ELSEVIER

Physica A 263 (1999) 26–38

PHYSICA A

Entropy-driven phase transitions

Daan Frenkel

FOM Institute for Atomic and Molecular Physics
Kruislaan 407, 1098 SJ Amsterdam, the Netherlands

Abstract

Increase in visible order can be associated with an increase in microscopic disorder. This phenomenon leads to many counter-intuitive phenomena such as entropy driven crystallization and phase separation. I devote special attention to the entropic depletion interaction as a means to tune the range of attraction between colloids. The range of the intermolecular potential determines whether or not stable liquid-vapor coexistence is possible. For short range attraction, the liquid-vapor transition may be located below the sublimation line. Under those conditions, meta-stable critical fluctuations may enhance the rate of crystal nucleation

1 Introduction

The second law of thermodynamics tells us that any spontaneous change in a closed system results in an increase of the entropy, S. In this sense, all spontaneous transformations of one phase into another are entropy driven. However, this is not what the term "entropic phase transitions" is meant to describe. It is more common to consider the behavior of a system that is not isolated, but can exchange energy with its surroundings. In that case, the second law of thermodynamics implies that the system will tend to minimize its Helmholtz free energy $F = E - TS$, where E is the internal energy of the system and T the temperature. Clearly, a system at constant temperature can lower its free energy in two ways: either by *increasing* the entropy S, or by *decreasing* the internal energy E. In order to gain a better understanding of the factors that influence phase transitions, we must look at the statistical mechanical expressions for entropy. The simplest starting point is to use Boltzmann's expression for the entropy of an isolated system of N particles in volume V at an energy E,

$$S = k_B \ln \Omega \tag{1}$$

where k_B, the Boltzmann constant, is simply a constant of proportionality. Ω is the total number of (quantum) states that is accessible to the system. In the remainder of this paper, I shall choose my units such that k_B=1. The usual interpretation of Eqn. 1 is that Ω, the number of accessible states of a system, is a measure for the "disorder" in that system. The larger the disorder, the larger the entropy. This interpretation of entropy suggests that a phase transition from a disordered to a more ordered phase can

PII: S0378-4371(98)00501-9

only take place if the loss in entropy is compensated by the decrease in internal energy. This statement is completely correct, provided that we use Eqn. 1 to *define* the amount of disorder in a system. However, we also have an *intuitive* idea of order and disorder: we consider crystalline solids "ordered", and isotropic liquids "disordered". This intuitive picture suggests that a spontaneous phase transition from the fluid to the crystalline state can only take place if the freezing lowers the internal energy of the system sufficiently to outweigh the loss in entropy: i.e. the ordering transition is "energy driven". In many cases, this is precisely what happens. It would, however, be a mistake to assume that our intuitive definition of order always coincides with the one based on Eqn. 1. In fact, the aim of this paper is to show that many "ordering"-transitions that are usually considered to be energy-driven may, in fact, be entropy driven. I stress that the idea of entropy-driven phase transitions is an old one. However, it has only become clear during the past few years that such phase transformations may not be interesting exceptions, but the rule!

In order to observe "pure" entropic phase transitions, we should consider systems for which the internal energy is a function of the temperature, but not of the density. Using elementary statistical mechanics, it is easy to show that this condition is satisfied for classical hard-core systems. Whenever these systems order at a fixed density and temperature, they can only do so by increasing their entropy (because, at constant temperature, their internal energy is fixed). Such systems are conveniently studied in computer simulations. But, increasingly, experimentalists - in particular, colloid scientists, have succeeded in making real systems that behave very nearly as ideal hard-core systems. Hence, the phase transitions discussed below can, and in many cases do, occur in nature. Below I list examples of entropic ordering in hard-core systems. But I stress that the list is far from complete.

2 (Liquid) Crystals

The earliest example of an entropy-driven ordering transition is described in a classic paper of Onsager [1], on the isotropic-nematic transition in a (three-dimensional) system of thin hard rods. Onsager showed that, on compression, a fluid of thin hard rods of length L and diameter D *must* undergo a transition from the isotropic fluid phase, where the molecules are translationally and orientationally disordered, to the nematic phase. In the latter phase, the molecules are translationally disordered, but their orientations are, on average, aligned. This transition takes place at a density such that $(N/V)L^2D = \mathcal{O}(1)$. Onsager considered the limit $L/D \to \infty$. In this case, the phase transition of the hard-rod model can be found exactly (see e.g. [2]). At first sight it may seem strange that the hard rod system can *increase* its entropy by going from a disordered fluid phase to an orientationally ordered phase. Indeed, due to the orientational ordering of the system, the orientational entropy of the system decreases. However, this loss in entropy is more than offset by the increase in translational entropy of the system: the available space for any one rod increases as the rods become more aligned. In fact, we shall see this mechanism returning time-and-again in ordering transitions of hard-core systems: the entropy *decreases* because the density is no longer uniform in orientation or position, but the entropy *increases* because the free-volume per particle is larger in the ordered than in the disordered phase.

The most famous, and for a long time controversial, example of an entropy-driven ordering transition is the freezing transition in a system of hard spheres. This transition had been predicted by Kirkwood in the early fifties [3] on basis of an approximate theoretical description of the hard-sphere model. As this prediction was quite counter-intuitive and not based on any rigorous theoretical results, it met with wide-spread skepticism until Alder and Wainwright [4] and Wood and Jacobson [5] performed numerical simulations of the hard-sphere system that showed direct evidence for this freezing transition. Even then, the acceptance of the idea that freezing could be an *entropy* driven transition, came only slowly [6]. However, by now, the idea that hard spheres undergo a first-order freezing transition is generally accepted. And, although the hard-sphere model was originally devised as an idealized and highly unrealistic model of an atomic fluid, it is now realized that this model provides a good description of certain classes of colloidal systems.

The next step in this sequence came in the mid-eighties when computer simulations [7] showed that hard-core interactions alone could also explain the formation of more complex liquid crystals. In particular, it was found that a system of hard sphero-cylinders (i.e. cylinders with hemi-spherical caps) can form a smectic liquid crystal, in addition to the isotropic liquid, the nematic phase and the crystalline solid. In the smectic (A) phase, the molecules are orientationally ordered but, in addition, the translational symmetry is broken: the system exhibits a one-dimensional density-modulation. Subsequently, it was found that some hard-core models could also exhibit columnar ordering [8]. In the latter case, the molecules assemble in liquid-like stacks, but these stacks order to form a two-dimensional crystal. In summary, hard-core interaction can induce orientational ordering and one-, two- and three-dimensional positional ordering. This is rather surprising because, in particular for the smectic and the columnar phase, it was generally believed that their formation required specific energetic interactions.

3 Binary mixtures

Phase separation in binary mixtures is the example that is used in many textbooks to illustrate the competition between energy and entropy in a phase transformation. For a mixture at constant total volume V, the Helmholtz free energy F, should be minimal. As a first approximation, the entropy of mixing of a mixture of two species A and B, is replaced by the entropy of mixing of an ideal mixture

$$S_{id}(X) = -Nk_B[X \ln X + (1-X)\ln(1-X)] \tag{2}$$

where X denotes the mole-fraction of one component (say A): $X = N_A/(N_A + N_B)$. The entropy of mixing given by Eqn. 2 is a convex function of X. As a consequence, $S_{id}(X)$ will always decrease if phase separation takes place. This implies that phase separation can only take place if the resulting decrease in energy E outweighs the increase in $-TS_{id}$. In a hard-core mixture, there is no energy change upon mixing. Hence, if Eqn. 2 were exact, we should never observe phase separation in a hard-core mixture. And, even though Eqn. 2 is known to be only an approximation, it was commonly thought that a fluid mixture of dissimilar hard spheres would not phase separate. This belief was, at least partly, based on the work of Lebowitz and Rowlinson [9], who studied the phase-behavior of such binary mixtures of dissimilar hard spheres, using a more accurate approximation for the entropy of mixing, based on the Percus-Yevick (PY) integral equation. Lebowitz and Rowlinson found that, at least within that approximation, hard spheres of arbitrary size ratio will mix in all proportions in the fluid phase. The implication of this result was that entropic effects are not enough to cause a miscibility gap in a simple fluid mixture. In th early nineties, Biben and Hansen [10] applied a more sophisticated analytical theory for dense fluid mixtures to the same problem. Unlike the PY approximation, this theory predicts that an asymmetric binary hard-sphere mixture should phase separate if the sizes of the two spheres are sufficiently dissimilar (typically, if the size ratio is less than 0.2). However, as in the case of [9], it is based on an approximate theory for the hard-sphere mixture. Hence, one may wonder to what extent the result found in [10] depends on the approximations that are used to compute the equation-of-state of the mixture. In fact, additional theoretical evidence for the de-mixing of dissimilar hard spheres comes from the work of Lekkerkerker and Stroobants [11] who used a completely different theoretical approach. Still, it would be highly desirable to have a model system of a binary mixture for which the existence of a purely entropic demixing transition can be proven exactly. It turns out that, in a special case [12], this can indeed be done by constructing a simple lattice model of binary hard-core mixture. This binary hard-core mixture can be mapped onto one-component lattice gas with attractive nearest neighbor interactions which, in turn, can be mapped onto an Ising model for which the phase behavior is either known exactly (in 2d), or with high accuracy (in 3d). In this model, the order-disorder transition of the Ising model, corresponds to the (entropic) de-mixing transition of the hard-core system. One would hope that computer simulations would provide a more direct test of the Biben-Hansen prediction. In fact, evidence for the occurrence of spontaneous phase separation in mixtures of hard spheres comes from a recent simulation by Buhot and Krauth [13] (and from a smaller-scale simulation by Biben et al. [14]). However, it is likely that this transition occurs in the regime where the fluid phase is meta-stable with respect to the solid [15]. A full study of the phase diagram of strongly asymmetric hard-sphere mixtures has not yet been reported. However, in simulations of dissimilar hard spherocylinders, Dijkstra and van Roij [15] do observe the de-mixing of thermodynamically stable isotropic fluids.

4 Depletion Interaction

A slightly more complex example of an entropy-driven phase separation in a binary mixture is polymer-induced flocculation of colloids. Experimentally, it is well known that the addition of a small amount of free, non-adsorbing polymer to a colloidal suspension induces an effective attraction between the colloidal particles and may even lead to coagulation. This effect has been studied extensively and is well understood, at least qualitatively. As in the example discussed above, the polymer-induced attraction between colloids is an *entropic* effect: when the colloidal particles are close together, the total number of accessible polymer conformations is larger than when the colloidal particles are far apart. This is the picture underlying the original picture of Asakura and Oosawa [16], and the subsequent theories of Vrij [17], Gast et al. [18] and Lekkerkerker et al. [19]. Numerical simulations of the effect of added polymer on the phase diagrams of hard-core particles are also feasible [21][22]. This is not obvious because the part of the simulations is the calculation of the exact partition function of a (lattice) polymer in the presence of hard-core colloids. Fortunately, it is possible to construct a recursive Monte Carlo scheme to do this [20,21]. Consider a chain of length $\ell - 1$ on a lattice. For convenience, we assume that the external potential on the lattice points is either zero or infinite. The total number of accessible ideal chain conformations that terminate on lattice site i is denoted by $\omega_{\ell-1}(i)$. The total partition function $\Omega_{\ell-1}$ is equal to $\sum_i \omega_{\ell-1}(i)$, where the sum runs over all lattice sites. The total number of chains of length ℓ that terminate on site i is clearly equal to the sum of the total number of chains of length $\ell - 1$ that terminate on any of the neighbors of i, multiplied by the Boltzmann factor associated with site i. Using such a recursive scheme, we can compute *exactly* Ω_ℓ, the partition function of a single ideal polymer of arbitrary length ℓ on a lattice, in an arbitrary external potential. We now assume that this potential is due to the presence of N hard, spherical colloidal particles each of which occupies many lattice sites. The polymer partition function clearly depends on the coordinates $\mathbf{r}^N$ of the colloidal particles: $\Omega_\ell(\mathbf{r}^N)$. The configurational part of the partition function of the system of N colloids plus one polymer of length ℓ in volume V is then given by:

$$Z(V,N,1) = \int_V d\mathbf{r}^N e^{-U_{hs}(\mathbf{r}^N)}(\Omega_\ell(\mathbf{r}^N)), \tag{3}$$

where $U_{hs}(\mathbf{r}^N)$ denotes the hard-sphere interaction. Next, we make use of the fact that we are considering *ideal* polymers. In that case we can immediately write down the corresponding partition function for N colloids and M ideal polymers:

$$Z(V,N,M) = \int_V d\mathbf{r}^N e^{-U_{hs}(\mathbf{r}^N)}(\Omega_\ell(\mathbf{r}^N))^M/M!, \tag{4}$$

where the factor $1/M!$ accounts for the fact that the polymers are indistinguishable. Using Eqn. 4 it is straightforward to transform to an ensemble where the polymer chemical potential (i.e. the osmotic pressure) is kept fixed. The corresponding grand-canonical partition function is given by:

$$\begin{aligned}\Xi(V,N,\mu) &= \sum_{M=0}^{\infty} e^{M\mu_{ch}}\, Z(V,N,M)/M! \\ &= \int_V d\mathbf{r}^N e^{-U_{hs}(\mathbf{r}^N)} \sum_{M=0}^{\infty} e^{M\mu_{ch}}(\Omega_\ell(\mathbf{r}^N))^M/M! \\ &= \int_V d\mathbf{r}^N e^{-U_{hs}(\mathbf{r}^N)}\, e^{z\Omega_\ell(\mathbf{r}^N)}\,. \end{aligned} \tag{5}$$

In the last line of Eqn. 5, we have introduced the polymer activity $z \equiv e^{\mu}_{ch}$, where μ_{ch} denotes the chemical potential of the chain molecules.

The important point to note is that Eqn. 5 allows us to evaluate the properties of the colloidal particles in osmotic equilibrium with a polymer reservoir. In particular, it shows that we can perform Monte Carlo sampling of the colloidal particles. The polymers only affect $U_{eff}(\mathbf{r}^N)$, the effective interaction between the colloidal particles:

$$U_{eff}(\mathbf{r}^N) \equiv U_{hs}(\mathbf{r}^N) - z\Omega_\ell(\mathbf{r}^N). \tag{6}$$

$z\Omega_\ell(\mathbf{r}^N)$ measures the entropic interaction between the colloids due to *all* possible polymer conformations. This entropic interaction is, in principle, not pairwise additive. In fact, it is shown in [21][22], that for all but the shortest chain molecules, this non-additivity of the polymer-induced interaction between the colloids, has a pronounced effect on the structure and stability of the mixture.

An interesting feature of the depletion interaction is that it is *tunable*. By varying the size and concentration of the added polymers, we can vary the range and strength of the attractive interaction between the colloids. As we shall see in the next section, varying the range of the attractive interaction can have a pronounced effect on the phase diagram of the colloids.

5 The liquid-vapor transition

Why do liquids exist? We are so used to the occurrence of phenomena such as boiling and freezing that we rarely pause to ask ourselves if things could have been different. Yet the fact that liquids must exist is not obvious *a priori*. This point is eloquently made in an essay by V. F. Weisskopf [23]:

...The existence and general properties of solids and gases are relatively easy to understand once it is realized that atoms or molecules have certain typical properties and interactions that follow from quantum mechanics. Liquids are harder to understand. Assume that a group of intelligent theoretical physicists had lived in closed buildings from birth such that they never had occasion to see any natural structures. Let us forget that it may be impossible to prevent them to see their own bodies and their inputs and outputs. What would they be able to predict from a fundamental knowledge of quantum mechanics? They probably would predict the existence of atoms, of molecules, of solid crystals, both metals and insulators, of gases, but most likely not the existence of liquids.

This statement may seem a bit bold. Surely, the liquid-vapor transition could have been predicted *a priori*. This is a hypothetical question that can never be answered. But, as I shall discuss below, there exists an analogous phase transition that has not yet been observed experimentally and that was found in simulation before it had been predicted.

But let us first consider the question of the liquid-vapor transition. In his 1873 thesis, van der Waals gave the correct explanation for a well known, yet puzzling feature of liquids and gases, namely that there is no essential distinction between the two: above a critical temperature T_c, a vapor can be compressed continuously all the way to the freezing point. Yet below T_c, a first-order phase transition separates the dilute fluid (vapor) from the dense fluid (liquid) [24]. From the work of Longuet-Higgins and Widom [26], we know that the van der Waals model (molecules are described as hard spheres with an infinitely weak, infinitely long-ranged attraction[25]) is even richer than originally expected: it exhibits not only the liquid-vapor transition but also crystallization. The liquid-vapor transition is possible between the critical point and the triple point, and in the van der Waals model, the temperature of the critical point is about a factor two larger than that of the triple

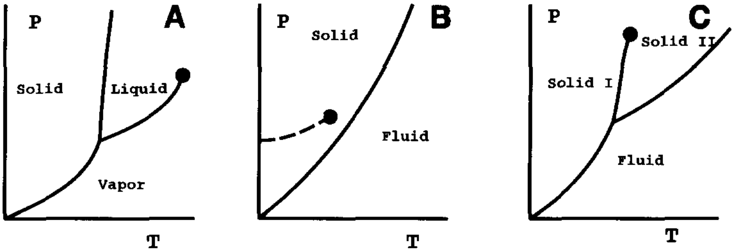

Figure 1: Schematic drawing of the PT phase diagram of a system of spherical particles with (A): an attractive interaction with a range larger than one third of the hard-core diameter. (B): range of attractive interaction between 5 and 20 % of the hard-core diameter. (C) range of the attractive interaction less than 5% of the hard-core diameter.

point. There is, however, no fundamental reason why this transition should occur in every atomic or molecular substance, nor is there any rule that forbids the existence of more than one fluid-fluid transition.

Whether a given compound will have a liquid phase, depends sensitively on the range of the intermolecular potential: as this range is decreased, the critical temperature approaches the triple-point temperature, and when T_c drops below the latter, only a single stable fluid phase remains. This phenomenon is well known in mixtures of spherical colloidal particles and non-adsorbing polymer, where the range of the attractive part of the effective colloid-colloid interaction can be varied by changing the size of the polymer [18,16,17,19,21,22]. Experiment, theory and simulation all suggest that when the width of the attractive well becomes less than approximately one third of the diameter of the colloidal spheres, the colloidal 'liquid' phase disappears. Figure 1 shows schematically the evolution of the phase-diagram of a system of spherical particles with a variable ranged attraction. As the range of attraction decreases, the liquid-vapor curve moves into the meta-stable regime. For very short-ranged attraction (less than 5% of the hard-core diameter), a first-order iso-structural solid-solid transition appears in the solid phase [27]. It should be stressed that phase diagrams of type **B** in figure 1 are common for colloidal systems, but rare for simple molecular systems. A possible exception is C_{60} [28]. Phase diagrams of type **C** have, thus far, not been observed in colloidal systems. Nor had they been predicted before the simulations appeared (this suggests that Weisskopf was right).

The fact that the liquid-vapor transition may become meta-stable, has important consequences for crystal nucleation. This will be discussed in the next section, in the context of the crystallization of globular proteins [29]. In doing so, I make a small digression into a field that seems far removed from statistical mechanics. It is, in itself, not an example of an entropic phase transition. But it illustrates how our understanding of entropic phase transitions can help us in understanding other phenomena of practical importance.

6 Protein crystallization

The human genome codes for some hundred thousand proteins. To understand the function of these proteins, we need to know their three-dimensional structure. At present,

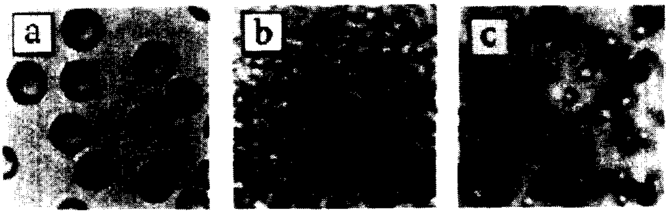

Figure 2: Optical micro-graphs of liquid-liquid phase separation of calf γIVa-crystallin solutions for three different protein concentrations quenched below the coexistence curve between solid and dilute solution. (**a**): droplets of protein-rich phase in protein poor solution. (**b**): bi-continuous structure of protein-rich and protein poor phase, near the meta-stable critical point, (**c**): Droplets of protein-poor phase in a protein-rich solution. For details, see [36]. Photograph by courtesy of Michael Broide.

only some four thousand protein structures have been determined (almost all of them globular proteins – less than ten membrane-protein structures have been resolved). One of the bottlenecks in the determination of the three-dimensional structures of proteins by X-ray crystallography is the difficulty of growing good protein crystals. In his book on this subject, McPherson [30] wrote *"The problem of crystallization is less approachable from a classical analytical standpoint, contains a substantial component of trial and error, and draws more from the collective experience of the past century. [$\cdots$] It is much like prospecting for gold"*. The experiments clearly indicate that the success of protein crystallization depends sensitively on the physical conditions of the initial solution [30,31]. It is therefore crucial to understand the physical factors that determine whether a given solution is likely to produce good crystals.

During the past few years, evidence has accumulated that not just the strength, but also the range of the interactions between protein molecules is of crucial importance for crystal nucleation. In 1994, George and Wilson [32] showed that the success of protein crystallization appears to correlate with the value of B_2, the second osmotic virial coefficient of the protein solution. George and Wilson measured B_2 for a number of proteins in various solvents. They found that for those solvent conditions that are known to promote crystallization, B_2 was always restricted to a narrow "slot". If B_2 was too large, crystallization did not occur at all, while for large negative values of B_2 protein aggregation, rather than crystallization, took place.

More recently, Rosenbaum *et al.* [33] established a link between the work of George and Wilson and earlier studies of the phase behavior of spherical, uncharged colloids. As explained above, for sufficiently short-ranged attractive forces, the liquid-vapor critical point crosses the triple point (see figure 1B) and only a meta-stable liquid-vapor coexistence curve survives below the equilibrium sublimation curve. This fact is relevant for protein solutions, because globular proteins often have relatively short-ranged attractive interactions. In fact, a series of studies by Benedek and Broide and collaborators [36,37] show that the phase diagram of a wide variety of proteins is of the kind shown in figure 1B (see figure 2). Moreover, the range of the effective interactions between proteins can be changed by the addition of non-ionic polymer (e.g. poly-ethylene glycol) to the solution (see [35]).

The interesting observation presented by Rosenbaum *et al.* [33], is that the conditions under which a large number of globular proteins can be made to crystallize, map onto a narrow temperature range – or, more precisely, a narrow range in the value of the osmotic second virial coefficient – of the computed fluid-solid sublimation curve of colloids with short-ranged attraction [34]. Starting with the work of Kose and Hachisu, several authors had already noted that a similarly narrow crystallization window exists for colloidal suspensions [38]. The question that we address here is: what is the physical origin of this nucleation window?

The rate-limiting step in crystal nucleation is the crossing of a free-energy barrier. In our simulations we computed the barrier for homogeneous crystal nucleation for a model "globular protein". Our model system exhibited some of the essential features needed to get a "protein-like" phase diagram of the type shown in figure 1B: the particles repel strongly at short distances and attract at larger distances.

Conventional Molecular Dynamics simulations cannot be used to study crystal nucleation under realistic conditions. The reason is that the formation of a critical nucleus is a rare event – crystallization in real protein solutions may take days or weeks. In a simulation, the situation would be worse because the volume that can be conveniently studied by simulation is some fifteen orders of magnitude smaller, and the probability of forming a crystal is decreased by the same amount. Moreover, the computational costs of Molecular Dynamics simulations that cover more than 10^{-8} s becomes prohibitive. Hence, the problem has to be approached in a different way. We used a technique that we had developed to study crystal nucleation in simple liquids [39]. In general, we can write the nucleation rate as the product of a kinetic prefactor, ν, and the part that describes the probability that a spontaneous fluctuation will bring the system to the top of the nucleation barrier: $\exp(-\Delta G^*/k_BT)$, where ΔG^* is the height of the (Gibbs) free-energy barrier separating the meta-stable liquid from the crystal phase. Unless the system is close to a glass or gel transition, the temperature-dependence of the nucleation rate is dominated by the variation of $\exp(-\Delta G^*/k_BT)$. The model that we study is not close to gelation, and hence we can safely focus on the variation of the free energy barrier. A rough estimate of ΔG^* is given by classical nucleation theory [40],

$$\frac{\Delta G^*}{k_BT} = \frac{16\pi\gamma^3}{3k_BT\rho^2\Delta\mu^2} \tag{7}$$

where γ is the free-energy density per unit area of the solid-fluid interface, ρ is the number density of the solid phase, and $\Delta\mu$ is the difference in chemical potential between the fluid and the solid – it is the thermodynamic driving force for crystallization.

To compute the free energy barrier that the system must overcome to form a critical crystal nucleus, we use a suitable modification of the umbrella-sampling Monte Carlo scheme of Valleau [39,41]. We denote the number of solid-like particles belonging to a given crystal nucleus by N_{crys}. We find that crystallization near the meta-stable fluid-fluid critical point is strongly influenced by the large density fluctuations that occur in the vicinity of such a critical point. We therefore also consider the free energy barrier associated with formation of dense, liquid-like droplets. We define the size of a high-density cluster (be it solid or liquid-like), as the number N_ρ of (connected) particles that

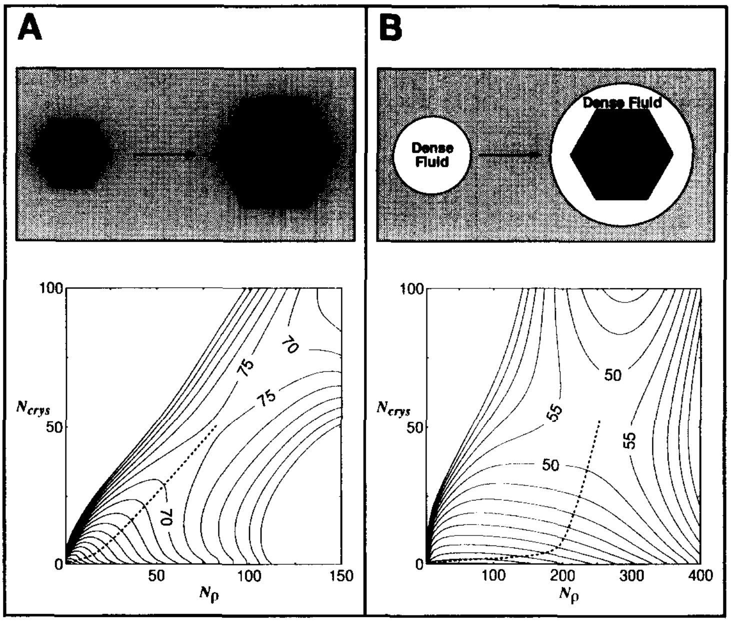

Figure 3: Contour plots of the free-energy landscape along the path from the meta-stable fluid to the critical crystal nucleus, for our system of spherical particles with short-ranged attraction. The curves of constant free energy are drawn as a function of N_ρ and N_{crys} (see text) and are separated by $5k_BT$. If a liquid-like droplet forms in the system, we expect N_ρ to become large, while N_{crys} remains essentially zero. In contrast, for a normal crystallite, we expect that N_ρ is proportional to N_{crys}.

Figure 3A shows the free energy landscape well below the critical temperature ($T/T_c = 0.89$). The lowest free-energy path to the critical nucleus is indicated by a dashed curve. Note that this curve corresponds to the formation and growth of a highly crystalline cluster.

Figure 3B: Idem, but now for $T = T_c$. In this case, the free-energy valley (dashed curve) first runs parallel to the N_ρ axis (formation of a liquid-like droplet), and moves towards a structure with a higher crystallinity (crystallite embedded in a liquid-like droplet). The free energy barrier for this route is much lower than the one shown in figure 3A.

have a significantly denser local environment than particles in the remainder of the system. In our simulations, we determine the free-energy "landscape"of the system, as a function of the two coordinates N_{crys} and N_ρ. In a crystal nucleation event, we start from the homogeneous liquid ($N_{crys} \approx N_\rho \approx 0$) - the free energy then increases, until it reaches a saddle-point (the critical nucleus). From there on, the crystal will grow spontaneously.

We first computed the phase diagram of our model system. Subsequently, we studied the free-energy barrier for crystal nucleation at four different points in the phase diagram: one well above the meta-stable critical point ($T = 2.23T_c$), one at T_c, and the remaining two at $0.89T_c$ and $1.09T_c$. All systems were prepared at a comparable degree of super-cooling – to be more precise, we chose the degree of super-cooling such that classical nucleation theory would predict the same value of $\Delta G^*/(k_BT)$ for all systems. To estimate ΔG^* from Eqn. 7, we used

$$\Delta\mu \approx \Delta H\frac{T_m - T}{T_m} \tag{8}$$

where ΔH is the enthalpy of melting at the coexistence temperature T_m. To estimate the surface free-energy γ, we used Turnbull's empirical rule [40] which states that γ is proportional to ΔH. For all points, we studied the free-energy landscape and the lowest free-energy path to the critical nucleus.

We find that away from T_c (both above and below), the path of lowest free energy is one where the increase in N_ρ is proportional to the increase in N_{crys} (see figure 3A). Such behavior is expected if the incipient nucleus is simply a small crystallite. However, we observe a striking change in the free-energy landscape around T_c (see figure 3B). First, the route to the critical nucleus leads through a region where N_ρ increases while N_{crys} is still essentially zero – in words: the first step towards the critical nucleus is the formation of a *liquid-like* droplet. Then, beyond a certain critical size, the increase in N_ρ is proportional to N_{crys} – a crystalline nucleus forms inside the liquid-like droplet. Near the fluid-fluid critical point, the wetting of the crystal nucleus by a liquid-like layer results in a value of the interfacial free-energy γ, and therefore of the barrier height ΔG^*, that is much lower than would be estimated on the basis of Turnbull's rule. In fact, there is experimental evidence[42] that the experimentally determined interfacial free energy of small protein crystals [43] is much smaller than the value predicted on the basis of their version of Turnbull's rule. Clearly, the presence of large density fluctuations close to a fluid-fluid critical point, has a pronounced effect on the route to crystal nucleation. But, more importantly, the nucleation barrier close to T_c is much lower than at either higher or lower temperatures.

Note that the observed reduction in ΔG^* near T_c by some $30k_BT$ corresponds to an increase in nucleation rate by a factor 10^{13}. The crucial point to note is that, at near the critical point, the incipient crystallite is wetted by a nearly critical liquid. This has a pronounced effect on the surface free energy of the nucleus. Let us denote the free energy density of the solid surface in contact with the "vapor" phase by γ_{sv}. This is the interfacial free-energy density to which Turnbull's rule should apply. However, if the crystallite is covered by a thin liquid layer, then (ignoring curvature effects) the surface free-energy density becomes $\gamma_{sl} + \gamma_{lv}$, where γ_{sl} is the solid-liquid interfacial free-energy density and γ_{lv} the liquid-vapor surface tension. The first point to note is that γ_{sl} is typically an order of magnitude less than γ_{sv}. But, in addition, at the critical point γ_{lv} vanishes. Hence it is not surprising that the surface free energy of a crystallite embedded in a critical droplet is much less than that the same crystallite in contact with the dilute vapor phase.

Let us consider the implications of this reduction of the crystal nucleation barrier near T_c. An alternative way to lower the crystal nucleation barrier would be to quench the solution deeper into the meta-stable region below the solid-liquid coexistence curve. However, such deep quenches often result in the formation of amorphous aggregates [32,33,35,44]. Moreover, in a deep quench, the thermodynamic driving force for crystallization (μ_{liq} –

μ_{cryst}) is also enhanced. As a consequence, the crystallites that nucleate will grow rapidly and far from perfectly [31]. In contrast, by adjusting the solvent conditions (e.g. by the addition of non-ionic polymer) such that a meta-stable fluid-fluid critical point is located just below the sublimation curve, we can selectively speed up the rate of crystal *nucleation*, but not the rate of crystal growth, nor the rate at which amorphous aggregates form.

Clearly, our description of the early stages of protein crystallization is highly simplified. Yet, we believe that the mechanism for enhanced crystal nucleation that we find is quite general. We conclude by noting that the phase diagram shown in figure 1B is likely to be the rule, rather than the exception for compact macromolecules. It is tempting to speculate that nature already makes extensive use of "piggy-back riding" on critical density fluctuations to facilitate the formation of ordered structures.

Acknowledgments

The work of the FOM Institute is supported by FOM ("Stichting Fundamenteel Onderzoek der Materie") with financial aid from NWO ('Nederlandse Organisatie voor Wetenschappelijk Onderzoek') . I thank Michael Broide for the permission to reproduce figure 2. And I thank my many co-authors, be they post-docs or graduate students, for carrying out the actual hard work.

References

[1] L. Onsager, Proc. NY. Acad. Sci. **51**,627(1949).
[2] R. F. Kayser and H. J. Raveche, Phys. Rev. **A17**,2067(1978)
[3] J.E.Kirkwood in *Phase Transformations in Solids*, R.Smoluchowski, J.E.Mayer and W.A.Weyl (eds.),Wiley, New York (1951), p.67.
[4] B. J. Alder and T. E. Wainwright, J. Chem. Phys. **27**,1208 (1957).
[5] W.W.Wood and J.D.Jacobson, J. Chem. Phys. **27**,1207 (1957).
[6] *The Many-Body Problem*, J. K. Percus, editor, Interscience, New York, 1963.
[7] D. Frenkel, H. N. W. Lekkerkerker and A. Stroobants, Nature **332**,822 (1988).
[8] J.A.C.Veerman and D.Frenkel, Phys. Rev. **A45**,5633(1992)
[9] J. L. Lebowitz and J. S. Rowlinson, J. Chem. Phys. **41**,133(1964).
[10] T. Biben and J.P. Hansen, Phys.Rev.Lett. **66**,2215(1991)
[11] H.N.W.Lekkerkerker and A. Stroobants, Physica A 195, 387 (1993)
[12] D.Frenkel and A.A. Louis, Phys. Rev. Lett. **68**,3363(1992)
[13] A. Buhot and W. Krauth, Phys. Rev. Lett. 80, 3787(1998)
[14] T. Biben, P. Bladon and D. Frenkel, J. Phys. Condensed Matter 8, 10799 (1996)
[15] M. Dijkstra and R. van Roij, Phys. Rev. E 56, 5594(1997)
[16] S. Asakura and F. Oosawa, J. Pol. Sci. **33**,183(1958).
[17] A. Vrij. Pure Appl. Chem., 48,471(1976).
[18] A.P. Gast, C.K. Hall and W.B. Russel, J. Coll. Inter. Sci. **96**,251(1983).

[19] H.N.W. Lekkerkerker, W.C-K. Poon, P.N. Pusey, A. Stroobants and P.B. Warren. Europhys. Lett., 20,559(1992).

[20] D. Frenkel, J. Phys. Condens. Matter **2**,SA265(1990)

[21] Computer simulation of polymer-induced clustering of colloids. E.J.Meijer and D.Frenkel, Phys. Rev. Lett. **67**,1110(1991)

[22] E.J. Meijer and D. Frenkel, J. Chem Phys. **100**,6873(1994).

[23] V.F. Weissskopf, Trans. NY Acad. Sci. II, **38**,202(1977)

[24] See, e.g. J.S. Rowlinson, *Studies in Statistical Mechanics*, Vol. XIV, J.L. Lebowitz (editor), North Holland, Amsterdam, 1988.

[25] P.C. Hemmer and J.L. Lebowitz, in *Critical Phenomena and Phase Transitions 5b*, C. Domb and M. Green (editors), Academic Press, New York, (1976)

[26] H.C. Longuet-Higgins and B. Widom, Mol. Phys. **8**,549(1964).

[27] P.G. Bolhuis and D. Frenkel, Phys. Rev. Lett. **72**,221(1994).
P.G. Bolhuis, M.H.J. Hagen and D. Frenkel, Phys. Rev. E **50**,4880(1994).

[28] M.H.J. Hagen et al., Nature, **365**,425(1993).

[29] P. R. ten Wolde and D. Frenkel, Science **277**,1975(1997).

[30] A. McPherson *Preparation and analysis of protein crystals*, Krieger Publishing, Malabar, 1982.

[31] S.D. Durbin and G. Feher, Ann. Rev. Phys. Chem. **47**,171(1996), F. Rosenberger, J. Crystal Growth **166**,40(1996).

[32] A. George and W.W. Wilson, Acta Crystallogr. D **50**,361(1994).

[33] D. Rosenbaum, P.C. Zamora, and C.F. Zukoski, Phys. Rev. Lett. **76**,150(1996).

[34] M.H.J. Hagen and D. Frenkel, J. Chem. Phys. **101**,4093(1994).

[35] S.M. Ilett, A. Orrock, W.C.K. Poon, and P.N. Pusey, Phys. Rev. E **51**,1344(1995).

[36] M.L. Broide et al., Proc. Natl. Acad. Sci. USA **88**,5660(1991). C.R. Berland et al., Proc. Natl. Acad. Sci. USA **89**, 1214(1992). N. Asherie, A. Lomakin, and G.B. Benedek, Phys. Rev. Lett. **77**,4832(1996).

[37] M.L. Broide, T.M. Tominc, and M.D. Saxowsky, Phys. Rev. E **53**(1996) 6325.

[38] A. Kose and S. Hachisu, J. Coll. Interface Sci. **55**,487(1976). C. Smits et al., Phase Transitions **21**(1990)157.

[39] P.R. ten Wolde, M.J. Ruiz-Montero, and D. Frenkel, Phys. Rev. Lett. **75**,2714(1995), and J. Chem. Phys. **104**,9932(1996).

[40] See e.g.: K.F. Kelton, in *Crystal Nucleation in Liquids and Glasses*, H. Ehrenreich and D. Turnbull editors, (Academic, Boston, 1991), Vol. 45, pp.75-177.

[41] G.M. Torrie and J.P. Valleau, Chem. Phys. Lett. **28**,578(1974).

[42] C. Haas and J. Drenth, J. Crystal Growth, **154**,126(1995).

[43] A.J Malkin and A. McPherson, J. Crystal Growth, **128**,1232(1992), ibid. **133**,29(1993).

[44] W.C.K. Poon, A.D. Pirie and P.N. Pusey, Faraday Discuss. **101**,65(1995. W.C.K. Poon, Phys. Rev. E **55**,3762(1997).