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The role of the peptides at the origin of life

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ABSTRACT

The peptides in biosystems are polymers of L-amino acids, but they racemize slowly by an active isomerization kinetics. The chemical reactions in biosystems are, however, reversible and here we show by a thermodynamics analysis and by comprehensive Molecular Dynamics simulations of models of peptides, that the isomerization kinetics racemizes the peptides at high water activity, in agreement with experimental observations of aging of peptides, but enhances homochirality at a smaller water activity. The main conclusion of the simulations is that it is only possible to obtain and maintain homochirality in the presence of a hydrophobic compact core in a peptide of hundreds of chiral units and at a low water activity, and thus the establishment of homochirality at the origin of life and aging of proteins in biosystems might be strongly connected.

1. Introduction

Biosystems consist of polymers, where the building units are L-amino acids and D-carbohydrates. Another general behavior of the polymers in the cells, the peptides, RNA and DNA, is, that they have "higher-order" conformational structures (Hecht et al., 2004; Levene, 1919; Minsky, 2004; Pauling and Corey, 1951; Watson and Crick, 1953; Zuker and Sankoff, 1984). But neither the peptides, nor DNA in the cells (Lahue et al., 1989; Lindahl, 1974; Sancar and Rupp, 1983) are long-time stable. The L-amino acids in aqueous solutions (Bada, 1972; Helfman and Bada, 1976), and the peptides in the cells racemize slowly (Fujii et al., 2010, 2015; Geiger and Clarke, 1987; Hooi and Truscoot, 2011; Truscott and Friedrich, 2016).

The origin of homochirality in the biosystems is unknown. There have, however been many models for spontaneously obtained homochirality during self-assembly from a racemic mixture of the building blocks. Almost all of them are Frank models (Frank, 1953), where one assumes, that the isomerization kinetics has an autocatalytic amplifying and inhibitory role and a corresponding positive or negative feedback during the self-assembly. For recent reviews see Blackmond (2010) and Saito and Hyuga (2013).

Racemization of peptides in biosystems is associated with an increased concentration of water molecules in the peptides and lost β-sheet structure (Fujii et al., 2010). The water activity in biosystems differs with respect to the extracellular- and intracellular water activity. Primarily the activity is given by the mole fraction of water and the ionic concentrations. But whereas the extracellular fluid in biosystems can be characterized as a rather ideal ionic solution ("saline solution") of ≈ 0.1 M NaCl, the intracellular (cytosol) fluid does not behave as a diluted aqueous solution. It consists of ≈ 0.1 M KCl, but the water activity, given by the vapor pressure for water in the cytomatrix, indicates that the water inside the cell is bound and behaves differently than bulk water (K. Luby-Phelps, 2000; Shepherd, 2006). Since the homochirality of the peptides in the cells degenerates over time, the homochirality must have been established at a condition which deviates somewhat from the physicochemical condition in the cytosol.

The influence of water on the stability of homochirality is investigated by simulating simple models of amino acids and peptides in aqueous solutions. The Molecular Dynamics model is described in the Appendix. The investigation shows that, whereas chiral monomers in aqueous solutions are unstable with respect to preservation of homochirality, the hydrophobic peptides in the aqueous solutions with more than of the order a few hundred amino acid units perform spontaneous chiral purification. This behaviour is well understood from a physicochemical theory, derived in the next section and indicates, that the hydrophobic core in the peptides has played a central role for obtaining the homochirality at the origin of life.

2. The physicochemical condition for stable homochirality in aqueous solutions

The physicochemical condition for stable homochirality of chiral molecules can be obtained for a pure ideal mixture and for ideal diluted solutions.

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A pure racemic mixture of D- and L-molecules can separate into homochiral domains if the gain in enthalpy, due to the chiral discrimination, is more than the loss of entropy by demixing, just as in the case of Pasteur's experiment (Pasteur, 1848), but now in a fluid state. A racemic mixture of chiral molecules and without an isomerization kinetics can separate in homochiral subdomains by molecular diffusion. This more ordered state can spontaneously be obtained from a state with racemic portions of the building units (sugars and amino acids) provided that the reaction Gibbs free energy, $\Delta_r G = \Delta_r H - T\Delta_r S < 0$, is negative.

The separation of a racemic mixture into two homochiral states (D and L) has a negative reaction entropy, $\Delta_r S < 0$. If the temperature, T, times the reaction entropy, $T\Delta_r S < 0$ by a separation from the racemic state to the two homochiral states is less negative than the corresponding reaction enthalpy, $\Delta_r H < 0$ it will ensure a negative reaction Gibbs free energy. An "ideal mixture" estimate of the entropy contribution to the reaction Gibbs free energy gives (Toxvaerd, 2009)

$$T\Delta_r S \approx -RT\ln 2 \approx -2 \ \ \mathrm{kJmol}^{-1} \tag{1}$$

at moderate and biological relevant temperatures, and the system will phase separate into homochiral domains, if the gain of reaction enthalpy given by a "chiral discrimination" is strong enough, i.e.

$$\Delta_r H < -2 \ \mathrm{kJ\ mol}^{-1}. \tag{2}$$

This fundamental physicochemical mechanism has recently been observed for spontaneous phase separation in a fluid mixture into homochiral coexisting fluid domains (Dressel et al., 2014).

An active isomerization kinetics in a racemic mixture with a chiral discrimination given by the reaction enthalpy, $\Delta_r H < T\Delta_r S$ can, however, also ensure the establishment of only one homochiral domain (Toxvaerd, 2000). Biochemical reactions are typically bimolecular. The bimolecular isomerization kinetics for chiral units is

$$\mathrm{D+D} \underset{k_{\mathrm{DL}}}{\overset{k_{\mathrm{DD}}}{\rightleftharpoons}} \mathrm{D+L} \underset{k_{\mathrm{LL}}}{\overset{k_{\mathrm{DL}}}{\rightleftharpoons}} \mathrm{L+L} \tag{3}$$

with the rate constants k_{DL} and $k_{\mathrm{LL}} = k_{\mathrm{DD}}$ between the two chiral species, D and L. Let the rate constants be given by Arrhenius expressions:

$$k_{\mathrm{DL}} = A_{\mathrm{DL}}\exp(-E_{\mathrm{DL}}/RT)$$
$$k_{\mathrm{LL}} = A_{\mathrm{LL}}\exp(-E_{\mathrm{LL}}/RT), \tag{4}$$

where the collision frequency factors for the isomerization kinetics in ideal dilute solutions must be equal, i.e. $A_{\mathrm{DL}} \approx A_{\mathrm{LL}} = A_{\mathrm{DD}}$. The relation between the activation energies and the reaction enthalpy is

$$E_{\mathrm{DL}} - E_{\mathrm{LL}} = \Delta_r H, \tag{5}$$

The chiral discrimination, given by the value of $\Delta_r H$, is the difference in enthalpy between a homochiral and a racemic system. But during a purification to homochirality a gain in enthalpy, $\Delta_r H(x)$, depends, however, on the instantaneous local composition, x, at the position, $\mathbf{r}$.

The strength of the chiral discrimination depends on how well the chiral molecules fit into a compact structure, and it is given by the complex potential function between a chiral molecule and its chiral neighbours. Primarily $\Delta_r H(x)$ depends on the excess number of homochiral neighbours by a change of a configuration. Consider a simple example: let a molecule (or a chiral unit in a peptide) at the position $\mathbf{r}$ be in e.g. an L configuration before it is activated to an (intramolecular) transition state configuration. It will with a Boltzmann probability choose the configuration with lowest potential energy. A molecule in a liquid mixture has typically eleven to twelve nearest neighbours. Let e.g. five of them be in a D configuration, four of the neighbours in a L configuration and three neighbours be indifferent water molecules. It corresponds to a local racemic composition near $\mathbf{r}$ of thirteen molecules with an equal amount of D and L configurations before the activation of the L molecule at $\mathbf{r}$. But due to the local excess of D molecules around the activated molecule, it will most likely turn into a D configuration by which the system has a lower energy, but now with an excess of D configurations. 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 chiral units into homochiral clusters and subdomains. The same kinetics for homochirality must also be valid for the chiral units in the peptides, where the symmetry breaking is caused by the chiral discrimination in the domain of nearest chiral units.

The homochiral dominance is obtained by, what could be expressed as *self-stabilizing chance* (Toxvaerd, 2009). The deviation from a racemic mixture is self-stabilizing, because homochiral clusters or subdomains catalyze 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 conversion of the configurations which are unfavorable. Still one needs to explain the observed dominance, since the kinetics seems only to enhance the separation, but *it does not favour one of thechiral species*. The breaking of symmetry on a macroscopic scale, and the establishment of only one stable homochiral domain will appear, when one of the homochiral domains encapsulates the other domain (Toxvaerd, 2000, 2013).

Simple carbohydrates and amino acids are soluble in water. Chiral discrimination in an *ideal* solution of amino acids or simple carbohydrates in water with the mole fraction x_w, is reduced proportionally to the number of chiral neighbours, and is approximately

$$\Delta_r H(aq) \approx (1 - x_w)\Delta_r H. \tag{6}$$

The chiral discrimination near a surface, $\Delta_r H_{surf.}(aq) \approx 0.5(1 - x_w)\Delta_r H$, is further reduced by a factor of order two due to halving of the number of nearest neighbours, and with the result, that a chiral purification is only possible for an extremely high concentration of chiral units or an extremely high strength of chiral discrimination, no matter where in the fluid. This explains, why the presence of water molecules affects the quatenary structure of a peptide and reduces the chiral order (Fujii et al., 2010, 2015).

The stability of chiral order in the presence of water can be obtained for ideal mixtures. The equilibrium constant K for a diluted solution of e.g. L-chiral molecules or a peptide with L- amino units in equilibrium with a small fraction of its enantiomer by an active isomerization kinetics, is

$$K = \frac{x_{\mathrm{L}}^2}{x_{\mathrm{L}}x_{\mathrm{D}}} = \frac{x_{\mathrm{L}}}{(1 - x_{\mathrm{L}} - x_w)}$$
$$= \frac{k_{\mathrm{DL}}}{k_{\mathrm{LL}}} \approx e^{(E_{\mathrm{LL}} - E_{\mathrm{DL}})/RT} = e^{-(1-x_w)\Delta_r H/RT}. \tag{7}$$

The equation determines the mole fractions x_{L} and x_{D} as a function of x_w and $\Delta_r H$ for an aqueous solution of chiral molecules in equilibrium with a small fraction of its enantiomer by the isomerization kinetics.

3. Chiral molecules and peptides in aqueous solutions

The Molecular Dynamics model and the simulations with isomerization kinetics are described in the Appendix. The simulations of amino acids and peptides in aqueous solutions confirm the thermodynamic derivations in Section 2. It is only possible to obtain a symmetry breaking and a chiral dominance in the MD systems for concentrated solutions of chiral molecules, here with $x_w \leq 0.20$

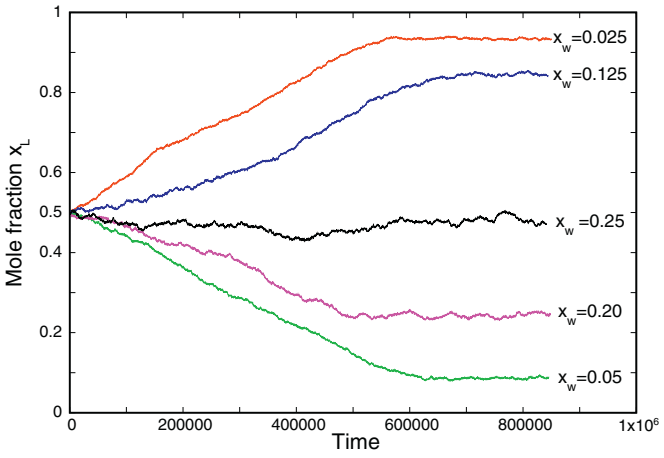

Fig. 1. Mole fraction $x_L(t)$ as a function of time (steps) in aqueous solutions of simple chiral molecules (e.g. amino acids) with isomerization kinetics and a strong chiral discrimination. The start composition is racemic ($x_L(0) = 0.5$). Red curve is $x_L(t)$ for a solution with a mole fraction of water molecules $x_w = 0.025$; green curve: $x_w = 0.05$; blue curve: $x_w = 0.125$; magenta curve: $x_w = 0.2$ and black curve: $x_w = 0.25$. The isomerization kinetics does not favour one of the chiral conformations, and a L or D dominance is obtained by chance with equal probability, as illustrated by the examples in the figure. The equilibrium mean fractions after the symmetry breaking are given by Eq. (7). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

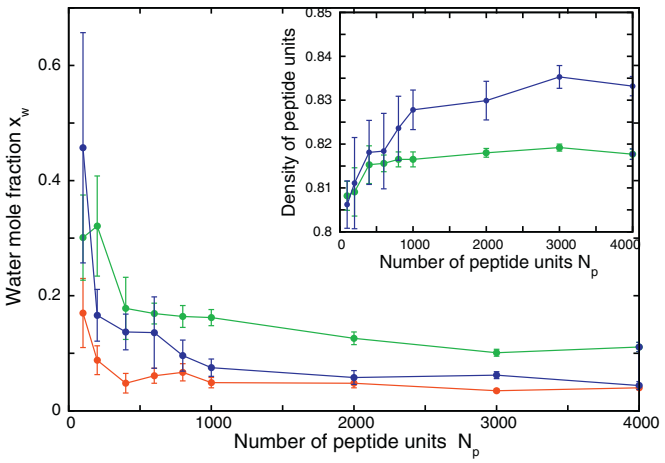

Fig. 2. Mole fraction, x_w, of water molecules in the sphere with radius equal to the radius of gyration for peptides with N_p hydrophobic units with strong chiral discriminations. The red points are for homochiral peptides and the green points are for racemic peptides, both without isomerization kinetics. The blue points are for peptides with isomerization kinetics and they have only a chiral dominance for $N_p \geq 400$. The inset shows the corresponding densities of the units for the racemic peptides (green) and the peptides with isomerization kinetics (blue). The uncertainties are obtained from ten independent simulations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 1). But although all simple carbohydrates and amino acids are soluble in water for low or moderate concentrations, they separate and crystallize at higher concentrations. Biosystems are, however in a fluid state, and there seems to be only one possibility for a self-organized chiral purification and maintenance of homochirality in aqueous solutions: *peptides with a hydrophobic core.*

We have constructed chains with different numbers, N_p, of chiral hydrophobic or hydrophilic units, and in aqueous solutions. The hydrophobic peptides have a compact globular form with a low fraction of water molecules in the peptides, whereas the chains swell up at a higher water activities. There are also differences in the conformations for chains with a racemic (random D- and L-) composition and a homochiral composition of hydrophobic units. The racemic peptides (Fig. 2, green points) have a significantly higher water content than the homochiral peptides (red points), exceeding $x_w \approx 0.20$ for the racemic peptides with chain lengths less than $N_p \approx 400$. The blue points are for hydrophobic peptides with isomerization kinetics. These properties shown in Fig. 2 are in qualitative agreement with the experimental observation of a peptide after aging with loss of homochirality (Fujii et al., 2010).

Fig. 3 shows the evolution of chiral dominance for different lengths of the hydrophobic peptides. The presence of water with a mole fraction, $x_w \geq 0.20$, makes the homochiral state unstable (Fig. 1) and favours the racemic state according to the thermodynamics. The results in Fig. 2 (blue line and points) shows that the short peptides with hydrophobic units and isomerization kinetics contain water molecules with a fraction which exceeds this stability limit. In accordance with these results we observe that peptides of hydrophobic units with isomerization kinetics and chiral discriminations cannot maintain homochirality when $N_p \leq 400$, and Fig. 3 demonstrates this fact. The fraction of the L-state, x_L, for a short peptide of $N_p = 400$ units (red line) fluctuates, but remains racemic in mean. For longer chains one obtains, however, a symmetry breaking to a state with a dominating chirality, either to a D-state (N_p =1000: green), or to a L -state (N_p =2000: blue).

The hydrophobic peptide with $N_p = 1000$ units, with x_L(t) shown in Fig. 3 (green line) is rather compact and globular. The peptide was simulated over a longer time period, where it maintained the chiral D dominance. The configuration at the end of the simulation is shown in Fig. 4. The strong hydrophobicity corresponds to a low water activity. If this peptide, however, is exposed to a higher water activity it swells up with a larger water content in the core, and the peptide looses its homochirality (Fig. 5).

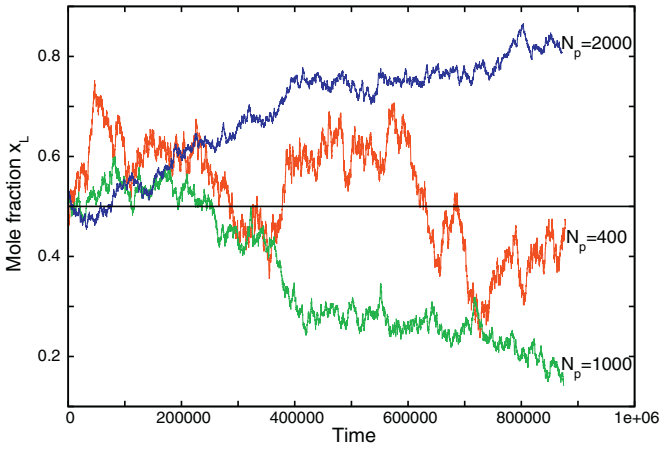

Fig. 3. Mole fraction x_L of L-units in chains with $N_p = 400$ (red), $N_p = 1000$ (green) and $N_p = 2000$ (blue) chiral units, and with isomerization kinetics. The chains have a random and racemic distribution of chiral units at the start. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We have performed many simulations, for different strengths of hydrophobicity, water activity and chiral discrimination ($E_{DL} - E_{LL}$), and they conform the results, shown in the figures. The spontaneous homochirality is only achieved for sufficient strength of chiral discrimination, $E_{LL} - E_{DL} = E_{DD} - E_{DL} \geq 2$, and for hydrophobic peptides with a mole fraction of water which is less than $x_w \approx 0.20$, in accordance with the thermodynamic conditions for obtaining spontaneous homochirality.

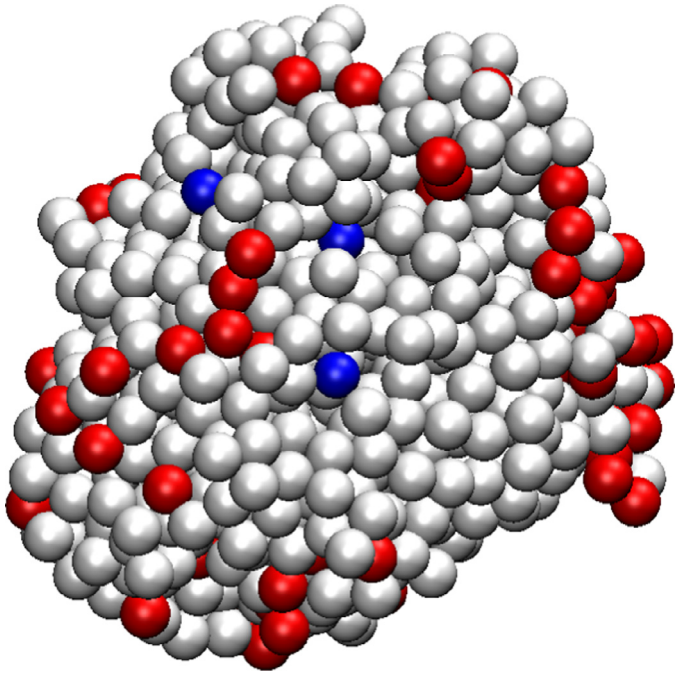

Fig. 4. The peptide with $N_p = 1000$ hydrophobic units and with isomerization kinetics. The peptide is compact and rather homochiral ($x_L \approx 0.15$) with dominating D-units (white). The L-units (red) are mainly located in the water-peptide interface. There are 15 water molecules (blue), mainly located in pockets of the compact peptide and with a few water molecules in the interior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

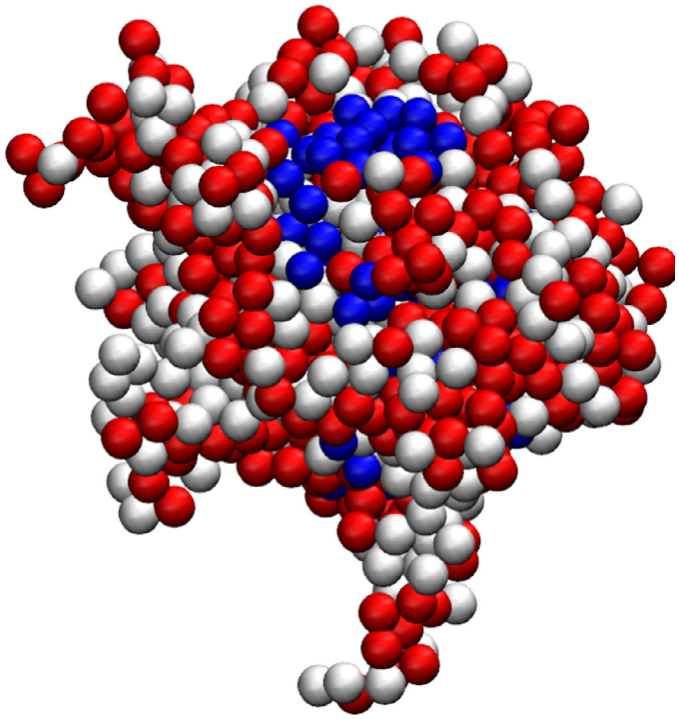

Fig. 5. The peptide with $N_p = 1000$ units at a higher water activity, and with isomerization kinetics. The composition (L/D=red/white) is now ≈ racemic and the concentration of the water molecules is increased to 39. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Conclusion

The intra- and extracellular aqueous solutions contain ions (Na^+,K^+,Cl^-,HCO_3^-,...) in dilute concentrations with an ionic strength of the order 0.15, but whereas the extracellular aqueous (saline-like) fluid behaves as a dilute aqueous solution, the intracellular (cytosol) fluid is not well described by the dilute paradigm (K. Luby-Phelps, 2000; Shepherd, 2006). Enzymes are examples of relatively short peptides with hydrophobic cores. The number of amino acid units in enzymes varies from less than hundred units to more than two thousand units, and the enzymes are present in all living systems. The physicochemical description in Section 2, and the MD simulations are for simple peptide-like polymers in dilute water-like solutions. The number of units in the chains cover the range of amino acid units in the enzymes, and the behaviour of the MD systems is in agreement with the theory in Section 2 and agrees qualitatively with experimental observations of the chiral stability. The conclusion from the comprehensive MD simulations is that it is only possible to obtain and maintain homochirality in the presence of hydrophobic compact cores of hundreds of chiral units and at a low water activity.

The strength of chiral discrimination depends on how well a chiral molecule or the mirror form of the molecule packs with chiral molecules. Normally one associates it with how well a molecule fits in with a copy of itself, compared with how well it fits in with its mirror image molecule. But there are also chiral discriminations between different amino acids (Taresevych et al., 2015; Viedma et al., 2012), and between simple carbohydrates and amino acids (Breslow and Cheng, 2010; Hein and Blackmond, 2012; Kock et al., 2002; Takats et al., 2003). There is a chiral discrimination between a simple carbon hydrate, D-Glyceraldehyde, and the amino acid L-Serine (Kock et al., 2002; Takats et al., 2003).

The investigation indicates that the function of the peptides, at the origin of homochirality and life, *first* were to stabilize homochirality in aqueous solutions by means of the hydrophobic core of the peptides, whereby they can act as the "backbones" with a stereo specific surfaces for the homochiral purification of carbohydrates and amino acids by the isomerization kinetics. An example is the peptide Triose Phosphate Isomerase, which catalyzes the isomerization of D-Glyseraldehyde-3-Phosphate at the central place in the Glycolysis metabolism. This enzyme was presumably in the proteome before the last universal common ancestor (LUCA) (de Farias et al., 2016; Sobolevsky et al., 2013). The presence of such a stable homochiral protein together with the binding of D-Glyceraldehyde to L-Serine can explain the overall dominance of D-carbohydrates and L-amino acids in biosystems.

The chemical reactions in biosystems are reversible, and what ensures homochirality at low water activity will racemize the system at higher water activity. The water activity at the establishment of homochirality must necessarily have been somewhat smaller than the aqueous cytosol solutions in the cells. A low water activity can e.g. be obtained by solutions of amino acids, carbohydrates and peptides at a higher ionic strength and concentrations than in the cytosol. Experiments on such aqueous solutions can reveal, whether it is possible to obtain spontaneous chiral purification and to maintain homochirality in the presence of peptides with hydrophobic cores.

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Appendix A. Molecular Dynamics simulations of amino acids and peptides in aqueous solutions and with isomerization kinetics

The chiral discrimination, $\Delta_r H$, depends on how well a chiral molecule, or a mirror image of the molecule, packs with other chiral molecules (e.g. amino acids or carbohydrates). The net energy difference is given by complex potential functions. But since it is the net gain of energy which gives the strength, it can be obtained by an energy function, which just ensures a correct gain of energy from the interactions between the molecule and its neighbour molecules. Here we simulate, by Molecular Dynamics (MD), such systems of amino acids and peptides of "united atom" units with chiral energy differentiation in aqueous solutions.

The system consists of $N = 40000$ Lennard Jones (LJ) particles in a cubic box with periodical boundaries.[1] The MD simulations are performed with the central difference algorithm in the leap-frog version, and the forces for particle distances greater than r_{cut} are ignored. There are different ways to take the non-analyticity of the force at r_{cut} into account. The most stable and energy conserving way is to cut and shift the forces (SF), (Toxvaerd and Dyre, 2011a) by which one avoids a nonphysical force gradient at the cut. The SF-MD simulations are performed for a temperature T=1.00 and a density ρ =0.80, which corresponds to a condensed liquid at a moderate ("room") temperature.

The peptide chains are constructed by linking LJ-units together by reflecting the LJ potential between two neighbour units in the chain at the potential minimum (Akkermans et al., 1998). This anharmonic bond potential is LJ-like and ensures a smooth interaction of an "amino acid unit" in the peptide with the water particles, as well as with the other units in the chain molecule.

A1. Potentials for hydrophobic and hydrophilic behaviour

The structure of a condensed fluid is determined by the forces within the first coordination shell of nearest neighbour particles (Toxvaerd and Dyre, 2011b), and it is also the short range attractive forces which determines the strength of the chiral discrimination. At the state point (T, ρ) =(1.00,0.80) the range of the first coordination shell (fcs) in the LJ system is $r_{\rm frc} \approx 1.55$.

The range of attraction for homochiral pairs (DD) or (LL) is taken to be equal to the radius of the first coordination shell, $r_{cut}(\rm DD) = r_{cut}(\rm LL) = r_{\rm frc} = 1.55$, by which one obtains a maximum attraction between homochiral pairs. A smaller mean energy for a racemic composition is then achieved by using a shorter range of attraction between enantiomers. The range of attraction between two enantiomers is taken to be r_{cut}(DL)=1.35, by which the mean potential energy difference, Δu, between a racemic mixture and a homochiral fluid is determined to be $\approx Tln2$. (The MD is for canonical ensemble dynamics (NVT), where the chiral discrimination is given, not by an enthalpy difference , but with the corresponding potential energy difference.) Consistent with this choice, MD simulations of a racemic mixture without isomerization kinetics separate slowly into a D- and a L- reach domains for a short range, r_{cut}(DL) < 1.35, of the attraction between enantiomers as one shall expect from thermodynamics considerations (Toxvaerd, 2009).

Molecules can be sorted into hydrophilic- and hydrophobic molecules according to their solubility in water. But the word "hydrophilicity" is perhaps a bit misleading, since there is only one molecule which is hydrophilic, and this is H_2O. And although all simple carbohydrates and amino acids perform hydrogen bonds and are soluble in water for small or moderate concentrations, they separate at higher concentrations. The strong hydrophilicity between LJ "water" molecules (W) is achieved by using $r_{cut}(\rm WW) = 1.55$, i.e. a strong mean attraction between pairs of water molecules, equal to the strong attraction between two homochiral units.

The hydrophilicity or hydrophobicity between a water molecule and a chiral molecule -or chiral unit in a peptide, is also monitored by the range of attraction. A hydrophobic D or L unit have a relative weak attraction to a water molecule. This hydrophobicity is achieved by using a cut $r_{cut}(\rm DW) = r_{cut}(\rm LW) \leq 1.35$, i.e. less or equal to the attraction between two enantiomers, whereas a more hydrophilic unit in the peptide has an attraction $r_{cut}(\rm DW) = r_{cut}(\rm LW) \geq 1.40$, which corresponds to a higher water activity.

We have constructed chains with different numbers, N_p, of LJ-units and in aqueous solutions with $N_w = N - N_p$ water molecules. The hydrophobic peptides have a compact globular form with a low fraction of water molecules in the peptides, whereas the chains swell up at a higher water activity.

A2. Chiral units with isomerization kinetics

The isomerization kinetics is performed as described in Toxvaerd (2000). A particle, i, at time t is activated by a collision with one of its nearest neighbours, j, if the potential energy, u_{ij}, between i and j at the collision exceeds the activation energy for the isomerization

$$u_{ij}(t) \geq E, \tag{8}$$

where E is equal to $E_{\rm DD} = E_{\rm LL}$, if j has the same chirality as i, and equal to $E_{\rm DL}$ if not.

The potential energy of particle i, at the time where it collides with j, is

$$u_i(t) = \frac{1}{2}\Sigma_k u_{ik}(t) \tag{9}$$

for the sum over interactions with i's nearest neighbours. Correspondingly the potential energy of i is

$$\tilde{u}_i(t) = \frac{1}{2}\Sigma_k \tilde{u}_{ik}(t), \tag{10}$$

if i's chirality is changed. The chirality of particle i is then changed in the traditional way by a Boltzmann probability from $\Delta_r u = \tilde{u}_i(t) - u_i(t)$ (Toxvaerd, 2000).

According to the thermodynamics, the strength of the chiral discrimination can be obtained from the activation energies, $E_{\rm DL}$ and $E_{\rm LL} = E_{\rm DD}$. The activation energies per chiral unit in favor of homochirality has to be

$$E_{\rm LL} - E_{\rm DL} = -\Delta_r H \geq T\Delta_r S = Tln2. \tag{11}$$

The MD systems perform symmetry breaks with chiral purification for $E_{\rm LL} - E_{\rm DL} = E_{\rm DD} - E_{\rm DL} \geq 2T$, in agreement with the thermodynamics (ideal mixture) estimate (Toxvaerd, 2009). The isomerization kinetics in the Section 3 are for $E_{\rm LL} - E_{\rm DL} = E_{\rm DD} - E_{\rm DL} = 8T - 5T$.

[1] In MD the mass m is usually included in the time unit. The unit length, energy and time used for LJ systems are, respectively, σ, ϵ and $\sigma\sqrt{m/\epsilon}$.

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