Materials for the onset. A story of necessity and chance

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## 1. ABSTRACT

We review the reactions that take place in the $HCN/NH_2COH$/catalysts system. In a vision of origin-of-life as emergence of new properties in complexity, the effectiveness of $HCN/NH_2COH$ chemistry is so robust and variegate to look unreasonable. In a logic close to Occamian simplicity, this chemistry embodies *necessity*. The evolution of the necessary fruits of this chemistry towards organismic level entails Darwinism. The role of *chance* enters into the process as an answer to evolving environments.

## 2. INTRODUCTION. CHANCE AND/OR NECESSITY ?

"Life belongs to the very fabric of the Universe . . . Were (the emergence of life) not an obligatory manifestation of the combinatorial properties of matter, it could not possibly have arisen naturally".  With these words (1) Christian de Duve spelled out in 1991 a concept that a posteriori looks obvious and difficult to contradict. We adhere to these statements, each of them explaining the reasons for the existence of life by physical-chemical *necessity*.

A different way of tackling the problem was proposed a quarter of century before by Jacques Monod who accompanied *necessity* to *chance* (2). The key point of Monod's thought did not consist in the confrontation of the two terms "*necessity*" versus "*chance*" but, rather, in their juxtaposition. *Chance* <u>and</u> *necessity*, one fulfilling and justifying the other. The bias between the two positions (pure *necessity* versus *necessity* <u>and</u> *chance*) is not solved. Has *chance* a role in the origin and evolution of life? And, if so, at which point along the path that goes between the Big Bang and the mind/consciousness of who reads these lines did *chance* play its role? We will come back to this problem, but not before having

a) presented our experiment-based opinions on the initial part of the path, and having recalled the words attributed to Friedrich Engels:

b) "Causality can only be understood in relation to the category of objective *chance*, which is a form of manifestation of *necessity*" (3). Our use of the terms *chance* and *necessity* is in the Engel's and Monod's purport.

**3. DISREGARDING THE CONCEPTS OF "EMERGENCE" AND "COMPLEXITY"**

Both *emergence* and *complexity* are multi-purpose terms. Beyond understandable initial confusion, semi-rigorous largely accepted definitions were formulated. *Emergence* is considered "a key concept in *complexity* theory in which certain features of a complex system occur as a result of a collective behaviour of the system" (4). This definition has the advantage of boiling down these concepts as defined by John Holland (5) and Stephen J. Fromm (6), but has limited practical use. Especially so if one applies it to "what-is-life." The definition of complexity turns out to be more elaborate. In the first place, the term complexity has two distinct usages (7), categorized as either a quality or a quantity. Both are unified by the concept of *information*, as derived from the work of Claude Shannon (8). The more information is required to specify a system, the more complex it is**.** Emergence refers to extra information arising above a certain level of complexity, which is not entailed in the specification of the system. In "what-is-life," emergence, complexity and information appear to be intricately and self-referentially                                   connected.

Did life as-we-know-it emerge as a consequence of the properties of its composing elements: H, O, C and N (plus those of the relevant but potentially replaceable P and S) upon their interaction? Approaching the problem first requires a clear definition of what we mean by the word *life*. Cutting short the intricate analysis of the long-standing problem of life's definition, we adhere to the conclusion reached by Edward Trifonov (9). Through the structural analysis of a largely comprehensive list of the existing definitions (123 in total), Trifonov's proposal resulting from their analytical and comparative consensus is: "life is self-reproduction with variations". This is only partially related to a largely popular previous definition ("Life is a

self-sustained chemical system capable of undergoing Darwinian evolution" (10)). A comparison between the two definitions reveals that the only common term is "self". Which is possibly the minimal but most robust definition of life: "self". In this definition, every added word would become a mere adjective describing coordinated series of chemical reactions.

This takes us to consider life as something unrepeatable in its manifestations, each one of them being the fruit of endless successive combinations of extremely complex clusters of information. The two direct consequences are that, in looking for an answer (or at least for a falsifiable Popperian approach to the title of this discussion), the categories of *emergence*, *complexity* and *information* become useless, and that life can only be described, not defined or classified.

Consequently life, as definable Aristotelian or Kantian Category, does not exist.

There is no point in space-time after which those clusters of chemical processes become animated, or before which they are inanimate**.**

The question: "how did an inanimate environment accomplish the steering toward functional success and eventual life?" then becomes informationally meaningless (it is not repeatable exactly) but experimentally approachable (its surrogates may be falsified).

Thus, let us adopt an apparently radical but logically formally correct point of view: there is no life to be defined. There are only endlessly complex clusters of reactions to be described. We are consequently immediately allowed to forget about fuzzy prebiotic scenarios or no-answer questions as "genetics-first or metabolism-first?", and are left with experimentally faceable problems.

In other words, our approach is based on the most extreme minimalism possible, reached through application of every possible form of reductionism. An important (and operationally functional) consequence of this logic is that one is allowed to resort to the Occam's razor method: the simpler alternative is the closest to truth.

**4. NH$_2$COH FORMAMIDE**

The four most abundant elements in the Universe are H, C, N and O, disregarding inert He. An estimation of the possible number of covalently bonded compounds with this elemental composition and with molecular weight lower than 300 Da yields millions of possible candidates (11). Obviously, at higher molecular weights their number increases exponentially.

Focusing  on the compounds made of these atoms which bear an intermediate chemical complexity (say, three atoms), and looking for their actual presence in circum-  and  interstellar  space,  one  finds (www.astrochemistry.net) that the most abundant three-

atoms inorganic compound is $H_2O$, the most abundant three-atoms organic is HCN hydrogen cyanide. The same analysis on two-atoms compounds is much less informative while that on four-atoms compounds is, in the "*necessity* versus *chance*" problem, too imbalanced in the deterministic direction.

The reaction of HCN with $H_2O$ yields formamide $NH_2COH$. The key facts here are that, from the formation point of view, HCN can be prepared from gaseous mixtures of methane $CH_4$ and ammonia $NH_3$ by corona discharge (12) and by ion-irradiation and/or UV photolysis of $NH_2$-rich ice containing $CH_4$ (13). Thus, in space-wise conditions HCN is an easily formed compound. HCN preparation from $CH_4$ and $NH_3$ is also promptly catalyzed by platinum (14), by $Al_2O_3$ in the presence of Pt group metal and nitrides of Al, B, Ti and Si (15) or zirconia (16). In our perspective, formation of HCN is *necessary*.

$NH_2COH$ may be formed from the same mixture of reagents leading to the production of HCN, i.e. from $CH_4$ and $NH_3$ through proton irradiation (17), through ultraviolet irradiation of icy mixture of HCN, NH3 and H2O (18), photolysis of ices (19), pyrolysis of mixtures of carbon monoxide (CO), NH3 and H2O (20). The basic chemistry of formamide has been recently reviewed (21,22) and is schematically reported in Figure 1, panel A.

As considered for HCN, also the formation of $NH_2COH$ has not occurred (and presumably is still not occurring) by *chance.* Its facility and widespread generality point to its *necessity*.

## 5. THE CHICKEN/EGG PARADOX

The very nature of extant organisms consists of the alternation of genotype and phenotype. The genetic material maintains and transmits information and, given the possibility, transforms part of this information into the elaborate mixture of compounds which make up the phenotype and which, among other things, replicate the genome. With the important corollary that the genetic material is itself part of the phenotype. This is the core of the chicken/egg paradox.

The original formulation of the paradox is due to Censorinus, a roman science writer of II Century who said " … quod negant omnino posse reperiri, avesne ante an ova generata sint, cum et ovum sine ave et ave sine ovo gigni non possit." (De die natali, IV, 3) (it is totally denied that it may be established that birds were generated before eggs, given that both egg without bird and bird without egg cannot be born) (23). The concept is very clearly exposed. The key word is *ante,* stressing the relationship of causality that in contemporary terms we would look for in the genotype/phenotype relationship.

The paradox is solved by the coexistence of both terms in the same cycle of alternations. This points to their contemporaneous origin, which is still reflected in their absolute interdependence in contemporary organisms.

However, genetics and metabolism are based on different chemical compounds (even though juxtapositions and border-crossings are numerous). This caused the formulation of the bias that has so far characterized the origin-of-life field: genetics-first or metabolism-first?

We suggest that the question has no real sense and that the solution consists in the parallel and possibly cooperative evolution of genetics and metabolism from mixtures of simple compounds, produced in a single chemical frame. The following sections report the analysis of the compounds that are synthesized from formamide (Figure 1, panel B) in the presence of one out of many different catalysts.

## 6. EASY SYNTHESES

The chemical potentiality of HCN/$NH_2COH$ was initially shown by the synthesis of a small number of heterocycles including, as a nucleic base, only adenine (24,25). Adenine was shown to derive in this chemical frame by a multi-step condensation process (26,27). We have explored for more than a decade the syntheses obtained from formamide in the presence of numerous classes of catalysts, starting in 2001 from the analysis of the catalytic effects of simple metal oxides (28). The results have been recently reviewed (21,22). We report here the most indicative.

### 6.1. Nucleic bases

The gentle warming of $NH_2COH$ at 160 °C in the presence of catalytic amounts of calcium carbonate ($CaCO_3$), alumina ($Al_2O_3$), silica ($SiO_2$), and zeolite (Y type) yielded cytosine and *4 (3H)*-pyrimidinone, in addition to purine and adenine (28,29). In 2003 thymine was synthesized from $NH_2COH$ in the presence of titanium dioxide ($TiO_2$) (30). In this case three novel purine acyclonucleosides, in which the heterocyclic base is bonded to a sugar-like side-chain in the *N (9)*-position, were obtained in addition to 5-hydroxymethyl uracil (5-HMU).

Uracil, adenine, cytosine and hypoxanthine were obtained in 2004 by thermal condensation of $NH_2COH$ in the presence of clays of the montmorillonite family (31). The ribonucleoside corresponding to hypoxanthine (inosine) is the starting material for the biosynthesis of adenosine and guanosine. 5-aminoimidazole-4-carboxamide (AICA) and 5-formamidoimidazole-4-carboxamide (fAICA), the imidazole intermediates for hypoxanthine in the cell, were also detected in the condensation mixture (31,32).

### 6.2. Chemiomimesis

Interestingly, the $NH_2COH$ /montmorillonite syntheses appeared to be the first documented example of a chemiomimetic system (33-35). "Chemiomimesis" refers to defined biosynthetic pathways considered as mimetic of abiotic chemistry, as originally proposed and defined by Albert Eschenmoser (35). In a prebiotic perspective, chemiomimesis entails a relatively complex chemical setting: defined catalyst (s), specific (series of) reactions leading to one or more new chemical structures. If in order
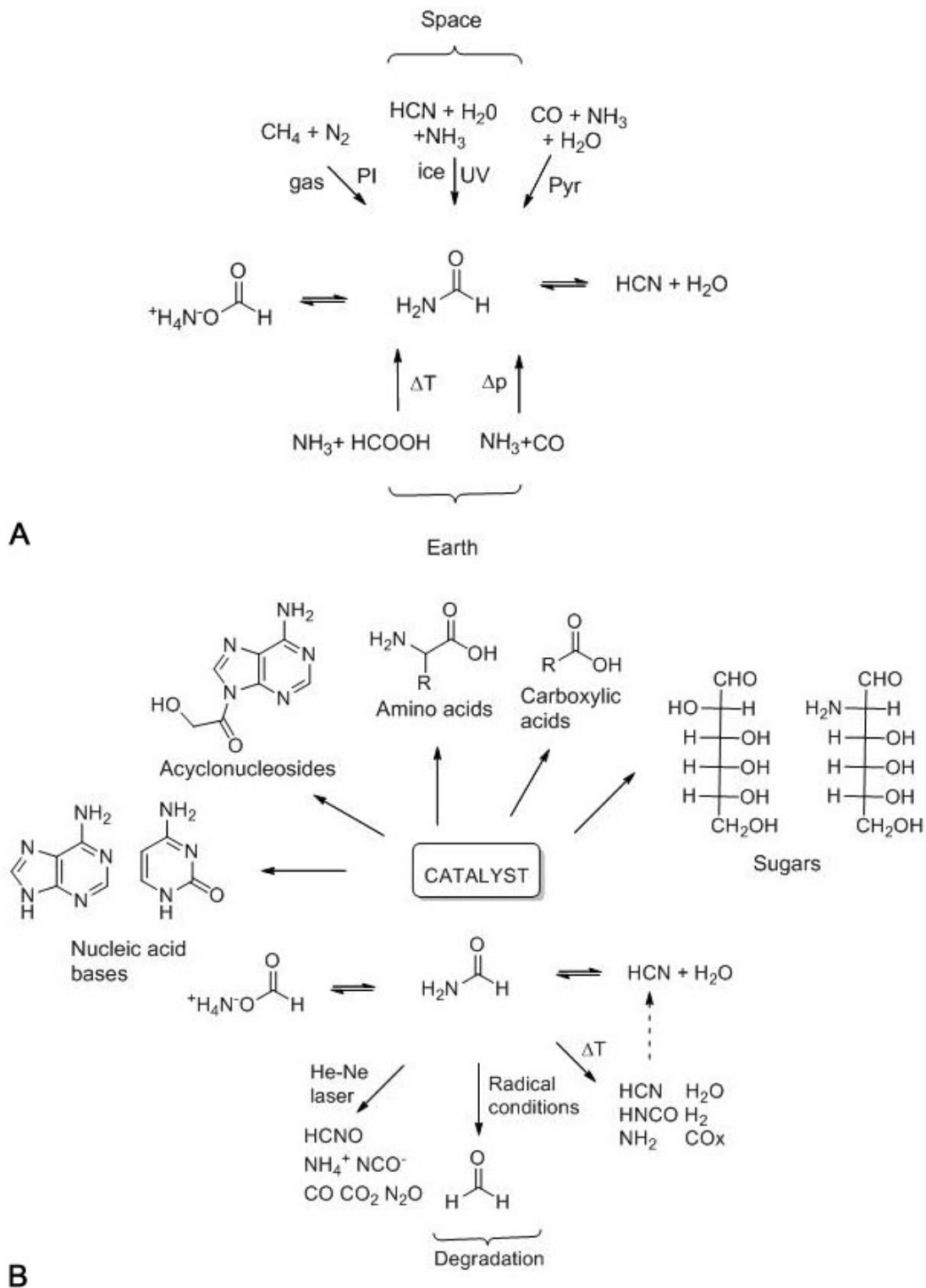
**Figure 1.** Basic chemistry of HCN/ NH2COH. Panel A: formamide is synthesized in space-wise (upper) and terrestrial (lower) conditions. PI = Photon Irradiation, Pyr = Pyrolysis, DT and DP = high temperature and/or high pressure (21,22). Panel B: formamide affords numerous biogenic molecules when reacted in the presence of catalysts (upper) or undergoes degradation (lower). See Text and references 21,22.

to fulfil a given biochemical need extant or archetypal organisms adopted a chemiomimetic route, starting from those very precursors to yield those very products, then a posteriori also the involved biological process can be defined as chemiomimetic. It seems to us that in chemiomimesis *necessity* and *chance* coexist. Chemical *necessity* and evolutionary *chance* can be dubbed as such only a posteriori, after that evolution has run its course and after that chemically favoured routes have been adopted and biologically fine-tuned.

### 6.3. More nucleic bases

In 2005 the pyrimidine nucleobases uracil and cytosine were selectively synthesized from $NH_2COH$ and cosmic dust analogues (CDAs) of terrestrial olivines (from fayalite to forsterite). The efficacy and selectivity of the reaction was determined by the content of iron in the catalyst, suggesting a redox process as a key step in the formation of the pyrimidin- (*1H,3H*)dione scaffold (36). In 2006, adenine, cytosine and uracil were obtained by warming $NH_2COH$ in the presence of one out of a large panel of mineral phosphates, confirming the possibility of the simultaneous synthesis of purine and pyrimidine nucleobases under simple conditions (37,38).

UV light irradiation of $NH_2COH$ on the surface of a $TiO_2$ (001) single crystal at low temperature in ultra-high vacuum conditions showed the formation of all five nucleic bases, including guanine (39). The possibility to synthesize guanine from $NH_2COH$ was confirmed in 2010 by a combined UV-irradiation/thermal condensation process in the presence of phosphate minerals (40).

In conclusion, all the five natural nucleobases are obtained by heating $NH_2COH$ in the presence of one out of a number of different catalysts. The results were extended to numerous other catalysts. In total: silicates and other metal oxides, clays, titanium dioxide, cosmic dust analogues, mineral phosphates, iron-sulphur minerals, zirconium minerals, borate minerals and meteoritic Murchison materials were analyzed, as reviewed (21,22, and as shown in Figure 2).

Summarizing, the formation of the nucleic bases present in all the organisms we know derives from the stabilization of hydrogen cyanide by water, leading to formamide. In the presence of all sorts of catalysts, formamide becomes nucleic bases. Although these reactions were carried out in our laboratories, they are so little fastidious that the probability of their occurrence anywhere in the universe, we guess, is rather high. The key word here is *stabilization*. That is: thermodynamic *necessity*.

### 6.4. Nucleic acids

The origin of extant genetic materials of terrestrial organisms is presumably connected with the unmatched autocatalytic versatility of RNA (41-46). RNA reactivity potentialities have lead to the shared vision of an "RNA world" (47,48) as the start of it all, confining DNA to the role of information depository, to be developed later by cellular or, at best, by (pre)cellular structures.

The synthesis of non-canonical polymers capable of heredity and evolution has been recently reported (49). These xeno-nucleic acids are an important example of nucleic bases-based polymers with structures different from those that have Darwinianly won the competition and rule extant biology on this planet. Numerous other examples have been reported over the years (50-53 and references therein), including the particularly interesting Peptide Nucleic Acid (54-56). All these compounds share one property: they are products of elaborate laboratory chemistry. This leaves unsolved, in the origin of life perspective, the problems related to their abiotic origin and relevance, if any.

Solutions to the problem of how a self-replicating system might have originated have been proposed (57,58 and references therein). Efficient enzyme-free copying of all four nucleobases templated immobilized RNA was recently reported (59). In general, these polymerization studies rely on the use of chemically activated precursors (typically phosphorymidazolides), which decreases their prebiotic valence but allows detailed analyses of *in vitro* non-enzymatic kinetics, sequence evolution and analysis of environmental effects.

The strong reactivity of ribonucleotides (to be considered in their natural form as nucleosides activated by phosphorylation) and the ribozyme capacities of oligonucleotides (60) may provide a solution to the conundrum of the initial formation of reproducible and transmittable (pre)genetic information.

The three major polymerization reactions of RNA in natural systems (polymerization from monomers, ligation of preformed oligonucleotides, cyclization) share a key step: the 3'-hydroxyl of one nucleotide attacks the 5'-triphosphate of another to form a 3',5'-phosphodiester. These reactions are carried out by highly evolved enzymes, all requiring triphosphate forms of nucleosides and the cleavage of the highest-energy bond. Triphosphates are not plausible prebiotic compounds, both for the energy cost of their formation and for their limited stability. This increases the likelihood that the initial prebiotic reactions were based on different compounds, possibly simpler to make and stable enough to allow their accumulation.

The prebiotic origin of purine and pyrimidine nucleosides is not understood. The formation of the β-glycosidic bond, connecting a nitrogen atom of a nucleic base and the anomeric carbon of the sugar has important regio- and stereo-chemical limitations (30). These prevent a direct reaction of preformed nucleic acids bases and sugars by a dehydration process, favouring multisteps construction of the nucleic acid base on a sugar or viceversa. Examples of both routes were reported (30,61). The formation of acyclic nucleotides consisting of aliphatic chains growing on the correct N position of the nucleic acid base appears a sufficiently simple and robust process to be prebiotically plausible.
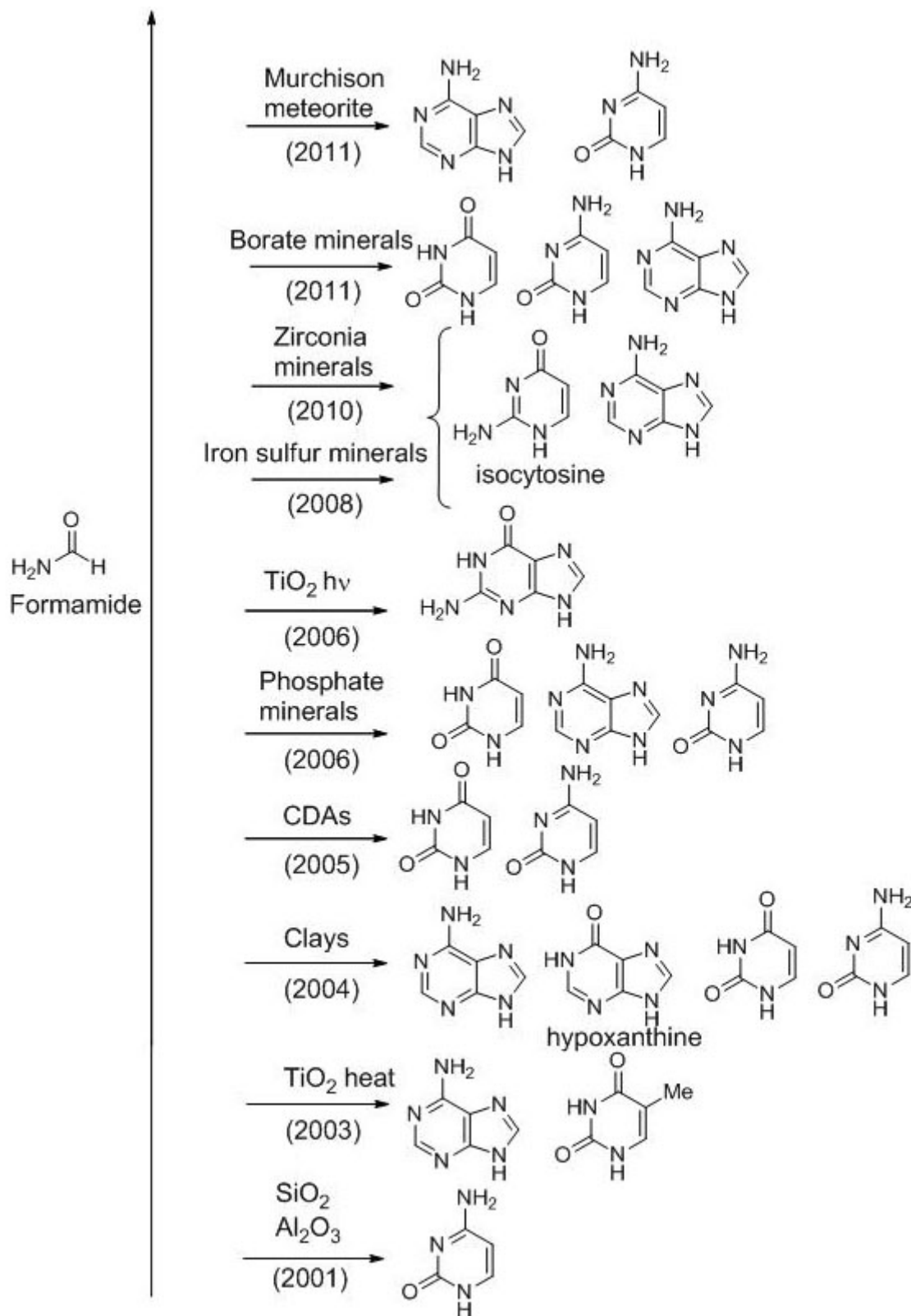
**Figure 2.** The nucleic acid bases synthesized by formamide in the presence of catalysts. The relevant and most abundant nucleic bases synthesized are shown, along with the indication of the catalyst (s) used and the year of discovery (bottom to top). See Text for specific references and details.
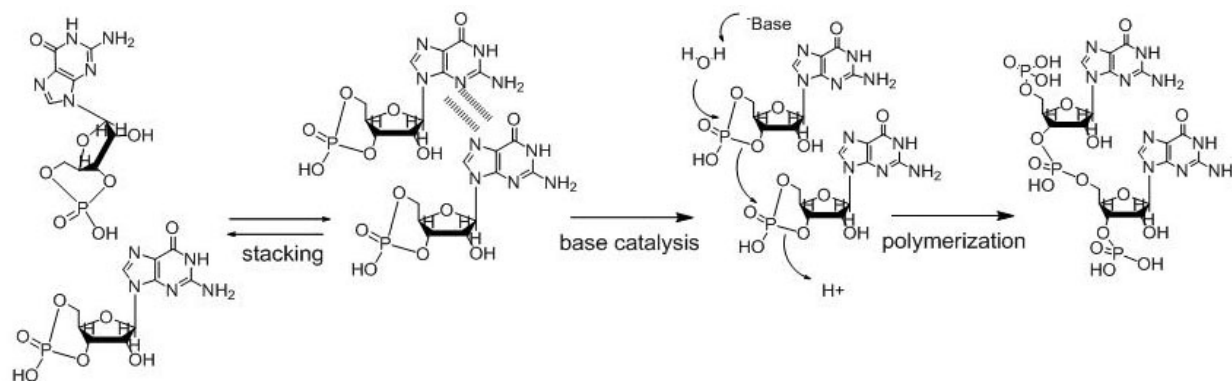
**Figure 3.** From cyclic nucleotides to RNA. The non-enzymatic polymerization of RNA from 3',5' cyclic nucleotides is schematically shown. See Text and references 66,67 for details.

Phosphorylation of nucleosides occurs in every possible position (2', 3' and 5') in the presence of a phosphate source and formamide (62,63). The nucleotides spontaneously cyclize to yield the 2',3' and 3',5' cyclic forms which, being more stable of the open forms in the conditions in which the reaction has occurred, may accumulate.

The polymerization of 2',3' cyclic phosphates was explored (64) and the role of this cyclic bond in the formation of phosphoester bonds connecting preformed oligonucleotides was studied (65). However, it was not until 2009 (66) that polymerization of 3',5' cyclic nucleotides was reported showing that 3',5' cGMP and, to lesser extent, 3',5' cAMP afford short oligomers in water (Figure 3). This reaction was recently analyzed in further detail (67) showing that it may occur in pure water but that it is stimulated by Brønsted bases such as 1,8-diazabicycloundec-7-ene (which is not prebiotic) and efficiently occurs also in formamide or in dimethylformamide (which are prebiotically plausible compounds).

The reaction is untemplated, does not require enzymatic activities, is thermodynamically favoured and selectively yields 3',5'-bonded ribopolymers containing as many as 25 nucleotides. This polymerization, which has several of the attributes of a click-like reaction (67), is based on the preliminary stacking of monomers, followed by the base-catalyzed opening of the cyclic P-bond and by its reformation on the OH of the anomeric carbon of a stacked adjacent nucleotide.

Given the presence of the 3',5' cyclic nucleotides at sufficient concentration (namely: $\geq 3$ mM), their hydrophobic character determines their interaction favouring the pillaring by stacking. The presence of a base (and water can be base enough) necessarily leads, at moderate temperature, to their polymerization. The polymer survives as such because the weakest bond in RNA, the 3' phosphoester, is more stable when part of a polymer than when present on a monomer (68) .

The formation of RNA polymers (Figure 3) appears to be, in the right conditions, chemically *necessary*.

It is probably at this level of chemical evolution of genetic materials that one should look for the border between *necessity* and *chance*. The survival of the polymeric information beyond its pure thermodynamic limits requires replication

This entails formation of complementary sequences, which requires the presence of the right complementary monomers, in the right concentrations, at the right temperature, and so on. If by *chance* all the conditions are met, replication follows. Meeting all these conditions outside a favourable programmed and well-fed laboratory or cellular environment is not a *necessary* happenstance.

Darwinian selection works a posteriori, favouring the fittest variants for a given, already existing function. Molecular replication is probably the key function for the initial selection. Hence the relevance of the observation of the formation of spontaneous networks among cooperative RNA replicators, recently reported (69). Nevertheless the question "what was there before the early replicators?" is still open. Watson and Crick end their seminal paper (70) by the words: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material". How did the first strand get synthesized? The observation that stacking pillars nucleic bases which, if connected with a bond-exchanging moiety, may covalently bind, suggests a solution. Base pairing provides the selected mechanism for the synthesis of the second strand. But, supposedly, stacking came first. Base pairing requires *chance* encounters, while stacking is a *necessary* property.

In addition: if life is "self-reproduction with variations" (9), it is at this point that errors (read: evolution) may start appearing in the not-completely faithful replication system.

The non-enzymatic generation of RNA oligonucleotides does occur also on complementary-sequence templates (66). In this case it is actually largely more efficient than when occurring in a solution of free-floating monomers. By exploiting this templated nonenzymatic polymerization

reaction, the possibility of introducing errors was observed (71). Introducing errors in a replicating mixture and transmitting (encoding) the errors corresponds to an increase of its information content, progressively moving from pure thermodynamic chemical *necessity* to genetic *chance*. A general treatment of these matters has appeared (72), connecting the ur-genotypic and ur-phenotypic realms. In particular, the relevance of *mistakes* was highlighted (ibidem).

### 6.5. Aminoacids and condensing agents

The same chemical system affords at least two amino acids, pointing to the possibility that others might be synthesized in yet-to-be-determined conditions. Remarkably, the synthesis is also observed of carbodiimide and urea, the components of a condensation cycle potentially able to release the synthesis of peptides from complex (pre)biological constraints and down-the-line evolutionary requirements. In particular glycine and alanine were observed, catalyzed by numerous borates, by zirconium minerals and by Murchison meteorite material (as reviewed in 21,22). Production of carbodiimide and urea were also observed in the presence of numerous phosphate minerals (37). The formation of aminoacids in space conditions is well documented (73-75).

### 6.6. Carboxylic acids and possibility of starting cycles

Carboxylic acids, notably dicarboxylic ones, are produced in different combinations from formamide in the presence of different catalysts. We have observed that formamide affords: Oxalic acid in various yields upon heating at 160°C in the presence of iron sulphur copper minerals: (pyrite ($FS_2$), pyrrhotine (FeS), bornite ($FeCu_5S_4$) and covellite (CuS)) (76); in the presence of zirconium minerals: (baddeleyte (zirconium dioxide, $ZrO_2$), cerium zirconium oxide (CeZrO4, as a mixture of ZrO2 and CeO2), zircon (zirconium silicate, ZrSiO4), different metal zirconates (lithium zirconate, Li2ZrO3), lead zirconate (PbZrO3), barium zirconate (BaZrO3) and zirconium oxinitrate ZrO (NO3)2) it affords glyoxylamide, glycolic, lactic, succinic, oxalic, fumaric and maleic acids, in various yields and combinations (77);

in the presence of borates: (borax ($Na_2B_4O_7$·10 ($H_2O$)), colemanite ($CaB_3O_4$ $(OH)_3$·$H_2O$), hydroboracite ($CaMgB_6O_8$ $(OH)_6$·3 ($H_2O$), kernite ($Na_2B_4O_6$ $(OH)_2$·3 ($H_2O$), kurnakovite ($MgB_3O_3$ $(OH)_5$·5 ($H_2O$), ulexite ($NaCaB_5O_6$ $(OH)_6$·5 ($H_2O$), chambersite ($Mn_3B_7O_{13}Cl$), hambergite ($Be_2$ $(BO_3)$ $(OH)$, ludwigite ($Mg_2Fe_3$+$BO_5$), rhodizite (K,Cs)Al_4Be_4 (B,Be)_{12}O_{28}), vonsenite ($Fe^{22+}Fe^{3+}BO_5$), dravite ($NaMg_3Al_6$ $(BO_3)_3Si_6O_{18}$ $(OH)_4$), dumortierite ($Al_{6.9}$ $(BO_3)$ $(SiO_4)_3O_{2.5}$ $(OH)_{0.5}$), elbaite ($NaLi_{2.5}Al_{6.5}C_3Si_6O_{18}$ $(OH)_4$), kornerupine ($Mg,Fe^{+2}$)4 ($Al,Fe^{3+}$)6 ($SiO_4,BO_4)_5$ $(O,OH)_2$), axinite- (Mn) ($Ca2Mn^{2+}A_{l2}$ $(BO_3)Si_4O_{12}$ $(OH)$, schorl ($NaFe^{+2}Al_6$ $(BO_3)_3Si_6O_{18}$ $(OH)_4$), canavesite ($Mg_2$ $(CO_3)$ (HBO_3)·5 ($H_2O$), painite ($CaZrB$ ($A_{l9}O_{18}$), boric anhydride ($B_2O_3$) and sodium perborate ($NaBO_3$·4 ($H_2O$)) it affords lactic, oxalic, pyruvic and glyoxylic acids, in various yields and combinations (see refs 21 and 78).

Murchison minerals afford lactic, malic, oxaloacetic and oxalic acids (79).

In summary, a large part of the essential components of both the glyoxylic and citric cycles and of gluconeogenesis are observed as products of nonenzymatic abiotic condensation of formamide.

### 7. CYCLES

Cycles essentially consist of ordered, teleologically potentially futile successive transformations of one component into a related one. The series of transformations exists in the form of closed loops, with no beginning and no end.

Cycles find their reason-of-being in the fact that at given points external compounds enter the flow, while others are released somewhere else. The so-called citric acid cycle enters $O_2$ and turning clockwise releases high-energy compounds (ATP and thus aminoacids, nucleic acid bases, sugars and lipids).

Vice versa, when turning counterclockwise, in eubacteria and archea, $CO_2$ is accepted and long-chain compounds are produced (Figure 4). Each one of the two directions is univocal, well defined for each organism, being genetically and biologically determined. The very existence of actual alternative directions indicates the flexibility of the principles on which the existence and the biological role of cycles are based.

The plausibility of metabolic cycles on the prebiotic Earth was questioned (80). Reasons for skepticism were the difficult optimization of the various catalyses, the presumable clogging of the reactions by the possibly very large complexity of secondary products, the difficulty in obtaining the right assembly of catalytic minerals, lack of coherent chemical plausibility and the right combination of efficiencies and specificities.

An interesting logical point is thus defined: ordered, smoothly running, clockwork-like, coordinated cycles exist. The very existence of cellular life is based on harnessing energy and channeling it through the biochemical ana- and cata-bolic pathways that are collectively dubbed metabolism. On the other hand, if considered from a chemist's point of view, their reconstruction and reproduction (in other words, lighting-up a cycle in a test tube) are prohibitive. Each one of the reasons pointed out (80) is valid and solid. Nevertheless, cycles exist. Even more, evolution has selected one or the other between possible directions. This suggests the frame into which the solution to the conundrum hides: evolution. Add to it Occam's logics and some observations start making sense:

• Under formose condensation formaldehyde H2CO is converted into a mixture of monosaccharides by an aldol-like reaction (81). As lateral products of the occasional conversion of formaldehyde to its dimer glycolaldehyde HCOCH2OH, higher complexity sugar chains are produced, ribose among others. In this case formaldehyde acts as a substrate and as a catalyst at the same time, in an autocatalytic process that (building on the
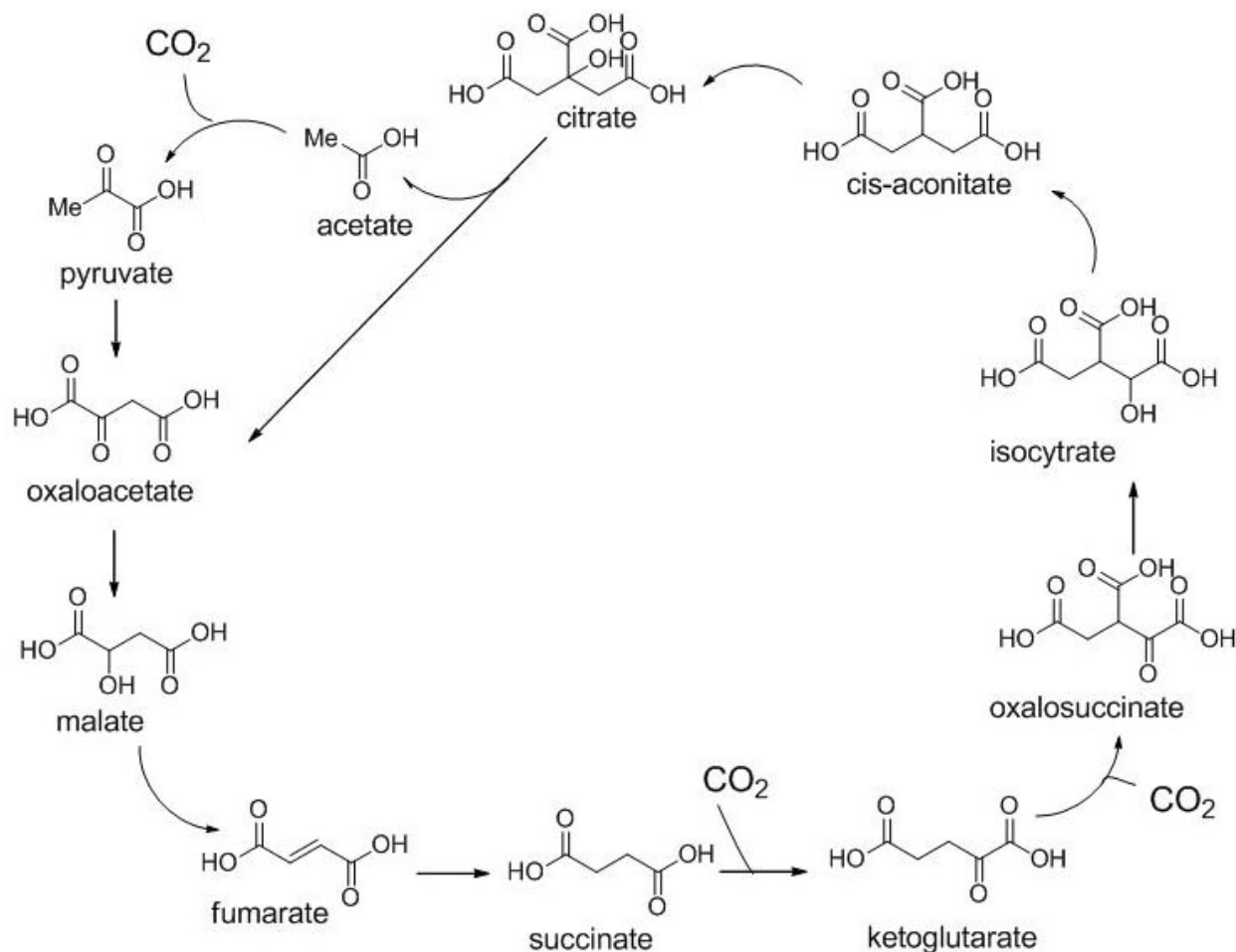
**Figure 4.** The reductive version of the citric acid cycle.

- 1861 report by Butlerow) was detailed by Breslow (82) (Figure 5).

- Cyclic aspects of the acceleration of HCN oligomerization by formaldehyde (83) and of the autocatalysis of the treose-ammonia reaction (84) were reported.

- Several steps of the rTCA cycle can be photochemically run in the presence of preformed acids in the presence of ZnS (85): oxaloacetate to malate, fumarate to succinate, ketoglutarate to oxalosuccinate. This chemistry suggests the chemical plausibility of the cyclic transformation oxalacetate → malate → fumarate →succinate →oxalacetate.

Thus simple cycles are not unprecedented. Their chemical simplicity speaks in favor of their being product of thermodynamical *necessity*, whenever the right concentrations of the reactants and physical-chemical conditions are met. Whether and how autocatalytic cycles spontaneously established themselves is matter of debate (86-90). Our view here is similar to that lying at the basis of spontaneous RNA polymerization. Given the presence of

the appropriate starting compounds (i.e., an uninterrupted series of carboxylic acids which, as reported above, necessarily form given the right conditions, precursors and catalysts. That is: given a Planet) simple cycling light up as thermodynamic necessity. Darwinian selection follows. If one starts from the consideration that the environment in which all this would have happened was a highly evolved system, the mise-en-place of these reactions might a posteriori not look that absurd.

Another possible key-point in the passage between *necessity* and *chance* may be identified considering the following: formamide condenses into pools of more stable chemical structures, whose composition mostly depends on the catalyst present, typically at temperatures moderately higher than 100°C, nothing else being required. Presence of water is allowed for synthetic reactions occurring below 100°C. The fact that purine is synthesized in the absence of catalysts (and that it is always present as a product, whatever catalyst is used) tells that formamide acts as a substrate and as a catalyst at the same time. Which is to say that it acts as agent of an autocatalytic process. The same role in autocatalysis was established for formaldehyde in the formose reaction leading to sugars
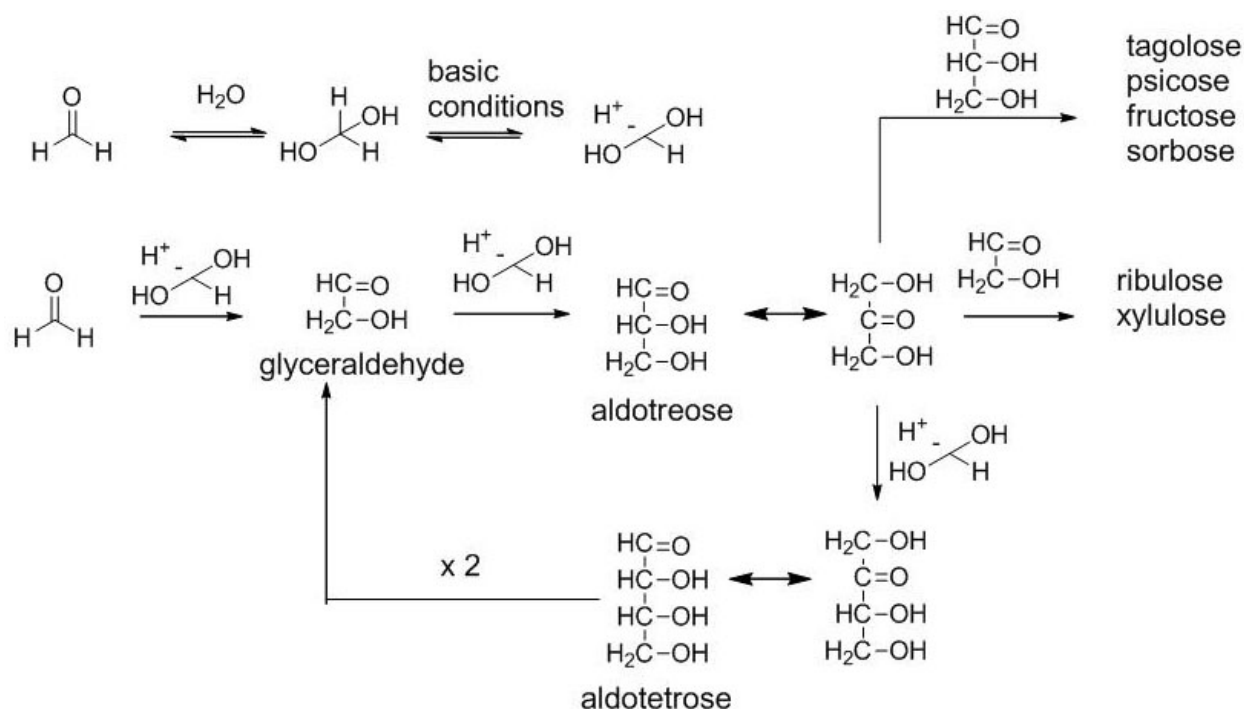
**Figure 5.** The formose reaction for the prebiotic synthesis of sugars. See Text, Section 7.

(81,82) and was hypothesized for HCN by Albert Eschenmoser (91). Some cycles may thus be seen as core groups of reactions built around a simple compound (i.e. $H_2CO$ or HCN) whose lateral products may play no direct role in the cycle, thus accumulating and becoming players in other cycles or in linear metabolic pathways, or simply be present and used as end-products.

Cycles as the citric acid cycle (both in its reductive or oxidative versions) obey the same general logics, but are established at a higher complexity level. Instead of one-carbon atom compounds, three-carbon atoms compounds are involved. In our perspective consideration, the $H_2CO$ or HCN substrate/catalyst cyclic functions would be *necessary* (mostly because of autocatalysis), while the tricarboxylic acid cycle would result from more sophisticated choices and selections, closer to evolutionary rules, conditioned by the availability of specific catalysts and ecological constraints. To the point of the possibility of its complete reversal: catabolic versus anabolic, O2 versus CO2, eubacteria versus eucaria.

In conclusion, the key logical point remains unsolved: are the elaborate cycles that we observe today due to casualty or to deterministic relationship with the environment? Their very complexity leans for the second alternative, with the specification that the term "environment" encompasses the local and actual chemical complexity and the general biological frame in consideration. In this perspective, extant cycles are fruit of evolution and fine-tuning, not withstanding the fact that the easy synthesis of the large number of carboxylic acids observed (76-79) indicates a solid starting level of *necessity*. In this context, *chemiomimesis* and *necessity* essentially coincide.

## 8. PERSPECTIVES

We have described a set of reactions taking place non-fastidiously whenever formamide is given the possibility to encounter a catalyst (or a mixture of catalysts) in a rather large set of conditions. These and other reactions may presumably occur in a wider, not yet fully explored and determined physical-chemical setting, waiting for further studies.

$HCN/NH_2COH$ afford numerous nucleic bases, including all the ones known to be primary components (i.e., not metabolic derivatives) of extant genetic materials. They also provide a credible scenario for their transformation into nucleosides and show prebiotically plausible means to the production of phosphorylated derivatives, noteworthy of the cyclic forms that were shown to be able to polymerize spontaneously. The experimental limits of the observed non-enzymatic polymerizations are discussed above.

The fact that carboxylic acids, notably dicarboxylic ones, are produced in the presence of numerous catalysts in various combinations is another relevant point for the shaping of a unitary perspective.

Formamide chemistry as a whole has numerous aspects of autocatalysis, as mentioned above, which apply to the first part of the scheme summarizing its reactions (Figure 1), concerning the synthesis of nucleic acid bases and of one-carbon atom compounds. In the phosphorylation of nucleosides and in their polymerization to oligonucleotides, formamide has only a catalyst role and

can be substituted by water, by dimethylformamide, or by strong Brønsted bases as DBU (1,8-diazabicycloundec-7-ene) (67).

As observed for formaldehyde, formamide plays a *necessary* role in the first part of its action, till the formation of nucleic acid bases, carboxylic acids, condensing agents, aminoacids. After this, the higher level interplay of its products becomes independent from its presence. The stimulation of RNA polymerization by formamide has presumably no special meaning and is possibly related to its chemical properties, easily substituted by other compounds (see above).

The fact that the basic components of the three major informational systems (nucleic acids, proteins, metabolic cycles) are all synthesized in the same chemical frame points to a possible unitary solution of the starting interactions among the systems. In addition, for each of the three systems a way towards the nucleation of higher level information appears to be possible: 3',5' cyclic nucleotides spontaneously generate oligonucleotides; glycine and alanine are synthesized along with carbodiimide and urea, agents of their condensation; carboxylic acids are synthesized which form gap-free tracts of extant metabolic cycles. Life as-we-know-it-by-description appears to be hard-wired by a precise set of chemical *necessities* whose solution, we propose, relied for its very first steps on the HCN/NH$_2$COH chemistry.

Summarizing, *necessity* characterizes the synthesis of simple compounds, up to three-carbon atoms carboxylic acids and relatively complex molecules as adenine, guanine, imidazoles and acyclonucleosides. Higher level interactions leading to the establishment of cycles of transformations and polymerizations involve more demanding sets of conditions, always relying on the *necessity* to obey to the second principle of thermodynamics and locating themselves and their products at the most convenient level of stability.

Nevertheless, complex series of reactions can only be obtained starting from pools of lower-information precursors. HCN/NH$_2$COH embodies the possibility that the precursors of nucleic acids, of proteins and of metabolic cycles are made in the same chemical frame, favored by the same catalysts. The very fact that all the numerous classes of catalysts tested showed catalytic activity and favored different and composite pools of precursors, indicates that this chemistry is robust and, at the same time, is able to modulate its response to the variations of the catalytic environment and of its physical-chemical conditions. It is presumably at the environmental level that *chance* started playing its role in the steer toward life.

The word *chance* is ridden with ambiguity. As phrased by David Abel: "*chance* doesn't cause or even influence any physical event to happen. *Chance* is only a descriptive mental construct, not a physical cause of effects" (92). And: "statistical predictions are neither determinative nor controlling" (ibidem).

We agree that, in this perspective, *chance* can be verified only a posteriori. When describing what has happened, *chance* acquires a Popperian purport and probabilistic verification only after things have happened. This is actually the interpretation that, through Abel's point of view (see also ref 93), can be given to Engels' words (quoted in the Introduction "…. causality can only be understood in relation to the category of objective *chance*, which is a form of manifestation of *necessity* (3)"). The key word there is "manifestation", which indicates the point in space-time where *chance* and *necessity* have met and where what was possible has actually occurred, being eventually ascertained by an Observer (94).

## 9. ACKNOWLEDGEMENTS

## 10. REFERENCES

1. de Duve C.: Blueprint for a Cell: The Nature and Origin of Life. Burlington NC. N. Patterson, 217 (1991)

2. Monod J. : Le hasard et la nécessité. In "Essai sur la philosophie naturelle de la biologie moderne", Eds. du Seuil. Paris (1970)

3. These words by Friedrich Engels are quoted in André Breton's "Les vases communicants", Paris Cahiers Libres, 1932 (repris in O.C. II, p. 168) and were commonly deemed to be present in F. Engels' "Herrn Eugen Dühring's Umwälzung der Wissenschaft" (1877). These sentences cannot be found nor in the work by Engels nor in the revolutionary literature of those times, according to the research carried out by Marguerite Bonnet and Etienne-Alain Hubert. However, several similar statements are present in his letters (*Notice,* pp. 1363-1365).

4. Oxford Dictionary of Science, 5$^{th}$ Edition.

5. Holland J. H.: Emergence: From Chaos to Order. Addison Wesley Ed. Redwood City, CA (1997)

6. Fromm S. J.: The emergence of Complexity. Kassel, University Press (2004)

7. Standish, R.K.: Concept and Definition of Complexity. In: Yang, A., Shan, Y. (Eds.), Intelligent Complex Adaptive Systems. IGI Global, London. (2008)

8. Shannon C.E.: A Mathematical Theory of Communication. Reprinted with corrections from *The Bell System Technical Journal,* 27, 623–656 (1948)

9. Trifonov, E. N.: Vocabulary of definitions of life suggests a definition, *J Biomolec Str Dyn* 29, 259-266 (2011)

10. Joyce J.: in Deamer DW & Fleischaker GR Eds, the forward of "Origins of Life: the Central Concepts", Jones and Bartlett, Boston (1994)

11. Fink T., H. Brugesser & J.L. Raymond: Virtual exploration of the small molecule chemical universe below 160 daltons. *Angew Chem Int Ed* 44, 2-6 (2005)

12. Stribling R. & S.L. Miller: Electric discharge synthesis of HCN in simulated Jovian Atmospheres. *Icarus* 72, 48–52 (1987)

13. Moore M.H., R.L. Hudson & R.F. Ferrante: Synthesis of HCN and HNC in Ion-Irradiated $N_2$-Rich Ices , *NASA Laboratory Astrophysics Workshop* 208–212 (2002)

14. Herceg E., & M Trenary: Carbon-Nitrogen Coupling on Pt (111) and its Relevance to the Catalytic Synthesis of HCN *Ciencia* 14, 104–113 (2006)

15. von Hippel L., Bussek C., Sauer J., Sauer M., Arntz D.: German Pat., DE, 19617040 C1 19971030, (1997)

16. McKenna E., A. Othoneos, N. Kiratzis & M. Stoukides: Synthesis of HCN in a Solid-Electrolyte Cell. Ind & Eng *Chem Res* 32, 1904–1913 (1993)

17. Koike T., T. Kaneko, K. Kobayashi, S. Miyakawa & Y. Takano: Formation of organic compounds from simulated Titan atmosphere: Perspectives of the Cassini mission. *Biol Sci Space* 17,188–189 (2003)

18. Gerakines, P.A., M. H. Moore, & R.L. Hudson: Ultraviolet Photolysis and Proton Irradiation of Astrophysical Ice Analogs Containing Hydrogen Cyanide. *Icarus* 170, 202-213 (2004)

19. Takano Y., T. Tsuboi, T. Kaneko, K. Kobayashi & K. Marumo: Pyrolysis of High-Molecular-Weight Complex Organics Synthesized from a Simulated Interstellar Gas Mixture Irradiated with 3 MeV Proton Beam. *Bull Chem Soc Jpn* 77, 779–783 (2004)

20. Bernstein M.P., L.J. Allamandola & S.A. Sandford: Complex organics in laboratory simulations of interstellar/cometary ices. *Adv. Space Res* 19, 991–998 (1997)

21. Saladino R., C. Crestini, S. Pino, G. Costanzo, & E. Di Mauro: Formamide and the origin of life. *Phys Life Rev* 9, 84-104 (2012)

22. Saladino R., Botta G., Pino S., Costanzo G. & E. Di Mauro, Genetics first or metabolism first? The formamide clue. *Chem Soc Rev* 41,5526-65 (2012)

23. Censorino, De die natali, IV, 3. For translation see the "De Die Natali" by Holt N. Parker (trans.): Censorinus. The Birthday Book. Chicago: The University of Chicago Press, 2007; Pp. xiv, 102.

24. Bredereck H., R. Gompper, H.G. Schur & G. Theilig: Neuere Methoden der präparativen organischen Chemie II. 16. Synthesen mit Säure-amiden, insbesondere mit Formamid. *Angew Chem* 71, 753-774 (1959)

25. Oró J.: Synthesis of adenine from ammonium cyanide. *Biochem Biophys Res Commun* 2, 407-412 (1960)

26. Yamada M., M. Hirobe, K. Higashiyama, H. Takaha & K.T. Suzuki: Reaction mechanism for purine ring formation as studied by carbon 13-nitrogen-15 coupling. *Tetrahedron Lett* 42, 4039 (1978)

27. Koyama T., T. Hirota, C. Bashou, T. Namba, S. Ohmori & M. Yamato: Polycyclic N-hetero compounds. XIV. Reactions of methylpyridine with formamide. *Chem Pharm Bull* 23,1923–1927 (1977)

28. Saladino R., C. Crestini, G. Costanzo, R. Negri & E. Di Mauro: A possible prebiotic synthesis of purine, adenine, cytosine and 4 (3H)-pyrimidinone from formamide: Implications for the origin of life. *Bioorg Med Chem* 9,1249-1253 (2001)

29. Saladino R., C Crestini, G. Costanzo, & E. Di Mauro: Advances in the prebiotic synthesis of nucleic acid bases: Implications for the origin of life. *Curr Org Chem* 8,1425-1443 (2004)

30. Saladino R., U. Ciambecchini, C. Crestini, G. Costanzo, R. Negri, & E. Di Mauro: One-pot $TiO_2$-catalyzed synthesis of nucleic bases and acyclonucleosides from formamide: Implications for the origin of life. *ChemBioChem* 4, 514-521 (2003)

31. Saladino R., C Crestini, U. Ciambecchini, F. Ciciriello, G. Costanzo, & E. Di Mauro: Synthesis and degradation of nucleobases and nucleic acids by formamide in the presence of montmorillonites. *ChemBioChem* 5, 1558-1566 (2004)

32. For reviews on prebiotic chemistry of $H_2NCHO$ see Ref. (21 and 22) and Saladino R., Crestini C., Costanzo G., & Di Mauro E: On the prebiotic synthesis of nucleobases, nucleotides, oligonucleotides, pre-RNA and pre-DNA molecules. *Top Curr Chem* 259, 29–68 (2005).

33. de Duve C.: Chemistry and selection. *Chem Biodiv* 4,574-583 (2007)

34. Breslow R.: Biomimetic chemistry: biology as an inspiration. *J Biol Chem* 284,1337–1342 (2009)

35. Eschenmoser A. & E. Loewenthal: Chemistry of potentially prebiological natural products. *Chem Soc Rev* 21,1-16 (1992)

36. Saladino R., C. Crestini, V. Neri, J.R. Brucato, L. Colangeli, F. Ciciriello, E. Di Mauro & G. Costanzo: Synthesis and degradation of nucleic acid components by formamide and cosmic dust analogues. *ChemBioChem* 6,1368–1374. (2005)

37. Saladino R., C. Crestini, V. Neri, F. Ciciriello, G. Costanzo & E. Di Mauro: Origin of informational polymers: The concurrent roles of formamide and phosphates. *ChemBioChem* 7,1707-1714 (2006)

38. Costanzo G., R. Saladino, C. Crestini, F. Ciciriello & E. Di Mauro: Formamide as the main building block in the origin of nucleic acids. *BMC Evol Biol* 7,1–8 (2007)

39. Senanayake S.D. & H. Idriss Photocatalysis and the origin of life: synthesis of nucleoside bases from formamide on TiO2 (001) single surfaces. Proc Natl Acad Sci USA 2006;103:1194–8.

40. Bark H.L., R. Buckley, G.A. Grieves, E. Di Mauro, N.V. Hud & T.M. Orlando: Guanine, adenine, and hypoxanthine production in UV-irradiation formamide solutions: relaxation of the requirement for prebiotic purine nucleobases formation. *ChemBioChem* 11,1240-1243 (2010)

41. Guerrier-Takada C., K. Gardiner, T. Marsh, N. Pace & S. Altman: The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35, 849-857. (1983)

42. Zaug AJ, P.J. Grabowski & T.R. Cech: Autocatalytic cyclization of an excised intervening sequence RNA is a cleavage-ligation reaction. *Nature* 301, 578-583 (1983)

43. Cech T.R.: The chemistry of self-splicing RNA and RNA enzymes. *Science* 236, 1532-1539 (1987)

44. Zaug, A.J.& T.R. Cech: The intervening sequence RNA of Tetrahymena is an enzyme. *Science* 231, 470-475 (1996)

45. Doherty, E.A. & J.A. Doudna: Ribozyme structures and mechanisms. *Annu Rev Biochem* 69, 597-615 (2000)

46. De Rose, V.J.: Two Decades of RNA Catalysis. *Chem Biol* 9, 961-969 (2002)

47. Gilbert, W.: Origin of life: The RNA world. *Nature* 319 (6055), 618 (1986)

48. Yarus, M.: Life from an RNA World: The Ancestor Within. Harvard University Press, Cambridge, MA, US. (2010)

49. Pinheiro V.B., A.I. Taylor, C. Cozens, M. Abramov, M. Renders, S. Zhang, J.C. Chaput, J. Wengel, S.Y. Peak-Chew, S.H. McLaughlin, P. Herdewijn &, P. Holliger: Synthetic Genetic Polymers Capable of Heredity and Evolution. *Science* 336, 341-344 (2012)

50. Pitha, J., P.M. Pitha & P.O. Ts'o: Poly (1-vinyluracil): The preparation and interactions with adenosine derivatives *Biochim. Biophys. Acta 204,* 39-48 (1970)

51. Schwartz A. & L. Orgel Template-Directed Synthesis of Novel, Nucleic Acid-Like Structures. *Science* 228, 585-587 (1985)

52. Benner, S.A., A. Ricardo & M.A. Cardigan: Is there a common chemical model for life in the universe? *Curr Op Chem Biol* 8, 672–689 (2004)

53. Renders, M., M. Abramov, M. Froeyen & P. Herdewijn: Polymerase-Catalysed Incorporation of Glucose Nucleotides into a DNA Duplex. *Chemistry* 15, 5463-5470 (2009)

54. Nielsen P.E., M. Egholm, R.H. Berg & O. Buchardt: Sequence-selective recognition of DNA by strand displacement with a thymine-substituted polyamide. *Science* 254, 1497-1500 (1991)

55. Nelson K.E, M. Levy & S.L. Miller: Peptide nucleic acids rather than RNA may have been the first genetic molecule. *Proc Natl Acad Sci USA* 97, 3868-3871 (2000)

56. Nielsen, P.E.: Self-assembling, dynamic alphaPNAs. *Chem Biol* 16, 689-690 (2009)

57. Reader J.S. & G.F. Joyce: A ribozyme composed of only two different nucleotides. *Nature* 420, 841-844 (2002)

58. Lincoln TA. & GF Joyce: Self-sustained replication of an RNA enzyme. *Science* 323, 1229-1232 (2009)

59. Deck C., M. Jauker & C. Richert: Efficient enzyme-free copying of all four nucleobases templated by immobilized RNA. *Nature chemistry* 3, 603-608 (2011)

60. Zaug A.J. & T.R. Cech: The intervening sequence RNA of Tetrahymena is an enzyme. *Science* 231, 470-475 (1996)

61. Powner, M.W., B. Gerland, & J.D. Sutherland: Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. *Nature* 459, 239-242 (2009)

62. Costanzo G., R. Saladino, C. Crestini, F. Ciciriello & E. Di Mauro: Nucleoside phosphorylation by phosphate minerals, *J Biol Chem* 282, 16729-16735 (2007)

63. Saladino R., C. Crestini, F. Ciciriello, S. Pino, G. Costanzo & E. Di Mauro: From formamide to RNA: the roles of formamide and water in the evolution of chemical information Special Issue on "The Origin of life and Microbiology" *Res Microbiol* 160, 441-448 (2009)

64. Verlander, M.S., R. Lohrmann & L.E. Orgel: Catalysts for the self-polymerization of adenosine cyclic 2', 3'-phosphate *J Mol Evol* 2, 303-316 (1973)

65. Usher, D.A & A.H McHale: Nonenzymic joining of oligoadenylates on a polyuridylic acid template. *Science* 192, 53-54 (1976)

66. Costanzo G., S. Pino, F. Ciciriello & E. Di Mauro: Generation of long RNA chains in water. *J Biol Chem* 284, 33206-33216 (2009)

67. Costanzo, G., R. Saladino, G. Botta, A. Giorgi, A. Scipioni, S. Pino & E. Di Mauro: Generation of RNA molecules by base catalyzed click-like reaction. *ChemBioChem* 13, 999-1008 (2012)

68. Saladino R., C. Crestini, F. Ciciriello, E. Di Mauro & G. Costanzo: Origin of informational polymers: differential stability of phosphoester bonds in ribomonomers and ribooligomers. *J Biol Chem* 281, 5790-5796. (2006)

69. Vaidya, N., M.L. Manapat, I. A. Chen, R. Xulvi-Brunet, E. J. Hayden & N. Lehman: Spontaneous network formation among cooperative RNA replicators. *Nature* 491, 72–77 (2012)

70. Watson J. & FJ Crick: A structure for Deoxyribose Nucleic Acid. *Nature*, 171, 737-738 (1953)

71. Pino, S., E. Trifonov & E. Di Mauro: On the observable transition to living matter. *Genom, Proteom & Bioinform* 9,7-14 (2011)

72. Di Mauro, E., A. K. Dunker & E. N. Trifonov: Disorder to order, non-life to life. In the beginning there was …a mistake. GENESIS - In "The Beginning Precursors of Life", Chemical Models and Early Biological Evolution Series: Cellular Origin, Life in Extreme Habitats and Astrobiology, Vol. 22, Part 3, 415-435, (Joseph Seckbach and Richard Gordon editors) (COLE), Springer. (2012)

73. Bernstein, M. P., Dworkin, J. P., Sandford, S. A., Cooper, G. W. & Allamandola, L. J. Racemic Amino Acids from the Ultraviolet Photolysis of Interstellar Ice Analogues, *Nature* 416, 401-403 (2002).

74. Meierhenrich U.J., Muñoz Caro G.M., Bredehöft J.H., Jessberger E.K. & Thiemann W.H.-P.: Identification of diamino acids in the Murchison meteorite. *Proc. Natl. Acad. Sci.* 101, 9182-9186 (2004).

75. Muñoz Caro G.M., Meierhenrich U.J., Schutte W.A., Barbier B., Arcones Segovia A., Rosenbauer H., Thiemann W.H., Brack A., Greenberg J.M.: Amino acids from ultraviolet irradiation of interstellar ice analogues. *Nature* 416, 403-406 (2002)

76. Saladino R., V. Neri, C. Crestini, G. Costanzo, M. Graciotti & Di Mauro E.: Synthesis and degradation of nucleic acid components by formamide and iron sulphur minerals. *J Am Chem Soc* 130, 15512-15518 (2008)

77. Saladino R., V. Neri, C. Crestini, G. Costanzo, M. Graciotti & E. Di Mauro: The role of the formamide/zirconia system in the synthesis of nucleobases and biogenic carboxylic acid derivatives. *J Mol Evol* 71, 100-110 (2010)

78. Saladino R., M. Barontini, C. Cosetti, E. Di Mauro & C. Crestini: The effects of borate minerals on the synthesis of nucleic acid bases, amino acids and biogenic carboxylic acids from formamide. *Orig Life Evol Biosph* 41, 317-330 (2011)

79. Saladino R., C. Crestini, C. Cossetti, E., Di Mauro & D. Deamer: Catalytic effects of Murchison material: Prebiotic synthesis and degradation of RNA precursors. *Orig. Life Evol. Biosph* 41, 437-451 (2011)

80. Orgel L.E.: The Implausibility of Metabolic Cycles on the Prebiotic Earth. *PLoS Biol* 6, 5-13 (2008)

81. Butlerow A.: Formation synthetique d'une substance sucrée. *Acad Sci* 53,145-147 (1861)

82. Breslow R.: On the mechanism of the formose reaction. *Tetrahedron Lett* 21, 22-26 (1959)

83. Schwartz A.W. & M. Goverde: Acceleration of HCN oligomerization by formaldehyde and related compounds: implications for prebiotic syntheses. *J Mol Evol* 18, 351–353 (1982)

84. Weber A.L.: The sugar model: autocatalytic activity of the triose-ammonia reaction. *Orig Life Evol Biosph* 37, 105–111 (2007)

85. Zhang X.V. & S.T. Martin: Driving parts of Krebs cycle in reverse through mineral photochemistry. *J Am Chem Soc* 128,16032–16033 (2006)

86. Smith E. & H.J. Morowitz: Universality in intermediary metabolism. *Proc Natl Acad Sci USA* 101,13168–13173 (2004)

87. Lane N., J.F. Allen & W. Martin: How did LUCA make a living? Chemiosmosis in the origin of life. *Bioessays* 32, 271–280 (2010)

88. Lane N.: Chance or *necessity*? Bioenergetics and the probability of life. *J Cosmol* 10, 7 (2010)

89. Russell M.J., A.J., Hall & W. Martin: Serpentinization and its contribution to the energy for th89emergence of life. *Geobiology* 8,355–371 (2010)

90. Strinivasan V. & H.J. Morowitz: The canonical network of autotrophic intermediary metabolism: Minimal metabolome of a reductive chemoautotroph. *Biol Bull* 216,126–130 (2009)

91. Eschenmoser, A: On a Hypothetical Generational Relationship between HCN and Constituents of the Reductive Citric Acid Cycle. *Chem Biodivers* 4, 554–573 (2007)

92. Abel, D.L.: The Formalism > Physicality (F > P) Principle. In *The First Gene: The Birth of Programming, Messaging and Formal Control*; Abel, D.L., Ed.; LongView Press-Academic: New York, NY, USA, 2011; pp. 325-356.

93. Trevors J.T. & D.L. Abel: Chance and necessity do not explain the origin of life. *Cell Biol In,* 28, 729–739 (2004)

94. For a deeper look at this concept, the reader is referred to the treatment of the terms "Ereignis", "Ereignen" and "Ereignishafte" in M. Heidegger's "Holzwege", Vittorio Klostermann GmbH, Frankfurt am Main (1950)

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