Prebiotic macromolecules and today's biomacromolecules in the light of polymerology

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Abstract:

The appearance of life and thus of biomacromolecules on Earth is related to the presence of small organic molecules, polymerized under prebiotic environmental conditions. However, none of proteins, polynucleotides or polysaccharides taken individually is a true biomacromolecule, because biomacromolecules result from mutual involvements in complex biological processes. Logically, the biomacromolecules involved in the first living cells were first macromolecules formed under early Earth environmental conditions. The appearance of such living cells required macromolecules with fundamental features like controlled synthesis and structures, compatibility with aqueous media, chirality, memory, replication, and recycling that had to respect corresponding fundamentals of polymer science referred to as polymerology. After a recall of relevant basics of chemical reactions, the prebiotic appearance of macromolecules is critically compared with today's polymer science including chirality, stability, degradation, and recycling. Instead of providing arguments in favor of consistent routes to the first biomacromolecules, the reference to polymerology emphasizes obstacles that complement those occasionally found in the origin of life literature. In front of this conclusion, the discussion is extended to the other ends of these routes, i.e. today's biomacromolecules. The comparison with polymerology emphasizes the pertinence of the natural choices that led to the outstanding smartness of biomacromolecules. Polymerology is still in its cradle after less than a century of existence. For the future, it is suggested to pay increasing attention to chiral, multimeric multifunctional macromolecules to enrich the population of smart polymers, to solve the problem of plastic pollution, and, maybe, to enlighten the mystery of biomacromolecules emergence under unfavorable conditions.

Keywords: prebiotic chemistry, origin of macromolecules, chirality, polymer science, biomacromolecules, origin of life.

1. Introduction

"Bang", a sudden event that may have occurred about 13.7 billion years ago is the favorite vision of the birth of the Universe proposed by astrophysicists under the form of a huge condensed energy that started evolving towards particles, atoms and matter to finally form galaxies, stars, and planets [1]. The origin of the Universe is still a matter of debate. Anyhow, the Universe is definitely very old compared with the formation of our planet, about 4.5 billion years ago [2]. Earth comes from extremely hot condensed matter. Only temperature-resistant inorganic compounds existed until environmental conditions became compatible with organic matter [3-4]. Chemical elements were available individually or combined as inorganic compounds: sulfur as depot from volcanos, carbon and oxygen probably as carbonates, phosphor and oxygen as phosphates, nitrogen and oxygen as nitrates, nitrogen and hydrogen as ammonium salts, for instance. In the early times, there was no oxygen gas and no water on Earth [5]. The origin of oxygen is often assigned to the activity of newly-formed protobacteria [6]. However such assignment faces a dilemma since these protobacteria and

chemical precursors needed oxygen to appear and multiply. As for water, it has been supposedly issued from the inner Earth or from space via meteorites [7-8]

It is reasonably assumed that prebiotic chemical evolution started with the formation of a first hydrosphere on Earth and then the appearance of organic molecules, followed by macromolecules. In the literature, the formation of prebiotic macromolecules is generally considered relative to the origin of life and thus to the availability of organic molecules like α-amino acids [9], sugars [10], and nucleotides [11]. The present understanding of prebiotic chemistry was recently discussed from the chemical engineering viewpoint [12]. The review emphasized the richness in speculations and the lack of experimental findings that leave the mystery total, despite the many attempts to raise the curtain. The authors took into account chemical and thermodynamic obstacles relative to the synthesis of high molar mass molecules under prebiotic conditions. The rest of the review recalls and discusses scenarios extracted from the literature, particularly those relative to polynucleotides. The prebiotic formation of polynucleotides and proteins was also discussed recently but in rather different terms [13]. In this critical contribution, some of the main chemical constraints affecting prebiotic chemical evolution towards these biomacromolecules were examined together with the notion of contingency seen as a very important organizing process subjected to chemistry. Kinetic control is assumed critically important to determine and constrain the prebiotic evolutionary process. It is also pointed out that the concentration threshold for prebiotic reactions is often not taken into account in the literature, particularly in the field of the fashioned prebiotic RNA-world. The general question of self-replication and the problem of homochirality are discussed but rather briefly. Like frequently in the origin of life literature [14-16], these two recent controversial discussions concerned the formation of proteins and polynucleotides. They agree to emphasize the existence of multi-parameter hurdles and constrains. In this domain, the main goal of scientists is finding feasible pathways from lab experimentations complemented by speculations. The explored routes are essentially based on organic molecules like α-amino acids [17], nucleotides [18], formamide [19], hydrogen cyanide [20], etc. An important particularity of living systems is confinement of biomacromolecules in closed spaces, the smaller being unicellular micro-organisms or cells organized in tissues that constitute plant and animal organisms [21]. Therefore, primitive cell-like compartments had to be formed during the prebiotic period in parallel to the formation of prebiotic macromolecules. The evolution of prebiotic chemistry had thus to follow two tracks, one of macromolecules, the other of self-assembling molecules such as lipids and other amphipathic molecules [22-23]. Plausible scenarios of what is called protobiology were reviewed with emphasis on the design, construction, and operation of protocell models [4]. Surprisingly enough, little attention has been paid to the fact that prebiotic precursors of the first biomacromolecules were certainly formed in parallel to or among many other macromolecules.

In this contribution which is an essay-like discussion and not a review, I wish to first consider the mysteries of macromolecules and biomacromolecules emergences on Earth with respect to the components of polymerology, namely chemistry, physical-chemistry, chirality, stability, degradation, replication and self-assembling that were all and together essential to end up to life. Indeed there is no reason to believe that present fundamentals of chemistry and of polymer science were different in prebiotic times, even if environmental conditions were largely different. In the absence of consistent clues to imagine the early time macromolecules that may have led to bioactive macromolecules necessary to form protocells, the other ends of the routes to macromolecules involved in living systems, i.e. today's biomacromolecules, were compared with polymerology. These unusual approaches made voluntarily broad and

multidisciplinary intend to favor facts over speculations, to promote cross-fertilization between origin of life, biology and polymers fields, and to propose perspectives for the future of the latter.

2. Chemical basics

When small organic molecules appeared on Earth regardless of whether they came from existing elements or from the Universe, any following step had to respect the basics of chemical reactions. Any chemical reaction leading to a new organic compound depends on the concentrations of reagents and on a rate constant k according to one of the typical reactions shown in **Figure 1**.

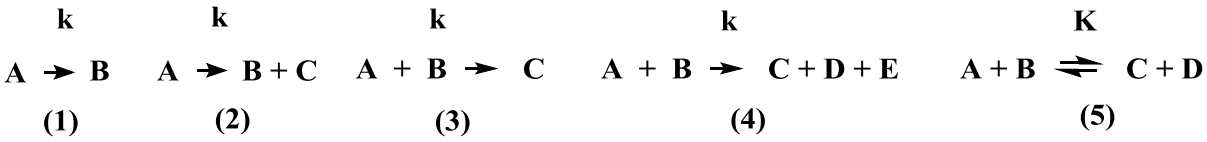


Figure 1: Typical chemical reactions in organic chemistry

The rate constant k gives the measure of fastness of a reaction. It depends on both the milieu and the temperature that conditions movements and collisions of molecules. The lower the temperature and/or the smaller the concentrations, the smaller the reaction rate is. Low temperature, low concentration and high dilution are thus unfavorable factors for chemical reactions.

Some reactions are unimolecular (**1**); others involve two or more precursors (**3-5**) or generate two or more products (**2, 4,** and **5**). In most cases an organic reaction leads to several products, including unreacted precursors. To reach high yields, purification of reagents is essential, especially in the case of successive reactions. Purification is relatively easy to achieve in a laboratory but it is difficult to imagine under outdoor conditions like in prebiotic environments. When they do not preclude a reaction, impurities lead generally to poor yields and to mixtures of more products and reagents when it is not to inhibition. In the absence of intermediate purifications, the probability of such detrimental consequences increases with the number of successive reactions.

Some reactions are reversible because of equilibrium between reagents and products reflected by the constant K which is the ratio of rate constants specific to the opposite reactions (**5**). To shift the equilibrium to full production, one of the products must be eliminated from the reaction medium by evaporation, crystallization, or extraction. If the concentration in one of the products increases independently by external supply, the reaction proceeds backwards and reagents are regenerated. It is often the case in condensation reactions like esterification in which the produced water limits the advance unless it is eliminated (**Figure 2**).

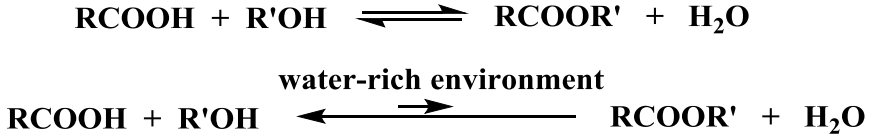


Figure 2: Equilibrium of ester formation by reaction of a carboxylic acid and an alcohol (top) shifted to the left in the presence of large amounts of water (bottom)

To be a monomer under prebiotic conditions, any prebiotic molecule had to respect these fundamental rules. Oceans are frequently proposed as sites of prebiotic chemistry. Formed in oceanic soups, soluble monomers could hardly avoid dispersion by dilution and were likely mixed with many other molecules and impurities. Atmospheric electric discharges are also proposed as source of organic molecules [24], but absence of mixtures is again difficult to imagine. Let us now see the role of these constrains with respect to polymerology as one can summarize it today.

3. Polymerology 3.4 billion years after the appearance of organic molecules

The concept of macromolecules was introduced by H. Staudinger less than 100 years ago [25]. Soon after, proteins, DNA and the first synthetic polymers were used to develop theories and identify the fundamentals of polymer science [26]. Year after year, the knowledge increased so that, today, one can talk of polymerology. Let us consider some of its components that may have played important roles on the route to biomacromolecules.

3.1. Macromolecule syntheses

Basically, there are three main routes to make macromolecules: chain polymerization, condensation polymerization, and modification of preformed macromolecules.

3.1.1. Chain polymerization

Chain polymerization is typical of unsaturated and heterocyclic monomers. It requires initiators to create the first reactive species that can be free radicals, anions or cations. Once the process of chain growth is initiated, macromolecules with different molar masses and dispersity are generally obtained because of different events: i) continuous initiation of new growing chains; ii) transfer reactions that initiate also new chain formation; and iii) termination reactions that stop chain growth. Under prebiotic conditions, isolated monomers were unlikely relative to mixtures. The addition of different monomers to a growing chain depends on the reactivity of each monomer. Accordingly, the intramolecular composition of copolymer macromolecules changes with time, a feature that favors diversity in compositions. Chains are enriched in units derived from the more reactive comonomer at the beginning and from the less reactive at the end of the polymerization. In prebiotic times, initiation, if there was any, could hardly occur in the absence of purification to eliminate terminating or inhibiting species.

- *the case of unsaturated monomers*

The chain polymerization of monomers with double or triple carbon-carbon bonds can be initiated by radicals, anionic and cationic species. The last two initiation processes require binding conditions difficult to satisfy, even in a laboratory. The prebiotic formation of radicals was possible and could result from chemical, thermic, photolytic or radiolytic cleavages of prebiotic molecules. To better control molar mass and co-unit distributions, polymer chemists have developed controlled radical polymerization techniques that could hardly be exploited under prebiotic conditions in the presence of water and oxygen [27-28]. Finally, only free radical polymerization in bulk or in aqueous media was reasonably compatible with prebiotic environmental conditions provided these conditions did not cause simultaneous dramatic degradation of the resulting macromolecules. Assuming radical polymerization possible, unsaturated monomers had to be present, pure and rather concentrated. Interestingly, calcium

carbide has been proposed as a mineral source of organic compounds [29-30]. Calcium carbide is formed at high temperature from calcium oxide and carbon, two minerals probably present at the stage of primitive Earth as results of volcanic activity. If so, calcium carbide remained stable until it came in contact with appearing water and generated acetylene locally according to a well-known reaction in chemistry. Therefore, acetylene is presently considered as a reasonable bridge between mineral and organic matters. Under anoxic laboratory conditions, ultraviolet irradiation of acetylene in the 185–254 nm UVC range led to hydantoin, 5-hydroxyhydantoin, the purines uric acid, xanthine, and guanine, and the pyrimidines uracil and cytosine. The authors concluded that an acetylene-containing atmosphere may have contributed to the origin of nucleobases. From the sole polymerology viewpoint, acetylene is also a source of many unsaturated compounds [31-32] suitable for free-radical polymerization and post-polymerization chemical modification, at least under laboratory conditions.

- *The case of heterocyclic compounds*

Functional strained cyclic molecules like lactones, lactams, oxiranes, thiiranes, etc. can lead to macromolecules by chain polymerization referred to as polyaddition in these cases. Free radical initiation is not applicable. The cycle is generally attacked ionically to yield activated opened species capable of reacting with another identical or different cyclic molecule. The process is a source of macromolecules with functions in backbones. However ionic initiation of heterocycles was unsuitable under prebiotic conditions, unless initiation and polymerization occur in a water-free closed space, a condition difficult to assume satisfied. Like in the case of unsaturated monomers, high purity is necessary to avoid termination reactions and to give access to high molar masses.

Polyamides can be synthesized by ring opening polymerization of lactams [33]. However α-amino acids that may be at the origin of proteins are exceptions because they dimerize rapidly to form cyclic diketopiperazines so stable that ring opening polymerization is not possible [34]. Avoiding cyclization was reported possible, but under drastic conditions [35]. In general, the chemical synthesis of poly(α-amino acid)-type polymers require complex processes based on cyclic carboxyanhydrides and high yield protection-deprotection steps in organic media incompatible with outdoor conditions [36].

3.1.2. Condensation polymerization

In condensation polymerization, bi-reactive and multi-reactive monomers are involved in a repeated condensation process that leads to linear and cross-linked systems, respectively [37]. Like chain polymerization, condensation polymerization does not lead to isomolecular macromolecules. Furthermore, stoichiometry in reacting groups is essential to end up with high molar masses. In practice, stoichiometry is difficult to achieve when complementary reagents are mixed. In contrast, stoichiometry is basic when both reactive groups are located on the same molecule like in hydroxy-acids or amino-acids. In any case, purity is a critical factor again. Reactive monomers must be exempt of any mono-functional compound that may generate inert end groups and preclude further condensation and chain growth. Condensation polymerization in water cannot lead to high molar masses when water is the released small molecule because the large excess of water acts against condensation. This route looks inappropriate, especially relative to the hypothetic ocean soup origin of organic chemicals.

3.1.3. Chemical modification

Almost any macromolecule can be chemically modified using suitable reactions taken from the panel of chemical reactions available in organic chemistry. For instance: i) additions can be performed on polyunsaturated macromolecules; ii) esterification or amidation can modify side-chain carboxylic acid group; iii) radical-based coupling can modify backbones, etc. Under prebiotic conditions, one of the problems was achieving 100% yield because in the case of macromolecules modified groups decrease the reactivity of unreacted ones when the modification advances. Another problem is related to side reactions. There is no possibility to eliminate the undesired modifications by distillation, chromatography or crystallization as organic chemists do with small molecules (Fig. 3 top). Therefore, in most cases, irregular new macromolecules of the copolymer-type are obtained (Fig. 3 middle) [38]. Under prebiotic conditions, the chemical modification of existing macromolecules may be seen as a means to create new macromolecules but it can also be a source of unsuitable perturbation of structures and properties of already existing ones, a dramatic possibility for precursors of biomacromolecules. On another hand, copolymers with more or less heterogeneous backbones resulting from copolymerization or from chemical modifications can be fractionated according to purification-like processes depending on outdoor conditions (solubilization or reactivity for instance) (Fig. 3 bottom right).

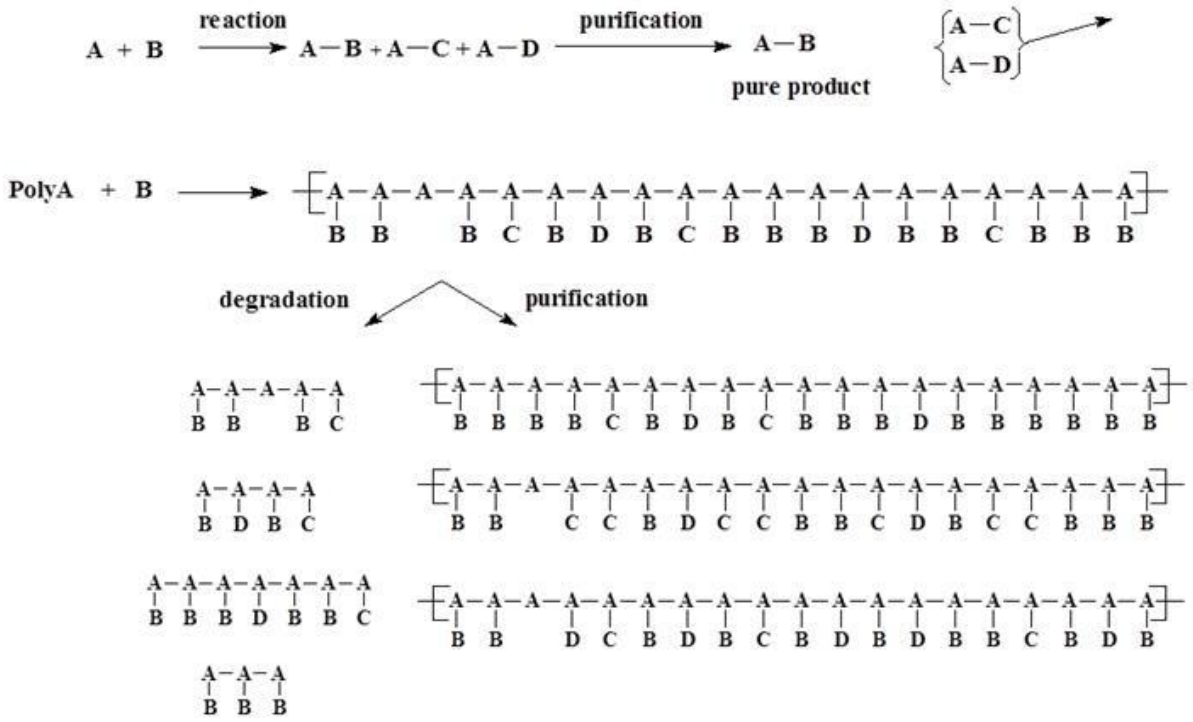


Figure 3 Schematic representations of the difference between the results of a similar chemical reaction with side reactions occurring in organic chemistry and in polymer chemistry (top) and of the consequences on the pool of resulting multimeric macromolecules of preferential degradation at weaker A(-B)-A(-C) inter-unit junctions that enrich in A(-B) units the resulting fragments (bottom left) and of purification-like fractionations that lead to new macromolecules and polymers of different structures and characteristics, including molar mass (bottom right).

3.1.4. Conclusion

Basically, there were chemical routes available to make prebiotic macromolecules under prebiotic conditions. However, polymerology does not provide any consistent clue to make macromolecules with specific, absolutely similar molecular characteristics, including the ordering of co-repeating unit distribution necessary for replication and, thus, for life. Ordering repeating units requires the control of unit introduction in growing chains, something which is still impossible in macromolecule synthesis, except by stepwise addition of units using complex protection and deprotection of reactive groups with the risk of uncomplete intermediate yield and of side reactions. The process is frequently exploited in polypeptide and polynucleotide syntheses [39-40], but seldom in the case of other polymers mainly because of the required tedious protection-deprotection stages [41-42]. Under prebiotic conditions, water was the sole or at least the most probable solvent medium in which the first macromolecules ended up once synthesized. Physical chemistry in this solvent was thus a key factor on the route to bioactive macromolecules.

3.2 Physical-chemistry

Despite the previous synthesis-related obstacles, force is to conclude that some prebiotic macromolecules appeared on Earth. In terms of physical chemistry, these macromolecules had to have, or to acquire, sooner or later, the main characteristics of today's biomacromolecules, namely solubility or nanodispersion in aqueous media. Many macromolecules are composed of hydrophilic and hydrophobic zones. Solubility in aqueous media is observed when solvation of hydrophilic zones is more energetic than inter-macromolecule interactions. This is the case when hydrophilic functions are present in the backbone and/or when functions like OH or ionized groups like COO- or R_3NH^+ or NR_4^+ are present in side chains [43].

Individually, polymers can be soluble, swollen, dispersed as micro or nanophase, or insoluble if inter-macromolecule interactions are strong. Inter-unit hydrogen bonds, ionic interactions, and van der Waals interactions are sources of weak interactive energy but strong macroscopic binding can be observed for derived polymers and preclude their solubilization because of cooperativity. Cooperative interactions between macromolecules can be set up or suppressed for very small changes of environmental conditions (pH, temperature, chemical composition and ionic strength in the case of oppositely charged polyelectrolytes). Such changes are exploited in pH-responsive, salt concentration-responsive, photo-responsive or thermo-responsive smart polymers [44]. Hydrogen bonds and van der Waals interactions are active at shorter distances than electrostatic ones. They contribute to the stability of conformations once electrostatic interactions are established if there are some, as it is the case in polyelectrolytes, where ionic interactions and ion condensation with dehydration of the ions depend on factors like pH, charge density, acid or base strength, concentration and presence of salt. A small change in salt concentration is a means to fractionate the components of a polyelectrolyte complex selectively according to charge densities and acid-base strength. When the salt concentration is high, polyanion-polycation interactions are precluded and complex formation can be fully suppressed. Such phenomena were normally available to select some prebiotic macromolecules from a pool [45].

Solutions of macromolecules are more or less viscous depending on concentration and conformation with, in addition, charge density and presence of salt in the case of polyelectrolyte. For a given molar mass, linear conformations lead to higher viscosity than coiled ones and much higher than hyper-coiled or globular ones. If different macromolecules are mixed, as it was possible under prebiotic conditions, phase separation is observed unless

concentrations are very low or if affine interactions exist like: i) hydrogen-bonds in polycarboxylic acid-polyether gels stable under acidic conditions [46]; ii) isotactic macromolecules with opposite tacticity [47]; and iii) homochiral macromolecules with opposite chirality [48].

In conclusion, the physicochemical behaviors of macromolecules in aqueous media depend on their structure and on environmental conditions. Minor changes in these conditions can cause cooperative changes of structures and of interactions. Under prebiotic conditions, differences in the physicochemical environments may have contributed to fractionation or separation of some existing macromolecules from multi-macromolecular mixtures.

3.3. Self-assembling of amphiphilic molecules and macromolecules

Amphiphilic small molecules interact to form various self-assemblies. Self-assembly can lead to micelles, sheets or also form vesicles (liposomes) that enclose an aqueous medium. Micelles are made of one layer whereas two layers are associated with hydrophobic tails facing each other in sheets and vesicles. Outer surfaces are composed of hydrophilic parts that stabilize dispersions. The ability of forming space-enclosing bilayer membranes is essential for life since a large part of the cell machinery proceeds within such vesicles (cells and organelles) [49]. Which amphiphilic compounds were available to self-assemble and form the first protocell? How such membranes could function as permeability barriers? These are two questions recently considered in the literature [50].

From the polymer viewpoint, self-assembled lipidic systems can be regarded as kinds of supramolecular polymers whose units are physically linked by hydrophobic tails interactions less energetic than covalent bonds but strong enough to fix the self-assemblies cooperatively. It is the case in cell membranes at body temperature. Physical associations of phospholipids are easily reversible by solvent, temperature or interaction with a polyelectrolyte [51]. Interestingly, liposomes made of unsaturated phospholipids were submitted to free-radical polymerization that, on the one hand, fixed the self-assembled structure and, on the other hand, formed patches of macromolecules [52]. Free radical polymerization involving unsaturated lipids was basically possible under prebiotic conditions. However, there is no residue of prebiotic inter-lipid polymerization in today's cell membranes despite the presence of unsaturated lipids.

Some amphiphilic macromolecules can also self-assemble to form macromolecular micelles, aggregates and vesicles (polymersomes). Weak interactions, cooperativity and reversibility drive the ability of macromolecules to self-assemble and disassemble in aqueous media. Di-block copolymers form macromolecular micelles, cylinders, bilayers, or vesicles depending on concentration and on structural and environmental parameters [53-56]. Comb-like co-polymer macromolecules with amphipathic structural elements do not form micelles or vesicles. They form aggregates of entangled macromolecules where hydrophobic segments interact to form lipophilic micro- or nanophases with hydrophilic segments located at the surface to ensure compatibility with water. Being not at equilibrium with unimers in contrast to micelles and vesicles, aggregates are much more stable in water. For some particular composition, comb-like macromolecules can collapse to hypercoiled polysoaps [57] or globular monomolecular conformations instead of forming aggregates [58]. Hydrophobic micellar cores, inner parts of bilayers, lipophilic pockets in aggregates, core of monomolecular globules are confined domains where water-insoluble lipophilic chemicals

can be accommodated with apparent solubility [59] Polymersomes can also accommodate hydrophilic molecules in their internal aqueous space and hydrophobic guests in the hydrophobic layer [60]. The temporary accommodation of molecules in lipophilic domains of amphiphilic macromolecular systems looks close to the behavior of transport proteins like albumin [60-62].

Like in the case of lipidic self-assemblies, confined domains present in self-assembled macromolecular systems can act as nanoreactors combining accommodation of reagents and catalytic activity [63]. The case of comb-like dibasic polyelectrolytes of the partially quaternized poly[thio-1-(N,N-diethylaminomethyl) ethylene]-type is remarkable. These co-polymer macromolecules are bifunctional with the presence of weak base (tertiary amine) and strong base (quaternary ammonium) functions pending from the same backbone. The presence of weakly basic amine groups is a source of variable charge density and hydrophobicity related to the protonation-deprotonation. When tertiary amine groups are deprotonated and for some degree of quaternization, the macromolecules collapse to form nanosized monomolecular globules with hydrophobic tertiary amine groups in the core and hydrophilic quaternary ammonium charges as stabilizing corona. Progressive protonation of tertiary amine groups in the presence of sub-equivalence quantities of acid destabilizes the globular conformation at almost constant pH because of simultaneous cooperative tertiary amine protonation and globule-to-open coil transitions, a process rather comparable to the denaturation of proteins [64]. The core of the globules can accommodate hydrophobic molecules like drugs [65]. Interestingly, it can also acts as a nanoreactor and accommodate hydrophobic carboxylic ester molecules, hydrolyze them and release the generated water-soluble carboxylic acid in the surrounding aqueous medium with rate increases as high as c.a. 3,000 times relative to the rate in the absence of polymer [66]. The hydrolytic activity was assigned to the presence of the amine groups within the core of the globules. When continuously fed, the globules exhibited a real enzyme-like hydrolytic action but so far without stereoselectivity when chirality was present in the globule [67]. Partially quaternized poly[thio-1-(N,N-diethylaminomethyl) ethylene] globules were even able to remove the protecting groups used to synthesize a polypeptide on Merrifield beads. The reaction occurred in water instead of in strongly acidic media [68]. Therefore, some synthetic macromolecules can show enzyme-like catalytic activity although this activity is still far from what is observed for enzymes involved in living entities.

3.4. Degradation

The routes to make macromolecules and polymers and the physical-chemistry of macromolecules in solution of man-made polymers have been extensively investigated during the last 90 years. Another important property for life is degradation. In general, macromolecules can be degraded by the action of aggressive environments like heat, electromagnetic radiations and individual or combined chemical reactions (solvolysis, aminolysis, hydrolysis, oxidation, etc.). Basically all these mechanisms were available once chemistry was established on Earth. Main chain degradation can occur through back-biting from a chain-end or through intra-chain cleavages. Both mechanisms lead to shorter segments, then oligomers, and finally small molecules that are not necessarily the initial monomers, a particularity that may have contributed to generate new chemicals on early Earth. Occasionally, degradation is limited to side chains with main-chain preservation. Detrimental to macromolecules and polymers, degradation, especially hydrolysis, was a key condition for the turn-over of the first biomacromolecules involved in protocells and for the biorecycling of the derived living matter.

C-C bonds present in hydrocarbon macromolecular backbones derived from double bond monomers are very stable. The cleavage of saturated hydrocarbon macromolecules requires highly energetic aggressions that encompass the cleaving potential of water, even in the presence of catalysts. If unsaturated functions are present like in poly(cis-1-4-isoprene), natural rubber, main chain double bonds can be cleaved or chemically modified but these macromolecules are not necessarily soluble in water [69]. In contrast, some macromolecular backbones obtained by condensation or by ring opening polymerization are repeatedly functionalized in main chains and are thus potentially hydrolysable if the intra-chain functions can be attacked by water with or without catalysts like acids or bases. Basically, it is the case for backbones composed of units linked by ester, amide, anhydride, urethane and some other groups. Today, some enzymes are able to cleave synthetic polymers but this is exceptional. There is no logical reason to believe that macromolecules presenting enzymatic activities were formed prior to any other prebiotic macromolecules. Therefore, prebiotic macromolecules could only be degraded by individual or combined actions of heat, radiation, oxidation and hydrolysis, once oxygen and water were present [70].

Whereas aromatic polyesters are stable in aqueous media, aliphatic ones are more or less sensitive to hydrolysis. Hydrolysis rates and fates of degradation by-products depend on many factors acting separately or jointly [71]. The hydrolytic degradation of poly(α-hydroxy acid)s has been extensively investigated because the exceptional structural characteristics of these polyesters provide means to adjust their material properties and functional duration to the requirements of specific temporary applications in various domains like surgery, pharmacology, environment, etc., [72]. In contrast, highly crystalline and hydrophobic poly(ε-caprolactone) [73] and poly(β-hydroxybutyrate), PHB [74] can last for months and even years in aqueous media in the absence of enzymes. This is an important property for PHB because this biopolymer serves as energy storage in bacteria, a function that requires hydrolytic stability. Bacteria use a specific depolymerase to degrade PHB rapidly [75]. Poly(β-malic acid)s are analogues of PHB with carboxyl-functions as pendent substituents and stereogenic centers in the main chain. These polyesters and many derivatives have been studied as hydrolytically degradable polymers from the viewpoints of polymerology and of biology as well since the poly[(R)-β-malic acid] is a biopolymer found in microorganisms [76]. Poly(malic acid) was also investigated as possible source of proto-proteins [77]. It was shown that synthesis is possible in solid state under alternating dry/hot and cold-wet cycles under different environmental conditions. However, the discussion did not take into account the chemical and chiral structures of the resulting small oligomers and their hydrolytic degradability identified in polymerology from synthetic and natural poly(β-malic acid)s [76, 78].

From a general viewpoint, the hydrolytic degradation of functional homopolymers depends primarily on the characteristics of cleavable functions, on the structure of inter-function segments and on the morphology of matrices. The hydrolytic degradation of copolymers depends in addition on the presence of zones with different reactivity. Preferential chain cleavage in the weaker zones of copolymer chains results in composition enrichments in favor of the more resistant zones and segments [79]. Therefore, hydrolytic degradation was a source of composition and properties changes for prebiotic macromolecules, at least basically. It was also a means to select some macromolecules from a pool containing degradation-resistant ones (Fig. 3, bottom left).

3.5. Chirality

Chirality is a property related to asymmetry in the spatial organization of groups of atoms and of conformations of molecules that results in non-superposable isomers. Chirality is also observed when non-planar 3D zones are blocked in space. Chiral isomers with one stereogenic center, generally a carbon atom, are called enantiomers whereas if two such centers are present the chiral isomers are referred to as diastereoisomers. From the chemistry viewpoint, two enantiomers have similar chemical properties except in the presence of an asymmetric reagent or an asymmetric environment. In contrast diastereoisomers have different chemical properties. In physics, chirality is related to the action on a plane polarized light composed of two opposite circular polarized lights to each of which correspond different refractive indices (optical rotation of the plan polarized light) and absorptions (circular dichroism). These chiroptical phenomena have been extensively used to investigate the conformations of small molecules and biomacromolecules [80].

According to chemistry the first chiral prebiotic molecules that may have served as monomers were necessarily racemic. In one way or another, deracemization or enantioselection was necessary to account for the appearance of optical activity in small molecule precursors of prebiotic biomacromolecules. Various possibilities have been proposed. The simplest hypothesis proposes that small molecules with enantiomeric excess came from space [8]. This is a possibility that may solve the problem on Earth but not at the Universe level. Another possibility is based on the unbalanced action of opposite circularly polarized lights on a chemical reaction. Such polarized lights may result from refractive or absorptive interactions with a birefringent crystalline mineral.

Synthetic polymers are chiral when stereogenic structural elements are present in some or all repeating units [81]. In the absence of defined stereo-ordered structures in solution, chiroptical phenomena can be used to monitor chemical modifications of optically active macromolecules, including ionization of polyelectrolytes and complex formation, even in the presence of achiral chemical species [82-83].

Polymer chains derived from substituted unsaturated monomers are sometime considered as chiral because of the presence of repeating units that look chiral locally. Actually, such macromolecules are only pseudo-chiral in the sense that they are not optically active because of intra-chain mirror image compensations. In contrast chiral macromolecules with enantiomeric excess are optically active and show optical rotation and circular dichroism phenomena. Research on the chiroptical properties of macromolecules was active several decades ago using biomacromolecules [80] and to a lesser extent chiral synthetic polymers [84]. Today, the domain is no longer attractive despite its obvious interest for biomacromolecules, and for synthetic smart macromolecular systems as well as previously emphasized in the case of degradation phenomena.

A particular source of optically active polymers and monomers is asymmetric enantiomer-differentiating polymerization of racemic feeds of cyclic monomers that leaves one enantiomer free [85]. But this process is conducted in organic medium and requires an enantiomeric chiral catalyst. Under prebiotic conditions, such catalyst could hardly exist but some chiral minerals may have played the role.

Among synthetic chiral polymers, lactic acid-based aliphatic polyesters are predominant because of their interest as degradable polymers in medicine and pharmacology. The enantiomers of lactic acid are largely exploited as sources of hydrolytically degradable

polyesters having different chemical, physical and material properties [86]. Homochiral monomers (homochiral lactides or lactic acids) lead to homopolymers composed of only one type of chiral units. In contrast, there is a multitude of chiral unit distributions in the case of stereocopolymer chains where the two enantiomeric units are present. Let us illustrate this multitude in the model case of 30-unit oligomers obtained by random condensation polymerization of racemic lactic acid. The number of stereocopolymers with different compositions is then 30!/(k!)(30-k!) where k stands for the number of equivalent units. k is 15 for a racemic feed whereas it is 30 for L or D-units only. The respective numbers of different distributions are then 30!/(15!) (15!) = 155117520 against 30!/30! = 1 for homochiral poly(L-lactic acid) and poly(D-lactic acid). Chirality in a polymer chain is thus a source of structure, property and performance diversification in addition to other factors typical of the polymeric matter like molar mass, molar mass dispersity, morphology, etc.

It is unfortunate that studying synthetic chiral polymers and their chiral properties is no longer a priority. The loss of interest is probably due to the fact that only few optically active synthetic polymers are commercially available and because syntheses may be rather tedious. Their interest as materials is also limited by the cost.

3.6. Conclusion

Small molecules issued from prebiotic chemistry may have served as meccano-kit to make prebiotic macromolecules. However, molecules susceptible to serve as monomers had to be present under conditions compatible with polymerology, i.e. rather high concentrations, high purity and suitable polymerization processes to end up with high molar mass molecules, something which looks unlikely presently. On the way to living systems, prebiotic chemistry had to solve many other problems that polymer scientists face regularly like controls of molar mass, molar mass dispersity, structures and functionality. In addition functionality duration and timing of macromolecule breakdown were also binding requisites for the beneficial controlled degradation required by living systems. In the case of equilibrated condensation reactions, hydrolysis was inevitably favored and normally precluded the formation of polyethers, polyesters and other molecules by dehydration. Condensation polymerization that involved activated hydrophobic monomers may have occurred at aqueous interfaces, but such reactions required the unlikely presence of a non-miscible organic solvent. Intervention of mineral initiators and catalysts is evoked in the literature, but these compounds also require purity. Polymerization of prebiotic monomers was proposed after adsorption onto a mineral surface [87] or absorption into porous minerals like mica [88] or clay [89] or zeolites [90]. However suitable monomers and catalytic minerals had to be present at the same place. The lipophilic core of micelles and the hydrophilic interior of vesicles are closed spaces that could accommodate monomers. However, chemistry tells us that concentrations in a closed space must be maintained high enough to allow collisions of precursors and formation of new products. Therefore, any closed space had to be fed continuously by monomers to allow chain growing again and again like in emulsion polymerization [91]. Physical chemistry and polymerology teach several important requirements: i) reagents must have affinity to the inner medium of the closed space; ii) the enclosing wall must allow diffusion between outer and inner media; iii) catalytic species must be present in the inner part or able to diffuse prior to the monomer(s); iv) the produced macromolecules must be soluble in the outer medium and able to cross the wall to diffuse outward [92]. Analogous obstacles exist in the case of adsorbed macromolecules and of absorbed newly-formed macromolecules that can hardly

leave the surface or the pores unless they undergo a chemical modification that minimizes the adsorption forces, or unless the outer medium is changed.

As it is today, polymerology does not provide any consistent clue to account for the appearance and the selection of macromolecules and thus of bioactive macromolecules under prebiotic conditions. This observation supports the doubts expressed in the literature relative to protein and polynucleotide prebiotic formation [12-13]. Today's polymerology fails to explain how simultaneous properties like stability, recognition, replication, reparation and recycling properties may have found natural solutions. Alternatively, biomacromolecules, the results of the mysteries, must be regarded as members of corresponding polymer families, namely polyamides, polyphosphates and polyethers, respectively, prior to be considered as macromolecules with biological activities.

4. Main characteristics of parent families of biomacromolecules

4.1. Polyamides

Polyamides are characterized by the presence of –CO-NH- amide functions in the main chains. Generally synthetic polyamides are homopolymers or copolymers composed of two different repeating units. Copolymerization is used to enlarge the range of properties and adapt them to meet application requirements. The properties of polyamides depend on the repeated hydrogen-bonded amide groups and on the segments in between. These segments are more or less hydrophobic depending on the number of carbon atoms intercalated between amide groups [93]. Repeated weak intra- and inter-chain H-bonds are at the origin of the excellent material properties of polyamides. Hydrophobic backbones complement H-bonds to make macromolecule interactions so strong that trifluoracetic acid, sulfuric acid or concentrated H-bond-breaking salts in alcohols are necessary to solubilize some of them. These structural particularities make polyamides insoluble in water unless some hydrophilic substituents are present in side-chains [94-95].

Oligomers of the glycine α-amino acid were reported as accessible abiotically. However it was by subjecting glycine monomers to ~40 h of supercritical water conditions at 270 °C and high 10 MPa pressure. Despite such drastic conditions only oligomers were obtained, with a majority limited to tetramers [96].

Some polyamides present in the literature are chiral. They generally derive from chemically modified α-amino acids to obtain di-carboxylic acids or diamines suitable to serve as monomers in condensation polymerization by reaction with complementary bifunctional compounds [33-34]. Optically active substituted polyamides were also made by ring opening polymerization of chiral lactams [97-98]. However, as mentioned in the previous section α-amino acids are not adapted to condensation polymerization.

4.2. Polyphosphates

Although polyphosphates play important roles in Biology, polymer scientists did not pay much attention to this kind of synthetic polymers. The precursor for polymeric phosphates is phosphoric acid (H_3PO_4), although there are also chemical routes based on phosphoric acid derivatives rather than the free acid. The main characteristics of diphosphate-type polyphosphates that correspond to the polynucleotide backbone are acidity and remarkable

resistance to degradation in aqueous media [99-100]. To the most of our knowledge, only very few optically active polyphosphates have been reported so far [101].

4.3 Polyethers

Polyethers are characterized by the -R'-O-R- functions in their backbone. They can be broadly classified in three categories based on the type of ether linkage present in the backbone, i.e. diaryl ether, aryl-alkyl ether, and dialkyl ether. The most extensively investigated polyethers belong to the first and the second categories. Polyethers are involved in many human activities [102]. Intrachain ether linkages can be generated by ring opening polymerization of epoxides or by condensation of diols. Repeated ether functions are sources of hydrophilicity and thus polymers with high ether densities are water-soluble as it is the case of poly(ethylene glycol)s and poly(ethylene oxide)s. If hydrophobic segments are intercalated between these functions, water-solubility requires the presence of hydrophilic functions in side chains. The ether link is chemically stable and requires rather drastic conditions to be cleaved hydrolytically. Many polyethers bearing chiral structural elements in main and/or side chains have been synthesized from epoxides [103-104] or from activated sugars [105].

4.4 Conclusion

If one characteristic common to polyamides, polyphosphates and polyethers is to be emphasized, it is certainly their remarkable resistance to degradation in aqueous media at neutral pH, a beneficial property for the integrity of biomacromolecule members that work in aqueous media, but a major inconvenient relative to degradation and recycling that are essential for biomacromolecules as they are today.

5. Biomacromolecules 3.5 billion years after prebiotic chemistry

As previously emphasized, today's polymerology does not provide any consistent clue to imagine how macromolecules and more specifically the first biomacromolecules were synthesized and replicated to allow the appearance of living entities. There are a few examples in the literature relative to self-reproduction of molecules but they can hardly be considered as pertinent with respect to polymerology and biology requirements [106-107]. To produce and replicate biomacromolecules, Nature called on complex macromolecular machineries that involve several types of chiral macromolecules interacting more or less in concert in the confined interior of cells. Let us consider the main ones in the light of polymerology.

5.1. Peptides and proteins

The backbones of peptides and of proteins are composed of α-amino acids linked together by amide bonds known as "peptide" bonds. The selection of a poly(α-amino acid) backbone for these polyamides is remarkable for several reasons: i) high density of amide functions and of side-chains; ii) regular head-to-tail enchainment of repeating units that provides regularity; iii) property diversification via side-chain chemical characteristics (aliphatic, acidic, basic, neutral, …) and roles (promoting hydrophobic interactions, solubility or insolubility, ionic interactions, etc.); iv) presence of stereogenic centers to enlarge the diversification and give access to a huge number of different polypeptides using the same backbone.

Poly(α-amino acid)s are copolymers derived from 20 α-amino-acids with achiral substituents. Since each of these α-amino acids can be included several times in a main chain, a huge number of different macromolecules can be formed as exemplified in Section 3.5 in the case of poly(lactic acid)s. Whereas L- and D-lactic acid are exploited by chemists, the poly(α-amino acid) part of protein backbones is based on L-enantiomers only, with rare exceptions depending on the living system. This limitation may look inconsistent since it decreases very much the number of combinations for a given gross composition. However, combined with the choice of regular enchainment of amide functions sources of intramolecular H-bonding, the choice of homochirality appears remarkable because it allows the formation of reversible ordered secondary structures like α-helices or β-sheets. These conformations depend on cooperative weak interactions that can be modified when external conditions like temperature, pH and ions or small molecules concentrations are changed [108]. Some sequences of units do not allow the formation of ordered secondary structures and correspond to flexible zones that contribute to the formation of tertiary structures with 3D-related specific properties.

According to polymer physical-chemistry, solutions of macromolecules are generally viscous and highly viscous if molecules are linear. The viscosity increases with concentration, molar mass, extended conformation and decreases when temperature increases. These dependences are problematic for dynamic phenomena like chemical reactions and flowing, especially when large molecules are used at high concentration like albumin and some other proteins in blood. To minimize viscosity, physical-chemistry recommends hypercoiled or globular conformations instead of extended chains. This solution was taken into account for some proteins. For instance the c.a. 68,000 Da albumin presents at ca. 40 g/L in blood has a condensed ellipsoid conformation particularly adapted to limit the viscosity and facilitate blood flowing.

A polyamide backbone was also a pertinent choice to provide stability in neutral aqueous biological media but it was also a major obstacle relative to life appearance. Life requires degradability to allow repairing, bioassimilation and biorecycling. As seen in the previous section, polymer chemists know how to promote and modulate the degradation of macromolecules, including by hydrolysis. However, they do not know how to control the initiation process and the duration [109]. Solving the stability/degradation dilemma required a particular and more complex process based on specific catalysts. The solution was brought by proteins with catalytic activity. From the chemical viewpoint, the synthesis of a macromolecular catalyst is a chemical process that requires time. In many instances, fast responses are required by some biological actions. Furthermore, hydrolysis has to be specific to respect the other proteins. The logical solution to shorten delays is to have a catalyst present, temporarily inhibited or dormant, and ready to be activated by removing the inhibition. This is exactly what some proteins, in particular enzymes, provide in present biology. To avoid any synthesis-related delay, many active proteins are present and inhibited or present in small amounts ahead of a buckle of amplification. Typical examples are the cascades of proteins involved in blood coagulation [110] and the non-specific immune system referred to as the complement [111].

Deracemization has been hypothesized as source of L-enantiomers of α-amino acids. Even if L-isomers were isolated, D-ones were still present on Earth and available to perturb any homochirality in polymers. To exceed these obstacles, Nature called on a much more sophisticated solution based on the involvement of other biomacromolecules, namely polynucleotides.

5.2. Polynucleotides (DNAs and RNAs)

In terms of polymerology, poly(2-deoxyribonucleic acid) or DNA is the generic name of a multitude of single and double-strand helical copolymers. DNA properties depend on many combined particularities: chirality; - presence of charges; - resistance to hydrolytic degradation; - ability for two similar but antiparallel DNA macromolecules to pair as double-strand helix; - reversibility of chain pairing; and, last but not least, - storage of information known as genetic code. DNA macromolecules have in common an oriented backbone of the polyphosphodiester-type composed of repeating units based on a substituted sugar, the D- (2-deoxyribose), connected by phosphoester links via the 3- and 5-hydroxyl functions of the sugar. The esterification of two of the three acidic functions present in phosphoric acid generates a single strand polymer chain and leaves one free phosphate group per repeating unit available for electrostatic interactions, making DNA a polyelectrolyte. Since two of the hydrophilic hydroxyl functions of the sugar part are esterified, the presence of electrostatic charges along the chain is essential to ensure solubility in aqueous media and to participate in the recognition of other chemical entities via long distance electrostatic interactions prior to more specific short distance ones. The chirality of each constitutive unit of single strand DNA is provided by the sugar and thus is unique despite the presence of several stereogenic centers. Homochirality, already observed for proteins, is essential for the formation of single and double helical conformations. Furthermore and like for proteins, side chains are achiral and the diversification of DNA macromolecules results from combinations of four different side-chains, namely cytosine (C), guanine (G), adenine (A) and thymine (T) bases, one per repeating unit. The structures of these bases are remarkable because they allow flat pairing by formation of cyclic H-bond interactions between A and T and C and G. The presence of associated bases in side chains and the possibility of 5'→3'/3'→5' antiparallel unit associations are exceptional in polymerology. Pairing allows the formation of the double-strand helix and isolates the bases from the outer medium and from other interactions than flat pairing although they allow intercalation of small molecules. In the double-strand helix the repulsion between pending ionized groups of the charged hydrophilic backbone and the attraction between H-bonded bases act against each other. Reversibility of the H-bond-based association is thus possible when local physicochemical changes or interactions with other species (proteins, small molecules, ions, etc.) act in favor of repulsion or association forces. Reversibility is essential for DNA dissociation and duplication. In the field of synthetic polymers, there is no example of association of two similar macromolecules to form double strain systems in solution.

In an aqueous medium, the very long negatively charged DNA macromolecules with several million g/mol molar mass would be the source of enormous viscosity, even in the presence of salt and of charge screening. To condense a negatively charged polyelectrolyte, polymer scientists make polyelectrolyte complexes with positively charged polycations. Though the partners and the results are much more complex, this is what is done in the cell nucleus where DNA is wrapped up onto positive histones to end up with nanometric particles involved in nucleosomes and chromosomes [112].

The second class of polynucleotides is composed of ribonucleic acids or RNAs. The chemical structure of RNAs is rather similar to that of DNA, but with two important differences. RNAs are based on D-ribose instead of D-2-deoxyribose, and the uracyl base replaces thymine, both bases having similar pairing ability. Among the members of the RNA family, the messenger RNA (mRNA) carries information from DNA to the sites of protein synthesis in a cell and determines the sequence of amino-acids in the produced protein macromolecule. mRNA is

transcribed from DNA and reflects the DNA coding necessary for ribosomes to synthesize proteins. According to this complex process, a coded polynucleotide chain is transcribed in a specific poly(α-amino acid) chain. Many other RNAs exist that do not code for protein. They play different roles (transfers, gene regulation and even catalysts (ribozymes localized in ribosomes for cutting and ligating other molecules) that depend on co-unit arrangements [113].

The mechanisms by which DNA, RNAs and proteins are produced or replicated are now well understood [114]. The replication of the precise unit ordering typical of a particular protein results from a complex machinery that involves other polynucleotides (polyribonucleic acid)s and also some proteins. Replicating a multimeric macromolecule like a protein implies the existence of a precise code to pick up the right monomer and add it to the backbone in formation via specific interactions. In polynucleotides, the coding memory is based on combinations of three of the bases or codons, one for each amino-acid. Homochirality is important in the case of proteins. It is essential for polynucleotides and their involvement in replications. If D-α-amino acids had been included in protein chains, more nucleotide-based codons and opposite sugar enantiomers had been necessary to control the distribution of diasteroisomeric units, thus resulting in plurichirality and directly penalizing pairing and secondary structure formation; not to say precluding life appearance. In contrast, plurichirality appears as an advantage in the case of carbohydrate-based biomacromolecules.

5.3. Carbohydrate-based polymers

Carbohydrates also known as sugars or saccharides are hydroxylated cyclic molecules composed of carbon, oxygen, hydrogen, and occasionally nitrogen. When two of the ring hydroxyl groups react with elimination of water, a disaccharide is formed where the two rings are linked by an ether bond also named osidic bond. If the process is repeated, polysaccharides are formed. Polysaccharides constitute a huge family of biopolymers of the stereo-copolymer type. The properties of the members of this family are differentiated through molar mass, ring conformation, inter-ring junction, side chains, chemical modifications of hydroxyl groups and chirality exploited in main- and in side-chains, including in branched and cross-linked networks. Because of the multitude of structures, polysaccharides are involved in many roles such as scaffolding (cellulose in plants and chitin in many animal shells), energy storage (starch and glycogen), and bioactivity (sialic acids that render negative the potential of the surface of cells, heparin, curdlan, etc.). The ether connections present in polysaccharides are very stable in water at neutral pH and enzymes are necessary to degrade polysaccharidic macromolecules. The biosynthesis of most polysaccharides begins with the formation of a nucleoside diphosphate glycosyl derivative from a nucleotide triphosphate and a glycosyl phosphate ester. Among the biomacromolecules, carbohydrate-based polymers present the particularity of fully exploiting the potentials of copolymerization and stereocopolymerization to provide multitudes of macromolecules and polymer properties based on the same type of backbones.

5.4. Biomacromolecules recognition and interactions

Life results from the formation and release of interactions between chemical entities among which biopolymers play exceptional roles. We have previously indicated that formation of macromolecules from soups of prebiotic chemicals was questionable since purity is a major requirement. However, small multimeric macromolecules may have been formed in these soups or in confined mineral spaces. If so, the question is then: what may have permitted the

necessary selections of precursors of biopolymers among the oligomeric components present in such media? A logical answer may be: "by specific interaction between complementary partners". In the physical-chemistry section, it was indicated that different polymers are generally incompatible and phase separate in solid state and in solution as well, unless weak attractive interactions are present repeatedly along the chains or if the concentrations of mixed macromolecules are very low. In polynucleotides, the phosphate negative charges are repeated regularly whereas in proteins the distribution of positive and negative amino acids generates charge density modulation. Peaks of charge densities may serve as first stage of recognition. Such a mechanism was proposed to account for heparin/thrombin interactions via the tri-sulfated pentasaccharide zone present in heparin and the lysine-rich zone in thrombin [115]. Once these long distance interactions are effective, the attraction can be stabilized by short-distance ones which are dependent on local chemical and configurational structures. Once appeared, prebiotic charged macromolecules were submitted to the physical-chemistry of polyelectrolytes and thus only some of them, those presenting suitable structural and electrostatic conditions, could form polyelectrolyte complexes. Complexation depends also on environmental conditions. Small changes of these conditions were also means to select some charged macromolecules from pools of uncharged or even weakly charged ones, a mechanism of selection available for the first poly(α-amino acids)s and polynucleotides. In addition, the homochirality of proteins and polynucleotides was highly favorable to the detection and recognition of different macromolecules as well as for base-pairing in DNA or amino acid-codon recognition.

5.5. Deracemization and homochirality

It has been shown that asymmetric enantiomer-differentiating polymerization of a racemic cyclic monomer can yield one of the chiral enantiomer enriched but this route requires a chiral initiator and an organic solvent. Polymerology offers other possibilities of backbone enantiomeric enrichment. Basically, deracemization is possible if one of the optical isomers is preferentially adsorbed onto an asymmetric crystalline surface [116] or absorbed into an asymmetric porous medium like chiral zeolites [117]. Such stereoselectivity is illustrated by the preferential adsorption of L-alanine from a racemic mixture in contact with l-(-)-quartz [118-119].

An interesting and original source of deracemization is based on the stereoselective degradation of chiral polymers. Indeed, the distribution of the enantiomeric units present in optically inactive chiral backbone includes homochiral segments in addition to heterochiral zones distributed according to polymerization-related statistics as observed in the case of racemic lactide [120] and α-amino acid carboxyanhydrides [121] ring-opening polymerizations. Sequences with opposite chiral structures have different lengths but same probability to respect the overall optical inactivity. Since diastereoisomeric heterochiral and homochiral segments have different reactivity with respect to cleaving reactions such as hydrolysis, thermolysis and photolysis, they are chemically cleaved at different rates. This phenomenon has been studied in details in the case of the hydrolysis of racemic aliphatic polyesters derived from lactic acid and lactides [122]. The preferential cleavage of ester bonds present in heterochiral domains respective to homochiral ones leads to residues enriched in equal amounts of opposite homochiral oligomers [123] The stereoselective adsorption of one of these isomeric oligomers onto a asymmetric chiral crystalline surface or absorption into a porous chiral mineral combined with degradation may leave the less captured oligomer free and available for chemical modification or degradation, thus for evolution. This mechanism of deracemization based on combined polymer degradation and stereoselective adsorption on or

into chiral minerals is, in principle, applicable to any chemically cleavable prebiotic racemic macromolecules. It has not been tested experimentally yet to the best of our knowledge.

6. Conclusions

Although the formation of chemicals that may serve as monomers was possible under prebiotic conditions, their evolution towards high molar mass molecules faced many obstacles in the light of today's polymerology. Fulfilling concentration, purity and absence of inhibition requirements may be relatively easy in a laboratory but very unlikely in ocean soups, in atmosphere, as well as on mineral surfaces or in confined spaces. As it is presently, polymerology does not provide any clue to imagine credible origins of macromolecules under prebiotic environmental conditions although macromolecules did appear. Some of the features typical of biomacromolecules, like chirality, reversible associations and selective inter-interactions in more or less salted and buffered aqueous media, stability and last but not least degradation, are currently investigated as parts of polymerology and exploited individually or in some concert to make smart polymers. However, coding, templating, controlled molar mass, unit dispatching, and degradation, all essential for replication and recycling, are still out of reach. The available knowledge accumulated in polymerology was collected from synthetic macromolecules composed of no-more than three co-units. Today there is no polymeric backbone that may lead to macromolecules as smart as biomacromolecules, i.e. combining controlled stereogenic centers, functional multi-repeating units based on a unique backbone, ionic groups, controlled molar mass and unit distribution, stability with degradation on command, replication and memory.

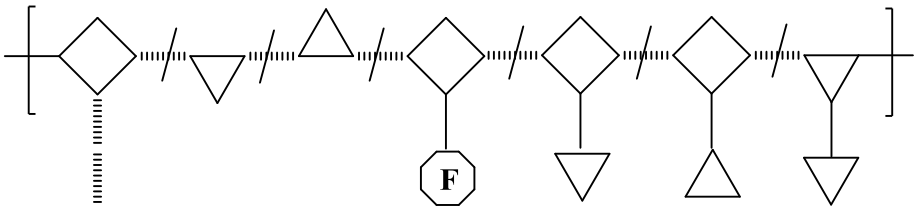
Polymerology is less than hundred years old and the study of artificial chiral polymers was scarce so far. In the future, polymer scientists should orientate their attention to multimeric and multifunctional chiral macromolecules of increasing complexity in parallel or in complement to the work done by chemists and biologists to find the prebiotic sources of biomacromolecules.

The case of the so-called "Artificial Biopolymers", i.e. synthetic degradable polymers and polyelectrolytes made of chiral metabolites exemplifies such strategies (See Table 1). Such polymers are already of interest for time-limited therapeutic applications [124] and environmental protection as well [125]. The family of lactic acid-based polymers is the archetype [126].

If one day the mysterious pathways that led from minerals to biotic macromolecules are identified, this will not be an end, since polymerology will have then to consider the mysteries of cells, then tissues, then organs and finally animals and plants formations, all based on macromolecular assemblies and composites. After the appearance of the first biotic macromolecules, cells (prokaryotes and then eukaryotes) evolved and organized themselves into multicellular forms; but it took a long time to reach large organisms. For ca. 3 billion years, life was mostly microscopic and simple. The evolution of animals, the Metazoans, as shown by the fossils of the Burgess Shale is a comparatively recent phenomenon [127]. According to today's visions, chemicals, including biotic molecules and macromolecules, that were involved in prokaryotes appeared within a period of a few hundreds of million years; then it took almost three billions years for cells to evolve up to the first multicellular animals which appear 600 million years ago, followed by complex animals like reptiles ca. 350 million years later, and finally by mammals 65 million years ago with humans rather lately.

The historical divergence between synthetic polymers and biomacromolecular sciences should be remedied if one wants to have a chance to solve the mysteries and maybe find on the way new smart polymers, macromolecular drugs (artificial macromolecules showing pharmacological activity), enantioselective synthetic enzymes, or new biomaterials as in the recent case of protein-based self-assembled hydrogels that showed unexpected advantages when D-α-amino acids were present in the poly(α-amino acid) backbone [128].

Table 1 Some structural elements available to make degradable and recyclable polymers composed of different metabolites repeating units linked through labile bonds and diversified by using various structural factors such as chirality, repeating unit distribution, substitution and functionalization : the so-called artificial biopolymers.



Metabolite-derived Units		Intra- and inter-chain labile links	Side-chain functional groups	Unit distribution	Main chain and side chain chirality	Sources of diversification
Achiral ◇	Chiral* ▽△	⁞⁞⁞⁞⁞⁞⁞⁞	F			
Glycolyl	Lactyl	Ester	Ester	Homopolymer	Homochiral	Hydrophiles
Alanyl	Malyl	Anhydride	Amide	Copolymer	Heterochiral	Hydrophobes
Glyceryl	Citryl	Amide	Amine	Multimer		Ionized groups
……	Lysyl	Phosphate	Carboxyl	Random		Ligands
	Seryl	Urethane	Hydroxyl	Blocky		Complexants
	……	Di-sulfide	……			Chiral entities
		……				……

* enantiomers

Acknowledgments: I am indebted to CNRS, University of Rouen, INSA of Rouen and University of Montpellier for personal and financial supports and to the numerous co-workers who contributed indirectly to the present essay by their contributions to studies of chiral and degradable functional polymers and polyelectrolytes.

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