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BIOGENIC BIPOLARITY
A NEW APPROACH TO THE ORIGIN OF LIFE

BY

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ABSTRACT

Involvement of electric bipolarity in the "sparking of life" which followed the breaking of the original, annihilating symmetry is reviewed in its evolutive span from nucleosynthesized atoms – with H the starter – to molecules – with the biogenic electric dipole H_2O – complexified into macromolecules and supramolecular self-assemblies. Intermolecular recognition mediated by H and other week bipolar bondings could have further driven life-like self-replications involving primitive bipolar codings by anticodonic doublets of nucleobases locked up by pH-controlled phosphoramide bondings, bypassing the nucleosidic stage in prenucleotidic, prenucleic infopolymers.

Key-words: Biogenesis, bipolarity, coding, prenucleic.

PROLOGUE

Polarity is a principle of wide interdisciplinary interest that we have attempted to survey in its whole span from 1989 to 1994. Its deep connection with the problems of Biogenesis has led us, since 1995, to switch our main interest to the enigma of the Origin of Life on the central assumption that it could be viewed as a result of the evolutionary superseding of primordial electromagnetic bipolarity by complexifying chemostructural biogenetic processes. We have therefore designed our Survey along these two parallel but interconnected axes: (1) the scaled precellular chapters of our 1994 book on Polarity, (due to space limitation, all citations drawn from it have not been referred); (2) our sequence of communications in the Archives of Sciences devoted since 1995 to the Origin of Life. In pursuing this goal, we have scanned the Evolution of the Universe from its inanimate start to its first animate expression, expecting thereby to have teleologically reduced the large gap between them.

I. ELECTROMAGNETIC BIPOLARITY IN THE PHYSICAL-CHEMICAL EVOLUTION

Following that start of the universal clock, the material Universe began to differentiate from the four previously unified basic forces of nature: (1) gravity was first to separate, followed by the tearing away of (2) the strong force (10^{-36} sec) and, only later (10^{-12} sec), that of the last two forces, previously united as electroweak symmetry; (3) electromagnetism – attraction and repulsion of electrically charged particles – carried by

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quanta of electromagnetic energy, the photons, and (4) the weak force controlling the radioactive decay.

1. The "radiation era" of photons

The inflation of the Universe triggered by the strong force was predominantly leptonic, namely filled with the low mass particles of matter, the electrons (-), and of antimatter, their antielectrons or positrons (+), bathed in a "sea" of probably massless neutrinos.

These primeval electric pairs of oppositely charged particles electrically symmetric could not stabilize because they were vanishing in a burst of pure radiation when their partners collided each other, thus returning to massless and chargeless original photons in a continuously reversible cyclic process. Such duality could never have been evolutionarily productive without the take-over of the light electrons+ (positrons) by the "giant" protonic particles, their first partners in atomic nucleo-synthesis (see I.3).

The electric particulate partners of these primordial, but evolutionless, dual couples, electrons (-) and positrons (+), have the same mass but opposite electric charge. They could only be created as diverging pairs if there was enough energy available to conserve momentum and provide mass according to the famous Einstein's equation of equivalence $E = m.c^2$ while when particles and antiparticles were free, they could annihilate each other when they collided, releasing a burst of energy in the form of ψ-rays.

2. The symmetry principle and its breaking

This principle of physical interactions, classically known since the work of PIERRE CURIE in 1894, is coupled with the weak force as an essential part of the laws of physical conservation. Three types of symmetry are known: C, or "charge conjugation", means changing particles for antiparticles, P or "parity", which means taking the mirror image (left and right are interchanged) and T, which points to reverse the direction of motion (backward) of all particles. It is satisfied when two different qualities are equivalent, as in the complementary "couple" matter/antimatter: charge symmetry implies that the antiworld with opposite charges is equivalent to ours (WEISSKOPF, 1969). This idea of antiworld and antiparticle arose from DIRAC (1929-30, see DAVIES, 1980) who made the bold suggestion that perhaps there are really two types of matter: ordinary particles like electrons, and "mirror" particles of antimatter. To each particle should correspond an antiparticle endowed with an equal mass but an opposite electrical charge: the matter atom of H is formed of a positive proton plus a negative electron while the antimatter antihydrogen is formed of a negative antiproton plus a positive antielectron or positron (HUGHES, 1991). It is expected that such an antiworld would look essentially like ours, but with opposite electric charges. If all properties of particles and antiparticles are completely symmetric the question therefore arises as to why our world is made of particles and not of antiparticles, and what happened after the Big Bang, so that only matter survived? The fact that the weak force shows important left-hand - right-hand asymmetries could be an answer to this universe's option for a lopsided, matter-dominated arrangement (von EGIDY, 1987).

To the question "Why then post Big Bang Universe should now contain more quarks than antiquarks, even if it started out with equal numbers of each"? It might then be answered that it is because there are forces that do not obey the symmetry T which points to reverse the direction of motion (backward) of all particles. The consequences would be that as the Universe expanded (hot early phase of the Big Bang), these forces could have caused more antielectrons to turn into quarks than electrons into antiquarks. However, as the Universe then cooled, the antiquarks would annihilate with the quarks and "since there would be more quarks than antiquarks, a small excess of quarks would have remained" (see HAWKING, 1990, p. 78). These quarks were those that made up the matter and thus our very existence would be regarded as a confirmation of grand unified theories (GUT).

The main crack in the edifice of perfect symmetry was LEE and YANG suggestion in 1956 that the charge-parity or CP symmetry might be violated in the weak interactions (see HUNTER, 1991). This mechanism and that of baryon-number violation have been extended in 1967 by SAKHAROV (see FREEDMAN, 1991) to explain skewing the Universe toward matter. However, SAKHAROV conceded there were few clues as to how these conditions of "charge-parity symmetry violation" have been met. One type of "CP violation" in specific particles decays had already been observed in 1964 by FITCH and CRONIN. More recent speculative scenarios about the origin of matter asymmetry have attempted to meet such clues relying on a version of the inflationary model of cosmology (DINE & MACLERRAN, 1991, in FREEDMAN, 1991). If such hypotheses had survived the test of experiment, the symmetry flaw of the weak force could well turn out to be "the crack through which the universe of matter emerged" (CLINE, 1993). Spontaneous symmetry-breaking is a property according to which a number of completely different particles at low energies are in fact found to be all the same type of particle but only in different state (WEINBERG & SALAM, 1967). Without it, all cosmic matter would have differentiated at expanse of indistinguishable mass-energy into distinct particles-antiparticles driven by separate forces during the first split-second of Big Bang material creation.

In his life-long "Dreams of a Final Theory", WEINBERG (1993) summarizes the story of the search for an ultimate "theory of everything" which leans on the recent superstring theory — superceding the simple string theory — an attempt to carry out Einstein's dream of unifying the theory of gravity with the theory of the three other forces of nature. The level of particle (electron–) antiparticle (positron+) asymmetry which determines the entropy, is not absolutely invariant. It occurred after the early instants of the universe, when the decay processes of proton were abundant. Since that remote event, a stable level of asymmetry between particles and antiparticles was eventually frozen and the predicted value became close to the observed asymmetry of one part in 10^8 (BARROW & SILK, 1980). Such rupture of original symmetry was generative of evolutive complementation rather than annihilation between dipolar electromagnetic charges in fitting with NIELS BOHR's quotation of his family's coat of arms: "Contraria sunt complementa" and thus was of fundamental importance for the evolution of matter and thereby of life in its primal sparking phase.

3. The "matter era" of elementary particles

The electron, the carrier of ordinary electric current, is a light-matter particle or lepton, which corresponds to one unit of electric charge (first measured by MILIKAN in 1911), one among the conserved quantities in nature to which can be attributed a symmetry considered by convention as negative.

Since 1925, it is known that every electron has a property called spin which became an important element in the development of quantum mechanics and atomic physics, particularly in the work of P.A.M. Dirac. A spin is the quantum number of electron. It makes this particle behave like a bar magnet, giving it a magnetic moment with north and south poles and, recently, many scientists believe that harnessing spin could push back the frontiers of information processing.

The proton, a heavier matter particle or hadron, was the unit of positive charge composed of quarks that are bound together by the exchange of massless gluons for which the biologist does not need (at least for now!) to consider its constituent quarks which have never been observed in the free state. It is in their allowed combinations that the fractional electric charges of these quarks add to yield the integral total charge 1+: the 2u (up) quarks have a charge of $+^2/_3$ while the charge of the d (down) quarks is $-^1/_3$; the charged proton has the quark composition uud thus giving it a total electric charge of +1. That positive electric charge carried by the proton is equal in magnitude but opposite in sign to that of its partner, the 1,820 times lighter electron (the rest mass of the electron is 1/2000 that of the hydrogen atom). Interestingly, the down quarks ($d-^1/_3$) can be changed into up ($u + ^2/_3$) quarks by the weak force. Consequently, another nucleon, the neutron (*udd*), can become a proton (*uud*) when the weak force changes one of its down quarks to an up (an electron and an antineutrino are also emitted in the process).

The transition from initial unconfined quark-gluon phase to the confined hadronic phase took place just after the Big Bang (t about 10^{-5} s). It could be explained by the gauge theory of strong interaction as described by quantum chromodynamics (QCD) in terms of quarks and gluons, a theory which explains the strong force by which quarks interact on the basis of their "color" (HARARI, 1983): while electrodynamic charge has only an alternate state — positive or negative — the color charge has three (red, green and blue quarks).

The central question remains of the nature of the two opposite electric charges. In first attempts to answer it, SCHERK & SCHWARZ in 1974 (see HAWKING, 1990) originally developed a string theory of the strong force which was then abandoned in favor of a theory based on quarks and gluons. This new, so-called heterotic string theory (SCHWARZ & GREEN, 1984, see HAWKING, 1990) proposed that the two charges +1 or -1 would result from a string deformation into knots, one (+) being perpendicular (up) to the string axis and the other (-) parallel (down) to it. The primordial positively charged knot was baptised quark by MURRAY GELL-MANN in 1963. It would be from the interactions between two differently or similarly oriented and electrically charged knots that would arise the attractive and the repulsive phenomena, respectively (see BOUNIAS, 1990). The electromagnetic attraction between negatively charged electrons and positively charged protons, has been more thoroughly pictured as being caused by the exchange of large

numbers of virtual massless particles of spin 1 (see C), the photons. By contrast, the repulsion between two electrons would be due to the exchange of force-carrying photons (see HAWKING, 1990). These similarly charged particles repel each other with a force inversely proportional to the square of their distances (COULOMB's law).

At the scale of elementary particles, there is symmetry within an atom only when it is regarded as governed by the electromagnetic force and its associated law of conservation of parity. This law states that the total number of right-handed particles and the total number of left-handed ones can never change. In the ordinary world of protons, electrons and similar particles, handedness or chirality clearly is not conserved and there is violation of the conservation law. The symmetry-breaking mechanism implies that the weak charge, and the associated handedness of particles, should only be conserved at extremely high energy, where a particle mass is a negligeable fraction of its kinetic energy (HARARI, 1983). Chiral asymmetry at the subatomic level is thus fundamentally connected to parity nonconservation.

It has been further considered that if only the magnitude of the electric charges of the electron and the proton were slightly different, the expansion of the Universe would be accounted for as a stroke. As EINSTEIN suggested in 1924, electrostatic repulsion would blow it apart. Anyway, the charge difference between electron and proton cannot be large, for that would force the Universe to expand more rapidly than is observed. It is therefore reasonable to admit that the charges of the electron and the proton are equal in magnitude but opposite in sign, so that an intact hydrogen atom is electrically neutral. This implies general support for the idea that electric charge is strictly quantized in units of the elementary charge and that electromagnetism accounts for this quantization of electric charge, i.e. that charge always comes in discrete multiples of a fundamental smallest charge (GEORGI, 1981, in MADDOX 1992). However, the quantization of electric charge (particle's charges are integral multiples of the proton's charge) implies the exact neutrality of the atom. This means that the strength of any given electromagnetic interaction is dependent on the size of the participating charges. Its measure is the so-called electromagnetic coupling constant (GEORGI, 1981).

A change in the strength of the strong interaction coupling constant of only a few percent would have dramatic consequences for the inert and living matters. As small an increase as two percent would block the formation of protons out of quarks and hence the formation of hydrogen atom. Comparable decrease would make certain nuclei essential to life unstable and small changes in the electric charge of the electron would block any kind of chemistry and, by extension of biochemistry (BARROW & SILK, 1980). Consequently, adjustment between both charges in the H atom must have been extremely precise to meet the evolutionary constraints. Would the charges on the electron and proton have been a factor of three higher, the periodic table would have ended at the element boron! In other respects, would the charge on the electron have exceeded that on the proton by one part in 1018, the overall electrical repulsion between a human and earth would equal the gravitational attraction (WILKINSON, 1991).

4. Atomic scale

The birth of the atoms occurred by the post-Big Bang process of nucleosynthesis which involved the gluonic confinement of protons+ (and neutrons) into nucleons orbited by electrons$^-$.

Unionized atoms are electrically neutral because the negative charges on the electrons precisely balance the positive charges on the nuclear protons (GEORGI, 1981). However, this deeply-rooted concept of balancing is worth a second thought: why should electrons and protons which seem to be independent forms of matter know so precisely the magnitude of each other's electrical charge? An answer that has suggested itself to many is that ultimately there is but one type of matter: electrons and protons are twins. If so, this would be the culmination of a long search for an underlying unity in nature. This startling result is a consequence of the electrical charge equality between the electrons and protons.

a) Primal H

Most of the "observable" universe is made of about 98% hydrogen H (including helium He) and, for the remaining 2% of matter, approximately 1% is made by five of the other biogenic atoms: C, N, O, S, P (ORÓ, 2001).

Hydrogen, the essential element (RIGDEN, 2002), was born during the cooling phase of the Big Bang from the successful association of an electron and a proton, thereby becoming the basic "brick" or protium of matter. Its opposite electric charges remain separate by the spinning of the light, negative electron on multiple lemniscatic, elliptic orbitals, imaging a planet circling the sun and maintaining it at an energy-dependent variable distance from the central, 1820 times heavier proton. According to quantum physics, the electron in the H atom is randomly positioned around the unique proton (spin-polarized model of EINSTEIN-BOSE, FARAGO, 1974). Therefore, it can thus be considered as a probabilistic dipole and as such must not be considered as a particle orbiting the proton, but as a rather nebulous "wave packet". Ionization high energy will delocalize the wave packet, namely the electron will become "spread out" over several energy levels, an event corresponding to the chaos in the classical motion of the electron (quantum chaos? see POOL, 1989). However, and paradoxically, it is because of its feeble ionization in neutral H_2O (10-7M H+) that the H atom could provide the fundamental ionization ($H^+ + e^-$) implicated in the bioenergetic redox reactions.

The hydrogen atom has integer value (1) of spin and belongs therefore, as the photon (0) to the boson class of particles. However, hydrogen is a composite boson and its constituents proton and electron which have half-integer value of spin ($^1/_2$) are fermions (SILVERA & WALRAVEN, 1982). Contrarily to bosons, fermions obey the quantum mechanical rule called the Pauli exclusion principle. According to this principle, two fermions (electrons, protons, neutrons) cannot occupy the same orbit if they have identical quantum numbers.

The scattering of spin-polarized electrons by spin-polarized "one electron" atoms, such as hydrogen or the alkali atoms, is denoted by specifying the direction of the spin orientation as parallel or antiparallel to an arbitrary axis of quantization (LALOË & FREED,

1988). The spin vector can thus point in one of two directions, either "up" or "down". For instance, the two electrons of a helium atom have antiparallel spins and so the magnetic moments cancel. In paronic helium, however, the spins are parallel and the magnetic moments add up. Thus each atomic orbit — in succession at progressively higher levels — can accommodate up to two electrons as long as their spins point in opposite directions. However, the Pauli's exclusion principle could be violated in rare "paronic" states in which two identical fermions would occupy a site simultaneously; one of the orbits would be filled by two electrons whose spins are parallel (GREENBERG & MOHAPATRA, 1987).

As a gas made up of isolated atoms, hydrogen is not stable in the conditions that prevail on the surface of the earth and the atoms combine explosively to form the diatomic molecule of hydrogen (H_2) in which the two charged particles are maintained by electromagnetic forces.

Quite recently, antihydrogen atoms with inverse electric bipolarity, i.e. by mixing at very low energy antiprotons– and positrons (electron+) have been produced in the CERN (AMORETTI *et al.*, Nature October 2nd, 2002).

b) Other biogenic atoms

To produce the carbon atom C, four nucleides of H were condensed into 1 He (α-particle) and 3 α-particles were then condensed by star's thermonuclear reaction into this central biogenic element. Also of high significance for prebiotic-biotic evolution was the fusion of 2C nuclei to form magnesium (Mg) and, in ensuing thermal processes, the production of heavier atoms up to and including iron (Fe).

The birth of atoms opened the possibility of the evolutionarily meaningful bipolar interaction acid-base and reduction-oxydation. Thus, the relatively light elements are endowed with electro-chemical properties by either gaining or losing electrons when they are dissolved in water, thus forming ions: cations, electrons-deficient in Na^+, K^+, Ca^{++} and Mg^{++}, or anions with surplus electrons in C^-, S^{-4}, and $P^{-3/5}$. Such oppositely charged ions are valued in the acid-base interactions while redox interactions are mediated by the heavier atoms of so-called trace (oligo)-elements such as $Cu^{+1/2}$, $Fe^{+2/3}$, etc.

When we consider the primordial nucleosynthesis of atoms in the stars, it has been shown by computer calculation that, if the values of the strong nuclear interaction or those of the electromagnetic forces (see I.) had been slightly different, the stars could not have built carbon atoms and consequently no biogenic evolution would have occurred (C. MCKAY, 2002).

5. Molecular scale and its evolution

It was produced by the sharing of electrons covalently bonding to H atoms into the primal dihydrogen molecule H_2. Such type of homodiatomic molecule further including O_2, N_2, S_2 was followed by the homotriatomic ozonium O_3 (the screener of atmospheric UV) and through the crucially biogenic heterodiatomic H_2O, NH_3 and CH_4 to reach the heterotriatomic level of monomers of prebiotic polymers (see III.1).

H_2

As the most abundant molecule in the universe (75% of all), hydrogen is the central species in all interstellar chemistry models according to which it is assumed to form by H-atom recombination on dust grains in dense molecular clouds (ref. in SANDFORD *et al.*, 1993).

To build this simplest molecule it is requested that the bipolar electric repulsion be overcome to pair electrons between the two H atoms. The two electrons can now circulate on complex orbitals around the two adjacent protons (MCWEENEY, 1986) and the hydrogen molecule formed is then a closed system with increased stability.

Nuclear spins of hydrogen atoms can be either parallel or antiparallel with respect to the spin of the polarized electron. Consequently, molecular hydrogen can only gradually form when atoms with antiparallel nuclear spins become slightly depolarized and thus can recombine with one another (SILVERA & WALRAVEN, 1982). Otherwise, when stabilized H atoms were produced by spin-polarizing all the electrons in the same direction instead of binding into pairs during a collision, they separated and H_2 did not form (LALOË & FREED, 1988).

O_2

There was a weakly reducing mixture of CO_2, N_2 and H_2O in the primitive Earth atmosphere with lesser amounts of CO and H_2 (see KASTING & BROWN, 1998) which controlled the O_2 abundance by producing H_2O. The further abiotic photolysis of H_2O vapor produced OH radicals which could react with O atoms themselves produced by photolysis of CO_2 to produce O_2.

H_2O

A landmark event of chemical evolution was the sharing of two electron pairs between the two H atoms and the O atom in the water molecule. That bipolar acid-base reactivity of H_2O was evolutionarily conserved in primordial organic molecules such as the biogenic amino acids built with covalently bonded backbone residues but with ampholytic terminals conferring them pH-depending "zwitterion" properties at their isoelectric point.

Evolutionarily, water was abiotically generated from the interaction of H2 and iron oxides ($Fe_2O_3 + H_2 = 2\ FeO + H_2O$) in the cooling phase of the primaeval lithosphere. Now, it can also be produced in artificial fuel cells in which DYER (1990) observed gas - electrical energy conversion processes occurring within very thin films of gas-permeable, ionically conducting prototypical membranes of hydrated aluminium oxide. The covered inner platinum electrode was positive and the polarity of the cell could be changed in $H_2 + O_2$ mixtures only when the outer platinum catalyst was changed to a nickel catalyst. This shows the strong dependence of cell polarity on the metals used and their sequence, suggesting that "different electrochemical kinetics might establish the polarity observed". A further clue of the origin of water on Earth (ROBERT, 2001) comes from carbonaceous meteorites which contain two distinct hydrogen carriers: water, present in clay minerals, and organic hydrogen, present mostly in macromolecular structures.

N nitride compounds

N_2 is relatively inert and has probably remained in the atmosphere throughout the entirety of Earth history.

This biogenic dimer is considered in the traditional view as a nearly universal proton acceptor as confirmed by NELSON *et al.* (1987). As dipole it can combine with H^+ to form the cations $(HNH_3)+$ or NH_4^+. Electrostatically, the cations H_3O^+ and NH_4^+ are thus comparable: the nucleus H^+ is fixed in the same way on both H_2O and NH_3 molecules acting as dipoles. Nevertheless, it has been recently shown that NH_3 can also act as a proton donor — even with argon as acceptor — in contrast with Nelson's conclusions that NH_3 never acts as a donor (SAYKALLY & BLAKE, 1993).

In H_2O the hydrogen atoms approximate naked protons on the surface of the oxygen atom. The net charge for the molecules as a whole is neutral (same number of electrons and protons). From spectroscopic and X-ray analyses the precise H-O-H bond angle is 104° 45' (PAULING, 1960). It is not absolutely stable but represents an average sharing of electrons and distribution of charges (SALISBURY & ROSS, 1985). The protons, thus distributed apart on the surface of the oxygen atom, provide a slight positive charge on one side of the molecule. This is balanced by an equal negative charge on the other side of the molecule. Such a polar molecule in which the electrons are asymmetrically distributed has a dipole moment. Thus, although the water molecule is electrically neutral, its partial positive and partial negative charges are separated, with the result that the molecule is an electric dipole.

The fact that the hydrogen bond is considerably weaker than the covalent bond is conventionally denoted by O-H...O. As a result of the asymmetric arrangement of the two covalent bonds, the distribution of electric charges within the neutral molecule of water is such that the hydrogen nuclei appear to be positive with respect to the oxygen which has taken up two electrons. Such dipolar structure of H_2O leaves weakly negative regions near the central oxygen atom at the other two corners of an imaginary tetrahedron. Consequently, when molecules of water join together transiently in a hydrogen-bond lattice, one molecule becomes the center of four-components clusters. These small clusters can then join to other water molecules to constitute short-lived assemblies known as "flickering clusters".

Following H_2O as maximal dipole with a permanent electric moment or Debye unit l of 1.8, there are SO_2 (l = 1.7), NH_3 (l = 1.5), HCl (l = 1.03) and H_2S (l = 1.0). Oppositely, CCl_4 and CO_2 have no electric moment (l = 0) (EGGERT and HOCK, 1947). Polar molecules can be associated either in series or as parallel dipoles and quadrupoles. Among the six dimeric species that may be formed from the first row hydrides, HF, H_2O and NH_3 monomers, all the predicted structures illustrated by the van der Waals stereochemistry were in essential agreement with experimental data obtained by high-resolution spectroscopy, except for the NH_3 dimer.

It was of decisive consequence for the further prebiotic evolution that H_2O could combine its structural covalent bonding with a possibility of partial ionic bonding authorized by the breakage of one of its H to O covalent bonds. Such reversible ionization of H_2O which proceeds to only a very slight extent at standard temperature (25° C) and

pressure produces an equilibrated proportion of a hydroxide anion (OH^-) and a hydrogen cation or proton (H^+, generally noted as the hydronium ion H_3O^+ by bonding to H_3O). Interestingly, in following the Bronsted-Lowry definition of a base as a proton acceptor and an acid as a proton donor, H_2O which accepts a proton as H_3O^+ is a base in the reaction while H+ can be considered as the simplest, so-called Lewis acid. Thus, it is plausible that "all phenomena of the world are the reactions of one kind of acid with one kind of base" (ATKINS, 1991), if such reactions are considered in the realm of the unifying principle of electric bipolarity.

C carbide compounds

The abundance of carbon in the primordial nebula and its ability to form complex species from CO-CO_2, confers a key-role in the chemical evolution toward life. WÄCHTERSHÄUSER (1988) suggested that life started from carbon dioxide, which, like hydrogen, oxygen and nitrogen it is capable of forming covalent bonds with its partners. While the hydrogen atom needs one electron, oxygen needs two, nitrogen three and the carbon atom needs four to fill their respective outer shells. Thus, a carbon atom can share four electron pairs with four hydrogen atoms to form the reduced molecule methane (CH_4) in which each of the shared electron pairs is a single bond. However, carbon can also form double bonds to oxygen (CO → CO_2) and triple bonds to nitrogen atoms in HCN.

Silicon, which is directly below carbon in the periodic table of the elements, also forms four covalent bonds. However, contrarily to CO_2, SiO_2 is insoluble in water and only forms relatively short chains with itself which impeded Si to have played a major part in directing biogenic chemistry.

Oxydo-reduction of C led to formaldehyde CH_2O, the precursor of the sugar ribose. It was produced in copious quantities in a weakly reducing, $CO_2 - N_2 - H_2O$ atmosphere by a complex mechanism (see KASTING & BROWN, 1998).

CH_4 methane, as the primordial molecule of the so-called organic carbon chemistry, is structurally isometric and apolar: its single C atom shares four electrons with four H atoms and the shared electron pairs form four covalent single bonds isometrically spaced in tetrahedral arrangement. According to CATLING *et al.* (2001), biogenic methane would have been involved in the irreversible oxidation of early Earth.

HCN cyanide is an anisometric and bipolar molecule difficult to form in a weakly reducing atmosphere but easily formed from spark discharge in gas mixtures containing N_2 and CH_4 (ZAHNLE, 1986).

S sulfide compounds

H_2S is involved in the oxidative formation of pyrite FeS_2 from iron sulfide and thereby has been considered by WÄCHTERSHÄUSER (1988) as the primordial biogenic energy source.

Complexified molecular steps:

Oxidative steps of methane can lead, through the neutral hydrophilic methanol (CH_3OH), to the first negative "monopole" formic acid ($HCOO^-$) while the reductively

produced methylamine ($CH_3NH_3^+$) features a primitive positive "monopole". Moreover, by formose polycondensation, formaldehyde (CH_2O) was the building stone for the ose series from C_2 glyoxylic acid to the biotic pentoses of nucleic acids.

It was the further biologically very significant ability of C atoms to share electron pairs with each other to form very stable carbon-carbon single bonds which has led to anisometric molecules, with ethane (CH_3CH_3) as prototype of the hydrocarbon series of homologues. This neutral and hydrophobic molecule has evolved to the primordial biogenic molecules through the hydrophilic ethanol (CH_3CH_2OH) and electrically monopolar such as acetic acid (CH_3COOH), precursor of the hydrocarbon chains of fatty acids.

Heterodipolar tri-tetratomic molecules: amino-acids

All life on Earth is constructed from the same basic biochemical building blocks, consisting of 20 amino acids with left-handed symmetry, five nucleotides, few sugars of right-handed symmetry and some lipids (LEHNINGER, 1975). Using the metaphore of computers, "this is equivalent to saying that all life shares the same hardware. Beyond hardware similarities, it is now known that all life has fundamentally the same software".

The 20 natural proteinic amino acids bear heterodipolar terminal groups (–COOH (-) *versus* $-NH_2$ (+)). They have been classified in five groups based on the degree to which the amino acid's side chain is polarized at pH 7 (DOOLITTLE, 1985): amino acids can be separated into non-polar side chains molecules (alanine, valine, leucine, iso-leucine); uncharged, polar chains molecules (glycine, serine, S-containing pentatomic threonine and cysteine); basic, positively charged side chains molecules (lysine, arginine, histidine); acidic, negatively charged side chains molecules (aspartic and glutamic acids); other side chains (generally those made up exclusively of carbon and hydrogen) are non polar.

With its simple H- as residue (R) group, glycine is the only a-amino acid having no asymmetrical carbon atom. It belongs to the electrically bipolar (+-) and therefore uncharged R group. The high degree of polarity of its α-amino and α-carboxyl groups is not influenced by either a hydroxyl (serine, etc.), amide (asparagine, etc.) or thiol (cysteine, etc.) group. These polar amino acids are also electrically neutral overall (+-). Their polarization results from the presence of oxygen or nitrogen atoms, which have a strong affinity for electrons. Other amino acids not only are polar but also carry a net electric charge; in other words, they are ionized under physiological conditions. Thus lysine, arginine and histidine carry a net positive charge (++–) while aspartic and glutamic acids carry a net negative charge (+--). When a polar or charged side chain projects into the aqueous environment, the strongly polar H_2O molecules assume an orderly arrangement.

The dipolar nature of amino acids was first suggested by the fact that crystalline amino acids have melting points that are much higher than those of organic molecules of similar size. The crystal lattice of amino acids is held together by strong electronegative forces between positively and negatively charged functional groups of neighboring molecules. When a crystalline polar amino acid such as alanine is dissolved in water, it

occurs as a dipolar ion which can act either as an acid (proton donor) or as a base (proton acceptor). Amino acids having this two-way property are amphoteric or ampholytes (from "amphoteric electrolytes"). Simple monoamino monocarboxylic a-amino acids such as glycine and alanine are considered as diprotic acids when they are fully protonated (see LEHNINGER, 1982); in this bipolar form they have two groups that can ionize to yield protons.

Those α-amino acids having a single amino group and a single carboxyl group crystallize from neutral aqueous solutions in a fully ionized species are called a dipolar ion or zwitterion (German for "hybrid ion"). The characteristic pH at which the amino acid is present as its fully ionized but electrically neutral dipolar form is called the isoelectric pH or isoelectric point (pHi or PI). Although such dipolar ions are electrically neutral and do not move in an electric field, they have opposite equal electric charges at their two "poles". Glycine ($^{+}H_3N\text{-}CH_2\text{-}COO^{-}$) is the prototype of such electrically heterodipolar molecules.

Nucleobases

They are also tetratomic molecules. Purine, such as adenine, can be abiotically synthesized from cyanide (CN) molecules (ORO, 1995) and pyrimidines from cyanoacetylene or cyanoacetaldehyde (FERRIS *et al.*, 1974). They are chemo-structurally bipolar with the anterior pole of their heterocyclic molecule reserved for base pairings by H bonds and the posterior pole for P-N bondings of nucleobases, (N^1 in pyrimidines, N^9 in purines) bypassing in prenucleic acids, their deficient β-glycosidic bonding with the C_5 sugar (ribose / deoxyribose) (see III.1).

Ribose precursors

C_1 formaldehyde combined with 2 C_2 carbohydrate has been described as a precursor of ribose in the formose reaction (see SCHWARTZ in BRACK, 1998).

Lipid precursors

Fatty acids are known to be synthesized from the heterotriatomic acetic acid.

6. Macromolecular polymers

Polymerization is an essential step in prebiological evolution and SIMAKOV & KUZICHEVA (2001) have shown "that this process probably could have taken place even at early stage of the Solar system formation, before planet accretion".

Chemically, the peptide bond is a substituted amide linkage between the anionic α-carboxyl (C) group and the cationic α-amino (N) group which removes one molecule of H_2O to close the covalent bond by the sharing of one pair of electrons between C and N atoms. However, at around neutral pH in pure H_2O, amino acids are not very reactive to polymerize because of their "zwitterions" form in which the negative charge on the carboxyl group (COO-) destroys the electrophilic character of its C atom; simultaneously, the nucleophilic character of the N atom is destroyed by protonation (NH^{3+}) of its pair of electrons. Therefore, to bond efficiently, amino acids need to be in an activated form provided either by the coupling of the COOH group with adenylate as well known for

"modern" protein synthesis or by its condensation with linear-cyclic polyphosphates, dicyanimides or carbodiimides (see PONNAMPERUMA, 1978). In prevital simulated conditions, alanyl adenylate was made to polymerize in aqueous solutions in the presence of the clay montmorillonite (BRACK, 1976). Another primordial way to shift the thermodynamic equilibrium of the reaction toward the end-product (peptide) has been the separation of the other end product, H_2O, by heat (FOX & HARADA, 1960).

Only amino acids bearing heteropolar terminal groups (-$COOH^{(-)}$ *versus* –$NH^{3(+)}$), and no other prebiotic molecules, such as dicarboxylic acids bearing only repulsive (-COOH) homopolar terminals, could insure polymeric chains formation. However, after such oligo-polypeptides are completed, only the two α-amino (+) and α-carboxyl (-) terminal groups continue to ionize and to present differences in their acid-base behavior and polarity at different pH values. All the other intrachain groups of the constituent amino acids are covalently joined in a repetitive pattern of peptide bonds.

A peptide chain is endowed with bipolarity; it starts at one end with a-amino group that does not participate in peptide linkage while the terminal end of the chain contains an a-carboxyl group that is also free. Consequently, and on the prototypic model of covalently-structured H_2O molecules "inter-netted" by electrostatic interactions the CO-NH peptide bonds between their constituent amino acids remain potentially electrically bipolar and endowed with reciprocal electrostatic affinities potentially generating interchain H bondings.

Many amino acids, the most abundant being glycine and alanine, have been produced in laboratory simulation (MILLER, 1953) and abiogenically self-condensed into peptides or protein-like polymers called proteinoids (see FOX, 1965). Concentration by evaporation of amino acids from 10^{-7} M as supposed to occur in primitive oceans to the levels of concentrations that may be needed to form polymers (at least $\approx 10^{-6}$-10^{-5} M) might have been reached on clays (CAIRNS-SMITH, 1982). Such synthesis of polypeptides proceeds more readily in the absence of H_2O, the basic idea being at least to separate the products, H_2O and polymers. The condensing force — used largely for intermolecular dehydration — would be drawn from the anhydrization and peptidizing conditions produced by cations such as Mg^{2+} ions (TURIAN, 1995).

In fitting with the polarity principles proposed by WÄCHTERSHAUSER (1998), the earliest polypeptides were polyanionic and made up exclusively of anionic amino acids. Consequently, on positively charged mineral surfaces, these will have the proper definitive orientation for producing polyanionic polypeptide. This prediction has been corroborated experimentally by FERRIS *et al.* (1996) who selected aspartic and glutamic acids as anions for anchoring nascent peptides on mineral surfaces cationized by magnesium ions.

II. PREBIOTIC RECOGNITION SYSTEMS

1. Supramolecular self-assemblies

While molecules are built by connecting atoms with strong covalent bonds, supramolecular compounds, as first defined in 1969 by JEAN-MARIE LEHN, are built by linking

molecules with weak intermolecular interactions. Their self-assembly was inspired by nature, where entities as simple as a raindrop arise from physical principles or instructions implicit in their components. In the case of the liquid drop which takes the spherical form that maximizes its energetic stability, self-assembly is known as an example of thermodynamic self-assembly (WHITESIDES, 1995). Recently it has been further defined (WHITESIDES & GRZYBAWSKI, 2002) as "a process that involves preexisting components, is reversible and can be controlled by proper design of the components".

There are two main kinds of self-assembly: 1) static, which involve systems that are at global or local equilibrium and do not dissipate energy and 2) dynamic in which the interactions responsible for the formation of structures or patterns between components only occur if the system is dissipating energy. Another variant is templated self-assembly in which "interactions between the components and regular features in their environment determine the structures that form" (WHITESIDES & GRZYBAWSKI, 2002).

Weak intermolecular interactions are divided into two classes: a) isotropic, medium-range forces which define the shape of the individual molecules, as well as their size and close packing; b) anisotropic, long-range forces which determine intermolecular orientations and functions. Isotropic interactions include the weak van der Waals forces, which act between all atoms and molecules. These individually weak forces (bond energies of 8 kJ mol-1) can be repulsive or attractive depending on the distance between the interacting non-bonded atoms. By contrast, in anisotropic interaction, it is the hydrogen bond which is the master key (DESIRAJU, 2001).

Self-assembling H and other weak bonds

According to the definition of H bonding proposed by PIMENTEL and MCCLELLAN (1960), the H bond specifically involves a hydrogen atom to another atom in a flexible enough way to include the fundamental examples of hydrogen-bonding small mineral molecules such as the biogenic dipole H_2O. This is the consequence of the differential attraction that atomic nuclei have for their orbital electrons, an attraction called electrophilia. For example, the hydrogen nucleus is far less electrophilic than the nitrogen nucleus and this insures that partial charges are distributed. As the electron and the nucleus of the hydrogen atoms are both polarized (LALOË & FREED, 1988), they are well fitted to bind to two negatively charged (d-) atoms, most commonly oxygen atoms, but also oxygen and nitrogen or two nitrogen atoms. The charges shared, respectively denoted d+ and d-, are called partial charges because they do not represent full electrostatic units.

The origin of hydrogen bonding is generally understood to be primarily electrostatic, but with significant contributions arising from short-range charge transfer interactions (RODHAM *et al.*, 1993). Typical hydrogen bond strengths in neutral systems fall in the range from 2 to 5 Kcal/mol, whereas those involving ions are much stronger. The preponderance of modern research has shown that hydrogen bonds usually adopt a nearly linear M-H...X: arrangement between a donor bond (M) and a proton acceptor (X:), typically a Lewis base.

H bonds are regarded as the strongest and the most directional of the weak intermolecular interactions ($1/10^{th}$ the strength of covalent bonds) that cause molecules to

form either liquids or solids. All intermolecular H bonds are broken by small changes in temperature, as occurs at the liquid/vapor (gas) transition in H_2O or between the double helical strands of warmed up DNA. Uncharged H bonds contribute to both binding energy and specificity (discrimination energy). The presence of mispairs (=NH HN=) in DNA duplexes will amplify this specificity, leading to the paradoxical conclusion that "the single most important factors in specificity are steric repulsion and unsolvated charges at the interfaces of complexes" (FERSHT, 1987). H bonding is therefore a major determinant of specificity, molecular recognition and, finally, for information transfer (JEFFREY & SAENGER, 1994).

Forces weaker than those of H bonds, the van der Waals interactions, are often assumed to be less "directional". Nevertheless, the distinction with the hydrophobic van der Waals bond seems moot; both are weak but van der Waals forces occur between uncharged atoms. However, the low energy of an hydrogen bond pair atomic group being greater than that of van der Waals contacts, those molecules still can form H bonds in preference to van der Waals contacts.

Evolutionarily, H bonds first appeared between successive H_2O molecules. At this primitive level and like the other low strength van der Waals bonds (CH_3...CH_3, etc.) they can be considered as homopolar cohesive forces (O-H···O). H bonds became heteropolar cohesive forces (N-H···O) when they linked opposite, amide bonded amino acids (a.a.) of neighbouring polypeptide chains. However, as in both cases H bonds provide their forces to link unit-to-unit similar molecular templates, they can still be considered as (1) homopolar-*homotemplates* for H_2O--H_2O bondings and (2) as heteropolar-*homotemplates* for a.a::a.a. peptidic bondings of proteins. It was only later that homopolar (N-H···N) and heteropolar (O-H···N) cohesive bonds provided *heterotemplate* forces when they started to link different nitrogen bases, i.e. purines versus pyrimidines in the nucleobase pairs of prenucleic-nucleic acids (see III).

By their direct involvement in bipolar interactions, H bonds are of fundamental importance for the cohesion of all inert matter and, without such bonding, all living things would disintegrate into random dispersions of inert matter (JEFFREY & SAENGER, 1994).

H-homobonded water networks

The primordial model of self-assembly is that of H_2O molecules, constituting water, the "cradle of life", singular as a liquid because of its ability to form three-dimensional molecular networks, mutually hydrogen bonded. Its molecules are in a state of high energy if they fail to make the maximal number of hydrogen bonds possible either with one another or with solutes or surfaces (FINNEY, 1979; WIGGINS, 1990).

Water biophysics relevant to polarity is mainly concerned with the relationships between hydration water and hydrogen bonds (SAENGER, 1987). Hydrogen bonding dynamics involves flip-flops and movement of water along the surface of macromolecules. Water would not have its particular properties if the molecules were not associated by hydrogen bonds O-H...O. If the O-H group is involved in hydrogen bonding it becomes polarized. In the association of water molecules to the surface of

proteins or nucleic acids, hydrogen bonding of type (water) O-H...Y is the main attractive force. When the O-H...O bonds all run in the same direction, this is called homodromic; it is indicative of the influence of the cooperative effect. When a water molecule donates two hydrogen bonds this gives rise to *heterodromic* situation, where hydrogen bonds are randomly oriented (SAENGER, 1987).

Liquid water is normally symmetrical but, eventually, through its phase transition to ice crystals its translational and rotational symmetry is broken, the system takes on the discrete symmetry of the ice crystal (CHUANG *et al.*, 1991). It has recently been discovered that an unusual kind of water frozen in an amorphous state is absent from Earth but ubiquitous in interstellar space. This interstellar ice may actually have played an intrinsic role in the origins of life (BLAKE & JENNISKENS, 2001).

Considering the many different crystalline ices known, and the nature of their structures, RICE (1975) had suggested that a modest arrangement of the positions of a group of water molecules can (and does) generate new minima in the potential energy surface, and that these new minima correspond to qualitatively different connectivities of the hydrogen-bond network. The strong, totally connected random tetrahedral network of hydrogen bonds should confer it rigidity rather than its familiar fluidity which can be ascribed to defects characterized geometrically by the presence of an extra, fifth molecule in the first coordination shell, or topologically "bifurcated" hydrogen bonds (SCIORTINO *et al.*, 1991 and refer. herein).

In summary, water can be considered as the agent that drives the conformation of organic molecules, which have a dual structure containing both hydrophobic and hydrophilic groups (BRACK, 1993). As such, it is "the support of life" (see Science, 2004).

H-heterobonded polypeptidic configurations

Polypeptides possess not only primary structure, i.e., a strong covalent backbone, but also a characteristic secondary structure, the manner in which amino acid residues are arranged in space. Their α-helix and β-structures are stabilized by H bonds between peptide groups, intrachain in the case of the α-helix and *interchain* in the case of β-structure; these bonds, although individually relatively weak, collectively give such structures considerable stability. The β-pleated sheets can consist of only two strands in parallel or antiparallel orientation. However, since the sheet has free H-bonding groups at both edges, more strands can be added to form a multitude of strands.

It is known that to form a b-strand from segment of polypeptide chain with one hydrophilic face and one hydrophobic face, the sequence must be designed with a periodicity of polar and nonpolar residues that matches the repeat for that type of secondary structure (KAMTEKAR *et al.*, 1993). For the design of a stable β-sheet protein, the sequence must be composed predominantly of alternating polar and nonpolar residues constituting some type of *binary* code.

In contrast to the α-helix which is formed by a continuous segment of a polypeptide chain, the β-pleated is formed by different segments of the polypeptide. These sheets can coil to form cylinder-like structures referred to as β-barrels (which, as a ring, are "-infinite" β-sheets, see JEFFREY & SAENGER, 1994). However, these circularly folded

segments can form either (a) pseudorings remaining connected by b-turns insured by vertical peptide bonds but leaving a possibility of free, weak H bondings at both edges of the turn or (b) complete rings individualized by horizontal, planar peptide bond closure of a circular polypeptide segment, thereby corresponding to a cyclic peptide.

Different kinds of constraints act on the conformation in space of an isolated polypeptide chain, among which the rigidity and *trans* configuration of the peptide bonds, the electrostatic repulsion or attraction between amino acid residues with charged R groups, the bulkiness of adjacent R groups.

In interchain pairings, attraction of opposites versus self-attraction processes intervene. Most effective are attractions between amino acids with side groups which have opposite or complementary features. Such interactions between residues conform to PAULING's (1960) laws of chemical bonding which involve weak ionic bonds, hydrogen bonds in which an electropositive H atom is attracted to electronegative atoms such as O or N, van der Waals forces which arise from a nonspecific attractive force originating when two atoms come close to each other (H ... H), hydrophobic forces between methyl groups, etc. H bonds also occur both in salt bridges with charged donor and acceptor groups and with uncharged groups (see JEFFREY & SAENGER, 1994).

2. Template recognition

Continuity of the emergent life processes required a depository of information insured by some type of genetic protocoding. Its first letters were the amino acids of primitive peptides (see DE DUVE, 2002). They recognized themselves by *homologous* self-replicated processes (II.2.a) secondarily taken over by intermolecular *heterologous*, heterocyclic nucleobases (II.2.b) among the 4 ones (A, U, C and G) experimentally first proposed by CHARGAFF (1951). We have chosen doublets of these bases to "pinch" the 16 possibly selected amino acids (TURIAN, 1998). In this encoding process, the stereo specifically chosen doublets had to be evolutively frozen by their locking up in the phosphate group of prenucleic polyphosphate chains by phosphoramide (P~N) bonding, bypassing the carbonaceous preribose-ribose chain of the backbone of the "modern" RNAs (III.1). The encoding would be finalized by decoding of the genetic information with a possibility of its amplification in life-like self-entrained processes (III.2).

a) Homologous monomers

In molecular evolution, the first peptides abiotically formed might have been cyclic ones rather than the self-replicated linear ones proposed by CALVIN in 1969, on the model of bacterial cyclic peptidic antibiotics (gramicidin, valinomycin) known to be synthesized without an RNA template (see LIPMANN, 1971).

The sequential specification of their amino acids has further been shown to occur in the interannular association of b-type rings which are formed through linear regular L,D polypeptides resulting into parallel and antiparallel cylindrical structures as first suggested by DE SANTIS *et al.* (1974). Later, construction of nanotubular structures has been realised by synthesis of some cyclic oligopeptides with S_{2n} symmetry (TOMASIC & LORENZI, 1987). On this principle, self-assembled organic nanotubes have recently been

produced on a cyclic peptide architecture (GHADIRI *et al.*, 1993). The interest of this model is the convergent approach in which "numerous ring-shaped peptide subunits interact through an extensive network of hydrogen bonds to form nanotube structures". In 1995, it inspired us to propose a model of prevital nanotube integrating (1) ORGEL's first proposal (1972), experimentally concretized by BRACK & ORGEL (1975), of a dimeric polymerization into an antiparallel β-pleated sheet of alternating hydrophobic-hydrophilic chains of amino acids closed upon itself into the polypeptidic nanotube built by vertical stacking of rings of intensively H-bonded cyclic peptides. This proposal could be experimentally confirmed when molecules of the monomeric cyclo-tetrapeptide β-alanine-glycine-β-alanine-glycine dissolved in an anhydrizing Mg^{2+}-rich saline solution acted as templates for their autocatalytic replication (TURIAN, 1996) parallely reported by GHADIRI's group (LEE *et al.*, 1996): a 32-residue α-helical peptide could also act auto-catalytically in templating its own synthesis in neutral aqueous solution. This template-directed ligation of peptides used the thioester-dependent mechanism devised in 1994 by DAWSON (see DE DUVE, 1998).

In the process of supramolecular evolution, interesting examples of self-replication are also those which use oligopeptides as templates. In these processes of auto-catalysis, cyclic α-peptides consisting of alternating D- and L- aminoacids self-assembled via H-bonding to the tubular, open-ended and hollow structures of nanotubes (SAGHAHELIAN *et al.*, 2001, FERNANDEZ-LOPEZ, 2001). The small repetitive units involved in this tubular formation were called supramolecular synthors by DESIRAJU (1995 in 2001).

Recently, GHADIRI *et al.* (2001) have demonstrated that chiroselectivity in peptide self-replication is a direct consequence of complementary noncovalent interactions that transfer simultaneously both binding and stereochemical information. This process of self-recognition between amino acids by point-point complementarity ordered by mutual H bonding could be an answer, especially exhibited by the regularly ordered organization of proteinous β-sheets. In 1972, ORGEL had imagined some very simple proprotein structure which could be based on just two kinds of amino acids, one hydrophobic and one hydrophilic. He suggested that, with such an alternation, coherent β-structures would tend to form the sheets made from aligned polyamino acid chains in which one surface would be covered with hydrophilic and the other with hydrophobic groups. Such β-structures might then be expected to assemble further into water-dispersible bilayers (see Figs in CAIRNS-SMITH, 1982). The tendency of linear heteropolymeric polypeptides to form antiparallel β-pleated sheets could thus provide self-reproducing sequential information.

In summary, the specific H bondings between intrachain peptide bonds (-NH ... OC-) play an indirect directional role in the self-recognition processes between opposite chain sequences. Such directive electrostatic interactions operate in an alternate way by inversely polarized H-bonds ordered by the opposite positionings of CO and NH groups, themselves inversed between the antiparallel chains of β-sheets. The challenge of the genetical evolutionary sequence remains therefore: *how* information-coding systems have developed from the simplest prebiotic precursor replicating molecules using H bonding template forces?

b) Heterologous prenucleic dimers

Peptide nucleic acids

While modern recognition of an amino acid by a trinucleotidic codon is effected indirectly through a tRNA molecule, recognition in pregenetical evolution may have occurred through direct amino acid-template interactions (WOESE *et al.*, 1966). The feasibility of interpolymer hydrogen bonding between the peptide backbone and nucleobases is thus pertinent to the evolutionary study of nucleic acid-protein interactions (NIU & BLACK, 1979, NIU *et al.*, 1987) in which a 5'-uracil substituent could recognize the side chain of a peptide-bound amino acid, and cytosine would have formed two hydrogen bonds to the peptide backbone plus one to the hydroxy-amino acids. The pregenetical material was not yet ribose-phosphate linked but peptide-linked. This noticeable principle was successfully followed in the synthesis described below of a new class of DNA and RNA analogs in which the sugar-phosphate backbone has been replaced by a similar linear structure of amino acids directly bonded to nucleobases.

The backbone of such peptide nucleic acid or PNA bimolecular structure is a polymer of N-(2-aminoethyl) glycine (AEG), first designed by computer modeling (NIELSEN *et al.* 1991) and synthesized in 1993 by EGHOLM's group. AEG has since been produced directly in electric discharge reactions from CH_4, N_2, NH_3, H_2O and the robust STRECKER synthesis with ethylenediamine (NELSON *et al.*, 2000).

In such PNAs, nucleobases are attached as side chains by carbonyl methylene linkers to the AEG units. A polycytidine decamer of PNA acted as a template for oligomerization of activated guanosine mononucleotides in the presence of Na and Mg ions.

Nonetheless, the PNA template was not as efficient as the corresponding DNA template (BOHLER *et al.*, 1995), even though the known propensity of PNA molecules to pair with RNA and DNA according to the WATSON-CRICK base-pairing rules suggested a good starting point for the evolution of the possibility of pregenetic takeover (MILLER & NELSON, 1994, see MILLS & BADA, 2000).

The molecular system of PNA can indeed serve as a template both for its own replication and for the formation of RNA from its subcomponents by the acquisition of the phosphodiester-(α-N (3/1 or 9)-glycosyl bonds connecting D-ribose to the phosphate groups and the nucleobases (see HORGAN, 1996). Nevertheless, it should neither be considered as "the primary replicator" nor that it even existed under prebiotic conditions (ORGEL, 1994).

Polynucleobase-phosphoramides (pre-RNAs)

There are serious difficulties in the prebiotic synthesis of D-ribose (JOYCE & ORGEL, 1999), this had led us to propose a deterministic scheme involving primal riboseless prenucleic polymers (TURIAN, 1996-1998) produced in the two following steps: (1) stereospecific coding of amino acids by doublets of nucleobases; (2) locking and, thereby, validation of such doublets by straight phosphoramide bonding of the NH groups of the bases (N1 in pyrimidines / N9 in purines) on one phosphate group of presumably triphosphates further polymerized into polyphosphate chains.

We then thought that in this most restrictive, primordial situation of a total absence of ribosidic linkages of the coding nucleobases (nucleosides would be too difficult to be made, see in BRACK, 1998) their doublets would have to be someway straightfully stabilized by their lining up on a macromolecular backbone (see III.1). Consequently and inspired by the well-known example of creatine phosphate ("phosphagene") we have visualized the possibility of a covalent amide bonding (P-N) of the nitrogenous nucleobases on phosphate groups, one per diphosphate unit of such so-called prenucleic polyphosphate polymers (Fig. 1 in TURIAN, 2000), thereby actualizing KORNBERG's (1995) suggestion of a vicariant role of polyphosphates in the prebiotic evolution.

By 1997, preliminary evidence for that hypothesis was obtained from the UV hypochromaticity of nucleobases incubated with linear triphosphate (TURIAN & SCHOENENBERGER, 1997). Since 1998, we have further investigated such presumed phosphoramidate production by ^{31}P-NMR in close comparison with imidazole which shares the same type of azole ring as nucleobase. This nitrogenous aromatic base was chosen because of its nucleophilic activity toward phosphate (P) thereby phosphoramido (P-N) bonded as imidazolylphosphate acting either as phosphorylating catalyst (SHABAROVA, 1970; RABINOWITZ & HAMPAI, 1979) or linker of nucleotides (GRYAZNOV & CHEN, 1994; ERTEM & FERRIS, 1996). We have then assayed by comparison with imidazole. To improve the efficiency of their condensation with linear triphosphate, we have added the water-soluble agent EDC, a derivative of carbodiimide, itself a tautomer of prebiotic cyanamide, capable of synthesizing phosphoramidate by catalysis of the dehydrating change from the linear triphosphate to the cyclic trimetaphosphate (BECK & ORGEL, 1965; KEEFE & MILLER, 1995), a ring structure which could thus provide high energy bonds (7.0 Kcal.mol^{-1} in CORBRIDGE, 1978) favorable to drive the presumed phosphoramidations of both imidazole and nucleobases. We have interpreted this activation by either imidazolides or nucleobases of the carbodiimide (EDC)-catalyzed condensation of linear triphosphate to the cyclic trimetaphosphate (TMP) as due to the simultaneous opening of the triphosphate cycle by the bases thereby displacing the chemical equilibrium in favor of further cyclic condensation (TURIAN *et al.*, 1998). We have pursued our ^{31}P-NMR spectral analyses with the couple TMP-nucleobase which provided more direct evidence for such phosphoramide bondings by Mg^{2+} enhanced nucleophilic attack of the TMP. Similar opening of the triphosphate cycle (TURIAN *et al.*, 1999) was reported with other >NH containing azole bases (WALSH, 1979; VOGEL, 1984) as directed on the electrophilic phosphorus atom of one of the anhydride bonds of the triphosphate cycle. The enhancing effect of Mg^{2+} ions on the cycle opening by either imidazole or nuclebase could be considered as being due to both their shielding effect of the charged phosphate groups (see WESTHEIMER, 1987) and their synergetic nucleophilic action (controls with Mg^{2+} alone).

P-N bonds are fairly strong and comparable with P-P while stronger than N-N but a little weaker than P-C (CORBRIDGE, 1978). Moreover, phosphoramides are more stable in alkaline than under acid condition. Their simplest compound, amidophosphate $Na_3HPO_3O_9$-NH_2 produced by condensation of linear TP with aqueous ammonia reverts to trimetaphosphate with loss of ammonia on acidifying the solution as proposed by QUIMBY & FLAUTT (1958) and THILO (1962).

A straight phosphoramide or N-P bond. the simplest occurring in $H_2N\text{-}PO_3H_2$, is more stable at alkaline than acid pH values as well-known in a biological phosphoramidate compound, creatine-phosphate or "phosphagen" energized (N~P) from ATP. Other phosphoramidates could be synthesized in neutral aqueous solutions on oligonucleotides by SHABAROVA (1988). SIEVERS and von KIEDROWSKI (1994) have used phosphoramide bondings as condensing agents for the replication of hexameric DNA oligomers while FERRIS *et al.* (1996) have used adenosine 5'-monophosphoramidate as precursor of the nucleoside 5'-phosphorimidazolide oligomerized on mineral surfaces.

The prebiotic, endo- or exogenous synthesis of the amino acid precursors of peptides was easier than that of the precursors of ribonucleic acid such as nucleobases (see ÓRO, 1995) and, especially, ribose (see SCHWARTZ, 1998). Then, in the riboseless, prenucleic phase of the pre-RNA world, autocatalytic sets of randomly produced primeval peptides could have been coupled to - and coded by - the template-replicating prenucleic sequences (TURIAN, 1998). Catalytic acylation-phosphorylation at the level of the phosphoramidic P~N bonds could have further entrailed peptide bond formation from imidazole or nucleobase polyphosphates (such as adenyl-diP, TURIAN 2002) by a self-reinforced cyclic mechanism of primary translation into more of the primally coded peptides providing secondary templates (see model in III.2).

Finally, the pH-modulable P~N bonds between nucleobases and phosphates could have been key prebiotic elements in the chemoevolutive transition toward the more wide range of pH-stable ribonucleotides, thereby securing the necessary coding accuracy of the RNA world submitted to pH-homeostasis.

III. BIOGENETIC EVOLUTION

1. Primal encodings

According to the conceptual scenario about the coding of amino acids, as biochemically determined by NIRENBERG & MATTHEI in the sixties (see L. KAY, 2000), the two first nucleobases of the triplet codon for glycine are guanines G + G. Applying the complementary base rules, these nucleobases should then pair with the anticodal cytosines C + C which thus would have prebiotically functioned as primal codons for glycine (TURIAN, 1996), i.e. by selective weak bonded pinching of the nucleobases (see anticodonic table I in TURIAN, 1998). The pregenetic encoding of peptidic amino acids by specifically selected doublets of anticodonic nucleobases (glycine-CC, alanine-CG, etc.) would have been impaired by the known deficient prebiotic synthesis of ribose (SHAPIRO, 1988, see JOYCE and ORGEL, 1999). The bypass of such blocked nucleosidic steps of t-RNA might have been evolutively insured by phosphoramidic (N-P) lock-and-key of the selected nucleobases on polyphosphate prenucleic chains, thereby fixing-validating the protocode (TURIAN, 2004) potentially evolvable by base-pairing into the biochemically identified codons of the genetic code.

2. Prebiotic self-replicating systems

A possible "protein first" evolutionary period provided the primeval templates of a pregenetical code of approximate accuracy but endowed with the selective advantage of

amide-bonded esters of amino acid coding letter sequences not easily hydrolyzed and thus relatively resistant to the hard environmental conditions of the prebiotic world. A selection pressure must have then developed in favor of template sequences better fitted to recognize mutually and pair code than amino acids. Therefore, prenucleic acids would have had to takeover the approximate information encoded in the primordial peptide sequences before having been themselves taken over by true nucleic acids.

In this takeover process, the pregenetic information present in a primordial peptide molecule could direct for the first time the order of specific nucleobases. This would necessarily implicate recognition of the mutual specific partners and a direct correspondence between certain amino acids and certain nucleobases, itself founded on preferential electrostatic affinities, hydrophobic-philic interactions, etc. Recognition by uracil side chains of specific hydrophilic amino acid side chains has been described since 1973 by BLACK. Even the number of atoms in an amino acid chain played a role in relation to pairs of coding bases and many other plausible arguments have been proposed on a physico-chemical basis for the establishment of the genetic code (JUNGCK, 1978, 1984).

The sparking event of this first phase of "coding evolution" could have been the progressively increased environmental proximity of newly synthesized nucleobases around amino acids lined up in preformed peptide sequences which would have led to their selective interactions directed by conformations] affinities. Steric constraints around and bulkiness of the specific residues of amino acids would have restricted to couples (doublets) the number of bases habilitated to bilaterally "pinch" and weakly bound each selected amino acid as it is known that the 1st and 2nd letters of each "modern" codon are the primary determinants (JUNGCK, 1963 in 1978). This would necessarily mean that the formation of the first doublets of nucleobases was mediated by the physico-chemical affinities inherent to the amino acids-nucleobases partners.

Hydrogen bonds are strongest when the bonded molecules are oriented to allow maximum electrostatic interaction. They are thus directional and capable of holding two hydrogen-bonded molecules or groups in a specific geometrical arrangement. Consequently, following PAULING'S proposal (1960), we have considered that these oriented bondings could have been the main drivers of the stereospecific interactions in the loose cavities or "pockets" modeled by the base doublets thereby acting as specific receptors of the amino acids (table I in TURIAN 1998).

Complementary to this intrinsic positioning of reactive atomic groups, steric hindrance also contributes to the restriction of interactions between amino acids and bases and leads to the exclusion of certain amino acids from cavities formed by the doublets of bases and at the encoding process. Such a principle of exclusion is well emphasized in the hydrophobic series of amino acids in which the principle is more constraining for heavy leucine which could only fit the large cavity left between two purines (G-A) bases than for light glycine which is good choice for two tightly bonded, light pyrimidines (C-C), a cavity otherwise exclusive for the other amino acids starting with alanine.

Non-enzymatic self-replicating systems based not only on nucleotidic but also non-nucleotidic precursors as initiated by REBEK's team (1994) were based on the minimal

system proposed by TERFORT & VON KIEDROWSKI (1992) who used the condensation of 3-aminobenzenidine and (2-formylphenoxy)-acetic acid. Other systems of interacting molecules can be envisaged which could have yielded prebiotic replicators capable of further evolution by mutation - selection. Among those, there are our riboseless pre-nucleic infopolymers directly, i.e. phosphoramidically, condensing on polyphosphate nucleobase doublets and having thus validated the specifically encoded amino acid sequence of a primitive, environmentally formed peptide.

The process of acylation-amination leading to the peptide bond formation can be catalytically activated by imidazole presumably phosphoramidically bonded on the tri-phosphate (RABINOWITZ & HAMPAI, 1978, 1980), an effect which is imitated by other azoles such as the 4 nucleobases as recently evidenced by ^{31}P-NMR (TURIAN *et al.*, 1999). Consequently, we have thought that the process of P-N phosphoramide locking of nucleobases and its possible opening for peptide bond formation should be highly relevant for the decoding of the polynucleobasephosphate sequences. However, to be fully effective and repetitive, such phosphorylamide acylation on the N-H groups of bases should be followed by their P-N rebonding to restore the continuity of the decoding chain. During its bonding process, the assembled peptide strand would be polarly displaced and freed to become available as additional template for the next PBPs replicative encodings, thereby reinforcing the number of PBP copies available for the following cycles (model in Fig. 4, TURIAN 2000). The translated peptides could then have functioned as templates for further affinity-encoding by additionally produced poly-nucleobasephosphates (PBPs) functioning as primary replicators by positive feedback in coupled self-reinforcing cycles.

3. Transition from dimeric prenucleotides to the trimeric nucleotide of nucleic acids (RNA-DNA) worlds

To achieve RNA takeover from prenucleic phosphoramidates, acid hydrolytic opening of nucleobase-phosphates could provide molecular topology and energy powering for the intercalation of D-ribose on the corner of each monomer, by N (1/9)-glycosyl ester with the nucleobase, on one side, and phosphoester (5') bonding, on the other (TURIAN, 1997). However, ribose as such was difficult to synthesize prebiotically (see discussion in JOYCE & ORGEL 1999), and we rather have to rely on its C_1-C_4 precursors.

The whole autocatalytic reaction sequence of ribose prebiotic synthesis would proceed as following (see MILLER 1998):

$$\begin{array}{lll} & \text{CHO} \quad\quad\quad \text{CH}_2\text{O} \quad\quad\quad \text{CHO} \\ \text{CH}_2\text{O} + \text{CH}_2\text{O} \rightarrow & \quad | \quad\quad\quad \rightarrow \quad\quad\quad \text{CHOH} \\ & \text{CH}_2\text{OH} \quad\quad\quad\quad\quad\quad \text{CH}_2\text{OH} \end{array}$$

Formaldehyde C_2 Glycolaldehyde + C_3 Glyceraldehyde = C_5 pentose

The acid-induced, opening by electric charge repulsion (+...+) of the P~N bond of nucleobase-phosphate would make available the intrinsic high energy necessary for the intermediate linking of C_1-C_5 ribose precursors such as methylene glycol $CH_2(OH)_2$ (see

KASTING & BROWN, 1998), as the shorter bridge over the open P...N bond (see in TURIAN 2001).

As first member of their sequence, formaldehyde CH_2O, can oligomerize by the formose reaction to a mixture of sugars from which only low concentrations of D-ribose could be resolved (see CAIRNS-SMITH, 1982; JOYCE, 1989, 1992). According to YUASA *et al.* (1995), polycondensation of formaldehyde could yield glycolaldehyde and a further triose condensation provide some ribose. Moreover, atmospheric CH_2O is soluble in rainwater precipitation and, once in the ocean, it might be hydrolyzed to the C_1 compound intermediate precursor, methylene glycol.

The C_2 glycolaldehyde when condensed by two (C_4) on the already phosphorylated C_1 of methylene glycol could close the pentose cycle of a ribonucleoside. The role of C_2 glycolaldehyde as dimerized product of CH_2O has been promoted by ESCHENMOSER's team (MÜLLER *et al.*, 1990; PITSCH *et al.*, 1995 in BRACK 1998). "Realizing that in biochemistry, sugar phosphate rather than free sugars are formed, this research leader studied the condensation of glycolaldehyde phosphate in the presence of a limited amount of formaldehyde and base". However, phosphorylation would require "modern" ATP, while cyclic triphosphate alone could have provided the prebiotic high energy required by the synthesis.

C_3 glyceraldehyde provides with its terminal C the phosphorylation site as C_5 of ribose after its condensation with glycolaldehyde C_2 thereby closing the pentose cycle. Another C_3, glycerol, proposed to replace ribose in simpler informational molecules (BRACK, 1998) can be condensed with 1 CH_2O into the C_4 of the acyclonucleoside (see JOYCE, 1989; ORGEL, 1992) or, possibly, with 2, thereby directly providing the C_5 ribose.

Synthesis of a *ribonucleoside* could start from both its molecular extremities: from a nucleobase ribosylated into nucleoside -- a difficult process requiring heating (FULLER *et al.*, 1972 in SCHWARTZ, 1998) - or from phosphate phosphorylating ribose into ribose-phosphate (see BRACK, 1998).

The final synthesis of a *ribonucleotide* could occur in a number of ways. According to the recent authoritative comments by JOYCE & ORGEL (1999) "the simplest, conceptually, would be to synthesize a nucleoside base, couple it to ribose, and finally phosphorylate the resulting "nucleoside". However, a number of other routes are feasible; for example, the assembly of the base on a preformed ribose or ribose phosphate or, as in our present proposal, the building, from its C_1-C_3 precursors, of ribose between opened P~N bondings bypassing the nucleosidic step in the prebiotic absence of ribose. Such intercalation process would be powered by the high energy released at the acid-induced opening of the phosphoramide bond and its further bridging electrically driven by the bilateral attraction of the – charged hydroxyl groups of the C-precursors spanning the following scale of increased complexity. C_1 methylene glycol might form the shortest bridge between a base and a phosphate group. The resulting trivalent monomer could be considered as the prototype of a nucleotide or protonucleotide (TURIAN, 2001).

Finally, to fully enter into the "RNA world", the ribonucleosides, by either way produced (see above) have still to be assembled into polymers capable to replicate prebiotically (non enzymatically). For that, clay-type minerals have been found (see FERRIS,

1996) to catalyze the joining of imidazole-activated nucleosides and the oligo nucleotides produced in vitro were pyro(di)phosphate linked (VISSCHER *et al.*, 1990 in FERRIS, 1998) as proposed for our phosphoramidic polyphosphates (see Fig. in TURIAN, 2000).

In summary, the transition from our prenucleic polybase phosphates to nucleotides could have been triggered by the "eco-transition" from slightly alkaline hydrothermal oceanic sources or from basaltic rocks to acidic ones (see RUSSELL *et al.*, 1998), favourable to the bridging by C-precursors of ribose (TURIAN, 2001). The homeostatic, eco-pH trend would then have led to this transition, acting as a "prime mover" to C-bridge the prenucleotides into the nucleotides of the RNA-DNA worlds.

EPILOGUE

Living matter and its lifelike precursors can be considered as both an information processing and a replicating system. Concerning information, prenucleic-nucleic acids and peptides-proteins deal with each other via a digital channel which uses software rather than hardware written in a double-triplet mathematical code. As for replication, it relies on bipolar recognition implicating the H bondings between paired nucleobases having selectively encoded aminoacids of primal peptides. It has thus a clear physical basis (see ABDUS SALAM, 1992 in DAVIES, 2001) while the informative message depends on a chemistry medium involving primal synthesis of the coding nucleobase letters of the genetic alphabet. We expect that our Survey could have correlated extrinsic electromagnetic bipolarity "sparking life" from its asymmetric origin to the pH-controlled phosphoramidic bypass fixing the information content of anticodonic nucleobase doublets to evolve towards the RNA-DNA worlds highlithing the principle of biopolarity.

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RÉSUMÉ

L'implication de la bipolarité électrique dans le "sparking of life", qui a suivi la rupture de la symétrie originelle annihilante est passée en revue dans son ampleur évolutive à partir des atomes nucleosynthétisés – avec H comme amorceur – aux molécules – avec le dipole électrique biogène H_2O – complexifiées en macromolécules et autoassemblages supramoléculaires. La reconnaissance intermoléculaire produite par les liaisons H et d'autres liaisons bipolaires faibles pourrait avoir conduit à des autoréplications simulant la vie, impliquant des codages par des doublets anticodoniques de nucléobases, bloqués par des liaisons phosphoramidiques contrôlées par le pH et court-circuitant l'étape nucléosidique dans les infopolymers prénucléiques prénucléotidiques.

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