

Micellesation vs aggregation in dilute solutions of amphiphilic heteropolymers

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Abstract

In recent experiments involving PNIPAM copolymers it has been observed that stable spherical nanoparticles are being formed by association of several chains in poor aqueous solution instead of aggregation. This type of mesoscopic structures called mesoglobules has an extremely monodispersed size distribution. Previously we have studied theoretically formation of clusters consisting of several chains in dilute solutions of amphiphilic heteropolymers. We have seen that the mesoglobules often possess an essentially micellar structure. In the current work we argue that formation of mesoglobules is strongly sequence and concentration dependent. In particular, by means of lattice Monte Carlo simulation we consider structures formed by a number of tri-block sequences and their certain mutations. For sequences consisting of two hydrophilic ends with a hydrophobic middle the size distribution of the resulting particles is rather narrow, i.e. mesoglobules are being formed. However, in the case of sequences with two hydrophobic ends and a hydrophilic middle a new type of structures seems to be prevalent. These consist of small mesoglobules interconnected by hydrophilic bridges. Clearly, on increasing the concentration these networked structures would play an important role resulting in a rapid onset of a gel-like behaviour. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

In recent years there were numerous works devoted to the behaviour of water soluble polymers near the lower critical solubility temperature (LCST). Typical systems include poly-*N*-iso-

propylacrylamide (PNIPAM) homopolymer and block copolymers [1,2] of the poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide), or PEO–PPO systems briefly [3,4]. The latter copolymers are widely used in pharmaceutical, agricultural and food industries due to their low toxicity and surfactant characteristics (EO is hydrophilic and PO is hydrophobic). These are commercially available as Pluronic or Synperonic polymers and they have been quite well studied experimentally [4,3]. Speaking of tri-block copoly-

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mers in particular there are two types which have rather distinct properties. First, a PEO–PPO–PEO polymer with the hydrophilic ends and hydrophobic middle is the standard Pluronic which forms stable micelles. Second, a polymer with the inverse structure would tend to bridge hydrophobic end ‘stickers’ by hydrophilic bridges. These are so-called telechelic associating polymers [5], which form telechelic gels possessing nontrivial rheological properties at higher concentrations.

The phase behaviour of PNIPAM homopolymer has been well investigated [1,2]. PNIPAM serves as an important model polymer due to its convenient LCST in water which is at approximately 32°C, i.e. near the room temperature. One of the important applications of this polymer is based on the use of temperature and pH responsive PNIPAM gels, which exhibit dramatic conformational changes such as swelling upon small changes of the external conditions such as temperature or pH. One of popular modifications is achieved by grafting PNIPAM main chain with PEO side-groups. After collapse of the backbone chain the PEO side chains solubilise it in water.

Polymers which form micellar structures generally are of great interest for biological and pharmaceutical applications because they may be used in a drug delivery process due to their ability to solubilise hydrophobic compounds and due to an improved stability as compared to low molecular weight systems. At higher concentrations these systems display a very rich variety of phases and corresponding morphologies [3]. One is particularly interested in the properties of dilute solutions as they are determined by the fundamental intra-molecular interactions. Experiments in this area [6–8] are quite difficult and often obscured by inter-polymer aggregation phenomena.

Perhaps one of the most striking recent experimental observations was the formation of rather size monodispersed nanoparticles [8]. This phenomenon has been recently observed by a number of groups worldwide: R. Pelton et al. [9] at McMaster University, by Chi Wu et al. [10] in Hong Kong, A.V. Gorelov et al. [8] at

UCD, and some indications in favour of these structures have also been seen in Lund University [11]. The appearance of spherical particles in dilute solutions of Poly(*N*-isopropylacrylamide) has been clearly observed by dynamic light scattering (DLS). Significantly, these particles have a relatively narrow size distribution and remain stable for many days. Thus, the size of the particles is thermodynamically controlled and it increases with increasing polymer concentration and increasing strength of inter-monomer attraction. Electron microscopy further confirms that these spherical particles have mean size and distribution in agreement with DLS.

We have recently been able to explain the stability of the mesoglobules based on the extended version of the Gaussian variational theory [12] as well as to determine the histograms of their size distributions via lattice Monte Carlo simulations in [13]. The existence of such mesoscopic structures is maintained by a delicate balance of the energetic and entropic terms under the connectivity constraints. In recent paper [14] we have examined some more complex heteropolymer sequences, such as tri-block copolymers. The main conclusion from such a study was that in the case of tri-blocks with outer hydrophilic blocks mesoglobules are thermodynamically stable in a narrow region of the phase diagram in accordance with the expectations from our theory. The case of tri-blocks with the outer hydrophobic blocks, however, generally does not have this property since the hydrophobic end ‘stickers’ can attach to similar blocks from other macromolecular clusters which thus are becoming connected via extended hydrophilic bridges. This picture is quite familiar from theory of associating polymers. Indeed, telechelic polymers [5] at higher concentrations would become highly inter-connected producing a physical gel.

The purpose of the current work is to consider a wider range of heteropolymer sequences in order to examine the competition of aggregation vs micellesation when the latter is accompanied by formation of mesoglobules. First, we shall proceed from the tri-block copolymers and apply certain ‘mutations’ obtained by permuta-

tion of some monomers to examine the stability of the clusters and how the mean size and dispersion of cluster sizes would be affected. Second, we shall examine the effect of decreasing the chain length with a simultaneous increase of the concentration at a constant total number of monomers in the system.

2. Results

We adopt the Metropolis technique in the lattice model of [13]. This model, apart from the connectivity and excluded volume constraints, includes short-ranged pair-wise interactions between lattice sites. The system is completely characterised by three Flory interaction parameters, X_{aa} , X_{ab} and X_{bb} , along with N , M and linear lattice size L . In addition to local monomer moves [13], we include translational moves representing diffusion of chains. The latter moves are applied to all clusters of chains with a probability inversely proportional to the number of monomers within (Stokes law).

To address the question about the size polydispersity of the mesoglobules we have obtained a large ensemble of independent equilibrium states in the region of the phase diagram where mesoglobules can be formed. Then by using the histogram technique we obtain the probability densities of the number of chains in a cluster (aggregation number), M_{cl} , and of the radius of gyration of a cluster (size), R_{cl} for different considered sequences.

In Fig. 1 we present these distributions for the OUTER-H (s1) and OUTER-P (s2) tri-blocks, as well as for their mutations s3 and s4, respectively, which are obtained by point-like permutations of two monomers near the points where a and b blocks join each other. The s2 sequence has a single high and narrow peak in both distributions, which corresponds to a well defined mean size of the well monodispersed mesoglobules. Sequence s1, however, has two peaks, which are also broader and less pronounced, as well as a high population of the macro-aggregate (cluster of $M_{cl} = M = 20$). This is due to bridging of hydrophobic clusters by the hydrophilic middle blocks. Mutated sequences s3 and s4 have quite close

distributions for the aggregation numbers $P(M_{cl})$ to their respective tri-blocks s1 and s2, demonstrating the stability of these two types of struc-

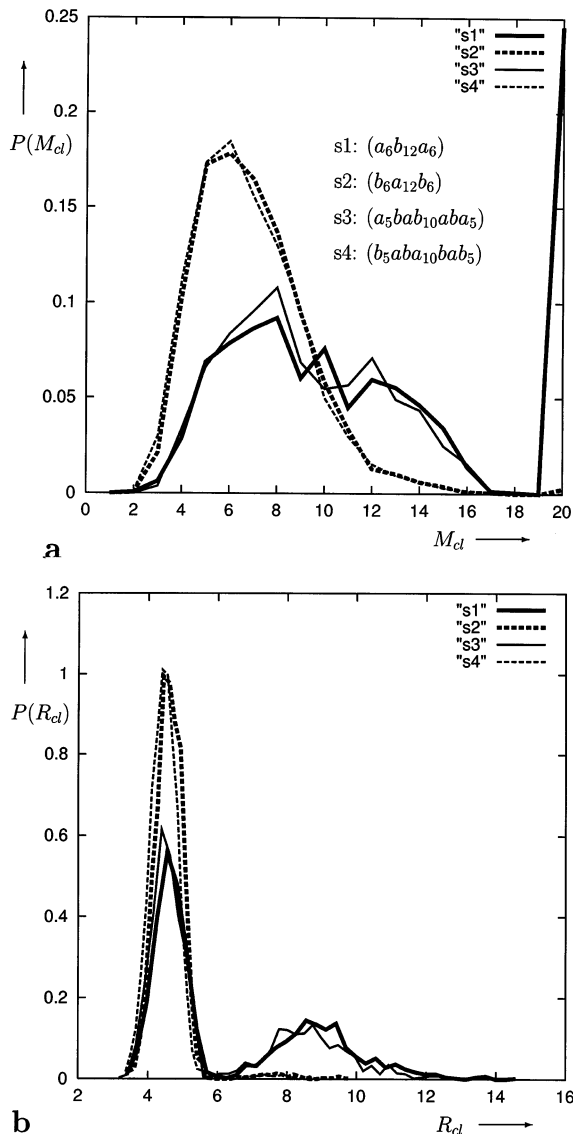


Fig. 1. Probability densities of the number of chains in a cluster (aggregation number), M_{cl} (a) and of the radius of gyration of a cluster (size), R_{cl} (b) for tri-blocks (thick lines) and mutated tri-blocks (thin lines) sequences. These results have been obtained by analyzing data for the ensemble size $Q = 1000$ for each sequence. Here the equilibration time was 1.92×10^9 of attempted Monte Carlo moves and other parameters were: linear lattice size $L = 60$, degree of polymerisation $N = 24$, number of chains $M = 20$, and the Flory interaction parameters $X_{aa} = 1$, $X_{ab} = 0.4$ and $X_{bb} = -0.2$.

tures with respect to slight perturbations in the primary sequence. However, in the size distributions $P(R_{cl})$ the locations of the peaks have shifted somewhat to the left. Therefore, both the mesoglobules and the aggregates for the mutated sequences have become somewhat smaller compared to those of the tri-blocks. This is natural since the outstretched hydrophilic tails or loops have become somewhat shorter.

In Fig. 2 we exhibit the two distributions for the system composed of twice the number of chains $M=40$ with half-long polymers $N=12$ in the same simulation box as compared to Fig. 1. For OUTER-P sequence s2 there is still a single peak corresponding to mesoglobules. A typical snapshot for these is presented in Fig. 3a, where one can see four micelles of essentially equal size. Compared to the twice longer sequence in Fig. 1 the size of the mesoglobules has become smaller, although the aggregation numbers have increased in approximately 1.5 times. The distributions for s1 sequence still have two peaks, the second corresponding to a population of the macro-aggregate. Thus, the nearly equal sized clusters are present there also, but in a small fraction, but many members of the ensemble have joined into dimers, trimers and so on formed from spherical clusters as shown in Fig. 3b. Interestingly, both s1 and s2 have rather small populations of the globules of single chains, which is due to the short length of the chains.

Distributions for the mutated sequences s3 and s4, however, are quite different from those of s1 and s2. Namely, for s4 the mesoglobules have become considerably larger and somewhat less pronounced due to an increased population of single chain globules compared to s2. The shape of distributions for s3 compared to s1 have undergone quite dramatic changes. First, the population of single chain globules have increased considerably. Second, the mean size of large clusters have increased and these have become more monodispersed. Third, the population of macro-aggregate has decreased. A typical snapshot for this situation is presented in Fig. 3c, where one can see a macro-aggregate of

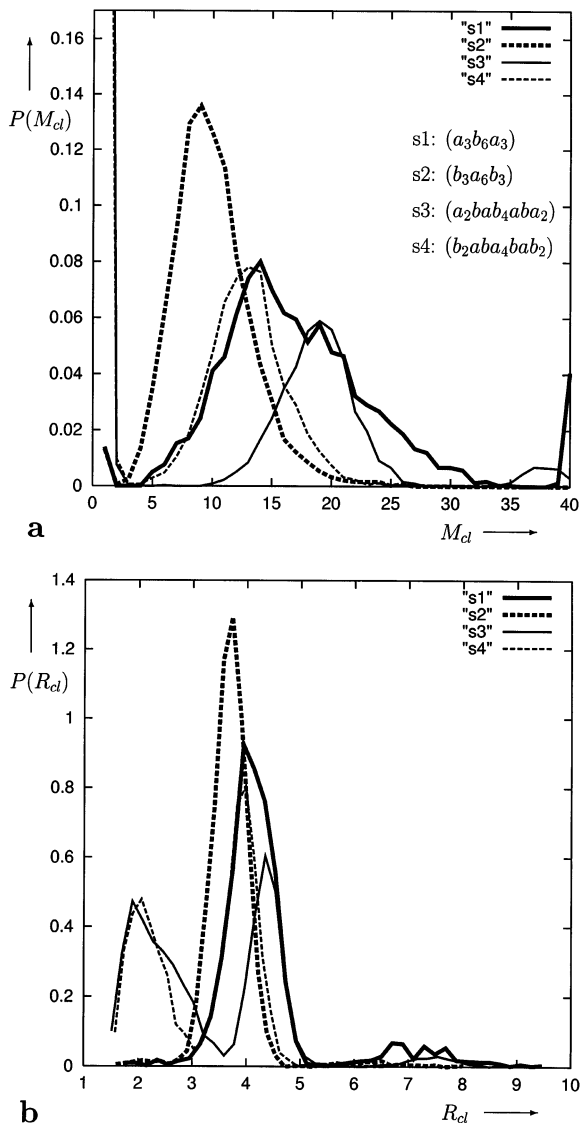


Fig. 2. Probability densities of the number of chains in a cluster (aggregation number), M_{cl} , (a), and the radius of gyration of a cluster (size), R_{cl} (b) for short tri-blocks (thick lines) and mutated tri-blocks (thin lines) sequences. Here $N=12$ and $M=40$, while other parameters are as in Fig. 1.

$M_{cl}=36$ chains coexisting with four single chain globules. Quite remarkably, the mutations of s1 has helped to stabilise average sized clusters leading to more size monodispersed 'mesoglobules'.

3. Conclusion

In this paper we have studied the effect of point-like mutations in tri-block copolymers on aggregates and mesoglobules in dilute solutions. For sufficiently long chains the effect of small

mutations is rather weak and corresponding structures remain stable. However, larger-scale mutations may produce stronger influence.

We then looked at solutions of twice the number of half-long chains for similar sequences. In this case, however, the shortness of the chains has

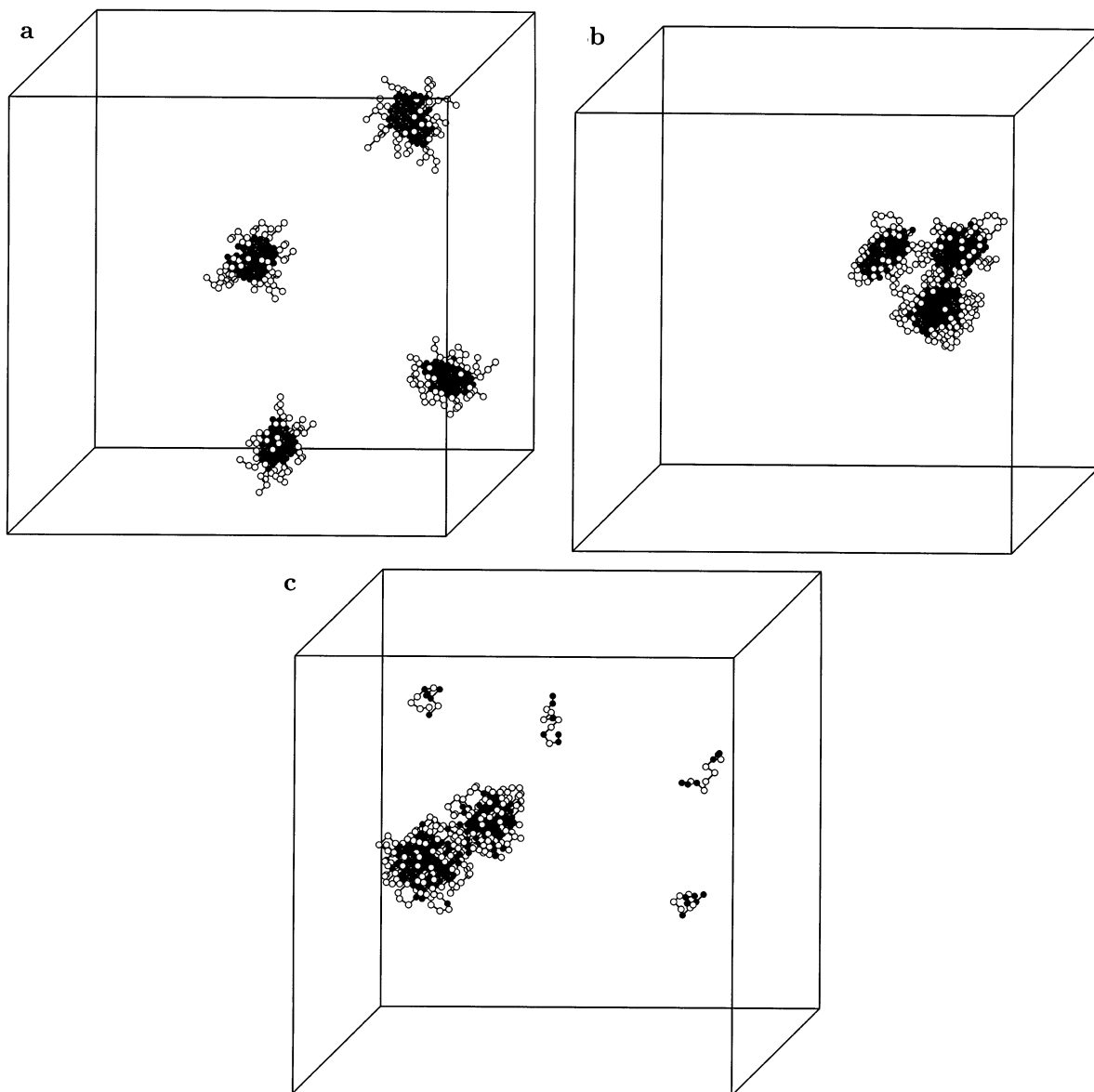


Fig. 3. Snapshots of typical conformations from simulation for different sequences. (a; b; c) correspond to sequences $b_3a_6b_3$, $a_3b_6a_3$ and $a_2bab_4aba_2$, respectively (these were denoted as s2, s1 and s3, respectively in Fig. 2). Here black (white) circles correspond to hydrophobic (hydrophilic) monomers, while other parameters are as in Fig. 2.

added certain populations of single chain globules for all sequences. The main effect of mutations was in dramatically increasing the populations of single chain globules as compared to the original tri-blocks. Perhaps the most unexpected result of mutations was in pronounced increase of the mesoglobules size (both in terms of radius and aggregation number) for mutated sequences compared to the tri-blocks. In [13] we have argued that the size of the mesoglobules is determined by a characteristic scale of micro-phase separation, which in turn is related to the lengths of the blocks. Thus, mesoglobules of shorter blocks should be smaller according to this line of arguing. This was so for sequences of length $N=24$ in Fig. 1 because mutations effectively decrease the lengths of blocks. However, in Fig. 2 the mutations have produced the opposite effect of pronounced magnitude. This paradoxical result reflects the complexity of the competitions of different interactions and the entropy and it does not have a simple explanation as yet.

The results of this work are important for understanding the role of various factors and imperfections in the design of polymers capable of producing stable mono dispersed mesoglobules. Mesoglobules with well controlled size distribution can find a range of applications in pharmaceutical, biotechnological and cosmetic industries. Moreover, these studies may also help understanding the problems of competition aggregation vs folding in protein solutions and, possibly, self-organisation of the quaternary structures in multimeric proteins.

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