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Coordination Chemistry Reviews
190-192 (1999) 1085-1099

COORDINATION CHEMISTRY REVIEWS

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The possible role of Cu(II) for the origin of life

Bernd Michael Rode *, Yuttana Suwannachot

Department of Theoretical Chemistry, Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innrain 52 a, A-6020 Innsbruck, Austria

Contents

Abstract

The most crucial prerequisite for the origin of life—most probably long before RNA/DNA-based reproduction could develop—was the formation of peptides and proteins under the conditions of the primitive earth. All reactions formerly proposed to have enabled this step of chemical evolution are highly questionable concerning their realizability under prebiotic conditions. However, the salt-induced peptide formation (SIPF) reaction, found some years ago, provides much more encouraging aspects for the creation of various peptides under such conditions. The necessary reagents—besides amino acids—are only sodium

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* Corresponding author. Tel.: +43-512-507-5160; fax: +43-512-507-2714.
E-mail address: theochem@uibk.ac.at (B.M. Rode)

PII: S0010-8545(99)00159-9

chloride and copper ions, and for both there is sufficient evidence of their presence on the primitive earth. The SIPF reaction occurs readily within a wide spectrum of environmental conditions (atmosphere, temperature etc.) and combines preferentially α-amino acids to peptides. Since it is applicable to all amino acids investigated so far, it has been possible to compare its preferentially formed peptide linkages with those found in the membrane proteins of the oldest still living organisms, namely archebacteria. The coincidence of these preferences is so high that it could have occurred by chance only with a probability of 10^{-18}. This leads to the conclusions that the SIPF reaction has been the basis for the formation of first peptide and protein matrices on earth (later reproduced by other, more efficient mechanisms and thus conserved, with some evolutionary variations, in these old organisms until now) and that, hence, Cu(II) has played a most significant role in the origin of life on earth.

Keywords: Role of Cu(II); Origin of life; Salt-induced peptide formation (SIPF); Chemical evolution

1. Introduction

1.1. Geochemical foundations

Modern geochemistry assumes that the secondary atmosphere (i.e. after diffusion of hydrogen and helium into space) of the primitive earth was formed by outgassing of volcanoes, and therefore to have consisted mainly of carbon dioxide, nitrogen, water, sulfur dioxide and even small amounts of oxygen [1]. Such a mixture can produce amino acids when exposed to electrical discharges mimicking those occurring in thunderstorms to UV light, heat and/or other radiation of atmospheric or cosmic origin [2]. According to geochemical estimations, this situation was reached about 3900 million years ago. On the other hand, the first fossil remainders of a cell-like structure were located in minerals dated back 3500 million years from now, the first indications of some kind of 'bio-activity' based on isotopically 'light' carbon even being found in 3800-million-year-old rocks [3]. This means that one has to assume that chemical evolution had 'only' 100–400 million years to produce a first mono-cellular structure from simple gaseous inorganic compounds.

1.2. Prebiotic reaction scenarios for peptide formation

After formation of a first hydrosphere, the increasing amount of liquid water started not only to readily dissolve soluble compounds formed by such processes, but also substances present in the crust of earth, such as inorganic salts (in particular chlorides), and one has therefore to assume a dominance of such inorganic solutes in whatever 'primordial soup' emerged through the dissolution of organic products stemming from atmospheric gas-phase reactions. These inorganic substances have been widely neglected in most assumed prebiotic scenarios so far, although they imply some important consequences for the stability of precursors of bio-molecules. As was found recently, nucleotides in particular are almost immediately decomposed into their constituents in the presence of high salt concentrations

[4]. On the other hand, in such a scenario peptides are considerably more stable than nucleotides, and thus the assumption of a primary chemical evolution of peptides and proteins seems much more plausible.

The general problem of peptide formation from amino acids in aqueous solution is the thermodynamically and kinetically unfavorable process of removal of water in a condensation reaction. A large number of proposals were made on how to overcome this difficulty, but a reevaluation of these reactions in the light of modern knowledge concerning environmental conditions on the primitive earth and according to the plausibility of the scenario required for the occurrence of these processes, has shown that most of them cannot have occurred or at least only with marginal probability at specific locations [5].

Generally, the proposed 'condensation reactions' of amino acids can be divided into three categories, corresponding to melt processes [6], heterogeneous systems involving mineral catalysis and condensation reactions induced by various reagents in homogeneous solution, respectively. Three arguments contradict strongly the relevance of melt reactions for the formation of peptides on the primitive earth: firstly, all processes producing amino acids from simple atmospheric components never lead to the required excess of acidic or basic amino acids; secondly, the mixture of amino acids in these experiments was chemically pure, but all the inorganic matter contained in the primordial 'soup' would rather dominate the residue after evaporation and form a serious obstacle for this process; thirdly, the resulting so-called 'proteinoids' are polymers containing only minor amounts of peptide bonds. Recent re-investigations of peptide formation based on clay catalysis [7] have clearly proven the feasibility of this reaction, albeit only for the simplest amino acids and in very small yields [8]. Although it must be assumed, therefore, that clay catalysts may have played rather a minor role in the production of the first peptides compared with other reactions, they could have been of major importance for other, subsequent processes such as chain elongation and stabilization against hydrolysis [8].

Several condensation reagents have been proposed as having linked amino acids in homogeneous aqueous solution, but they are often needed in excess of water, which also makes the related scenarios very unlikely. Typical examples of such reagents are imidazol [9], triazol [15] and dicyanamide [10]. Besides the difficulty in explaining the availability of the necessary large amounts of these reagents under primitive earth conditions, the inevitable presence of inorganic salts has mostly been neglected. Energy-rich phosphates have also been proposed as potential condensation reagents [11], but their availability under hydrolyzing conditions and in the presence of metal ions is rather questionable, which strongly reduces the significance of such a scenario.

Huber and Wächtershäuser have proposed another scenario for the formation of peptides from amino acids which assigns an important role to inorganic materials for the condensation process in an environment possibly occurring in volcanic vents [12]. In the simultaneous presence of freshly precipitated NiS and FeS and of H_2S or CH_3SH and a considerable amount of CO (partial pressure of ~ 1 kbar), some amino acids form dimers in yields of 0.2–5%. Such a reducing environment can be imagined—according to the aforementioned present view of geochemical conditions of the primitive earth—as being realizable only very locally, and the availability of the necessary high concentration of carbon monoxide has to be doubted [13]. Another problem with this scenario is that amino acid formation under such conditions could not be shown so far, raising the question, how amino acids formed in atmospheric processes could have been transported to such localities beyond the surface to be reacted to peptides.

Another condensation reaction, the so-called 'salt-induced peptide formation (SIPF)', was found in 1989: systems containing amino acid, NaCl and a small amount of $CuCl_2$ at temperatures of ~80°C form peptides easily [14]. This represents the simplest way so far to obtain peptides in aqueous solution, and the properties of this reaction are quite favorable for an important role in chemical evolution. While the first experiments were still performed with high concentrations of amino acid and salts, later series of investigations proved that it is also possible, even more favorable, to start from very dilute solutions [15] subjected to wetting/drying cycles [16] (evaporation experiments), thus, mimicking possible processes occurring as a consequence of day/night cycles, rain and tidal fluctuations. Referring to the plausibility of this reaction under primordial earth conditions, one can certainly assume a most likely presence of sodium chloride in oceans, lagoons and even lakes. A decisive role is also played by the catalyst Cu(II). For sufficient Cu(II) availability, the so-called 'green zones' in precambrian rock formations [17], consisting mostly of copper minerals, give strong evidence, and the modern estimations of the oxygen content of the secondary primitive earth atmosphere, ranging from 10^{-15} to 0.1 of the present atmospheric level [18,19], favor the presence of copper ions in the divalent state: a partial pressure of 10^{-35} atm is sufficient to oxidize Cu(I) to Cu(II) [20]. Temperatures between 80 and 100°C are most likely in the cooling process of earth after the first formation of a hydrosphere, and at such temperatures a regular occurrence of drying/wetting cycles has to be assumed, taking into consideration day–night cycles, heavy rainfalls and tidal fluctuations. On the basis of these considerations, the primitive earth environment should have provided very suitable conditions for the SIPF reaction. Important features of this reaction are its strong preference of the biologically relevant α- over β- and γ-amino acids in the formation of peptides [21] due to their better complex formation ability with the catalytic Cu(II) ion, its universal applicability as peptides are formed from all amino acids investigated so far, and a slow racemization, especially at low concentration of reagents.

2. The mechanism of the salt-induced peptide formation reaction

2.1. Reacting species

The first data collected from SIPF experiments strongly suggested that—besides the dehydrating activity of NaCl—a Cu(II)/amino acid complex might have played a crucial role in peptide formation, and that the readiness to form peptides depends on the 'electronegativity' of the amino acids side chains [22]. Both experimental and theoretical methods were employed to obtain detailed information about the reaction mechanism, starting with potentiometric and spectrophotometric titrations and subsequent species analysis [23]. The latter showed that at pH values between 1.5 and 5.0 several complex species exist: a protonated Cu(II) complex with two amino acid ligands (one most likely coordinated via carboxyl group only) coexists with the unprotonated 1:2 complex and—due to the high Cl^- concentrations—most of the Cu(II) species also carry a chloride ligand. Monte Carlo simulations of a 0.5 M $CuCl_2$/5 M NaCl solution [24] predicted $CuCl^+$ to be the dominant copper species, and this result was confirmed later by a more sophisticated simulation including full 3-body corrections and by neutron diffraction investigations with isotope substitution (NDIS) of this solution [25].

2.2. Experimental and theoretical investigations on the reaction mechanism

The mechanism illustrated in Fig. 1, based on the formation of a monochlorocuprate complex with two amino acids (or one peptide and one amino acid) can be assumed to lead to the new peptide linkage between the reactants. Ab initio calculations at Hartree—Fock level of such complex species have been performed [26], predicting a particular stability of this species and partial charges favoring a nucleophilic attack of the amino group of the chelated amino acid at the protonated amino acids carboxyl carbon. Further investigations of the mechanism showed that whenever one of the two reacting partners is a peptide and the second an amino acid, the amino acid will form the chelate ligand and the peptide will be coordinated via carboxyl oxygen only [27], providing a certain 'guideline' for the growth of oligopeptides. Experiments using salts other than NaCl as condensation

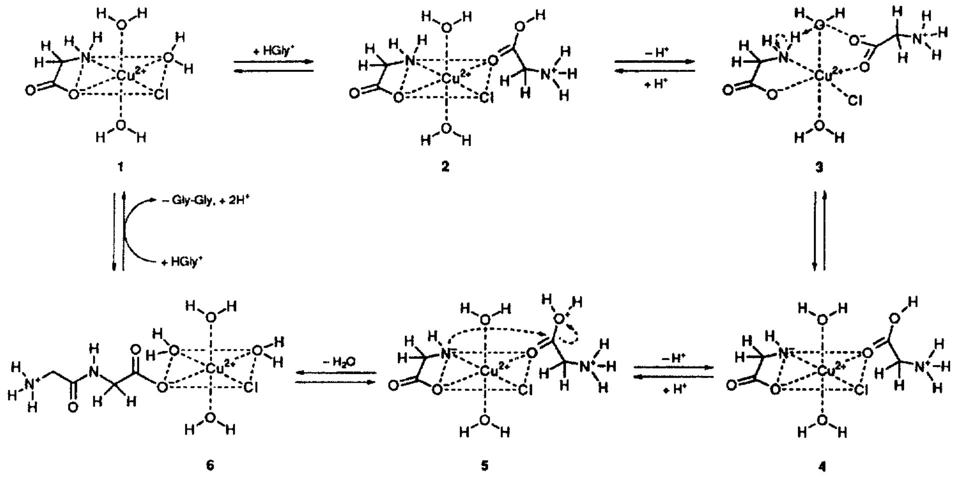

Fig. 1. Postulated reaction mechanism for the salt-induced peptide formation (example of diglycine formation).

agents proved the essential role of the chloride anion and thus of the monochlorocuprate species [27]. The dehydrating effect is directly related to the hydration enthalpy of the cations and reflected in the primary peptide formation. In this sense, Mg(II), Ca(II) and Ba(II) could produce peptides more readily, but their disadvantage is a shift of the pH to lower values, which increases hydrolysis rates and also shifts the Cu(II) complex species distribution away from its optimum. In this context Na(I) seems to be the best compromise between dehydrating effect and optimal complex formation conditions, aside from its highest probability among all cations to have been abundant under primordial conditions.

2.3. *The essential role of Cu(II) and Cl^- in the mechanism*

Other anions than Cl^- drastically reduce the formation of peptides and no other metal ion can replace Cu(II) in this mechanism, as investigations with a large number of transition and main group metal ions have shown. This unique role of Cu(II) has to be ascribed to its particular complex formation abilities with amino acids and peptides on the one hand, and its relative strength of binding chloride ions on the other hand. The particular stability of the complex held responsible has been confirmed by calculations at ab initio level [26], which also gave details of its structure and the electron distribution in the reacting amino acids. In terms of 'classical' considerations of complex chemistry, one could consider the complex a strongly and irregularly distorted octahedron, where the distortions are not only caused by the Jahn–Teller effect but also by the very different nature of ligands attached to the central ion. Although the data from the calculations are strictly valid only for the isolated complex in the gas phase, solvation can be assumed to produce only some minor changes in bond angles and lengths, comparing the strong interaction energies of the coordinated ligands and the ion with the strength of ligand–solvent interactions. Hence, the ab initio data form the most reliable data for the discussion of the structure of this complex in solution, for which experimental data would hardly be available under the conditions of the reaction by any method as NMR, X-ray or neutron diffraction.

3. Mutual amino acid catalysis in the salt-induced peptide formation

3.1. *Glycine as catalyst*

In the course of extended investigations on the formation of peptides from binary amino acid mixtures, it was found that some amino acids apparently catalyze the formation of homo-dipeptides not or only scarcely available from the corresponding amino acid alone [28]. Also in the case of other homo-peptides. e.g. di- tri- and tetraalanine, yields improved strongly in the presence of such a 'catalyzing' amino acid, particularly in very dilute solutions. Table 1 illustrates this effect for the case of Ala_2 and Ala_3. In very dilute alanine solutions, these peptides are not formed at all by the SIPF reaction, but in the presence of small amounts of glycine they result

Table 1

Dialanine yields resulting from 160, 80, 40 and 20 mM L-alanine solutions in the absence and presence of 5 mM glycine in the SIPF reaction[d]

Alanine concentration (mM)	Ala_2 yields (%) (absence of Gly)			Ala_2 yields (%) (in presence of Gly)			Ala_3 yields (%)	
	+/+[a]	+/−[b]	Ratio[c]	+/−[a]	+/+[b]	Ratio[c]	Without Gly	with Gly
160	2.37	2.56	0.48	2.42	2.22	0.48	0.48	0.55
80	3.53	0.85	0.81	1.15	3.09	0.73	0.57	0.67
40	Traces	–	1.00	0.10	4.02	0.98	–	0.67
20	–	–	–	–	2.62	1.00	–	0.51

[a] +/+ denotes L,L+D,D-Ala_2.

[b] +/− denotes L,D+D,L-Ala_2.

[c] Ratio, L,L+D,D-Ala_2/(L,L+D,D-Ala_2+L,D+D,L-Ala_2).

[d] Ala_3 is the sum of all isomers.

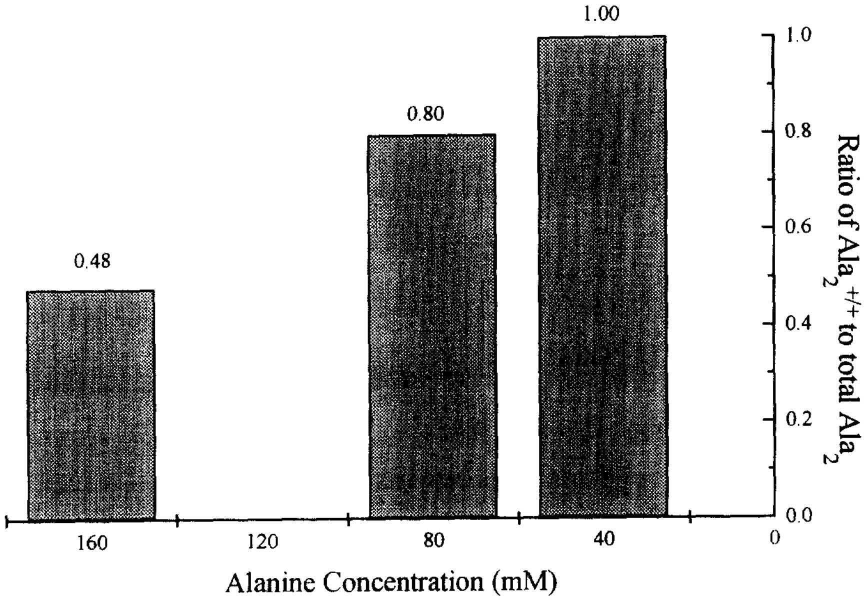

Fig. 2. Ratios of L-L-Ala$_2$ to total Ala$_2$ produced from solutions of pure L-alanine of varying concentrations.

in good yields, and with almost 100% conservation of the optical purity. Figs. 2 and 3 demonstrate these effects in detail. Fig. 2 (2,2,6) shows, how racemization depends on the initial concentration of alanine. Whereas a 160 mM alanine solution leads to a completely racemic mixture of dialanine after seven reaction cycles, the 40 mM solution, albeit producing Ala$_2$ in relatively better yield, contains only optically pure L/L-Ala$_2$. Fig. 3 (2.2.7) illustrates the production of (optically pure) di- and trialanine in this solution, starting from L- and D-alanine, respectively. It seems, as if L-alanine as starting material leads to slightly better yields than the D-form, but the differences are small (cf. error bars) and could be caused by the different production methods of L- and D-amino acids and hence, some impurities remaining even in analytical grade substances.

A 20 mM alanine solution does not form any oligomers in the absence of glycine, but if this solution contains 5 mM of glycine at the same time, the yields shown in Fig. 4 (2.2.8) result. Again, optical purity is conserved, and L-alanine seems to react slightly better than L-alanine. The trialanine concentration remains rather stable throughout the observation period, probably because new formation from dialanine/alanine and hydrolysis of the trimer reach an equilibrium state.

3.2. Other amino acids and peptides acting as catalysts

The results obtained for glycine led to a more systematic investigation of the 'mutual amino acid catalysis' phenomenon, focussed on the one hand on other amino acids and related compounds that could play such a role, and on the other hand on the homo-dipeptides not obtained so far from the SIPF reaction with the corresponding amino acid alone, namely Val, Leu and Lys.

Among all potential catalysts tested, glycine, diglycine, DKP and histidine proved to be effective (cf. Table 2). In particular, the first three compounds represent a most welcome result, as glycine is the compound most easily formed from simple atmospheric compounds and should always have accompanied other amino acids resulting from such syntheses, and as diglycine and DKP are the compounds most readily formed in the SIPF reaction.

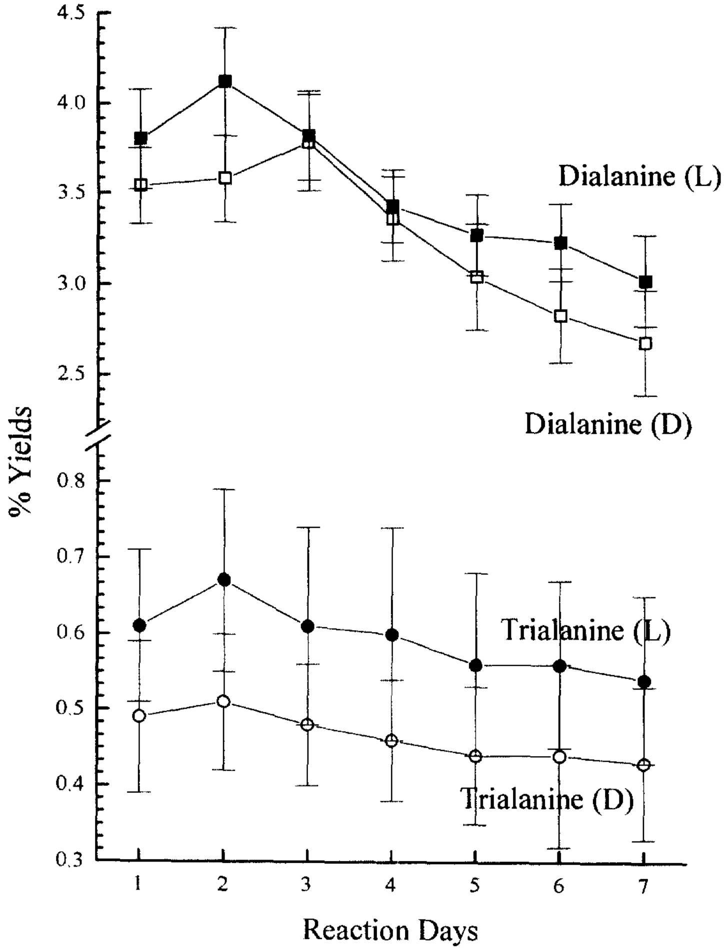

Fig. 3. Yields of dialanine and trialanine from 40 mM L- and D-alanine solutions in the presence of 5 mM glycine.

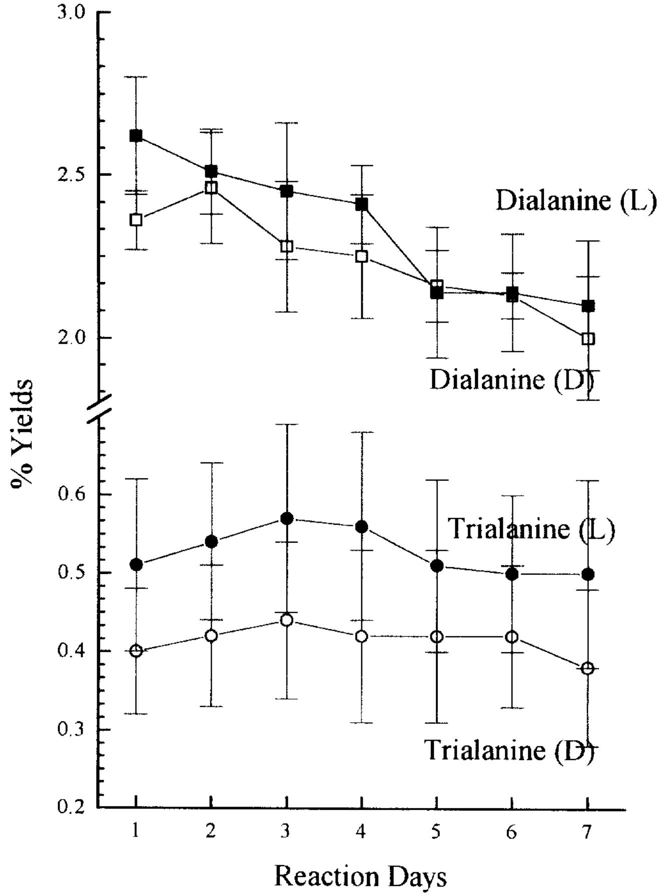

Fig. 4. Yields of dialanine and trialanine from 20 mM L- and D-alanine solutions in the presence of 5 mM glycine.

3.3. Interpretation of the mutual catalysis effect

The results obtained so far for the catalytic effect can be interpreted by the mechanism illustrated in Fig. 5. It involves the formation of higher oligopeptides and a subsequent hydrolysis. In the example given, Gly–Ala is formed first, reacting with a further Ala molecule to form Gly–Ala–Ala and then breaking into Ala–Ala and gly, which can react as a catalyst for other Ala molecules. In an analogous mechanism, the second important catalyst found, diglycine, would form Gly–Gly–Ala–Ala, and the –Gly–Ala– bond would be broken by hydrolysis. Another efficient catalytic substance, DKP, is assumed to act only after hydrolysis to diglycine, whereas the mechanism for His should be the same as for Gly.

If larger amounts of glycine are present (the optimal ratio for Gly/Ala is 1:8), glycine becomes more and more of a competing partner in peptide formation, and

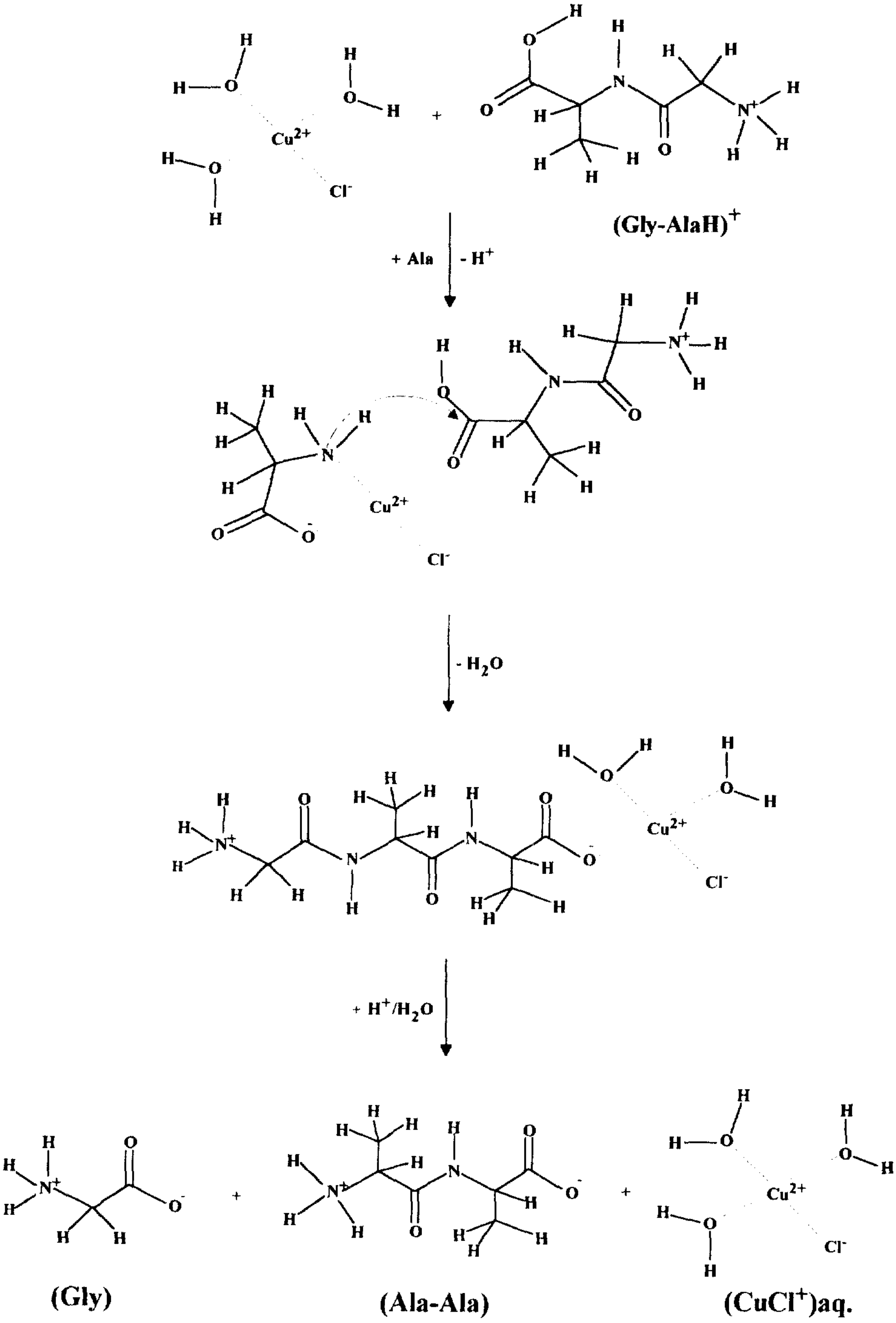

Fig. 5. Reaction scheme for dialanine formation under glycine catalysis.

the catalytic effect for Ala–Ala formation is gradually reduced to zero. The overall concentration of amino acids is also related to the effectiveness of the catalyst: starting the SIPF reaction from higher concentrations of amino acids a gradual diminishment of the effect is observed, until it vanishes at about 100 mM initial concentration in the case of alanine.

4. Amino acid sequences of the salt-induced peptide formation reaction

One of the important features of the SIPF reaction resulting from investigations of a larger number of amino acids as single and binary systems is the preferential formation of specific dipeptides, which implies the preference of certain amino acid sequences. This finding encouraged a comparison of the preferred SIPF sequences to those found in 'primitive' proteins, i.e. those found in organisms dating back to the beginning of biological evolution. The basic idea for such an endeavor was that any later developed replication mechanism for peptides and proteins would most probably not 'invent' its own new sequences, but rather reproduce peptide units already existing in nature. Hence, it should be possible to detect some kind of a 'fingerprint' for the reaction responsible for the evolution of the first peptides on earth in the proteins of primordial organisms. The recently reported existence of self-replicating peptides [29], which could have played an important role in protein growth and evolution before the appearance of the more efficient RNA/DNA-mechanism, seems to support this idea and to provide a transition stage in the evolution of biocompounds. It even allows one to think of a primary development of proteins forming cellular structures in which environment-sensitive bio-compounds as oligo- and polynucleotides could be formed and protected at a later stage of evolution.

Table 2
The yields of Val_2, Leu_2 and Lys_2 obtained within seven reaction cycles in the presence of Gly, His, Gly_2 and DKP

	Yields[a]		
	Val_2	Leu_2	Lys_2
Added amino acids			
Gly	0.92	0.07	0.10
His	0.82	0.04	0.26
none	nf[b]	nf[b]	0.09
Added peptides			
Gly_2	0.96	0.30	0.23
DKP	0.85	0.19	0.22

[a] Yields are given in % of initial amino acid concentration.

[b] nf, not found.

Table 3
Percentual occurrence of peptide linkages of hitherto investigated amino acids normalized to the value of 100 for the most frequent sequence of the SIPF reaction [a,b]

↓A, B →	Asp	Glu	Gly	Pro	Lys	His	Ala	Leu	Val
Asp	**5.8**	2.6	11.1	na	6.4	na	2.9	1.5	2.3
Glu	3.5	**12.0**	4.6	na	tr	na	tr	tr	nf
Gly	3.6	7.8	**100**	8.2	14.3	8.2	13.8	44.7	31.2
Pro	na	na	14.6	**nf**	na	na	23.6	13.1	1.8
Lys	16.1	tr	4.6	na	**4.0**	na	4.3	na	tr
His	na	na	3.8	na	na	**5.0**	4.9	2.9	20.2
Ala	5.6	3.8	18.3	3.8	9.7	12.9	**28.3**	3.0	17.8
Leu	1.7	nf	8.8	tr	na	3.0	4.1	**4.6**	5.8
Val	nf	tr	13.5	tr	tr	7.9	4.0	2.4	**14.6**

[a] Yields are given in % of initial amino acid concentration.

[b] na, not analyzed due to lack of generic reference compounds; tr, traces detected.

The fact that among all 'prebiotic' peptide synthesis reactions proposed so far only the SIPF reaction showed enough universality to investigate a sufficiently large number of amino acids, made it feasible to undertake the aforementioned comparison for the first time. The yields of homo- and heteropeptides from a number of amino acids achieved under identical conditions in evaporation cycle experiments are listed in Table 3 in the form of relative occurrence of the dipeptides. (For the homopeptides of Leu, Val and Lys, the yields obtained in the presence of small amounts of glycine have been considered.)

On the other hand, the membrane proteins of archaebacteria and prokaryonta have been analyzed with respect to the relative occurrence of peptide linkages between the same amino acids (data from [30]). In Table 4, coincidences of A-B and B-A sequences of the proteins with the corresponding sequences produced in largest amounts by the SIPF reaction are listed.

In the case of archaebacteria mostly 2–3 sequences coincide. This does not mean much for a single amino acid, where a single coincidence (based on the nine amino acids investigated) occurs with a probability of 4/9 in this comparison, a double with 1/6 and a triple with 1/21. However, the probability for the cumulative coincidence found for all 18 amino acid pairings A-B and B-A investigated is only 10^{-18} by chance. For prokaryonta in general, coincidences are still frequent, the corresponding 'by chance'-value is merely 10^{-16}.

These findings provide strong support for the assumption that the SIPF reaction has been indeed responsible for the production of the first peptides on the primitive earth and that, once created, peptide sequences have been conserved to a considerable extent in the course of further chemical evolution into the beginning of life and biological evolution.

Hence, as Cu(II) is essential for the occurrence of this reaction—no other metal ion investigated so far can replace it in the salt-induced peptide formation—a new and most important role can be ascribed to this ion, pertaining not only to some specific parts of biochemistry, but to the origin of life on earth as such.

Table 4
Coinciđences among the four most preferred peptide linkages of the SIPF reaction with those of archaebacteria (AB) and prokaryonta (PK)

Amino acid, A	Source	A-B linkage		B-A linkage	
		Amino acid, B	N.C. [a]	Amino acid, B	N.C. [a]
Asp	AB	Asp, Ala	2	Ala, Asp	2
	PK	Ala	1	Ala	1
Glu	AB	Glu, Asp	2	Glu, Asp, Ala, Gly	4
	PK	Glu	1	Glu, Ala	2
Gly	AB	Lys, Val, Gly	3	Ala, Gly	2
	PK	Gly, Val, Lys	3	Gly, Ala	2
Pro	AB	Gly, Ala, Leu	3	Gly, Ala	2
	PK	Ala, Gly, Val	3	Gly, Ala	2
Lys	AB	Ala, Lys, Gly	3	Gly, Lys	2
	PK	Gly, Ala, Lys	3	Gly, Ala, Lys	3
His	AB	Gly, Ala, Val	3	Gly, Ala	2
	PK	Val, Ala, Gly	3	Ala, Gly, Val	3
Ala	AB	Ala, Gly	2	Ala	1
	PK	Ala, Gly	2	Ala	1
Leu	AB	Ala, Gly	2	Ala	1
	PK	Gly, Ala	2	Ala	1
Val	AB	Ala, Val	2	Ala, Gly, Val	3
	PK	Val, Ala	2	Ala, Val	2
		Total AB	22	Total AB	19
		Total PK	20	Total PK	17

[a] N.C. denotes number of coincidences.

Acknowledgements

Thanks are due to the National Bank of Austria, Projects 5235 and 7054 and the Federal Ministry of Science and Transport, Project GZ 45.445/1-III/B/8a/99 for financial support, and to the Federal Ministry for Foreign Affairs for a scholarship granted to Yuttana Suwannachot.

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