A Statistical Theory of cosolvent-induced coil-globule transitions in dilute polymer solution

Yu. A. Budkov, A. L. Kolesnikov, N. Georgi, and M. G. Kiselev

1) Institute of Solution Chemistry of the Russian Academy of Sciences, Ivanovo, Russia
2) Ivanovo State University, Ivanovo, Russia
3) Institut für Nichtklassische Chemie e.V., Universitat Leipzig, Leipzig, Germany
4) Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany
We present a statistical model of a dilute polymer solution in good solvent in the presence of low-molecular weight cosolvent. We investigate the conformational changes of the polymer induced by a change of the cosolvent concentration and the type of interaction between the cosolvent and the polymer. We describe the polymer in solution by the Edwards model, where the partition function of the polymer chain with a fixed radius of gyration is described in the framework of the mean-field approximation. The contributions of polymer-cosolvent and the cosolvent-cosolvent interactions in the total Helmholtz free energy are treated also within the mean-field approximation. For convenience we separate the system volume on two parts: the volume occupied by the polymer chain expressed through its gyration volume and the bulk solution. Considering the equilibrium between the two subvolumes we obtain the total Helmholtz free energy of the solution as a function of radius of gyration and the cosolvent concentration within gyration volume. After minimization of the total Helmholtz free energy with respect to its arguments we obtain a system of coupled equations with respect to the radius of gyration of the polymer chain and the cosolvent concentration within the gyration volume. Varying the interaction strength between polymer and cosolvent we show that the polymer collapse occurs in two cases - either when the interaction between polymer and cosolvent is repulsive or when the interaction is attractive. The reported effects could be relevant for different disciplines where conformational transitions of macromolecules in the presence of a cosolvent are of interest, in particular in biology, chemistry and material science.
I. INTRODUCTION

The coil-globule transition in dilute polymer solutions is one of the most fascinating phenomena in physical chemistry of polymers. The mechanism of conformational transition of a chain molecule upon a change of environment has found many applications in recent technological advances ranging from encapsulation of drug molecules in a polymer coil and targeted delivery\cite{1,2}, to smart materials changing their properties in response to the environment\cite{4,8}. Numerous applications are based on a conformational transition of a polymer sensing the presence of specific molecules at low concentrations\cite{7}, inducing a phase change aggregation of suspensions of colloids coated with pH or temperature responsive polymers\cite{3,5}, gels comprising thermoresponsive polymer networks\cite{5,6}, to name only a few. In organisms proteins fold into a compact state attaining a well defined biological function by exposing functional groups to their environment. Viral DNA collapses to a condensed state to fit in the confined space of a viral capsid\cite{10}. First steps in DNA separation for subsequent analysis involve condensation of DNA using osmolytes or denaturants\cite{11,12}. Especially water soluble polymers are used to exert a lateral pressure on the DNA to induce a collapse\cite{9}. In the present article an alternative mechanism is outlined that could also lead to a collapse when the low molecular weight cosolvent has entered the coil of a chain molecule compressing the coil from within.

The ubiquitous presence of chain molecules and the principal possibility to control the conformational transition by an external stimulus has therefore attracted much attention from experimental point of view in chemistry, biology and material science.

Theoretical efforts on the other hand formulating a coil-globule transition theory contributed much to a qualitative understanding of this phenomenon. Today many theoretical contributions exist dedicated to the coil-globule transition ranging from simplified self-consistent field treatment of the solvent to theories based on the field-theoretic formalism\cite{15-22,24-28}. It has been shown that, as the solvent becomes poorer, the polymer coil shrinks leading eventually to a collapse of the polymer coil. Predominantly the theoretical models describe the solvent only implicitly, i.e. its influence on macromolecule taken into account through effective monomer-monomer interaction. However, nowadays, due to the importance of conformation control of macromolecules in solution by low-molecular weight cosolvents (for example, adding of osmolytes or denaturants in protein aqueous solutions\cite{30-34}) explicit account of the cosolvent in the model seems to be indispensable.
However, up to now only a few attempts considering the cosolvent explicitly have been reported. Notably in the work of Tanaka, et al.\textsuperscript{29} the conformational phase transition of an isolated polymer chain capable of forming physical bonds with solvent molecules treated the solvent explicitly. On the basis of a Flory type mean-field theory, a formula for the temperature dependence of the expansion parameter of the chain has been derived. The formation of the physical bonds between polymer and solvent molecules causes a reentrant conformational change between coiled and globular state of the polymer chain when temperature is varied.

In the work\textsuperscript{35} the collapse and swelling behavior of a homopolymer has been studied using implicit-solvent, explicit cosolvent Langevin dynamics computer simulations. Varying the interaction strength the results of two theoretical models have been compared with the simulation findings. The first model was based on an effective one-component description where the co-solutes have been averaged out - the second model treated the fully two-component system in a Flory-de Gennes type of approach. A conclusion has been reached that the simulation results were in accord with the predictions of the second model.

However, to our best knowledge, there does not seem to exist an approach starting from first principals of statistical mechanics describing the influence of the cosolvent on conformational behavior of the polymer chain – specifically the concentration dependence of the radius of gyration of the polymer chain taking into account the type of cosolvent interactions with the polymer. In the present work such a statistical model of a flexible polymer chain in good solvent in the presence of a low-molecular cosolvent is developed. The influence of cosolvent concentration and quality of its interaction with monomers on the collapse and swelling behavior of polymer chain is investigated.

The paper organized as follows. In Sec. II, we present our theoretical model and in Sec. III the numerical results are given. In Sec. IV, we discuss the obtained results and summarize our findings.

II. THEORY

We consider the case of a polymer chain immersed in a good solvent. We will describe the polymer in the framework of the Edwards model (flexible polymer chain with excluded volume)\textsuperscript{13,14}. The polymer chain molecule and the low-molecular weight cosolvent at a
specified concentration are immersed in a solvent described by a continuous, structureless medium. We assume further that the volume of the system consists of two parts: the gyration volume containing predominantly monomers of the polymer chain and a bulk solution (see, fig. 1). Thus, we consider the cosolvent concentration at equilibrium in the two subvolumes varying the strength of interaction of the polymer-cosolvent. In order to find the solution of the posed problem the minimum of total Helmholtz free energy of the system as function of the radius of gyration and the number of cosolvent molecules within gyration volume is sought.

We assume further that the interaction between cosolvent molecules is purely repulsive so that it can be described by simple hard-sphere potential. This assumption is reasonable if a thermodynamic state of cosolvent is far from binodal in region above the critical point or when it is in the field of liquid states where attraction between cosolvent molecules is not important. Basically, we consider the theory at the level of the mean-field approximation. However, we take into account the cosolvent density fluctuation effect on the monomer-monomer interaction. Our aim is to study the dependence of polymer chain conformations as a function of the cosolvent concentration and the type of interaction between cosolvent and monomers.

The partition function of the polymer-cosolvent system takes the form (for details, see Appendix)

$$Z(R_g, N_1) = Z_c(R_g, N_1)Z_p(R_g),$$  \(1\)

where

$$Z_c(R_g, N_1) = \frac{(V_g - N_1v_c - Nv_{mc})^{N_1}}{(N_c - N_1)!N_1!}e^{-\beta\Delta F_{int}(N_1)}$$  \(2\)

is a partition function of low-molecular weight cosolvent in solution;

$$\beta\Delta F_{int}(N_1) = \frac{w_{pc}N_1}{V_g - Nv_{mc}} - \frac{w_{pc}^2N_1\chi_TN^2}{2\chi_T^\text{id}V_g^2},$$  \(3\)

\(V\) is a volume of the system; \(N_1\) is a number of cosolvent molecules which are within the gyration volume \(V_g = \frac{4\pi R_g^3}{3}\) (\(R_g\) is the radius of gyration); \(N\) is a degree of polymerization - e.g. length of the polymer chain; \(w_{pc}\) is a parameter of volume interaction polymer-cosolvent corresponding to the second virial coefficient; \(N_c\) is a total number of cosolvent molecules, \(v_c = \frac{\pi d_c^3}{6}\) (\(d_c\) is cosolvent molecules diameter) is the excluded volume of cosolvent molecules, \(v_{mc} = \frac{\pi d_m^3}{6}\) (\(d_m = \frac{d_m + d_c}{2}\), \(d_m\) is a diameter of monomers; \(\chi_T\) is an isothermal compressibility
Figure 1. Pictorial representation of the model. The system consists of a polymer chain in a good solvent which is represented by a continuous, structureless medium and a low-molecular weight cosolvent at a specified concentration. The total volume of the system consists of two parts: the gyration volume containing predominantly monomers of the polymer chain and a bulk solution of cosolvent in the gyration volume and $\chi^{id}_T$ is an isothermal compressibility of ideal gas. The expression for the isothermal compressibility in the case of pure repulsive interaction within the mean-field approximation has a form

$$\chi_T(\rho, T) = \frac{1}{\rho} \left( \frac{\partial \rho}{\partial P} \right)_T = \frac{(1 - \rho v_c)^2}{\rho k_B T},$$  \hspace{1cm} (4)$$

where $\rho$ is a cosolvent concentration, $k_B$ is a Boltzmann constant, $T$ is a temperature, $P = \frac{\rho k_B T}{1 - \rho v_c}$ is a pressure. The first term in the right hand side of (3) is relates to the monomer-cosolvent interaction in the framework of mean-field approximation. The second term in (3) is a contribution of the effective monomer-monomer interaction due to cosolvent concentration fluctuations.

The second term in the product (1)

$$Z_p(R_g) = \int d\Gamma(R_g) e^{-\beta H_p}.$$  \hspace{1cm} (5)$$

is a partition function of the polymer chain with fixed radius of gyration; the symbol $\int d\Gamma(R_g)(...)$ denotes an integration over microstates of the polymer chain at a fixed radius
of gyration; \( H_p \) is a Hamiltonian of interaction monomer-monomer which includes the hard-core potential and simple 1-body monomer interaction potential due to the solvent influence (see Appendix). Using the mean-field approximation we obtain the following expression for the polymer Helmholtz free energy

\[
\beta F_p(R_g) = -\ln Z_p(R_g) = \beta F_{id}(R_g) + \frac{N^2 w_p}{2V_g} - N \ln \left( 1 - \frac{N v_m}{V_g} \right),
\]  

(6)

where \( \beta F_{id}(R_g) = -\ln Z_{id}(R_g) \) is the Helmholtz free energy of the ideal polymer chain, \( \beta = \frac{1}{k_B T} \), \( v_m = \frac{\pi d_m^3}{6} \) is a monomer excluded volume. The second term in (6) determines the contribution of monomer-monomer interaction due to solvent effect. The last term in (6) corresponds to the contribution of hard-sphere effect in the Helmholtz polymer free energy within the mean-field approximation. Based on the results of Fixman\(^{38}\) we construct an interpolation formula for the free energy of the ideal polymer chain:

\[
\beta F_{id}(R_g) = \frac{9}{4} \left( \alpha^2 + \frac{1}{\alpha^2} \right) - \frac{3}{2} \ln \alpha^2,
\]  

(7)

where \( \alpha = \frac{R_g}{R_{0g}} \) denotes the expansion parameter, \( R_{0g}^2 = \frac{N b^2}{6} \) is a mean-square radius of gyration of the ideal polymer chain and \( b \) is the Kuhn length of the segment. Rewriting the polymer free energy in terms of the expansion parameter \( \alpha \) we obtain

\[
\beta F_p(\alpha) = \frac{9}{4} \left( \alpha^2 + \frac{1}{\alpha^2} \right) - \frac{3}{2} \ln \alpha^2 + \frac{9\sqrt{6}w_p\sqrt{N}}{4\pi b^3\alpha^3} - N \ln \left( 1 - \frac{9\sqrt{6}v_m}{2\sqrt{N\alpha^3 b^2}} \right).
\]  

(8)

The expression for the cosolvent Helmholtz free energy takes the form

\[
\beta F_c(R_g, N_1) = -\ln Z_c(R_g, N_1) = \beta \Delta F_{int}(N_1) - N_1 \ln \left( V_g - N_1 v_c - N v_{mc} \right) - (N_c - N_1) \ln (V - V_g - (N_c - N_1)v_c) + N_1 (\ln N_1 - 1) + (N_c - N_1) (\ln(N_c - N_1) - 1).
\]  

(9)

Minimizing \( \beta F_c(R_g, N_1) \) with respect to \( N_1 \), i.e. equating to zero the derivative \( \frac{\partial (\beta F_c(R_g, N_1))}{\partial N_1} \) and introducing the notations \( \rho_1 = \frac{N_1}{V} \) and \( \rho = \frac{N_c}{V} \) we obtain the equation for the density of the cosolvent within the gyration volume \( \rho_1 \)

\[
\rho_1 \frac{1 - \rho_1 v_c}{1 - \rho v_c} - \frac{9\sqrt{6}v_{mc}}{2\pi\sqrt{N\alpha^3 b^2}} = \rho_1 v_c \left( 1 - \rho_1 v_c \right) - \frac{9\sqrt{6}v_{pc}}{2\pi\sqrt{N\alpha^3 b^2}} \frac{g_1}{g_{mc}} + \frac{243\omega_{pc}^2}{4\pi^2 N\alpha^3 b^2} A(\rho_1),
\]  

(10)

\[
\rho \frac{1 - \rho v_c}{1 - \rho v_c} - \frac{9\sqrt{6}v_{mc}}{2\pi\sqrt{N\alpha^3 b^2}} = \rho_1 v_c \left( 1 - \rho_1 v_c \right) - \frac{9\sqrt{6}v_{pc}}{2\pi\sqrt{N\alpha^3 b^2}} \frac{g_1}{g_{mc}} + \frac{243\omega_{pc}^2}{4\pi^2 N\alpha^3 b^2} A(\rho_1),
\]  

(11)

which valid for \( V \gg V_g \) and \( N_c \gg N_1 \); \( A(\rho_1) = (1 - \rho_1 v_c) (1 - 3\rho_1 v_c) \).
It should be noted that the value of the expansion parameter, which corresponds to a minimum of the total Helmholtz free energy. Thus, using the equations (4, 8, 10), and calculating a derivative of the total free energy with respect to $\alpha$ and equating it to zero, we obtain the equation

$$\alpha^5 - \frac{2}{3} \alpha^3 - \alpha = \frac{3\sqrt{6}}{2\pi} \sqrt{N} \left( \tilde{w}_p + \frac{\tilde{v}_m}{1 - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3}} - B(\tilde{\rho}_1) \right) -$$

$$- \frac{2\pi\sqrt{6}}{81} N^{3/2}\alpha^6 \left( \frac{\tilde{\rho}}{1 - \tilde{\rho}\tilde{v}_c} - \frac{\tilde{\rho}_1}{1 - \tilde{\rho}_1\tilde{v}_c} - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3} \right) + \frac{2N\tilde{w}_{pc}\tilde{\rho}_1\alpha^3}{3 \left( 1 - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3} \right)},$$

(12)

where $\tilde{w}_p = w_p b^{-3}$, $\tilde{w}_{pc} = w_{pc} b^{-3}$, $\tilde{\rho} = \rho b^3$, $\tilde{v}_c = \frac{v_c}{b^3}$, $\tilde{v}_{mc} = \frac{v_{mc}}{b}$, $\tilde{v}_m = \frac{v_m}{b}$, $B(\tilde{\rho}_1) = 2\tilde{w}_{pc}\tilde{\rho}_1 \left( 1 - 2\tilde{\rho}_1\tilde{v}_c \right) \left( 1 - \tilde{\rho}_1\tilde{v}_c \right)$. The first term in a right hand side of equation (12) relates to the monomer-monomer interaction due to solvent effect, monomer hard-core effect and effect of cosolvent concentration fluctuations. The second term relates to a pressure difference between the cosolvent molecules within gyration volume and in the bulk solution. The last term is related to the polymer-cosolvent interaction.

The dimensionless cosolvent concentration $\tilde{\rho}_1 = \rho_1 b^3$ within gyration volume satisfies the equation

$$\tilde{\rho}_1 = \frac{1}{1 - \tilde{\rho}_1\tilde{v}_c} - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3} =$$

$$= \frac{\tilde{\rho}}{1 - \tilde{\rho}\tilde{v}_c} - \frac{\tilde{v}_c}{1 - \tilde{\rho}_1\tilde{v}_c} + \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3} \left( 1 - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3} \right) + \frac{2\pi^2\tilde{w}_{pc}^2}{4\pi^2 N\alpha^6} A(\tilde{\rho}_1).$$

(13)

Let us analyze some limiting regimes. At $\tilde{\rho} \to 0$ we have a swelling regime $\alpha \sim (\tilde{w}_p + \tilde{v}_m)^{1/5} N^{1/10}$ that is described by the classical mean-field Flory theory. Now, we consider the situation when $\tilde{w}_{pc} \gg 1$, i.e. when interaction cosolvent-polymer is strongly repulsive. In this case $\tilde{\rho}_1 \ll \tilde{\rho}$ and the equation (12) simplifies to

$$\alpha^5 - \frac{2}{3} \alpha^3 - \alpha = \frac{3\sqrt{6}}{2\pi} \sqrt{N} \frac{\tilde{v}_m}{1 - \frac{9\sqrt{6}\tilde{v}_m}{2\pi\sqrt{N}\alpha^3}} - \frac{2\pi\sqrt{6}}{81} \frac{\rho N^{3/2}\alpha^6}{1 - \tilde{\rho}\tilde{v}_c}.$$  

(14)

If the second term on the right hand side of equation (14) dominates then neglecting all except the first and second terms we obtain the following relations for expansion parameter and radius of gyration

$$\alpha \simeq a^{1/3} N^{-1/3}, \quad \frac{R_g}{b} \simeq \frac{\sqrt{6}}{6} a^{1/3} N^{1/3},$$

(15)
which corresponds to a globular conformation; \( a = \frac{9\sqrt{6}v_{mc}}{4\pi} + \sqrt{\left(\frac{9\sqrt{6}v_{mc}}{4\pi}\right)^2 + \frac{243\tilde{v}_m(1-\tilde{\rho}_c)}{4\pi^2\rho}}. \)

We turn now to the opposite limiting case when \( \tilde{w}_{pc} < 0 \) and \( |\tilde{w}_{pc}| \gg 1 \), i.e. when interaction cosolvent-polymer is strongly attractive. In this case \( \tilde{\rho}_1 \gg \tilde{\rho} \). Therefore the difference of cosolvent pressures between interior of the gyration volume and the bulk can lead to an additional swelling the polymer coil. The excluded volume of cosolvent molecules and monomers has the same affect. However, the strong attraction between cosolvent and monomers leads to a shrinking of the polymer coil. Due to the competition between these trends the coil-globule transition can occur. The equation (12) in this case simplifies to

\[
\frac{2\sqrt{N}|\tilde{w}_{pc}|\tilde{\rho}_1\alpha^3}{3\left(1 - \frac{9\sqrt{6}v_{mc}}{2\pi\sqrt{N}a^3}\right)} \approx \frac{2\pi\sqrt{6}N\alpha^6}{81} \frac{\tilde{\rho}_1}{1 - \tilde{\rho}_1\tilde{v}_c - \frac{9\sqrt{6}v_{mc}}{2\pi\sqrt{N}a^3}} + \frac{3\sqrt{6}}{2\pi} - \frac{\tilde{v}_m}{1 - \frac{9\sqrt{6}v_{mc}}{2\pi\sqrt{N}a^3}}. \quad (16)
\]

The equation (16) can be simplified by the substitution \( \alpha = sN^{-1/6} \). Thus we obtain the equation with respect to \( s \) which already does not contain the degree of polymerization \( N \)

\[
\frac{\pi\sqrt{6}}{27} - \frac{s^6\tilde{\rho}_1}{1 - \tilde{\rho}_1\tilde{v}_c - \frac{9\sqrt{6}v_{mc}}{2\pi s^3}} + \frac{9\sqrt{6}}{4\pi} - \frac{\tilde{v}_m}{1 - \frac{9\sqrt{6}v_{mc}}{2\pi s^3}} - |\tilde{w}_{pc}|\tilde{\rho}_1s^3 = 0. \quad (17)
\]

Therefore, the equation (17) determines the globule size as function of \( \tilde{v}_c, \tilde{v}_m, \tilde{v}_{mc} \) and \( \tilde{w}_{pc} \):

\[
\alpha \approx sN^{-1/6}, \quad \frac{R_g}{b} \approx \frac{\sqrt{6}}{6}sN^{1/3}. \quad (18)
\]

In this case size of the globule is determined by a competition between cosolvent-polymer attraction and monomer and cosolvent excluded volume effect. We would like to stress that in the globular regimes the cosolvent concentration \( \tilde{\rho}_1 \) within gyration volume does not depend on the expansion parameter.

### III. NUMERICAL RESULTS AND DISCUSSION

Turning to the numerical analysis of the system of equations (12-13) we will fix the diameters (in units of Kuhn’s length of the segment \( b \)) \( \tilde{d}_c = \tilde{d}_m = \tilde{d}_{mc} = 1 \), parameter of volume interactions monomer-monomer \( \tilde{w}_p = 1 \), and degree of polymerization \( N = 10^4 \).

We first discuss the case when the interaction polymer-cosolvent is a pure repulsive. Fig. 2 (a) shows the expansion parameter \( \alpha \) as a function of the cosolvent concentration \( \tilde{\rho} \) at different values of \( \tilde{w}_{pc} \). At increasing cosolvent concentration the expansion parameter monotonically decreases and is asymptotically close to limit given by (15) corresponding to a
globular conformation. Increasing the interaction parameter \( \tilde{w}_{pc} \) the coil-globule transition becomes sharper. Fig. 2 (b) shows the cosolvent concentration in the gyration volume as a function of cosolvent concentration in the bulk for two values of polymer-cosolvent interaction parameters. In the region of coil-globule transition the cosolvent concentration within the gyration volume shows a sufficiently pronounced maximum. Such behavior can be interpreted as follows. At small values of cosolvent concentrations in the bulk the gyration volume offers enough space for the cosolvent to intrude leading to a swelling of the polymer coil. In contrast, increasing the size of polymer coil decreases leading to a more confined space increasing therefore the repulsion between cosolvent and monomers and as consequence the cosolvent is expelled from polymer coil. Thus, when the cosolvent concentration in the bulk drops below a certain value the cosolvent concentration within the gyration volume monotonically decreases.

For the case when the polymer-cosolvent interaction is attractive (\( \tilde{w}_{pc} < 0 \)) an abrupt collapse of the polymer chain takes place. Fig. 3 (a) shows the expansion parameter \( \alpha \) as a function cosolvent concentration for different values of \( \tilde{w}_{pc} \). At values of bulk cosolvent concentration at which the collapse occurs there is also a jump of cosolvent concentration in the gyration volume to very dense packing (fig. 3 (b)). In contrast to the previous case, in this regime the polymer collapse happens as a first - order phase transition at which the jump of the cosolvent concentration takes place. As mentioned above, this phase transition is due to the competition between polymer - cosolvent attraction, which tends to shrink the polymer chain, and a steric factor of the cosolvent molecules and monomers, which tends to expand it.

It is interesting to consider the dependence of the expansion parameter \( \alpha \) on the polymer-cosolvent interaction parameter \( \tilde{w}_{pc} \). As shown in fig. 4 this dependence is sufficiently non-monotonic. The collapse of polymer chain takes place in the range of negative values of \( \tilde{w}_{pc} \). At increasing \( \tilde{w}_{pc} \) the expansion parameter towards zero a maximum occurs. Further increasing (towards positive values) \( \tilde{w}_{pc} \) the expansion parameter again monotonically decreases and smoothly approach the globule regime. Such behavior is in agreement with results of computer simulations obtained in \cite{35}. 

10
IV. SUMMARY

We have outlined a first principles mean-field theory of conformational changes of a polymer chain depending on the cosolvent concentration and the type of interactions between cosolvent and the polymer. The explicit account of the cosolvent leads to the fundamentally new effects, namely polymer chain collapse occurs in two limiting cases. The first case, when the cosolvent-polymer interaction is a strongly repulsive and, in the opposite case, when this interaction is strongly attractive. In the second case when polymer-cosolvent interaction is attractive the collapse occurs as a first-order phase transition, i.e. discontinuous change of the radius of gyration and the cosolvent density within the gyration volume. We call these phenomena “cosolvent-induced coil-globule transitions”.

The described phenomena may be relevant for applications, where the mixed-solvent polymer solutions are used. In particular where the solvent conditions are used to induce a change in polymer conformation the described mechanism might offer an additional routine to exert control on the polymer conformational transition. In particular, the present theory may be useful for description of stabilization of proteins in aqueous solution by adding osmolytes, such as trimethylamine N-oxide (TMAO), glycine, betaine, glycerol, and sugars\textsuperscript{32}. We would like to stress that the effect of the polymer collapse in the case of strong attraction between monomers and cosolvent molecules is very similar to the collapse of polypeptide PNIPAM due to cooperative generating of hydrogen bonding of urea with the polypeptide backbone\textsuperscript{42}. However, these speculations require more detailed investigations involving the computer simulations and comparisons with real experimental data, that is a subject of the forthcoming publications.

Instructively to provide an estimation in physical units of values of cosolvent concentration in the bulk $\rho$ and second virial coefficient of interaction monomer-cosolvent $w_{pc}$ at which the coil-globule transitions can take place. We consider the case when the value of Kuhn’s length of the segment is approximately equal to $b \approx d_m \approx d_c \approx d_{mc} \approx 0.4 \text{ nm}$, that is quite reasonable for real polymer solutions\textsuperscript{35,42}. In the case when interaction of monomer-cosolvent is pure repulsive one can get the following estimates: $\rho \sim 10 \text{ M}$, $w_{pc} \sim 10^2 \text{ A}^3$. In the case of attractive interaction we obtain the estimates: $\rho \sim 1 \text{ M}$ and $|w_{pc}| \sim 10^2 \text{ A}^3$. These estimates show that the reported coil-globule transitions may be observed under ambient conditions in reality.
The present theory, however, has natural limitations. Firstly, it can not describe a dilute polyelectrolyte solutions, where many-body effects due to long-range electrostatic interactions play crucial role. Such a first-principals theories, which can describe the collapse of the charged polymer chain in dilute polyelectrolyte solution, has been recently developed in works \textsuperscript{43,44}. Moreover, our theory does not take into account a possibility the formation of chemical bonds between polymer and cosolvent molecules. Apart from the above limitations our theory does not explicitly account for specific interactions, such as hydrogen bonds formation. We note that work in this direction has been recently published \textsuperscript{45}, where the problem of the helix-coil transition in explicit solvent has been addressed analytically. Employing a spin-based models the influence of the hydrogen bonds formation on the helix-coil transition has been investigated. It would be interesting to investigate how the chemical bond formation and explicit accounting specific interactions influence on the coil-globule transition in dilute polymer solutions. We believe, that these problems also can be a subject worthwhile for forthcoming publications.

V. ACKNOWLEDGMENTS

The research leading to these results has received funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement №//247500 with //project acronym "Biosol".

We are grateful to prof. N.V. Brilliantov for his remarks which allowed to do a more rigorous theory.

We thank anonymous referees for their valuable suggestions and comments.

VI. APPENDIX: DERIVATION OF FORMULA (2)

To address a derivation of the expression (2) for the partition function of the cosolvent we start from the canonical partition function of the solution, which can be written as follows

\[ Z(R_g) = \int d\Gamma_p(R_g) \int d\Gamma_c \exp \left[ -\beta H_p - \beta H_c - \beta H_{pc} \right] , \]

where the symbol \( \int d\Gamma(R_g)(..) \) denotes the integration over microstates of the polymer chain performed at a fixed radius of gyration; the symbol \( \int d\Gamma_c(\ldots) = \frac{1}{N_c} \int d\vec{r}_{1c} \ldots \int d\vec{r}_{N_c}(\ldots) \) denotes
the integration over cosolvent molecules’ coordinates; \( V \) is a volume of the system;
\[
\beta H_p = \frac{w_p^N}{2} \int ds_1 \int ds_2 \delta (\vec{r}(s_1) - \vec{r}(s_2)) + \frac{\beta}{2} \int ds_1 \int ds_2 V_{hc}^{(m)}(\vec{r}(s_1) - \vec{r}(s_2))
\] (20)
is the Hamiltonian of the monomer-monomer interaction; \( w_p \) is a second virial coefficient for the monomer-monomer interaction and
\[
V_{hc}^{(m)}(\vec{r}) = \begin{cases} 
\infty, & |\vec{r}| \leq d_m \\
0, & |\vec{r}| > d_m 
\end{cases}
\] (21)
is a hard-core potential of interaction monomer-monomer; \( d_m \) is a diameter of monomers;
\[
\beta H_{pc} = w_{pc} \int ds \sum_{j=1}^{N_c} \delta (\vec{r}(s) - \vec{r}_j) + \beta \int ds \sum_{j=1}^{N_c} V_{hc}^{(mc)}(\vec{r}(s) - \vec{r}_j)
\] (22)
\[
= w_{pc} \int V \hat{\rho}_c(\vec{x}) \hat{\rho}_p(\vec{x}) + \beta H_{pc}^{(hc)}
\] (23)
is the Hamiltonian of the polymer-cosolvent interaction; \( \hat{\rho}_c(\vec{x}) = \sum_{i=1}^{N_c} \delta (\vec{x} - \vec{r}_i) \) and \( \hat{\rho}_p(\vec{x}) = \int d\vec{r} \delta(\vec{x} - \vec{r}(s)) \) are the local densities of the cosolvent molecules and monomers, respectively; \( w_{pc} \) is the second virial coefficient for the polymer-cosolvent interaction,
\[
V_{hc}^{(mc)}(\vec{r}) = \begin{cases} 
\infty, & |\vec{r}| \leq d_{mc} \\
0, & |\vec{r}| > d_{mc} 
\end{cases}
\] (24)
is a hard-core potential of the monomer-cosolvent interaction ;
\[
\beta H_c = \frac{\beta}{2} \sum_{j \neq i} V_{hc}^{(c)}(\vec{r}_i - \vec{r}_j)
\] (25)
is the Hamiltonian of the cosolvent-cosolvent interaction;
\[
V_{hc}^{(c)}(\vec{r}) = \begin{cases} 
\infty, & |\vec{r}| \leq d_c \\
0, & |\vec{r}| > d_c 
\end{cases}
\] (26)
is the hard-core potential (\( d_c \) is a cosolvent molecule diameter). Thus we describe the cosolvent-cosolvent interaction as an excluded volume interaction.

Making the following identity transformation
\[
Z(R_g) = \int d\Gamma_p(R_g)e^{-\beta H_p} \int d\Gamma_c e^{-\beta H_c - \beta H_{pc}} = Z_p(R_g) \int d\Gamma_c e^{-\beta H_c} \langle e^{-\beta H_{pc}} \rangle_p,
\] (27)
where

\[ Z_p(R_g) = \int d\Gamma_p(R_g) e^{-\beta H_p} \]  

(28)
is the polymer partition function; the symbol \( \langle \ldots \rangle_p = \frac{1}{Z_p(R_g)} \int d\Gamma_p(R_g) e^{-\beta H_p} \langle \ldots \rangle \) denotes averaging over polymer microstates with a fixed radius of gyration. To take into account the polymer-cosolvent hard-sphere effect we will assume that the contribution of the polymer-cosolvent hard-core interaction in the total Hamiltonian just leads to a renormalization of the cosolvent configurational space. This amounts to

\[ \int d\Gamma_c e^{-\beta H_{pc}(..)} \rightarrow \int d\Gamma'_c(..), \]  

(29)

where

\[ \int d\Gamma'_c(\ldots) = \frac{1}{N_c!} \int_{V-V_{Mc}} d\vec{r}_c \ldots \int_{V-V_{Mc}} d\vec{r}_N(\ldots). \]  

It should be noted that the approximation (29) is the simplest method to account for the so-called depletion forces which may lead to an additional repulsion of the cosolvent molecules from the gyration volume due to the presence of monomers. Keeping in mind the "mean-field" assumption (29) we arrive at

\[ Z(R_g) = Z_p(R_g) \int d\Gamma'_c e^{-\beta H_c} \left\langle e^{-\int \hat{\rho}_c(\vec{x}) \hat{\rho}_p(\vec{x})} \right\rangle_p. \]  

(30)

Truncating the cumulant expansion at the first order we obtain

\[ \left\langle e^{-\int \hat{\rho}_c(\vec{x}) \hat{\rho}_p(\vec{x})} \right\rangle_p \approx e^{-w_{pc} \int V \hat{\rho}_c(\vec{x}) \hat{\rho}_p(\vec{x})}. \]  

(31)

Thus one can get

\[ w_{pc} \int V \hat{\rho}_c(\vec{x}) \langle \hat{\rho}_p(\vec{x}) \rangle_p \approx w_{pc} \frac{N}{V_g} \int V \hat{\rho}_c(\vec{x}), \]  

(32)

where the approximation

\[ \langle \hat{\rho}(\vec{x}) \rangle_p \approx \begin{cases} \frac{N}{V_g}, & |\vec{x}| \leq R_g \\ 0, & |\vec{x}| > R_g, \end{cases} \]  

(33)

has been introduced. Therefore, we obtain the following expression for the partition function of the solution

\[ Z(R_g) = Z_p(R_g) Z_c(R_g), \]  

(34)

where \( Z_c(R_g) \) has a form

\[ Z_c(R_g) = \int d\Gamma'_c e^{-\beta H_c - w_{pc} \frac{N}{V_g} \int V \hat{\rho}_c(\vec{x})}. \]  

(35)
Rewriting the last expression in the form

\[ Z_c(R_g) = \frac{1}{N_c} \sum_{n=0}^{N_c} Z_c(R_g, n), \tag{36} \]

where

\[ Z_c(R_g, n) = \frac{N_c!}{(N_c - n)! n!} \int_{V_g - N\nu_{mc}} \int_{V_g - N\nu_{mc}} d\vec{x}_1 \ldots \int_{V_g - V_g} \int_{V_g - V_g} d\vec{x}_n \int_{V_g - V_g} d\vec{y}_n \int_{V_g - V_g} d\vec{y}_{n-1} \ldots d\vec{y}_1 e^{-\beta H_c - \beta H_{int}} \tag{37} \]

is the cosolvent partition function with a fixed number \( n \) of cosolvent molecules in the gyration volume; \( \beta H_{int} = \frac{w_{pc} N}{V_g} \int d\vec{x} \hat{\rho}_c(\vec{x}) \) is an effective Hamiltonian which describes the monomer-cosolvent interactions. To evaluate \( Z_c(R_g, n) \) we introduce the approximation \( H_c = H_c^{(N_c)} \approx H_c^{(n)} + H_c^{(N_c-n)} \) which is accurate for sufficiently large gyration volumes. This leads to

\[ Z_c(R_g, n) \approx \frac{N_c!}{(N_c - n)! n!} Z_c^{(N_c-n)} Z_c^{(n)} \tag{38} \]

where

\[ Z_c^{(N_c-n)} = \int_{V_g - N\nu_{mc}} \int_{V_g - V_g} d\vec{y}_1 \ldots \int_{V_g - V_g} d\vec{y}_{N_c-n} e^{-\beta H_c^{(N_c-n)}}, \tag{39} \]

\[ Z_c^{(n)} = \int_{V_g - N\nu_{mc}} \int_{V_g - V_g} d\vec{x}_1 \ldots \int_{V_g - V_g} d\vec{x}_n e^{-\beta H_c^{(n)} - \beta H_{int}} = Q_c^{(n)} \langle e^{-\beta H_{int}} \rangle_c, \tag{40} \]

\[ Q_c^{(n)} = \int_{V_g - N\nu_{mc}} \int_{V_g - V_g} d\vec{x}_1 \ldots \int_{V_g - V_g} d\vec{x}_n e^{-\beta H_c^{(n)}} \]

is a configurational integral of the cosolvent in gyration volume; the symbol \( \langle (..) \rangle_c = \frac{1}{Q_c^{(n)}} \int_{V_g - N\nu_{mc}} \int_{V_g - V_g} d\vec{x}_1 \ldots \int_{V_g - V_g} d\vec{x}_n e^{-\beta H_c^{(n)}} (..) \) means an averaging over cosolvent microstates in gyration volume. Now we have to evaluate the cosolvent partition function \( Z_c^{(n)} \) in the gyration volume.

Truncating the cumulant expansion at the second order we obtain:

\[ Z_c^{(n)} = Q_c^{(n)} \exp \left[ -\beta \langle H_{int} \rangle_c + \frac{\beta^2}{2} \left( \langle H_{int}^2 \rangle_c - \langle H_{int} \rangle_c^2 \right) \right]. \tag{41} \]

Then we obtain:

\[ \beta \langle H_{int} \rangle_c - \frac{\beta^2}{2} \left( \langle H_{int}^2 \rangle_c - \langle H_{int} \rangle_c^2 \right) = \frac{w_{pc} N}{V_g} \int_{V_g} d\vec{x} \langle \hat{\rho}_c(\vec{x}) \rangle_c - \frac{w_{pc}^2 N^2}{2V_g^2} \int_{V_g} d\vec{x} \int_{V_g} d\vec{y} \langle \delta \hat{\rho}_c(\vec{x}) \delta \hat{\rho}_c(\vec{y}) \rangle_c. \tag{42} \]

Using a local approximation for the correlation function of the cosolvent density fluctuations in the gyration volume

\[ \langle \delta \hat{\rho}_c(\vec{x}) \delta \hat{\rho}_c(\vec{y}) \rangle_c = \frac{n}{V_g^2 \chi_T^2} \delta(\vec{x} - \vec{y}). \tag{43} \]
and keeping in mind that \( \langle \hat{\rho}_c(x) \rangle_c = \frac{n}{V_g - N v_{mc}} \) we arrive at

\[
Z_c^{(n)} = Q_c^{(n)} \exp \left[ - \frac{w_{pc} n N}{V_g - N v_{mc}} + \frac{w_{pc}^2 N^2 n \chi_T}{2 V_g^2 \chi_{id}^2} \right],
\]  

(44)

where \( \chi_T \) is an isothermal compressibility of cosolvent in the gyration volume and \( \chi_{id}^2 \) is an isothermal compressibility of the ideal gas.

Applying the mean-field approximation to \( Z_c^{(N_c-n)} \) and \( Q_c^{(n)} \) we finally arrive at

\[
Z_c(R_g) = \sum_{n=0}^{N_c} \frac{(V_g - n v_c - N v_{mc})^n (V - V_g - (N_c - n) v_c)^{N_c-n}}{(N_c - n)! n!} e^{-\beta \Delta F_{int}(n)},
\]  

(45)

where

\[
\beta \Delta F_{int}(n) = \frac{w_{pc} N n}{V_g - N v_{mc}} - \frac{w_{pc}^2 N^2 n \chi_T}{2 V_g^2 \chi_{id}^2},
\]  

(46)

\( v_c = \frac{\pi d^3}{6} \) is an excluded volume of the cosolvent molecules. The first term on the right hand side of (46) determines the contribution of monomer-cosolvent interaction in the framework the mean-field approximation. The second term is related to an effective monomer-monomer interaction due to the cosolvent concentration fluctuations. In the thermodynamic limit \((N_c \to \infty)\) in the sum (45) only the highest order term giving the main contribution is relevant. This term corresponds to the number \( n = N_1 \) which can be obtained from the extremum condition

\[
\frac{\partial}{\partial n} \ln \left( \frac{(V_g - n v_c - N v_{mc})^n (V - V_g - (N_c - n) v_c)^{N_c-n}}{(N_c - n)! n!} e^{-\beta \Delta F_{int}(n)} \right) = 0.
\]  

(47)

Therefore we arrive at the expression for the cosolvent partition function in the framework of the mean-field approximation which already has been used in the main text

\[
Z_c(R_g) \simeq \frac{(V_g - N_1 v_c - N v_{mc})^{N_1} (V - V_g - (N_c - N_1) v_c)^{N_c-N_1}}{(N_c - N_1)! N_1!} e^{-\beta \Delta F_{int}(N_1)}.
\]  

(48)
REFERENCES

1. Priya Bawa, Viness Pillay, Yahya E Choonara and Lisa C du Toit. Stimuli-responsive polymers and their applications in drug delivery // Biomed. Mater. 4, (2009) 022001

2. Fitzpatrick S.D., Lindsay E.F., Thakur A., et.al. Temperature-sensitive polymers for drug delivery // Expert Review of Medical Devices 2012, Vol 9, 4 ,P. 339

3. Kost, J., Langer R. Responsive polymeric delivery systems // Advanced Drug Delivery Reviews, 2001, 46, 125 - 148

4. Somali Chaterji, Il Keum Kwon, Kinam Park. Smart polymeric gels: Redefining the limits of biomedical devices // Prog. Polym. Sci. 32 (2007) 1083–1122

5. Liang-Yin Chu, Rui Xie, Xiao-Jie Ju, Wei Wang. Smart Hydrogel Functional Materials // Springer, Chemical Industry Press, DOI 10.1007/978-3-642-39538-3

6. Volume Editor: Walter Richtering. Smart Colloidal Materials// Springer, Progress in Colloid and Polymer Science Volume 133, 2006

7. Anis Zribi, Jeffrey Fortin. Functional Thin Films and Nanostructures for Sensors Synthesis, Physics, and Applications // Springer Series, Integrated Analytical Systems 2009

8. Ashok Kumara, Akshay Srivastava, Igor Yu Galaev, Bo Mattiasson. Smart polymers: Physical forms and bioengineering applications // Prog. Polym. Sci. 32 (2007) 1205–1237

9. Vladimir B. Teif, Klemen Bohinc. Condensed DNA: Condensing the concepts // Progress in Biophysics and Molecular Biology 105 (2011) 208-222

10. Gelbart, W.M., Bruinsma, R., Pincus, P.A., Parsegian. DNA-inspired electrostatics. Phys. Today 53, 38.

11. Rita Dias, Bjorn Lindman. DNA Interactions with Polymers and Surfactants 2008 Wiley

12. Koutsoukos, Petros G. Trends in Colloid and Interface Science XV Series: Progress in Colloid and Polymer Science, Vol. 118

13. Edwards S.F. The statistical mechanics of polymers with excluded volume. // Proc. Phys. Soc. - 1965. - Vol. 85 - p. 613.

14. Edwards S.F. The theory of polymer solutions at intermediate concentration. // Proc. Phys. Soc. - 1966. - Vol. 88 - p. 265.

15. Birshtein T.M., Pryamitsyn V.A. Coil-Globule Type Transitions in Polymers. 2. Theory of Coil-Globule Transition in Linear Macromolecules // Macromolecules. - V. 24. - 1991.
16 Moore M.A. Theory of the polymer coil-globule transition // J. Phys. A: Math. Gen. - V. 10 (2) - 1977. - P. 305.

17 de Gennes P.G. Collapse of a polymer chain in poor solvents // Le Journal De Physique Letters. - V. 36 (2) - 1975. - P. L-55.

18 Lifshitz I.M., Grosberg A.Yu State diagram of a polymer globule and the problem of self-organization of its spatial structure // Soviet physics JETP. - V. 38 (6). - 1974. - P. 1198.

19 Lifshitz I.M. Some problems of the statistical theory of biopolymers // Soviet physics JETP. - V. 28 (6) - 1975. - P. L-55.

20 Muthukumar M. Collapse transition of a stiff chain // J. Chem. Phys. - V. 81. - 1984. - P. 6272.

21 Sanchez I.C. Phase Transition Behavior of the Isolated Polymer Chain // Macromolecules. - V. 12 (5). - 1979. - P. 980.

22 Birshtein T.M., Pryamitsyn V.A. Theory of the coil-globule transition // Polymer Science U.S.S.R. - V. 29 (9). - 1987. - P. 2039.

23 Grosberg A.Yu., Kuznetsov D.V. Quantitative Theory of the Globule-to-Coil Transition. 1. Link Density Distribution in a Globule and Its Radius of Gyration // Macromolecules. - V. 25. - 1992. - P. 1970.

24 Khohlov A.R. Theory of the polymer chain collapse for the d-dimensional case // Physica. - V. 105 A. - 1981. - P. 357.

25 van den Oever J.P.M., Leermakers F.A.M., Fleer G.J., et.al. Coil-globule transition for regular, random, and specially designed copolymers: Monte Carlo simulation and self-consistent field theory // Phys. Rev. E. - V. 65. - P. 041708.

26 Wu C., Wang X. Globule-to-Coil Transition of a Single Homopolymer Chain in Solution // Phys. Rev. Lett. - V. 80 (18). - P. 4092.

27 Kholodenko A.L., Freed K.F. Globule-to-Coil Transition of a Single Homopolymer Chain in Solution // J. Phys. A: Math. Gen. - V. 17. - 1984 - P. 2703.

28 Sear R.P. The coil–globule transition of polymers of long rigid monomers connected by flexible spacers // J. Chem. Phys. - V. 107. - 1997. -

29 Matsuyama M., Tanaka F. Theory of solvation-induced reentrant coil-globule transition of an isolated polymer chain // J. Chem. Phys. - V. 94 (1). - 1991. - P. 781.
30 Batchelor D.R., Paschek D., Garcia A.E. Equilibrium Study of Protein Denaturation by Urea // J. Am. Chem. Soc. - 2010. - V. 132. - P. 2338.
31 Canchi J.D., Olteanu A., Tripathy A., Pielak G.J. Impact of Protein Denaturants and Stabilizers on Water Structure // J. Am. Chem. Soc. - 2004. - V. 126 (7). - P. 1959.
32 Canchi D.R., Garcia A.E. Cosolvent Effects on Protein Stability // Annu. Rev. Phys. Chem. - 2013. - V. 64. - P. 273.
33 Haran G. How, when and why proteins collapse: the relation to folding // Current Opinion in Structural Biology. - 2012. - V. 22. - P. 14.
34 Ziv G., Thirumalai D., Haran G. Collapse transition in proteins // Phys. Chem. Chem. Phys - 2009. - V. 11. - P. 83.
35 Heyda J., Muzdalo A., Dzubiella J. Rationalizing Polymer Swelling and Collapse under Attractive Cosolvent Conditions // Macromolecules. - V. 46 - 2013. - P. 1231.
36 Das P., Xia Z., Zhou R. Collapse of a Hydrophobic Polymer in a Mixture of Denaturants // Langmur. - V. 29 (15) - 2013. - P. 4877.
37 Matysiak S., Das P. Effects of Sequence and Solvation on the Temperature-Pressure Conformational Landscape of Proteinlike Heteropolymers // Phys. Rev. Lett. - V. 111. - 2013. - P. 058103.
38 Fixman M. Radius of Gyration of Polymer Chains // J. Chem. Phys. - V. 36 (2) - 1962. - P. 306.
39 Doi, M., Edwards, S. F. The Theory of Polymer Dynamics // Clarendon Press: Oxford, 1986.
40 Flory P. Statistical Mechanics of Chain Molecules // New York: Wiley-Interscience. - 1969.
41 Kubo R. Generalized cumulant Expansion Method // J. Phys. Soc. Jap. - V.17 - 1962 - P. 1100.
42 Zhang Y., Cremer P.S. Chemistry of Hofmeister Anions and Osmolytes // Annu. Rev. Phys. Chem. - 2010. - V. 61. - P. 63-83.
43 Brilliantov N.V., Kuznetsov D.V., Klein R. Chain Collapse and Counterion Condensation in Dilute Polyelectrolyte Solutions. // Phys. Rev. Lett. - 1998. - Vol. 81 (7). - P. 1433.
44 Schiessel H., Pincus P. Counterion-Condensation-Induced Collapse of Highly Charged Polyelectrolytes // Macromolecules. - 1998. - V. 31. - P. 7953.
45 Badasyan A., Tonoyan S.A., Giacometti A., et.al. A unified description of solvent effects in the helix-coil transition // arXiv:1401.0281v1.
46 Barrat J.-L., Hansen J.-P. University Press, Cambridge: 2003.
Figure 2. Repulsive polymer-cosolvent interaction (e.g. $\tilde{w}_{pc} > 0$). (a) The expansion parameter $\alpha$ as a function of cosolvent concentration $\tilde{\rho}$ in the bulk solution. (b) The cosolvent concentration in gyration volume $\tilde{\rho}_1$ as a function on the cosolvent bulk concentration $\tilde{\rho}$ at different positive parameter of interaction polymer-cosolvent $\tilde{w}_{pc}$. It is seen that at increasing of cosolvent concentration the expansion parameter is monotonically decrease and asymptotically close to limit (25) corresponding to globular conformation. It is easy to seen that at increasing of parameter $\tilde{w}_{pc}$ the coil-globule transition becomes sharper. In the region of coil-globule transition the cosolvent concentration within the gyration volume shows a sufficiently pronounced maximum. We use $\tilde{w}_{p} = 1$, $N = 10^4$, $\tilde{d}_m = \tilde{d}_c = \tilde{d}_{mc} = 1$. 

\[ \tilde{w}_{pc} = 1.8 \quad \tilde{w}_{pc} = 2 \]

\[ \tilde{\rho} \]

\[ \tilde{\rho}_1 \]
Figure 3. Attractive polymer-cosolvent interaction (e.g. $\tilde{w}_{pc} < 0$). (a) The expansion parameter $\alpha$ as a function of the cosolvent bulk concentration $\tilde{\rho}$. (b) The cosolvent concentration in the gyration volume $\tilde{\rho}_1$ as a function of cosolvent concentration in the bulk shown for polymer-cosolvent interaction parameter $\tilde{w}_{pc} = -3; -5$. The bulk cosolvent concentration at which the chain collapse occurs coincides with the jump in the cosolvent concentration within the gyration volume. In this regime the polymer collapse happens as a first-order phase transition. Values are shown for $\tilde{w}_p = 1$, $N = 10^4$, $\tilde{d}_m = \tilde{d}_c = \tilde{d}_{mc} = 1$. 
Figure 4. The expansion parameter $\alpha$ as a function of polymer-cosolvent interaction parameter $\tilde{w}_{pc}$ at different cosolvent bulk concentrations $\tilde{\rho}$. At negative values of $\tilde{w}_{pc}$ the collapse of polymer chain takes place. Increasing $\tilde{w}_{pc}$ towards zero a maximum occurs. Further increasing (towards positive values) $\tilde{w}_{pc}$ the expansion parameter again monotonically decreases and smoothly approach the globule regime. Shown here for $\tilde{w}_p = 1$, $N = 10^4$, $\tilde{d}_m = \tilde{d}_c = \tilde{d}_{mc} = 1$. 

\[
\alpha
\]