The First Steps of Chemical Evolution towards the Origin of Life

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1. Introduction. – Numerous experiments in the past fifty years have strongly changed the ideas how life could have emerged on the primitive earth. Many of the new results have given indications towards the formation of the precursors of biomolecules, and of larger polymers of these biomolecules, which are essential for life forms as we know them today. However, we cannot expect that the first forms showing signs of life have been identical to the biomolecules in their complexity as we encounter them today in modern life forms. Therefore, it is difficult to predict what were the first steps from an inanimate, inorganic world consisting of minerals, on the one hand, and of small, mostly gaseous molecules, on the other, to form organic molecules in a larger variety and in the diversity that was needed in order to achieve the complexity of an emerging and more and more organized system showing the basic principles of life, namely metabolism, reproduction, and information transfer.

It is certainly not possible to deal with the question of chemical evolution without knowing much about the scenario by which this evolution had taken place. The results of geochemical research in the past fifty years have also changed, to a large extent, the ideas about the possibilities and pathways of chemical evolution and have to be taken into account as a prioritary item, therefore. In the following, this scenario will be discussed, and, starting from the conditions of this scenario, the possible evolution of the first and essential biomolecules will be discussed.

2. The Geochemical Scenario and the Stability of Biomolecules. – Geochemists unanimously assume that the first hydrosphere was formed on earth ca. 3.8 billion years ago or even earlier [1][2]. This was the time when the earth had cooled down sufficiently to allow water to exist in its liquid form. Still the earth was very hot, near the boiling point of water, and through atmospheric events, volcanic eruptions, and other changes of temperature water was frequently evaporated, then precipitated again in form of rain falls. In such a hot atmosphere, events like wind and thunderstorms must have been much more violent than they are today. Since it cannot easily be assumed that chemical evolution could have happened rapidly enough and in larger amounts before the existence of liquid water as a solvent accumulating its products was granted, one has to consider the geochemical scenario for a chemical evolution towards biomolecule precursors at that time, i.e., 3.8 billion years ago.
know that the first fossil cells have been assigned an age of 3.5 billion years [3], which means that chemical evolution leading from the first organic molecules to the first cell-like structures took not more than 300 million years. About the atmosphere of the primitive earth, many new findings have altered the general picture. While, in the middle of the 20th century, people were still considering a strongly reducing atmosphere consisting of hydrogen, methane, ammonia, and carbon dioxide to have prevailed, this opinion has changed in the past decades. First of all, it was recognized that the gravitation of earth was not sufficient to keep hydrogen in its atmosphere, and, therefore, hydrogen would have escaped into space at an early stage of Earth’s existence [2]. On the other hand, the mean life times of methane and ammonia are relatively short on an astronomic scale [4]. Therefore, they could have been only main components of the primitive atmosphere if they were continuously delivered to the atmosphere. For this assumption, we do not have any evidence, however. Therefore, the modern geochemical view of the primitive atmosphere is rather based on the idea that a secondary atmosphere was formed by outgassing of volcanoes [2], and that the composition of these volcanic gases was quite similar to that of today’s volcanoes. Hence, the atmosphere should have been composed mainly of carbon dioxide and nitrogen, and – to a small extent – sulfur dioxide and some other gases [2]. Another principle component of the atmosphere was, due to the high temperature of the earth, water in its gaseous form, i.e., water vapor. Many of the experiments carried out in the second half of the 20th century have tried to reproduce chemical evolution in the previously assumed reducing atmosphere [5–14]. These experiments led to a large number of organic compounds which were sufficiently complex to give rise to optimism that the secrets of chemical evolution could be easily revealed. When the geochemists denied the existence of a reducing atmosphere – and they do this in their large majority today – one had to think of new experiments taking into account their findings and to assess whether the same chemical evolution could have taken place in a neutral or even slightly oxidizing atmosphere as well.

Further considerations have to be devoted to the solid and liquid surface of the primordial earth. For the solids, we know rather few details about precambrian rock formations, but what we know indicates that clay minerals where abundant on the primitive earth [15]. Interestingly, inside these precambrian rocks, large, so-called ‘green zones’ were found, containing mostly the copper minerals azurite and malachite [16]. These minerals will play a significant role at a later stage of our discussion. About the liquid phase, namely the primordial oceans, which should have successively collected all soluble inorganic and organic substances in the course of time to form what is often termed the ‘primordial soup’, it should be pointed out that most of the scientists discussing chemical evolution have taken into consideration only the organic substances dissolved in this ‘primordial soup’ and completely neglected the inorganic materials dissolved. A large number of salts are soluble in water, and, therefore, they should have formed a major component of the primordial sea. For example, it is estimated that the content of sodium chloride (NaCl) of the primitive ocean was approximately the same as of nowadays’ oceans [2]. We will see that, for some reactions, this salt content can have played a detrimental role, whereas, for others, it might have been a very essential ingredient of the ‘soup’. In particular, when we are discussing the stability of biomolecules in this primordial soup we have to consider first
of all the main constituents of today's living organisms, i.e., RNA, DNA, and proteins. The stability of the constituents of RNA, namely the nucleic bases, the sugars, and the phosphate, does not constitute much of a problem except for the phosphates, which in the presence of the heavier metal ions would have been precipitated and thus become a part of the solid phase and not be easily available for the formation of RNA. Interestingly, a few peptides are able to stabilize phosphate via hydrogen bonds [17] and thus prevent it from precipitation at least to a certain extent. The formation of nucleotides, however, under the condition of a hot, salty ocean, does not seem to be realistic, as experiments have shown that sufficient NaCl concentrations would decompose any polynucleotides into their constituents within minutes [18].

The strong UV radiation on the primordial earth not being protected yet by an ozone layer is another factor strongly contradicting the formation of polynucleotides [19].

While the conditions of the primordial ocean appear very unfavorable for a stable formation or lasting presence of polynucleotides, the situation is quite different in the case of the other group of essential biomolecules, i.e., the amino acids and peptides. These compounds are relatively insensitive to UV radiation, they are rather stable against salts, even in higher concentrations, and the only process that can gradually destroy peptides is hydrolysis. However, many experiments have shown that hydrolysis does not happen so easily, even at elevated temperatures, and that peptides can remain stable in solutions for a considerable time, even under hot and salt-rich conditions [20–22]. In addition to that, it has been shown that adsorption to clay minerals could prevent hydrolysis for a much longer time and, therefore, stabilize oligomers and polymers bound together by peptide bonds [23]. In the light of this knowledge, it seems appropriate to reconsider the possibilities of the first steps towards life, namely whether they happened in the form of an early RNA world or in the form of an amino acid, peptide, and protein world. The next chapter will be devoted to that question.

3. RNA or Protein World First? – Although chemical stability discussed in the previous chapter already gives a very strong indication towards a much higher probability of the development of peptides and proteins under primordial world conditions than for the existence of polynucleotides and thus RNA, there are still other arguments which lend a strong preference to the protein world as an initial step.

One of these arguments is based on the development of so-called ‘hyper-cycles’ as proposed by Eigen and Schuster [24]. To reproduce an RNA sequence, it is necessary to reduce the error probability to such an extent that this can be achieved by modern organisms only with the help of complicated enzyme-controlled mechanisms. For any abiotic RNA application, the error tolerance possibly achieved is only $10^{-2}$, which would limit the number of constituents of the RNA to 100 elements, which is definitely not enough for any higher-level biochemical process. Further, computer simulations of hyper-cycles and quasi-species lead to a stable system only with a very limited population size and within a very narrow bandwidth, and they are subject to so-called ‘catastrophic events’ by short circuits, population collapse, or so called ‘selfish RNA’ which all would limit the possibility of a higher organization proceeding through these ‘hyper-cycles’ [25].

There is still another very striking argument which was proposed by Dyson [26], with his model calculation for a primitive cell system, for which it is assumed that,
within a given system, higher-organized units are formed from discrete monomer chemical species, thus showing a primitive form of metabolism and evolution to more complex species. From the formula describing this model, one can see that there is an optimal number of chemical species in order to proceed to higher-organized systems with a given preferential binding of the different monomer species to each other, as illustrated in Fig. 1. This specific preference of binding can be compared to the specificity of catalysts. Whereas modern enzymes can reach a specificity factor of ca. 5,000, inorganic catalysts, which should have been the only ones present on the primitive earth, usually reach a factor in the range of 60 to 100. Such a model works well with a number of species involved between 2,000 and 20,000, which guarantees a sufficient complexity. The number of basic species needed to achieve continuous development to higher forms should be ideally between eight and ten, with a smaller number of species, e.g., the four basic units making up modern polynucleotides such as RNA and DNA, this development cannot be achieved with the specificity factor of

\[ \phi(x) = \frac{1}{1 + ab^{-x}} \]

**Fig. 1.** Dyson’s [26] model for the evolution of higher-organized systems, depending on the number of building blocks \( a \) and catalytic preference factor \( b \)
inorganic catalysts. On the other hand, the model conditions with 8–10 basic species also increases the error tolerance of the system to a remarkable 30% [27].

If one takes into account this information-theoretical argument together with the chemical stability of biopolymers, one can only arrive at the conclusion that four nucleotides cannot have been the first step in the evolution of life, in particular because chemical diversity would have been too low to allow a development to higher organization. Thus, the only alternative to consider the first steps of chemical evolution towards origin of life, is to come back to the models proposed by Oparin [28], Cairns-Smith [29], and Lancet and co-workers [30], which are sometimes referred to as the ‘genes-last model’: Starting with a number of amino acids, ideally around ten, with 2,000 to 20,000 units for the formation of the higher-organized system, small droplets could be formed as cell precursors. This process would also imply that enzymes developed before the genes, and that the initial catalysts used might be clay minerals or other inorganic substances, eventually also metal-ion complexes with amino acids and/or peptides.

For a final consideration of this problem – what was the first ‘world’ leading towards life? – one still has to address the question whether amino acids and peptides could have provided the necessary conditions which are required in the definition of life processes. Metabolism does not provide any difficulty in this aspect, whereas the questions of carrying on information, of self-replication, and of auto-catalytic processes have to be answered. While these processes are well-known to occur with RNA and DNA – although with the help of complicated protein-based enzymes – it has to be shown that this type of processes is also possible with peptides alone. In the eighties of the 20th century, it was demonstrated that there are a number of peptides which are able to reproduce themselves from smaller constituents [31], thus replicating their structure and their properties. On the other hand, it was found that amino acids themselves can catalyze peptide-formation processes, which can be seen as a good example of auto-catalysis in the production of oligomers [32]. If one considers all of these aspects and findings, one arrives at the conclusion that the most likely way to initiate chemical evolution towards some primitive life forms was a beginning with a number of amino acids, forming peptides and later on the larger polymers, namely the proteins. Thus, the question of RNA world or protein world does not seem any more a hen-and-egg problem but a clearly-to-answer problem in favor of a ‘protein-first world’, starting from smaller peptides and forming in the end some cell-like organisms with first simple characteristics of life. One could ask at this point why one does not observe such primitive organisms any more. Here, one has to acknowledge that evolution has always replaced less efficient mechanisms by improved ones, eliminating thus the less favorable life forms. Hence, it is not difficult to postulate that as soon as RNA and DNA came into the ‘game of life’, any older organisms would have been eliminated. In that context, it seems very interesting that, although chemical evolution took only ca. 300 million years to lead to the first form of cells from simple atmospheric molecules, it required 2–2.5 billion years more to come from monocellular to multicellular organisms. This actually means that there must have been some more or less abrupt changes in the mechanisms of life which then led to the famous ‘Cambrian explosion’ of species, where a large number of increasingly complex life forms evolved in a much shorter time than the evolution from monocellular to multicellular organisms took. It
sounds plausible that, before the ‘Cambrian explosion’, life was based on a mainly protein-governed world, whereas later on RNA and DNA, which could remain stable within the protected cells of this ‘protein world’ even in an otherwise hostile environment of a salty ocean, could have gradually been used to build new, faster, and more efficient mechanisms, to find better ways of reproduction and thus to lead to a much richer scenario for the development of new species through mutations. Margulis [33] has already proposed a similar scenario for the appearance of RNA and DNA in evolution, and the considerations presented here seem to support this hypothesis. We certainly have to expect that the old ‘protein world’ has vanished and been replaced by the modern life forms based on polynucleotide processes.

It has to be mentioned at this point that the idea that RNA and DNA are a rather late-appearing form of biomolecules in chemical evolution has been expressed by prominent scientists already quite some time ago. Francis Crick [34] and Joshua Lederberg [35] have both indicated in famous statements that they assume that the nucleic acids have not formed the first genes, partly because they are so complex, and partly because their perfection rather indicates a late stage of chemical evolution. Sidney Fox [36], who is well-known for a number of famous experiments related to peptide formation under primitive earth conditions has once stated that ‘the attempt to understand evolution in a reductionist way, i.e., starting from todays living organisms equals an attempt to learn baking of a cake by disbaking an existing one’. From these statements, we can see that several prominent scientists involved in research on chemical evolution have already argued that the RNA and DNA world is rather a later step, a perfection of mechanisms that have started from much more simple and primitive systems. Based on these ideas and results, it seems reasonable to concentrate the further discussion of the first steps of chemical evolution to the possibilities to form amino acids, their oligomers, and polymers rather than to speculate on the complicated assembly of nucleotides and their polymers. The next chapter will be devoted, therefore, to the first step of this, namely the evolution of amino acids from the constituents of the primitive atmosphere in the presence of the solid and liquid environment available at that time.

4. The Evolution of Amino Acids on the Primitive Earth. – As indicated in the previously cited statement of Sidney Fox, it seems impossible to reconstruct the evolution of the first biomolecules by studying present organisms. The only way to investigate the processes leading to these biomolecules on the primitive earth is, therefore, to simulate such chemical reactions under the environmental conditions of the primordial earth. The best known example for such a simulation experiment, which gave rise to numerous subsequent similar laboratory works, was performed by Miller in 1953 [5]. Miller assumed for his experiment the reducing atmosphere being the common idea at his time. By electric discharges mimicking thunderstorms in an atmosphere of water vapor, ammonia, methane, and hydrogen, he obtained a large number of organic compounds within a few days, among them also some amino acids. This spectacular result was the reason why, in the following years, a number of research groups tried to obtain similar data from different, slightly modified atmospheres, and with various energy sources which could have been present on the primitive earth [5–14]. A few of these experiments were also carried out with a non-reducing atmosphere,
but they did not lead to amino acids as Miller’s experiment did [37]. It was only three years ago that an experiment of this kind with a neutral atmosphere was repeated. In this case, whose setting is illustrated in Fig. 2, an atmosphere consisting of the geochemically nowadays accepted gases, namely carbon dioxide, nitrogen, and water vapor was subjected to electric discharges above liquid water. At a temperature of around 80°, a large number of organic compounds was produced within a few weeks, and several amino acids were detected in different amounts [38], among them even quite complicated molecules such as histidine and proline. HPLC Chromatograms of amino acids obtained by such an experiment compared to reference amino acids are shown in Fig. 3.

Fig. 2. Apparatus for discharge experiments in N₂/CO₂/water vapor atmosphere

Such experiments are still carried out with some variations of environmental conditions and composition of the atmosphere. What is known up to now from such experiments makes it quite clear that Miller’s idea was right in principle, and that the formation of amino acids on the primitive earth should not have encountered much difficulty and should thus have been a quite ubiquitous process, leading, in a short time, to large amounts of these compounds essential for the further chemical evolution.

It should be mentioned here that experiments of Miller type had been performed already in the early 20th century by Loeb, but at that time – before Oparin’s famous book on the origin of life – no one was thinking of simulating the primordial earth, but rather in terms of a novel synthetic organic chemistry. These experiments published in
1906 [39] and 1913 [40] can be considered, however, as the first attempts to obtain larger organic molecules from simple inorganic gases with the help of electric discharges.

Table 1 presents some of the results of simulation experiments of Miller type, and one can estimate the relative relevance of these experiments for the actually assumed geochemical scenario on the earth 3.8 billion years ago. From this data, it can be seen that a number of other energy sources could also have led to the production of more or less complex organic molecules, and that one has to assume, therefore, that chemical evolution could proceed at a quite fast pace during that time. Accumulation of these compounds should then indeed have produced a quite promising ‘primordial soup’ for further processes. Besides amino acids, a number of reactions have been reported that could have produced other components of modern biomolecules, inter alia sugars starting from formaldehyde as a basis for their formation, or compounds like nucleic bases which are also needed for the later assembly of RNA and DNA molecules. One
Table 1. Some Examples of Miller-Type Experiments Simulating Assumed Primordial Earth Scenarios

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reactants</th>
<th>Energy source</th>
<th>Results reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller [5]</td>
<td>CH₄, NH₃, H₂O, H₂</td>
<td>Electric discharges</td>
<td>Simple amino acids, organic compounds</td>
</tr>
<tr>
<td>Abelson [6]</td>
<td>CO, CO₂, N₂, NH₃, H₂, H₂O</td>
<td>Electric discharges</td>
<td>Simple amino acids, HCN</td>
</tr>
<tr>
<td>Bar-Nun et al. [7]</td>
<td>CH₄, NH₃, H₂O</td>
<td>Shock wave</td>
<td>Simple amino acids</td>
</tr>
<tr>
<td>Hanada and Fox [8]</td>
<td>CH₄, NH₃, H₂O</td>
<td>Thermal energy (900–1200°C)</td>
<td>14 proteinogenic amino acids</td>
</tr>
<tr>
<td>Lawless and Boynton [9]</td>
<td>CH₄, NH₃, H₂O</td>
<td>Thermal energy</td>
<td>Glycine, alanine, aspartic acid, β-alanine, N-methyl-β-alanine, β-aminobutanoic acid</td>
</tr>
<tr>
<td>Groth and Weyssenhoff [10]</td>
<td>CH₄, NH₃, H₂O</td>
<td>Ultraviolet light (1470 and 1294 Å)</td>
<td>Simple amino acids (low yields)</td>
</tr>
<tr>
<td>Yoshino et al. [12]</td>
<td>H₂, CO, NH₃, montmorillonite</td>
<td>Temperature of 700°C</td>
<td>Glycine, alanine, glutamic acid, aspartic acid, histidine, lysine, arginine</td>
</tr>
<tr>
<td>Palm and Calvin [13]</td>
<td>H₂, CH₄, NH₃, H₂O</td>
<td>Electron irradiation</td>
<td>Glycine, alanine, aspartic acid</td>
</tr>
<tr>
<td>Miyakawa et al. [14]</td>
<td>CO, N₂, H₂, H₂O</td>
<td>High-temperature plasma</td>
<td>Glycine, alanine, aspartic acid</td>
</tr>
<tr>
<td>Rode and co-workers [38]</td>
<td>CO₂, N₂, H₂O</td>
<td>Electric discharges</td>
<td>Glycine, alanine, valine, serine, proline, lysine, histidine</td>
</tr>
</tbody>
</table>
somehow disturbing fact is that, among all of the sugar molecules formed under condensation reactions from formaldehyde, ribose, another essential constituent of RNA/DNA, was found in only marginal amounts [41]. This also indicates that the formation of nucleotides might indeed have been something that happened at a much later stage of chemical evolution.

While the formation of amino acids seems to be quite simple and plausible under primitive earth conditions, the next step, namely their oligomerization to form peptides is a much less simple step and will be discussed in the next chapter.

5. From Amino Acids to Peptides. — One of the critical points in the discussions about the evolution of ever larger chemical subunits is the approach to describe separate steps in this process and then to assume that all these processes could have been linked together, finally leading to the desired complex molecules. In this stepwise procedure, environmental conditions are sometimes entirely different. Some of them take place in an aqueous environment, others in the gas phase, others again consist of solid-state or melt reactions – and then it is assumed that all of this could have taken place subsequently without any interaction or mutual perturbation of the processes. In the laboratory, usually in every step analytical-grade pure chemicals are utilized to perform the reactions, and the possible influence of any impurities (for which one has to assume even large amounts in a realistic scenario of the primitive earth) is neglected. So, it looks as if by some mysterious process chemicals of some kind were produced, than purified, transported to another place with a completely different environment, and then reacted in a subsequent step. And again, the products were transferred to another environment to perform the next reaction …. This is certainly a too simplistic description of the complicated evolutionary processes which, in order to be generally realizable, must have taken place under similar environmental conditions. The only differences and changes in the common environment that have to be assumed to have occurred everywhere are changes in temperature, changes in the amount of the solvent water, and changes in various energy sources other than thermal. Within these variations, however, these processes must have been compatible with each other in order to perform regularly and ubiquitously and to lead to larger amounts of evolutionary products.

The process of the condensation of amino acids to peptides is a classical example, where such assumptions have to be made or at least had to be made in the past decades to explain how the proposed mechanisms could occur on the primitive earth. Basically, the reactions proposed for the evolution of peptides can be divided into a few classes, the first one being a solid-state reaction, based on the melting of amino acids [42][43], the other mechanisms related to condensation reagents [44–46] or to chemical modifications of amino acids to produce more easily condensating compounds, in particular esters [47]. A third general proposal took into account inorganic substances, namely minerals present on the primordial earth [22][48], working as catalysts and condensation reagent at the same time. These inorganic catalysts have retained their importance even in the most modern theories of peptide evolution [49].

The other condensation reagents proposed will be discussed only briefly. Most of them are organic molecules such as triazole [44], imidazole [45], and similar heterocyclic compounds which, however, would have to be present in large amounts
to enable the reaction. Energy-rich phosphates [46] also belong to the typical condensation reagents frequently considered as possible ‘assistants’ in prebiotic peptide synthesis. Later on, we will critically evaluate the possible availability of all proposed ‘actors’ in peptide evolution, and thus the relevance and plausibility of each scenario.

To understand the processes occurring in such condensation reactions, one has to consider the thermodynamic and kinetic properties of the peptide formation from amino acids. The combination of two amino acids to a peptide by forming the so-called ‘peptide bond’ requires the removal of one H\textsubscript{2}O molecule per peptide bond. It is obvious that such a process is thermodynamically unfavorable in aqueous solution. Additionally, there is a kinetic barrier that would also prevent this reaction from occurring readily. For these reasons, reaction conditions have to be adapted specifically in order to provide the condensation of amino acids to dimers or oligomers. This process of peptide-bond formation is absolutely essential to arrive at the final goal of this evolutionary pathway, the proteins.

It is clear, therefore, that a large number of attempts were made to explain how this process could have occurred under primitive-earth conditions. Most researchers have focussed their work on the aforementioned condensation reagents enabling the removal of water set free during the peptide-bond formation. The previously mentioned organic condensation reagents, namely imidazol, triazol, and other heterocyclic compounds [44–45] can achieve this, at least if they are provided in excess. However, it seems rather bizarre to assume an excess of such chemicals to have existed in the primordial oceans, although some compounds of this type can be formed in the Miller-type experiments in small amounts.

Another way to explain peptide formation involves esterification of amino acids and subsequent condensation [47]. Even that is not a process with much probability, as it would require the presence of alcohols and suitable conditions to form the esters.

Wächtershäuser and co-workers [50] have proposed a deep-sea vent scenario for the formation of peptides, driven by iron sulfide catalysis and the high local temperatures. However, the realization of this reaction requires an extremely high partial pressure of carbon monoxide which makes it, together with the very confined locality of the reaction, rather a very special but not general scenario.

Another proposal that attracted much attention and is still cited by a few authors as the ‘way from amino acids to proteins’ was the reaction of solid amino acids on a hot surface where they would melt at temperatures of around 120 to 180° [42][43]. Temperatures below that could achieve the same reactions in the presence of phosphoric acid in high concentrations [43], which, however, does not appear to be plausible for any primitive-earth scenario. At higher temperatures, one has to be aware that amino acids start to decompose, which sets narrow limits for the reaction conditions. There are some more problems related to this reaction. First of all, the amino acids have to be present in very pure form. A larger amount of inorganic purities, in particular of salts, would prevent the melting and thus the polymerization reaction. Second, the result of this reaction is not exactly what one would expect on the way to proteins. Although dissolving the reaction products in water, one obtains small cell-like structures which resemble micelles formed by proteins – a reason why they were optimistically termed ‘proteinoids’ by Fox and Harada [43], who performed these
experiments first—they do not really represent any protein-like compound. Analysis of the structure and composition of these ‘proteinoids’ soon revealed that most of the bonds in these polymers were not peptide bonds but rather ester bonds, proving the name given to these polymers misleading [51].

Another problem of the melt reaction is the requirement of acidic or basic amino acids in large amounts [43]. This is in contrast to the yields obtained by all kinds of Miller-type experiments, in which the simpler amino acids glycine, alanine, and other aliphatic amino acids are forming the majority of the products, and acidic and basic amino acids have rarely been identified.

Thus, until recently the only plausible way to peptides in a primordial earth environment appeared to be the interaction of the amino acids with inorganic minerals on the solid surface, water being removed by the layers of the minerals. Indeed, it was possible to show that in heating–drying–wetting cycles peptides are formed from certain amino acids on minerals like kaolinite, montmorillonite, hectorite, or other smectites [52][53], mostly in the form of dimer and some trimer peptides. However, this reaction worked well only with the simplest amino acids, in particular with glycine, which is known to be very easily polymerizable [54]. The yields in the case of the next simple amino acid alanine was already very small, even after long reaction periods, and thus not very encouraging to consider this clay-catalyzed peptide formation as the main process for the formation of peptides from amino acids in chemical evolution.

It was only in the late 1980s that a new reaction was discovered, which also utilizes inorganic materials as catalyst and condensation reagent, but not in the form of solid minerals as heterogeneous catalysts, but as homogeneous catalysts present in the aqueous phase. This new reaction, the so-called ‘salt-induced peptide formation reaction’ (SIPF reaction), will be discussed in a separate chapter, as it has provided completely new aspects of a very simple peptide evolution under primordial earth conditions.

6. The Salt-Induced Peptide Formation (SIPF) Reaction. – The SIPF reaction was discovered in 1988 [55] on the basis of theoretical investigations of electrolyte solutions and of metal complexes. Simulations of concentrated NaCl solutions by Monte Carlo methods [56–57] had shown that, above a concentration of 3M, the Na\(^+\) ions cannot access sufficient solvent molecules in order to fill their regular first hydration shell, which normally contains six H\(_2\)O molecules. Due to the strong binding energy of Na\(^+\) ion to the hydration shell, this would mean that the Na\(^+\) ions with lower coordinations can be considered as a strongly dehydrating system, thus being able to assist any reaction in which H\(_2\)O would have to be removed. This gave rise to the idea that NaCl at certain concentrations could be considered as a condensation reagent, helping amino acids to form oligomers through peptide linkages. At the same time, preliminary ab initio calculations had shown that metal complexes could be an ideal means to lower the kinetic barrier of condensation reactions between organic ligands [58]. These two findings together led to the idea to attempt peptide formation reactions to be induced in the presence of NaCl in higher concentrations by some suitable transition metal ions serving as a central ion to form complexes with the amino acids. Numerous metal ions were tested in this reaction system in the laboratory, and finally copper turned out to be the most suitable ion to form complexes with the amino acids, and to bring them
together into a suitable position and polarization state to allow peptide formation to take place with the help of the dehydrating agent NaCl [55][59]. Other metal ions were also investigated, but only molybdenum reached to a small extent the capability of copper as a complex former in this reaction. Among different salts, NaCl proved to be almost the best dehydrating agent [60], as other ions with stronger dehydrating ability would lead to too low pH values of the solutions, and others with less dehydrating power, i.e., with less binding energy for H$_2$O molecules in their hydration sphere, would not achieve the necessary level of removing H$_2$O in larger amounts.

Once this reaction with the only ingredients water, amino acids, NaCl, and copper ions was established, it could be optimized and tested for varying environmental conditions. Whereas the first experiments had still been performed at constant volume, a temperature of around 80°C, and with relatively high concentrations of all substances, namely 0.8m concentration of amino acids, 0.4m of copper, and 5m NaCl concentration [55][59][61], soon new experiments were developed which actually followed the idea of concentrating the solutions by elevated temperature, starting from low concentrations in the millimolar range, and gradually achieving the higher concentrations needed by evaporation [59][62]. In daily cycles of evaporation and subsequent take-up of the residues by water, processes happening in a primordial earth environment, namely in lagunas or shallow lakes, where the heat of the day would have led to evaporation of water and the rainfalls, or tide would have re-diluted the systems, were mimicked. These reactions were first performed with simple amino acids like glycine and alanine, and immediately – which means after a few days already – peptides could be identified [62]. Additionally, it was not only dipeptides, but also larger oligomers up to heptapeptides that could be detected after a few days. This encouraging result led to further experiments with a number of other amino acids, and soon it was observed that the reaction works under varying conditions and with almost all amino acids, as long as the ingredients were present, and the temperature was high enough to guarantee evaporation in a day’s cycle [62–63].

Investigations by various methods, in particular potentiometric and spectrophotometric titrations with subsequent species analysis [64], but also by varying the ingredients and concentrations of the reactions, soon revealed that the main species responsible for the formation of peptides was a Cu complex where one amino acid is bound to the Cu-atom in a chelating way, i.e., via its N and O coordination sites, one Cl$^-$/C0 ion due to the high NaCl concentration, and another amino acid only by its carboxylic group [64–65]. Two more H$_2$O molecules should be bound to this complex rather loosely at distant positions due to the Jahn–Teller effect. This complex is illustrated in Fig. 4 and shown with distances evaluated through an *ab initio* quantum-mechanical optimization of the system.

Further investigations were directed at specific properties of the reaction, and a number of interesting results was obtained. First of all, due to the complex formation properties, it was found that the biologically relevant $\alpha$-amino acids are strongly preferred over $\beta$- or $\gamma$-amino acids [66]. This could be a good explanation why contemporary biological systems almost exclusively involve $\alpha$-amino acids. It was found that almost all amino acids formed dimers, some in larger amounts, some not so easily when they were present alone. However, it was soon detected that the presence of glycine or its dimer diglycine can catalyze the formation of dimers and oligomers of
other amino acids [32][67]. This catalytic property was later found for histidine as well [68]. Even a quite wide variation of the environmental conditions, namely temperatures between 60 and 100°C, smaller or larger initial concentration of the reactants, in particular of NaCl, did not have much influence on the feasibility of the reaction. In all cases, peptide formation starts from the first day and increases in the subsequent cycles. In some cases, hydrolysis occurs, slowing down the production of peptides, but, in all cases, the peptides never vanished. Thus, the reaction as such offers a possibility of a rapid and easy peptide evolution within a very realistic primordial earth scenario which could be encountered along all the coastal regions or inside lakes and lagunas nearby the sea.

It was also observed, when using optically pure amino acids, that racemization took place very slowly, in particular when the initial concentrations were low [69]. This finding will be discussed in detail below.

Later on, mixtures of amino acids were employed in the experiments, and it was shown that various kinds of hetero-dimers and hetero-oligomers were readily produced [62][70]. Not all amino acid sequences were found in the same amounts, however, and this gave rise to the idea that the SIPF reaction could have been a governing mechanism to determine what amino acid sequences were preferred and formed first from the amino acids present, thus leading to specific compositions of polymers and proteins [63]. This aspect will be further discussed later.
Another essential part of the investigations related to the SIPF reaction was the possibility to carry out this reaction in the presence of clays and other substances modelling mineral surfaces such as silica and alumina. In all of these cases, it was observed that the SIPF reaction was the determining step for the formation of the initial dipeptides. However, in the presence of clays, yields were better, and in particular larger oligomers were formed in higher yields [23] as illustrated in Fig. 5.

These findings indicated that the role of the clay minerals in chemical evolution could have been, on the one hand, a protection of the formed oligomers against hydrolysis by adsorption and, on the other hand, a connection of smaller oligomers to larger units by bringing these peptides into a suitable position on the surface to react with each other by forming new peptide bonds as illustrated in Fig. 6. Thus, the role of clay minerals in peptide evolution can be considered a very important one, albeit not for the formation of peptides from amino acids, but for linking smaller peptides to larger units and thus helping to perform further steps on the way to larger biomolecules up to proteins. The stabilizing effect of the surface of the clay minerals, e.g., montmorillonite and hectorite, was also investigated in separate experiments [23] and could be seen as an important factor for the conservation of larger compounds, stabilizing them against hydrolytic and other decomposition processes. Another important result of these investigations was that both reactions could take place in the same environment, under the same conditions and without any mutual perturbation.
Fig. 6. Schematic representation of adsorption of small peptides to clay minerals, showing their arrangement in a suitable conformation for chain elongation.
Altogether, the SIPF reaction and its interplay with reactions on the surface of minerals believed to have made up a large part of the surface on the primordial earth led to a quite plausible scenario with very simple reaction partners.

The plausibility of the reaction scenario is further supported by the fact that, according to all geochemical data, NaCl should have been ubiquitously present [2] and, thus, does not require any specific explanation for its existence in the scenario. Further, the ‘green zones’ in the precambrian rock formations [16], mostly consisting of malachite and azurite, indicate that copper was available in sufficient amounts to play the catalytic role needed in the SIPF reaction. Even the question whether copper was present at that time in its divalent form employed in the complexes can be answered positively. The estimations of the oxygen content of the primitive atmosphere formed by outgassing from volcanoes and influenced by energy impacts of different kinds in the atmosphere reach from $10^{-15}$ to $10^{-1}$ of present atmospheric level [71]. However, a partial pressure of $10^{-35}$ of oxygen is sufficient to oxidize copper to its divalent form [72]. Therefore, the whole scenario does not only seem to be the simplest one ever proposed for the formation and evolution of peptides under primitive earth conditions, but also the most plausible one, as it does not need any further and difficult assumptions for its realization. In the next chapter, we will look for further indications that the SIPF reaction was an essential step on the way to life by comparing the properties of the SIPF reaction with properties of the oldest still living organisms on Earth.

### 7. The SIPF Reactions and Modern Life Forms

Although it seemed very daring to try to relate the first steps of peptide evolution to still living organisms, this attempt proved quite interesting and successful in the end. It was found that the SIPF reaction did not produce arbitrary amino acid sequences with equal probability. Indeed, there are some clear preferences for certain amino acid linkages, and this indicated that the compositions of any larger polymers, namely peptides in the form of oligo- or polypeptides up to proteins, should not be a statistical mixture of all possible combinations of amino acids but rather follow a certain framework set by the reaction conditions, in particular the individual probability of yields according to the SIPF reaction [22][63]. For a comparison, it was obvious to consider the oldest still living organisms, in the first line archaea and, in the second line, all procaryontic organisms. As it could be assumed that the first proteins formed in chemical evolution would also form the first cell-like structures, the membrane proteins of these old organisms were the first candidates for a comparison with sequence preferences of the SIPF reaction.

Therefore, membrane proteins of archaea and procaryonta were analyzed with respect to their most frequently occurring pair sequences of amino acids, employing all available protein data from a protein data bank [73]. A comparison with the most preferred sequences of the SIPF reaction was performed, and it was found that there is a remarkable coincidence between the two sets of data [63]. Table 2 illustrates such coincidences for A–B and B–A linkages of amino acids, and, although the coincidence in the case of a single amino acid is by no means something very striking, the total of coincidences for all investigated amino acids is quite exciting. The probability for such a coincidence to exist merely by chance is as low as $10^{-15}$ in the case of archaea. This indicates that there might exist a ‘finger print’ of the SIPF reaction in the structure and composition of these old proteins. If one proceeds to the procaryonta, one also finds
these coincidences, and, in this case, the probability of coincidence by chance is still as low as $10^{-14}$. Once the possible catalytic processes by other amino acids were taken into account in the yields of peptides produced by the SIPF reaction, the coincidences still increased in the case of archaea, finally leading to a probability to occur by chance of $10^{-18}$ [22]. These results lend a high probability to the assumption that it was indeed the SIPF reaction that had produced the first peptides and proteins on the primitive earth.

There is another type of proteins or at least protein-like structures which have attracted much attention in the past years as the reasons for various diseases, from Scrapie and Mad-Cow Disease to Kuru-Kuru and Creutzfeld–Jacob Disease [74]. These substances called prions have not been assigned any important role in the living organisms so far. Therefore, the idea was proposed that they might be a relic from an early stage of evolution [75]. Indeed, if one compares the frequencies of preferred sequences between the SIPF reaction and prions, the similarity is striking again, as illustrated in Fig. 7. In particular, the high amount of gly-gly linkages is remarkable as glycine is the most easily produced amino acid in all Miller-type experiments, and as it has to be expected that, in a first stage of chemical evolution, glycine–glycine bonds were most widespread. For this reason, one can assume that prions are indeed similar to the very first peptides formed in prebiotic evolution, and that they could give us another indication that the SIPF reaction was the decisive step in chemical evolution towards proteins.

Table 2. Comparison of Amino Acid Linkages in Archaea (A) and Most Produced Sequences of the SIPF Reaction*)

<table>
<thead>
<tr>
<th>AB-Linkages</th>
<th></th>
<th>BA-Linkages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid A</td>
<td>Amino acid B</td>
<td>Coincidences</td>
</tr>
<tr>
<td>Asp</td>
<td>A</td>
<td>glu, val, asp, ala</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>glu, lys, asp, ala</td>
</tr>
<tr>
<td>Glu</td>
<td>A</td>
<td>glu, leu, val, asp</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>glu, gly, asp</td>
</tr>
<tr>
<td>Gly</td>
<td>A</td>
<td>glu, lys, val, gly</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>gly, leu, val, lys</td>
</tr>
<tr>
<td>Pro</td>
<td>A</td>
<td>glu, gly, ala, leu</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>ala, gly, leu, val</td>
</tr>
<tr>
<td>Lys</td>
<td>A</td>
<td>ala, gly, glu = val, gly</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>asp, gly, ala</td>
</tr>
<tr>
<td>His</td>
<td>A</td>
<td>lys, gly, ala, val = asp</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>val, his, ala, gly</td>
</tr>
<tr>
<td>Ala</td>
<td>A</td>
<td>ala, asp = glu, gly, leu</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>ala, gly, val, his</td>
</tr>
<tr>
<td>Leu</td>
<td>A</td>
<td>ala, gly, glu, lys</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>gly, val, ala, his</td>
</tr>
<tr>
<td>Val</td>
<td>A</td>
<td>ala, glu, asp, leu = val</td>
</tr>
<tr>
<td></td>
<td>SIFP</td>
<td>gly, his, ala, leu</td>
</tr>
</tbody>
</table>

*) Probability for incidental coincidence: $1:10,000,000,000,000,000$. 
The data presented in this chapter give a very high plausibility to the importance of the SIPF reaction in chemical evolution, and we will see in the following chapter that there is still another important argument which reinforces the credibility of the SIPF reaction as a first and most relevant step in the evolution of peptides and proteins.

8. The SIPF Reaction and Biohomochirality. – Biohomochirality is one of the great riddles of chemical evolution and life. It is known that all proteins of living organisms are made up exclusively of l-amino acids. It is clear that a mixture of l- and d-amino acids would lead to problems in the tertiary structure of proteins, as it would make it difficult to form the structural entities known as α-helices and β-sheets [76]. However, the same conditions could be achieved either with l- or with d-amino acids. The question is, therefore, why nature has decided to select the l-forms of these molecules.

There is a number of hypotheses that has been published in the past decades to explain this selectivity for the l-amino acids, the most simple one being the hypothesis of chance [77], which means that some initial process that led to the first active biomolecules started accidentally with l-amino acids, and thus all subsequent molecules followed the same direction. One knows that autocatalytic crystallization processes can be initiated with either l- or d-molecules, leading to a large excess of either l- or d-crystals and, by this way, laying the foundation of an exclusive use of one form [78]. However, such a hypothesis does not sound very satisfactory as one cannot see a reason why the relevant biomolecules should have formed only in one specific place with an incidental ‘starter’ leading to l.

One of the explanations employed to explain the preference for l-amino acids was and is its extraterritorial origin [79]. It has been observed that, near some clouds in the universe, e.g., the Orion cloud, strong sources of polarized infrared light are existing.
Such polarized light could certainly lead to a favorization of one of the optical isomers and thereby to a ‘chirality success’ over the other [80]. The preference would depend, however, on the polarization direction of the light available, and again one does not find a real explanation why \( \text{l} \) and not \( \text{d} \) has been preferred.

However, investigations of meteorites containing amino acids have lent some support to the hypothesis of \( \text{l} \)-preference in the Universe (or at least in our galaxy). For example, for the Murchison meteorite [81] of Australia, it was found that, in its inner zones, a slight excess of \( \text{l} \)-amino acids over \( \text{d} \)-amino acids exists. This could either give support to an extraterrestrial origin of the preference of \( \text{l} \)-amino acids on Earth, but it could also simply mean that the process leading to this preference is an ubiquitously present reaction mechanism causing a preference of the \( \text{l} \)-forms at any place in the universe.

In considerations about a terrestrial origin of biohomochirality, the most common hypotheses are based on the adsorption of amino acids onto chiral surfaces [82] [83]. This could have happened, however, only in a local environment as optically active crystals are in average equally distributed as \( \text{l} \)- and \( \text{d} \)-forms. The main material mentioned in such hypotheses is quartz [83], as it consists of the very common material silica and is found in nature in both isomers, namely the \( \text{l} \)- and \( \text{d} \)-form of the crystals. In this case, one would again have to stress the chance hypothesis, namely that, in some selected or specific local environment with an abundance of one of the two optomers, the process to form the first biomolecules would have started, and by chance this would have determined the future direction of the development.

There is another possibility, however, how \( \text{l} \)-forms could have been preferred. Among the forces in nature known so far there is only one that violates parity. This is the weak nuclear force, and it is known that it does not act completely symmetrically [84], thus leading to a certain preference for \( \text{l} \)-forms [85] [86]. In the case of simple organic compounds, where the C-atom is the main atom to determine the chirality, the energetic difference based on this weak nuclear force in combination with the electromagnetic force (together they are called electroweak force) would lead only to an excess of \( \text{ca.} \, 10^7 \) molecules per mole [86] of the \( \text{l} \)-form. This is by far not enough to explain the final preference of \( \text{l} \), even over many millions of years. However, the effect of the weak force increases with something between the fifth and sixth power of the nuclear charge [87]. Therefore, this effect is already measurable for heavier elements, where it becomes pronounced enough to be seen in experiments [88]. There are some arguments to explain biohomochirality by assuming that the electroweak effect could have been augmented by some kind of amplification mechanism, but, so far, these attempts of explanation were rather hypothetical [89] and did not provide any experimental verification.

In the course of the investigations of the SIPF reaction with different amino acids, it was studied whether optically pure amino acids or racemic mixtures would lead to different yields. For this reason, alanine was investigated both in its \( \text{l} \)- and \( \text{d} \)-form, and with a racemic mixture. The first result of this investigation was that racemization takes place very slowly if low amino acid concentrations are employed [62]. Second, it was found that \( \text{l} \)-alanine apparently always gave a slightly better yield of the dipeptide than the \( \text{d} \)-form [62]. This was first attributed to impurities of the chemicals or to some other side effects, but when the experiments were repeated in numerous new series,
employing amino acids from different manufacturers, at different concentrations, and by different investigators, and the result turned out to be always the same, it became obvious that there might be some yet unknown mechanism that constantly favored L-amino acids [69]. The same experiments were then repeated with other amino acids, and it was found that not all amino acids showed this effect but only a few ones, in particular alanine, valine, and some other simple amino acids [90][91].

After this effect had thus been reconfirmed, it became necessary to seek an explanation for a possible mechanism in the selection of L-amino acids as a slightly preferred educt of the SIPF reaction. In this context, a possible influence of the electroweak force was primarily considered, in particular, as it was known that the complex leading to peptide formation involved copper ions and thus a heavier element. Copper with its nuclear charge of 29 would show a much more pronounced effect of the electroweak difference between L- and D-conformers, due to the \( Z^p \) or even \( Z^q \) dependence. Fig. 8 illustrates the exponential increase of parity violation effects with increasing atomic number for \( Z^p \) dependence, for the range of H to Cu.

![Fig. 8. Schematic illustration of parity violation effects provided by the elements H to Cu for a \( Z^p \) dependence](image)

The first investigation directed at such a possible effect was the determination of the stability of Cu complexes with L- and D-alanine. Although differences between the stability constants were only marginal, they seemed to be reproducible [69]. At the same time, circular-dichroism (CD) spectra of the solutions leading to the SIPF reaction also showed slight differences between L- and D-alanine [69], as shown in Fig. 9.
Fig. 9. Circular dichroic titration of an aqueous solution of 0.04M a) l-alanine, b) d-alanine and 0.02M CuCl₂/5.0M NaCl, c) at 650 nm: l-alanine (×), d-alanine (*), d) magnified, with sixth degree polynomial fitting: l-alanine (—) with the minimum at pH 3.94 and d-alanine (—) with the minimum at pH 4.00. In graphs c and d, the CD of l-alanine has been inverted for better comparability.
All of this would not explain, however, the experimentally observed considerable excess of l-l- over d-d-dipeptide yields. An indication towards a potential amplification mechanism of the effect of the electroweak force came from the structure of the SIPF complex illustrated in the previous chapter in Fig. 4. If one takes into account that the two H$_2$O ligands should be rather loosely bound due to the Jahn–Teller effect, one obtains a more or less tetracoordinated Cu complex with four different binding sites, one being the amino acid binding as a chelate with O and N, the other ligands being a Cl-atom and an amino acid bound via the carboxylic group. If one could assume a distortion of the plane of these binding sites towards a pseudo-tetrahedral coordination, one would obtain a stereogenic center at the Cu-atom itself. Such stereogenic centers at transition metal ions are a well-known phenomenon in a number of complexes [92] and thus not very unusual.

To clarify whether such an effect could be observed, complexes of Cu with two identical optically active amino acids and a Cl-atom were calculated by means of quantum-mechanical ab initio methods, taking into account the solvent effect by means of PCM (polarizable continuum model) contained in the Gaussian 03 package [93]. The results of these calculations clearly showed that not all amino acids would lead to such a distorted tetrahedral conformation, but only a few of them. Comparing these results with the experimental data, namely with the yield differences related to preferential reaction with l- or d-amino acids, it was finally recognized that, wherever such a distortion was found in the complex structure, the corresponding amino acids showed a more or less pronounced preference for l-amino acids [91]. Figs. 10 and 11 show two examples of complexes, one formed with alanine, the other one with proline. Whereas, in the case of alanine, one observes a distortion of the complex, one does not see this in the case of proline. In the SIPF experiments, there is no difference in dipeptide yields starting from either l- or d-proline, whereas, for alanine and valine, this difference is clearly observable.

Fig. 12 shows the experimental results for the amino acid valine that shows the most distinct preference for its l-form among all amino acids investigated so far in the SIPF reaction.

However, if only a part of the amino acids would have shown this preference for l-amino acids in peptide evolution, it is clear that, in the long run, l-forms would have dominated the units utilized in the construction of larger biomolecules. As mentioned previously, the overall composition of large biomolecules, in particular proteins, should have contained only one type of optical isomers in order to form a suitable tertiary structure, and this would have led to the homochiral forms containing only the favored l-amino acids.

Summarizing these results, one could conclude that the electroweak effect seems to be augmented by the formation of a stereogenic center in the SIPF complex. Binding of a chiral amino acid within that complex would provide a differentiation by the formation of diastereoisomers. Thus, the SIPF reaction appears to be a very plausible explanation for the preference of l-amino acids in peptides and proteins, and thus for the phenomenon of biohomochirality.

Conclusions. – Summarizing the data presented here and the considerations of the previous chapters, one can come to some quite intriguing conclusions concerning the
Fig. 10. *SIPF* Complex with two alanine ligands with a distorted conformation of the central Cu-atom and amino acid coordination sites.

Fig. 11. *SIPF* Complex with two proline ligands with a nearly planar conformation of the central Cu-atom and amino acid coordination sites.
first steps of chemical evolution towards biomolecules and thus towards life. First of all, it seems quite clear that the production of amino acids as the building blocks of proteins does not mean any miraculous event on the primitive earth with its geochemical environment, but rather a necessary process that should have happened readily and ubiquitously. Second, the oligomerization and polymerization of amino acids to form peptides and later proteins also seems to have been a quite easy process with many possibilities to be realized in different scenarios along the coastal regions and in inland lakes, and thus a quite high concentration of such peptides can be expected to have prevailed in the ‘primordial soup’. With the help of minerals, such peptides could easily have been protected from hydrolytic processes, but they could also have been enlarged in cooperation of the mechanism of the SIPF reaction with the catalytic activity of the minerals themselves, leading to higher polymers, and thus have paved the way for the formation of proteins. The SIPF reaction presented here also seems to explain in a simple way a number of biological questions, for example, why it is mainly \ensuremath{\alpha}-amino acids that are involved in biological molecules, and why certain amino acid sequences are dominating or less favorable in the formation of polymers. The question of the formation of biomolecules in the form we encounter them today, thus, becomes initially a matter of chemical stability of complexes, reactivity of the partners, and not any more a matter of merely statistical events. The fact that the preferred SIPF sequences are found in the protein membranes of the oldest still living organisms speaks for a high

Fig. 12. Dipeptide yields obtained in the SIPF reaction of \(l\)- and \(\alpha\)-valine with different starting concentrations
probability that this reaction has been the basis for protein formation on the primordial earth. Last but not least, the reaction also provides a plausible explanation for the preference of L-amino acids in biohomochirality and thus leadsto an overall conclusive picture of the role that this reaction could have played in chemical evolution. All of these reactions are fully compatible with the geochemical scenario as proposed today, and they also enable an evolution of peptides under considerably varying environmental conditions.

It is clear that the evolutionary scenario presented here represents only the very first steps on the way to life, but most probably some very crucial steps. One must be very modest, however, when thinking of the many further evolutionary steps needed to lead to modern life forms. It is understood that, on the one hand, the formation of proteins following the pathways presented here could have happened in a relatively short time span. The formation of modern life forms as we know them, however, took at least another two billion years – the first multicellular organisms are at least two billion years younger than the first fossil cell-like structures! – and thus leaves much to explain about mechanistic changes, new reactions, and the increasing complexity of biochemistry that produced the biology as we know it in its modern form.

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