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The coenzyme/protein pair and the molecular evolution of life

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What was first? Coenzymes or proteins? These questions are archetypal examples of causal circularity in living systems. Classically, this "chicken-and-egg" problem was discussed for the macromolecules RNA, DNA and proteins. This report focuses on coenzymes and cofactors and discusses the coenzyme/protein pair as another example of causal circularity in life. Reflections on the origin of life and hypotheses on possible prebiotic worlds led to the current notion that RNA was the first macromolecule, long before functional proteins and hence DNA. So these causal circularities of living systems were solved by a time travel into the past. To tackle the "chicken-and-egg" problem of the protein–coenzyme pair, this report addresses this problem by looking for clues (a) in the first hypothetical biotic life forms such as protoviroids and the last unified common ancestor (LUCA) and (b) in considerations and evidence of the possible prebiotic production of amino acids and coenzymes before life arose. According to these considerations, coenzymes and cofactors can be regarded as very old molecular players in the origin and evolution of life, and at least some of them developed independently of α-amino acids, which here are evolutionarily synonymous with proteins. Discussions on "*chicken-and-egg*" problems open further doors to the understanding of evolution.

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1. Introduction

"*If there has been a first man he must have been born without father or mother – which is repugnant to Nature*" Aristotle.[1]

The "*chicken and egg*" problem is the archetypal example of causal circularity found in all living systems. Such scenarios are relevant when we need B for A, but for B first A.[2] If we look at the molecular evolution of life, we encounter several such metaphorical paradoxes that deal with this specific problem.[3]

In molecular evolution, the "*chicken-and-egg*" problem has been discussed primarily in relation to the major classes of macromolecules: DNA, RNA and proteins (Fig. 1). These are responsible for information storage, replication and

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transformation into function. It boils down to the question which of these three privileged macromolecules was the first. The RNA world theory[4] is not the only one that can explain the origin of life.[5] However, no other theory has been subjected to a similar number of experiments to either vary or falsify it. Biosynthetic and probably evolutionary RNA is a precursor to DNA, and if the RNA world theory is correct, the hen's egg dilemma is left to RNA and proteins. It is rather unlikely that these two different types of macromolecules were formed simultaneously.

The discovery that RNA has catalytic properties[6] was used as an argument for a possible solution. Originally, a single macromolecule could have performed both replication and catalysis. However, two further objections[7] were raised to the RNA world hypothesis in relation to its catalytic properties. Only long RNA sequences show catalytic properties, and the catalytic repertoire of RNA is small and chemically not diverse.

Nevertheless, it has been postulated that RNA fragments were first formed from simple prebiotic molecules, which led to the early appearance of kind of ribozymes. These might have been involved in the binding and condensation of prebiotically generated amino acids to produce the first peptides and non-coded chains that might be comparable to modern peptidyl-transferase centres (PTC). Such ancient complexes have occasionally been referred to as proto-ribosomes.[8] Biotically speaking, the highly complicated translation system is necessary for its own formation.

Over time, larger peptides formed a tertiary structure with catalytic properties. Their greater chemical stability might be the reason why the RNA used as catalyst was to a great extent replaced by peptides and hence proteins.

From a chemical point of view, this was the entry into the world of today's enzymes. At that time, DNA formation was possibly facilitated by the occurrence of an iron-dependent ribonucleotide reductase.[9] Therefore, the theory of the RNA world assumes that RNA preceded the proteins that preceded DNA (Fig. 1).[10]

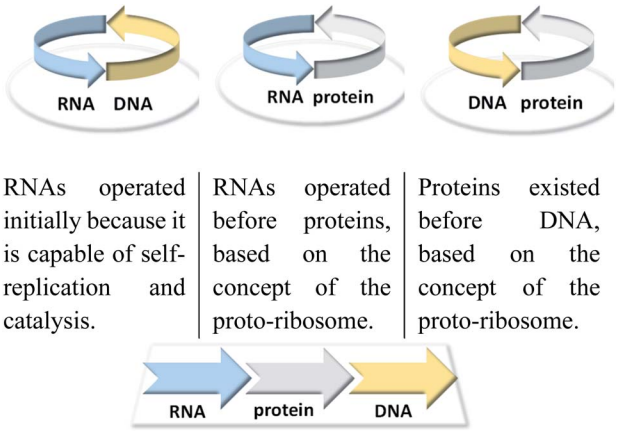

Fig. 1 Classical problems of circular causality in biomolecular systems and how this are resolved with reference to the RNA world hypothesis.

Important chemical players in metabolism and proto-metabolism – the coenzymes and cofactors – have been largely neglected. These are small organic non-protein molecules that bind specifically to proteins and actively participate in catalytic biotransformations (Fig. 2). This alliance is effective because it is able to promote site-specific oxidations and reductions, group transfer reactions such as acylation, phosphorylation, methylation and formal acylanion transfer reactions. The protein part itself is generally not capable of promoting such reactions, but often are involved in general acid–base catalysis.[11] In fact, it can be argued that coenzymes and cofactors are the most chemical species in nature of all molecular architectures, because accept for a few new roles that came into play much later in evolution, their sole purpose is to promote chemical reactions.

A closer look at the biosynthetic origin and biological role of coenzymes reveals another biomolecular "*chicken and egg*" problem, namely the relationship between the pair coenzymes/

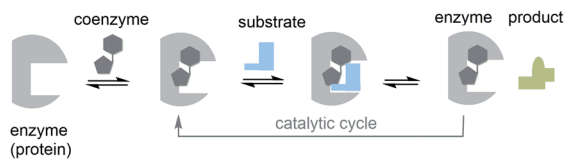

Fig. 2 The role of cofactors/coenzymes in enzyme catalysis (the case of reversibly bound coenzymes are shown; prosthetic groups are commonly covalently attached to the protein template).

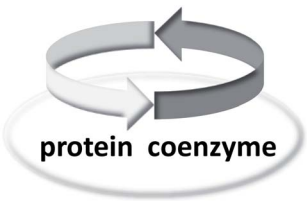

Fig. 3 The "*chicken-and-egg*" problem of coenzymes and proteins.

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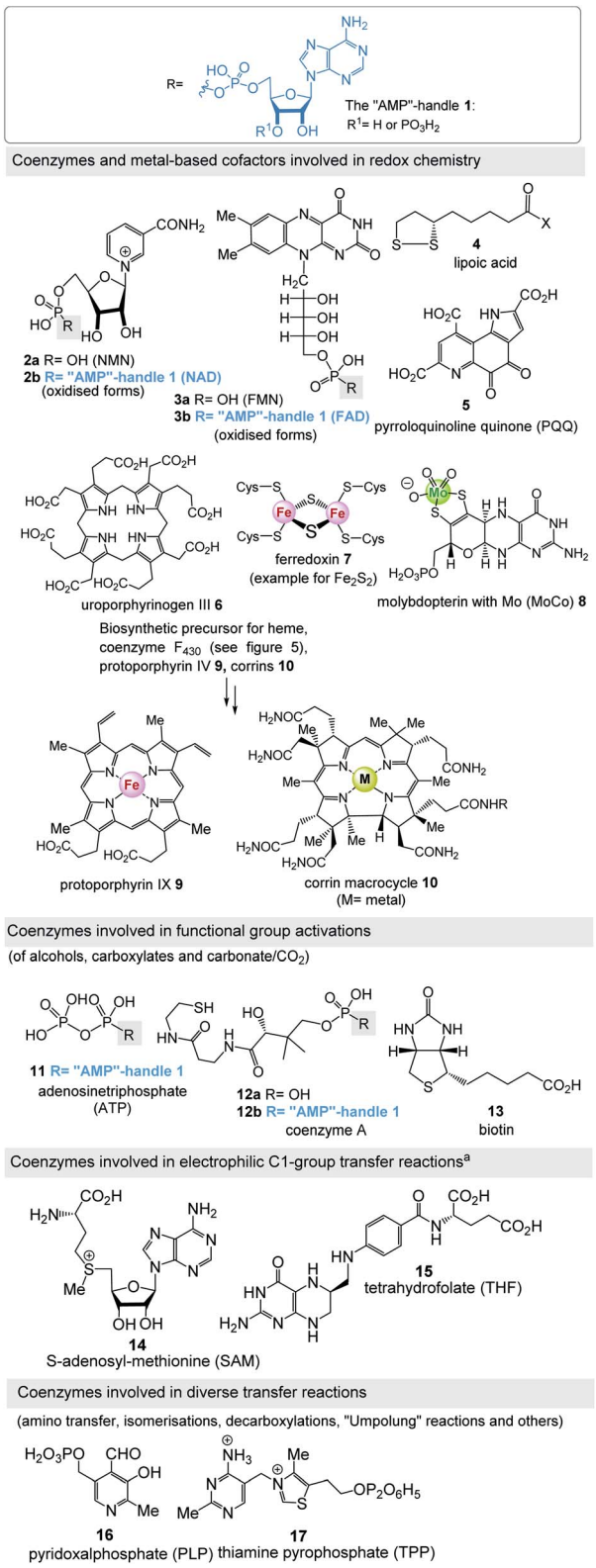

Fig. 4 "AMP"-handle **1** and coenzymes and cofactors **2–17** (phosphates are depicted in fully protonated form throughout the text). [a]SAM is also involved in S-ylide chemistry and in combination with FeS-clusters also responsible for isomerisations triggered by radicals.

cofactors and proteins (Fig. 3). In this report it will be shown that an evolutionary view can serve as a basis for solving the dilemma whether coenzymes and cofactors or proteins were the first. It should not be overlooked that there is still a debate about whether the RNA world hypothesis is valid or not.[10] Nevertheless, speculations about the origin of life, as covered by the RNA world hypothesis, may point the way that causal cycles in biomolecular systems can be solved if prebiotic milieus are included in the considerations. Biomolecular causal cycles are broken if at least one element of such systems is a molecular remnant from prebiotic time. Based on these fundamental considerations, the "*chicken and egg*" problem of coenzymes and proteins is discussed here.

2. Coenzymes/cofactors and proteins in the biotic world

2.1 Coenzymes/cofactors – a brief overview

Fig. 4 lists the most important coenzymes and metal-based cofactors **2–17**.[10] These are categorised according to their chemical properties and their role in metabolism. Most of them are distributed across all phylogenetic kingdoms.

Uroporphyrinogen III (**6**) is the biosynthetic precursor for many macrocyclic ligands such as heme including protoporphyrin IX **9** and cobalamin **10**.[12] Structurally, several of the coenzymes contain elements of nucleotides, which is manifested in the "AMP handle" **1**. This fact was seen as a strong indication that RNA and coenzymes, or simpler analogues derived from them, may have occurred on earth under prebiotic conditions at about the same time.[13] Furthermore, methanogens are dependent on several coenzymes that do not occur in other organisms (Fig. 5).[14] These prokaryotes belong to the domain of the archaea and are exclusively capable of

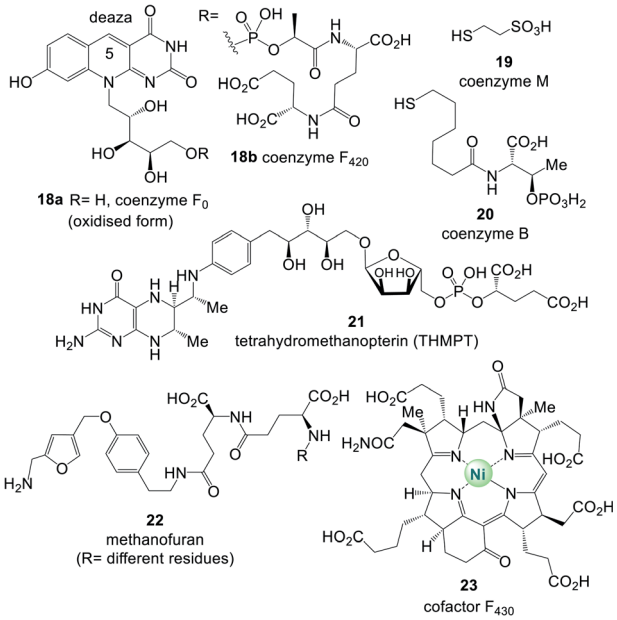

Fig. 5 Coenzymes and cofactors **18–23** found in methanogens.

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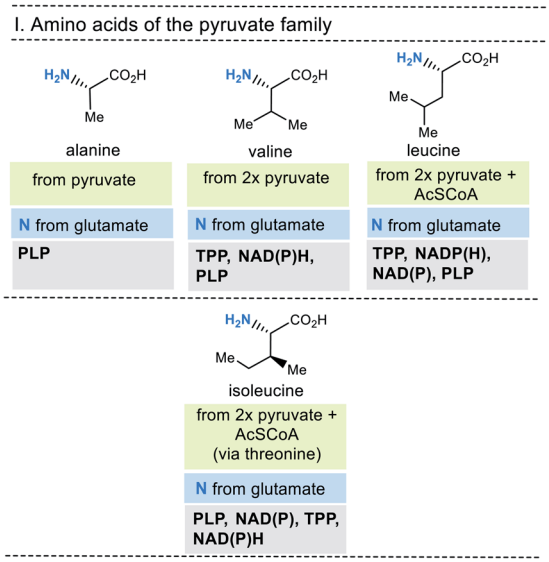

Fig. 6 Summary of amino acid biosyntheses of the pyruvate family with reference to starting building blocks and coenzymes.

synthesising methane. As such they are limited to carbon dioxide, formate, methanol, methylamines and acetate as carbon sources. Coenzymes and cofactors are involved in this energy process, such as the 5-deazaflavines, the coenzymes F_0 and F_{420} (**18a**,**b**) (structurally related to FMN **3a** and FAD **3b**), coenzyme M (**19**), 7-mercaptoheptanoylthreonine phosphate (coenzyme B, **20**), tetrahydromethanopterin (THMPT, **21**), methanofuran (**22**) and cofactor F_{430} (**23**). Most of them are specialised in their role in methanogenesis.[15] Surprisingly none of the coenzymes specific to methanogenesis contains the "AMP handle" **1**.

Methanogens are hydrogen-dependent autotrophs that have been suggested as good candidates for the ancestral state of physiology.[16]

Intriguingly, besides the "AMP-handle" some coenzymes possess an (oligo)-gamma-glutamate handle such as (THF **15**, THMPT **21**, F_{420} **18b**, methanofuran **22** and glutathione).

2.2 Casual circularity is a relevant dilemma for the coenzyme/protein pair

2.2.1 Principles of amino acid biosynthesis. The pair of coenzymes/cofactors and proteins has not yet been discussed in the context of causal circularity. Enzymes, like all proteins, are biosynthesised from proteinogenic amino acids, and the ribosome is the macromolecular assembly line for protein biosynthesis, a process known as translation.[17] Ribosomes are found in the three domains of life that are remarkably similar, which has been interpreted as evidence of a common origin.[18]

At this stage it is useful to ask where the proteinogenic amino acids come from and how they are biosynthesised. The essential information on these questions are summarised in Fig. 6-10. They are grouped in a classical way, and this classification is linked to biosynthetic considerations.[19] For example, the members of the pyruvate family of amino acids all use pyruvate as the starting building block for their biosynthesis. In fact, all 20 proteinogenic amino acids use carbohydrate-containing building blocks or carboxylic acids to build their carbon backbones.

In selected cases (*e.g.* isoleucine, proline, arginine) other amino acids serve as precursors, but these in turn are derived from simpler building blocks. With the exception of glutamate itself, the nitrogen atom of the amino group usually comes from the amino acid glutamate. Finally, the nitrogen atom in glutamate is recruited from ammonium (NH_4^+). Other nitrogen atoms in amino acids, such as in asparagine, glutamine, arginine, lysine, histidine and tryptophane, are taken from glutamate, glutamine, aspartate or ATP. Finally, the sulfur atoms in cysteine and methionine come from H_2S or thiosulfate.

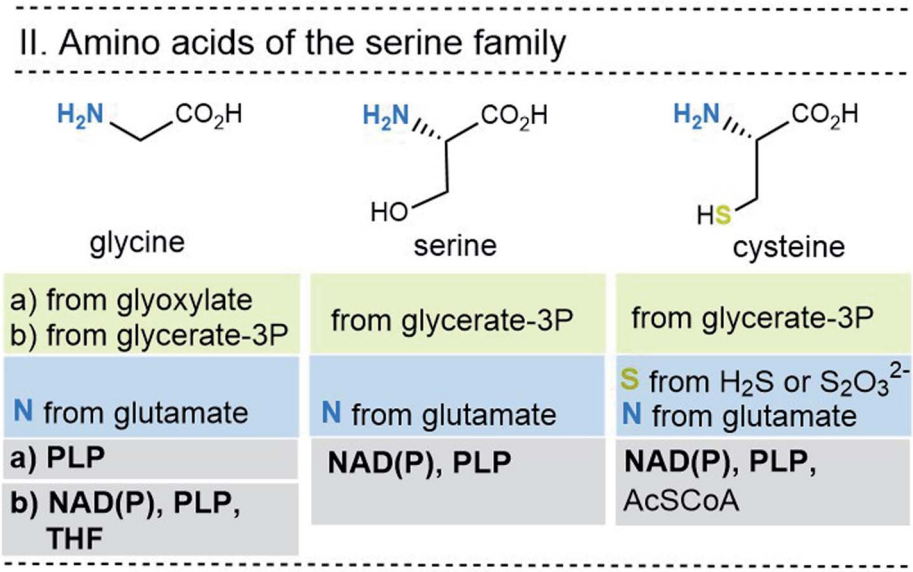

Fig. 7 Summary of the amino acid biosyntheses of the serine family with reference to the required starting building blocks and coenzymes.

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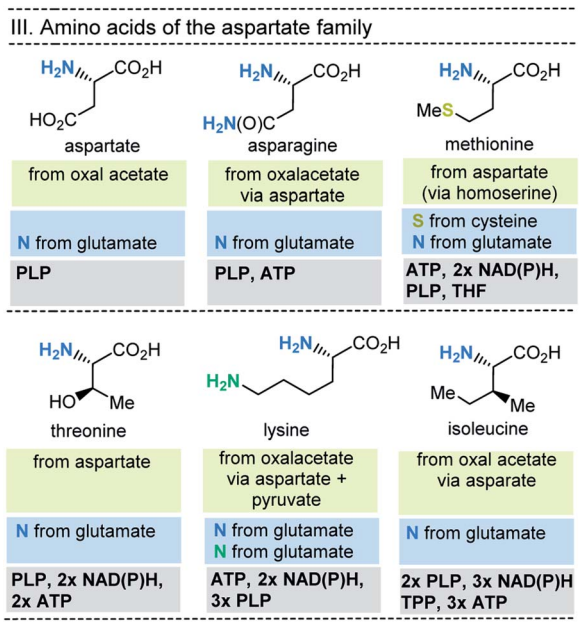

Fig. 8 Summary of amino acid biosynthesis of the aspartate family with reference to starting building blocks and coenzymes required.

This condensed presentation is far from comprehensive. It does not include the biosyntheses of the building blocks (marked on light green ground) and the question which coenzymes that are required for their biosyntheses. For example, thiamine pyrophosphate (TPP, **17**) is a coenzyme that plays an important role in carbohydrate metabolism such as in the pentose phosphate pathway. In addition, the amino acid biosynthetic pathways vary greatly between species. Fig. 6–10 also do not cover the variations found in archaea, bacteria and eukarya, as these details are not essential to convey the message underlying this report. This message is that, based on the listed building blocks, the biosyntheses of all 20 amino acids require different sets of coenzymes. These coenzymes serve as catalytically active units (PLP **16**, TPP **17**) or as group transfer agents, usually for chemical activation (ATP **11**), redox reactions (NAD(P)/NAD(P)H **2**) and for the transfer of methyl groups (THF **15**). Note, that metal-based cofactors, which are considered evolutionary ancient, are not found in this list.

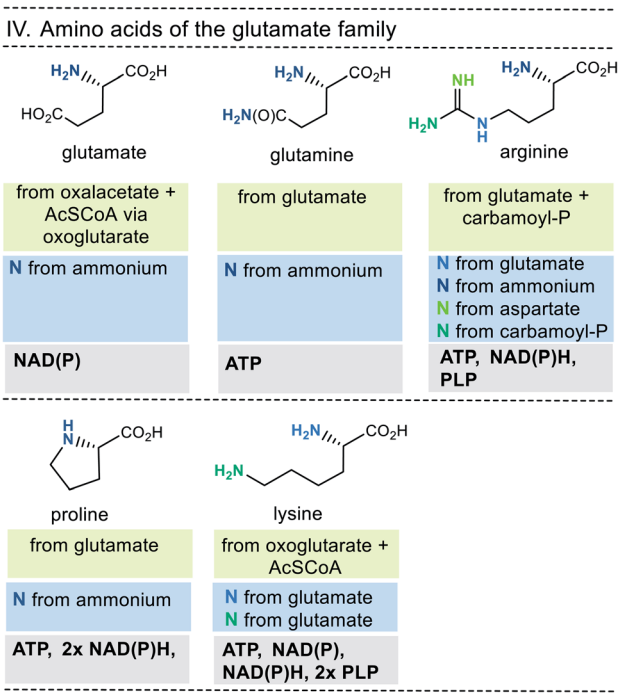

Fig. 9 Summary of amino acid biosyntheses of the glutamate family with reference to starting building blocks and coenzymes.

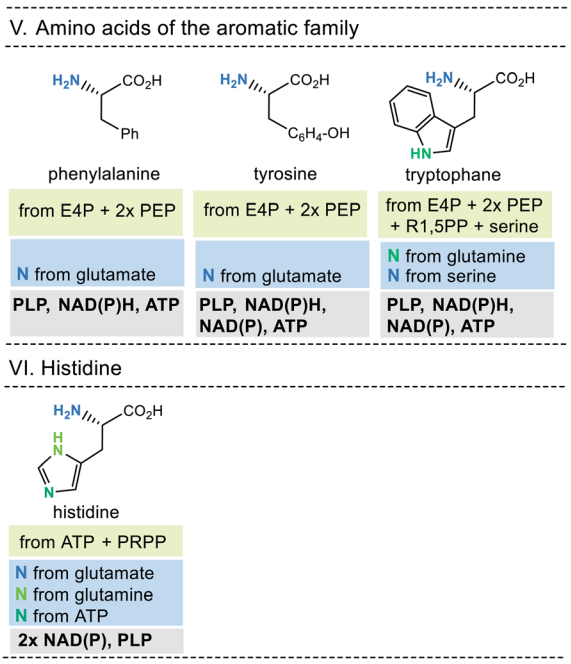

Fig. 10 Summary of amino acid biosyntheses of the aromatic family and histidine with reference to starting building blocks and coenzymes required.

2.2.2 Examples of coenzyme/cofactor biosyntheses. Coenzymes are required for the biosynthesis of amino acids and proteins. However, all coenzymes are biotically formed by series of enzymatic steps. For illustration purposes, the biosyntheses of the coenzymes NAD **2b**, PLP **16** and M **18** as well as the cofactor uroporphyrinogen III **6** (Schemes 1–4) are briefly described. The first two examples **2b** and **16** are almost ubiquitous in amino acid biosyntheses (see previous chapter), while the latter two play a key role in the bioenergetic apparatus of anaerobes, including the one proposed for the metabolism of the last unified common ancestor (LUCA, discussed below), which is a purely theoretical model organism.

*2.2.2.1 NAD **2b**.* The past years have seen a revival of NAD **2b**. It was found that besides its well-established role in redox biochemistry and energetic metabolism, nicotinamide cofactors can also function as signaling molecules in a variety of cellular processes.[20] NAD(P) also serves as substrate in mono- and poly-ADP ribosylation reactions that lead to the covalent modification of proteins.[21]

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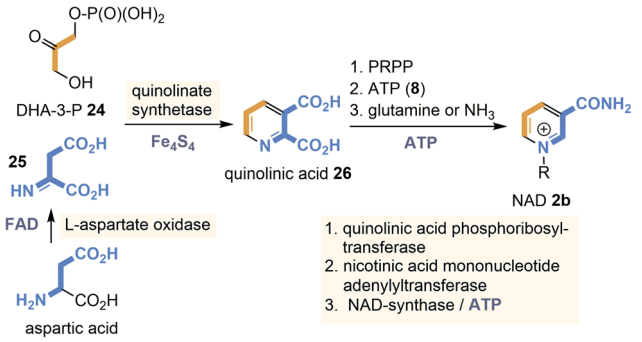


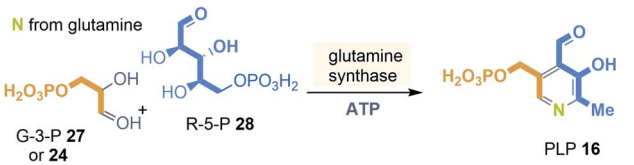
Scheme 1 NAD biosyntheses in bacteria and archaea: building blocks are marked in orange and blue including positions where they end up in quinolic acid (**26**) and finally in NAD **2b** (coenzymes required for individual steps are also given).

Currently, two different NAD(P) biosyntheses are known with quinolinic acid (**26**) and niacin being the key intermediates for both pathways (Scheme 1). In bacteria quinolinic acid (**26**) derives from dihydroxyacetone phosphate (DHA-3-P, **24**) and L-aspartate,[22] while in plants L-tryptophane is the precursor,[23] a route not discussed here. In bacteria, aspartic acid is first oxidised to the corresponding imine **25** by L-aspartase oxidase with FAD **3b** as redox coenzyme. In some archaea and thermotogales, this step is catalysed by aspartate dehydrogenase rather than aspartate oxidase.[24]

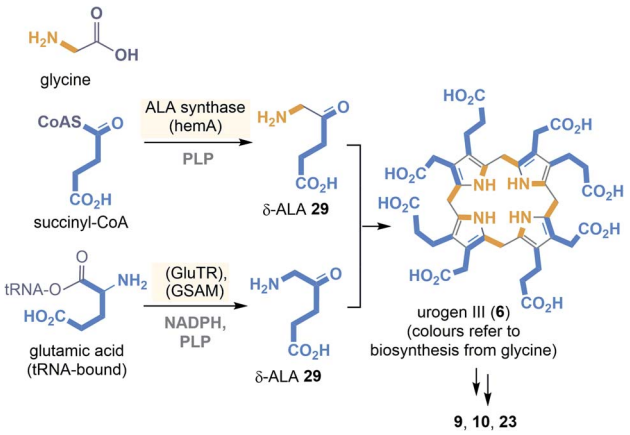
Next, condensation with DHA-3-P **24** occurs which is catalysed by the quinolinate synthase. This step is controlled by a [4Fe–4S] cluster that does not act as a redox cofactor but rather as a Lewis acid.[25] Decarboxylation provides niacin whose pyridine nitrogen atom is quaternised with 5-phospho-α-D-ribose-1-diphosphate (PRPP) as electrophilic building block to furnish NAD **2b**. The amide functionality is introduced in the final step and almost all archaea utilise ammonia as a nitrogen source for this transformation.

*2.2.2.2 PLP **16**.* Pyridoxal phosphate (**16**), and its "amino sister" pyridoxamine phosphate are coenzymes that promote myriads of biotransformations especially in amino acid metabolism. Typical reactions are transaminations, decarboxylations, racemisations, retro-aldol reactions and Michael additions.[26] It also participates as "coworker" in radical mediated reactions with radical SAM, *e.g.* in the lysine 2,3-aminomutase.[27]

In nature two principal biosynthetic pathways are found. Here, only the simpler of the two is briefly covered, that starts from glyceraldehyde-3-phosphate (GA3P, **27**) and ribose-5-phosphate (**28**) and *e.g.* was studied in *Bacillus subtilis* (Scheme 2). The nitrogen atom is recruited in form of ammonia from glutamine.[28] The PLP-synthase that bears an additional glutaminase site for providing ammonia directly condenses **27** and **28** to straightforwardly yield PLP **16**. Noteworthy, the whole pathway does not require any additional coenzyme except that ATP is needed for the regeneration of glutamine from glutamate.



Scheme 2 Ribosephosphate-dependent biosynthetic pathway of pyridoxal phosphate (**16**): building blocks marked in orange, blue and yellow and positions where they end up in PLP **16**.



Scheme 3 Summary of uroporphyrinogen III (**6**) biosyntheses: building blocks (orange and blue) (GSAM = glutamyl-tRNA reductase, GluTR = glutamate-L-semialdehyde aminomutase).

*2.2.2.3 Uroporphyrinogen III (**6**).* Uroporphyrinogen is an important biosynthetic precursor for heme, coenzyme F_{430}, cobalamins and protoporphyrin IX (**9**) and is the last common biosynthetic precursor for all tetrapyrroles.[12,29] Porphyrin containing proteins are ubiquitously distributed in all kingdoms of life and among those heme and chlorophylls are the most important ones. Remarkably, cytochrome P450 enzymes, that contain the heme core, are thought to have existed for more than 3.5 billion years.[11]

The two known biosynthetic pathways to uroporphyrinogen III (**6**), present in all kingdoms of life including archaea,[29,30] utilise 5-amino-levulinic acid (δ-ALA, **29**) as linear precursor (Scheme 3). δ-ALA is either biosynthesised from glycine and succinyl-CoA or in a two-step enzymatic process from glutamyl-tRNA. In the first case, ALA synthase catalyses the decarboxylative coupling of glycine to succinyl-CoA catalysed by PLP **16**. For the second route NADPH **2b** and PLP **16** are coenzyme involved in the biosynthesis of δ-ALA **29**. Next, eight molecules of δ-ALA are condensed to yield the macrocycle **6**.

*2.2.2.4 Coenzyme M (**19**).* Coenzyme M is found in methanogenic archaea and plays a key role in methane formation.[31] The *S*-methyl derivative is generated from coenzyme M (**19**) in methyl transfer reactions catalysed by proteins that contain zinc. In 1990 it was reported that coenzyme M is also involved in the bacterial metabolism (*e.g.* in proteobacterium *Xanthobacter autotrophicus*) of alkenes and oxiranes, the corresponding oxidation products.[32]

In methanogens two biosynthetic pathways are known for coenzyme M (**19**) in which the carbon backbone is derived either from phosphoenolpyruvate (PEP) or L-phosphoserine (Scheme

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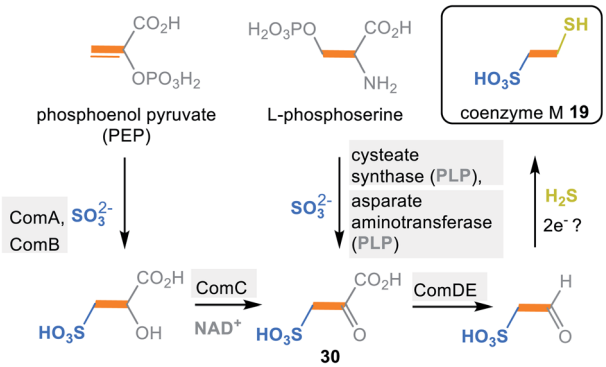


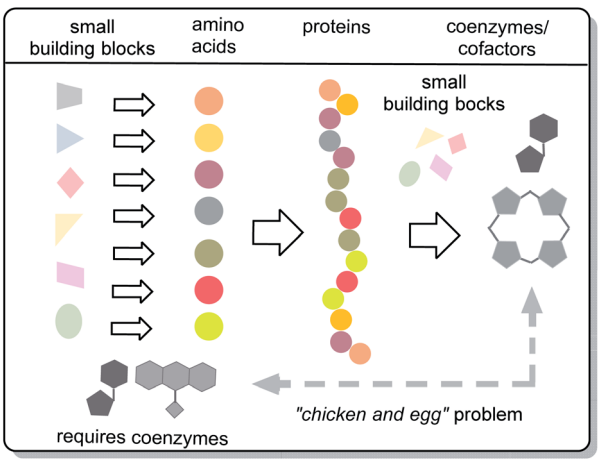
Scheme 4 Summary of coenzyme M biosyntheses: building blocks marked in orange, blue and yellow (ComA = phosphosulfolactate synthase, ComB = phosphosulfolactate phosphatase, ComC = NAD-dependent dehydrogenase, ComDE = sulfopyruvate decarboxylase).

4).[33] The PEP-dependent pathway is initiated by a Michael addition of sulfite. This step is followed by phosphate hydrolysis and oxidation to the α-keto acid **30**. Finally, decarboxylation and reductive introduction of H_2S furnishes coenzyme M (**19**). Details about the electron donor involved in this last step have not yet been clarified.

The L-phosphoserine-dependent pathway is based on the concerted elimination of phosphate and the addition of sulfite. The resulting L-cysteate is transaminated to form the joint intermediate sulfopyruvate **30**, with α-ketoglutarate serving as co-substrate. From here, the pathway supposedly follows the first one.

2.2.3 Summary of the coenzyme/protein dilemma. From the principal information collected in this and the previous chapter it is evident that proteins and coenzymes represent another archetypal example of causal circularity in living systems (Scheme 5).

Coenzymes, especially PLP, NAD(P), TPP, THF and ATP, are involved in the biosyntheses of all amino acids and consequently for proteins. Proteins are needed for the biosynthesis of coenzymes. At this point, the causal circularity for the coenzyme/protein pair is clearly revealed, and the question arises again: what came first? Proteins or coenzymes?



Scheme 5 The "*chicken-and-egg*" problem of the protein/coenzyme pair.

3. How can this "*chicken-and-egg*" *problem* of the protein/coenzyme pair be tackled?

The causal circularity of the three biomacromolecular pairs RNA–DNA, DNA–protein and RNA–protein was solved under the assumption that the RNA world hypothesis is correct by going back in time and making considerations about the origin of life and hypotheses about prebiotic protometabolism (see Fig. 1). It can therefore be assumed that a retrospective approach will help to break the causal circularity of coenzymes and proteins and that time travel either back to the origin of biotic evolution or to prebiotics world can solve this dilemma.

3.1 Back in biotic time

3.1.1 Viroids. A remarkable aspect of the RNA world hypothesis is the link to viral forms of Life, especially RNA viruses.[34] Positioning viruses at the beginning of biotic evolution presents a dilemma, since a virus is an obligatory parasite. Therefore, it is commonly argued that the viruses could only have emerged when cells already existed. But strictly speaking, we know that viruses parasitise on any replication system, including that of other viruses. Any replicator that is created anywhere is susceptible to parasitism, and not only is it susceptible to parasitism, but it will inevitably attract parasites. There is therefore no point at which we can speak of viruses with any certainty. The theory of viral evolution assumes that at the transition from the prebiotic world to the biotic world there were probably genetic parasites or parasites of those self-replicating units that later became genes.

According to this idea, viruses did not have to wait for the arrival of bacteria or the archaea; their ancestors could have entered the stage earlier, so that the DNA era was preceded by an epoch of far more primitive, fiercely competing self-replicating RNA chains – in essence the RNA world. Under these circumstances, simple ancestors of the RNA viruses, including retroviruses, could have already appeared in this archaic world. Their independence is manifested in the observation that the vast majority of viral genes are not found in bacteria, plants, animals or any other hosts. Viruses are thus able to create complex genes of their own accord, which are then assembled from other viral pieces. The link is manifested to contemporary protein-free viroids[34] often called "living fossils" of primordial RNAs.[35,36]

Another line of discussing earliest viral forms of life are nucleocytoplasmic large DNA viruses (NCLDV) and the related giant mimivirus (giant refers to >500 kb). The mimivirus has a capsid diameter of 400 nm, comparable to the size of small intracellular bacteria such as *Rickettsia conorii*.[37] Remarkably, mimivirus contains, among others, genes for sugar, lipid and amino acid metabolism. Details on coded biosynthetic pathways of amino acids and especially of coenzymes have not been

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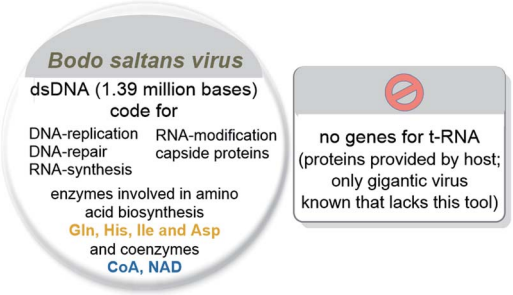
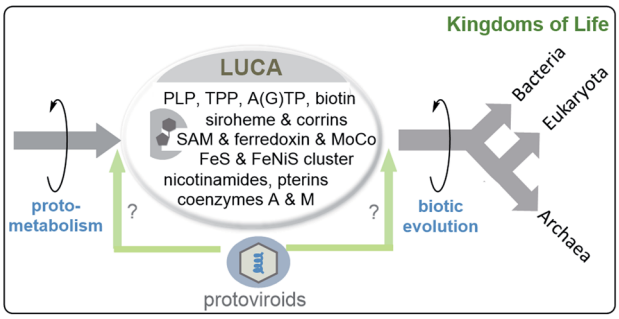


Scheme 6 Bioinformatic analysis of the giant virus *Bodo saltans* virus (BsV).



Scheme 7 Last unified common ancestor (LUCA) and its coenzymes and cofactors as suggested by bioinformatic analyses disclosed in ref. 44*a* (including ESI). LUCA is regarded to be the ancestor of bacteria and archaea while eukaryotes arise from archaea (structures of coenzymes and metal cofactors see Fig. 4 and 5).[49] the possible role of protoviroids and how there origin may relate to LUCA are included ("virus first" hypothesis).[36]

published for the mimivirus.[37] The major difference in the mimivirus genome compared to small intracellular bacteria is the absence of genes coding for ribosomal proteins. They harbor missing building blocks as incomplete sets not sufficient for independent protein synthesis preventing them from leading an autonomous life.[37b,c] These giant viruses have been placed at the boundary between living and non-living[38a] and indicate that the evolutionary transition from virus to cell may have been a continuum (Scheme 6).[39,40]

Overall, the "virus first" approach does not solve the "*chicken-and-egg*" problem of the coenzyme/protein pair and does not provide an answer to the question of what came first.

3.1.2 Last unified common ancestor (LUCA). At the cellular level, the progenote or LUCA models are discussed to describe the starting point of life. Several bioinformatic retrospective approaches were followed to get an idea of the metabolism of LUCA. As oxygen must have been absent before biological evolution it is widely assumed that LUCA was an anaerob and among the diverse known members hydrogen dependent autotrophs, namely acetogens and methanogens, were suggested to look like promising candidates for the ancestral state of physiology.[16,41]

Boyd *et al.*[42] studied the possible origin and evolution of flavin-based electron bifurcating enzymes using a bioinformatics approach.[43] Electron bifurcation is called the disproportionation of two electrons at the same redox potential to one electron with a higher and one with a lower redox potential and utilise coenzymes and cofactors such as NAD (**2b**), FAD (**3b**), ferredoxins (**7**), flavodoxin and ubiquinone.

With this mechanism in hand microorganisms generate low-potential electrons for the reduction of ferredoxins and flavodoxins, one central cellular process relevant for anaerobs that inhabit highly reductive environments.[44a] The phylogenetic analysis of twelve such bifurcating enzymes revealed that these redox systems were not part of LUCA but must have appeared at a later stage of life.

A comprehensive bioinformatic investigation on the (bio) molecular and pysiological basis of LUCA was carried out by Martin *et al.* They genetically analysed 6.1 million protein-coding genes and 286 514 protein clusters from sequenced prokaryotic genomes of various phylogenetic trees.[44b,c] Search for genes was conducted that are involved in the physiology, cells access to carbon, energy and nutrients. 355 Protein clusters were found to be indicative for LUCA's metabolism being likely dominated by iron–sulfur clusters and radical reaction mechanisms.[45]

Cofactor analysis unravelled the presence of biosynthetic pathways for basically all coenzymes and cofactors listed in Fig. 4 and 5 (this list includes those found in the ESI of ref. 44*a*) (Scheme 7). Important members are pterins such as molybdopterin **8**, 5-deazaflavins (coenzyme F_{420}, **18b**), *S*-adenosylmethionine (SAM, **14**), coenzymes A (CoA, **12b**) and M (**19**), thiamine pyrophosphate (TPP, **17**), ferredoxin (Fe–S proteins, **7**), protoporphyrin IX (**9**) and corrin (**10**) (see Scheme 3).[46] This list of coenzymes and cofactors covers members found in methanogens[47] but also bacteria. This comprehensive list means that the biosynthetic machinery of LUCA already utilised all coenzymes and cofactors now found in all kingdoms of life. How can this be rationalised? The authors interpreted the list of cofactors as a strong indication that LUCA must have relied on the Wood–Ljungdahl pathway a noncyclic reductive carbon fixation path from CO_2 and other C_1 building blocks to (activated) acetic acid.[48] A deeper analysis suggests that LUCA could have lived from the gases H_2, CO_2 and N_2.

The Wood–Ljungdahl pathway relies on a metalloprotein complex with iron and nickel[50] playing a central role as metals. It is composed of a carbon monoxide-dehydrogenase and acetyl-CoA synthase (CODH/ACS). The ferredoxin part promotes the reduction of CO_2 to CO.[51] In primordial metabolism CO itself could have formed through the gas water shift reaction or by transition metal catalysis. It was also found that LUCA must have contained the reverse gyrase, an enzyme typically associated with hyperthermophiles,[48] which supports the assumption that LUCA must have been an autotrophic thermophile.

Returning to the starting point of this article and the "*chicken-and-egg*" problem, it must be stressed that neither the viral hypothesis nor the current view on the metabolism of LUCA can answer the question of what came first, coenzymes/cofactors or proteins.

Interestingly, Martin and colleagues noted that LUCA could only have had nine nucleotide and five amino acid biosynthetic

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pathways. The absence of some essential pathways was justified by the possibility that LUCA had not yet developed the genes in question before the phylogenetic separation of bacteria and archaea took place. Instead, the missing products or building blocks could have been provided to LUCA externally from the prebiotic pool.

This statement is important because it shifts the central question of this report further into the past, namely the transitional phase between prebiotic metabolism and the development of LUCA.

3.1.3 Nanoarchaeota. Indeed, there are special life forms, the Nanoarchaeota, which survive with reduced genomes and an incomplete metabolism. They require essential cell nutrients that are supplied from outside. These very small ectosymbiotic Nanoarchaeota live on the surface of other archaic hosts in order to grow and replicate.[52] Only a few Nanoarchaeota have been successfully co-cultivated with their hosts, the most famous pair being the one of the marine hyperthermophilic and chemolithoautotrophic archaea *Ignicoccus hospitalis*[53] and the Nanoarchaeota *Nanoarchaeum equitans*.[54,55] Almost all genes required for information processing are present while genes for many metabolic and *de novo* biosynthetic pathways as well as energy production are absent.[55b] These include those that code for amino acid-, nucleotide-, coenzyme and cofactor and lipid biosynthesis.

Consequently, essential components are provided primarily through cell–cell contacts with the host *I. hospitalis* (Scheme 8). *N. equitans* are "incomplete" cells that can exist, provided that the missing nutrients are collected externally from the environment.[56] However, it has to be pointed out that parasitic *nanoarchaeota* has to be regarded as a model for early forms of life but itself is no remnant of life before LUCA. Similar to Martin's analysis they must externally recruit a large number of different metabolites such as amino acids and coenzymes/cofactors.

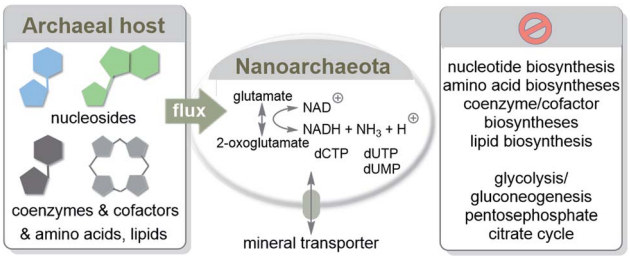
This recruitment scenario resembles to some degree the retrograde theory of evolution,[57] It says that the first living being was a completely heterotrophic entity that reproduced itself at the expense of prebiotically formed organic molecules (I–III) in its environment. The organism will then deplete the environmental reserves of these molecules, *e.g.* I and exhaust them to a point where growth is limited. In such an environment, any organism that develops an enzyme or catalytic system capable of synthesizing a molecule I from the precursors II and III would have a clear selection advantage and would spread rapidly in the environment.

Horowitz, who suggested this theory, further proposed that next evolution was probably based on the random combination of genes. For example, the simultaneous unavailability of two intermediates (*e.g.* II and III) would favour a symbiotic association between two mutants, one of which is able to synthesise B and the other able to synthesise C from other precursors in the environment. This would lead to the development of short reaction chains using substances whose synthesis was previously acquired. It is of interest to note that this theory includes the idea of parasitism as a driving force of evolution.

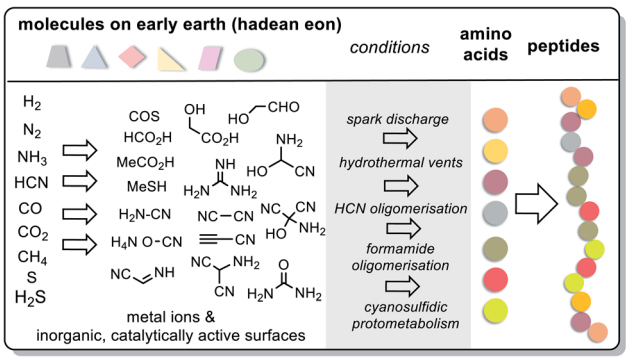
3.2 Back in prebiotic times

3.2.1 Protometabolism of amino acids. The transition from abiotic world to the first life forms is still largely unresolved. The message of the previous chapter is that a journey back on the biotic time arrow does not solve the "*chicken-and-egg*" problem of the coenzyme/protein pair, because the current hypothesis on LUCA's metabolism, as suggested by the analysis of Martin *et al.* says that both enzymes as well as basically all currently known coenzymes and cofactors were part of its set of metabolic tools. As theorised above, a pre-LUCA organism or protocells must have existed that likely relied on the influx of essential building blocks from outside similar to archaeota. In this case, these building blocks would be products of a protometabolism that had developed under prebiotic conditions. Therefore, this chapter deals with the second approach to overcome the causal dilemma of the coenzyme/protein pair. Could amino acids and coenzymes have existed and been produced before the appearance of LUCA?

For amino acids, the answer is briefly yes. Amino acids and consequently simple peptides must have formed under different geochemical scenarios as these have been experimentally probed. Conditions include three different electrical charge experiments by Miller and Urey[58–60] (spark discharge),



Scheme 8 Transfer of biomolecules from the marine hyperthermophilic and chemolithoautotrophic archaea *I. hosptalis* to *N. equitans* to supplement its metabolism. Elements of this metabolism are depicted according to ref. 55*a*.



Scheme 9 Summary on the prebiotic formation of amino acids and peptides (further details are described in the text) from prebiotically formed small molecules. The list of privileged building blocks is not complete; for example, higher sugars (C3, C4) and sugar acids (glycerate, pyruvate) are missing.

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the iron–sulfur world of Wächtershäuser and Huber[61–63] (hydrothermal vents), oligomerisations of HCN[64] and formamide[65,66] as well as Sutherland's cyanosulfidic protometabolism (Scheme 9).[67] Key reactions are the Strecker reaction and its phosphoro variant[68] and the photochemical Kiliani–Fischer reaction.

These experimental designs provided a wide variety of canonical amino acids such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, asparagine, asparagine, glutamate, glutamine, proline methionine, arginine and phenylalanine, as well as various non-canonical amino acids. Di- and tripeptides were also found in experiments mimicking hydrothermal vents.[61,62]

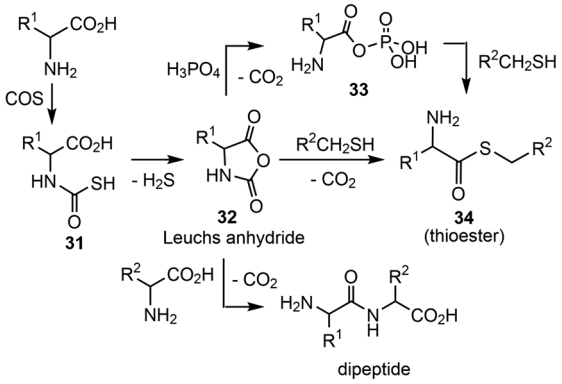
In addition, it has been shown that α-amino acids can be chemically activated by *e.g.* COS, a product from hydrothermal sources according to Wächtershäuser and Huber.[63] *Via* the corresponding thiocarbamates **31** (Scheme 10), carbohydrides **32** (Leuchs anhydride) are formed,[69–71] a process that is kinetically accelerated in the presence of metal cations. Leuchs anhydride is also a precursor for highly reactive aminoacyl phosphate anhydrides,[33] which are potential precursors for the formation of peptides and thioesters.[35]

3.2.2 Protometabolism of coenzymes/cofactors. In essence, both amino acids and simple peptides may have existed long before the beginning of biotic evolution. And what about coenzymes and cofactors? The scenarios listed in Scheme 8, spark discharge, hydrothermal vents, HCN and formamide oligomerisation and cyanosulfidic protometabolism did not specifically address this question. In general, coenzymes and cofactors were rarely considered in the development of hypotheses on prebiotic protometabolisms, although White III[13a] suspected as early as 1976 that the original "enzymes" were nucleic acids and that the coenzymes were vestiges of that system that remained as proteinous enzymes developed. White III did not only mention the AMP handle **12b** but also referred to nitrogen-containing heterocycles of several coenzymes that form the catalytically active portion of cofactors like flavins **3**, folate **15**, PLP **16** and TPP **17**. The AMP-handle, whose key function is the interaction with enzymes, provide an obvious hint for an origin of some coenzymes in the RNA world and it was even speculated that cofactor binding-sites like the highly conserved Rossmann-fold might have continued to evolve from generic nucleotide-binding properties of ancient proteins. In the framework of these hypotheses, RNA-derived cofactors might have existed in a prebiotic RNA-world as part of RNA–enzymes.

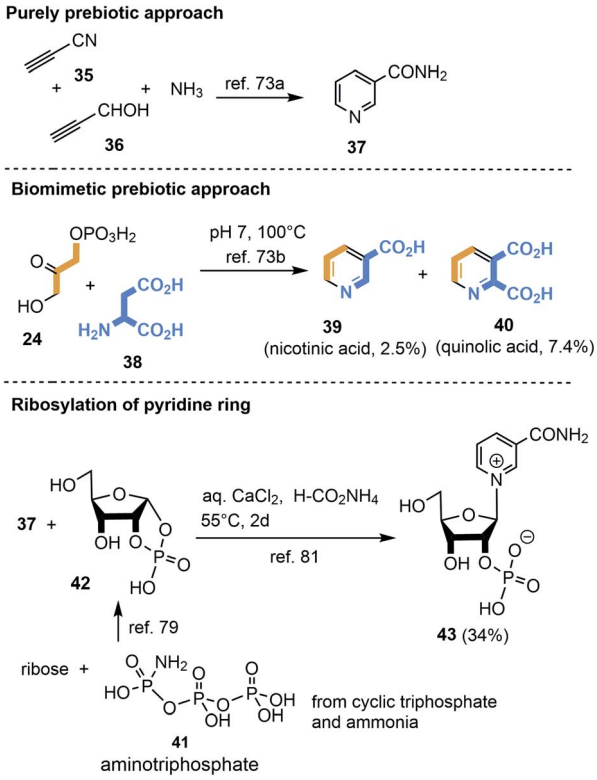
Following this hypothesis, King explained that the earliest biochemicals were not only reproduced by autocatalytic pathways, but that they were actually autocatalytic molecules and that evolution took place through a succession of symbiotic unions.[13b]

Since arguments for the formation and operation of coenzymes or cofactors did not appear in the experiments listed under "conditions" in Scheme 9, more direct chemical assessments had to be made and fossils collected.[72] Since White III first directed a beam of light at coenzymes, various efforts have been made to find and establish conditions for the formation of coenzymes or simplified but functional derivatives under prebiotic conditions.[5] Here, too, the focus is on the four representative examples NAD **2b**, PLP **16**, uroporphyrinogen III (**6**) and coenzyme M (**19**), which were already chosen in chapter 2.2.2 with regard to their biotic synthesis.

*3.2.2.1 NAD **2b**.* First attempts to produce the pyridine unit in NAD **2b** under ostensibly prebiotic conditions were reported by Orgel *et al.* The group showed that propiolonitrile **35**, propiolaldehyde **36** and ammonia yielded nicotinamide **37** (Scheme 11).[73a,b]



Scheme 10 COS-mediated amino acid activation and peptide as well as thioester formation.



Scheme 11 *De novo* syntheses of nicotinamide **37**, nicotinic acid **39**, quinolic acid **40** as well as generation of nicotinamide nucleotide **43**.

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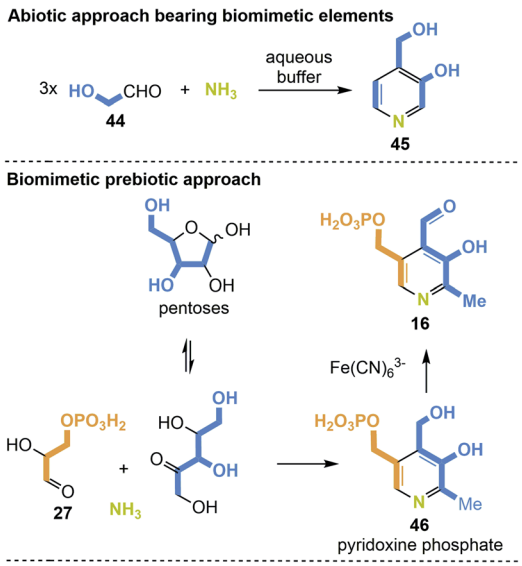
Cleaves and Miller suggested that the prokaryotic biosynthetic pathway[20c] should in principal be chemically mimicked in a prebiotic environment (Scheme 11).[74] Thus, mixing dihydroxyacetone phosphate **24** with aspartic acid **38** (ref. 75) provided nicotinic acid **39** and quinolic acid **40**. Is it realistic to assume that phosphorylated small carbohydrate-containing building blocks already existed in such early times? An important finding was that cyclotriphosphate[76] reacts with ammonia to aminotriphosphate (**41**)[77] which is a powerful phosphorylating agent *e.g.* for α-hydroxyaldehydes.[78,79] Importantly, water-soluble polyphosphates like cyclotriphosphate are known to be generated in the vicinity of volcanoes.[80]

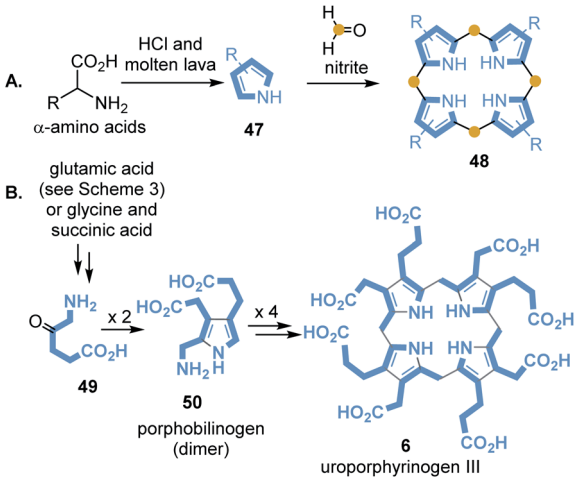
Kim and Benner combined the findings of Orgel[73a,b] and Eschenmoser[79] by reacting nicotinamide **37** with ribose-1,2-cyclic phosphate **42** under prebiotically plausible conditions and obtained the nicotinamide nucleotide.[81]

3.2.2.2 PLP 16. PLP promotes a large and diversified number of biotransformations mainly in amino acid metabolism. Transamination and decarboxylation of α-amino acids are the two key reactions of PLP **16**. Due to its central role in the formation of amino acids and especially in the context of this review article, it is worth considering a protometabolic scenario for this coenzyme.

The first example of a simplified pyridoxine derivative formed under putative prebiotic conditions is based on the trimerisation of glycol aldehyde **44** in a heated buffered solution in the presence of ammonia (Scheme 12, top). Glycoladehyde is a small aldose that can undergo aldol reactions forming higher sugars. Against this background, the synthesis to 4-(hydroxymethyl) pyridin-3-ol (**45**) carries biomimetic elements.[82] A prebiotic approach, which is more similar to one of the two principle biosyntheses of PLP, precisely the one that does not require additional coenzymes, is depicted in Scheme 12 (bottom).[28] The condensation of ribose or any other pentose with glyceraldehyde-3-phosphate (**27**) in the presence of ammonia could yield



Scheme 12 *De novo* syntheses of 4-(hydroxymethyl)pyridine-3-ol (**45**) pyridoxine phosphate (**46**) and PLP **16** under supposedly prebiotic conditions.



Scheme 13 Abiotic (A) and biomimetic (B) formation of porphyrine core structures.

pyridoxine phosphate (**46**). Finally, the final oxidation to PLP **16** could be carried out by ferric salts such as $Fe(CN)_6$.[83]

3.2.2.3 Uroporphyrinogen III (6). Cofactors of the porphyrin type such as uroporphyrinogen III (**6**) carry a macrocyclic tetrapyrrole ligand which is suited for the binding of various metals, as is the case with protoporphyrin IX (**9**) and cofactor F_{430} (**23**).[15]

Porphyrin-containing proteins are ubiquitously distributed in the biotic world. It is assumed that some representatives have existed for more than 3.5 billion years, so it can be assumed that they also played a role in the prebiotic world.[84] Baker and coworkers reported on first attempts to synthesise porphyrin from pyrrole and formaldehyde under simulated geochemical conditions.[85] Interestingly, simple pyrroles **48** can be detected when seawater that contains amino acids is exposed to molten lava. Strasdeit *et al.* suggested that on primordial volcanic islands the volatile pyrroles and HCl must have condensed in cooler places.

Under these concentration conditions, pyrrole oligomerisation may have taken place.[86] It has also been found that 2,4-diethylpyrrole (**47**) and HCl in the presence of formaldehyde and nitrite provides octaethylporphyrin **48** and other oligomers (Scheme 13A).

Lindsey and collaborators included biosynthetic considerations in their studies on more water-soluble uroporphyrinogen III (**6**).[87] Porphyrinogens are formed by self-condensation from aminoketones **49** and diketones or ketoesters in water under prebiotic conditions (Scheme 13B). Remarkably, these synthetic studies confirmed that dimer **50** is the most important intermediate in this process, similar to uroporphyrinogen III biosynthesis (see Scheme 3).[87]

It needs to be emphasised that the transfer of basic prebiotic molecules to the starting building blocks, in particular succinic acid and further downstream 5-aminolevulinic acid (**49**), has not yet been experimentally clarified.

3.2.2.4 Coenzyme M (19). As early as 1993 Miller and coworkers searched for prebiotic conditions that could result in the formation of coenzyme M (**19**).[88] They proposed ethene as a possible C2 building block that can form during prebiotic

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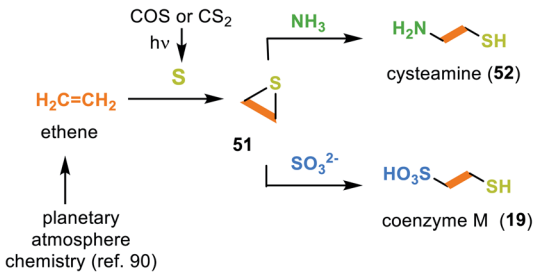


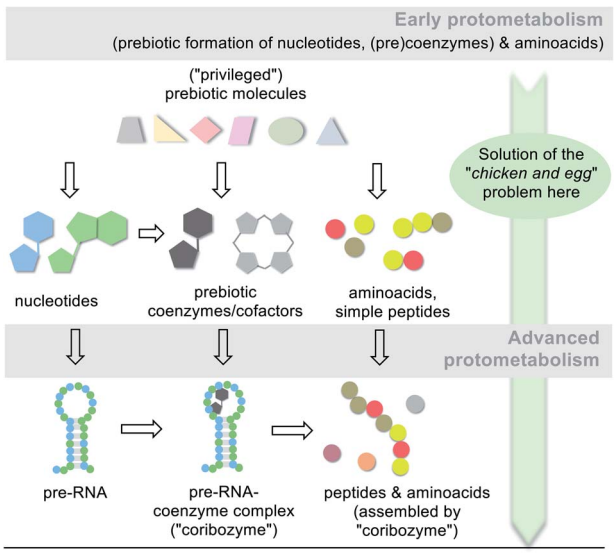
Scheme 14 Experimental evidence for the prebiotic formation of cysteamine (52) and coenzyme M (19) from ethene and sulfur.

processes in planetary atmospheres.[89] Under photolytic conditions, CS_2 or COS serve as a source of 3p-sulfur atoms, which end up in ethylene sulfide (51) after collision with ethene (Scheme 14).[90] In the following, cysteamine (52) is generated during the ring opening of ethylene sulfide (51) with ammonia.[88] In a similar way, the presence of sulfite leads to the coenzyme M (19).

For a more comprehensive overview of a chemistry that mimics the formation of coenzymes under prebiotic conditions, the reader is referred to ref. 72.

4. Integration of the coenzyme/protein pair in an evolutionary context

It can be concluded from the previous chapters that amino acids and selected coenzymes or simpler analogues must have been present before the first life forms appeared (Scheme 15; early protometabolism). These may have been involved in molecular and biological evolution from the very beginning and have played an active role since then.



Scheme 15 Simplified graphical representation of the protometabolic evolution of life from simple building blocks to key metabolic building blocks (amino acids, nucleotides and coenzymes/cofactors) and finally to biomacromolecules (pre-RNA, peptides,[96a] RNA/coenzyme–cofactor complexes[72]). Note, that a network of diverse molecules make up this molecular evolution with RNA playing one key role.

The "*chicken-and-egg*" problem is solved at this very early stage of chemical evolution, because no circular dependence existed at that time. Both molecular entities could be formed independently of each other under prebiotic conditions. This is because they are the result of the inherent chemical reactivity of molecules that were available under the conditions of the Hadian eon about 4 billion years ago. It has to be stressed that α-amino acids are formed under all the postulated prebiotic scenarios listed in Scheme 9.

Certainly the original evolutionary role of RNA was linked to its catalytic properties. Chemically, however, the known ribozyme-catalysed transformations are rather limited in their diversity. More sophisticated chemical transformations such as redox chemistry, alkylations and C–C bond forming reactions depend on co-catalysts, which, as discussed here, are typically represented by coenzymes and cofactors. To broaden the scope of protometabolism, these co-catalytic small molecules (or simpler analogues) may have bound to RNA that served as a template. Such an association could have taken place *via* hydrogen bonds and/or electrostatic interactions similar to existing coenzyme/protein complexes (Scheme 15; advanced protometabolism).[91] Alternatively, coenzyme-like co-catalysts may be covalently bound to the 5′ terminus of a ribozyme.[4a,92]

A strong argument for such coenzyme–RNA complexes can already be found in the biotic world. The ability of coenzymes such as TPP **17**,[93a,b] FMN **3a**,[92c,d] SAM **14**,[93e,f] THF **15**,[93g] and adenosylcobalamine (AdoCbl)[93h] to bind to RNA is found in riboswitches. These short, relatively simple sequences in mRNAs bind metabolites directly and are responsible for regulating gene translation.[94] As a result activation or deactivation of gene expression occurs, a role, however, that became relevant later in biotic evolution.

Without explicitly mentioning the coenzymes, Stewart proposed such a scenario by linking the protometabolism to the RNA world.[95] The controlled metabolism hypothesis suggests that RNA benefits from the protometabolism by overcoming what he called the cooperation barrier. The RNA would become a manager that manages the metabolism and uses its power to increase its productivity. This corresponds to a trend in the field of molecular evolution of life not to only consider and experimentally verify prebiotic routes towards selected molecules and oligomers but rather to consider cooperative interactions and networks among diverse classes of molecules that include peptides[96] and small molecules present in primary metabolisms such as the reversed Krebs cycle.[97] What is occasionally framed with the word "system chemistry" has led to a broader focus on cooperative coevolution among the diverse classes of molecules from the earliest times.[98]

One of several possible geological sites where such an advanced protometabolism could thrive are terrestrial hydrothermal freshwater fields and ponds.[99] The conditions in such fields are highly dynamic in that evaporation to dryness occurs either over long periods of time or at high frequency through nearby geysers. Both the concentration of solutions, which preferably contain small molecules and precursors for

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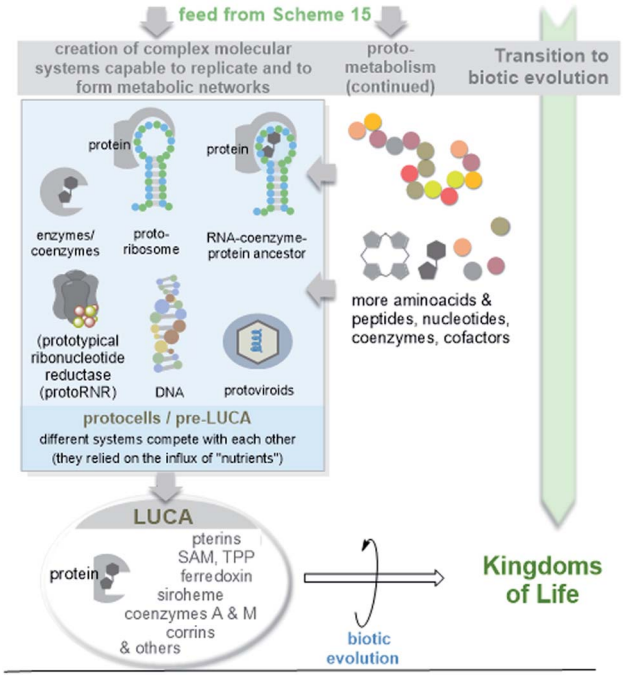
nucleotides, amino acids and (pre)coenzymes/cofactors,[100] and the precipitation on inorganic surfaces and their redilution represent unique changing chemical environments from which more complex peptides, oligonucleotides and coenzyme/cofactor RNA complexes may have formed (Scheme 15). Some evidence has already been collected that wet–dry cycles can drive the polymerization of mononucleotide mixtures and yield polymers 10 to >100 nucleotides in length.[99]

As soon as nucleotides, amino acids, small peptides and oligonucleotides as well as selected coenzymes and cofactors or their simpler analogues became available, they actively participated in the transition to biotic evolution. The RNA world hypothesis (Scheme 16, advanced protometabolism) assigns an evolutionary leadership position to this polymer, being a part of a collaborative network of diverse molecules including peptides that all coevolved.[96] This prominent role has been linked to the ability of RNA to act as a catalyst, as known for ribozymes. From a chemical point of view, however, the variety of RNA-catalysed transformations is rather small, so that, as first suggested by White III,[13a] it is assumed that co-catalytically active coenzymes (or simpler analogues thereof) must have already been present to form functional co-ribozymes.[101] RNA served as a template here to form hydrogen bonds and/or electrostatic interactions with the coenzyme, which are similar to most existing coenzyme/protein complexes.

Remarkably, RNA can be related to a virus-like state, and the formation of LUCA and modern cells then becomes a subsequent event.[102] Viroids, the smallest and simplest replicating RNA molecules known today, have been proposed as subviral descendants of the earliest biomolecules on Earth.[103–105] Special features are their small size, the circular structure, high G + C content and lack of protein coding capability compatible with a ribosome-free habitat. Later in evolution, these ancient viroids (protoviroids) may have become parasites, and today they depend on cellular enzymes such as RNA polymerase, RNAaseH and RNA ligase for replication.[105] However, protoviroids would always have depended on some kind of ATP-dependent cell metabolism, so that it was speculated that such ancient viroids and protocells likely co-evolved.[106]



Scheme 16 Simplified graphical representation of the evolution of protoviroids, protocells and LUCA (according to ref. 44a) as early life forms. Due to their importance in the evolution of macromolecules, the cofactor-mediated radical transformation of RNA to DNA is highlighted.

While access to LUCA is possible *via* a phylogenetic and bioinformatics approach, ideas about the transformation to compartmentalized forms of early life before LUCA appeared on planet Earth are much more speculative. It is likely that LUCA evolved from a confusing variety of different pre-metabolic forms of protocells (pre-LUCA), which are even more difficult to grasp in practice. However, dramatic molecular renewals must have occurred during this transitional phase towards biotic evolution.[107] Protoribosomes allowed the controlled synthesis of peptides and from these, enzymes and coenzyme–protein conjugates with extended catalytic potential were formed. The coenzymes and cofactors have changed their macromolecular template (from RNA to protein). And at one point DNA must have appeared on the scene.

Ribonucleotide reduction is a key step in the transformation of the RNA world into a world in which DNA macromolecules became central to information storage. Ribonucleotide reductase (RNR) catalyses the deoxygenation of ribose *via* a radical process. Lundin *et al.* drew a picture on the evolution of this process and possible ancestors of the proteins, which they called prototypical ribonucleotide reductase (protoRNR).[108] Their analysis revealed that metals or cofactors must have played an important role in this deoxygenation process, initially with a lack of chemoselectivity with respect to the radical abstraction of H from given nucleotides. In anaerobes, the 5′-deoxyadenosyl-5′-radical (dAdo radical) generated by cobalamin-type redox systems or radical SAM/iron–sulfur clusters acts as a redox promoter, and the analysis suggests that these early types of redox systems serve as a raw model for modern RNR.[109] In particular, extant B_{12}-dependent class II RNRs have been proposed as the most promising first candidates for modern RNRs that originate from protoRNRs. The discussion about the evolution of this key transformation provides a further argument for the fact that both amino acids/proteins and coenzymes/co-factors must have been present long before the appearance of biotic life in the form of LUCA, which already belonged to the DNA world.

5. Conclusions and outlook

This overview does by no means cover all geological, chemical and biological facets that are important for proposing scenarios on the origin and evolution of life. Indeed, our journey began with the question of what came first: coenzymes or proteins? It turned out that this is a real but overall neglected "*chicken-and-egg problem*" of the biotic world. Coenzymes or cofactors, which

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have played the role of small chemical catalysts or promoters of chemical reactions for most of molecular evolution, have often not been included in hypothetical considerations and theories of the origin of life. It is often mentioned that they are part of (pre-)metabolic networks, but their origin has hardly been discussed. But this biorelevant class of molecules is ancient, even in LUCA they are said to have been found,[44a] but remarkably they have hardly changed their structures and function until today. Coenzymes and co-factors are mainly designed to promote chemical reactions. This was the case in connection with protometabolism and is to a large extent still the case today.

The journey took us on a time arrow back to the early days of life with analyses of the existence and role of coenzymes, cofactors and also proteins in viroids, the last common ancestor (LUCA) and *nanoarchaeota*. While these analyses did not solve the circular dilemma of coenzymes and proteins, they did provide a deeper understanding of coenzymes and cofactors and their role in early life forms, as they are key promoters of metabolism in methanogens, especially the reductive Wood-Ljungdahl pathway. Like proteins, coenzymes and cofactors are old. The "*chicken-and-egg*" problem can be solved by considering prebiotic formation of amino acids, small peptides and coenzymes.

In the scenario of the RNA world, coenzymes and cofactors were partners of RNA rather than proteins. Only later did it appear that they were brought together in the form of enzyme–coenzyme complexes, and the development of biosynthetic pathways to these led to the circular dilemma that is the starting point of this overview.

This report is intended to provide new ideas and food for thought on the origin of life, which will eventually have to be reinvented, much as A. Eschenmoser would put it.[110] Finally, coenzymes and cofactors will hopefully attract more interest as a fourth key player in the molecular evolution of metabolism.

6. Conflicts of interest

There are no conflicts to declare.

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