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Chirality Driven Twisting as a Driving Force of Primitive Folding in Binary Mixtures

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Abstract

The N-trifluoroacetylated α-aminoalcohols (TFAAAs) are able to form quasi-one-dimensional supramolecular fibers (strings) when chirally pure, and isometric precipitates in the racemate. The strings' formation leads to the reversible gelation of the solution. The fresh gels occupy all the available volume, however during the incubation, they contract and concentrate in the central region of the tube. The microscopic observations revealed the growth of the strings' diameter and their rotation in the course of the incubation at the hour time-scale. The rotation provides for the hairpins forming that serve as hooks on the rotating string, which provides for coiling of the strings, which was observed as gel contraction. The morphology of the twisted strings resembles the structures observed in modern proteins, which allows drawing an analogy between the folding of biopolymers and the formation of the clew of strings. In addition, the rotation found in the TFAAA gels is an example of a simple system converting the energy of intermolecular agglutination to the rotational movement, so they could be considered as molecular motors.

Keywords Self-assembly · Folding · Supercoiling

Introduction

The folding of the modern proteins is a very complex and highly specialized process (Finkelstein and Galzitskaya 2004) which complicated and evolved for many ages to adapt the final

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spatial structure of each distinct molecule to its functions. So, the analysis of the folding dynamics of modern proteins brings little data on its early development and origin. Nevertheless, it is very unlikely that the folding process appeared at once and as it is. Some simple processes should have been taking place in the early protobiological matrix before they evolved, complicated, and the became resembling the modern folding.

Some of the most common features of the early processes evolved into the modern folding process should have been inherited and should be observed at present. There could be many ways of speculation on how to find these ancient signs, but all of them have to split the whole folding process into some elementary stages. First of all, any complex 3D protein structure can be separated into a set of turns and more or less straight parts of the backbone, that could be considered as the hairpins (Serrano 2000). So, the hairpin could be considered as one of the simplest elements of the whole structure. Basing on the results of the MD simulation of the folding of short peptides and nucleic acids, it became possible to identify some principal features of the formation of the hairpins. In short peptides, the β-hairpins formation can start with the peptide termini association provided by the hydrophobic forces between the edges of the peptide or directly from the hairpin tip formation (Wei et al. 2004; Suenaga et al. 2007). At the same time, in the single-stranded nucleic acids, the formation of the hairpins usually begins from the pairing of the bases at the hairpin tip followed by a rapid "zipping" of the rest of the structure (Pörschke 1974; Menger et al. 2000). Thus, the structure of the hairpin tip (the sequence in the modern polymers) on its own can induce the hairpin formation.

The ancient processes that evolved into modern folding can be modeled in the ultimately simplified biomimetic systems. Indeed, at the beginning of the evolution, there were no special adaptations complicating the folding process, so the process should have been proceeding in rather simple systems. The physical driving force of the processes in the simplified models should be clearly visible and easily identifiable, in contrast to the full modern biological objects. The latter provides for the main advantage of the biomimetic systems as research objects.

Hairpins can also form in reaction to the torsional stressing, for example, induced in DNA by the ATP-dependent enzymes called gyrases (Cozzarelli 1980). In prokaryotes, gyrases introduce negative supercoiling in the DNA that causes the formation of the positive hairpin-like structures (Cozzarelli 1980; Tverdislov et al. 2017). Moreover, the same mechanism ("phone cord effect") was proposed for the explanation of the topology of some of the regular structural domains in proteins (Cole and Bystroff 2009). So, the torsional stressing can serve as a driving force of the folding in the modern proteins and nucleic acids.

Recently we have formulated a mechanism of the spatial segregation of the chiral molecules capable of supramolecular self-assembly (Zlenko et al. 2019; Stovbun et al. 2019). Some low molecular weight substances, such as N-trifluoroacetylated α-aminoalcohols (TFAAAs, (Stovbun et al. 2018)) or phenylalanine (Adler-Abramovich et al. 2012) are capable of self-assembly into highly-elongated strings when chirally pure, while form the isometric (not elongated) aggregates in racemate (Breslow and Levine 2006; Zlenko et al. 2019). Moreover, if the system for some reason became a bit asymmetric, and the concentration of one of the enantiomers became higher than of the other, the racemic precipitate would form at the first stage until the rest of the system became chirally pure (Breslow and Cheng 2009; Zlenko et al. 2019). At the next step, the chiral strings can form, and they could be separated from racemic precipitate due to the differences in their rheological properties. This simple mechanical process could lead to the spatial segregation of some of the selected chemical species, which could have become an initial substrate for the further evolution of life.

Strings can concentrate in some areas of the specimen, while other regions were clear of them. On the other hand, in the xerogels, we have usually observed the "star-like" structures where numerous strings emanated from the nucleation point and were often bent at the scale of hundreds of microns (Stovbun et al. 2018). The spatial concentration of the strings creates opportunities for their interaction and compactization while bending of the strings reflects the mechanical stress emerging in the course of their growth (Stovbun et al. 2018). Moreover, the mechanical stress was large enough to force the strings twisting to each other and forming structures of greater diameter. The observed bending and mutual twisting of strings could be considered as a prototype of folding observed in modern bio-polymers (Stovbun et al. 2018).

The presented work is devoted to the description of the phenomenon of the spatial concentration and supramolecular structure complication observed in the binary solutions of TFAAAs in nonpolar organic solvents (heptane). We consider the role of the mechanical load in the behavior of the long elastic rods and demonstrate that the torque can cause the formation of the hairpin in even a binary mixture of a solvent and solute. Moreover, we demonstrate how mechanical stressing spontaneously arises in the described system due to the interaction and agglomeration of the chiral strings and does not require any additional factors or components.

Materials and Methods

The supercoiling was modeled using a copper multi-wire cable of 3 m long, having a diameter of 4 mm, and a round cross-section. One end of the cable was fixed, while the second one was twisting using an ordinary electric drill (60 rpm, positive direction). The process was held until the supercoiled negative hairpins were formed. The experiments were done for the intact cable and a cable with the damaged shell. The latter was used to model a defect in the initially uniform cord. Experiments were repeated several dozen times.

N-trifluoroacetylated α-aminoalcohols (TFAAA) were synthesized, as was described earlier (Kostyanovsky et al. 2005). Hot (60–80 °C) solutions of TFAAA-4 (Stovbun et al. 2018) in heptane and isopropanol were cooled down (to the room temperature) in the sealed glass tubes that was accompanied by supramolecular strings formation (Stovbun et al. 2018). The obtained specimens were incubated for several days and analyzed with an optical microscope MIKMED-6 (LOMO, Russia).

Results

Aging of the Gels

The fresh gels formed by the supramolecular strings were a whitish jelly-like substance occupying the whole volume of the tube (Fig. 1b). In the course of the incubation for several hours, the whitish substance contracted and concentrated in the center of the tube (Fig. 1c). The surrounding solution, in its turn, became liquid and transparent. Thereby, the gel spontaneously concentrated in the central area of the tube. The phenomenon of spatial concentration of the gel was observed for all available TFAAA species, but here we present the results only for TFAAA-4 solutions in heptane, for clarity. TFAAA-4 molecule has two chiral centers (Stovbun et al. 2018), and the effect was the most prominent for this type of TFAAA .
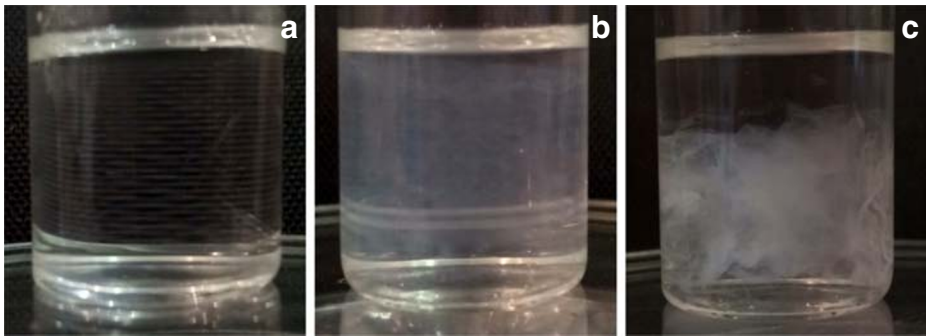
Fig. 1 Aging of the TFAAA gel. **a** The fresh solution of TFAAA-4 in heptane (1 mg/ml, $\sim 70\,^{\circ}$C), **b** The gel after two hours. **c** The gel after a week of incubation

Optical microscopy observation of the fresh and aged gels revealed the growth of the strings' diameter in the course of the aging. The thickness of the strings in the fresh gels was in the range of 1–5 μm. In the gels incubated for a month, significant fraction of the strings had a diameter of several dozens of microns or even up to 100 μm (Fig. 2a). According to the optical microscopy observations, the 100 μm strings were braid of the strings having a diameter of several microns (up to 10 μm). The strings found in the aged gels were always much thicker than the elementary strings having a diameter of about several nanometers (Stovbun et al. 2018), so we would refer them as "thick strings".

Topology of the Thick Strings

The thick strings usually demonstrated a prominent helical structure, clearly visible under the optical microscope. The helical pitch of thick strings lied in the range of 10–60 μm (Fig. 2b). The ends of the thick strings were often formed by numerous thinner ones converging together and forming a cone-shaped structure (Fig. 3). The cone-shaped bundles of the thin strings were observed both in relatively fresh gels (incubated for an hour) contained rather thin strings (~ 1 μm, Fig. 2a) and in the aged gels (incubated for a week) contained a significant amount of the thicker strings (~ 20 μm, Fig. 2b). In both cases, the
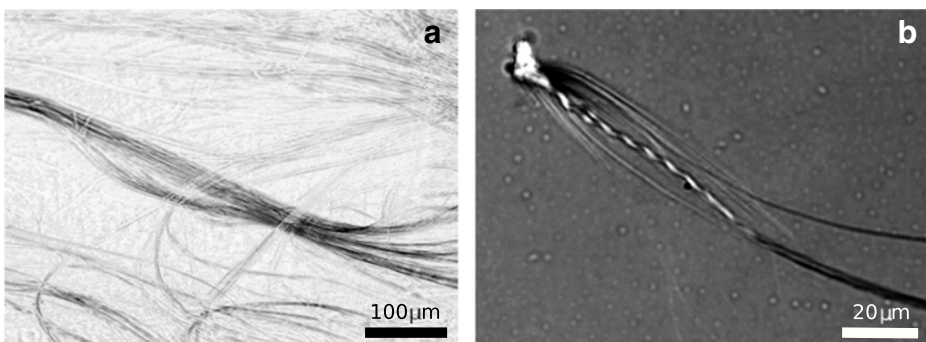
Fig. 2 a Typical thick string having a diameter of 50–70 μm braid of the thinner ones of a micrometer diameter. **b** The thick string having a prominent helical structure. The image in A is represented in negative colors for clarity. 0.4 mg/ml, TFAAA-4, heptane
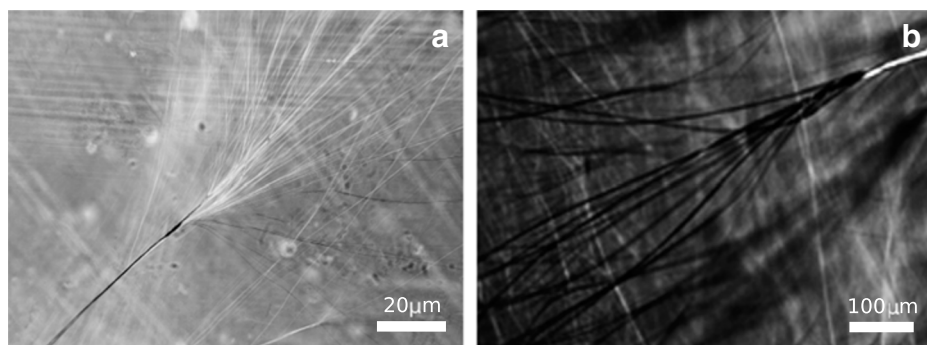
Fig. 3 Typical optical microscopy images of the ends of the thick strings formed by thinner ones. In A the sthick string has a diameter of about a micron, wile in B the diameter of the thick string is about $10\,\mu$m. 0.4 mg/ml, TFAAA-4, heptane

thicker strings were twisted of the thinner ones. Therefore, in the aging gels, we observed the formation of the hierarchy of the structural levels described earlier for different biological systems, such as proteins (Tverdislov et al. 2017), or cellulose (Nikolsky et al. 2019).

The thick strings grew, and the convergence point of the thin strings moved with the velocity of $0.1–10\,\mu$m/sec. The growing velocity and helix pitch were constant for each string and depended on their thickness: the thicker strings grew slowly and had greater helical pitch (Stovbun et al. 2018). The size and shape of the thin strings cone remained stable in the course of the thick strings' growth. As a rule, the semi-vertex angle of the cone was in the range of 40–50 °, and the length of the cone was about $100\,\mu$m.

In the aged gels, strings having one end to be fixed were usually curved (Stovbun et al. 2018) right up to the formation of the circle structures (Fig. 4a) and occasionally twisted with each other. In some cases, the helices formed by a couple of strings resembled the DNA double helix (Fig. 2b), but in the case of TFAAAs these helices were supramolecular structures and were not maintained by the covalent bonds in the polymer chain. Moreover, the thick strings were able to form loops and hairpins (Fig. 4b and c) strongly resembling the hairpins formed in prokaryotic DNA under the DNA-gyrases' action (Cozzarelli 1980).

The right-handed twisting of the electrical cable by the electric drill caused the formation of the left-handed hairpins (Fig. 4c). In the intact, uniform cable, the hairpin tips formed randomly at any point of the long wire. On the other hand, if the cable shell was damaged, the hairpin tip always formed close to this damage. Therefore, even in such a simple mechanical model, the hairpin formation can be promoted by the local peculiarities of the rod structure. This result, to a certain degree, correlates with the hairpins formation in DNA and proteins whose position is determined by the sequence of the biopolymers.

Discussion

Mechanics of Twisting

The thick strings (having a length $L_1 \sim 1$ mm and radius $r_1 \sim 1$ mkm) grew due to mutual twisting of the thinner strings forming a cone-like structure on the thick string's end (Fig. 3). The length of the thin strings (L_2) was about $100\,\mu$m, while the velocity of the thick string formation (v) was in the range of $0.1–10\,\mu$m/sec (Stovbun et al. 2018). The helical pitch of
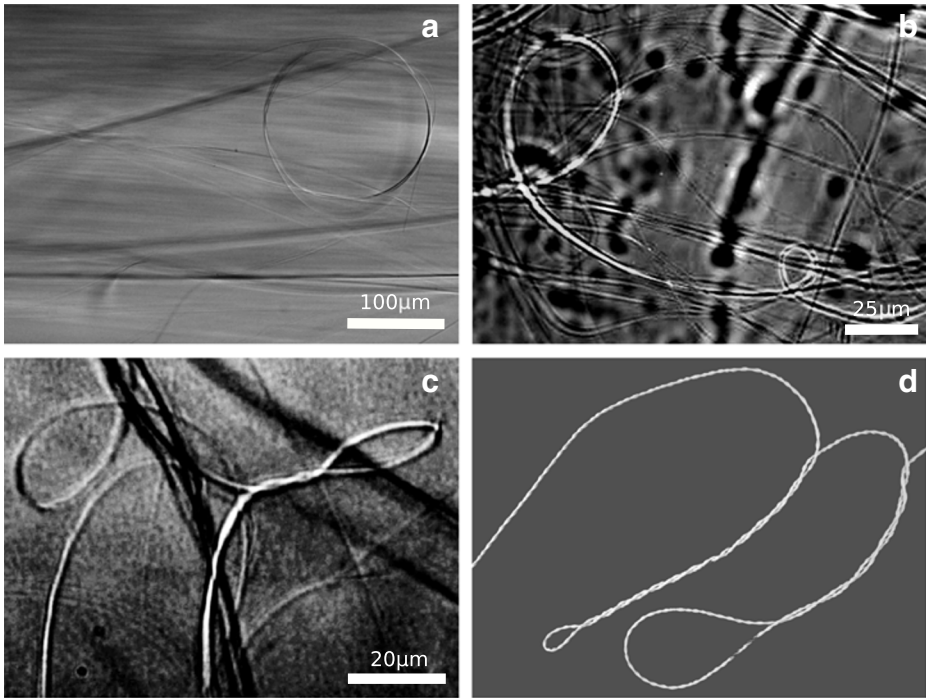
Fig. 4 A circle-shaped (**a**), loop-shaped (**b**), and formed a hairpin (**c**) thick string of TFAAA-4 in heptane (0.4 mg/ml). **d** Typical hairpins, formed by a copper cable twisted by the electrical drill

the thick string (l_h) was about several dozens of microns (10–60, Fig. 2b). Therefore, each time when the length of the thick strings grows by a helix pitch, the cone of the thin strings should come a full-circle turn. So, the thick string and the cone must rotate in respect to each other to provide for the observed helical structure forming. The angular velocity of their mutual rotation (ω) could be assessed as follows:

$$\omega = \frac{2\pi v}{l_h} \approx 10^{-2} - 10^{0} \text{rad/sec}$$

The mutual rotation of the thick string and the cone was a result of the action of some angular momentum provided by the thin strings twisting in the course of their agglutination. This rotational force should have been equilibrated by the angular momentum of the viscous forces. For the thick string rotating with the angular velocity ω_1, the torque (M_1) could be estimated as the angular momentum of viscous forces acting on the cylinder of the radius r_1 and length L_1:

$$M_1 = 4\pi \eta \omega_1 r_1^2 L_1$$

where $\eta \approx 10^{-3}$ Pa·sec – is the dynamic viscosity of the solvent (heptane).

The viscous torque for the cone of the thin strings (M_2) can be lower bound estimated considering the cone as a solid one. If α – is a semi-vertex angle ($tg\alpha \sim 1$, Fig. 3), and ω_2 – is the angular velocity of the cone rotation, then for the circular fragment of the cone surface of length dz, the angular momentum of viscous forces (dM_2) can be assessed as:

$$dM_2 \approx 4\pi \eta \omega_2 \left(tg\alpha\right)^2 z^2 dz$$

where z – is the distance to the cone vertex, and $z\,tg\alpha$ – is the radius of the circular fragment of the cone. Integrating of the above expression brings us the lower-bound estimate for the full momentum M_2:

$$M_2 \approx \frac{4\pi}{3}\eta\omega_2\,(tg\alpha)^2\,L_2^3$$

Given that, the angular momenta of the viscous forces (M_1 and M_2) are equal in absolute value, the angular velocity of the cone (ω_2) would be:

$$|\omega_2| = \frac{3r_1^2 L_1}{(tg\alpha)^2\,L_2^3}\,|\omega_1| \sim 10^{-3}|\omega_1|$$

Thus, the angular velocity of the thick string rotation appears to be much greater than that of the cone. As the angular velocity ω equals the difference between the angular velocities of the thick string (ω_1) and the cone (ω_2), the angular velocity of the cone $\omega_2 \approx 10^{-5}$–10^{-3} rad/sec. According to the obtained estimate, the cone made not more than one turn per an hour and, therefore, cannot be revealed experimentally. This was confirmed by the microscopic observations that did not reveal any rotation of the cone, although its size allows observing this process. The rotation of the thick strings also cannot be observed microscopically as they are too thin (~ 1–$10\,\mu$m), and their rotation also was not revealed microscopically.

Nevertheless, the rotation of the thick string can be detected in case if one end of the string was fixed for some reason. In this case, the twisting caused by the string growth would cause the accumulation of the stress that would cause bending. Indeed, as one of the ends was fixed, the string cannot rotate anymore. Therefore, the angular momentum acting on the string would be equal to the viscous torque acting on the cone of the thin strings:

$$M_2 \approx \frac{8\pi^2}{3}\,\eta\,(tg\alpha)^2\,L_2^3\,\frac{v}{l_h}$$

where we have replaced the expression for angular velocity $\omega_2 \approx \omega = 2\pi v/l_h$. The thick string as any other elastic rod loose its stability under stress if (Landau and Lifshits 1987):

$$M_2 L_1 > 2\pi\,A$$

where A – is a bending stiffness, which for uniform cylindrical rod equals:

$$A = \frac{\pi}{4}\,E\,r_1^4$$

where E – is the Young modulus (Landau and Lifshits 1987). Given that the strings of the radius r_1 of about one micron lose their straightness at the length of about several millimeters, the Young modulus could be assessed as $\sim 10^7$–10^8 Pa. The resulting assessment appeared to be several orders of magnitude lower than Young's modulus of the elementary string (Litvin et al. 2016). The difference in stiffness between the strings of different thickness reflects the lacy structure of the thick strings composed of many thin ones and some amount of the solvent between them. The persisting positive twisting of the thick string with the fixed end would cause its bending and formation of the negative hairpins after the accumulation of sufficient stress. The bent structures, as well as the hairpins, were regularly observed both in the gels and in the model cables, which confirms the credibility of the theory explicated above.

Spatial Concentration and Folding

In the tube having 20 mm in diameter, the characteristic time of the spatial concentration of the gel was about several days. On the other hand, the time required for the diffusion of the TFAAA molecule across the tube equals ~ 100 hours. Therefore, the spatial concentration cannot be explained by the mechanism based on the diffusion of the single molecules, resembling recrystallization.

We propose another, much faster mechanism for the explanation of the effect of spatial concentration based on the hairpins forming. The hairpins formed by mechanically stressed thick string releases the stress to some extent but never can relieve it completely. The continuing growth of the string would cause additional twisting, the hairpin growth in length, and also its rotation around the string's axis. This effect was repeatedly observed in the experiments with the cable and drill (Fig. 4d). The hairpins could be considered as the paddles, which can hook other strings and spool them to the one bearing the hairpin. Multiple hairpins on many different growing thick strings would hook and spool each other, forming a complex three-dimensional clew. So, the gel would act as a machine contracting itself in the space. According to the principle of the change of the chirality sign between the structural levels (Tverdislov et al. 2017), the direction of the strings rotation should depend on their thickness. So, the strings of similar thickness would rotate in the same direction and act as a coordinated integral machine. We suppose that precisely this effect is responsible for the spatial concentration of the gels (Fig. 1).

In the case of the strong rotational stress, several hairpins can be formed close to each other as it was observed in the model experiments (Fig. 4d). In this case, their interaction and mutual twisting can result in the formation of the compact globule. The localization of the hairpins in the string, as well as in any other elastic rod, can be predetermined by the local structure of the rod, as we have observed in the experiments with the cord having a damaged envelope. The same was found in the natural biopolymers, as the sequence of protein, for example, provides for the position of the hairpin, and in many cases, the hairpin tip appears to be the first morphological structure that forms in the course of the folding process (Wei et al. 2004; Suenaga et al. 2007; Pörschke 1974; Menger et al. 2000). Therefore, the described phenomenon of the spontaneous chirality-driven twisting and subsequent contracting of the gels can be considered as a possible mechanism that underlies the folding of the proteins. This proposition is supported by the observation made on the beta-alpha-beta helical crossovers, where the helices induce some torque on the beta-strand that determines the topology of the whole structure (Cole and Bystroff 2009) and clearly resembles the processes found in the TFAAA gels.

The phenomenon of spatial concentration itself may have been playing a role in the early stages of chemical evolution. According to our hypothesis on the role of the ability to self-organization in early stages of the development of Life (Zlenko et al. 2019; Stovbun et al. 2019), the ancestors of the modern amino-acids and carbohydrates were able to form either supramolecular highly-elongated fiber-like structures (in a chirally pure state), or form usual more or less isometric precipitate (in racemate). Due to the difference in the rheological properties between the racemic and chiral precipitates, they could have been separated by flows, waves, or even wind. This process could have been providing for the spatial segregation of some special chemical species, which on top of that were segregated in a chirally pure state. The observed effect of spatial concentration would increase the difference in the rheological properties between the racemic and chiral parts of the system. Indeed, the lone strings would have worse ability to soar in the solvent then the clew of strings. Therefore, the transfer of the clews would be more effective that should intensify the spatial

segregation. Moreover, the clew of the strings becomes an integrated body that can move as a whole and in such a way, provide for the cooperative transfer of some capable of self-ordering (and chirally pure) substances. Besides that, the effect of spatial concentration provides for rapid concentration of the substances as compared to the diffusion-based processes. As far as rates of chemical processes depends on the concentration, the spatial concentration would intensify all of them and push forward the development of early life. Both effects should also have been contributing to the processes of the spatial segregation of the biological monomers or their ancestors.

The lion's share of our observations was made on a rather exotic molecules (TFAAAs), which cannot be found in the living cells. However, the main feature – the ability to form fiber-like precipitates from chirally pure solutions (or in course of spontaneous resolution of enantiomers (Zlenko et al. 2019)) – was reported for several biological monomers, such as phenylalanine (Adler-Abramovich et al. 2012; Breslow and Levine 2006), or carbohydrate mixtures (Stovbun et al. 2019). Therefore, we propose, that the same mechanism has been provided for the selection of some "special" monomers from the wide range of the substances in the initially synthesized mixture at the young Earth (Stovbun et al. 2019). Moreover, the chiral purification of the selected range of the substances became the unavoidable consequence of the segregation process, rather than a serious theoretical problem requiring some additional explanation. In this work, we report the phenomenon of spatial concentration that should intensify and accelerate the processes of the mechanical sorting and segregation of the substances and enantiomers in the prebiotic mixture. The described mechanism of spatial concentration based on supercoiling and formation of hairpins resembles the folding of the modern proteins. As far as we propose that spatial concentration promoted the isolation of some particular chemical substances, this analogy allows considering the ability to fold in the compact globules as a necessary feature of the ancient ancestors of the modern bio-monomers. In other words, the ability to spatial concentration promoted the segregation at the prebiotic stage could be considered as a preadaptation to folding in modern biopolymers.

However, all of our observations demonstrate the principal possibility of the segregation and enantiomeric purification but do not demonstrate it explicitly for bio-monomers. The latter could be even impossible due to the billions of years of evolution of the living cells where the initial properties of the selected monomers lost their significance.

Conclusions

In conclusion, we would like to point out another analogy between the thick strings and modern biological objects. In strings, the torque arises due to the condensation of the chiral and helical thin strings (Stovbun et al. 2018) that can agglutinate only in the form of the thick helix having the opposite symmetry (Tverdislov et al. 2017). As far as the thickness of the string is related to the structural level, the direction of the string's rotation appears to be determined by its diameter. Given that the strings grow under cooling and melt under heating (Stovbun et al. 2018), the rotation seems to be reversible and changing its sign with the temperature oscillation in some range.

The rotation of the thick strings makes them a unique physical object. To our knowledge, the rotating quasi-one-dimensional objects are known only among the biological structures, such as bacterial flagella or enzymes like ATP-synthase. Therefore, in the aging gels of TFAAA, we found an example of a simple abiotic system that is able to convert the energy

of the intermolecular interaction to the rotational movement. This effect arises solely due to the chirality of the TFAAA, as the strings are always chiral (Stovbun et al. 2018; Zlenko et al. 2019). Thus, the chiral asymmetry and discrepancies between the structures of TFAAA molecules restrict the number of possible ways of their interaction and forces both the strings formation and their twisting. Similar effects force the rotation in the biological systems too. All of the biological motors are asymmetric and made of the chiral proteins, and it is very unlikely that they could have the symmetric structure. Indeed, in the achiral and fully symmetric system, both directions of rotation are equivalent, and the directional movement cannot be realized. Therefore, abstracting from the crucial differences in the structure of the procaryotic flagellum, for example, and the rotating thick string, the mechanism of their rotation seems to be generally similar.

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