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Bethe approximation for a model of polymer solvation

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The phase diagram of a recently proposed model for the solvation of monomers and polymers in water is studied in the homopolymer case, and several thermodynamic quantities are computed by means of pair approximation of the cluster variation method, i.e., the Bethe approximation. The model takes into account the water degrees of freedom in a simplified way, so that they can be integrated out analytically. The resulting effective Hamiltonian contains only a temperature-dependent water-monomer interaction and its phase diagram can be easily studied thanks to the simplicity of the Bethe approximation and exhibits, for a hydrophobic polymer, both cold and warm unfolding transitions in a wide region of the parameter space. This suggests that the present one might be a toy-model description of the phase behavior observed experimentally in water solutions of hydrophobic polymers, such as poly-*N*-isopropylacrylamide (PNIPAM), as well as a step to understand the mechanism of cold unfolding in proteins.

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Increasing attention has been devoted in recent years to the *cold unfolding* phenomenon. Both proteins [1] and homopolymers, such as poly(*N*-isopropylacrylamide) and poly (*N*-isopropylmethacrylamide) [2–4] in water solution, exhibit this phenomenon, that is, they change from a compact, globulelike configuration to a swollen, coil-like configuration upon *decreasing* the temperature. In both cases, hydrophobic interactions seem to play a crucial role in stabilizing the compact state.

Although the warm unfolding phenomenon has been widely studied in the past [5], theoretical studies of cold unfolding appeared only in the last years, focusing on the importance of explicitly taking into account solvent degrees of freedom [6–14]. This is not at all a trivial task, since the solvent to be considered is water, a tetrahedrally coordinated network-forming fluid, whose physics is rather complex, as revealed for example by the anomalous behavior of density and other observables.

Among several attempts, one of us proposed a model [13,14] capable of describing the solvation of both single monomers and polymeric chains, which takes into account, in a simplified way, the effect of hydrogen bonding on the arrangement of water molecules around solute molecules. The model is simple enough that water degrees of freedom can be integrated out analytically, yielding the solvation free energy in the case of a single molecule and, in the case of a polymer, an effective Hamiltonian depending only on the number of water-monomer contacts (or, equivalently, on the number of monomer-monomer contacts) with a temperature-dependent interaction strength.

The case of a nonpolar homopolymer of fixed, finite length has been studied in [13,14] by taking a Poissonian approximation, based on the results reported in [15], to the number of polymer configurations having a given number of contacts. In the present paper, we shall take a different approach by looking at the infinite length limit in the Bethe approximation [16]. This is particularly convenient since it allows a simple and reasonably accurate determination of phase transitions in the infinite length limit, essentially in a closed form.

We shall now describe in some detail the model proposed in [13,14], then the Bethe approximation [16], and finally, our results.

The model proposed in [13,14] deals with two-dimensional waterlike molecules with three equivalent hydrogen bonding arms, as those studied in [17–20]. The model is defined on a two-dimensional lattice of coordination number z. Every lattice site can be occupied by a monomer or by z clusters of m water molecules, each cluster being in contact with one of the z nearest neighbor sites. In this way an isolated monomer is in contact with z different clusters (which represent its hydration shell), while a monomer in a polymer chain can be in contact with $z-2$ water clusters at most. The relevant physics of water molecules is described in a simplified way up to the cluster scale, and interactions between different clusters are not explicitly considered.

Clusters are divided into two classes: *bulk* clusters, which are in contact with a site occupied by water, and *shell* ones, which are in contact with a site occupied by a monomer. The m water molecules belonging to a given cluster are allowed to form a maximum of $3m/2$ hydrogen bonds. In a *bulk* (*shell*) cluster, each hydrogen bond lowers the energy by an amount h_b (h_s). Hydrogen bonds are represented by harmonic oscillators, and can be broken independently of one another. An overall additional energy shift J, representing nonbonding contributions, is attributed to a shell cluster.

Bulk and shell clusters also differ in their allowed configurations [13,14]. Molecules in a bulk cluster can form (if they are correctly oriented) hydrogen bonds with the molecules in the adjacent cluster, up to a maximum of q_b bonds. Molecules in a shell cluster can form up to a maximum of q_s hydrogen bonds with the solute. A hydrophobic solute is represented by $q_s=0$.

With the above assumption, the density of states of a cluster, and hence its partition function, can be computed analytically, yielding

$$\mathcal{Z}_b^{\mathrm{clu}}=A_b,$$

$$\mathcal{Z}_s^{\mathrm{clu}}=A_s e^{-\beta K m}, \tag{1}$$

where b and s stand for bulk and shell, respectively, $\beta=1/T$ is the inverse temperature (taking Boltzmann's constant as unity), $K=\frac{3}{2}(h_b-h_s)+J$ and the functions $A_b \equiv A_b(\beta;h_b,q_b)$ and $A_s \equiv A_s(\beta;h_s,q_s)$ are reported in [13,14].

In the case of a homopolymer the above cluster partition function leads to an effective, temperature-dependent, water-monomer contact interaction given by $-T\log x$, where $x=A_sA_b^{-1}\exp(-\beta K m)$, and hence to the grand-canonical partition function

$$\Xi=\sum_{L=0}^{\infty}(\mathcal{Z}_b^{\mathrm{clu}})^{z(N-L)}\exp(\beta\mu L)\sum_{\mathcal{S}_L}x^{N_{wm}}, \tag{2}$$

where N is the number of lattice sites, μ is the chemical potential for monomers, $\mathcal{S}_L$ is the set of self-avoiding walks (SAWs) of length L, and N_{wm} denotes the number of water-monomer contacts in a walk.

Introducing the number N_{mm} of monomer-monomer contacts, which is related to N_{wm} by the identity

$$N_{wm}+2N_{mm}=(z-2)L+2, \tag{3}$$

the model can be mapped on a SAW model with an effective monomer-monomer contact interaction given by $2T\log x$.

Although we refer to [13,14] for the full analytic expression of x, it is important to notice here that, in the limit $T\to 0$, the effective water-monomer coupling $-T\log x$ tends to K. For $K<0$, corresponding to $\lim_{T\to 0}x=+\infty$, water-monomer contacts lower the energy, and hence the ground state of the polymer will be an extended one. On the other hand, for $K>0$, corresponding to $\lim_{T\to 0}x=0^+$, water-monomer contacts raise the energy, and the ground state will be a compact one.

The model described by the above grand-canonical partition function can be easily studied in the infinite length, infinite dilution limit $L\to\infty$, $L/N\to 0$, by means of the Bethe approximation for SAWs outlined in [16]. The variational free-energy density can be written in the form

$$f=-\tilde{\mu}\rho-n_{wm}T\log x-T\left[\frac{z}{2}S_2-(z-1)S_1\right], \tag{4}$$

where $\tilde{\mu}=\mu-zT\log\mathcal{Z}_b^{\mathrm{clu}}$, $\rho=L/N$ is the monomer density, $n_{wm}=N_{wm}/N$ is the density of water-monomer contacts (number of contacts per site), and S_1 and S_2 are the site and nearest neighbor pair entropies, respectively. The latter can be written in terms of the probabilities s_i (p_i) and multiplicities $m_s(i)$ [$m_p(i)$] of the site (pair) configurations, as

$$S_1=-\sum_{i=1}^{2}m_s(i)s_i\log s_i,$$

$$S_2=-\sum_{i=1}^{4}m_p(i)p_i\log p_i. \tag{5}$$

The site and pair independent configurations are those reported in [16] if we reinterpret an empty site as a water site. The site probability s_1 is that of a site occupied by a monomer and has a multiplicity $m_s(1)=z(z-1)/2$, which takes into account the possible orientations of the links in the polymer chain; s_2 is the probability of a site being occupied by water and has multiplicity $m_s(2)=1$. The pair probability p_1 is that of a pair occupied by two monomers that are consecutive in the polymer chain, and has multiplicity $m_p(1)=(z-1)^2$; p_2 is that of a pair occupied by two monomers that are not consecutive in the polymer chain (a monomer-monomer contact) and has multiplicity $m_p(2)=[(z-1)(z-2)/2]^2$; p_3 is the probability of a water-monomer contact and has multiplicity $m_p(3)=(z-1)(z-2)$; finally, p_4 is the probability of a pair of sites both occupied by water and has multiplicity 1. One can show that the probabilities can be written as functions of ρ and n_{wm} as

$$s_1=\frac{2\rho}{z(z-1)},$$

$$s_2=1-\rho,$$

$$p_1=\frac{2\rho}{z(z-1)^2},$$

$$p_2=\frac{4\rho}{z(z-1)^2(z-2)}-\frac{4n_{wm}}{z(z-1)^2(z-2)^2},$$

$$p_3=\frac{2n_{wm}}{z(z-1)(z-2)},$$

$$p_4=1-\rho-\frac{n_{wm}}{z}. \tag{6}$$

We are left with only two variational parameters, ρ and n_{wm}, and in order to study the infinite dilution limit we shall tune the chemical potential in such a way that ρ (and hence also n_{wm}) tends to zero (this is strictly true only for a homogeneous system, while for a phase separating system, the globule phase has a nonvanishing monomer density ρ and occupies a volume that tends to zero).

The first result of the Bethe approximation is that the above model has a coil-globule second-order phase transition at $x_c=\sqrt{(z-2)/(z-1)}$, which can be computed by means of a Landau expansion of the variational free energy (see also [16], where results are reported in terms of $\omega=-\frac{1}{2}\log x$). For $x>x_c$ the polymer is in a coil state, while for $x<x_c$ the system undergoes a phase separation into a pure water phase, and a globule phase with a monomer density that depends on x. In the square lattice case we have $x_c\simeq 0.8165$, while a recent Monte Carlo estimate is $x_c\simeq 0.717$ [21] and the prediction based on the Poissonian approximation [13,14] is $x_c\simeq 0.405$.

Following [13,14] we have considered the case $m=4$, $q_b=2$, $q_s=0$. In Fig. 1 we have compared sections of the

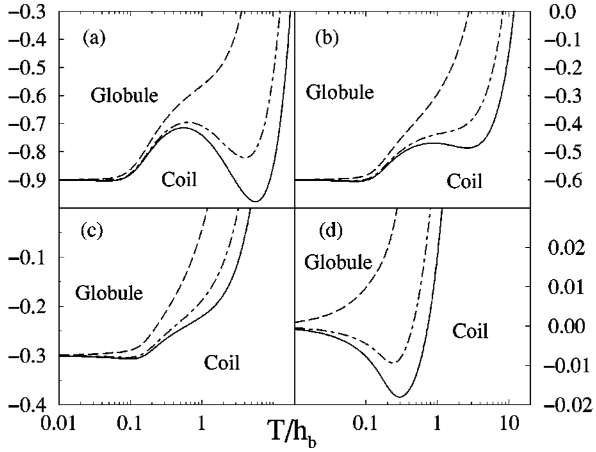

FIG. 1. Phase diagram in the J vs T plane, using the x_c estimates from Bethe approximation (solid line), Poissonian approximation (dashed), and Monte Carlo simulation (dash-dotted). $m=4$, $q_b=2$, $q_s=0$, $h_b=1$, and $h_s=0.4$ (a), 0.6 (b), 0.8 (c), 1 (d).

critical surface in the (J,T) space for several values of h_s/h_b, obtained using the x_c estimates from the Bethe approximation, Monte Carlo simulation and the Poissonian approximation.

The main features of the phase diagram are qualitatively the same for the three x_c estimates, and the phase diagrams obtained using the Bethe and Monte Carlo x_c estimates have also a rather good quantitative agreement.

For $J>-\frac{3}{2}(h_b-h_s)$ (i.e., $K>0$) the polymer is compact at low temperatures and swells, with a continuous phase transition, at a θ point: for $h_s/h_b \geqslant 1$ we can call this a strongly hydrophobic polymer. Indeed, $h_s/h_b>1$ yields the positive peak in the excess specific heat of single monomer hydration that is the experimental hallmark of hydrophobicity, together with a positive solvation free energy ([13,14]). In Fig. 2 we have reported the hydration free energy, monomer density, density of monomer-monomer contacts, and ex-

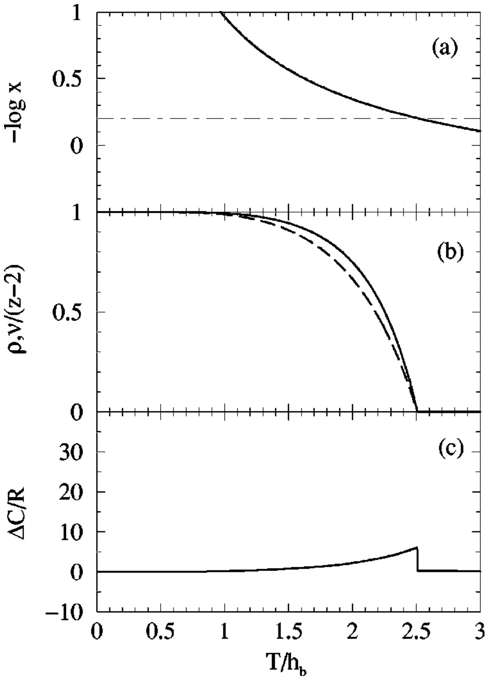

FIG. 2. Hydration free energy [(a); the dash-dotted line represents the critical value], monomer density (b, solid line), density of monomer-monomer contacts (b, dashed line), and excess specific heat (c). $m=4$, $q_b=2$, $q_s=0$, $h_s/h_b=1.25$, and $J/h_b=0.5$, corresponding to $K>0$.

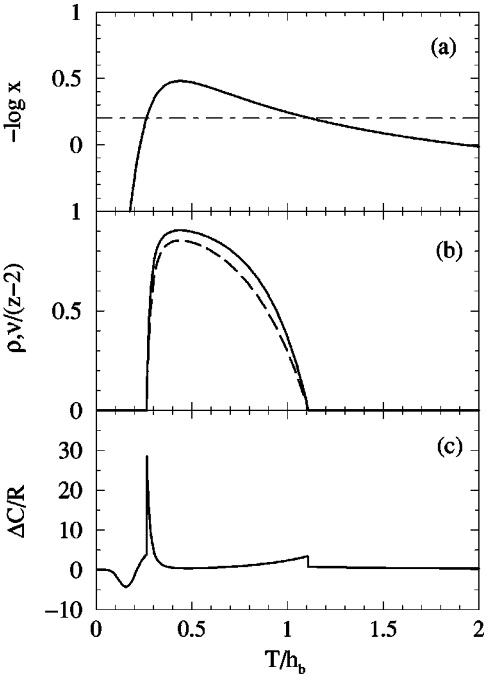

FIG. 3. The same as Fig. 2, but here $J/h_b=0.32$, corresponding to $K<0$.

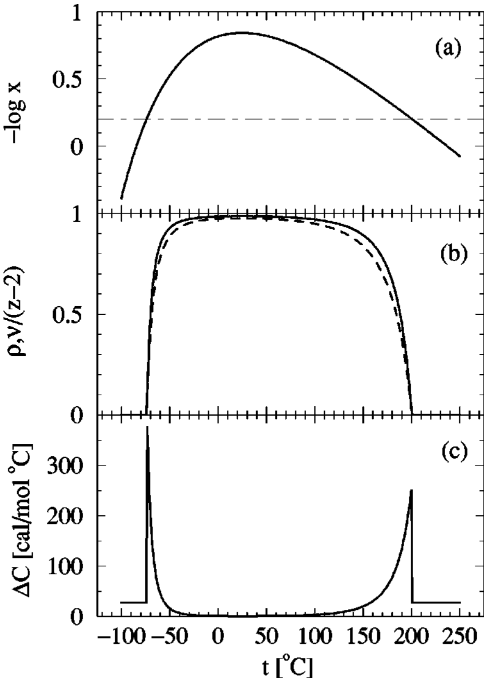

FIG. 4. The same as Fig. 2, calculated using the empiric hydration free energy from [22].

cess (with respect to pure water) specific heat in a typical case. The monomer density plot shows that the compact phase can include a significant amount of water, which indeed happens in poly(N-isopropylacrylamide) [2].

For $J<-\frac{3}{2}(h_b-h_s)$ (i.e., $K<0$) the polymer is swollen at low temperatures, but two regimes are present. If $|K|$ is large enough, the polymer is swollen at all temperatures. There is, however, a significantly wide range of values of $|K|$ where a reentrant behavior can be found. The polymer is compact in a certain range of temperatures, and swells with a second-order phase transition both at a lower and at an upper critical temperature. When $h_s/h_b>1$ this situation can describe (except for the order of the phase transition) the behavior of a ''moderately'' hydrophobic polymer such as poly(N-isopropylacrylamide) and poly (N-isopropylmethacrylamide) [2–4], which exhibits the cold unfolding transition. Again, a typical case is shown in Fig. 3.

In small regions around $K=0$, additional reentrance phenomena can appear, giving rise to more complicated sequences of phase transitions which, as far as we know, are not observed in experiments, that, by the way, can access only the limited range of temperatures where water is liquid. For $K>0$ and $h_s/h_b>1$ we do not detect cold unfolding, at difference with the results reported in [13,14]. That effect should therefore be attributed to the Poissonian approximation, which underestimates too much the x_c value.

Finally, we have repeated our calculations using the empiric hydration free energy for a hydrophobic monomer reported in [22]. It is noteworthy that the excess specific heat exhibits a feature that is found also in poly (N-isopropylacrylamide) [3], namely that the excess specific heat is smaller in the compact phase than in the expanded one (see Fig. 4).

In conclusion, we have mapped out the phase diagram of the model proposed in [13,14] for the solvation of monomers and polymers in the homopolymer case. We have also computed several thermodynamic quantities in the infinite length limit, by means of the Bethe approximation developed in [16]. The results show that the model can describe the behavior of both strongly and moderately hydrophobic polymers, including the cold unfolding transition.

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