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NEW TRENDS IN POLARITY
III. DIPOLAR HYDROGEN BONDINGS AS HOMOTEMPLATE FORCES FOR PREGENETICAL EVOLUTION

BY

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ABSTRACT

New trends in polarity. III. Dipolar hydrogen bondings as homotemplate forces for pregenetical evolution. - Intermolecular H bonding is bioevolutionarily motive by (1) promoting prototypic self-assembly of H_2O molecules, and (2) providing template forces for stacking cyclic peptides into prevital proproteinaceous nanotubes possibly endowed with self-reproductive competence.

Key-words: Hydrogen bonding, H_2O, cyclic peptides, nanotubes, homotemplate forces.

INTRODUCTION

Endowed with both electro-structural and informational polarity contents, hydrogen (H) bonding can be considered as "the unifying principle of continuity in the evolutive complexification of Polarity" (our Epilogue in Addenda IV, 1992) (TURIAN, 1989-92).

Electrostatic in origin, H bonding is the attraction to an acceptor atom of a hydrogen already bonded to a donor atom (PIMENTEL & MCCLELLAN, 1960; JOESTEN & SCHAAD, 1974; SCHUSTER *et al.*, 1976; JEFFREY & SAENGER, 1994). A fundamental question regarding H bonds is whether the potential energy for motion of the hydrogen has a single minimum or two minima. With two minima the hydrogen is closer to one acceptor than to the other. There are then two different tautomeric forms of H bonds which equilibrate rapidly with each other (PERRIN, 1994) and knowledge of their symmetry may be important for the design of small molecules that are to exhibit intermolecular recognition (GELLMAN *et al.*, 1991).

H bonds are regarded as the strongest and the most directional of the weak intermolecular interactions (1/10th the strength of covalent bonds) that cause molecules to form either liquids or solids. Nevertheless, all intermolecular H bonds are broken by small changes in temperature, as occurs at the liquid/vapor (gas) transition in H_2O (see p. 175) or between the double helical strands of warmed up DNA.

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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 factor 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). Consequently, it can be considered as a primary structure-determining template force in biological molecules which spans Polarity "from its electromagnetic origins to its biological take-over" (TURIAN, 1994).

Evolutionarily, H bonds first appeared between successive H_2O molecules. At this primitive level and like the other low strength van der Waals bonds ($CH_3 \cdots CH_3$, 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 as (2) 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 pairs adenine=uracile/thymine (O-H···N; N-H···N) or guanine≡cytosine (O-H···N; N-H···O; N-H···N) of the sequentially born RNA and DNA.

In our opinion, the challenge of the pregenetical evolutionary sequence remains therefore: how information-coding systems have developed from the simplest prebiotic precursor, H_2O, using H bonding template forces? and, according to ORGEL (1992), "how simple replicating molecules must have played a critical role in the origin of Life through that of protobionts".

1. SELF-ASSEMBLY OF H_2O DIPOLES

Molecules of H_2O not only provide a superb stable universal medium in which organic molecules can dissolve and interact (see SAGAN, 1994), they confer a structural order upon cells and they contribute to the stabilities of macromolecules by a redirection of H bonding interactions of water molecules thereby contributing directly to the properties of proteins by influencing their interactions with ligands such as sugars (QUIOCHO *et al.*, 1989).

In large part, the properties of water reflect the dipole that results from the greater electronegativity of the single oxygen atom over the two hydrogen atoms in each molecule. Water is singular as a liquid because of its ability to form three-dimensional network of mutually H-bonded molecules (WIGGINS, 1990). The fact that electrons in *sp*3 orbitals of oxygen atoms can easily be rehybridized to respond to the relative configurations of adjacent molecules may account for its two types of H bond. Spectra

of thin films of water suggest that only H bonds of the strong variety are present; these strongly H-bonded clusters should have all the properties reported for vicinal water (LI & ROSS, 1993).

Of fundamental importance in life processes, H_2O boils at a temperature 160°C higher than does H_2S (KLEMPERER, 1993). When this only nonvolatile, biological solvent is led to evaporate by provision of energy (heat of vaporization), this transition to the gas phase leads to the disruption of hydrogen bonds. However, when water is again condensed, at lower temperature, its H bonded lattice or "flickering cluster" is parallely reconstituted. The amount of energy required to bring water molecules from the interior of an aqueous phase to the air-water interface, to expand the surface area and to disrupt the hydrogen bond is the surface tension (see POTTS, 1994). Water molecules in aqueous solution continually escape into the surrounding gas phase — as third most prevalent in air after N_2 and O_2 — and the vapor pressure at equilibrium is dependent on the temperature and the amount of solutes in solution.

In the living cell, H_2O is modified by a special physical force called solvation which arises when water abuts a cell surface (DROST-HANSEN & SINGLETON, 1989) and which involves H bonding interactions with cations such as K^+, Mg^{2+}, etc. (see FRANKS & MATHIAS, 1982; VASILESCU *et al.*, 1990; WIGGINS, 1990). In these molecular networks, cations are hydrated: 6 H_2O encage the alcaline K^+ and also surround the alcaline earth metal Mg^{2+}. The hydration shells resulting from the self-assembly of water molecules thus sequester them in the immediate surroundings of the cations, an anhydrization process which creates the necessary microenvironment for condensation of amino acids into peptide bonds, and a condition for the salting-out of proteins.

Among the properties of water which make it so uniquely suited to the diverse roles it plays in cell processes (Potts, 1994), its electric dipole is preeminent. It results from the greater electronegativity of the single oxygen atom over its two hydrogen atoms. It is this bipolarity wich confers to water its capacity to H-bond to other H_2O molecules (see Fig. 2 in TURIAN, 1994). Such process of self-assembly into an expanding network, exerted between similar molecules by template forces is a characteristic feature of living matter and therefore allows us to consider water as prototypic, preliving molecules.

2. SELF-RECOGNITION OF AMINO ACIDS BETWEEN PEPTIDIC RINGS OF NANOTUBES

It has often been speculated (see KAUFFMAN, 1993) that perhaps enough information is present in the protein molecule for replication. This belief that life began with self-replicating proteins is widespread since OPARIN (1957), with his protobiontic coacervates, proposed that, contrarily to the current idea that only polynucleotides can replicate, polypeptides are capable of catalytic behaviours and thus could be produced abiotically on the primitive Earth as simulated by FOX & DOSE (1977) among others.

Many amino acids, the most abundant being glycine and alanine, have been produced in laboratory simulation 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 the cations mentioned above. As questioned by CAIRNS-SMITH (1982) "what the simplest useful proproteins might have been like — defining a poly-α-amino acid as (at least) a proprotein if it is both sufficiently accurately specified and long enough to fold, or otherwise "self-assemble", into some distinct higher order 'structure". Moreover, many processes of biological recognition require the stripping away (at least in part) of solvent water from interacting groups and hydration potentials of amino acid side chains have been measured (see WOLFENDEN *et al.*, 1979).

The suggestion has been made of a possible self-sustaining network of proteins in which the components mutually catalyse the synthesis of each other from monomeric starting materials (DYSON, 1982). A large enough assemblage of random polypeptides could thus catalyze peptide-bond formation (KAUFFMAN, 1986) even though leaving the difficulty of amino acid sequence specificity (JOYCE, 1989). A 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. ORGEL (1972) has 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 Fig. 9.11 (b) in CAIRNS-SMITH, 1982). The tendency of linear heteropolymeric polypeptides to form antiparallel β-pleated sheets could thus provide the self-reproducing sequential information as noted above (see ORGEL, 1992).

It is known that to form a β-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.

Sequential specification of amino acids has been shown to occur in the interannular association of β-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 then been realized

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 molecular evolution, the first peptides abiotically formed might also have been cyclic ones on the model of bacterial cyclic peptidic antibiotics (gramicidin, valinomycin) known to be synthesized without an RNA template (see LIPMANN, 1971). Stacking of such cyclic polypeptides therefore could concour to the self-assembly of cylindrical nanostructures of the type of the organic nanotubes — first described by IIJIMA (1991) and EBBESEN & AJAYAN (1992) — self-assembled according to the cyclic octapeptide architecture built by GHADIRI *et al.* (1993). The hollow cylinders provided by nanotubes have the physico-chemical advantage over the plain structures of wires, vesicles (budding microspheres, in FOX, 1965) and "marigranula" (BOUNIAS, 1990) to offer two interfaces for the energetic ionic exchanges required by prometabolic activities, i.e. external for exergonic forces, internal for endergonic ones.

These considerations lead us to propose a model of prevital nanotube (Fig. 1) 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 with (2) our visualization of such a β-sheet closed upon itself into the polypeptidic nanotube built by vertical stacking of rings of cyclic peptides, intensively H-bonded (Fig. 1b), according to the architectural model recently produced by GHADIRI *et al.* (1993).

In our model, two successive rings would constitute a unit of template replication (Fig. 1a) because the lowest ring could first attract and peptide bind amino acids of opposite electric charge (for ex. glutamic acid [–] facing lysine [+]) thereby building the second ring of the dimer. In short, the first ring formed by peptidization in the contact of the anhydrizing substrate (a Mg^{2+} nanocrystal?, see below) would thus serve as template for an electrically complementary ring below it and the H-bonded ring stacking process would basipetally proceed further up into the nanotube (Fig. 1c).

The recognition-interaction (attractive/repulsive) between hydrophilic amino acids would be vertically complemented by the hydrophobic forces between carbon side chains of amino acids either homologous (alanine-alanine, valine-valine, etc.) or closely related (alanine-glycine, etc.) but not between spatially too different ones because of steric hindrance (alanine-leucine, etc.). Such hydrophobic forces would provide the cohesion forces between rings when similar electric charges (+ in Fig. 1a) face each other due to the steric constraints of the antiparallel amino acid ring chains.

Nanocrystals emerging from rocks could have provided the primordial "seed" for the annular condensation of the primordial peptide ring according to a fortuitous sequence complementarily specified by the H-bond sequences of the mineral, a replicatory role attributed by CAIRNS-SMITH (1982) to primordial "mineral life" or by that of anhydrizing chemicals (polyphosphates, etc.) creating the necessary peptidizing

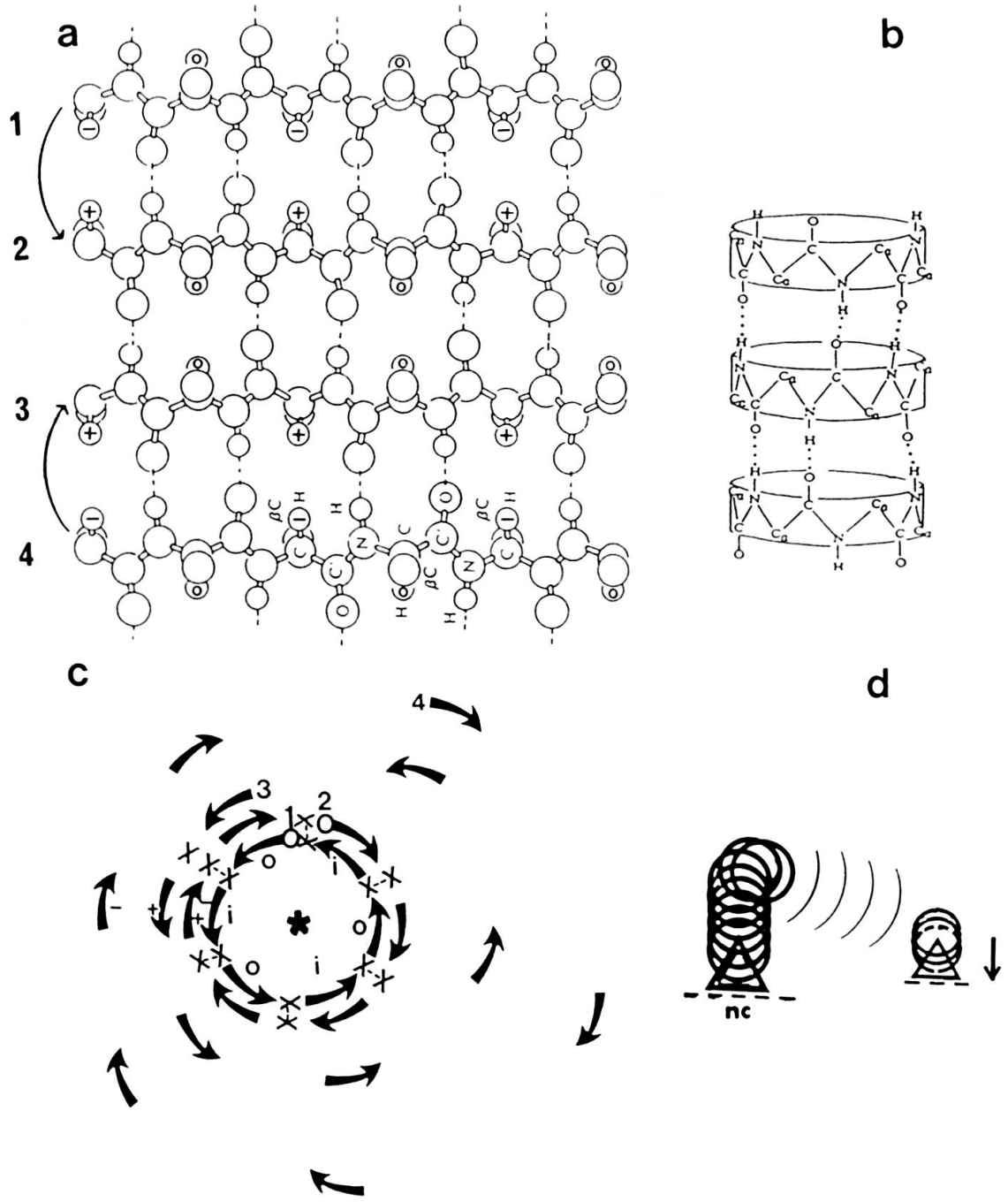

FIG. 1

(a) Antiparallel β-pleated polypeptide sheet with L-amino acid side chains alternating according to PAULING & COREY (1951), (b) patternized to be closed upon itself into a nanotube of self-assembled, H bonded cyclohexapeptide rings according to the model synthesized by DE SANTIS *et al.* (1974). (c). Alternation of hydrophobic (o) and hydrophilic (i –/+) amino acids residues modellized to insure self-replication of protobiontic nanotubes (d) from the 2-ring (a) template units.

0X = closure peptide bond of cyclohexapeptide rings condensing and then basipetally (↓) piling up (1→2→(3)→(4)→...) into a H-bonded (X···X) nanotube (o might be alanine; i^-, glutamic acid; i^+, lysine). ★ = anhydrizing and peptidizing core materials, possibly Mg^{2+} nanocrystal (nc) emerging from waterlogged rock.

conditions (LIPMANN, 1971). Our model would thus rely on such a dehydration requirement to shift the equilibrium of an amino acids-oligopeptide mixture towards larger heteropolymers, a process which appears to be especially enhanced by cations such as Mg^{2+}, an aquo ion surrounded by a shell of hexahedrically co-ordinated H_2O dipoles, known to be abundant in hydrated arche-rocks such as crystallized brucite [$Mg(OH_2)$], white asbestos, etc. (see CAIRNS-SMITH, 1982). Other possible anhydrizing chemicals such as poly- and metaphosphates have also been successfully used as condensing agents of oligopeptides (PONNAMPERUMA & PETERSON, 1965; RABINOWITZ *et al.*, 1969).

To insure their "viability", such nanocolumnar structures had naturally to be terminally plugged by proteinoids possibly playing the role of the recently proposed cationic metallo-oxides (GUERRET-PLECOURT *et al.*, 1994; TSANG *et al.*, 1994) to anticipate the rule of any living cells to be peripherally closed. Secondary, coaxial widening of the column by reciprocal, bipolar (+/–) and hydrophobic "semipermeable" boundary properties to meet environmental constraints could be envisaged either by "crystallization" of many primary cylinders according to the model of gramicidin (WALLACE & RAVIKUMAR, 1988) or by secondary widening of the column by progressive encasing of the primary polypeptidic sheath by secondary proteinoids selectively binding to side chains of the cyclic peptides; thus would be formed an equivalent of early "cytoplasm" surrounding the central hollow core, an equivalent of a "protonucleus" when possibly filled by negatively charged polyphosphates. These would have been further taken over in their primitive coding task by abiotically produced nucleic acid bases, the most important being adenine (A) to produce ATP and providing energy for further peptide bond formation by the concourse of primordial thioesters according to DE DUVE's hypothesis (1991). A necessary protective external layer involving hydrophobic residues of amino acids, isoprenoids or fatty acids, would have thus provided a "protoperiplasmic membrane" thereby completing the primitive "Russian nanodolls".

The ring structure of the nanotubes could theoretically be repeated so long mechanochemical constraints be met, contrarily to the tobacco mosaic virus in which the length of the particle is determined by the length of the internally coiled RNA (KLUG, 1969, in TURIAN, 1989). However, when reaching a critical length, the nanotubes would be prompt to dislocate as old tumbling-down chimneys (Fig. 1d), following rupture of their interrings H-bonds. This would be expected to occur preferentially between two successive dimeric template units where electric repulsions between similarly charged side chains (see Fig. 1a) might overcome both hydrophobic forces and the interannular H bondings. The separated oligorings would thus be competent to resume new cycles of self-replicative annealations by basipetal condensation of specific amino acids around surface nanocrystals and therefore perpetuate the breed. Such dislocation of the rod-like "nanochimneys" would prefigure the most primitive, binary fission process of cell reproduction still exhibited by most modern bacteria.

CONCLUSIONS

Grounded in the principle of Polarity (TURIAN, 1994), the universal prebiological and biological use of dipolar H templates enforces us to share with others the opinion that pregenetical evolution would have followed a route inverse that of the "central dogma" of genetic information which has already been challenged not only at the level of reverse transcriptase but also by the proposal of reverse translation (MEKLER, 1967; COOK, 1977; MEHTA, 1986) and therefore of protein first. In this molecular evolution, water molecules showed the way to replication by templating themselves through their prototypic homopolar H bonds. Such polar bondings were then exploited by homotemplation of the covalently linked peptide bonds between homologous amino acids heteropolarly bonded unit-to-unit in the stacked cyclic peptide rings of proproteinaceous nanotubes. Such "protein first" evolution would then have been taken over by the improved specification anticipating the more specific heterotemplate self-recognition provided by peptide nucleic acid (PNA) and the "RNA world" (see GESTELAND & ATKINS, 1993) announcing the "modern DNA world" endowed with its tremendous memory capacity.

ADDENDUM

According to our preliminary experiments, molecules of a simple, monomeric cyclotetrapeptide (β-Ala-Gly-β-Ala-Gly) dissolved in an anhydrizing Mg^{2+}-rich saline solution are not only stabilized but could also act as templates for their autocatalytic replication as evidenced at least by significant increases in dipeptide bondings obtained from only homologous amino acids (technical data in Communic. SPHN, November 2, 1995, Archs Sci. Genève, Vol. 49, Fasc. 1, 1996).

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