Macromolecules **1998,** *31,* 4635−4638

Protein-Induced Collapse of Polymer Chains

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Received February 18, 1998; Revised Manuscript Received April 29, 1998

ABSTRACT: The collapse of polymer chains in a good solvent due to the presence of small colloidal spheres, taken to model inert globular proteins, is discussed. It is argued that the large-scale properties of the chains in the mixture are adequately described using Edwards' type (δ function) interactions between all constituents, provided that the colloidal particles are very much smaller than the polymer coils and that their concentrations are not too high. Chain collapse occurs when the mutually excluded volumes of the segments, renormalized by the concentration fluctuations of the colloids, become negative. A closed expression for the colloid density at which the collapse transition should be expected is given and is compared with recently published computer simulation results. The agreement is reasonably good, even at densities which are outside of the range of validity of the theory.

Dispersions of colloidal particles can be destabilized by adding sufficient amounts of nonadsorbing polymer molecules. For colloids larger than the polymer coils, the demixing is thought to be due to a so-called depletion attraction between the colloidal particles.[1,2] The depletion interaction arises from an imbalance in the osmotic pressure when polymeric material is forced out of the gap between two colloidal particles at close separation. The study of this kind of entropy-driven phase separation has gained considerable momentum[3−6] since the pioneering work of Asakura and Oosawa[1] and of Vrij.[2] (For recent developments, see, e.g., refs 7 and 8.) Discussion often focuses on the case where the colloids are of a size similar to that of the polymeric chains, or where they are much larger than them, which appears to be the norm for conventional colloids. Theoretically less well-understood is the behavior of polymers mixed with particles significantly smaller than the macromolecules.[9] Examples of technological and biological importance include aqueous mixtures of long polymers and inert, globular proteins.[10−12] These too demix under appropriate conditions, although the driving force is, as shall become clear below, not necessarily solely a conventional (mean-field) depletion interaction.

In this paper, we consider theoretically highly idealized, mixed dispersions of spherical particles, taken to model globular proteins, and nonadsorbing polymer chains. The solvent quality shall be assumed good for all solutes, with all solute−solute interactions of the purely repulsive, excluded-volume type. As usual, the microscopic structure of the solvent is not explicitly taken into consideration. We restrict ourselves to the limit where the colloidal spheres are quite small compared to the typical length scale associated with the self-avoiding chains. In dilute solution, the typical length scale is given by the radius of gyration of the chains, R_g, and in semidilute solution it is given by the entanglement length, ξ. Integral equation theory[13,14] and computer simulation studies[15−17] show that hard particles can indeed cause model polymers to collapse or demix macroscopically, provided the particle density is sufficiently high. A plausible explanation[14] for the colloid-induced chain collapse relies on the ability of small particles to penetrate swollen coils, although this does reduce the configurational entropy of the chains.[18] The entropy loss is attenuated by the expulsion of colloidal particles from the interior of the coil. When this leads to a sufficiently large difference in colloid density the chains collapse in effect by osmotic stress. A similar mechanism is thought to lead to the demixing of polymers of different size.[19−21] Our aim is to estimate at what colloid density one might expect the collapse transition and/or phase separation to occur. The required minimum density decreases fairly rapidly with particle size, in accord with the computer simulations of Sanchez and co-workers.[17]

The starting point of our analysis is a solution of volume V, containing n self-avoiding flexible polymer chains of length L and Kuhn length l_K, as well as n_c globular particles of diameter σ. The polymers are labeled 1 through n, and modeled as nonoverlapping continuous space curves. Segmental position coordinates, $\mathbf{r}_a(s_a)$, can then be parametrized by the contour distance s_a from one end of each chain a. Temporarily ignoring the influence of the colloidal spheres, the Edwards Hamiltonian describing the chains may be written as[22]

$$H_E[\{\mathbf{r}_a\}] = \frac{3}{2l_K}\sum_a\int_0^L ds_a \left(\frac{\partial \mathbf{r}_a(s_a)}{\partial s_a}\right)^2 + \frac{u_{pp}}{2{l_K}^2}\sum_{a,b}\int_0^L ds_a \int_0^L ds_b\, \delta(\mathbf{r}_a(s_a) - \mathbf{r}_b(s_b)) \quad (1)$$

where the thermal energy is set equal to unity, $k_B T \equiv 1$, and the summations over a and b run from 1 to n. The first term represents the usual Gaussian elastic energy of the chains, while the second term accounts for the interactions between pairs of polymer segments. Within the Edwards treatment of polymer chains, the effective segment−segment interaction potential (actually the negative of a direct correlation function[23]) takes the form $u_{pp}(\mathbf{r}) = u_{pp}\delta(\mathbf{r})$. Here, $\mathbf{r}$ denotes a relative

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S0024-9297(98)00249-6 CCC: $15.00

position coordinate and u_{pp} the strength of the interaction, also known in polymer solution theory as the excluded volume parameter.[22,24] In a good solvent $u_{\mathrm{pp}} > 0$, while in a poor solvent $u_{\mathrm{pp}} < 0$. In a sufficiently poor solvent the chains collapse or phase separate. The precise conditions are determined by factors such as the three-body interaction terms neglected in eq 1, the molecular weight, and the polymer concentration.[24] Note finally that the use of a δ-correlated effective interaction in the description of interacting polymers is justified, because the microscopic details of the polymers do not play any significant role in the large-scale properties of the chains, at least not in the limit of high molecular weights. Microscopic length scales can be absorbed in quantities such as the Kuhn length l_{K} and excluded volume parameter u_{pp}.[25]

Also dispersed in the solution are the colloidal spheres, which not only experience each others excluded volumes but also interact with the polymer chains. We propose that the (effective) interaction between the polymers and the colloids can be described at the same (Edwards) level as that between polymer segments. This is obviously reasonable for the case where $l_{\mathrm{K}} \approx \sigma$, but remains a useful Ansatz when $l_{\mathrm{K}} \ll \sigma \ll R_{\mathrm{g}}$. The reason is that when a small colloidal particle enters the polymer coil, this particle induces a local disturbance of the segment density distribution only.[9,26,27] Indeed, the property of scale invariance of long, self-avoiding polymer chains demands that the size of this particle sets the length scale of the disturbance, in our case $\sigma \ll R_{\mathrm{g}}$. (See also ref 9.) Hence, it seems justifiable to use a δ-function potential $u_{\mathrm{pc}}(\mathbf{r}) = u_{\mathrm{pc}}\delta(\mathbf{r})$ for the effective interaction between a segment and a sphere, with the interaction strength u_{pc} to be specified later. Although our effective polymer−colloid interaction is highly localized, this does not suppress long-range inhomogeneities in the polymer segment−colloid pair correlation. (We demonstrate this below.) Our arguments carry over to the semidilute regime, provided $\sigma \ll \xi$.

The direct correlation function of hard spheres in a suspension without any added polymer rapidly approaches zero at separations beyond a particle diameter σ.[23] There are no indications that polymer-mediated interactions could alter this,[9] implying that the effective interaction between the colloids in the mixture must also be short-ranged on the scale of the polymer coils or blobs.[31] As our interest concerns the behavior of the polymer chains, we might attempt an approximate description of the (effective) sphere−sphere interaction by again choosing an expression of the form $u_{\mathrm{cc}}(\mathbf{r}) = u_{\mathrm{cc}}\delta(\mathbf{r})$. A possible impact of the fluctuating polymer background on the colloid-colloid interaction will be neglected, so we insert for the interaction strength a hard-core excluded volume $u_{\mathrm{cc}} = 4\pi\sigma^3/3$. Although hardly exact,[30,31] within the perturbation treatment presented below this seems a justifiable approximation. Our description of the hard sphere fluid is equivalent to a second virial approximation, and is consistent with the use of δ-function interactions. Both approximations break down when packing effects become important. The validity of the theory is restricted to relatively dilute colloidal suspensions, although we shall not hesitate to extrapolate to high densities in our comparison with computer simulation data.

The Hamiltonian of our (quasi) binary system of polymers plus colloidal spheres is

$$H\,[\{\mathbf{r}_a\},\{\mathbf{r}_i\}] \equiv H_{\mathrm{E}}[\{\mathbf{r}_a\}] + \frac{u_{\mathrm{pc}}}{l_{\mathrm{K}}}\sum_{a,i}\int_0^L \mathrm{d}s_a\,\delta(\mathbf{r}_a(s_a) - \mathbf{r}_i) + \frac{u_{\mathrm{cc}}}{2}\sum_{i,j}\delta(\mathbf{r}_i - \mathbf{r}_j) \quad (2)$$

As in eq 1 the subscript $a = 1, ..., n$ refers to the polymer chains. The subscripts i and j run from 1 to n_{c} and indicate degrees of freedom associated with the globular colloids. To explore the phase behavior of the mixture one would, in principle, need to evaluate the configurational integral $Z = \int\Pi_a D[r_a]\int\Pi_i\,\mathrm{d}\mathbf{r}_i\,\exp(-H)$. We instead choose to simplify the problem considerably by preaveraging Z over the positions $\mathbf{r}_i$ of the proteins. A similar mode of attack was followed by Shaw and Thirumalai[14] in their study of a polymer in a hard-sphere solvent and by Chandler and co-workers addressing the related problem of excess electrons in simple fluids.[13] The preaveraging is not performed exactly. Integrations are carried out assuming (i) that the polymers do not significantly perturb the colloid density fluctuations and (ii) that these fluctuations conform to a Gaussian distribution around a mean value $\rho_c = n_{\mathrm{c}}/V$.[32] The width of the distribution is obtainable from standard statistical mechanics,[23] where it should be noted that the fluctuations turn out to be independent of the wave vector on account of our choice for the effective interaction. Obviously, the treatment should be seen as a first step in a more formal perturbation scheme. It allows us to interpret the result of the calculation directly in terms of what is already known about the behavior of polymers in nonathermal solutions.[24]

Eliminating the colloid degrees of freedom gives an effective Hamiltonian $\tilde{H}_{\mathrm{E}}$ describing the polymer chains in a coarse-grained "solvent" that now includes the colloidal particles. The functional form of $\tilde{H}_{\mathrm{E}}$ is almost identical to eq 1, the only difference being that the "bare" excluded volume parameter u_{pp} is replaced by a renormalized one depending explicitly on the colloid density ρ_{c},

$$\tilde{u}_{\mathrm{pp}} = u_{\mathrm{pp}} - \rho_{\mathrm{c}}\frac{{u_{\mathrm{pc}}}^2}{1 + \rho_{\mathrm{c}}u_{\mathrm{cc}}} \quad (3)$$

Nonlocal contributions do not arise exactly because of our choice of Edwards' type interactions. Of course, a nonlocal "renormalized" segmental interaction would present itself in any other theory.[13,14,33] We stress again that although its range may be significant on the scale of a polymer segment, it remains local on the scale of the chain and should therefore become irrelevant in the infinite chain limit for any given finite ratio l_{K}/σ.[31] This does not imply that long-range pair correlations do not exist. It is easy to verify that within, e.g., a reference site interaction model (RISM), the polymer segment−colloid pair correlation function, $g_{\mathrm{pc}}(\mathbf{r})$, varies on the scale of the chain, even when the direct correlations are δ peaked.[13,14] Integration of the (Ornstein−Zernike type) RISM integral equation is at our level of approximation in fact trivial and gives

$$g_{\mathrm{pc}}(\mathbf{r}) = 1 - u_{\mathrm{pc}}\frac{g(\mathbf{r})}{1 + u_{\mathrm{cc}}\rho_{\mathrm{c}}} \quad (4)$$

with $g(\mathbf{r})$ the (to lowest order unperturbed) intrachain correlation function (the form function). Implied in eq 4 is the formal limit $L/l_{\mathrm{K}} \to \infty$. For swollen chains in dilute solution the form function, $g(\mathbf{r})$, at separations $l_K \ll |\mathbf{r}| \ll R_g$, is to a good approximation equal to $|\mathbf{r}|^{-4/3} l_K^{-5/3}$ but becomes exponentially small when $|\mathbf{r}| > R_g$.[24] Hence, $g_{pc} < 1$ inside and $g_{pc} \rightarrow 1$ outside the coil; the globular particles are indeed depleted from the interiors of the coils. In semidilute solution the segments and colloids also decorrelate beyond R_g, but the interpretation is less obvious.

We now focus attention on the implications of eq 3. When u_{pp} is positive, that is, when the (true) solvent is good, the renormalized excluded volume parameter $\tilde{u}_{pp} < u_{pp}$ is positive too, but only when the density of colloidal particles is low. The quality of the (colloidal, coarse-grained) solvent is in that case good, and the chains are swollen. The renormalized excluded volume parameter does, however, decrease with increasing density of the colloid, and with it the solvent quality; the size of the coil cannot remain unaffected by the presence of the colloidal particles. At sufficiently high particle density the interaction strength u_{pp} becomes negative, inducing chain contraction and eventually collapse. The collapse is, in our calculation, caused entirely by the coupling to the fluctuating background of particles. Had we ignored the colloid density fluctuations, the preaveraging procedure would have lead to the erroneous conclusion that the presence of inert globules does not influence the interactions between the segments, $\tilde{u}_{pp} = u_{pp}$. (See also ref 33.) It explains why in the *ad hoc* theory of ref 35, where fluctuation effects are ignored, small particles do not promote polymer collapse or phase separation.

One may, in analogy to the Θ-temperature of polymer solutions, define a colloid Θ-concentration ρ_Θ for which $\tilde{u}_{pp} = 0$, marking the crossover from good-to-bad solvent behavior of the polymers

$$\rho_\Theta = \frac{u_{pp}}{u_{pc}^{\,2} - u_{pp}u_{cc}} \tag{5}$$

We infer from polymer solution theory that chain collapse (and polymer phase separation) must occur at densities $\rho_c = \rho_\Theta(1 + O(l_K^{1/2}L^{-1/2}))$ very close to but in excess of the Θ-concentration.[24] The precise transition point should depend on the degree of polymerization of the chains, the various interactions strengths, and so forth.

The crossover density ρ_Θ is positive and finite provided $u_{pc}^2 - u_{pp}u_{cc} > 0$, a condition obeyed for any type of "additive" interaction such as the hard core volume exclusion. (Frenkel and Louis discussed some time ago the possibility that nonadditive repulsive interactions between solvent particles and a polymer molecule could induce chain collapse.[36]) An exception is the circumstance when $u_{pp} = u_{pc} = u_{cc} > 0$, in which case $\tilde{u}_{pp} > 0$ at all densities ρ_c. This contradicts the computer simulation results of Dijkstra and Frenkel,[16] who do find a polymer on a cubic lattice to collapse upon the addition of 0.7 volume fraction hard cubes of equal size as the polymer segments. Our approximate picture breaks down at colloid densities this high, so the disagreement is not entirely surprising.

To obtain a numerical estimate for the minimum volume fraction of colloid $\phi_\Theta \equiv \rho_\Theta\pi\sigma^3/6$ required to collapse or phase separate the polymer chains, we insert in eq 5 for the interaction strengths hard-core excluded volumes: $u_{cc} = 4\pi\sigma^3/3$, $u_{pp} = 4\pi l_K^2/3$, and $u_{pc} = 4\pi(^1/_2\sigma + {}^1/_2 l_K)^3/3$. Notice that this choice gives the expected $u_{pc} \sim \sigma^3$ scaling for $\sigma \gg l_K$. Our theoretical result is plotted in Figure 1, showing that ϕ_Θ decreases quite strongly with increasing colloid radius. Also indicated in the figure are the concentration intervals of the transition region in which, in the Monte Carlo simulations of Sanchez and co-workers, a lattice polymer of 64 segments reduces in size from the swollen to the fully collapsed state due to the presence of increasing volume fractions of hard cubes.[17] (As one can easily verify, the prediction plotted in Figure 1 does not depend on whether the particles are spheres or cubes.) One should, strictly speaking, only take seriously the agreement between theory and simulation for the case $\sigma = 3l_K$. The other data indicate rather wide transition regions, possibly due to finite size effects,[17] and are anyway outside of the range of validity of our second virial treatment, which becomes inaccurate at volume fractions in excess of about 10%. Still, even in the high density regime the agreement is quite remarkable, albeit probably only fortuitously so.

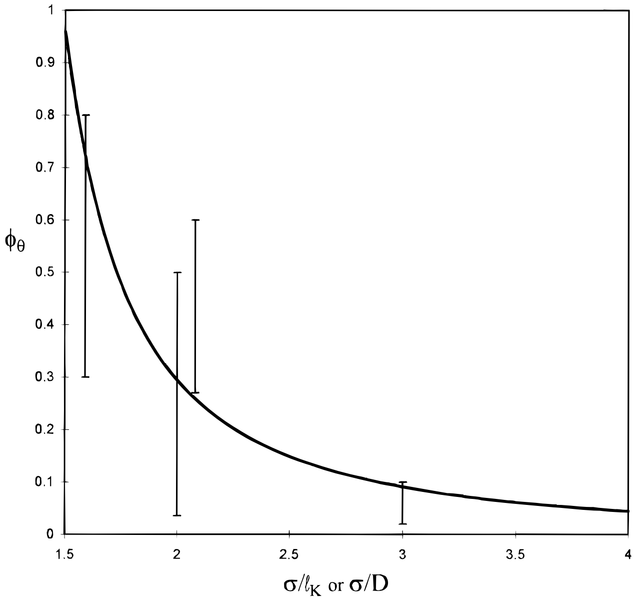

Figure 1. Volume fraction ϕ_Θ of hard particles needed to collapse a long polymer molecule in a good solvent, as a function of the ratio of hard sphere radius, σ, and the interaction radius. For flexible polymers the interaction radius is equal to the Kuhn length, l_K, and for semiflexible worms to the chain diameter D. The solid line gives the theoretical estimate according to eq 5, extrapolated to high volume fraction. The vertical bars indicate the collapse transition region as found in the simulations of Sanchez and co-workers,[17] which were performed on a cubic lattice. For l_K we used the polymer segment size, in the simulations equal to the lattice spacing, while for σ the cubic root of the volume of the particles. The simulation data with noninteger values of σ/l_K refer to data on nonisometric particles.

Although eq 5 was derived with flexible polymers in mind, it also applies approximately to semiflexible chains and should give a reasonably accurate indication of the location of the fluctuation-induced collapse transition of semiflexible polymers such as DNA. (DNA is a charged macromolecule, so one would have to impose conditions of excess salt.) The reasons are as follows. First, based on theoretical work describing the collapse transition of semiflexible chains in poor solvents, one should again expect the colloid-induced collapse of such chains to occur under conditions slightly worse than Θ-conditions.[24] (The order of the transition need not remain continuous, however.) Second, our calculation requires only minor modifications to apply to long, semiflexible chains. An obvious but for our purposes unimportant modification is the replacement of the first term of eq 1 by a bending energy of the form $^1/_2 P \sum_a \int ds_a (\partial^2 \mathbf{r}_a/\partial s_a{}^2)^2$, with $P = l_K/2$ being the persistence length.[37] More important is that within a bead-on-a-wire model for self-avoiding wormlike chains such as advanced by Yamakawa and Stockmayer,[37] the interacting units (the beads or segments) are not of size Kuhn length $l_K = 2P$ but of size chain diameter $D \ll l_K$. This does not affect integrating out the colloidal coordinates, so the general form of eq 5 remains valid for a wormlike chain of length $L \gg l_K \gg D$. The only difference is in the interaction strengths, which are now determined by the colloid size σ and chain diameter D. Inserting the hard-core interaction strengths $u_{pp} = 4\pi D^3/3$, $u_{pc} = \pi(\sigma + D)^3/6$, and $u_{cc} = 4\pi\sigma^3/3$, we find that the critical volume fraction is now a universal function of the ratio σ/D. See Figure 1.

In conclusion, the presence of small colloidal spheres can cause polymer molecules to collapse, even when the solvent quality is good for both globule and polymer. The collapse can be induced by fluctuations in the colloid density, which interfere with the configurations of the polymer chains through excluded volume interactions. The minimum density needed to condense the polymer decreases with increasing colloidal size. It should be stressed that our theory only applies when the particles are not only much smaller than the relevant polymer length scale but are at the same time in some sense sufficiently different from the polymer segments.

Acknowledgment. I thank Julian Shillcock for critically reading the manuscript, and Carina van der Veen for assistance with the presentation of the results. I am also indebted to Prof. Theo Odijk for several illuminating discussions.

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MA980249P