

DYNAMIC CO-EVOLUTION OF PEPTIDES AND CHEMICAL ENERGETICS, A GATEWAY TO THE EMERGENCE OF HOMOCHIRALITY AND THE CATALYTIC ACTIVITY OF PEPTIDES

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Abstract. We propose a scenario for the dynamic co-evolution of peptides and energy on the primitive Earth. From a multi component system consisting of hydrogen cyanide, several carbonyl compounds, ammonia, alkyl amine, carbonic anhydride, borate and isocyanic acid, we show that the reversibility of this system leads to several intermediate nitriles, that irreversibly evolve to α -amino acids and N-carbamoyl amino acids via selective catalytic processes. On the primitive Earth these N-carbamoyl amino acids combined with energetic molecules (NO_x) may have been the core of a molecular engine producing peptides permanently and assuring their recycling and evolution. We present this molecular engine, a production example, and its various selectivities. The perspectives for such a dynamic approach to the emergence of peptides are evoked in the conclusion.

Keywords: α -amino acids, chemical energetics, chiro-selectivity, chemo-selectivity, dynamic co-evolution, energy, homochirality, hydrophobic-selectivity, peptides, primary pump

1. Introduction

There are some obvious arguments that are hard to circumvent, such as: no dynamics without energy, no evolution without dynamics, no life without evolution, which result in postulating the existence of dynamic co-evolutionary processes at the origin of life. More elaborate approaches lead to the same conclusions (Kauffman, 1993).



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For several years we thought to build a primitive molecular system that would allow a dynamic co-evolutionary approach for peptides and energy to be modeled. Our model now consists of a group of molecules {H₂O, HCN, R₁COR₂, NH₃, R₃NH₂, CO₂, CO₃HNa, B(OH)₄⁻, HNCO, NO, O₂} evolving in an thermodynamic open system composed by the solar system, in which the primitive earth occupies a particular place. The energy needed is that of solar UV, lightning from electric storms, and impacts.

The selected molecules, chosen from among the central molecules of prebiotic chemistry, continuously supply the system, and react with each other at different rates.

2. Experimental

The experimental conditions are described in the quoted references.

3. Results and Discussion

3.1. α -AMINO ACIDS AND RELATED COMPOUNDS FROM A MULTI-COMPONENT REACTION MODEL

We start, in Figure 1, with some of the essential molecules of prebiotic chemistry (water, HCN, Carbonyl compounds, Ammonia or amines, carbon dioxide and borates).

3.1.1. *Reversible Reactions*

The first reaction between these molecules is the formation of the α -hydroxynitriles (I). This reaction is very fast. It is followed by the formation of amino alcohols (II). These amino alcohols lose the OH⁻ anion to give iminium ions (III). These iminium ions react with the cyanide anion to give α -amino nitriles (IV). These α -amino nitriles then react with the initial carbonyl derivatives to give new α -amino alcohols (V). As before, these new amino alcohols (V) lose OH⁻ and, together with the cyanide anion, give α -amino dinitriles (VII), but, in competition with that reaction, the amino alcohols (V) also lose H⁺, leading to amino alcoholates (VIII, Béjaud *et al.*, 1975; Béjaud *et al.*, 1976; Béjaud *et al.*, 1976; Béjaud *et al.*, 1975; Taillades *et al.*, 1974; Taillades *et al.*, 1974; Taillades *et al.*, 1974). Carbon dioxide, when present in the medium, specifically reacts with the α -amino nitriles (IV) to give carbamic acids (IX) and carbamates (X) (Rousset *et al.*, 1980; Rousset *et al.*, 1984). Boric acid, when present in the medium, specifically reacts with the α -hydroxynitriles (I) to give boric esters (XI) and corresponding borates (XII, Jammot *et al.*, 1989; Jammot *et al.*, 1990). All these reactions are reversible.

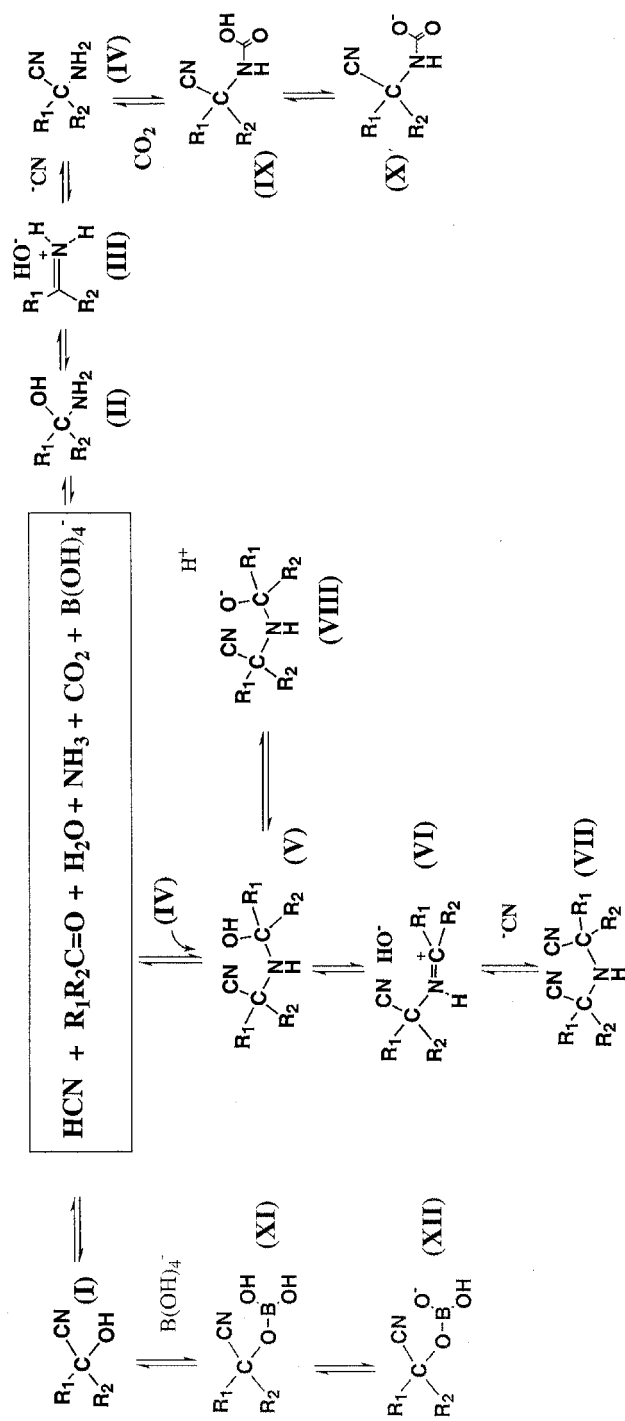


Figure 1. The initial system, made up of 6 compounds {H₂O, HCN, R₁R₂CO, NH₃, CO₂, B(OH)₄⁻} leads, at equilibrium, to all of the neutral or ionized molecules represented in this figure.

3.1.2. Non Reversible Reactions

In Figure 2 we examine the different possibilities for escaping from this reversibility. The first two possibilities are reactions (A) and (B). These reactions are the hydration of the nitrile functions by the hydroxide ion. These reactions lead competitively to α -hydroxyamides (XIIc) and α -amino amides (VIIIc). In the prebiotic literature they are known as the Strecker reaction* (Strecker 1850).

The rate constants for these reactions are low, and almost identical ($v_A \sim v_B = 710^{-6}$ [RCN]). In Miller-type reactions, in addition to these α -hydroxy amides (XIIc) and α -amino amides (VIIIc), imino diacids (VIIIb₃) are always formed. Miller intuitively considered the presence of these three compounds to be the signature of the Strecker reaction, without knowing the formation mechanism of imino diacids (VIIIb₃).

In addition to the reactions (A) and (B), we have discovered three new reactions (C), (D) and (E) which enable this system to escape from equilibrium.

The starting point for the first of these reactions (C) is the alcoholates (VIII). It leads to α -amino amides (VIIIc) via a reaction path that is catalyzed by the carbonyl derivatives (Pascal *et al.*, 1978a; Pascal *et al.*, 1978b; Pascal *et al.*, 1980). This reaction is chemically selective, and is part of the Strecker reaction. Indeed it is the most effective reaction path in the Strecker reaction. Its rate constant ($v_C = 0,3$ [RCN]) is very high compared with the previously mentioned reaction paths, (The rate constants are given for [RCN] = 1 mole·L⁻¹, to compare the different rates).

The second reaction (D) starts from the carbamates (X). It leads to hydantoins (Xc) via intermediary isocyanates (Xb). This reaction is also chemically selective. It is the Bucherer-Bergs reaction. Its rate constant ($v_D = 0,012$ [RCN]) is almost as high as that of the reaction (C) (Rousset *et al.*, 1980; Taillades *et al.*, 1986.)

The third reaction (E) starts from the borates (XII), which are used as catalysts. This reaction is also chemically selective. It leads to α -hydroxy amides (XIIc). Its rate constant ($v_E \sim 10^{-4}$ [RCN]) is lower than (C) and (D) (Jammot *et al.*, 1989; Jammot *et al.*, 1990).

All of the reactions (A) to (E) displace the species in equilibrium, preferentially to α -amino amides (VIIIc) and hydantoins (Xc), and less effectively to α -hydroxyamides (XIIc). It is a typical case of a kinetically controlled reaction process.

The amides (VIIIc, XIIc) and hydantoins (Xc) formed are hydrolysable. This hydrolysis leads to:

- α -hydroxyacids (XIId) ($v_{XIId} \sim 10^{-5}$ [XIIc]),
- α -amino acids (VIIIId) ($v_{VIIIId} \sim 10^{-5}$ [VIIIc]),
- and N-carbamoyl amino acids (Xd) ($v_{Xd} \sim 10^{-5}$ [Xc]).

* By referring to the experiments described by Strecker, the nomination 'Strecker reaction' was initially given to the synthesis of α -amino acids by acid hydrolysis of aqueous solutions of carbonyl compounds, hydrocyanic acid, ammonia. After that, the name 'Strecker reaction' was extended to all the experiment conditions (acidic and basic) using various reactional ways (A) + (B) + (C) figure 2.

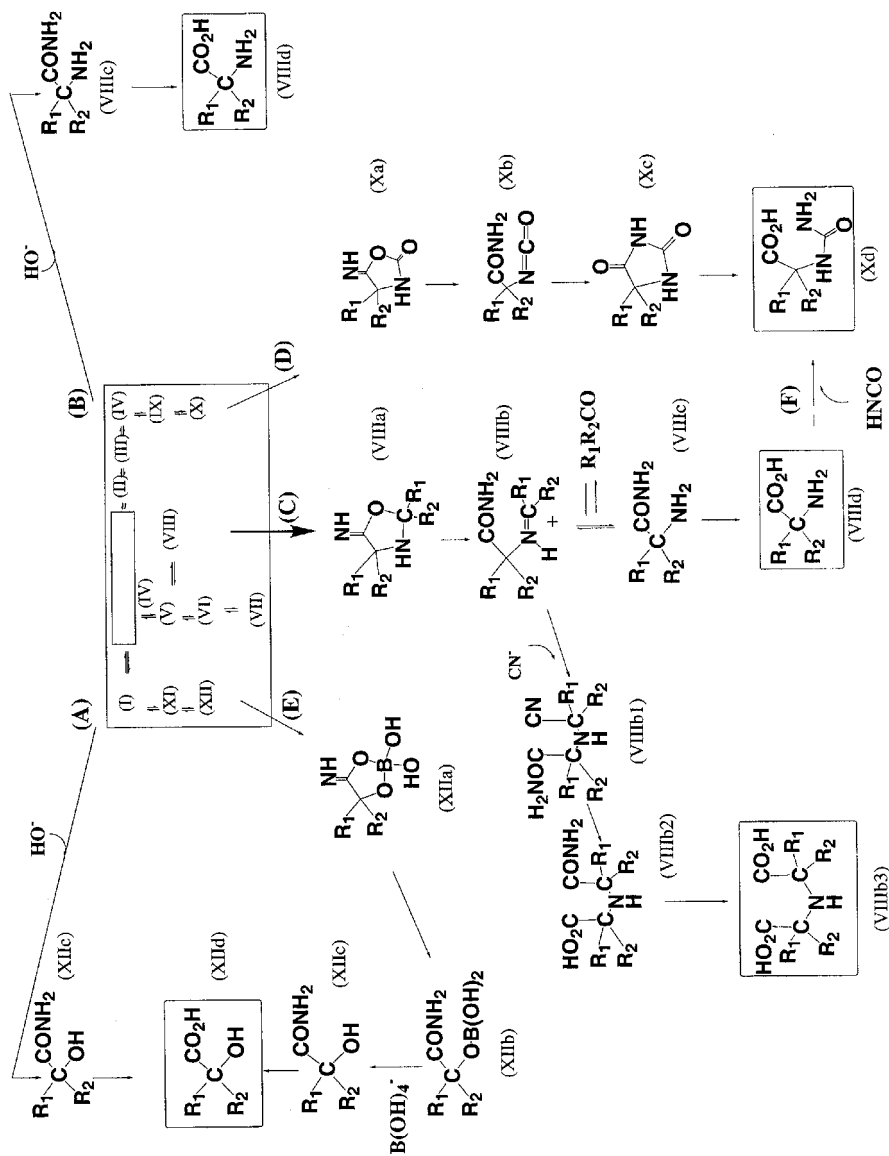


Figure 2. Five different and competitive irreversible reactions (A), (B), (C), (D), (E) enable the reversible system to escape from reversibility. The kinetics constants (see text) are only indicative. They are given for $[\text{substrate}] = 1 \text{ mole}^{-1}$ to compare the different rates. To take into account the information from 3.2, we have added the carbamoylation reaction (F), to this figure.

The rate constants of these hydrolysis reactions are low, and almost identical.

This means that the formation rate for these acids is kinetically controlled by the previously mentioned reactions (C), (D), (E).

3.2. CONSEQUENCES ON THE PREBIOTIC EMERGENCE OF α -AMINO ACIDS AND DERIVATIVES

According to Miller and others, the association of α -hydroxyacids (XIId), α -amino acids (VIIIId) and imino diacids (VIIIb₃) is the signature of the Strecker reaction, although the formation mechanism for imino diacids was unknown (Peltzer *et al.*, 1984).

When imino diacids were not found in meteorites, Cronin and Chang (Cronin *et al.*, 1993), while accepting that the Strecker reaction is the only way to explain the formation of meteoritic α -amino acids and α -hydroxyacids, wanted to understand why the imino diacids were absent. This question was by no means a trivial one. The status of the Strecker reaction rests directly upon it.

The answer to this question was provided by Narcinda Lerner (Lerner, 1997), Sandra Pizzarello (Pizzarello *et al.*, 2001) and Laurence Garrel (personal communication). Narcinda Lerner showed that the formation of imino diacids is only possible when the initial reagents (HCN, R₁COR₂, NH₃) are in certain proportions. Sandra Pizzarello showed that imino diacids are present in meteorites. Laurence Garrel showed that when the cyanide ion reacts on the imino amides (VIIIb), (intermediates in the catalyzed formation of α -amino amides through reaction (C)), imino nitrile amides (VIIIb₁) are formed, which lead to imino diacids (VIIIb₃) by hydrolysis. This reaction is catalyzed.

Consequently, we can conclude, as Miller anticipated, that imino diacids are secondary products of the Strecker reaction. These results confirm that the Strecker reaction is indeed prebiotic, and that it played a role in the formation of meteoritic α -amino acids and α -hydroxyacids. By extrapolation, we can consider after Miller that this reaction also played a role on the primitive Earth.

This reaction does not however explain the formation of meteoritic hydantoines. Yet hydantoines (Xc) have been identified in meteorites by Cooper and Cronin (Cooper *et al.*, 1995), and more recently by Shimoyama and Ogasawara (Shimoyama *et al.*, 2002). In order to explain the formation of α -aminoamides, hydantoines, and α -hydroxyamides in meteorites we must take in consideration (Figure 2) the compounds formed through the Strecker reaction (A+B+C), the Bucherer–Bergs reaction (D) and borates (E). This already complex global process needs to be completed by the action of cyanate (another prebiotic molecule) on α -amino acids (F). This reaction of cyanate on α -amino acids (reaction (F) Figure 2) quantitatively gives N-carbamoyl amino acids at pH levels between 5 and 7 (Taillades *et al.*, 2001), which are compatible with those of the primitive ocean (Mojzsis *et al.*, 1999). The rate of this reaction is lower than the rate of reactions (C), (D), (E). The consequence of this reaction, for the primitive Earth, is that the whole set of

reactions could have kinetically converged not towards free α -amino acids (VIIIId), but rather towards N-carbamoyl amino acids (Xd) (Taillades *et al.*, 1998). This reaction diagram is considerably more complete than the one (reactions (A) and (B)) generally used in prebiotic literature. These reactions become useful for the kinetic modeling of the formation of α -amino acids, N-carbamoyl amino acids, and related compounds on the primitive Earth.

3.3. PEPTIDES FROM N-CARBAMOYL AMINO ACIDS

According to George Wald's suggestions (Wald, 1957) the α -helical secondary structure of a growing homochiral polypeptide chain might ensure the selection of α -amino acids of the same chirality as those already present in the chain during its lengthening, thus preserving and augmenting the homochirality of the growing chain. These suggestions were proved by Idelson and Blout (Idelson *et al.*, 1958), Lundgbert and Doty (Lundberg *et al.*, 1957), by studying the polymerization of the NCA (in dioxane). Stereoselectivity was negligible at the simple peptide level and much higher for the α -helix at higher degrees of polymerization (around the octapeptide level) (still in dioxane). In the same paper George Wald said 'If one could grow such polymers in a reversible system in which synthesis was partly balanced by hydrolysis, the opportunity for selection would be greatly improved.' Obviously, George Wald was calling our attention to water, but since then not all activated amino acids studied in water have received the prebiotic status. For example Blair and Bonner (Blair *et al.*, 1981), studying the amplification of a small enantiomeric excess in Leucine-NCA polycondensation in dioxane, concluded that NCA is not prebiotically relevant. Liu and Orgel reached the same conclusion when they formed NCA in water through a carbonyldiimidazole activating molecule (Liu *et al.*, 1998). So George Wald's suggestions remain an open question.

3.3.1. *Molecular Engine*

In Figure 3, we propose a solution to this problem (Commeyras *et al.*, 2002; Commeyras *et al.*, 2001). The first step (**1**) is the formation of N-carbamoyl amino acids (see 3.1.2 and 3.2). These N-carbamoyl amino acids are stable in water

at the pH of the primitive ocean. The second step (**2**) is the concentration of these N-carbamoyl amino acids. This could have taken place on the shores of the Hadean continent, at low tide. In the dry phase, the NO_x in the primitive atmosphere (see 3.3.2), nitrosated the N-carbamoyl amino acids. These nitrosated intermediates are unstable and, through cyclization, lead to the NCAs step (**3**). This reaction is quantitative at ambient temperature. At the same time as producing NCAs, they form stoichiometric quantities of nitrogen, water and nitrous acid. The nitrous acid stabilizes the NCAs for several hours. If the NCAs stay too long in an acid medium, they are hydrolyzed into α -amino acids and recycled. When, step (**4**), the rising tide changes the pH of these NCAs back to between 5 and 7 (pH of the primitive ocean), then peptides form in a step lasting a few minutes (**5**) (this

change in pH is conceivable for tidal pools or lagoons). The peptides thus produced react with the cyanate, step (6), to give N-carbamoyl peptides. This reaction easily occurs at pH between 5 and 7. This reaction prevents subsequent elongation of the peptides. In water, the N-carbamoyl peptides slowly hydrolyze, step (7). This hydrolysis leads to shorter peptides, down to α -amino acids themselves. These peptides and amino acids are carbamoylated in their turn.

When these N-carbamoyl peptides arrive on the shore, they dry. We have shown that they are immediately unprotected by the NO_x (Collet *et al.*, 1999). This reaction, step (3') occurs under the same conditions as NCA formation. And, at the next high tide, the unprotected peptides get longer. The evolution of peptides could have been brought about by their partial hydrolysis and lengthening.

The formation rate for the peptides is fast, whereas their hydrolysis is slow. As a result, the peptides could have accumulated. When speaking of peptides, it is difficult not to associate homochirality with emergence (another of George Wald's hypotheses (Wald, 1957))

It is well known that the extraterrestrial input of α -amino acids was not totally racemic (see the work of Cronin and Pizzarello (Pizzarello *et al.*, 2000)). If these non-racemic α -amino acids played a role in the synthesis of peptides, (this remains to be proved), then these low enantiomeric excesses may have been amplified. Such amplification phenomena have been highlighted by Bonner (Blair *et al.*, 1980), but in organic solvents. Now, if chiral centers racemise more slowly in peptide chains than in isolated molecules (our recent unpublished results from L. Boiteau and G. Danger are consistent with this possibility), then the synthesis of peptides may have progressed towards homochirality. A lot of work still needs to be done to test this avenue of research.

3.3.2. NO_x: Reactivity and Origins

Concerning the reactivity of NO_x, figure 4 summarizes the reversible reactions between NO, O₂, N₂O₄ and N₂O₃ in the gaseous phase. The kinetics constants for the nitrosation of N-carbamoyl amino acids by HNO₂ in water ($k_{HNO_2} = 0.1 \cdot s^{-1}$), and by N₂O₄ ($k_{N_2O_4} = 1.7 \cdot s^{-1}$) and N₂O₃ ($k_{N_2O_3} = 1.0 \times 10^8 s^{-1}$) in the solid gas phase was measured, showing the very high reactivity of N₂O₃ (Lagrille, 2001; Lagrille *et al.*, 2002).

So, traces of N₂O₃ in the primitive atmosphere may have provided the energy for the molecular engine.

NO and O₂ could have different origins:

- for O₂: the photolysis of CO₂, abundant in the primitive atmosphere (Selsis *et al.*, 2002);
- for NO: volcanic lightning (Navarro-Gonzalez *et al.*, 2001; Navarro-Gonzalez *et al.*, 1998), impacts and meteors (Prinn *et al.*, 1987).

So the first ten kilometers of the primitive Earth's atmosphere could have contained non-negligible quantities of NO and O₂, with the best NO/O₂ ratios. This enables us to conclude that the NO_x energy of this molecular engine on the primitive Earth

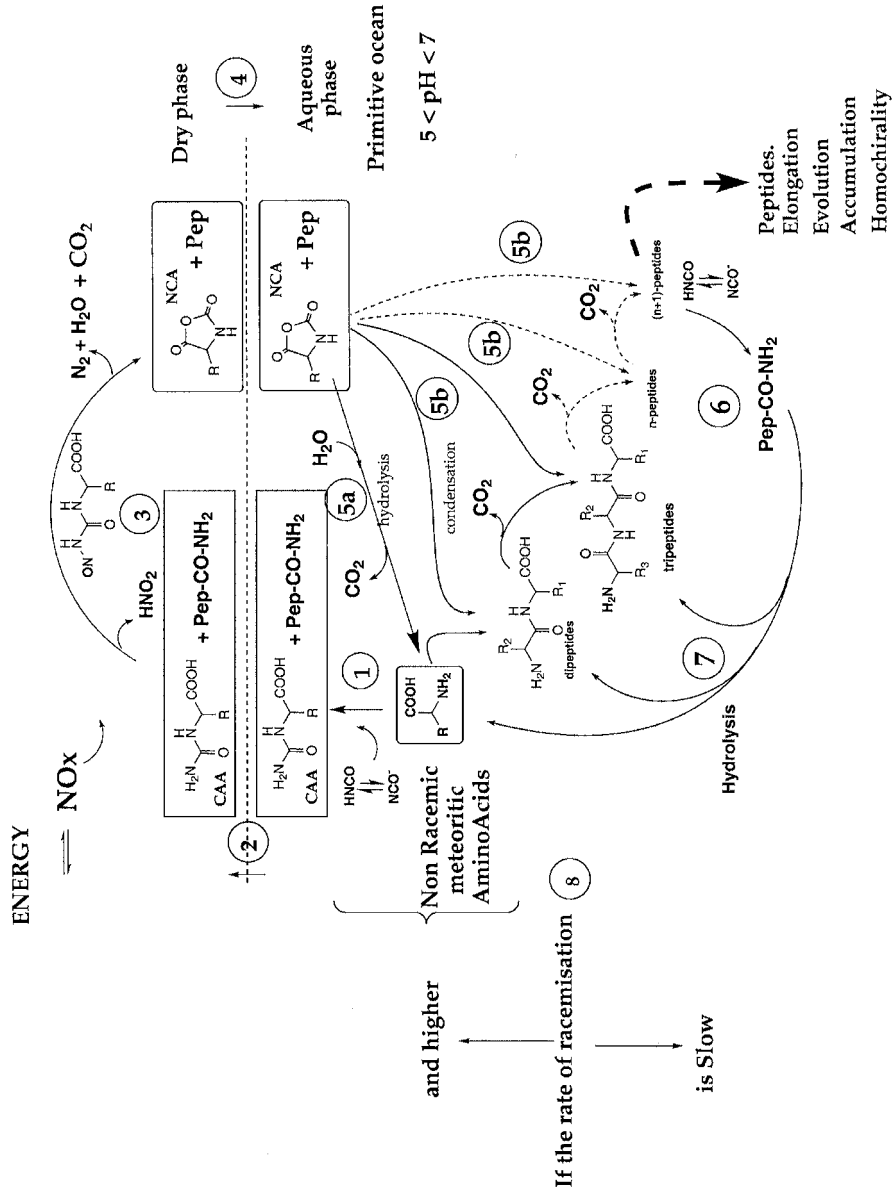


Figure 3. Molecular engine leading to the production of evolutionary sequential peptides, starting from N-carbamoyl amino acids and from CNO^- , NO , O_2 , HCO_3Na , H_2O .

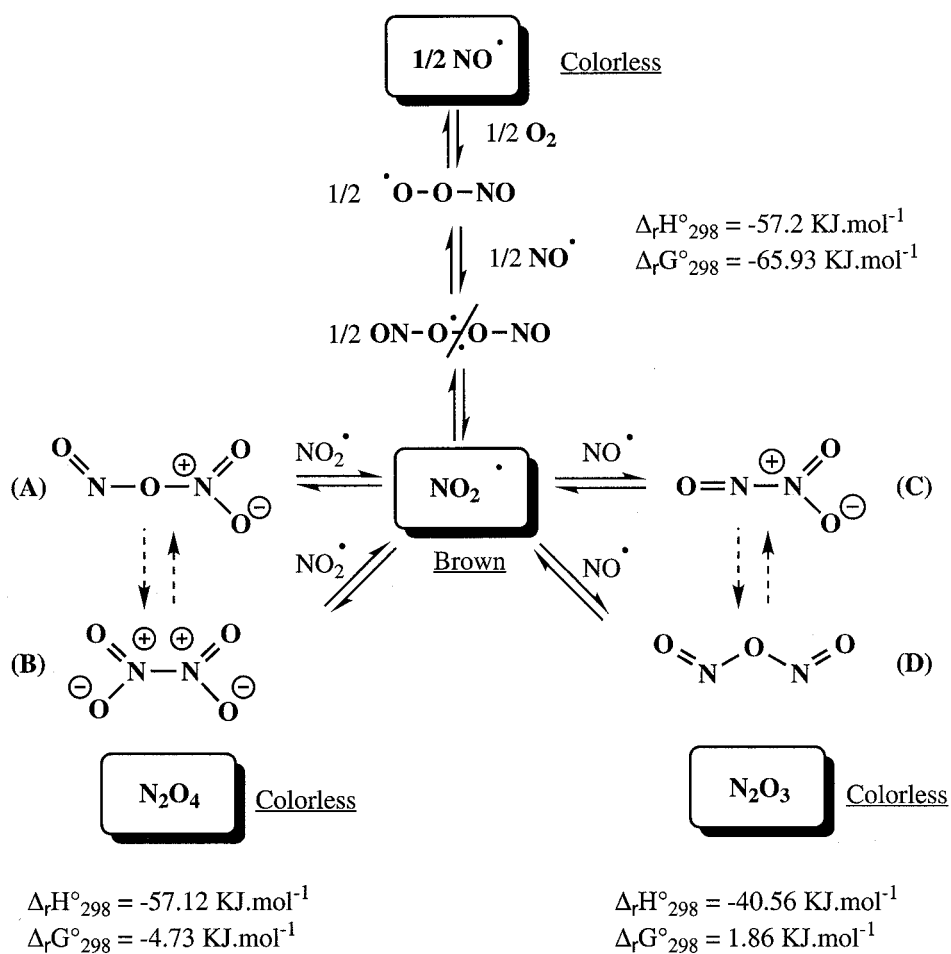


Figure 4. Equilibrium between NO and O₂ in the gaseous phase.

could have been a realistic possibility, even if complementary experimentation and modeling will be necessary in the future.

3.3.3. Details of peptide synthesis by the molecular engine

Having drawn up the plans of this molecular engine, we need to study each of the steps in detail. In this paper we draw your attention only to some details of peptide synthesis. NCAs in aqueous solutions undergo two competitive reactions during step (5), hydrolysis and condensation, with different kinetic laws:

$$v_{\text{hyd}} = k_{\text{hyd}}[\text{HO}^-][\text{NCA}]$$

and

$$v_{\text{condens}} = k_{\text{condens}}[-\text{NH}_2][\text{NCA}]$$

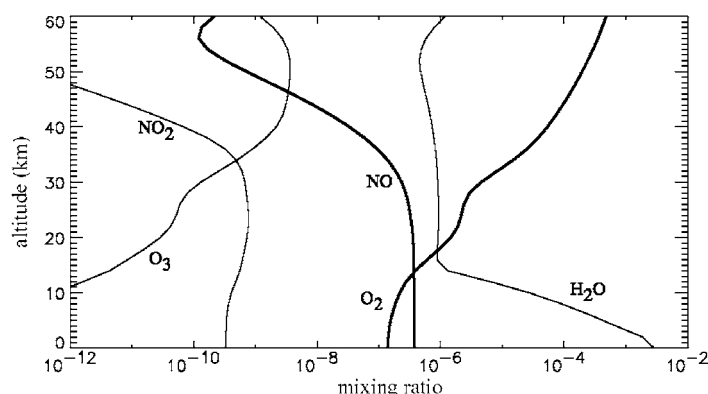


Figure 5. Simulation of a primitive atmosphere starting from an initial atmosphere of 1 bar containing 80% of N_2 and 20% of CO_2 including the NO production by volcanic lightning estimated by Navarro-Gonzalez *et al.*, 1998.

We took into consideration the work carried out by Bartlett (Bartlett *et al.*, 1957; Bartlett *et al.*, 1957), on the use of capillary electrophoresis. With this technique, we directly measured the hydrolysis rates of the NCAs and the formation rates of the peptides (Plasson *et al.*, 2002). Partial results for valine NCA give $k_{\text{hydrolysis}} = 4.40 \times 10^{-4} \text{s}^{-1}$ for hydrolysis, and $k_{\text{LL}} = 1.65 \times 10^{-2} \text{s}^{-1} \text{L mol}^{-1}$, and $k_{\text{LD}} = 1.14 \times 10^{-2} \text{s}^{-1} \text{L mol}^{-1}$ for the formation of Val-Val from L-val-NCA on L-Val and D-Val, respectively.

So, in water, the hydrolysis rate of the NCAs is low compared to the condensation rate. The condensation rate constant for K_{LL} is much greater than K_{LD} , and for the formation of dipeptide, the $K_{\text{LL}}/K_{\text{LD}}$ ratio is already much greater than 1. This ratio should be bigger for the synthesis of larger peptides (octapeptides and above), whose enantio-selectivity of the α -helix has been shown to be very high in organic mediums. Similar research concerning chiro-selectivity needs to be carried out and enlarged. In water, the formation rate of peptides is a function of their pKa and, paradoxically the PKa of peptides are not very well known. We (Plasson, Biron, Cottet, to be published) have developed a fast method for measuring pKa using capillary electrophoresis. This method is shown in Figures 6–8.

Figure 6 shows that the electrophoretic mobility of peptides depends on the pH.

From the electrophoretic mobilities, we obtained (Figure 7) the pKa of the peptides we studied. Figure 8 illustrates this with the example of the pKa of polyglycines.

From this information, we deduce, Figure 9, that in aqueous solution, at equal concentration, longer peptides (lower pKa) tend to lengthen faster than shorter peptides, by assuming that the kinetic lengthening constant is the same for all peptides.

This physico-chemical approach needs to be controlled by synthesis techniques because, in water, other parameters are involved in the lengthening of peptide

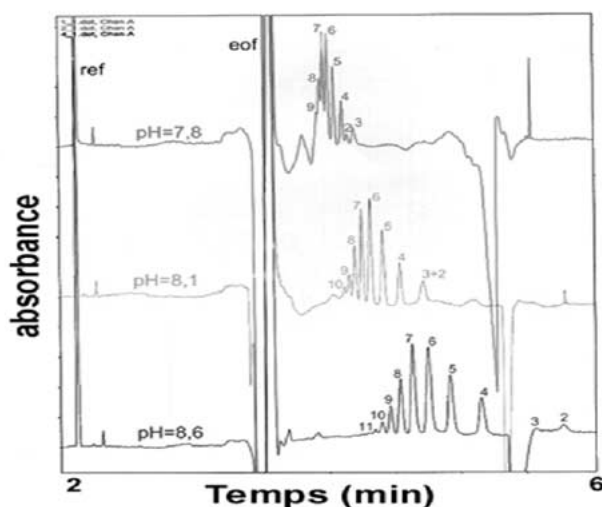


Figure 6. Capillary electrophoresis of polyglycines. Electrophoretic mobilities are pH dependent.

chains, and these parameters need to be understood. Figure 10 shows the results obtained by running the molecular engine with two amino acids: V and E. Many peptides are formed but not all of them (Commeyras *et al.*, 2002). Figure 11 shows the distribution of peptides formed in these experiments and a very effective chemo-selectivity during the lengthening process.

With four amino acids (V, E, G, A) as starting materials (Figure 12), MALDI-TOF analysis shows that the length of the peptides increases with the cycle number, but insoluble peptides are formed. The insoluble fraction (separated after 7 cycles) is made up of peptides whose molecular mass is distributed around 800 Daltons, whereas the mass of the soluble compounds is higher than 2000. So there is a selectivity process that is complementary to the others, due to hydrophobia.

The stimulating aspect of this point is that a stress (due to hydrophobia) eliminated the insoluble peptides. The only peptides capable of surviving (that is to say to evolve) were the soluble ones, in other words those that were best adapted to their environment. Note that the inappropriately adapted species, the insoluble ones, are completely recycled after hydrolysis (Commeyras *et al.*, 2003).

In conclusion we can consider that in aqueous solution, the described selectivities could have considerably decreased the number of peptides formed among the possible ones ($2 \cdot n^x$ with $n > 20$ and $x > 100$), and have thus made this synthesis realistic. Detailed analysis of these various selectivities will require considerable research investment.

3.4. ENERGY

The energy question is of primordial importance concerning the chemical evolution. The energy itself must have evolved. In the course of our research, we moved

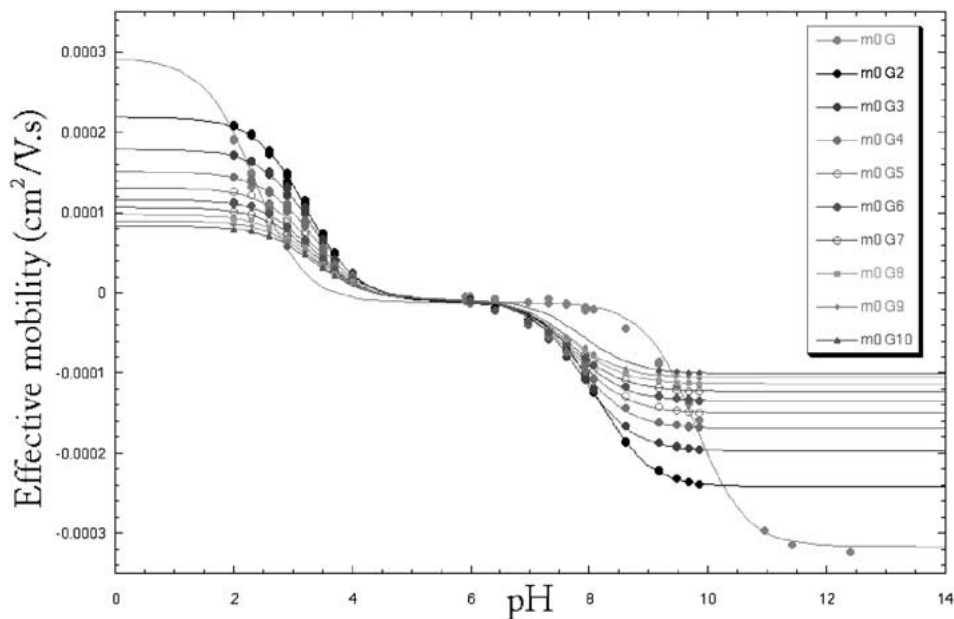


Figure 7. Electrophoretic mobilities of poly-glycine as a function of pH.

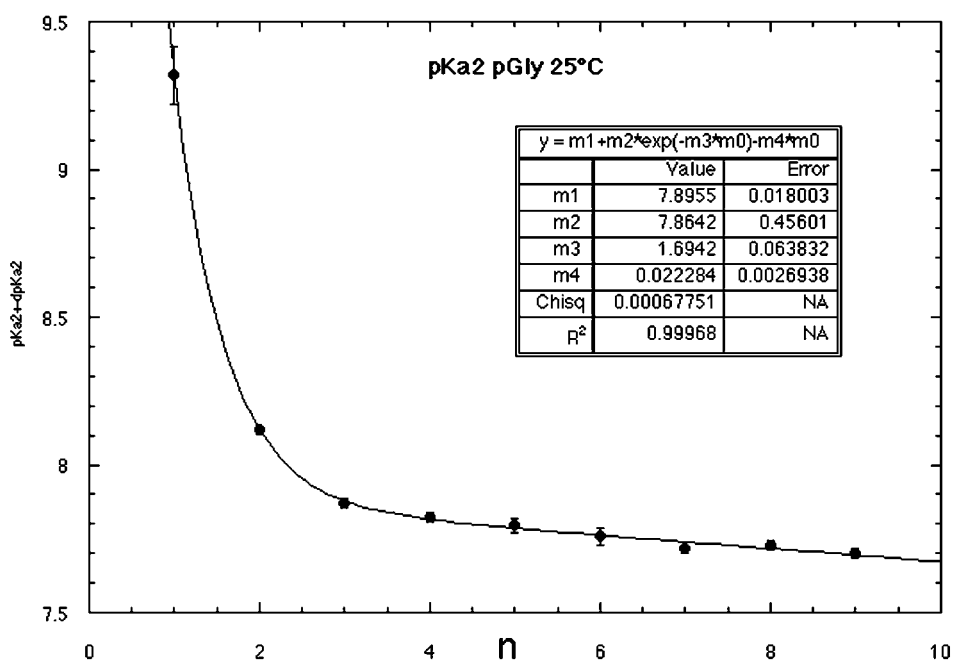


Figure 8. pKa of polyglycines from 1 to 9 residues.

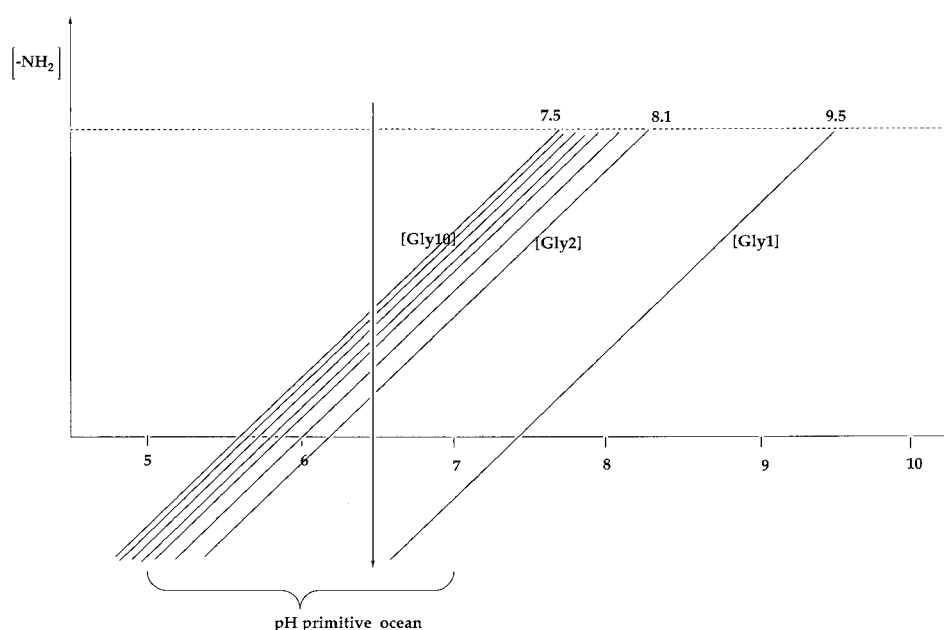


Figure 9. In aqueous solution, at equal concentration of peptides, the concentration of the non protonated amino group of the longer peptides (lower pKa) is higher than the concentration of the non protonated amino group of shorter peptides.

(Figure 13) from radiation energy to NO_x anhydrides. These NO_x, then evolved towards a second group of anhydrides, by which I mean the NCAs. Why not try to find a filiation between NCAs and ATPs?

3.4.1. Need for Kinetic Modeling

It is obvious that if we have this system evolving with too many carbonyl derivatives, it will make the model extremely complex, limiting experimentation. About 50 carbonyl derivatives are sufficient for studying the emergence of meteoritic α -amino acids, and terrestrial peptides. Nevertheless, the whole model will be a sizeable 'Multi-Component Reaction', and this MCR cannot be adequately dealt with by the techniques of combinatorial chemistry. To understand how this system can evolve, it will be necessary to use kinetic modeling. In this field, to construct a credible model, we must continue to study the mechanisms of these evolution and selection processes, and precisely determine the kinetics of the steps involved. That is the price to be paid if we seriously want to understand such a chemical evolution model.

3.4.2. Terrestrial energy

In order to work, the primary pump requires an alternation of dry and aqueous periods for instance on tidal beaches. This implies that both emerged continents and

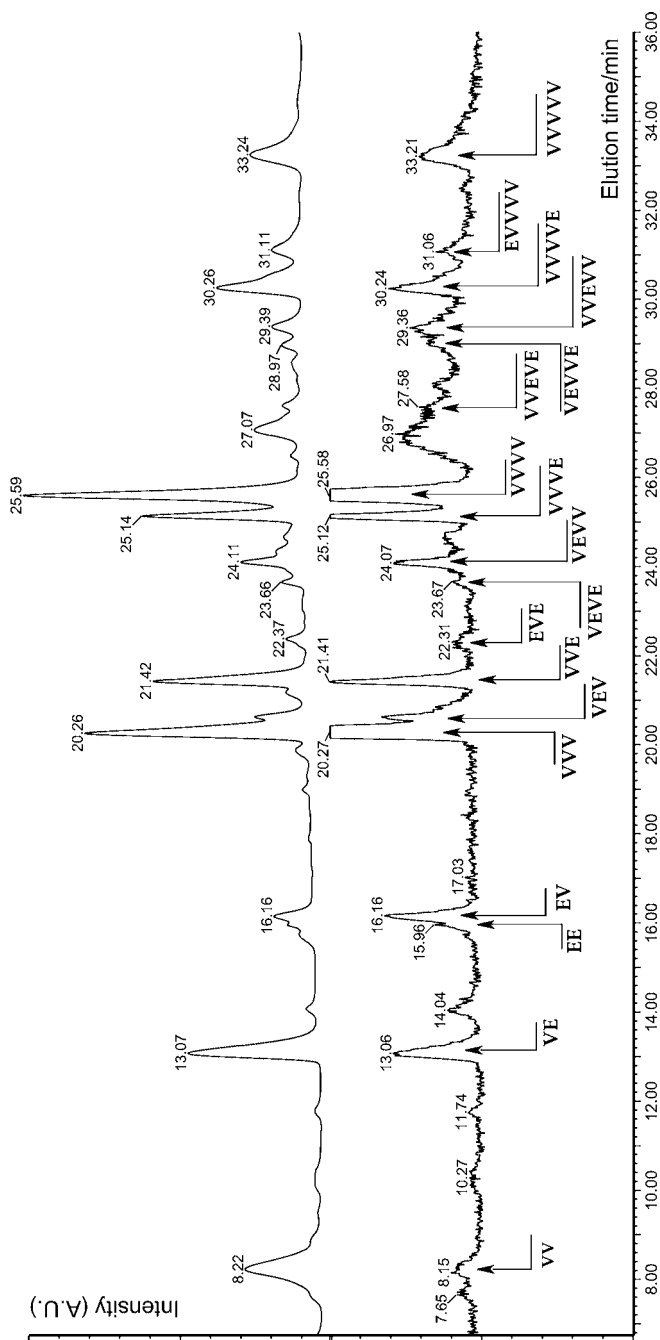


Figure 10. Molecular engine running with 2 amino acids Val (V) and Glu (E) (HPLC/MS/Q-TOF analysis).

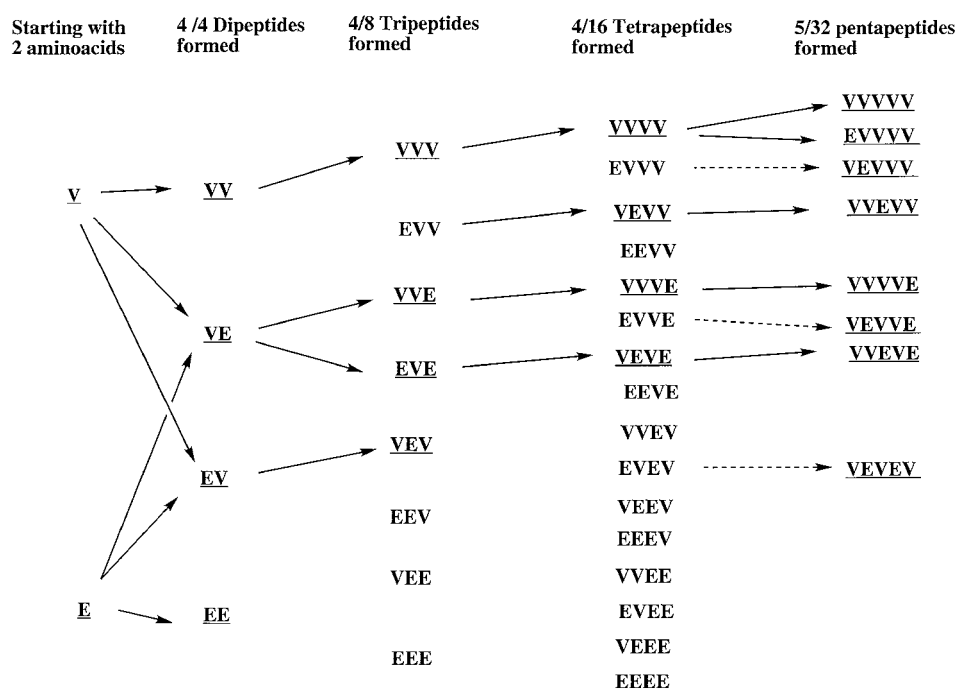


Figure 11. Chemo-selectivity during the formation of peptides from 2 amino acids as starting materials.

liquid water existed on Hadean Earth surface. Zircons crystals extracted very recently from Jack Hill metaquartzites (Australia) were dated at -4.404 ± 0.008 Gyr. Their chemical characteristics demonstrate that they formed in continental crust and that their host rock reacted with liquid water (Mojzsis *et al.*, 2001; Wilde *et al.*, 2001), thus demonstrating the existence of Hadean sea and continents. Continents formed from Earth mantle through partial melting processes and emerged due to plate tectonic activity. Consequently, in addition to chemical energy, an terrestrial source of energy was also required in order to allow Primary pump efficiency: this energy was not directly in the chemical reactions, but it initially created favourable conditions for their development.

4. Conclusions

To summarize, we have presented a scenario for the dynamic co-evolution of peptides and energy. This scenario is not necessarily the right one, it is chemically original, and could complete the previous scenario of asymmetric synthesis essentially of theoretical nature reviewed by De Min (De Min *et al.*, 1988). Over the course of these developments, we hope to open up a gateway to the emergence of homochirality and catalytic activities of peptides (Pascal, 2003).

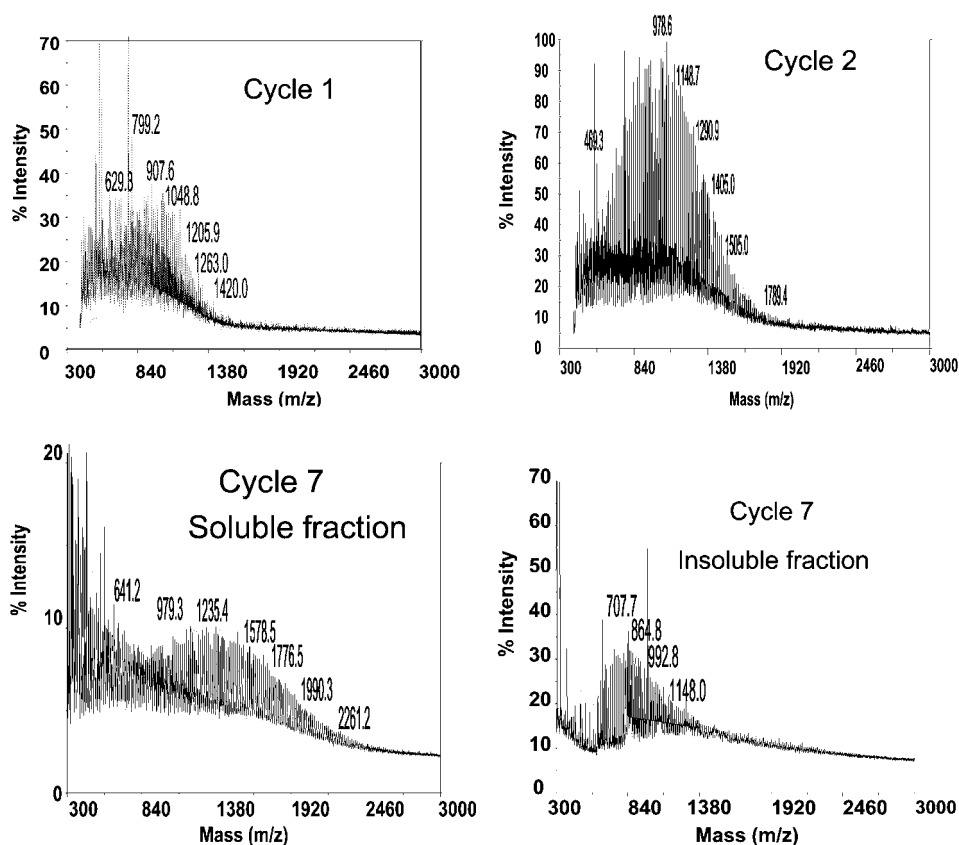


Figure 12. The molecular engine was run with 4 amino acids (V, E, G, A). MALDI-TOF analysis for the peptides formed is given for the cycle 1, 2, and 7 (soluble fraction and insoluble fraction).

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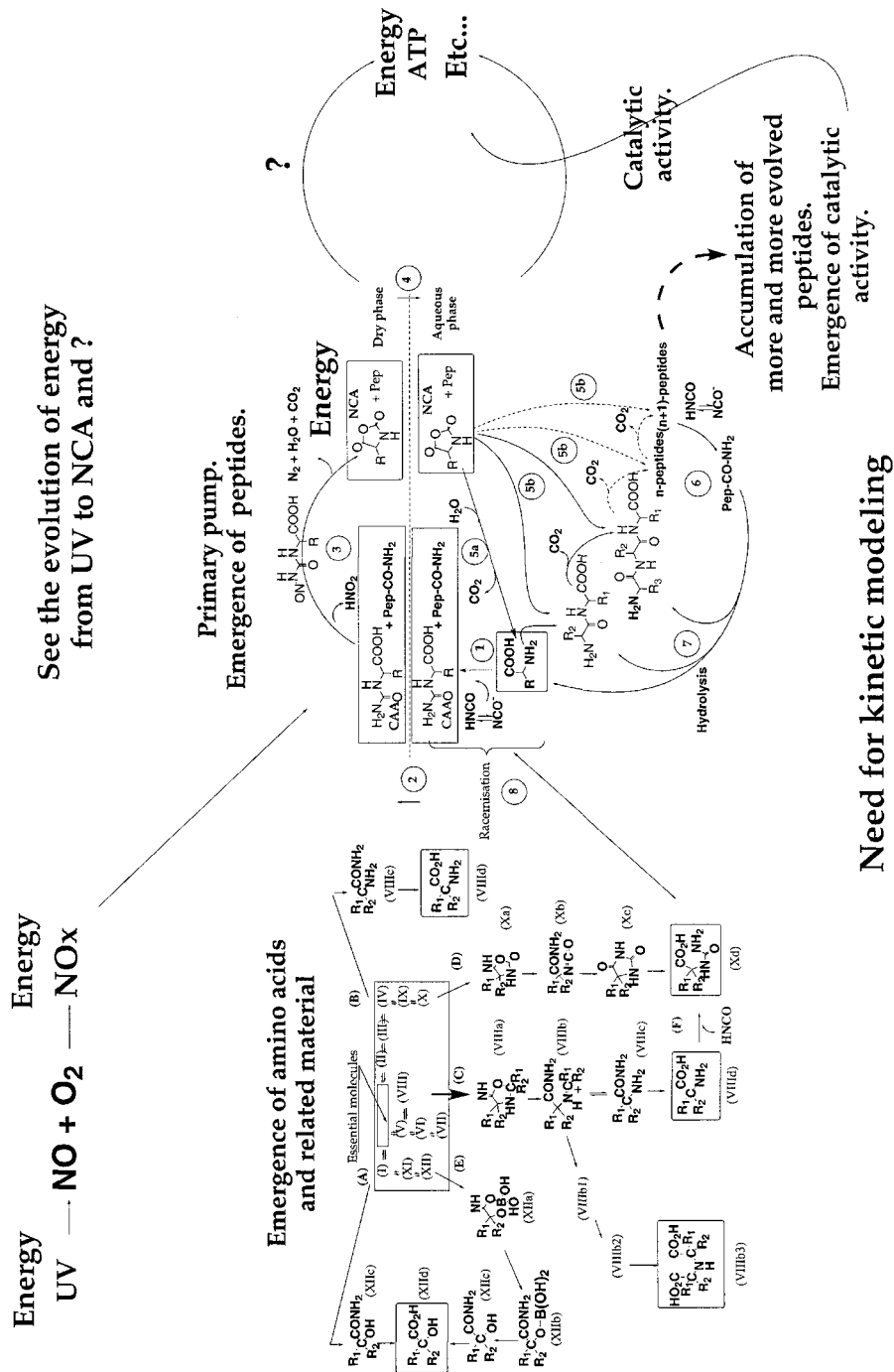


Figure 13. Global view of the molecular engine, fed with matter and energy.

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