synthesis of Biomonomers

In this section we shall review the progress that has been made, through 1968, in the laboratory synthesis, under the conditions 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 abiogenic synthesis of the amino acids, nucleic acid bases, nucleosides, nucleotides, sugars, fats, and porphyrins.

Since most of the abiogenic syntheses have come from the effects of high energy on methane–ammonia–water mixtures, we shall first consider the chemical-evolution-relevant radiation chemistry of each of these compounds. Most of our knowledge of this chemistry comes from the identifications of reactive fragments in the mass spectrometer, *i.e.*, after electron impact on the compound under observation. However, it is likely that the same fragments appear under the effects of other forms of ionizing radiation, some of which are of greater importance to chemical evolution (*e.g.*, electric discharges or ultraviolet light). To say that "the same fragments appear" does not imply that they necessarily end up in the same product. Different fragment densities, along the tracks of various ionizing rays or particles, may lead to quite different final products.

A. RADIATION CHEMISTRY OF METHANE, AMMONIA, AND WATER

1. Methane

The radiation chemistry of this compound has been extensively studied. Mass spectrometric investigations of the pure gas have shown that the principal carbon-containing ions formed are CH_4^+ (47%), CH_3^+ (40%), CH_2^+ (8%), CH^+ (4%), and C^+ (1%).[26] H^+ is also observed (about 1%), as is a trace of H_2^+. Additional mass spectrometric investigations, at higher pressures, have shown the predominance of the ion–molecule reactions.

$$CH_4^+ + CH_4 \longrightarrow CH_5^+ + \cdot CH_3$$
$$CH_3^+ + CH_4 \longrightarrow C_2H_5^+ + H_2$$

At pressures of about 0.2–2.0 mm the CH_5^+ and $C_2H_5^+$ account for about 70% of the ion current, and ions up to C_7 have been detected.[26,27] That these ions are branched, as well as straight-chained, is indicated by the identification of isobutane and isopentane among the radiolysis products of

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(23) E. I. Rabinowitch, "Photosynthesis," Vol. I, Interscience Publishers, New York, N. Y., 1945, p 82.

(24) W. M. Garrison, *et al.*, *Science*, **114**, 416 (1951).

(25) S. L. Miller, *ibid.*, **117**, 528 (1953).

(26) F. H. Field and M. S. B. Munson, *J. Am. Chem. Soc.*, **87**, 3289 (1965).

(27) S. Wexler and N. Jesse, *ibid.*, **84**, 3425 (1962).

methane.[28] The higher molecular weight ions and radicals arise, at least in part, from such additional reactions as

$$C_2H_5^+ + CH_4 \longrightarrow C_3H_7^+ + H_2$$

$$C_2H_5^+ + e^- \longrightarrow \cdot C_2H_5$$

The G values (molecules produced per 100 eV of absorbed energy) for the principal products observed on methane's radiolysis are[29]

Product	*G*	*Product*	*G*
H_2	6.4	n-C_4H_{10}	0.13
C_2H_4	0.13	i-C_4H_{10}	0.06
C_2H_6	2.1	i-C_5H_{10}	0.05
C_3H_8	0.26		

The prominent ethylene product (C_2H_4) is assumed to arise from

$$C_2H_5^+ + e^- \longrightarrow C_2H_4 + H\cdot$$

and

$$2CH_2 \longrightarrow C_2H_4$$

The ethylene may account for another route to higher molecular weight products

$$R\cdot + C_2H_4 \longrightarrow RCH_2CH_2\cdot \xrightarrow{C_2H_4} R(CH_2)_4\cdot, \text{ etc.}$$

where R· is a radical or a hydrogen atom.

Although acetylene has not been reported as a product of the radiolysis of pure methane, it has been observed when I_2 is present,[29] and $C_2H_2^+$ ions have been observed in the mass spectrum of pure methane.[26] The polymerization of acetylene is presumed to be the route to the benzene ring of the aromatic amino acids, phenylalanine and tyrosine, that have been reported as products of methane–ammonia–water radiolyses. A number of arenes, including benzene, naphthalene, acenaphthalene, phenanthracene, and pyrene, have appeared when CH_4 is passed over silica gel at 1000°.[30]

2. *Ammonia*

Mass spectrometric studies of gaseous ammonia have shown that NH_2^+, NH_3^+, and NH_4^+ are the principal ions produced.[31,32] The only molecular products are N_2, H_2, and N_2H_4 (hydrazine). The appearance of the hydrazine indicates the production of NH_2 radicals, as does mass spectral observations, indicating that the reaction $NH_3^+ + NH_3 \rightarrow NH_4^+ + NH_2$ occurs with high efficiency.[31] The NH_2 radical may be the source of the amino group of the amino acids that are formed in primitive-Earth atmospheres. That it is important in the formation of the nucleic acid base, adenine, on irradiation of such atmospheres is indicated by a decreased adenine yield with increases of H_2 in the CH_4–NH_3–H_2O–H_2 mixture.[33] The presence of H_2 probably decreases the NH_2 yield by the reaction: $NH_2 + H_2 \rightarrow NH_3 + H$.

3. *Water*

More radiation chemical studies have been devoted to water than to any other single compound. This is due not only to its importance in radiobiology. It has attracted the attention of the radiation chemists because highly purified samples are easily obtainable and because its relevant physical properties, such as bond angles and lengths, moment of inertia, dielectric constant, etc., are so well known; accurate knowledge of these properties is most useful in formulating radiolysis mechanisms.

Mass spectrometric studies on water have shown that the principal positive ions formed are H_2O^+, H_3O^+, OH^+, and H^+ (the relative intensities are approximately 5:1:1:1). A great variety of studies, of which the principal ones are electron spin resonance spectroscopy, pulse radiolysis accompanied by fast absorption spectroscopy, and addition of radical scavengers, have demonstrated that the principal reactive species in irradiated water are the ·OH radical, the ·H atom, and the hydrated electron (e_{aq}^-). The principal molecular products are H_2 and H_2O_2, resulting from combinations of ·H atoms and ·OH radicals. All of the effects of the participation of water in the radiolysis of methane–ammonia–water systems are interpretable on the basis of the participation of one of these reactive species (·H, ·OH, e_{aq}^-, H_2, H_2O_2, or of one of the ions listed above).[34]

B. AMINO ACIDS

It is the great successes in the abiogenic 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 indicate 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.[35–38] The characteristic formation of the amino acids seems also reflected in the preferred formation of α-aminonitriles, as reported by Ponnamperuma and Woeller.[39] 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.

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(28) K. Yang and P. J. Manno, *J. Am. Chem. Soc.*, **81**, 3507 (1959).

(29) G. G. Meisels, W. H. Hamill, and R. R. Williams, *J. Phys. Chem.*, **61**, 1456 (1957).

(30) J. Oró and J. Han, *Science*, **153**, 1393 (1966).

(31) L. M. Dorfman and P. C. Noble, *J. Phys. Chem.*, **63**, 980 (1959).

(32) B. P. Burtt and A. B. Zahlan, *J. Chem. Phys.*, **26**, 846 (1957).

(33) C. Ponnamperuma, R. M. Lemmon, R. Mariner, and M. Calvin, *Proc. Natl. Acad. Sci. U. S.*, **49**, 737 (1963).

(34) F. S. Dainton, *et al.*, in "Radiation Research," G. Silini, Ed., North Holland Publishing Co., Amsterdam, 1957 pp 161–262.

(35) S. L. Miller, *J. Am. Chem. Soc.*, **77**, 2351 (1955).

(36) S. L. Miller, *Ann. N. Y. Acad. Sci.*, **69**, 260 (1957).

(37) K. Harada and S. W. Fox, *Nature*, **201**, 335 (1964).

(38) C. U. Lowe, M. W. Rees, and R. Markham, *ibid.*, **199**, 219 (1963).

(39) C. Ponnamperuma and F. H. Woeller, *Currents Modern Biol.*, **1**, 156 (1967).

(a) The cyanohydrin mechanism, invoked by Miller[35] to explain his amino acid products

$$\mathrm{RCHO} \xrightarrow{\mathrm{NH_3,\ HCN}} \mathrm{RCH(NH_2)CN} \xrightarrow{\mathrm{H_2O}} \mathrm{RCH(NH_2)CO_2H}$$

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

(b) Since electric discharges in anhydrous methane–ammonia mixtures cause the formation of α-aminonitriles,[39] the intermediate aldehyde formation may not be necessary.

$$\mathrm{CH_4 + NH_3 \longrightarrow H_2NCH_2CN,\ H_3CCH(NH_2)CN} \xrightarrow{\mathrm{H_2O}} \mathrm{H_2NCH_2CO_2H,\ H_3CCH(NH_2)CO_2H}$$

(c) Sanchez, *et al.*,[40] have suggested a possibly important role for cyanoacetylene (a product of CH_4–N_2 irradiations) in amino acid syntheses. In the presence of NH_3 and HCN, this compound forms considerable asparagine and aspartic acid (*ca.* 10% yields); the suggested reactions are

$$\mathrm{NCC{\equiv}CH + NH_3 \longrightarrow NCCH{=}CHNH_2} \xrightarrow{\mathrm{HCN}} \mathrm{NCCH_2CH(NH_2)CN} \xrightarrow{\mathrm{H_2O}} \underset{\text{asparagine}}{\mathrm{HO_2CCH_2CH(NH_2)CONH_2}} \xrightarrow{\mathrm{H_2O}} \underset{\text{aspartic acid}}{\mathrm{HO_2CCH_2CH(NH_2)CO_2H}}$$

(d) Abelson,[17] Matthews, Claggett, and Moser,[41–44] and Harada[45] have emphasized a possible key role of HCN oligomers, produced by the base-catalyzed polymerization of HCN. They have found, for example, that the HCN trimer, aminoacetonitrile, and the HCN tetramer, diaminomaleonitrile, give, on heating in water for 24 hr at 100°, as many as 12 of the 20 α-amino acids commonly found in proteins.[43,44] Abelson reports that uv light (2536 Å) speeds HCN polymerization and that, on hydrolysis, glycine, alanine, serine, aspartic acid, and glutamic acid are found.[17]

With the data now available, it is impossible to decide which of the above routes was the most important path of amino acid formation in abiogenic syntheses. Probably all of them contributed to some degree.

Table II[46–54] is a summary of the amino acids whose syntheses have been reported during the past 16 years in "primitive Earth atmosphere" experiments. Yield data are omitted. However, in all primitive-Earth experiments yields are low, rarely exceeding 5% of the starting carbon (*e.g.*, methane) and usually below 1%. 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 II were performed on CH_4–NH_3–H_2O–H_2 mixtures; the exceptions are noted. In some cases, the H_2 was omitted; in others, varying amounts of CO, CO_2, or N_2 were added. In all cases the mixture was more reduced than oxidized.

The data of Table II leave no doubt that amino acids, at least those up to six 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 CH_4–NH_3–H_2O–H_2 mixtures to about 1000°. 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, Fla., in 1963.[55]

In addition to the amino acids whose formation from "primitive-Earth atmospheres" is recorded in Table II, 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 III.[56–66]

C. NUCLEIC ACID COMPONENTS

In reviewing the progress made in the abiogenic syntheses of the nucleic acid monomers (the nucleotides) we shall consider, in turn, synthesis of the purine and pyrimidine bases, the sugars, the nucleosides, and the nucleotides themselves.

1. 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 these nucleic acid bases. The more

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(45) K. Harada, *Nature*, **214**, 479 (1967).

(46) T. E. Pavlovskaya and A. G. Pasynskii in "The Origin of Life on Earth," Proceedings of the 1st International Symposium, Moscow, 1957, Pergamon Press, New York, N. Y., 1959, p 151.

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(57) K. Dose and C. Ponnamperuma, *Radiation Res.*, **31**, 650 (1967).

(58) T. Hasselstrom, M. C. Henry, and B. Murr, *Science*, **125**, 350 (1957).

(59) C. Reid in ref 46, p 619.

(60) S. W. Fox, *Science*, **132**, 200 (1960),

(61) J. Oró, A. Kimball, R. Fritz, and F. Master, *Arch. Biochem. Biophys.*, **85**, 115 (1959).

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(66) G. Steinman, E. A. Smith, and J. J. Silver, *Science*, **159**, 1108 (1968).

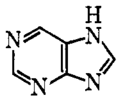
Table II

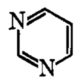
Production of Amino Acids in Simulated "Primitive-Earth Atmosphere" Experiments (1953–1968)

Amino acid formed	*Input energy*[a]	*Product identification*[b]	*Lit ref*
Glycine	A	I	35
	A	II	46
	A	II	47[e]
	C	I	48
	A	II	49
	B	II	50[c]
	A	II	51[f]
	A	II	52
	D	II	37
Alanine	A	I	35
	C	I	48
	A	II	46
	B	II	50[c]
	A	II	52
	D	II	37
	A	II	47[e]
	A	II	49
	A	II	51[f]
β-Alanine	A	I	35
	A	II	52
	A	II	46
	A	II	51[f]
Cysteic acid	A	I	53[d]
N-Methylglycine (sarcosine)	A	I	35
	D	II	37
	A	II	52
	A	II	51[f]
Serine	A	II	49
	D	II	37
Threonine	A	II	49
	D	II	37
α-Aminobutyric acid	A	I	35
	A	II	46
	B	II	51[f]
	D	II	37
	A	II	49
N-Methylalanine	A	I	35
Asparagine	A	II	47[e]
Aspartic acid	A	I	35
	C	I	48
	A	II	46
	A	II	47[e]
	A	II	49
	D	II	37
Glutamic acid	A	I	35
	A	II	46
	A	II	49
	D	II	37
Valine	D	II	37
Leucine	D	II	37
	D	II	54
	A	II	49
Isoleucine	D	II	37
	D	II	54
	A	II	49
Alloisoleucine	D	II	37
	D	II	54
Lysine	A	II	46
	A	II	49
Phenylalanine	D	II	37
	D	II	54
Tyrosine	D	II	37
	D	II	54

[a] A = electric discharge (spark or corona), B = uv radiation, C = ionizing radiation (γ-rays or electrons), D = heat (about 1000°). [b] (I) Product identification very secure; for example, absolute chromatographic coincidence between labeled product (from $^{14}CH_4$) 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 CH_4–NH_3–H_2O mixture. [e] Ethane was added to a CH_4–NH_3–H_2O–H_2 mixture. [f] Experiments on CO_2–N_2–H_2–H_2O mixtures.

complex structures of the latter indicate why this should be expected. The two purines (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.


purine


pyrimidine

Adenine is the only one of the five nucleic acid bases that has been synthesized in a "primitive-Earth atmosphere" experiment. In 1963, Ponnamperuma, *et al.*, found adenine after irradiating a CH_4–NH_3–H_2O–H_2 mixture with an electron beam.[38] 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. This H_2 effect is not surprising since methane carbon must be oxidized in order to appear finally in a purine. In the adenine synthesis, the principal species effecting the oxidations are probably OH and NH_2 radicals, and these would revert to the starting materials (water and ammonia) on reaction with hydrogen.

Table III

Formation of Amino Acids from Primitive-Earth Compounds (1953–1968)

Reactants	*Input energy*	*Amino acids reported*[a]	*Lit. ref*
1. Paraformaldehyde, H_2O, NO_3^-, Fe^{+3}	Sunlight	Gly, Ala, Asp, Val, His, Pro, Lys, Ser, Asp, Arg	56
2. N-Acetylglycine, H_2O, NH_3	γ-Rays	Gly, Asp, Thr	57
3. NH_4Ac, H_2O	e^- beam	Gly, Asp	58
4. H_2NOH, HCHO, CO_2	Uv	Gly, Ala	59
5. HCHO, NH_4Cl, NH_4NO_3	Uv	Ser, Gly, Ala, Glu, Val, Ile, Phe	46
6. HCN (at pH 8–9), followed by hydrolysis	Uv	Gly, Ala, Ser, Asp, Glu	17
7. Formamide	Pyrolysis at 250°, followed by hydrolysis of product	Gly, Ala, Asp, Ser, Thr, Val, Glu, Leu	47
8. Glucose, urea	150–200° hydrolysis of product	Gly	60
9. Malic acid, urea	As above	Asp	60
10. Hydroxyglutamic acid, NH_3	As above	Glu	60
11. HCN, NH_3, H_2O	90°	Asp, Thr, Ser, Glu, Gly, Ala, Ile, Leu, β-Ala, Abu	38
12. HCHO, H_2NOH, H_2O	80–100°	Gly, Ala, β-Ala, Ser, Thr, Asp	61
13. HCN, NH_3, H_2O	27–100°	Gly, Ala, Asp	62
14. $HC\equiv CCN$, NH_3, H_2O, HCN	100°	Asp, $AspNH_2$	40
15. $(NH_4)_2CO_3$ (solid)	γ-Rays	Gly	63
16. Glycine (on quartz)	260–280°	Ala, Asp	64
17. $EtNH_2$, HCO_3^-, S^{2-}	γ-Rays	Cys, $(Cys)_2$	65, 66

[a] Ala = alanine, β-Ala = β-alanine, Abu = α-aminobutyric acid, Arg = arginine, Asp = aspartic acid, $AspNH_2$ = asparagine, Cys = cysteine, $(Cys)_2$ = cystine, Gly = glycine, Glu = glutamic acid, His = histidine, Ile = isoleucine, Leu = leucine, Lys = lysine, Pro = proline, Phe = phenylalanine, Ser = serine, Thr = threonine, Val = valine.

$$\cdot OH + H_2 \longrightarrow H_2O + H\cdot$$

$$\cdot NH_2 + H_2 \longrightarrow NH_3 + H\cdot$$

The first reaction is energetically favored since the H–H bond energy is 104.2 kcal and the H–OH bond energy is 119 kcal.[67] The second is slightly unfavored (H–NH_2 bond energy is 103 kcal)[67] and may not occur. Another way in which H_2 may interfere with the production of purines would be through the back reaction $H_2 + \cdot CH_3 \rightarrow CH_4 + \cdot H$. Here, the bond energies are very similar: H–CH_3 (104.0 kcal), H–H (104.2 kcal).[67]

The mechanism of the formation of adenine from the CH_4–NH_3–H_2O mixture is unknown. However, it may be noted that adenine may be considered as a pentamer of HCN, *i.e.*, $(HCN)_5$, and that hydrogen cyanide was a prominent product of Miller's experiment.[35] Furthermore, the formation of adenine from HCN in basic aqueous solution (see below) appears to proceed through a trimer and a tetramer of HCN.

None of the other nucleic acid bases (guanine, cytosine, thymine, or uracil) has been detected after the irradiation of CH_4–NH_3–H_2O mixtures. The apparent preference for adenine synthesis may be related to multiple roles of adenine in biological systems. Not only is it a constituent of both DNA and RNA, but it is also present in many important cofactors, for example, ATP, ADP, DPN, TPN, FAD, and coenzyme A. In addition, molecular orbital calculations have shown that, of all the biologically important purines and pyrimidines, adenine has the greatest resonance energy.[68,69] This would not only make synthesis of adenine more likely but would, in addition, confer radiation stability upon it.

The first "primitive-Earth" synthesis of adenine was reported by Oró in 1960;[70] this work was elaborated in further publications[62,71] and confirmed by Lowe, *et al.*[38] 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 or diaminofumaronitrile (both HCN tetramers).[71–74] The probable reaction sequence is shown in eq 1. All of the compounds in the above sequence, with the exception of the HCN dimer, have been identified in the aqueous solution chemistry of HCN. Evidence for the existence of the dimer in the (presumably) lower energy form of its radical tautomer (aminocyanocarbene), as well as evi-

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(67) J. A. Kerr and A. F. Trotman-Dickenson, "Handbook of Chemistry and Physics," 48th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967–1968, pp F-149–F-154.

(68) B. Pullman and A. Pullman, *Nature*, **196**, 1137 (1962).

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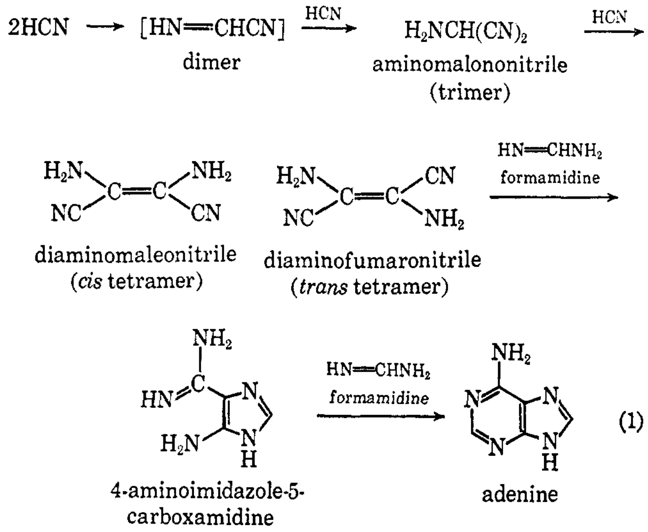
(71) J. Oró and A. P. Kimball, *Arch. Biochem. Biophys.*, **94**, 217 (1961).

(72) J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, **88**, 3829 (1966).

(73) R. A. Sanchez, J. P. Ferris, and L. E. Orgel, *J. Mol. Biol.*, **30**, 223 (1967).

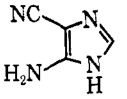
(74) R. A. Sanchez, J. P. Ferris, and L. E. Orgel, *ibid.*, **38**, 121 (1968).



(1)

dence for the spin ground state of the latter, have been presented in a recent publication.[75]

Both adenine and the other nucleic acid purine, guanine, have been synthesized by shining ultraviolet light on dilute solutions of HCN.[76] These two purines have also been reported as products of the reaction of aqueous solutions of HCN or cyanogen with 4-amino-5-cyanoimidazole.[73,74,77]



This compound is also a product that is formed in aqueous solutions of HCN and NH_3.[73] Upon reaction with ammonia it gives the 4-aminoimidazole-5-carboxamidine of the reaction sequence above.

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.[78] 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 transitory). Oró has also recorded the appearance of uracil under conditions he considers relevant to chemical evolution: heating (135°) urea with acrylonitrile (or β-aminopropionitrile, or β-aminopropionamide) in aqueous solution.[54]

The only reported abiogenetic synthesis of cytosine is that of Sanchez, *et al.*[40,79] They found a 5% yield of this pyrimidine upon heating 0.1 *M* aqueous cyanoacetylene (which they report as a product of the sparking of a mixture of CH_4 and N_2) with 1.0 *M* KCNO for 1 day at 100°. These authors also report that cytosine is obtained in a 1% yield when the same solution of the same reactants 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.[77] The abiogenic syntheses of the nucleic acid purines and pyrimidines are summarized in Table IV.

Table IV

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

Compound	*Experimental conditions*	*Lit ref*
Adenine	Aq NH_4CN, HCN, 90°, 1 day	38, 70
	CH_4—NH_3-H_2O; e^- beam	33
	Aq HCN, uv	76
	Aq diaminomaleonitrile + HCN, uv, 25°	73, 77
Guanine	Aq HCN, uv	76
	Aq diaminomaleonitrile + C_2N_2, uv, 100°	73, 77
Uracil	Malic acid, urea, $H_4P_2O_7$, 130°	78
	Acrylonitrile, urea, H_2O, 135°	54
Cytosine	HC≡CCN, KCNO, H_2O, 100°	79
Thymine	No recorded "primitive-Earth" synthesis	

2. 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.[80] Miller's early work produced evidence, not only for the production of formaldehyde on sparking the CH_4-NH_3-H_2O-H_2 mixture, but also ("possibly") for the appearance of sugars.[14] 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 CH_4-NH_3-H_2O 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 reported as products of the ultraviolet irradiation of formaldehyde.[76] In addition, a 3.8% yield of ribose has been reported to appear on the refluxing of 0.01 *M* HCHO over kaolinite (hydrated aluminum silicate).[81]

3. Nucleosides

The nucleosides represent a major gap in the synthesis of biologically important intermediates under primitive-Earth conditions. Experiments performed in 1963–1964 indicated the formations of adenosine and deoxyadenosine when 2537-Å light was shown on dilute (about 10^{-3} *M* in each reactant) solutions of adenosine, ribose (or deoxyribose), and NH_4-H_2PO_4 or NaCN.[82,83] Later work, however, showed that the products were not the natural nucleosides, but closely related (chemically and chromatographically) adenine–sugar adducts.[84] In addition, substitution of adenine by any one of the

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(75) R. E. Moser, J. M. Fritsch, T. L. Westman, R. M Kliss, and C. N. Matthews, *J. Am. Chem. Soc.*, **89**, 5673 (1967).

(76) C. Ponnamperuma, in ref 49, p 221.

(77) R. Sanchez, J. Ferris, and L. E. Orgel, *Science*, **153**, 72 (1966).

(78) S. W. Fox and K. Harada, *ibid.*, **133**, 1923 (1961).

(79) J. P. Ferris, R. A. Sanchez, and L. E. Orgel, *J. Mol. Biol.*, **33**, 693 (1968).

(80) A. Butlerov, *Ann.*, **120**, 296 (1861).

(81) N. W. Gabel and C. Ponnamperuma, *Nature*, **216**, 453 (1967).

(82) C. Ponnamperuma, C. Sagan, and R. Mariner, *ibid.*, **199**, 222 (1963).

(83) C. Ponnamperuma and P. Kirk, *ibid.*, **203**, 400 (1964).

(84) C. Reid, L. E. Orgel, and C. Ponnamperuma, *ibid.*, **216**, 936 (1967)

other four nucleic acid bases led to no detectable nucleoside formation.[85]

4. 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; the lower oxidation states of phosphorus are unstable except under higher H_2 pressures than are reasonable for a primitive-Earth atmosphere.[86] With respect to chemical evolution, the main problem is not the chemical form of the phosphorus, but rather the very low solubility of the alkaline earth phosphates. There would have been, just as today, very little phosphate dissolved in the ocean. However, the phosphate-incorporating reactions may have taken place at the surface of phosphate minerals. The adsorption of dissolved organic compounds onto the surface of such minerals, and their ensuing phosphorylation at those sites, may have been key steps in chemical evolution.

In the work quoted above regarding adenosine formation, the same workers found no detectable adenosine phosphate (adenylic acid) when adenosine was treated with phosphoric acid and ultraviolet light.[82] They did show that when "polyphosphate ester" (a complex mixture of compounds formed by reacting P_2O_5 with ethyl ether[87]) 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.[87]

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 2 hr.[88] 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 reactions would take place in the presence of small amounts of water. Evidence has been presented that these phosphorylations are effected by a prior formation of pyrophosphate (and higher condensed phosphates).[89]

Waehneldt and Fox have recently demonstrated the phosphorylation (on the hydroxyl group of the pentose moiety) of adenosine, cytidine, deoxycytidine, guanosine, uridine, and thymidine.[90] They employed temperatures from 0 to 22°, and their phosphorylating reagent was polyphosphoric acid; the latter compound may well have existed on the primitive Earth, both for the reason given above and because its principal constituent, pyrophosphoric acid, is formed in dilute aqueous solution by the action of cyanamide (a compound that results from CH_4–NH_3–H_2O irradiations[91]) on phosphoric acid.[92] Pyrophosphate has also been prepared by Miller and Parris by the reaction of potassium cyanate, KCNO, with hydroxyl apatite, $Ca_{10}(PO_4)_6(OH)_2$ (this is the Earth's commonest phosphorus-containing mineral).[93] From the standpoint of chemical evolution, the work of Waehneldt and Fox, with its low temperatures and high yields (25–45%) of nucleoside phosphates, is particularly attractive.

Orgel, *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.[94] The most effective inorganic phosphates in promoting this reaction were $Ca(H_2PO_4)_2$ and $(NH_4)_2HPO_4$. The authors suggest that of the two, the ammonium hydrogen phosphate is the more likely to have played a part in chemical evolution. $Ca(H_2PO_4)_2$ is precipitated only from acid solution, whereas in an ocean containing substantial amounts of ammonia the $(NH_4)_2HPO_4$ may have formed on the evaporation of shallow pools. Further work from the same laboratory has shown that approximately 1–4% yields of uridine 5′-phosphate are achieved by heating aqueous uridine (0.1 *M*) with $H_2PO_4^-$ (~1 *M*, pH 5–8) at 95° for 5 hr *in the presence of* a variety of cyanide derivatives (~1 *M*). Of the latter compounds, results of this work led the authors to believe that cyanogen (and its partial-hydrolysis products, cyanformamide and cyanate), cyanamide, and cyanamide dimer (dicyandiamide) were the most effective in producing these condensations.[95] (The latter two compounds are discussed later in this report under "Abiogenic Synthesis of Biopolymers.") The presence of cyanamide dimer (0.01 *M*, aqueous solution) has been found to produce a small (<1%) yield of adenosine 5′-phosphate when adenosine (0.01 *M*) and H_3PO_4 (0.01 *M*) are allowed to stand at room temperature for 4.5 hr.[96] The only difficulty about this work, with respect to chemical evolution, is the necessity of a low pH (2–3); at pH 7 the nucleotide formation is not observed.

D. FATS

The fatty (*i.e.*, aliphatic or carboxylic) acids are another class of compounds whose appearance on the primitive Earth is 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.[97,98] 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 ($RH + CO_2 \rightsquigarrow RCO_2$-

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(85) C. Ponnamperuma, private communication.

(86) N. H. Horowitz and S. L. Miller, *Progr. Chem. Org. Nat. Prod.*, **20**, 453 (1962).

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(90) T. V. Waehneldt and S. W. Fox, *Biochim. Biophys. Acta*, **134**, 1 (1967).

(91) A. Schimpl, R. M. Lemmon, and M. Calvin, *Science*, **147**, 149 (1964).

(92) G. Steinman, R. M. Lemmon, and M. Calvin, *Proc. Natl. Acad. Sci. U. S.*, **52**, 27 (1964).

(93) S. L. Miller and M. Parris, *Nature*, **204**, 1248 (1964).

(94) A. Beck, R. Lohrmann, and L. E. Orgel, *Science*, **157**, 952 (1967).

(95) R. Lohrmann and L. E. Orgel, *ibid.*, **161**, 64 (1968).

(96) G. Steinman, R. M. Lemmon, and M. Calvin, *ibid.*, **147**, 1574 (1965).

(97) S. C. Lind and D. C. Bardwell, *J. Am. Chem. Soc.*, **48**, 2335 (1926).

(98) W. Mund and W. Koch, *Bull. Soc. Chim. Belges*, **34**, 119 (1925).

H)[99] and to amines to form amino acids.[100] 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 Ponnamperuma 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}.[101] 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 (laboratory) 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.

E. PORPHYRINS

Another biologically very important class of compounds that need be considered are the porphyrins. Chlorophyll and heme are, respectively, magnesium and iron complexes (chelates) of substituted porphyrins. The porphyrins (or similar visible-light absorbing pigments) had to preexist the first alga. The established biosynthetic route to the porphyrins utilizes glycine and succinic acid (both known primitive-Earth compounds) and proceeds through a C_5 compound, δ-aminolevulinic acid.[102] The latter has been sought, but not found, as a product of CH_4–NH_3–H_2O irradiations.[103] 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.[104] Hodgson and Baker have reported[105] the formation of metal porphyrin complexes on heating (84°) formaldehyde and pyrrole in the presence of cations; the yields, however, were very low (10^{-3}–10^{-5}%). A very recent report asserts that porphyrins are detectable (no yields are given) after the passage of electric discharges through CH_4–NH_3–H_2O mixtures.[106]

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 1000, the catalytic effectiveness of the iron's ability to destroy peroxide.[107]

F. SUMMARY

The most important organic molecules (biomonomers) in living systems have been enumerated as the 20 amino acids of the natural proteins, the 5 nucleic acid bases, glucose, ribose, and deoxyribose.[108] Of these, laboratory experiments under conditions clearly relevant to probable conditions on the primitive Earth have resulted in the appearance of at least 15 of the 20 amino acids, 4 of the 5 nucleic acid bases, and 2 of the 3 sugars. In addition, representatives of the biologically important nucleosides, nucleotides, fatty acids, and porphyrins have been observed. This research has made it clear that these compounds would have accumulated on the primitive (prebiotic) Earth—that their formation is the inevitable result of the action of available high energies on the Earth's early atmosphere.

V. Abiogenic Synthesis of Biopolymers

Granted a primitive ocean with a lot of biomonomers in solution, and adsorbed on mineral surfaces, there now arises the problem of how these compounds may have gotten condensed to form the biopolymers. In all cases the monomers are condensed with a concomitant elimination of water (dehydration condensation). These attachments are shown in Scheme I 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.

Research in chemical evolution has 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.

A. PROTEINS

As was mentioned earlier under "Other Conditions on the Primitive Earth," 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°; in the presence of polyphosphoric acid, temperatures below 100° are effective.[109–112] The presence of sufficient excess of one of

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(99) B. C. McKusick, W. E. Mochel, and F. W. Stacey, *J. Am. Chem. Soc.*, **82,** 723 (1960).

(100) N. Getoff and G. O. Schenk, *Radiation Res.*, **31,** 486 (1967).

(101) W. V. Allen and C. Ponnamperuma, *Currents Mod. Biol.*, **1,** 24 (1967).

(102) D. Shemin, Proceedings of the 3rd International Congress on Biochemistry, Brussels, 1955, p 197.

(103) R. M. Lemmon, unpublished results.

(104) A. Szutka, *Nature*, **212,** 401 (1966).

(105) G. W. Hodgson and B. L. Baker, *ibid.*, **216,** 29 (1967).

(106) G. W. Hodgson and C. Ponnamperuma, *Proc. Natl. Acad. Sci. U. S.*, **59,** 22 (1968).

(107) M. Calvin, *Science*, **130,** 1170 (1960).

(108) G. Wald, *Proc. Natl. Acad. Sci. U. S.*, **52,** 595 (1964).

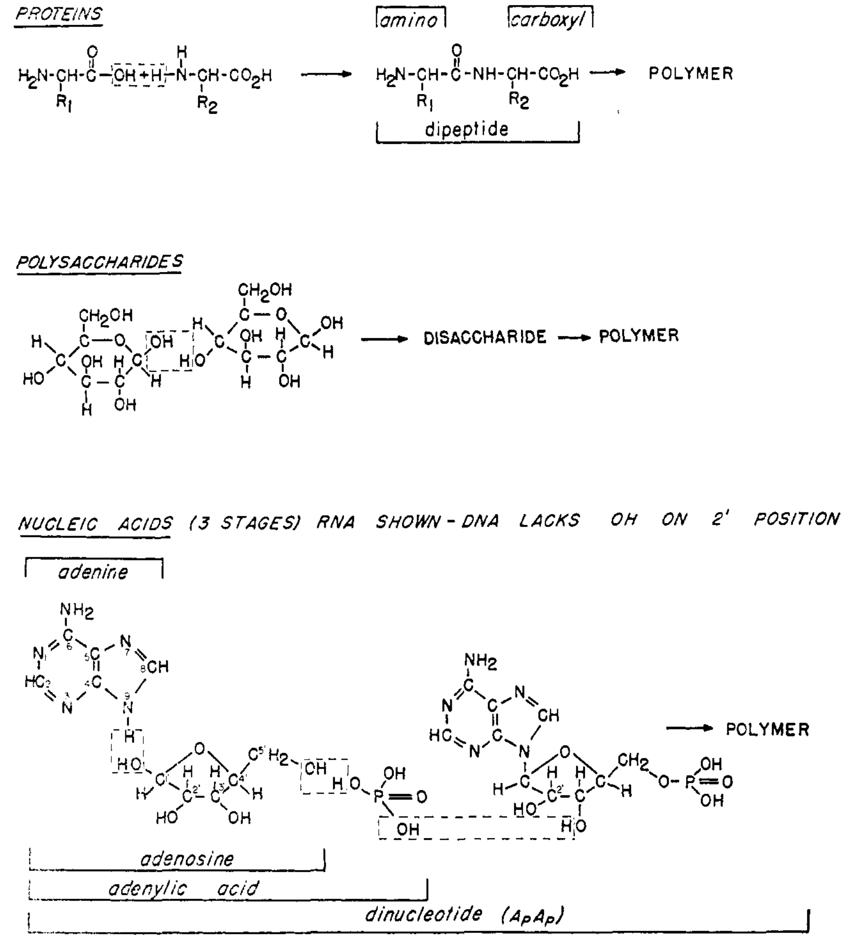
(109) S. W. Fox and K. Harada, *J. Am. Chem. Soc.*, **82,** 3745 (1960).

(110) S. W. Fox and S. Yuyama, *Ann. N. Y. Acad. Sci.*, **108,** 487 (1963).

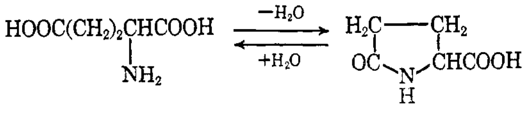
(111) K. Harada and S. W. Fox in ref 49, p 289.

(112) S. W. Fox and T. V. Waehneldt, *Biochim. Biophys. Acta*, **160,** 246 (1968).

Scheme I



the dicarboxylic amino acids, glutamic acid or aspartic acid, is necessary to achieve these condensations. In promoting these condensations, a special, but unexplained, role for lysine is also claimed.[113] When glutamic and aspartic acids 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. Glutamic acid is particularly effective in promoting these condensations, and it is presumed that its effectiveness lies in the thermal production of its lactam, 2-pyrrolidone-5-carboxylic acid, a five-membered cyclic anhydride



followed by the condensation of this lactam with an amino acid to give a mixed dipeptide.[114]

The amino acid thermal condensations are not completely random; aside from glutamic and aspartic acids, the incorporation of glycine, alanine, lysine, and methionine are slightly favored.[109] 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 bonds, (b) they have molecular weights in the thousands, (c) they give positive biuret reactions (color tests for peptide bonds), (d) they can be hydrolyzed to amino acids, (e) they are susceptible to attack by proteolytic enzymes, and (f) 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." [110,115] These globules have some properties that have led Fox and coworkers to call them proto- or precellular. They are about 2 μ 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. When one imagines the control over subsequent chemistry that these membranes would confer upon the proteinoid globules, it seems reasonable to refer to them as possible "protocells." [115]

Peptides have also been reported as products from heating glycine in aqueous NH_4OH,[116] products of the γ-irradiation of N-acetylglycine,[57] and indicated as products of the thermal (90°) treatment of ammonium cyanide solutions.[38] Matthews

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(113) D. L. Rohlfing, *Nature*, **216**, 657 (1967).

(114) K. Harada and S. W. Fox, *J. Am. Chem. Soc.*, **80**, 2694 (1958).

(115) S. W. Fox in ref 49, p 361.

(116) J. Oró and C. L. Guidry, *Arch. Biochem. Biophys.*, **93**, 166 (1961).

and Moser found peptide-like material upon hydrolysis of the products obtained from (a) sparking CH_4–NH_3 mixtures[41] and (b) heating HCN–NH_3 mixtures;[42] these experiments the authors advance as support for the idea that polypeptides may have resulted on the primitive Earth directly from the hydrolysis of HCN polymers.[117] 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 triglycine.[118–120]

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 ($RN{=}C{=}NR'$), reagents that have been used for over a decade in synthetic organic chemistry to effect dehydration condensations (in nonaqueous media).[121] Cyanamide, $H_2NC{\equiv}N$, a tautomer of the parent (and unknown) member of the carbodiimide series ($HN{=}C{=}NH$) has been used in the form of its dimer (dicyandiamide, $H_2NC({=}NH)N{=}C{=}NH$, a known primitive-Earth compound[91]) to prepare simple peptides (glycylleucine, leucylglycine, and alanylalanine)[92,96,122]. 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; considerable yields of triglycine (about 15%) and tetraglycine (about 7%) were also observed.[123]

The carbodiimide analogs referred to here, and the related cyanide derivatives (such as the cyanogen hydrolysis products referred to earlier under "Nucleotides"), have shown a wide usefulness in chemical evolution research. They not only promote the dehydration condensations, in dilute aqueous solution at room temperature, of amino acids to peptides, but under similarly mild conditions they produce glucose 6-phosphate from glucose and H_3PO_4, adenosine 5′-phosphate (AMP) from adenosine and H_3PO_4, and $H_4P_2O_7$ (pyrophosphate) from H_3PO_4.[96] These compounds thus show a preference to remove (react faster with) the elements of water from a variety of molecules (amino acids, sugars, H_3PO_4) in aqueous solution, rather than to react with the surrounding water molecules. The condensing agent itself is hydrolyzed, for example

$$\underset{\text{cyanamide}}{H_2N{-}CN} \xrightarrow{H_2O} \underset{\text{urea}}{H_2NCONH_2}$$

$$\underset{\text{dicyanamide}}{NC\text{-}NH\text{-}CN} \xrightarrow{H_2O} \underset{\text{cyanurea}}{NC\text{-}NH\text{-}CONH_2} \xrightarrow{H_2O} \underset{\text{biuret}}{H_2NCO\text{-}NH\text{-}CONH_2}$$

The mechanisms of the reaction of dicyanamide with aqueous glycine have been extensively investigated and are summarized in Scheme II.[123] The kinetic data indicate that the dipeptide, diglycine, is formed through the unstable N-cyano-O-aminoacetylurea (route to the right). The route to the left shows an overall catalytic effect of the glycine in promoting dimerization of the dicyanamide to N,N,N′-tricyanoguanidine; this route is, of course, useless in promoting peptide formation.

All that the ambient-temperature, dilute-solution "chemical evolution" experiments have so far achieved is some low-yield preparations of peptides—at most, the tetrapeptides. However, even if we do not wish to invoke the high-temperature "protenoid" route to proteins (but in no way denying that this route may have been the key one), we can still easily imagine protein syntheses in the prebiotic oceans. Although the coupling of amino acids to peptides is accompanied by a positive free-energy change, there probably existed on the primitive Earth far better combinations of conditions for protein synthesis (catalysts, coupling agents, etc.) than have yet been found in the laboratory "chemical evolution" experiments. Adsorption of oligopeptides on appropriate surfaces may have increased coupling rates and diminished hydrolysis rates, leading to net synthesis of polypeptides. The molar free energy ($-\Delta G$) of adsorption of glycine peptides to the clay mineral montmorillonite increases with increasing length of the peptide.[124] This same mineral has been reported to increase the rate of dicyanamide-promoted peptide synthesis.[125]

We have good reason to expect that polypeptides, once formed, would have tended to aggregate themselves into the conformations (secondary and tertiary structures) that we find in present-day proteins. This tendency is shown by the facile laboratory denaturation and renaturation of proteins. Either a raising of the temperature, or a lowering of the pH, disrupts the helical structure and produces a random coil. On subsequent reversal of the temperature or pH, the helical structure reappears. These shifts in conformation are revealed by the hypochromism of the helix; it shows a lesser optical absorptivity (at about 190 nm) than does the random coil.[126,127] Similar observations have been made with respect to the restoration of, or natural tendency to form, the tertiary structure of proteins. There is good reason to expect the accumulation, on the prebiotic Earth, of proteins similar in most, if not all, respects to the present-day biologically produced proteins.

B. NUCLEIC ACIDS

Just as some modest progress has been recorded in chemical evolution experiments in producing peptides and protein-like material, so also has progress been made in producing polynucleotides (on the way to the nucleic acids). Although it cannot be called a chemical evolution experiment (enzymes were used) the *in vitro* synthesis of nucleic acids by Ochoa, Kornberg, *et al.*, is of great relevance. They demonstrated the following reaction.[128,129]

$$\begin{array}{l}\text{nucleoside + triphosphate} \\ \text{"primer" nucleic acid}\end{array} \xrightarrow[Mg^{2+}]{\text{enzyme } (e.g., \text{ polymerase})} \begin{array}{l}\text{newly synthesized} \\ \text{nucleic acid}\end{array}$$

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(117) R. M. Kliss and C. N. Matthews, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1300 (1962).

(118) S. Akabori in ref 46, p 189.

(119) H. Hanfusa and S. Akabori, *Bull. Chem. Soc. Japan*, **32**, 626 (1959).

(120) J. H. Reuter, "On the Synthesis of Peptides under Primitive Earth Conditions," 3rd International Meeting on Organic Geochemistry, London, 1966.

(121) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(122) C. Ponnamperuma and E. Peterson, *Science*, **147**, 1572 (1965).

(123) G. Steinman, D. H. Kenyon, and M. Calvin, *Biochim. Biophys. Acta*, **124**, 339 (1966).

(124) D. J. Greenland, R. H. Laby, and J. P. Quirk, *Trans. Faraday Soc.*, **58**, 829 (1962).

(125) G. Steinman and M. N. Cole, *Proc. Natl. Acad. Sci. U. S.*, **58**, 735 (1967).

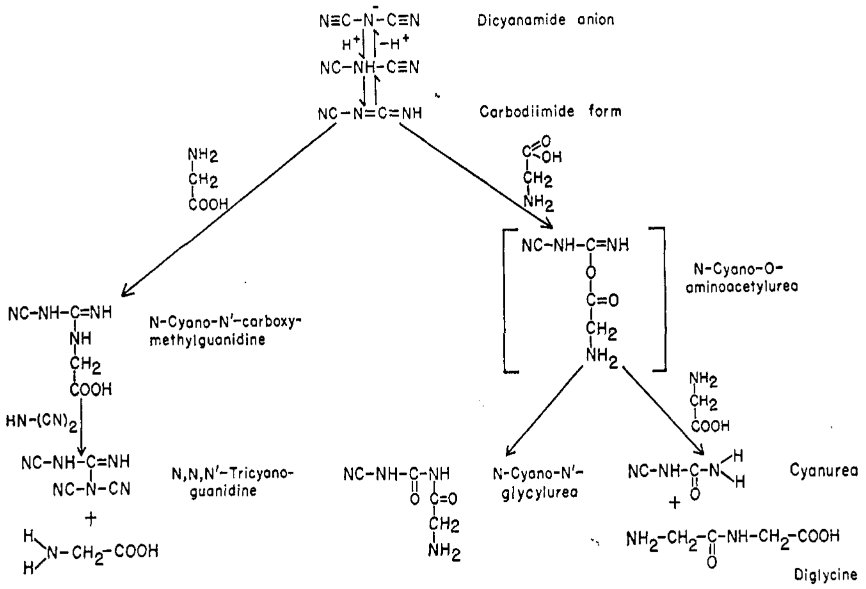
(126) I. Tinoco, Jr., A. Halpern, and W. T. Simpson, "Polyamino Acids, Polypeptides, and Proteins," University of Wisconsin Press, Madison, Wis., 1962, p 147.

(127) M. Calvin, *Proc. Royal Soc.* (London), **A288**, 441 (1965).

(128) A. Kornberg, "Enzymatic Synthesis of Deoxyribonucleic Acid," Academic Press, New York, N. Y., 1961, pp 83–112.

(129) M. Goulian, A. Kornberg, and R. L. Sinsheimer, *Proc. Natl. Acad. Sci. U. S.*, **58**, 2321 (1967).

Scheme



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 IV.C.4), and magnesium constitutes about 2 atom % of the Earth's crust.[130] The above reaction is not detected in the absence of enzyme. However, from the chemical-evolutionary viewpoint, for a given reaction, time can always be substituted for a catalyst. The demonstration of the above reaction in the laboratory is suggestive that nucleic acids could have accumulated on the prebiotic Earth. One can also visualize the concomitant accumulation, at that time, of both the polynucleotides and the polypeptides, each tending to catalyze the formation of the other.

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.[131] 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.[128,132] 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.[133]

It was mentioned earlier (section IV.C.4) that Schramm, *et al.*, have prepared a "polyphosphate ester" that has been used in dehydration condensation work.[87] The same authors also reported the preparation of polynucleotides (from nucleotides) with this reagent and have claimed some chemical-evolutionary relevance for their results.[87] 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 H_3PO_4, in dilute aqueous solution), *via* dehydration condensation, the sugar–phosphate ester bond characteristic of the nucleic acids.[92]

VI. Concluding Remarks

This review has concentrated on the "synthesis" aspects of chemical evolution. Outside of its scope is the subject of how the biomacromolecules progressed toward the degree of organization that we now see in the living cell. The principal ideas of how this took place are the "coacervate" theory of Oparin[134] and the "microsphere" concept of Fox.[115] Both of these ideas are but halting steps on the long road toward an understanding of the genesis of the tremendously complex organization of the living cell. However, they both are based on the notion that the emergence of life is the inevitable outcome of associational and organizational forces inherent in the macromolecules' chemistry.

An outstanding, and very often discussed, problem in chemical evolution is that of the origin of optical activity in biological compounds. We still do not know why, to pick the main example, the natural proteins are composed of L- instead of D-amino acids. Little further understanding of this problem has developed during the past decade, and the reader is referred to excellent discussions of the subject by Wald, in 1957,[135] and by Horowitz and Miller, in 1962.[86] A new possibility in understanding this problem, however, has been suggested in a recent paper by Garay.[136] This work suggests that β-ray emission results in circularly polarized bremsstrahlung, and that such γ-radiation might radiation-decompose one enantiomorph faster than the other. Indeed, this report is ac-

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(130) B. Mason, "Principles of Geochemistry," John Wiley and Sons, New York, N. Y., 1952, p 41.

(131) A. W. Schwartz and S. W. Fox, *Biochim. Biophys. Acta*, **134**, 9 (1967).

(132) A. P. Vinogradov in ref 46, p 23

(133) J. Morávek, *Tetrahedron Lett.*, **18**, 1707 (1967).

(134) A. I. Oparin, "The Chemical Origin of Life," translation by A. Synge, Charles Thomas Publishers, Chicago, Ill., 1964.

(135) G. Wald, *Ann. N. Y. Acad. Sci.*, **69**, 352 (1957).

(136) A. S. Garay, *Nature*, **219**, 338 (1968).

companied by experimental data that indicate that ^{90}Sr β-rays decompose D-tyrosine faster than L-tyrosine. Any evaluation of the importance of this process in chemical evolution must await a quantitative estimate of its effect, and a determination of how general the effect is.

The relatively 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 our knowledge of our origins, is assured.

VII. Addenda

Since the original writing of this manuscript, two monographs on chemical evolution have appeared, and the reader is referred to these for elaboration of many of the topics discussed in this review.[137,138]

The work of Degens and Matheja[139] has reinforced the notion that the minerals available in the primitive oceans would have provided excellent templates for protein synthesis. They have also presented evidence that certain amino acid adsorptions may change the subsequent peptide formation from thermodynamically unfavored to favored.

A series of recent papers by Sulston, *et al.*,[140–142] have shown that a water-soluble carbodiimide [1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride] induces in dilute water solution (about 0.01 *M* in all reactants) the formation of di- and trinucleotides from mixtures of nucleosides and nucleotides. The reaction is performed at ambient temperatures for several days, and the yields are good (a few per cent). Furthermore, these reactions are aided by the presence of synthetic polynucleotides, and the Watson–Crick pairing rules seem to apply. That is, the adenosine–adenylic acid condensations (but not those between adenylic acid and guanosine, cytidine, or uridine) are greatly aided by the presence of polyuridylic acid, and a polycytidylate template aids in the condensations of guanosine with guanylic acid. Although unnatural condensates are also formed (*e.g.*, 2′-5′ linkages), this work demonstrates a likely route for polynucleotide synthesis on the primitive Earth.

Friedmann and Miller have recently shown that phenylacetylene is synthesized in good yield from various hydrocarbons (of which ethane is the best) by high temperatures (1300°), electric discharge, and uv light.[143] They have also shown that the phenylacetylene can be hydrolyzed under primitive-Earth conditions to phenylacetaldehyde, and that the latter may be converted to phenylalanine on treatment with NH_3 and HCN, followed by hydrolysis. If the hydration step of phenylacetylene to acetaldehyde is carried out in the presence of H_2S and uv light, a better yield of phenylalanine (about 20% from the starting phenylacetylene) is obtained, accompanied by a trace of tyrosine. These results make it easier to envisage the appearance of the aromatic amino acids on the primitive Earth.

Krampitz and Fox have demonstrated that a carbodiimide (dicyclohexylcarbodiimide) causes the adenylates of the natural amino acids to condense easily in water solution at room temperature. The product is a high molecular weight, peptide-bond-containing material, similar in many respects to the "proteinoids" obtained in the anhydrous, high-temperature conditions. This work is a notable addition to our understanding of possible routes of protein synthesis on the prebiotic Earth.[144]

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(137) D. H. Kenyon and G. Steinman, "Biochemical Predestination," McGraw-Hill Book Co., Inc., New York, N. Y., 1969.

(138) M. Calvin, "Chemical Evolution," Oxford University Press, Oxford, 1969.

(139) E. T. Degens and J. Matheja, *J. Brit. Interplanet. Soc.*, **21**, 52 (1968).

(140) J. Sulston, *et al.*, *Proc. Natl. Acad. Sci. U. S.*, **59**, 726 (1968).

(141) J. Sulston, *et al.*, *ibid.*, **60**, 409 (1968).

(142) J. Sulston, *et al.*, *J. Mol. Biol.*, **40**, 227 (1969).

(143) N. Friedmann and S. L. Miller, *Science*, **166**, 766 (1969).

(144) G. Krampitz and S. W. Fox, *Proc. Natl. Acad. Sci. U. S.*, **62**, 399 (1969).