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ASTROBIOLOGY

The Role of Carbohydrates at the Origin of Homochirality in Biosystems

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Abstract Pasteur has demonstrated that the chiral components in a racemic mixture can separate in homochiral crystals. But with a strong chiral discrimination the chiral components in a concentrated mixture can also phase separate into homochiral fluid domains, and the isomerization kinetics can then perform a symmetry breaking into one thermodynamical stable homochiral system. Glyceraldehyde has a sufficient chiral discrimination to perform such a symmetry breaking. The requirement of a high concentration of the chiral reactant(s) in an aqueous solution in order to perform and *maintain* homochirality; the appearance of phosphorylation of almost all carbohydrates in the central machinery of life; the basic ideas that the biochemistry and the glycolysis and gluconeogenesis contain the trace of the biochemical evolution, all point in the direction of that homochirality was obtained just after- or at a phosphorylation of the very first products of the formose reaction, at high concentrations of the reactants in phosphate rich compartments in submarine hydrothermal vents. A racemic solution of D,L-glyceraldehyde-3-phosphate could be the template for obtaining homochiral D-glyceraldehyde-3-phosphate(aq) as well as L-amino acids.

Keywords Homochirality · Origin of life

Origin of Life and the Environment at Earth 4 Billion Year Ago

All carbohydrates and derivatives of carbohydrates in biosystems are D-configurations and all amino acids and derivatives of are L-configurations. This

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notation refers to the stereo specific configuration of ligands at the carbon atom next to the terminal $-CH_2OH$ for carbohydrates and to the configuration at the $(\alpha-)$ carbon atom with a carboxylic acid and an amine group attached. The homochirality is crucial for the coupled biochemical reactions in living systems. The origin of this specific order could may be have been evolved during a purification of simple biosystems, but a general assumption is that the homochirality of carbohydrates and amino acids have been present at the origin of life on Earth.

The oldest undisputed evidence of life on Earth is 3 Gyr (billion years) old (Brasier et al. 2006). It is fossilized bacteria, but older findings in rocks dated to about 3.5 Gyr (Altermann and Kazmierczak 2003) and 3.8 Gyr (Mojzsis et al. 1996) may also show sign of the presence of bacteria. From a biochemical and biological point of view a bacteria is, however, a very complex and highly ordered system and thus the purification of bio-molecules and the self-organisation into complex biological control systems must necessarily have appeared significantly earlier than the appearance of bacteria. The Earth is 4.56 Gyr old, and if life has originated on Earth, it has taken place in the time interval from the creation of the Earth and to the appearance of the first geological sign of life. To determine possible physicochemical models for the origin of homochirality and the origin of life it is thus necessary to know the physicochemical environment at this early time of the Earth's history.

Bacteria as well as all other biosystems are from a physicochemical point of view soft condensed matter, and one more fact is worth noticing. All the elementary bio-assembly of molecules are dehydrations (DNA,RNA,proteins, starch,fats) with release of one water molecule per polymerization step, with the consequence that H_2O must have been present at the self-organization of the complex biosystems at the origin of life. A part of the water in the oceans comes from meteors that contained ice and hit the Earth at the Late heavy bombardment 3.8–4 Gyr ago (Tera et al. 1974; Cohen et al. 2000). But the solid mantle of the Earth also contains water (Hirschmann and Kohlstedt 2012) and there is evidence of oceans on Earth 4.4–4.3 Gyr long before the late heavy bombardment (Wilde et al. 2001; Mojzsis et al. 2001). So a natural conclusion from these simple facts is that life with homochirality of carbohydrates and amino acids started as self-organization in a fluid containing water as one of its components.

Another fact worth noticing is that all known biosystems only exist at moderate temperatures, $T \leq 150^\circ$ C, and there are at least two reasons that life hardly could have started just after the creation of the Earth. First the temperature just after the condensation of the materials, which has led to the creation of the planet(s) was too high for living systems with membranes. Secondly the Earth is believed to have been involved in a collision 30–100 Myr (million years) just after its creation, a collision which created the Moon (Canup and Asphaug 2001; Canup 2004). This collision and the creation of the Moon had drastic consequences not only for the temperature, but also for the condition at the surface of the Earth (Zahnle et al. 2010). The moon was at the start much closer to the Earth and at that time a day was significant shorter. This is due to the tide waves which have pushed the Moon out to its present orbit and at the same time have damped the rotations of the Earth and the Moon. If Earth had oceans $\approx$ 4.3–4.4 Gyr ago there must have been very strong tide waves and a turbulent atmosphere. The extrapolation back to times just after the Moon's creation is difficult (Kagan 1997; Bills and Ray 1999), but all extrapolations indicate much stronger tide waves for $\approx$ 4–4.4 Gyr at the origin of life.

From a physicochemical point of view biosystems are non-equilibrium and open systems, and the refined self-organization must necessarily have taken place in an environment with high concentrations of the basic constituents and a smooth and continuous input over very long period of time of the constituents for the biosystems, which primarily are carbohydrates and amino acids. It is hard to imagine that this could have taken place in a turbulent atmosphere- or in the oceans of the Earth. But the right conditions could have been present at- or below the hydrothermal vents (Shock 1992; Russell et al. 2010).

Before analyzing the role of carbohydrates at the origin of homochirality in biosystems we need to summarize the appearance of carbohydrides and amino acids at the origin of life and their physicochemical behavior (Section "Aqueous Solutions of Amino Acids and Carbohydrates"), as well as the basic physicochemical-kinetics mechanism for obtaining and *maintaining* homochirality (Section "Spontaneous Symmetry Breaking in Concentrated Racemic Solutions").

Aqueous Solutions of Amino Acids and Carbohydrates

Prebiotic Appearance of Amino Acids and Carbohydrates on Earth

Amino Acids

There are at least three sources to prebiotic amino acids: by lightning in the atmosphere, injected into the Earth from the interstellar space, or already present in the Earth's upper mantle or synthesized from the released materials at or below the vents.

The spectacular experiment(s) performed by Miller (1953) and Miller and Urey (1959) demonstrated that more than 20 different amino acids were produced by sparks ignition in a prebiotic atmosphere of water, methane, ammonia and hydrogen. In the original experiments Miller focused on amino acids, but later spark experiments demonstrated that also formaldehyde and other carbohydrates are synthesised (Schlesinger and Miller 1983). So the lightning in this prebiotic atmosphere produced both the basic constituents in Earth's biological systems.

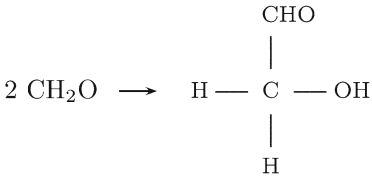
The carbonaceous meteorites contain amino acids and in a non-racemic proportion with a very small excess of L-amino acids. The composition of these meteorites is considered to be close to that of the solar nebula from which the solar system condensed. The two most prominent examples are the Murchison meteorite (Engel and Nagy 1982; Bada et al. 1983) and the Murray meteorite (Cronin and Moore 1971). From these meteorites compositional data and from an estimated impact rate of prebiotic meteorites, Pierazzo and Chyba (1999) suggested that meteorites might have contributed significantly by of the order up to 10^8 kg per year to amino acids on Earth at the time where the life could had started. But even with this injection of amino acids the concentration in the oceans must have been low. Earth's oceans now contain of the order 1.4×10^{21} kg H_2O. The simple amino acid glycine is observed in the interstellar space (Kuan et al. 2003), and the interstellar space could have seeded the Earth with organic molecules at the origin of life (Herbst and van Dishoeck 2009).

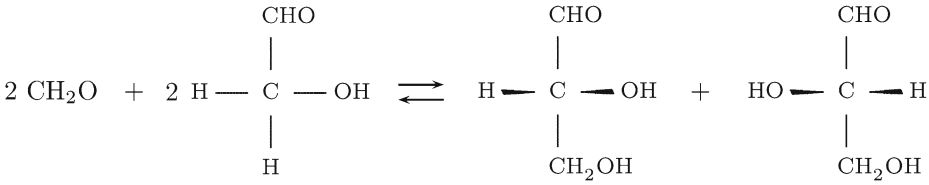
Amino acids can also be synthesized at conditions similar to the physicochemical conditions at or below the hydrothermal vents (Amend and Shock 1998; Imai et al.

1999; Huber and Wächtershäuser 2006). If the materials from which the solar system has condensed contained the same materials as the carbonaceous meteorites, there might have been a substantial amount of amino acids in the upper part of the mantle of the Earth at the origin of life.

Carbohydrates

The formose reaction is the spontaneous condensation of formaldehyde into carbohydrides, which was discovered already in 1861 (Butlerow 1861), and the aldol-like mechanism is described by Breslow (1959). The two first steps are





which gives a racemic mixture of D-glyceraldehyde and L-glyceraldehyde. Formaldehyde, CH_2O, is the simplest carbohydrate and it can be synthesized from carbon dioxide. It is produced in a reducing atmosphere containing CO_2 and methane (Schlesinger and Miller 1983). The condensation into carbohydrides is catalyzed by not only amino acids (Weber 2001); but also by naturally aluminosilicates occurring at the alkaline hydrothermal vents (Gabel and Ponnamperuma 1967; Martin et al. 2008).

Simple carbohydrates are also detected in the interstellar space (Herbst and van Dishoeck 2009) which must have seeded the Earth, not only by amino acids but also with carbohydrates, and simple carbohydrates (formaldehyde) might also have appeared in the upper part of Earth's mantel at the origin of life.

The formose reaction is well known and is believed to be the basic synthesis of biocarbohydrates and related bio-organic molecules (Gabel and Ponnamperuma 1967; Washington 2000; Kim et al. 2011; Jalbout et al. 2007; Lambert et al. 2010).

Stability and Isomerization Kinetics of Carbohydrates and Amino Acids

Both carbohydrates and amino acids are soluble in water due to the hydrophilic -OH groups in carbohydrates and to the hydrophilic -NH_2 and -COOH in amino acids which performs hydrogen bindings with water molecules. Both carbohydrates and amino acids are stable, but configurational unstable in the sense that they, by an isomerization kinetics, change configuration at an asymmetric carbon atom (i.e. an carbon atom with chemical bounds to four different atoms).

Carbohydrates

The kinetics which changes the configuration at a chiral center in a carbohydrate is a "keto-enol" kinetics. The simplest example is the kinetics for D-glyceraldehyde (GLA) in equilibrium with L-glyceraldehyde.

Glyceraldehyde has only one asymmetric carbon atom and the keto-enol kinetic converts the D-configuration to the mirror L-configuration. The hexoses glucose and fructose have four and three asymmetric carbon atoms, respectively. The initiator of the configurational change by the keto-enol kinetics is the oxo group at a carbon atom next to an asymmetric carbon atom, which at a hexose is either carbon atom No. 1 (e.g. glucose) or to carbon atom No. 2 (fructose). The keto-enol intermediate is a configuration with two double bounded carbon atoms, each with an −OH group, (see Fig. 1). It establishes a transformation between different configurational arrangements at carbon atoms next to the oxo group, in the case of glucose between D-glucose, D-fructose and D-manose, but not between the enantiomers D-glucose and L-glucose. The D-configuration of a carbohydrate refers to the configuration of the asymmetric carbon atom next to the terminal group -CH_2OH, in the case of glucose to carbon atom No. 5, and *this is not involved in the keto-enol kinetics*. To obtain a transformation between a D-carbohydrate and the enantiomer L-carbohydrate by the keto-enol kinetics one must go to the triose, as demonstrated in Fig. 1. L-hexoses do not occur naturally in biosystems, but must be synthesized in the laboratory. (E.g. the acetate derivative of L-glucose is found to stimulate insulin release, but it is produced synthetic (Malaisse 1998)).

Aqueous solutions of carbohydrates are reported to be unstable (Kopetzki and Antonietti 2011). Reid and Orgel observed that diluted solutions of carbohydrates under prebiotic conditions degrade within hours or days (Reid and Orgel 1967) and ribose decomposes even at low temperature and neutral pH (44 years at $0< T \leq 150°$ C) (Larralde et al. 1995). None of the experiments contain, however, any information about the quality of the water, used for the solutions. Even highly purified water contains organic materials and it requires special laboratories and technique to avoid bacteria in a solution. Bacteria, or their enzymes will degrade carbohydrates at low concentrations, but not at high concentrations. Carbohydrates at high concentrations are known to be very stable and they are used for conservation of food. Honey, which can be characterized as a fructose rich-solution with ≈ 17 % water is very stable, and fossil honey was found in in southern Georgia in a tomb from the bronze age, 27th–25th centuries B.C. (Kvavadze et al. 2007).

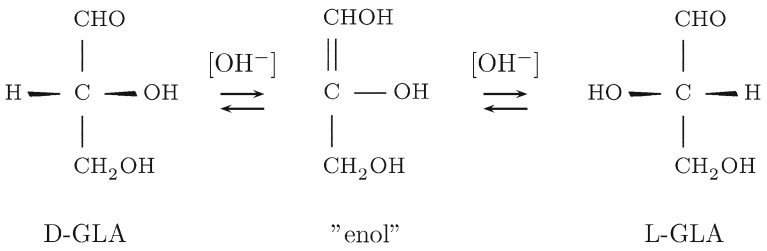


Fig. 1 Keto-enol isomerization kinetics for the triose glyceraldehyde

Amino Acids

Amino acids undergo also an isomerization kinetics (Bada 1972), but there are crucial differences between the keto-enol kinetics for glyceraldehyde, pentoses and hexoses on one hand and the isomerization kinetics for bio-amino acids on the other hand. The pentoses and hexoses maintain their D-configuration at the keto-enol kinetics and only the carbohydrates with one asymmetric carbon, glyceraldehyde, changes between the D- and L-configuration. But all the chiral bio-amino acids change the L-configuration to the D-configuration by their isomerization kinetics. This is because all bio-amino acids are α-amino acids, i. e. the D- and L-configurations refer to the asymmetric carbon atom with an amino and a carboxylic group attached.

The isomerization kinetics will drive a diluted solution of a homochiral L-amino acid toward a racemic solution (Bada 1972). Another difference between carbohydrates and amino acids is the values of the reaction constants for the isomerization kinetics. Amino acids change configurations within thousands of years (Bada 1972) (but might racemize much faster in the presence of a dipeptide (Boehm and Bada 1984)). Glyceraldehyde changes its configuration within hours, but with competing reactions (Fedoroňko and Königstein 1969).

Although the amino acids racemize they are, however, very (constitutional) stable in solid phases as well as in solutions, and even at relative high temperatures (423 K) (Conway and Libby 1958; Snider and Wolfenden 2000). So if the composition of the carbonaceous meteorites equals the composition of the materials that created the Earth it is actual possible that the mantle of the Earth has contained amino acids at the origin homochirality and life.

Spontaneous Symmetry Breaking in Concentrated Racemic Solutions

Pasteur has demonstrated that the chiral components in a racemic mixture can separate into homochiral crystals of each enantiomers. A racemic system can, however, perform a spontaneous symmetry breaking to *one* homochiral system. There are *two* necessary conditions for that this process takes place. The reaction must be exergonic, i,e. $\Delta_r G < 0$ and the system must have an isomerization kinetics between the two chiral configurations. Some amino acids may fulfill these two conditions, but in the case of carbohydrates only the triose glyceraldehyde and its derivatives, e.g. glyceraldehyde-3-phosphate fulfills it. This is due to the fact that whereas the isomerization kinetics for α-amino acids converts D- to L- and visa verse, the keto-enol kinetics for higher-order carbohydrates as mentioned does not change the stereo configuration at the carbon atom next to the terminal group.

Exergonic Reaction in a Racemic Mixture of Chiral Molecules with Strong Chiral Discrimination

The first and crucial condition for obtaining not only a spontaneous symmetry breaking, but also for maintaining homochirality over long times is that there is a (exergonic) gain of Gibbs free energy by a separation into homochiral sub domains. For the reaction

$$D, L \rightarrow D + L, \tag{1}$$

where D,L is an uniform mixture of molecules with D- and L configurations which separates into *sub domains* of the D and L forms, the the gain in Gibbs free energy,

$$\Delta_r G = \Delta_r H - T\Delta_r S \tag{2}$$

by this phase separation is primarily determined by the gain in enthalpy, $\Delta_r H < 0$ by the separation. This is because the change in free energy from the entropy term by the separation, $-T\Delta_r S > 0$, is positive and of the order $RT \ln 2 \approx 2$ kJ/mole for a racemic mixture of equal amount of molecules with D- and L configurations (obtained by approximating the D,L mixture with an ideal mixture with mixing entropy equal to $R[x \ln x + (1-x)\ln(1-x)]$ and with mole fraction $x = 1/2$ for the racemic mixture).

The gain in enthalpy is given by the strength of the chiral discrimination (cd). The existence of chiral discrimination was discovered by Louis Pasteur in 1848 (Pasteur 1848, 1850). It manifests itself in the crystallization from a racemic fluid mixture of enantiomers into crystals of homochiral molecules, as demonstrated by Pasteur. As is well known, it is due to the fact that for some molecules there is an enthalpy gain, $-\Delta_r H > 0$, by packing homochiral molecules together instead of in pairs of enantiomers. The enthalpy gain must be bigger than the temperature times the mixing entropy, which is of the order 2 kJ/mole at room temperature. For pure systems, $\Delta_r H$ in Eq. 2 for the change in enthalpy by the phase separation due to the chiral discrimination can be obtained from standard values as

$$\Delta_r H = \Delta_{\rm cd} H^{\ominus} = \Delta_{\rm f} H^{\ominus}(\text{enantiomer}) - \Delta_{\rm f} H^{\ominus}(\text{racemic}) \tag{3}$$

From a physicochemical point of view biosystems are, however, in an aqueous solution. Because the polymerization of amino acids, as well as of carbohydrides and Nucleic acids, are dehydrations with a release of one water molecule per covalent polymerization bond, the state where the synthesis of prebiotic systems appear is, what in physical chemistry is referred to by (aq) for the aqueous solution. On the other hand, the concentration of the chiral molecules, $[D]$ and $[L]$, at prebiotic self-assembling must necessarily have been high, with only a small concentration of water molecules, for two simple reasons. First

$$\Delta_{\rm cd} H \approx 0; [D], [L] \ll 1 \tag{4}$$

in diluted solution because there is no aggregation of homochiral clusters, so the reaction is endergonic ($\Delta_r G \approx -T\Delta_r S > 0$), and secondly the isomerization kinetics (the second general condition) in a diluted aqueous solution drives the system toward a racemic composition, as is observed in diluted aqueous solutions of L-amino acids (Bada 1972). So even if one, in one way or the other, starts with a homochiral system, it will tend to a racemic state if the concentration is low.

The difference between Pasteur's observation of the spontaneous separation of enantiomers from a racemic mixture and a corresponding spontaneous separation for a racemic mixture of carbohydrates or amino acids is that Pasteur's chiral constituents: D- and L-ammonium sodium tartrate are moderately soluble in water, but carbohydrates and amino acids are very soluble. But even if it is possible to obtain a separation of e.g. amino acids by a crystallization, biosystems are soft condensed matter and we need to find a mechanism which not only separates the two constituents in the racemic composition, but also stabilizes homochirality over (very) long times in a water environment. Therefore a measure of the strength of the

chiral discrimination should be obtained for a state with high concentration of the chiral molecules and where

$$\Delta_r H \approx \Delta_{cd} H^{\ominus}(l), \tag{5}$$

and this should at least be bigger (i.e. $\Delta_r H < -2$ kJ/mole) than the mixing entropy to ensure an exergonic process.

In general, physicochemical data for the strength of chiral discrimination, $\Delta_{cd} H^{\ominus}(l)$ in the fluid state do not exist. Only for the simple triose glyceraldehyde (Gla) where $\Delta_{cd} H^{\ominus}(l) = -11.7$ kJ/mole (Baer and Flehmig 1969), which is much more than what is needed to overcome the mixing entropy. For some amino acids there exist data for $\Delta_{cd} H^{\ominus}(c)$ for the enthalpy difference between an enantiomer crystal and a racemic crystal. This strength is, however, weakened at melting due to less effective packing in the fluid state. A collection of available data is given in Table 1. As can be seen from this table a few central amino acids (Phenylalanine, Isoleucine) might have the potential to maintain a homochiral aqueous state (aq). The simple triose, glyceraldehyde has, however, an exceptionally and sufficiently strong chiral discrimination.

The Isomerization Kinetics

The second general condition for obtaining a spontaneous symmetry breaking in a racemic mixture is the presence of an isomerization kinetics between the two enantiomeric configurations. The isomerization kinetics of amino acids and carbohydrides are complex (Bada 1972; Fedoroňko and Königstein 1969; Nagorski and Richard 2001). We shall simplify the reaction mechanism by bimolecular reactions

$$\begin{array}{ccc} & E_{DD} & \\ D + D & \rightleftharpoons & \\ & E_{DL} & \end{array} \quad \begin{array}{ccc} & E_{DL} & \\ D + L & \rightleftharpoons & \\ & E_{LL} & \end{array} \quad L + L \tag{6}$$

between the two chiral species. The activation energy, E_{DL}, for DL-collisions in an exergonic reaction, which may convert a D-molecule into a L-molecule or *vice versa*, is, in a condensed racemic fluid, less than the corresponding activation energy, $E_{DD} = E_{LL}$, thus allowing a conversion of one of the molecules in the collisions. The inequality

$$E_{DL} < E_{DD} = E_{LL} \tag{7}$$

Table 1 Strength of chiral discrimination for different molecules

Molecule	$\Delta_{cd} H^{\ominus}$/kJ mol^{-1}
Glyceraldehyde(l)	−11.7
Phenylalanine(c)	−6.7
Isoleucine(c)	−5.4
Lysine(c)	≈ 0.
Valine(c)	≈ 0.
Leucine(c)	3.1
Serine(c)	6.3
Proline(c)	16.6
Threonine(c)	16.9
Alanine(c)	18.9

Data taken from NIST Standard Reference Database Number 69 and references therein

accounts for the chiral discrimination with a lower potential energy in homochiral domains of one of the enantiomers corresponding to a sufficient strength of the chiral discrimination (Atkins and de Paula 2002). More specifically

$$E_{\mathrm{DL}} + \mid \Delta_r H(x) \mid = E_{\mathrm{DD}} = E_{\mathrm{LL}}, \tag{8}$$

where the gain in enthalpy, $\mid \Delta_r H(x) \mid$, by a conversion of the stereo configuration is a function of the *local* composition, $x(\mathbf{r})$ of the configurations at the position $\mathbf{r}$, and with a maximum (negative) value of $\mid \Delta_r H(x) \mid$ for a homochiral local composition ($x(\mathbf{r}) = 0$ or $x(\mathbf{r}) = 1$).

Primarily $\mid \Delta_r H(x) \mid$ is proportional with the excess number of homochiral neighbors by a change of a configuration. Consider a simple example: Let a molecule, e.g. in a L configuration be activated to a transition state (intramolecular) configuration. It will with a Boltzmann probability end in the configuration with lowest energy. A simple molecule has twelve nearest neighbours. Let e.g. five of them be in a D configuration, four of the neighbours in a L-configuration and two be indifferent water molecules. It corresponds to that the local environment before the molecule was activated was racemic with an equal amount of D and L configurations. But the activated molecule will most likely turn into a D configuration by which the system tends to a lower energy, but now with an excess of D configuration. Thus a strong chiral discrimination together with an isomerization kinetics will ensure a separation of a racemic mixture on a molecular level and tend to order the molecules in homochiral clusters and sub domains.

A racemic D,L-system tends to separate in homochiral domains of enantiomers if the enthalpy gain, due to the chiral discrimination, is bigger than the entropy of mixing, just as in the case of Pasteur's experiment, but now in a fluid state. Without an isomerization kinetics such a racemic mixture will separate into homochiral sub domains through molecular diffusion. An isomerization kinetics enhances the separation; but what is much more significant, the kinetics also ensures a break of symmetry as demonstrated by the simple example, and results in the dominance of one of the species at late times (Toxvaerd 2000).

The break of symmetry is obtained by, what could be expressed as *self-stabilizing chance* (Toxvaerd 2005). The deviation from a racemic mixture is self-stabilizing because a homochiral clusters- or sub domains catalyse their own growth by the isomerization kinetics which mainly takes place in the interface, whereas the chiral discrimination inside the homochiral domains slows down the kinetics and the conversions of the configurations, which always are unfavorable. Still one needs to explain the observed break of symmetry since the kinetics seems only to enhance the separation but *it does not favour one of the chiral species*. The break of symmetry on a macroscopic scale will appear when one of the homochiral domains encapsulates the other domain. In a *confined geometry* of e.g. a fluid in a bottle or a prebiotic racemic mixture in a solid chamber (Russell and Martin 2004; Martin and Russell 2003), one of the homochiral domains will dominate when, by a chance, it percolates in the confined volume and encapsulates the other domain.

A simple example (Fig. 2) illustrates this mechanism. Consider a system consisting of two homochiral (macroscopic) phases and let e.g. the D form be the dominating (red area in Fig. 2), but as a big droplet in the middle of a box surrounded by molecules with L configurations (white area). The D molecules in the droplet has a convex surface (and the L molecules around the droplet have correspondingly

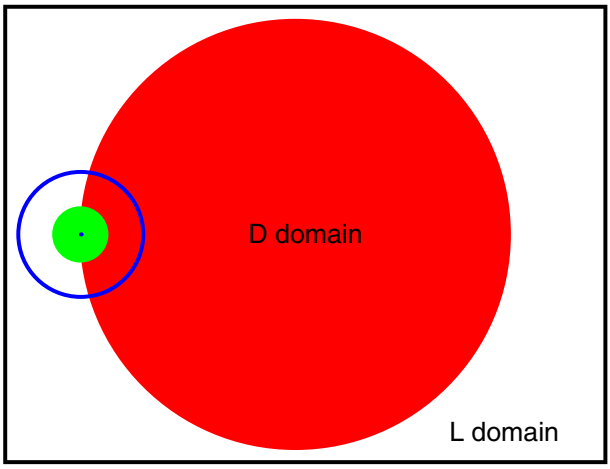


Fig. 2 Illustrative example of the topological mechanism for symmetry breaking and the dominance of one of the chiral species. The (*rectangular*) volume contains the two separated homochiral phases of the enantiomers. The L-rich domain is white and it percolates the volume, whereas the red D-rich domain in the droplet is encapsulated by the L-rich domain. An activated particle (*green*) in the interface between the two domains has a range of attraction (*blue*) to the nearest neighbours which together with the activated particle determine the strength of the chiral discrimination. Since the *white area* inside the *blue circle* is greater than the corresponding red area, there are an excess of L neighbours and the activated particle will end in the L-configuration with a Boltzmann probability. The *white area* will increase and the area of the red droplet decrease and the droplet will finally disappear

a concave surface). Let the green circle mark an activated molecule A^* which will tend to either a D configuration or a L configuration with a Boltzmann probability depending on the local strength of $\Delta_r H(x(\mathbf{r}))$. Due to the strong chiral discrimination $\Delta_r H(x(\mathbf{r}))$ is only negative in the interface and the isomerization kinetics is mainly active there. Even if there are more D molecules in the droplet than L molecules around the droplet, most neighbours to an activated molecule in the interface are L due to the concave L-rich neighbourhood, and the activated molecules will most likely end in a L configuration by which the (big) droplet decreases. It is a matter of *chance* which of the two enantiomers that dominates and encapsulates the other domain. The domain-catalytic behaviour is *self-stabilizing*, and the dominance of a percolating domain is self-stabilizing as well, because its concave interface will ensure the dominance. The topological determined condition for symmetry breaking and the dominance of one of the species is illustrated in Fig. 2 (for further details see Toxvaerd 2000).

Figure 3 shows the time evolution of chiral dominance in a fluid of particles with chiral discrimination, obtained by a realistic (molecular dynamics) computer simulation (Toxvaerd 2000). The kinetics are implemented at time $t = 0$ and the strength of the chiral discrimination is given by the difference in the two activation energies, E_{DL} and $E_{\mathrm{DD}} = E_{\mathrm{LL}}$. The dominance of a species is measured by the enantiomeric excess given by the difference in mole fraction, $x_{\mathrm{D}} - x_{\mathrm{L}}$. For $E_{\mathrm{DD}} - E_{\mathrm{DL}} = RT$ we do not obtain a break of symmetry even after very long times, and inspection of the (local) composition shows that the mixture remains in the racemic state. This

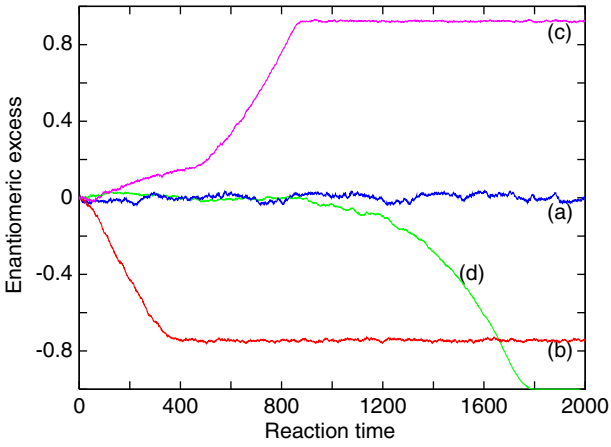


Fig. 3 The enantiomeric excess, i.e., the difference in mole fraction, $x_D - x_L$, as a function of time in a molecular dynamics system with isomerization kinetics and for different strength of chiral discrimination, accordingly to Eq. 8: **a** | $\Delta_{cd} H^{\ominus}$ |$= RT$, **b** $2RT$, **c** $3RT$ and **d** ∞

is also to be expected since the mixing entropy is $RT \ln 2$. But for a stronger chiral discrimination one observes a break of symmetry and a dominance of one of the enantiomers at late times. The figure only shows four cases; but many independent simulations gave an equal dominance of the D- and L- systems, within the statistical uncertainties, as one shall demand for a racemic system with no preference for one of the enantiomeric configurations. The dominance appears already for a strength of $2RT$ (b in the figure), but this strength is not sufficient to kill the isomerization kinetics within the dominating domain, and the system ends in a chiral fluid, but with a small homogeneous concentration of the loosing species. (Only for an infinite strong chiral dominance of $\Delta_r H(cd) = \infty$ (d in the figure) does this system end in a pure homochiral fluid.) Two other fluid systems have been investigated (Toxvaerd 2004a, b) in order to determine the sensitivity of the break of symmetry of the actual fluid systems, the conclusion being, that the isomerization kinetics which destabilizes homochirality in diluted solutions ensures homochirality at high concentrations, provided that the chiral discrimination is sufficiently strong.

The description of the spontaneous symmetry breaking is exact. It makes only use of the law of thermodynamics and that the kinetics is reversible. But it is formulated for an isomerization kinetics between the two enantiomeric configurations in a concentrated aqueous solution. There are other models for symmetry breaking and spontaneous homochirality in racemic systems. Some of these models differs by assuming that the low Gibbs free energy state is not a concentrated aqueous solution of the basic constituent, but e.g. the crystalline phase or adsorbed constituents at mineral surfaces (Hazen and Sverjensky 2010). The general condition cited above is of cause also valid for these models, but the reason for focusing on concentrated aqueous solutions is that it is not enough to obtain a homochirality by crystallization or through adsorption at a mineral surface. A bacterium is, from a physicochemical point of view, soft condensed matter containing chiral molecules including both the L-amino acids and simple D-carbohydrates in an aqueous solution (Ellis 2001; Spitzer and Poolman 2009), and the nucleus for life must from a physicochemical point of view, have been an open driven system with a steady state input of the chiral units for the self-assembly. So the homochirality must be maintained in this fluid over a very long period of time at the emergence of a living system.

In other models for the origin of homochirality in biosystems the chiral purification is obtained through the consecutive kinetic equations for the polymerization of the complex organic molecules. In the Frank model (Frank 1953; Brandenburg et al. 2005) the composition of the simple chiral units in the biopolymers is assumed to be racemic at the origin of the synthesis, and the overall homochirality is obtained by the kinetics during a period of time at the origin of life. The homochiral domains are here the polymers and the chiral discrimination is given by the Gibbs free energy difference between the formation of a polymer binding between two homochiral centre versus the corresponding energy of a polymer binding between units with L- and D- configurations. This asymmetry is expressed by the rate constants for cross-inhibition. This model is not at all in conflict with the present description. In both cases it is the kinetics in the open driven system which ensures homochirality, either by the isomerization kinetics between monomers or by the kinetics of polymerization, and in both cases governed by the gain of Gibbs free energy by homochiral (inter- or intramolecular) contacts. In fact both symmetry breaking kinetics might have been present at the origin of homochirality. But whereas the Frank model is an appealing model for purification of a racemic mixture of amino acids, the model is less appealing in the case of homochirality in polymers of carbohydrates such as the complex stereo-specific macromolecules DNA and RNA with a homochiral backbone of D-ribose. Here a model which ensures homochirality of the polymer units before the synthesis of the macromolecule is more appealing.

Homochirality of Carbohydrates and Amino Acids

The carbohydrates, amino acids and their derivatives in biosystems are all homochiral. Thus one needs to explain how a symmetry breaking appears for both constituents. No matter where the ordering has taken place it is likely that both constituents have been present. But it is in fact very simple to explain this apparent puzzle. The mechanism works primarily through the gain of Gibbs free energy produced by a homochiral clustering together with an isomerization kinetics, and works equally well for mixtures of carbohydrates and amino acids provided there is a sufficient gain in energy by clustering D-carbohydrate molecules together with L-amino acid molecules. Nowhere in the thermodynamic/kinetic description in Section "Spontaneous Symmetry Breaking in Concentrated Racemic Solutions" for symmetry breaking in a concentrated aqueous solution is it assumed that all the molecules should be of the same type, only that there is a gain in energy by ordering and an active isomerization kinetics in the mixture. It is only a matter of whether there is a sufficient gain of Gibbs free energy by clustering amino acids together with a carbohydrate and this is actually the case for some simple carbohydrates and some amino acids (Kock et al. 2002; Takats et al. 2003; Pizzarello and Weber 2004, 2010; Breslow and Cheng 2010).

In Kock et al. (2002), Takats et al. (2003) the authors observed a stereo selective coupling between L-serine octamers and D-glyceraldehyde and D-glucose. Serine furthermore performs coupling with phosphoric acid and some transition-metal ions. Serine has a unique ability to perform "magic-number" ionic clusters composed of eight acid units and with a stereo selective chiral discrimination (Nanita and Cooks 2006).

L-isovaline acts as a asymmetric catalyse of the threose and erythose from condensation of glycolaldehyde (Pizzarello and Weber 2004). Glycolaldehyde and racemic glyceraldehyde condensate to pentoses in non racemic proportions in the presence of (some) dipeptides of L,L- and D,D-amino acids (Pizzarello and Weber 2010).

The syntheses of glyceraldehyde from formaldehyde and glycolaldehyde in the present of homochiral amino acids gives a non racemic yield (Breslow and Cheng 2010). In Breslow and Cheng (2010) some L-amino acids were observed to give an excess amount of D-glyceraldehyde, e.g. L-phenylalanine, whereas e.g. L-proline gives a significant excess of L-glyceraldehyde.

These asymmetries, obtained in the synthesis of carbohydrates in the presence of excess L-amino acids, must be a result of the chiral discrimination (energy binding) between the carbohydrates and the amino acids. According to the model described above such gain of Gibbs free energy together with the isomerization kinetics of glyceraldehyde is sufficient to obtain a homochiral solution of D-glyceraldehyde. But the available experimental data show that only some of the L-amino acids favor an ordering of D,L-glyceraldehyde to D-glyceraldehyde. For some amino acids their L-configurations leads to an excess of L-glyceraldehyde (Pizzarello and Weber 2010; Breslow and Cheng 2010), e.g. L-proline. These catalysis works both ways so an excess of L-glyceraldehyde enhances the isomerization growth of L-proline, and correspondingly D-glyceraldehyde must enhance the isomerization growth of D-proline. According to Table 1 proline has a chiral discrimination which favors a racemic proportion even in a concentrated solution. Thus if the origin of homochirality of carbohydrates appeared via a catalyze by an L-amino acid, one needs to clarify how the homochirality of some L-amino acids, e.g. L-proline, has been obtained together with D-carbohydrates.

The chiral discrimination between amino acids and glyceraldehyde do not favour one of the constituents. But there is, however a significant difference between the isomerization kinetics of a carbohydrate and an amino acid. Whereas a diluted solution of an amino acid racemizes within thousand of years (Bada 1972) (see however Boehm and Bada 1984), the corresponding racemization of e.g. a diluted solution of D-glyceraldehyde is significant faster but with competing reactions (Fedoroňko and Königstein 1969). On one hand this may be taken to imply that it is only possible within days or years to observe an excess of chirality of carbohydrates, but not of amino acids in a mixture of the two constituents, and one the other hand, that homochirality is first obtained for the carbohydrate no matter what the excess of chirality of the two constituents at the start of the purification.

The Role of Phosphate at the Origin of Life

So far one important fact has been ignored. The role of phosphate at the origin of homochirality and life. Although all derivatives of carbohydrates have D-configurations they appear almost always as phosphate derivatives. The list is long: The central energy cycles, the glycolysis and gluconeogenesis, ATP, ADP, RNA, DNA and the most common anchor molecule in the membrane molecules. Phosphates did not, however, appear in high concentrations in the early oceans (Keefe and Miller 1995; Hagan et al. 2007), but they are widely distributed in many minerals. Phosphate rocks containing apatite ($Ca_{10}(PO_4)_6(OH,F,Cl)_2$), are widespread on Earth and there are

rare natural examples of condensed phosphates (e.g. canaphite, $Ca_2Na_2PO_7.4H_2O$ (Rouse et al. 1988); Kanonerovite $MnNa_3P_3O_{10}.12H_2O$ (Popova et al. 2002)).

A simple example illustrates the role of phosphate at the origin of life. There exist two different forms of simple living organism, Archaea and Bacteria. The central metabolisms (glycolysis and gluconeogenesis) are common but they differ on other biosynthetic pathways (Graham and White 2002; Genschel 2004), and by having different membrane molecules. Archaea membrane-molecules consist of (ether) derivatives of sn-glycerol-1-phosphate, whereas the molecules in the membranes of Bacteria and Eucarya consist of (ester) derivatives of sn-glycerol-3-phosphate. The membrane molecules are now synthesized by enzymes which, however, have no common sequence, and an analysis of these enzymes in different Achaea and Bacteria indicates that there is no common enzyme-ancestor (Koga et al. 1998). In a living organism the membrane building blocks are synthesized from e.g. glycerol with help of these stereospecifique enzymes (Peretó et al. 2004); but at the origin of life we must search for a reaction pathway of spontaneous self-assembling directly from the ingredients. There are two facts which together are notable.

All the elementary membrane molecules in a cell are homochiral, and all these molecules (in Archaea and Bacteria membrane of three carbon atoms) can be synthesized from glyceraldehyde or glycerol. These two facts are notable because one can obtain simple vesicles with membranes from amphiphiles with only one or two central carbon atoms and with only one hydrophobic chain in the membrane molecule (Ourisson and Nakatani 1999). But nature did it with three carbon atoms in the central chiral unit and with two hydrophobic chains linked to the amphiphilic head group; all which can be synthesized from glyceraldehyde (see Fig. 4). If the

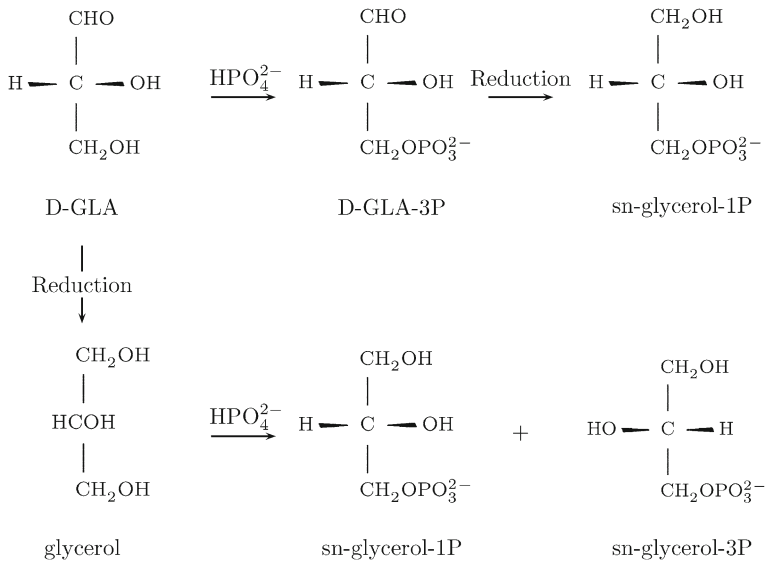


Fig. 4 Phosphorylation and reduction of glyceraldehyde. If phosphorylation precedes reduction one obtains the configuration found in Archaea; if the reduction precedes phosphorylation one obtains both the configurations in Archaea and Bacteria. (Notice that due to *IUPAC* nomenclature rules the reduced product of D-glyceraldehyde-3-phosphate is sn-glycerol-1-phosphate)

spontaneous self-assembly of cell-membranes had originated from a pool of simple bio-molecules, why would the spontaneous synthesis not have chosen the simplest track and synthesized simpler membrane molecules than diglycerides, phosphoro-lipids and phosphoro-ethers? The homochirality of the biomembranes are crucial for their functions and the first chiral component in the formose reaction is glycer-aldehyde from which D-glyceraldehyde-3-phosphate and all the different membrane molecules can be synthesized.

The Role of Carbohydrates at the Origin of Homochirality in Biosystems

The general opinion and the literature about the origin of homochirality favors amino acids as the initiator and catalyzer of homochirality (Higgs 2009). But inspection of the experiments and the present analysis reveals that it is more likely D,L-glyceraldehyde or rather D,L-glyceraldehyde-3-phosphate. The catalysis of sym-metry breaking by the chiral discrimination of carbohydrates and amino acids is neutral in the sense that it does not select one of the reactants, e.g. an amino acid, as the catalyzer and the other as the substrate. A differences in the reaction times of the isomerization kinetics in favor of carbohydrates implies, however, that a carbohydrate reaches the homochiral state faster, and thus will act as the catalyzing template for homochiral purification of the amino acids. But if it was a carbohydrate that first reached the homochiral state, there seems to be only one possibility, glyceraldehyde or more likely the derivative glyceraldehyde-3-phosphate. This is so because the isomerization kinetics of the higher order carbohydrates do not change the configuration at the carbon atom next to the terminal group, and because the spontaneous reaction of D,L-glyceraldehyde into pentoses and hexoses results in a spectrum of carbohydrates without an enantiomeric excess (Weber 1987). These fact favors a phosphorylation before or at a symmetry breaking and with the homochirality of D-sugars and L-amino acids obtained in a concentrated aqueous solution of D,L-glyceraldehyde-3-phosphate.

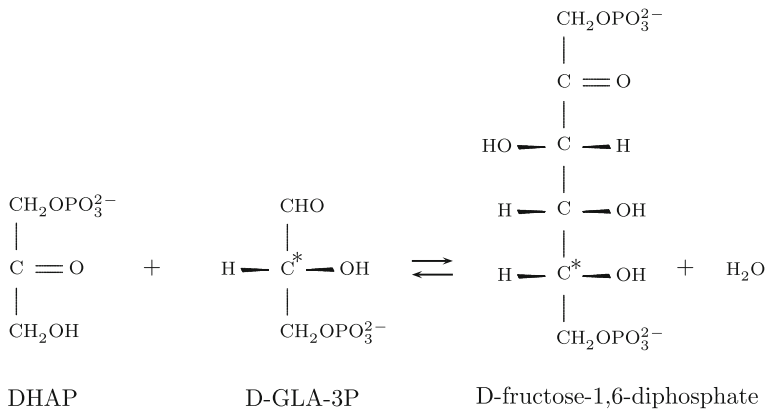


Fig. 5 The aldol condensation of dihydroxy acetone phosphate (DHAP) with D-glyceraldehyde-3-phosphate (D-GLA-3P) to D-fructose-1,6-diphosphate. The asymmetric carbon atom from D-GLA-3P which, by the condensation gives the D configuration in D-fructose-1,6-diphosphate is marked with *

If the formose reaction took place in a phosphate environment with a phosphorylation before the condensation it explains not only the diversity of the enantiomeric form of the membrane molecules but also the central step in the glycolysis and gluconeogenesis. In this step dihydroxyacetone phosphate (DHAP) condensates with D-glyceraldehyde-3-phosphate (D-GLA-3-P) to D-fructose-1,6-diphosphate with the release of one water molecule (Fig. 5). DHAP is one of the molecules in the isomerization reaction of D,L-glyceraldehyde-3-phosphate and will appear together with D-glyceraldehyde-3-phosphate. This aldol condensation is very exergonic at standard concentrations (molar concentrations at pH = 7) with a Gibbs free energy $\Delta G^{\ominus'} = -23.98$ kJ/mole and the reactants will react spontaneously (Nelson and Cox 2010). The reason why we obtain energy from the reverse reaction with hydrolysis of D-fructose-1,6-diphosphate in the glycolysis is that the concentration of D-fructose-1,6-diphosphate is usual quite low (<0.1 mM) by which the reverse reaction is entropy driven and exergonic.

In Summary

A break of symmetry and the ordering of a racemic solution into one homochiral domain only requires a strong chiral discrimination and an isomerization kinetics. These two conditions can be present in a concentrated racemic solution. The requirement of a high concentration of the chiral reactant(s) in an aqueous solution in order to perform and *maintain* homochirality; the appearance of phosphorylation of almost all carbohydrates in the central machinery of life; the basic ideas that the biochemistry and the glycolysis and gluconeogenesis contains the trace of the biochemical evolution (Romano and Conway 1996; Say and Fuchs 2010), all point in the direction of that homochirality was obtained just after- or at a phosphorylation of the very first products of the formose reaction at high concentrations of the reactants in phosphate-rich compartments.

An alkaline submarine hydrothermal mound is known to be compartmentalized and the inorganic membranes would offer low water activity traps and sites not only necessary for the phoshporylations (Russell et al. 2013) but also for the domain catalyzed and self-stabilizing mechanism by which the homochirality of simple organic chiral molecules can be obtained and maintained over long periods of time.

Although there have been many experimental investigations of possible spontaneous ordering of racemic systems into homochiral systems there do, however, not exist such experiments for D,L-glyceraldehyde-3-phosphate(aq).

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