

The Emergence of Bioenergetics: The Formation of a Gluconeogenesis System and Reductive Pentose Phosphate Pathway of CO₂ Fixation in Ancient Hydrothermal Systems

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Abstract

The origin of phosphorus metabolism is one of the central problems in the context of the emergence of life on Earth. It has been shown that the C–H–O system can be transformed into a four- component C–H–O–P system with the formation of a gluconeogenesis path in a possible Archean hydrothermal condition under the influence of a phosphorus chemical potential. This system became the energy supply basis for protometabolism, and facilitated the formation of a new CO₂ fixation cycle (the reductive pentose phosphate pathway).

The modular design of central metabolism in the C–H–O–P system is derived from the parageneses (associations) of certain substances, and the emerging modules in turn associate with each other in certain physical and chemical hydrothermal conditions. The assembly of malate, oxaloacetate, pyruvate, and phosphoenolpyruvate is a reversible "turnstile - like" mechanism with a switching of reaction direction that determines the trend of specific metabolic systems development.

Keywords: Origin of metabolism energetics; Autocatalytic cycles; Gluconeogenesis; CO₂ fixation; Modularity; Parageneses; Chemical potentials

Introduction

One of the most important concepts in the theories of the chemolithoautotrophic origin of life in the Archean volcanic hydrothermal environment is autocatalytic CO₂ fixation [1-9]. It has also been suggested that the last common ancestor (LCA) of all extant cell lineages was a chemolithoautotrophic thermophilic anaerobe [10-14] capable of synthesizing organic 'building blocks' from the inorganic carbon. Thus, these microorganisms can serve as a model for studying primordial metabolism. However, CO₂ fixation requires energy, which was provided by energy from high-energy intermediates, organic phosphates in particular, that are presently involved in the primary biochemical pathways.

In previous works we have considered the thermodynamic factors of natural selection in the coupled autocatalytic cycles of CO₂ fixation (redundant modular constructions) in the three - component C-H-O system [6,15]. It is rationalized that these systems are the primordial metabolic autocatalytic reductive citrate (RC) cycle (reductive tricarboxylic acid, Arnon-Buchanan cycles) and 3-hydroxypropionate (3-HP) cycle. An important factor in the stability and subsequent evolution of these coupled cycles is the reversibility of some key chemical reactions such as succinate ↔ fumarate, malate ↔ fumarate and others [16]. The further development of this system with negative feedback involves increasing the number of independent components by maintaining additional supply of phosphorus, nitrogen, and sulfur. Adding phosphorus (forming a four - component C–H–O–P system) leads to the development of the gluconeogenesis system, which

produces phosphorylated sugars, a basic source of energy for different biosynthetic pathways. The nodal intermediates and proposed autocatalysts in this process are malate, pyruvate, and oxaloacetate, the transformation of which into phosphoenolpyruvate permits the formation of phosphorylated trioses, pentoses, and hexoses.

The fundamental role of phosphorylated carbohydrates and the universality of the few modern metabolic interconversions suggest their origin at the earliest evolutionary stage. The possibility of gluconeogenesis first originating as a precursor to phosphorus metabolism in hyperthermophilic microorganisms was considered in [17]. Gluconeogenesis starting with phosphoenolpyruvate uses the unusual ancient enzyme fructose 1,6-bisphosphate aldolase/phosphatase, which converts triose phosphates to fructose 1,6-bisphosphate [18,13]. The ancient origin of gluconeogenesis with the consequent origin of the ancestral Aquificae, Chloroflexi, and Thermotogae taxa is postulated. Reactions converting triose phosphate into fructose 1,6-bisphosphate are generally reversible, but the reaction of fructose 1,6-bisphosphate into stable fructose 6-phosphate is irreversible and substantially determines the unidirectionality of gluconeogenesis, which precedes the emergence of glycolysis evolutionarily [17].

The early origin of gluconeogenesis is indirectly supported by data from the non-enzymatic metal - catalyzed formation of phosphorylated three-carbon sugars and pyruvate [19,20], and the widespread role of non-enzymatic catalysis in phosphate metabolism is considered in ref. [21]. It should be noted that both non-enzymatic and enzymatic reactions are based on the same fundamental thermodynamic laws. Experimental analysis of the conditions required for phosphorylated intermediate formation and stability in the pentose phosphate pathway is given in ref. [22].

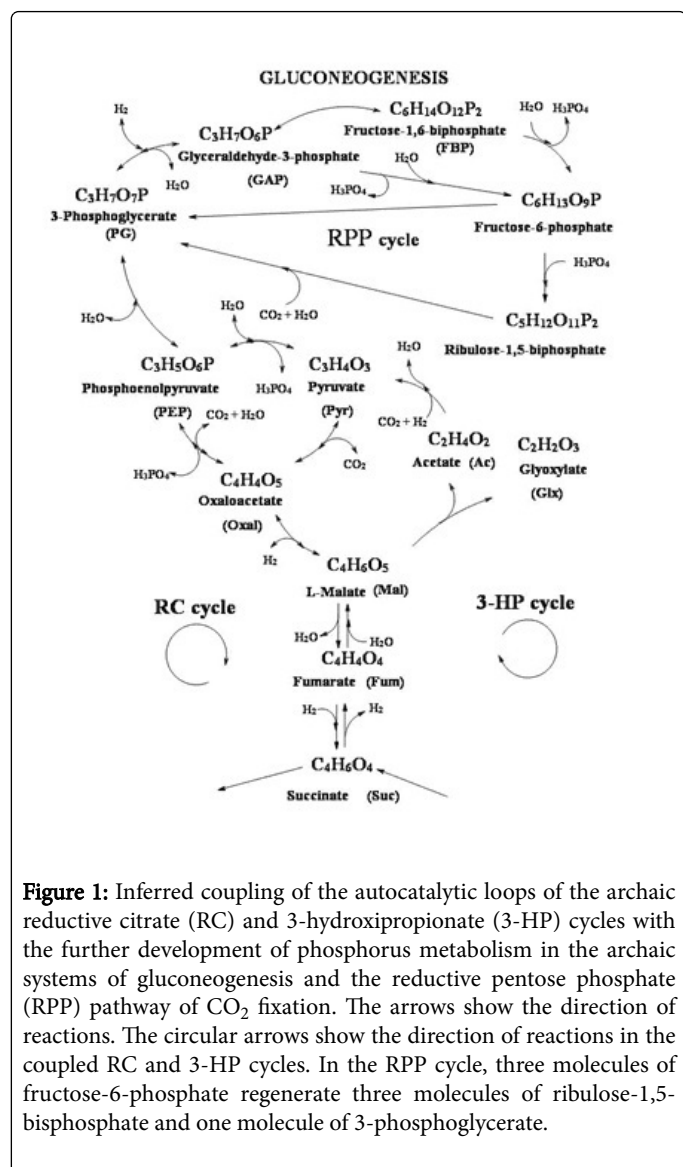


Figure 1: Inferred coupling of the autocatalytic loops of the archaic reductive citrate (RC) and 3-hydroxypropionate (3-HP) cycles with the further development of phosphorus metabolism in the archaic systems of gluconeogenesis and the reductive pentose phosphate (RPP) pathway of CO₂ fixation. The arrows show the direction of reactions. The circular arrows show the direction of reactions in the coupled RC and 3-HP cycles. In the RPP cycle, three molecules of fructose-6-phosphate regenerate three molecules of ribulose-1,5-bisphosphate and one molecule of 3-phosphoglycerate.

The reactions underlying the interconversion of phosphorylated carbohydrates were examined under the conditions found in a putative Archean ocean, which were determined based on the chemical composition of sedimentary rocks in this time period. It was shown that the simple inorganic ions (Fe (II), Co (II), Ni (II), Mo (IV)) found in rocks from the Archean period could catalyze the reactions observed in the extant metabolic pathways. It was also concluded that iron (at concentrations of 20 μM to 5 mM) was the most effective catalyst of metabolic reactions requiring substrate phosphorylation in early anoxygenic Archean ocean. It is assumed that the ancient ocean was enriched not only by ferro - ions but also phosphates [22-24] that emanated from high-temperature alkaline hydrothermal fluids to the surface of the Earth [25]. Nevertheless, it requires some thermodynamic analysis of the possibility of phosphorylated carbohydrates formation.

A simplified biomimetic image of primordial anaerobic central carbon metabolism in the form of branching metabolic reactions with the formation of gluconeogenesis and the reductive pentose phosphate (RPP) CO₂ fixation cycle (Calvin-Benson cycle) is presented in Figure

1, which shows the development of coupled autocatalytic systems (archaic RC and 3-HP cycles [26]) in the direction of phosphorus metabolites - triose phosphates and phosphorylate d sugars. It is assumed that these metabolic changes took place during of the origin of life energetics aspect.

Methodical Approach

The physicochemical analysis of parageneses (associations, assemblages) is widely used in geochemical researches of mineral systems [27]. This approach is based on a generalization of the thermodynamic and physical properties of minerals in order to detect the conditions responsible for the formation of the parageneses observed in rocks and ores. In this case, the thermodynamic potential method [27,28], which allows one to develop a system of geochemical mineral facies (thermodynamic stability areas), is used. Our preliminary calculations indicated that paragenetic analysis can be extended to organic substances, which form the systems listed below (the systems are listed in increasing complexity of chemical composition and structure): C-H-O, C-H-O-N, C-H-O-N-P and C-H-O-N-P-S [6,15,29].

The studies of organic substances assemblages (parageneses) and areas of their thermodynamic stability (facies) is based on the Gibbs phase rule, according to which the number of degrees of freedom for a thermodynamic system in equilibrium is equal to the number of system independent components plus two minus the number of phases. In this case, the number of independent components is the smallest number of chemical components; the compositions of all possible phases of the system can be obtained by their combination. The phase rule is not limited to consideration of the extensive parameters of the system and, hence, is completely applicable to open systems with chemical potential as an independent parameter [16,30]. Determining the total number of system independent parameters (intensive and extensive), and using this number together with the Gibbs phase rule provides a way to study the thermodynamic properties of organic systems.

The system state was calculated using free partial energy values for organic substance formation ($\Delta G_o f, T$), depending on external conditions. The state diagrams, which reflect the facies of organic compounds and their parageneses, are graphically presented. When considering these organic compounds in fluid and aqueous hydrothermal systems, the points of major importance are shown with diagrams: a) chemical composition - paragenesis (at constant pressure (P), temperature (T), and chemical potential (μ_i)), b) chemical potential - temperature (at constant P), c) the relationship between chemical potentials of the components: $\mu_{H_2O} - \mu_{CO_2}$, $\mu_{H_2} - \mu_{O_2}$, etc. (at constant P and T).

The major equilibrium factors in the physicochemical analysis of parageneses are the chemical potential (μ_i) of each component (representing its partial energy). The value μ_i is expressed through activity, a_i , and fugacity, f_i , as follows: ($\mu_i = (\mu_i^0) T, P + RT \ln a_i = (\mu_i^0) T, P + RT \ln f_i$).

The aqueous constants used were derived using the electrostatic model method, according to which the solvate constituent of a substance plays an essential role in the chemical potential at different temperatures, reflecting the contribution from electrostatic interactions between the substance and solvent (H₂O) [31-34]. Thermodynamic calculations of the Gibbs standard free energy and analysis of the geochemical constraints showed that the abiotic

synthesis of organic compounds in hydrothermal systems is limited by the metastable equilibrium that results from kinetic barriers, which prevent the achievement of stable equilibrium [32,35-37]. Most of the organic substances in condensed and dissolved phases are in a metastable state, i.e., these substances do not reach the minimum Gibbs free energy for the given composition of elements, and thus are "kinetic" or "metastable" phases [38,39].

Previously, we calculated a diagram of composition - paragenesis for the ternary C-H-O system [e.g., 6]. The addition of phosphorus to the C-H-O system forms the quaternary system C-H-O-P, in which the independent components - carbon, hydrogen, oxygen, and phosphorus - are extensive parameters (*lex*). Figure 2 presents the phase diagram of compositions for the compounds shown in Figure 1. In this ternary C-H-O diagram, the phases of the phosphorylated compounds are represented by the subtracting of orthophosphoric acid (H₃PO₄). If, in thermodynamic calculations, the chemical potential is

determined for H₃PO₄ ($\mu_{\text{H}_3\text{PO}_4}$), and phosphorus becomes an intensive parameter (*fin*), then the quaternary system becomes ternary (C-H-O). If the chemical potential is calculated for hydrogen or methane (μ_{CH_4} , μ_{H_2}), and hydrogen becomes intensive parameter (*fin*), then the ternary system becomes a binary system, C-O (Figure 2a and b). The dashed conodes connect CH₄ and H₂ with substances phases, which are represented by stars on the triangle side. The composition diagram (Figure 2c) shows that, if the chemical potential is calculated for CO₂ (μ_{CO_2}), and CO₂ becomes an intensive parameter (*fin*), then the ternary system becomes a binary system, C-H (dashed conodes connect the CO₂ point, and substance phases represented by rhombs on the triangle base). The free energies of aqueous ionized phosphorus substance formation were taken from ref. [40] and were designed for non-ionized forms using the method described in refs., [40,41]. The constants for substances in the C-H-O system were taken from [16].

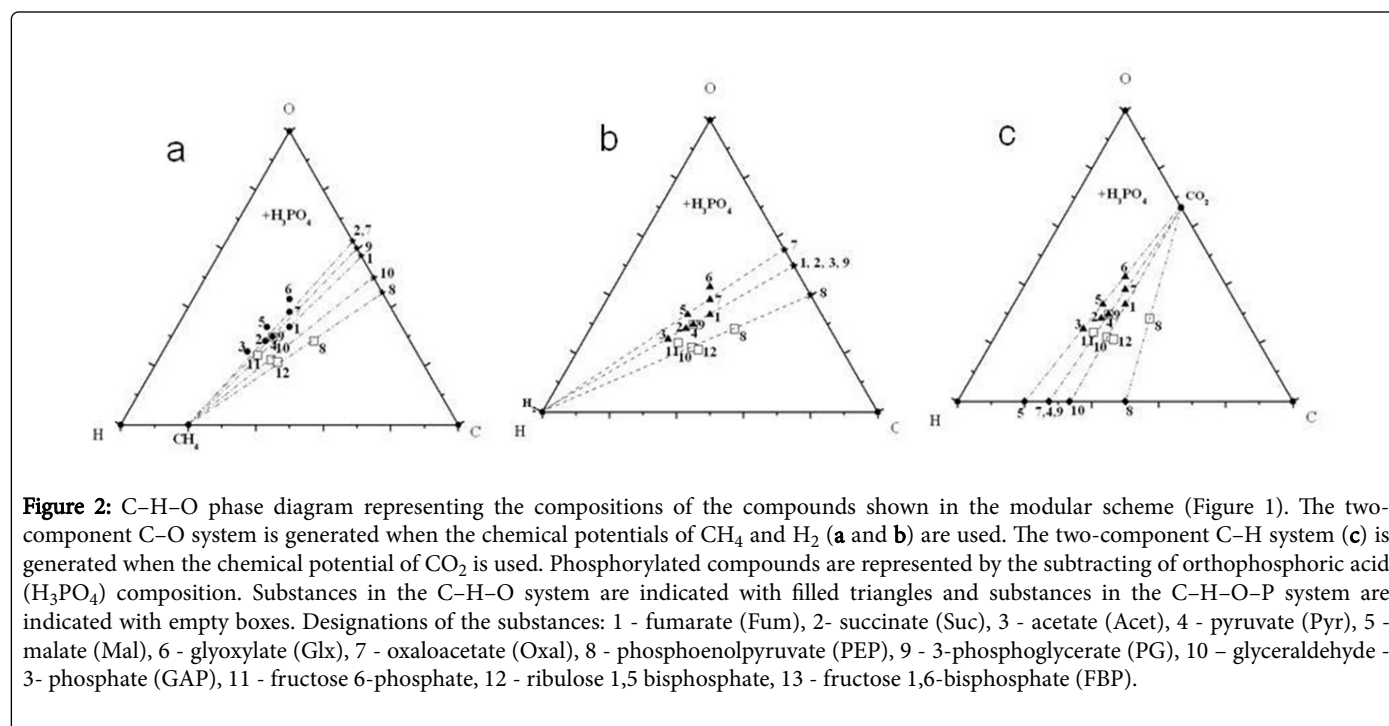


Figure 2: C-H-O phase diagram representing the compositions of the compounds shown in the modular scheme (Figure 1). The two-component C-O system is generated when the chemical potentials of CH₄ and H₂ (a and b) are used. The two-component C-H system (c) is generated when the chemical potential of CO₂ is used. Phosphorylated compounds are represented by the subtracting of orthophosphoric acid (H₃PO₄) composition. Substances in the C-H-O system are indicated with filled triangles and substances in the C-H-O-P system are indicated with empty boxes. Designations of the substances: 1 - fumarate (Fum), 2- succinate (Suc), 3 - acetate (Acet), 4 - pyruvate (Pyr), 5 - malate (Mal), 6 - glyoxylate (Glx), 7 - oxaloacetate (Oxal), 8 - phosphoenolpyruvate (PEP), 9 - 3-phosphoglycerate (PG), 10 - glyceraldehyde - 3- phosphate (GAP), 11 - fructose 6-phosphate, 12 - ribulose 1,5 bispophosphate, 13 - fructose 1,6-bisphosphate (FBP).

Certainly, the hydrothermal systems are generally characterized by a more high- pressure and high-temperature conditions. However, these conditions cannot fundamentally change the character the diagrams of chemical potentials - as a rule, the equilibria shifts in a direction of its higher values.

It is assumed that the anoxygenic Archean ocean saturated with siliceous compounds and Fe (II) contained a higher level of dissolved orthophosphate than the modern ocean [23,42,43]. These conditions have primarily been determined with the use of the orthophosphate chemical potential in thermodynamic calculations of the origin and the evolution of protometabolic pathways related to the four component C-H-O-P system.

The Chemical Potentials of Methane, Molecular Hydrogen, and Carbon Dioxide

The most important energy factors in the generation of organic compounds, which are intermediates of protometabolic pathways in

hydrothermal systems, are the chemical potentials of molecular hydrogen and hydrocarbons. The predominant widespread hydrocarbon is methane, the concentration of which (e.g., in volcanic oceanic emissions) is usually more than two orders of magnitude higher than the concentration of other hydrocarbons [44].

At the present time, the abiotic synthesis of organic compounds in the hydrothermal systems of mid-ocean ridges has been confirmed in a number of publications (e.g., [44-46]). Alkanes and carboxylic acids represent some of the most abundant organic structure types found in natural hydrothermal systems and sedimentary basin fluids.

The diagram in Figure 3 is based on aqueous constants at standard conditions and shows the formation and development of coupled C-H-O-P metabolic systems, Figure 1, under the influence of the chemical potentials of methane (μ_{CH_4}) and phosphoric acid ($\mu_{\text{H}_3\text{PO}_4}$).

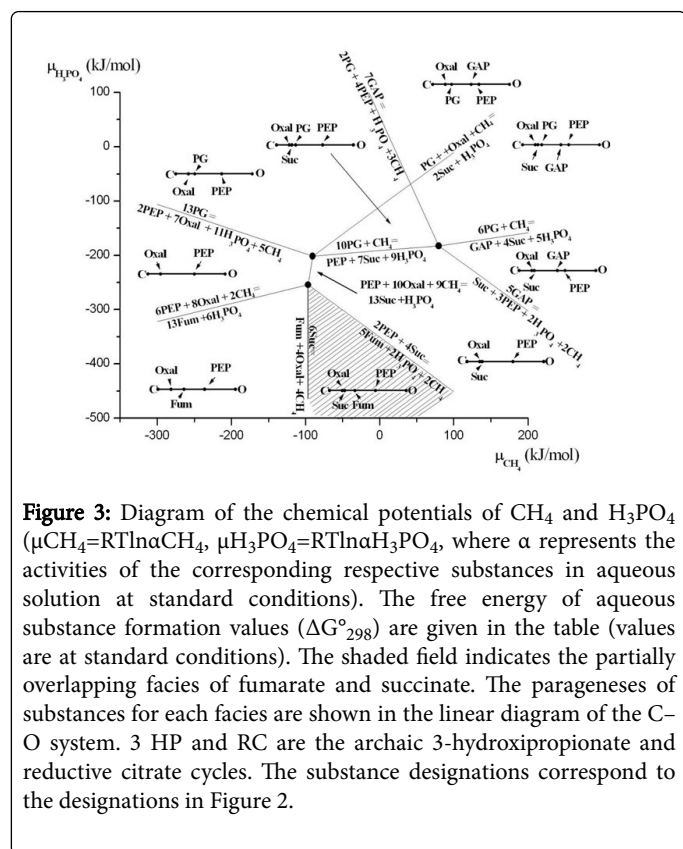


Figure 3: Diagram of the chemical potentials of CH₄ and H₃PO₄ ($\mu_{\text{CH}_4} = RT \ln a_{\text{CH}_4}$, $\mu_{\text{H}_3\text{PO}_4} = RT \ln a_{\text{H}_3\text{PO}_4}$, where a represents the activities of the corresponding respective substances in aqueous solution at standard conditions). The free energy of aqueous substance formation values (ΔG°_{298}) are given in the table (values are at standard conditions). The shaded field indicates the partially overlapping facies of fumarate and succinate. The parageneses of substances for each facies are shown in the linear diagram of the C–O system. 3 HP and RC are the archaic 3-hydroxipropionate and reductive citrate cycles. The substance designations correspond to the designations in Figure 2.

According to the Gibbs phase rule, the diagram represents the four-phase nonvariant equilibria in this two-component C–O system (see Figure 2a), whereas the monovariant equilibria are three-phase, separating divariant fields of phase stability and their parageneses and are identified by linear diagrams in the system facies. Increasing the H₃PO₄ chemical potential results in the stable paragenesis phosphoenolpyruvate - oxaloacetate at a relatively low chemical potential of methane (<-100 kJ/mol). Further development of the system leads to the facies formation of 3-phosphoglycerate and glyceraldehyde phosphate, permitting the development of the ancient pathway of substrate phosphorylation – gluconeogenesis and the reductive pentose phosphate (RPP) cycle of CO₂ fixation. Attention should be drawn to the overlapping facies (shaded field) of succinate (RC-cycle) and fumarate (3-HP cycle) with oxaloacetate - succinate - fumarate - phosphoenolpyruvate paragenesis. This field is an area of thermodynamic stability of coupled RC + 3-HP bicycle [6] and the new metabolic pathways apparently originated at the beginning of these redundant autocatalytic metabolic systems.

The chemical potential of H₂ divides the lower region of the diagram (Figure 4) on the facies of the dicarboxylic acids (succinate ↔ fumarate) and thus fixes the phase areas of stability of the archaic autotrophic 3-HP and RC cycles of CO₂ assimilation. With an increase in the chemical potential of H₃PO₄, facies of fumarate (3-HP cycle initiation) transform into facies of phosphoenolpyruvate - oxaloacetate, and a further increase in the chemical potentials of H₂ and H₃PO₄ leads to the decomposition of the metastable paragenesis with the formation of facies of 3-phosphoglycerate, which is a central metabolite (and autocatalyst [47]) in both gluconeogenesis and the RPP autocatalytic CO₂ fixation cycle (see Figure 1). Similarly, increasing the H₃PO₄ chemical potential in facies of succinate (RC

cycle initiation) also leads to the formation of facies with phosphoenolpyruvate - oxaloacetate paragenesis and further to facies of 3-phosphoglycerate.

According to [11], phosphoenolpyruvate and oxaloacetate are nodal molecules of all anabolic networks (in addition to acetate, pyruvate, and 2-oxoglutarate). From the diagrams in Figures 3 and 4, it is clear that facies with phosphoenolpyruvate - oxaloacetate paragenesis are an area of bifurcation (network node) that determines the development of the primordial 3-HP (fumarate) and RC cycles (succinate), system of gluconeogenesis (3-phosphoglycerate ↔ fructose 1,6-bisphosphate → fructose 6-phosphate) and the RPP cycle (3-phosphoglycerate → ribulose-1,5-bisphosphate → 3-phosphoglycerate). It is obvious that 3-phosphoglycerate must be added to the five nodal molecules of autotrophic anabolic networks mentioned above. Thus, the diagram in Figure 3 and 4 represents a thermodynamic basis of "encrustation" of the C-H-O system by a chemical "shell" of phosphorus under the influence of a chemical potential of methane and/or hydrogen and phosphorus. However, the autotrophic nature of the paragenesis formation of carboxylic acids and triose phosphates is manifested the best with consideration of the chemical potential of carbon dioxide.

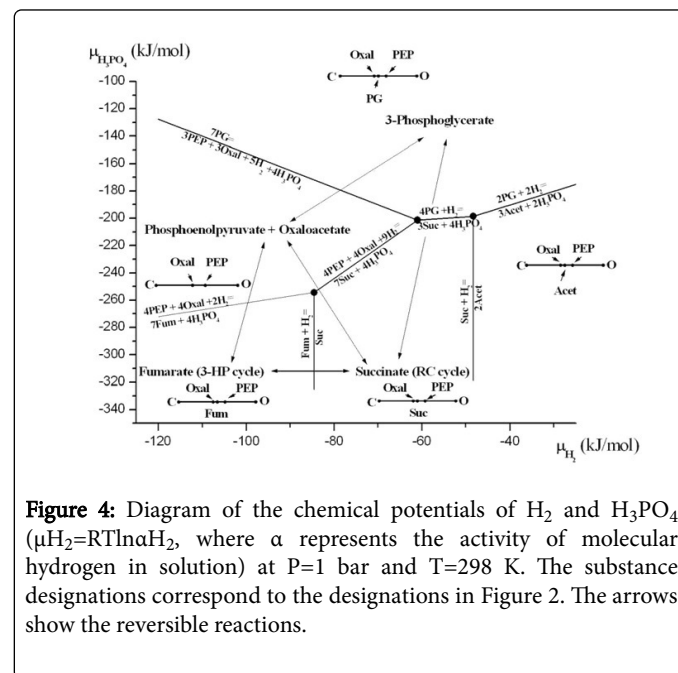


Figure 4: Diagram of the chemical potentials of H₂ and H₃PO₄ ($\mu_{\text{H}_2} = RT \ln a_{\text{H}_2}$, where a represents the activity of molecular hydrogen in solution) at P=1 bar and T=298 K. The substance designations correspond to the designations in Figure 2. The arrows show the reversible reactions.

Figure 4 shows a diagram of the chemical potentials of hydrogen and H₃PO₄. In general, this diagram is similar to Figure 3 (also see Figures 2a and 2b), and the monovariant equilibria are three-phase or degenerate two-phase. As we have shown previously [6,26], the association of succinate with fumarate acts as a redox switch, turning electron flow in the direction of archaic chemoautotrophic 3-HP and RC cycles in the wide temperature range.

On the diagram of CO₂ and H₃PO₄ chemical potentials (Figure 5), a phosphoenolpyruvate - malate paragenesis is located in a sufficiently limited range of the considered chemical potentials (center diagrams) and develops in the direction of the discussed metabolic systems (Figure 1) at varying chemical potentials. Thus, increasing the chemical potential of phosphorus leads to the emergence of phases of 3-phosphoglycerate and glyceraldehyde phosphate (emerging at a low chemical potential of CO₂), and these compounds (phosphorylated acid and aldehyde) are the initiators of gluconeogenesis and the RPP

cycle. It should be noted that glyceraldehyde phosphate is also one of the main centers of the ancient evolutionary development of the non-oxidative branch of the pentose phosphate pathway, which leads to the formation of a series of phosphorylated sugars [48].

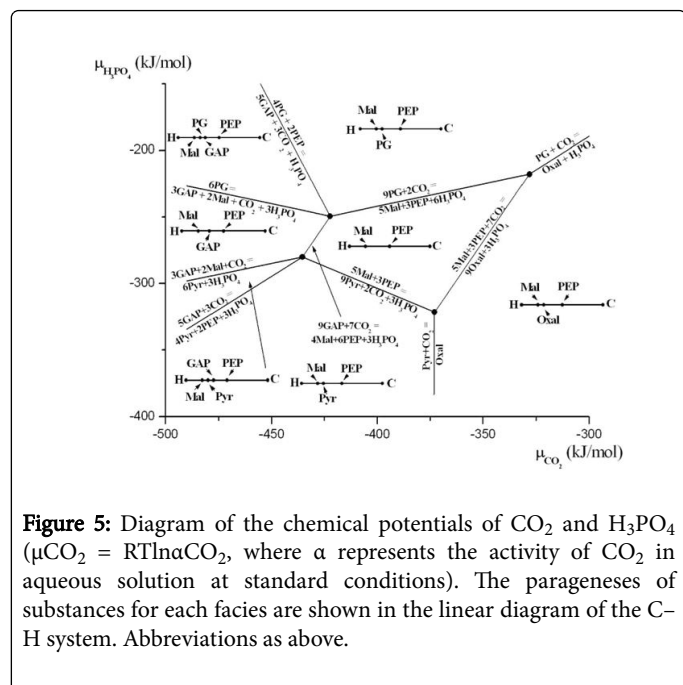


Figure 5: Diagram of the chemical potentials of CO₂ and H₃PO₄ ($\mu_{\text{CO}_2} = RT \ln a_{\text{CO}_2}$, where a represents the activity of CO₂ in aqueous solution at standard conditions). The parageneses of substances for each facies are shown in the linear diagram of the C–H system. Abbreviations as above.

Decreasing the chemical potential of phosphorus leads to the disappearance of the phosphoenolpyruvate - malate paragenesis and the appearance of phosphoenolpyruvate - pyruvate (with decreasing μ_{CO_2}) and phosphoenolpyruvate - oxaloacetate (with increasing μ_{CO_2}) parageneses. In general, increasing the CO₂ chemical potential leads to the carboxylation of compounds and their association with the formation of nodal facies - the center of phosphorus metabolism (malate - oxaloacetate - phosphoenolpyruvate). In this facies, as depicted in the diagram (Figures 3 and 4), the autocatalytic oxaloacetate - phosphoenolpyruvate paragenesis is also a "paragenesis bifurcation", meaning that this paragenesis determines the direction of natural selection of the primitive gluconeogenesis and CO₂ fixation metabolic pathways. According to Figure 1, phosphoenolpyruvate, oxaloacetate, and pyruvate assemblage are "turnstile - like" chemical mechanisms, allowing the direction of development of metabolic systems to change.

Conclusion

The energy processes within the living cells are chiefly determined by an element such as phosphorus, and phosphates play a crucial role in the activation of organic molecules through phosphorylation. Therefore, it is reasonable to assume that some types of phosphorylated compounds also played a major role in the formation of the first protometabolic systems on the early Earth. Early evolution likely ensured the storage and consumption of energy in the substrate phosphorylation process [e.g., 49], which was the main driving force behind the development of both other metabolic systems and replication, and allowed the further development of energy pathways in aerobic and anaerobic organisms in all three domains of life.

Unlike other designs, the modular systems of metabolism are much more capable of evolutionary development [50,51]. The modules of the

core metabolic pathways are derived from the parageneses of certain substances (micro modules - associations of chemical compounds which ultimately function together), and the resulting modules are in turn in paragenesis with each other in certain physical and chemical conditions. Malate, oxaloacetate, pyruvate, and phosphoenolpyruvate (Figure 1) form the reversible "turnstile - like" mechanism capable of switching reaction directions. A change in the external conditions shifts the coupled modular autocatalytic system toward developing in the direction that is most favorable to the formation of specific metabolic systems. The chemical C–H–O system acquired new "layers" from phosphorus, nitrogen, and sulfur. The present work investigated only the phosphorus "layer", which led to the development of new protometabolic energy systems. Thus, in early chemical protometabolic reactions of the CO₂ fixation energetics, which primordially was provided by the partial energy of environmental chemical potentials (mainly due to the endogenous flow of hydrogen and hydrocarbons), was then replaced with energy from high-energy organic phosphates.

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