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Diagram of State of Stiff Amphiphilic Macromolecules

Vladimir A. Markov,^{1,3} Valentina V. Vasilevskaya,^{*2} Pavel G. Khalatur,²
Gerrit ten Brinke,³ Alexei R. Khokhlov^{1,2}

Summary: We studied coil-globule transitions in stiff-chain amphiphilic macromolecules via computer modeling and constructed phase diagrams for such molecules in terms of solvent quality and persistence length. We showed that the shape of the phase diagram essentially depends on the macromolecule degree of polymerization. Relatively short amphiphilic molecules always form a spherical globule in a poor solvent, and the coil-globule transition includes one or two intermediate conformations, depending on the chain's stiffness. These are a disk-like globule in case of high enough Kuhn segment length, and a pearl necklace-like structure of spherical micelles and a disk-like globule in case of relatively flexible chains. The phase diagram of a long stiff amphiphilic chain was found to be more complex still. Thus three specific regions can be distinguished in the poor solvent region, depending on the chain stiffness. These correspond to a cylindrical globule without any specific backbone ordering, a cylindrical globule containing blobs with collagen-like ordering of the chain, and co-existence of collagen-like and toroidal globules. In the intermediate transition region in this case, apart from the pearl necklace-like conformations with spherical micelles, necklace conformations can be also observed where the polymeric chain has collagen-like ordering within each bead.

Keywords: amphiphiles; cylinder; phase; stiffness; tor

Introduction

Many synthetic and biological macromolecules belong to the stiff-chain type. The DNA double helix is among the stiffest ones. No wonder, therefore, that stiff chain macromolecules have been extensively studied over the last several decades.^[1–7] The ability to form globules of a complex form is one of the most remarkable properties of stiff-chain macromolecules. Thus, the DNA double helix is known to fold to a toroidal structure *in vivo*, within bacteriophage capsule, and *in vitro* during

compactization in solutions of multivalent ions and surfactants.^[8–16] Toroidal globules are formed by stiff-chain macromolecules of relatively small length and are intermediate states between coil and spherical globule in the conformational state *vs.* solvent quality phase diagram.^[3–4,6] A rod-like globule is another unusual conformation of stiff-chain macromolecules: the chain just folds onto itself several times. Rod-like globules co-exist with toroidal globules.^[4–16]

Homopolymer molecules with persistence or freely jointed flexibility mechanism are usually considered in theoretical and computer simulation studies.^[1–7]

However, many macromolecules (including a single-chain DNA and proteins) are amphiphilic, i.e. each monomer unit contains both hydrophobic and hydrophilic groups. This duality of monomer units causes the polymer's concurrent affinity and incompatibility both with polar and

¹ Physics Department, M.V. Lomonosov Moscow State University, 117234 Moscow, Russia

² A.N.Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov St.28, 119991 Moscow, Russia
E-mail: vvvas@ineos.ac.ru

³ Department of Polymer Chemistry, Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

non-polar solvents. Such macromolecules, being put into a mixture of organic and inorganic solvent incompatible with the former, prefer to concentrate not in the solvent bulk, but at the interface.^[17–18] A classification of monomer units based on this feature was suggested in ref.,^[18] and the simplest theoretical model was described in ref.,^[19] where the amphiphilic unit was considered as a dumbbell consisting of a hydrophobic and a hydrophilic bead. Computer modeling of macromolecules amphiphilic on the single unit scale was performed in a series of papers;^[19–22] it was shown therein that amphiphility of the monomer units leads to a significantly more complex and varied character of conformational changes compared to the case of usual homopolymer macromolecules.

We have studied stiff-chain amphiphilic macromolecules in ref.^[21] and found that such macromolecules can adopt a great number of thermodynamically stable conformations. These are cylindrical, toroidal, collagen-like globules, conformations of intramolecular micelle-beads connected by a string resembling a pearl-necklace. The number of possible conformational structures of such macromolecules greatly exceeds that of structures observed in usual (non-amphiphilic) stiff macromolecules. Remarkably, the structural details of conformations observed in both cases (such like toroidal and rod-like (or cylindrical) globule) are essentially different for homopolymeric and amphiphilic macromolecules.

We continue the study of the conformational properties of stiff-chain amphiphilic macromolecules in the present paper. We performed computer simulations to find out the details of various conformational structures and constructed phase diagrams of the states of such macromolecules in terms of solvent quality and persistence length.

Model and Experimental Technique

A schematic representation of the polymer model is shown in Figure 1. Each amphiphilic monomer unit is a dumbbell consist-

ing of a **H** and a **P** bead connected by a rigid bond of fixed length. These dumbbells form an amphiphilic polymeric chain of length N with a backbone of hydrophobic **H** beads and pendant hydrophilic **P** beads. The main chain of **H** beads is semi-flexible with preferred angle θ_0 between the neighboring bond vectors in the chain.

The temporal evolution of the system was found via solving a system of Newton's equations with molecular dynamics technique.^[23] Unity bond length in this macromolecule was chosen: $b = 1.0$ and ensured with RATTLE algorithm.^[24]

The excluded volume interaction between the non-connected beads was given by the repulsion potential of the Lennard-Jones type:

$$u_{ev} = \begin{cases} 4\varepsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 + \frac{1}{4} \right], & r_{ij} \leq r_0 \\ 0, & r_{ij} > r_0 \end{cases} \quad (1)$$

where r_{ij} is the distance between the interacting centers i and j , and $r_0 = 2^{1/6}$ is the cut-off radius of the potential. Parameter ε in Equation (1) determines the interaction strength and controls the energy scale, whereas parameter σ determines the spatial scale. We have set $\sigma = \varepsilon = 1$ for all the pair-wise interactions and all the results discussed below are given in terms of these parameters.

The solvent molecules were not considered explicitly in the calculations, but represented as a continuous medium. Terms describing friction and terms R_i for Langevin's uncorrelated noise were introduced into the equations of motion to account for the solvent being in contact with the external reservoir with temperature T .

The solvent-induced intrachain hydrophobic-hydrophilic interactions were described with a Yukawa-type potential:

$$u_s(r_{ij}) = \frac{\varepsilon_{ab}\sigma}{r_{ij}} f(r_{ij}, r_c) h(r_c - r_{ij}) \quad (2)$$

where $f(r_{ij}, r_c) = \left[1 - \left(\frac{r_{ij}}{r_c} \right)^2 \right]^2$ is the screening function; $r_c = 4\sigma$ is the screening radius of such interactions; $h(r)$ is the Heavyside function; parameters ε_{ab} ($= \varepsilon_{HH}, \varepsilon_{PP}, \varepsilon_{HP}$)

Figure 1.

Model of a stiff-chain amphiphilic macromolecule. Each unit of the amphiphilic chain consists of a hydrophobic **H** and a hydrophilic **P** bead connected by a rigid bond. The backbone formed by **H** beads is semiflexible with preferred angle $\theta_0 = 170^\circ$ between the bond vectors neighboring along the chain.

describe the strength of the interactions between the corresponding bead types.

Potential (2) describes the solvent-mediated short-range hydrophobic-hydrophilic interactions. In case of $\varepsilon_{\alpha\beta} = 0$ there are no additional interactions (attraction or repulsion) between the units except for the excluded volume interactions given by the potential (1).

We set the following values for the parameters in the computer experiments performed: $\varepsilon_{PP} = 0$, $\varepsilon_{HP} = 3$, and $\varepsilon_{HH} < 0$ was varied in the course of the experiment. The non-zero (positive) value of ε_{HP} stands for repulsion between the corresponding groups. The negative parameter ε_{HH} describes attraction between the hydrophobic groups. The behavior of the polymer chain in a selective solvent (poor for hydrophilic **H** groups and good for hydrophobic **P** groups) was modeled by varying the ε_{HH} parameter.

The stiffness of the polymer chains was described via an additional potential of interaction between the units neighboring along the chain:

$$U(\vartheta) = \varepsilon_{st}(\vartheta - \theta_0)^2 \quad (3)$$

where ε_{st} is the stiffness parameter; ϑ is the angle between the neighboring bond vectors in the chain; θ_0 is the preferred angle, which was set to 170° in this study.

The stiffness of the chain was characterized by the Kuhn segment length, which was determined via calculating the radius of inertia of equivalent chains without the excluded volume interactions for various

values of stiffness parameter ε_{st} (the calculation procedure is described in detail in paper^[21]).

The calculations were performed for various chain lengths $N = 64, 128, 256$ and various Kuhn segment lengths $L_k = 2.9; 8.2; 13.9; 19.6; 24.2; 29.2$ (corresponding to stiffness parameter $\varepsilon_{st} = 0; 2; 4; 6; 8; 10 \text{ } \varepsilon/\text{rad}^2$). The solvent quality was varied via changing the energy parameter ε_{HH} within the range of -5.5 up to -0.5 . The calculations were performed with simulated annealing technique. The ε_{HH} parameter was changed by no more than $\Delta\varepsilon_{HH} = -0.5$, and this change was introduced gradually over 5×10^6 time steps; the system was equilibrated for 5×10^6 time steps, and then measurements for each conformation were performed. In order to obtain accurate values of the radius of inertia squared, R_g^2 , and other parameters of the system, the calculations were carried out over the time interval greatly exceeding the fluctuation time for these parameters, and several independent experiments were performed.

Results and Analysis

The mean square radius of gyration R_g^2 is the basic parameter characterizing the dimensions of the macromolecule in describing its compactization.

Figure 2 shows the dependence of the mean square radius of inertia R_g^2 on the interaction energy ε_{HH} for chains with different Kuhn segment lengths L_k , contain-

Figure 2.

The dependence of the mean square radius of gyration R_g^2 of the macromolecule on the solvent quality ϵ_{HH} for macromolecules with $N=128$ and different Kuhn segment lengths $L_k=2.9$ (3), 19.2 (2), 29.2 (1).

ing the same number ($N=128$) of monomer units.

The macromolecule is in the coil state at small values of interaction parameter $-\epsilon_{HH}$. In this case, the greater is the molecule's stiffness, i.e. its Kuhn segment length L_k , the larger is the mean square radius of gyration R_g^2 . As the solvent becomes poorer (the parameter $-\epsilon_{HH}$ increases), the macromolecule undergoes a coil-globule transition. In case of relatively flexible chains ($L_k=2.9$) the coil-globule transition occurs smoothly, as a second order-type phase

transition (Figure 2, curve 1). The sharpness of the transition increases and its position shifts to higher $-\epsilon_{HH}$ as the chain's stiffness increases (Figure 2, curve 2–3). This behavior agrees with the theoretical and experimental conceptions of the impact of the chain's stiffness on the properties of coil-globule transitions in usual, non-amphiphilic stiff-chain macromolecules.^[25]

Figure 3 shows the dependence of the mean square radius of gyration R_g^2 on the attraction energy between the hydrophobic units $-\epsilon_{HH}$ for rather stiff ($L_k=29.2$) chains

Figure 3.

The dependence of the mean square radius of gyration R_g^2 of the macromolecule on the solvent quality ϵ_{HH} for $L_k=29.2$ and different polymerization degrees $N=64$ (3); 128 (2); 256 (1).

with different lengths N . We can see that R_g^2 increases with increasing degree of polymerization N both for the coil and for the globular state of the macromolecule; the coil-globule transition shifts to lower energies, and the sharpness of the transition increases. These results also agree with the common conceptions of the impact of the chain's stiffness on the coil-globule transitions in macromolecules.^[25]

Figure 4 shows the dependence of the mean square radius of gyration R_g^2 of the macromolecule on its degree of polymerization N for the coil (A) and the globular state (B). We can see that in both cases the scaling dependence ($R_g^2 \sim N^{1.8}$ for the coil

and $R_g^2 \sim N^{1.8}$ for the globule) are strong enough and differ from those observed in case of usual non-amphiphilic macromolecules. In the first case due to high stiffness (and therefore small number of Kuhn segments: $N/L_k \sim 500/29.2 \sim 17$), and also due to additional swelling caused by the repulsive interaction between the hydrophilic groups, the asymptotic characteristic for a coil in a good solvent is obviously not reached: $R_g^2 \sim N^{1.2}$. The nearly linear dependence $R_g \sim N^{0.9}$ in the globular state (note that $R_g \sim N^{1/3}$ for usual spherical globules) indicates that the macromolecule forms elongated cylindrical structures in the globular state. Note also that the nearly

Figure 4.

The dependence of the mean square radius of gyration R_g^2 of the macromolecule with $L_k=29.2$ in the coil state (A, $\epsilon_{HH}=3.5$) and in the globular (cylindrical) state (B, $\epsilon_{HH}=5.5$) on the degree of polymerization N .

linear R_g vs. N dependence was observed for flexible-chain amphiphilic macromolecules^[19] and for regular copolymers of amphiphilic and hydrophobic units,^[20] which form cylindrical globules in a poor solvent.

The formation of a cylindrical globule is characteristic for long macromolecules made of amphiphilic units especially due to the dualistic structure of their monomer units. The change from a spherical to a cylindrical globule for such monomer units has an advantage in terms of energy, because it leads to an essential increase of the globule's surface. This allows maximal exposure of the hydrophilic parts of the monomer units to the solvent, while keeping the hydrophobic parts inside the globule in close contact with each other.

The analysis we performed showed^[21] that packing of the chain in cylindrical globules is of a blob type. This means that the backbone fills consecutively parts (blobs) of the cylindrical globule so that backbone changes direction several times within each blob and parts of the chain belonging to different blobs have almost no intersections.

As the chain becomes stiffer, the length of the cylindrical blob remains practically the same, blobs become more elongated, and the total number of blobs decreases (see paper^[21] for details). Different branches within the blob are intertwined at relatively high chain stiffness. We call such blobs collagen-like. And, finally, a chain with still higher stiffness forms a collagen-like globule, which is, in fact, a limiting case of a cylindrical globule containing a single blob. The chain in such globule folds several times upon itself and parts of the chain intertwine with each other, which is similar to the behavior of collagen chains.

Other globule varieties formed by stiff-chain macromolecules are toroidal globule and a thin, practically two-layer, disk-like globule. Figure 5 shows snapshots of globules characteristic for the stiff-chain amphiphilic macromolecules. These are cylindrical globule (Fig. 5A), cylindrical globule with collagen-like blobs (Fig. 5B), as well as collagen-like

(Fig. 5C), toroidal (Fig. 5D), and disk-like (Fig. 5E) globules.

We performed visual analysis and analysis of distances between the monomer units neighboring along the chain (see paper^[21] for details). These analyses showed that an amphiphilic macromolecule with high molecular mass always adopts the form of a cylinder with blob type of backbone packing (Fig. 5A) in case of low stiffness, and the form of a cylindrical globule with collagen-like blobs (Fig. 5B) at higher stiffness. Collagen-like (Fig. 5C), toroidal (Fig. 5D), and disk-like (Fig. 5E) globules co-exist in the globular state at high stiffness (L_k). Notably, we only observed the latter globule type for a chain 128 units long. Stiff macromolecules of 256 monomer units long, formed only collagen-like and toroidal globules and the probabilities of adopting these conformations were approximately the same. We performed 23 independent experiments for a chain with $N=256$ and Kuhn segment length $L_k=29.2$, and 11 times the chain adopted the collagen-like globule conformation, and 12 times – that of toroidal globule. The $R_g^2(\epsilon_{HH})$ dependence shown in Figure 2, curves 2–3, have been averaged over all the experiments and all possible conformations.

Figure 6 shows the dependence of the form factors k_1 and k_2 on the solvent quality for a stiff ($L_k=29.2$) macromolecule 256 monomer units long. Factors k_1 and k_2 ($k_1 \leq k_2$) are determined as ratios of components of the tensor of inertia in diagonalized form (see paper^[25] for details on the procedure for calculating k_1 and k_2). The ratio of these factors helps evaluating the shape of the macromolecule. Thus $k_1 = k_2 = 1$ for a sphere, $k_1 \rightarrow 0$, $k_2 = 1$ for a cylinder, and $k_1 = k_2 \rightarrow 0.5$ for a disk with zero thickness.

Figure 6 shows the dependence of the k_1 and k_2 form factors for various scenarios of coil-globule transition, namely, those leading to formation of a collagen-like (A) and a toroidal (B) structure. Analysis of the form factor graphs was accompanied by visual analysis of conformations obtained;

Figure 5.

Characteristic conformations of stiff-chain macromolecules in a poor solvent ($\epsilon_{HH} = -5.5$). (A) Cylindrical globule with non-ordered blobs ($N = 256$, $L_k = 6$); (B) Cylindrical globule with collagen-like blobs ($N = 256$, $L_k = 19.2$); (C) Collagen-like globule, $N = 256$, $L_k = 29.2$; (D) Toroidal globule, $N = 256$, $L_k = 29.2$; (E) Disk-like globule, $N = 128$, $L_k = 29.2$.

we refer to the latter when discussing the graphs.

We can see that at relatively low values of $-\epsilon_{HH}$ ($-\epsilon_{HH} < 3.0$), when the macromolecule is in coil state, the k_1 and k_2 dependence is almost the same in both cases. The shape of the macromolecule is similar to ellipsoid in this region. As the parameter $-\epsilon_{HH}$ increases (which means increased attraction between the hydrophobic groups of the backbone) a nucleus is formed in the macromolecule – the center of future globule's formation. The morphology of this center can vary; it is determined by the kinetics and determines, in turn, the globule's shape.

In the first case, when the collapse leads to formation of a collagen-like globule (Fig. 6A) at the energy $\epsilon_{HH} \sim -3.5$, a part of the polymer chain folds and intertwines with another part of the chain thus forming a nucleus of the collagen-like conformation. As $-\epsilon_{HH}$ increases, other parts of the

macromolecule intertwine themselves with this part of the chain, which becomes longer. This results in formation of a collagen-like globule at $\epsilon_{HH} = -4.0$, which consists of six intertwining branches. Note that the coil-globule transition occurs within a rather narrow range of energies from $\epsilon_{HH} = -3.5$ to $\epsilon_{HH} = -4.0$. In fact, we can see (Fig. 6A) that factors k_1 and k_2 and, therefore, the globule's shape do not change within the range of $\epsilon_{HH} = -4.0 \div -5.5$.

In the second case, when the collapse leads to the formation of a toroidal globule (Fig. 6B), a loop is formed at $\epsilon_{HH} \sim -3.5$ that grows with further decrease of solvent quality, increasing in diameter and number of turns. Thus a toroidal globule is formed. Note that final formation of a toroidal globule extends over a much wider range of energies (from $\epsilon_{HH} = -3.5$ to $\epsilon_{HH} = -5.0$.) than formation of a collagen-like globule. Separate branches in the toroidal globule

Figure 6.

Form factors k_1 and k_2 ($k_1 \leq k_2$) versus solvent quality for a stiff-chain ($L_k = 29.2$) with degree of polymerization $N = 256$ for various scenarios of the coil-globule transition. (A) –collagen-like globule (B) –toroidal globule.

are also intertwined. However, the linking of such toroidal structures is zero, i.e. if the chain in such a globule is “pulled” by its ends, a straight line without any knots will be formed.

Visual analysis shows that less stiff macromolecules ($L_k = 2.9$ and 19.2) forming cylindrical globules in a poor solvent pass the stage of necklace of micelle-like beads during compactization. In case of relatively flexible macromolecules ($L_k = 2.9$) each of the micelle-beads has a spherical shape (Fig. 7A). Stiffer macromolecules ($L_k = 19.2$) form a necklace of collagen-like micelles, where parts of the chain belonging to each micelle are

intertwined (Fig. 7B). Collapse of such macromolecules results in formation of cylindrical globules with blob type of chain folding and no specific ordering of the chain (Fig. 5A) or with collagen-like ordering of the chain within the blob (Fig. 5B), respectively.

The results of the calculations, the visual analysis and the analysis of the macromolecule’s shape are summarized in Figures 8 and 9 in the form of state diagrams in terms of the Kuhn segment length L_k and the attraction energy between the hydrophobic units $-\epsilon_{HH}$.

Figure 8 shows a state diagram for a chain with number of units $N = 256$. The

Figure 7.

Snapshots of pearl necklace-like conformations. $N = 256$, $L_k = 2.9$, $\varepsilon_{HH} = 4.0$ (A); $N = 128$, $L_k = 19.2$, $\varepsilon_{HH} = 4.0$ (B).

following regions are marked: 1 – coil state; 2 – pearl-necklace conformation with spherical (2') and collagen-like (2'') micelle-beads; 3 – cylindrical globules with non-ordered (3') and collagen-like (3'') blobs; 4 – co-existence of collagen-like and toroidal

globules. The border between the coil and globular states (i.e. the border between region 1 and regions 2 and 4 co-existing with the former) connects the maxima in the heat capacity *vs.* attraction energy (ε_{HH}) dependence. In order to determine the

Figure 8.

Phase diagram of an amphiphilic macromolecule with high degree of polymerization ($N = 256$). 1-coil state (●); 2-pearl-necklace conformation with spherical (2') and collagen-like (2'') micelle-beads (■, □); 3-cylindrical globules with non-ordered (3') and collagen-like (3'') blobs (□, ○); 4-region of co-existence of collagen-like and toroidal structures (△).

Figure 9.

Phase diagram of an amphiphilic macromolecule with low degree of polymerization ($N = 64$). 1 – coil state (●); 2 – pearl-necklace conformation with spherical blobs (□); 3 – collagen-like globule (△); 4 – spherical globule (⊙).

border between regions 2 and 3 (i.e. between the pearl-necklace and cylindrical globule conformations) we calculated average cluster sizes. The border between the regions was defined as the set of points where the average cluster size equals the total number of units in the backbone. The border between regions 3' and 3'' (regions of cylindrical globules with collagen-like ordering of the backbone inside the blob and those without such ordering) was determined visually based on the conformation snapshots and via analyzing the dependence of distance between the monomer units (see paper^[21] for details).

As the chain length decreases, the main border dividing the coil and globular state shifts towards greater energies of attraction between the hydrophobic units. The border between regions 2 and 3 remains unchanged for chains with polymerization degrees $N > 64$, and the border of regions 2 and 4 shifts towards smaller chain stiffness. Besides, in case of chain with $N = 128$ the disk-like globule co-exists with the collagen-like and toroidal globules within region 4.

Both flexible and stiff amphiphilic macromolecules form spherical globules (Fig. 9) at low chain length ($N < 64$) in a poor solvent. Here the coil-globule transi-

tion of stiff macromolecule includes three consecutive stages: coil – disk-like globule – spherical globule. In case of relatively short Kuhn segment length the macromolecule, in addition to the stages listed above, also passes the stage of pearl-necklace comprised of spherical micelles.

Thus we constructed state diagrams for amphiphilic stiff-chain macromolecules in terms of the Kuhn segment length and the solvent quality. We showed that the shape of the diagram depends essentially on the degree of polymerization of the macromolecule. So, relatively short amphiphilic macromolecules always form spherical globules in poor solvent. The globule shape of long amphiphilic polymers depends both on chain stiffness and on kinetic factors, so that stiff macromolecules can form co-existing collagen-like, toroidal, and disk-like globules. Note that the degree of polymerization dependence of the shape of the phase diagram for a stiff-chain macromolecule was discussed in a series of papers^[3–4] for homopolymeric macromolecules. It was shown therein that collapsing stiff-chain macromolecules pass the three stages: coil – toroidal globule – spherical globule, and the higher the degree of polymerization is, the narrower is the range of parameters allowing the existence of a

toroidal globule. Thus, in the thermodynamic limit $N \rightarrow \infty$ the toroidal globule state is not realized at all.

The phase diagram of amphiphilic stiff-chain macromolecules is far more complex. Spherical globules of such macromolecules are observed only in case of rather short and flexible chains (i.e. for low polymerization degree N and Kuhn segment length L_k). In case of high degree of polymerization even flexible chains adopt cylindrical globule shape in a poor solvent. Amphiphility of each monomer unit is the reason for cylindrical globule formation, because it favors structures with rather large surface. This allows the amphiphilic monomer units to arrange themselves at the surface so that the hydrophobic units are on the inside of the globule, and the hydrophilic units are exposed to the solvent. Such monomer unit structure is, in particular, responsible for the stage of pearl-necklace comprised by micellar structures appearing in the coil-globule transition of amphiphilic macromolecules. The non-ordered backbone structure with many bends becomes disadvantageous in terms of energy as the chain stiffness increases. Collagen-like ordering occurs in micelle-beads when polymer chain folds several times within each bead and the branches intertwine themselves. This type of ordering remains within the cylindrical structure formed by such macromolecule in a poor solvent. Therefore we can call this structure a blob-type cylindrical globule meaning that the chain fills consecutively parts of the volume and parts of the chain belonging to different blob have almost no intersections (see paper^[21] for details). Blobs in such structures are elongated, and their length grows with the increase of chain stiffness. We call a cylindrical globule containing a single collagen-like blob a collagen-like globule. Collagen-like globules co-exist with toroidal (and sometimes even with disk-like) globules and the energies of all the three stages are approximately the same (the difference in energies is ca. 4%). The essential energy losses at the sharp bends on the edges of collagen-like globule are

obviously compensated for by the sum of small energy losses at a greater number of small bends in a chain forming a toroidal or a disk-like globule. The region of co-existence of different globule types (collagen-like, toroidal, and disk-like) is observed only in case of very stiff polymer chains and the coil-globule transition in this part of phase diagram is rather sharp, without the additional stage of pearl-necklace conformation.

Remarkable is that shorter amphiphilic macromolecules pass one or two intermediate stages during the coil-globule transition depending on the chain stiffness. These stages are disk-like globule in case of stiff short chains and micelle necklace and disk-like globule if the short amphiphilic chain is less stiff.

Thus it was shown that stiff-chain macromolecules with amphiphilic monomeric units can form a large number of different conformations and that the state diagrams are more complex and depend on the details of the structure and the degree of polymerization of the chains. No experimental studies of such systems in this context have been performed yet. Note, that also almost no systematic experiments have been performed to study structural conversions of stiff-chain macromolecules during coil-globule transitions. As far as we know, only one paper has been published so far^[3] on the study of the solvent quality dependence of globule's shape of DNA double helix. Therein was, in fact, the prediction made (and verified) that the toroidal globule is an intermediate stage between the coil and the spherical globule. The DNA double helix is, apparently, a stiff homopolymeric macromolecule able to form spherical, toroidal, and rod-like (where DNA chain folds upon itself several times) globule. The chains of many proteins participating in DNA metabolism are amphiphilic and, apparently, stiff enough and can therefore adopt toroidal form.^[27] We can expect that all the variety of structures predicted in the computer experiments described above can be in fact observed for these (or similar) protein

macromolecules. This makes studying conformational transitions in stiff-chain amphiphilic macromolecules very important and prospective.

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