Nucleation of First-Order Phase Transitions

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Introduction

A sample of distilled water can be held indefinitely at -10 °C without freezing; after further purification and division into tiny droplets in capillary tubes, water can be cooled below -30 °C. Emulsified droplets of liquid gallium can be undercooled more than 150 °C below their normal freezing point of 30 °C. Clean liquid samples can be superheated by tens or hundreds of degrees above the boiling point; this is avoided in the laboratory only by the use of boiling chips. A gas can be compressed to several times its equilibrium condensation pressure before a liquid drop suddenly appears and grows.

These observations all reflect the fact that there are kinetic barriers to first-order phase transitions, with metastable phases persisting over long periods of time. Small fluctuations of the new (stable) phase tend to disappear, while large fluctuations grow. The critical nucleus is that fluctuation which lies at the barrier between shrinking and growing regions of the new phase. The nucleation rate (the rate of appearance of such critical nuclei) then determines the time it takes for a phase transition to occur, as the growth beyond the critical nucleus is generally fast compared to its formation rate.

As an activated process, nucleation resembles chemical reaction kinetics in that its rate depends exponentially on the height of the barrier represented by the critical nucleus (the activated complex in reaction rate theory). An important distinction, however, is that in chemical kinetics

the activation energy depends only weakly, if at all, on temperature whereas in nucleation the activation (free) energy depends strongly on temperature. For example, the free energy barrier for gas-to-liquid nucleation is infinitely large at gas–liquid phase coexistence (the binodal) but falls rapidly and vanishes as the spinodal is approached. Because nucleation rates involve exponentials of rapidly varying free energies, they are extraordinarily sensitive to the conditions under which the experiment is run (pressure and impurity concentrations as well as temperature). Reproducibility of experimental data can be difficult to achieve, and theoretical prediction of nucleation rates is subject to large uncertainties. Nucleation theory is one of the few areas of science in which agreement of predicted and measured rates to within several orders of magnitude is considered a major success.

In this Account, I describe briefly the results of classical nucleation theory, an approach that began with the work of Becker, Döring, and Volmer in the 1930s, and then present a new approach developed by myself, my co-workers, and other scientists over the past decade, based on density functional theory in statistical mechanics.[1] I discuss a variety of situations in which classical theory fails both quantitatively and qualitatively and show how the new approach accounts for previously unexplained experimental phenomena. In several cases, I show that the critical nucleus can differ drastically from the eventual new phase in composition or structure.

Nucleation Theory: Classical and Nonclassical

Classical nucleation theory is based on the capillarity approximation, in which small portions of the new phase are treated as if they represent macroscopic regions of space. Because it is thermodynamically stable, the new phase has a lower free energy per unit volume than the original phase, but the introduction of an interface increases the free energy by an amount proportional to the surface area of the phase. A spherical nucleus minimizes this surface area for a given volume and is thus the shape of the critical nucleus in most cases. The free energy (Figure 1) is the sum of a (negative) volume term and a (positive) surface term:

$$\Delta\Omega(R) = -{}^4/_3\pi R^3 |\Delta F_v| + 4\pi R^2 \gamma$$

where R is the radius of the nucleus, ΔF_v is the bulk free energy difference per unit volume between the new and old phases, and γ is the surface free energy per unit area. The critical nucleus is the maximum in $\Delta\Omega(R)$; the barrier height, which appears exponentiated in the nucleation rate $J = J_0 \exp(-\Delta\Omega^*/kT)$, is equal to[1]

$$\Delta\Omega^* = 16\pi\gamma^3/3|\Delta F_v|^2$$

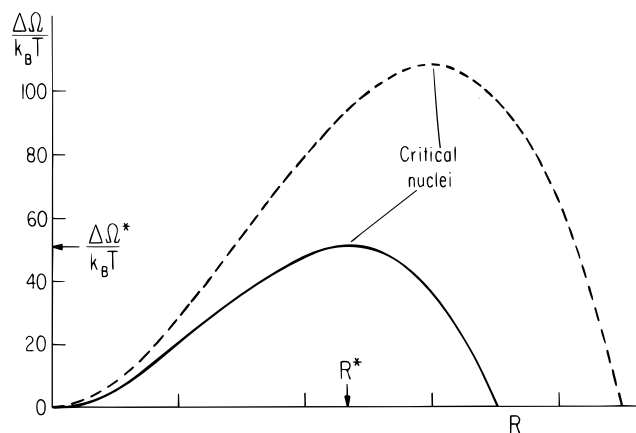and depends strongly on temperature and pressure,

FIGURE 1. Free energy to create a droplet of radius *R* increasing up to a maximum value of $\Delta\Omega^*$ at the critical nucleus. Subsequent growth lowers the free energy. $\Delta\Omega^*$ is larger at higher temperatures (dashed curve).

diverging as phase coexistence is approached and the driving force ΔF_v approaches zero.

Classical nucleation theory assumes that material at the center of the nucleus behaves like the new phase in bulk and that the surface free energy of a small cluster is the same as that of an infinite planar surface. Both assumptions become questionable for nuclei that may contain only 20–50 molecules, small enough that the center is not in the thermodynamic limit and the interface is sharply curved, changing its free energy. The nonclassical nucleation theory that we have developed goes beyond the classical approach by taking the free energy to depend not on a single parameter (the droplet radius *R*) but on the actual average spherical density profile $\rho(r)$. It calculates not a simple function $\Delta\Omega(R)$ but a *functional* $\Delta\Omega[\rho(r)]$, the free energy of an inhomogeneous fluid whose density varies from the center of the nucleus outward. In the nonclassical theory, the density at the center of the nucleus need not be that of the new bulk phase, nor must the surface behave like a planar interface. Instead, the critical nucleus density profile $\rho^*(r)$ is the *saddle point* in functional space separating "reactants" (small clusters that tend to shrink) from "products" (large clusters that tend to grow). At the saddle point, the functional derivative $\delta\Omega/\delta\rho$ vanishes, giving a mathematical equation for the critical nucleus profile.

To carry out the density functional program just described and calculate the shape and free energy of the critical nucleus, a theory is needed for the free energy of inhomogeneous fluids. Our approach is based on liquid-state perturbation theory and ideas that date back to van der Waals. It writes a spherical potential as the sum of a rapidly varying repulsive part and a slowly varying attractive part $V_{att}(r)$ (the traditional Weeks–Chandler–Andersen separation[2] of a potential in the theory of simple liquids). The repulsive part is then replaced by an effective hard sphere potential with diameter *d*. The free energy is the sum of a purely entropic hard-sphere contribution (treated using the local free energy f_{hs} per unit volume of a hard-sphere fluid) and an attractive

contribution (treated using perturbation theory):

$$\Omega[\rho(r)] = \int dr \, f_{hs}(\rho(r)) +$$
$$\int\int dr dr' \, V_{att}(|\boldsymbol{r} - \boldsymbol{r}'|) \, \rho(r) \, \rho(r')$$

Setting the functional derivative of this equation to zero for the critical nucleus gives a nonlinear integral equation for $\rho^*(r)$ which is solved by iteration. (Details are given in refs 3 and 4.) The nucleation rate is then the negative of the critical nucleus free energy divided by temperature, exponentiated, and multiplied by the prefactor J_0 from classical theory. Our approach does not incorporate the full kinetic theory required to modify this prefactor.

Gas–Liquid Nucleation

In recent years, direct experimental measurements of nucleation rates have become possible for the gas-to-liquid transition. (Before that time, only critical super-saturations were measured: the pressure at which the nucleation rate changes from very slow to very fast.) For this reason, the most quantitative tests of classical and nonclassical theory are for condensation from the vapor. Experiments show that for most nonpolar fluids the classical theory predicts nucleation rates accurate to within several orders of magnitude. For strongly polar fluids such as acetonitrile, on the other hand, classical theory is in error by many orders of magnitude. Even for nonpolar fluids the temperature dependence of classical nucleation theory is systematically in error: classical theory gives too high a nucleation rate at high temperatures and too low a rate a low temperatures. In most cases, there is an intermediate temperature where classical theory is correct.

We have not yet made real progress in understanding the difficult problem of nucleation in strongly polar liquids. On the other hand, our density functional approach has clarified some issues for weakly polar liquids and has helped significantly in explaining the behavior of nonpolar fluids. Using both a hard-sphere plus Yukawa[3] and a more realistic Lennard-Jones potential,[4] we have calculated free energies of critical nuclei. The density functional theory captures the observed temperature dependence of nucleation, which is not described correctly by classical theory (Figure 2). It should be emphasized that most experiments have been carried out on substances such as the alkanes (e.g., nonane), alcohols, and toluene, for which simple spherical potentials are not good quantitative models; no accurate data are available for simple substances such as the noble gases. Comparison with experiment is thus only qualitative, but it is encouraging that the observed trends in temperature correspond with those calculated from spherical potentials.

Moreover, because theoreticians can vary the potential at will, we have been able to probe the reasons for the failure of classical theory. We showed[3] that, if the range of the attractive tail on a realistic potential is made slightly (30%) greater, the qualitative agreement of classical theory
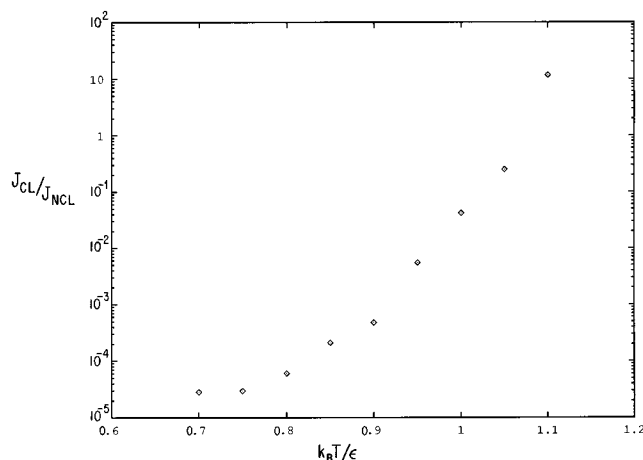
FIGURE 2. Ratio of classical to nonclassical nucleation rates as a function of temperature. The same trend is seen in experiments on nonane and the alcohols. Reprinted with permission from ref 4. Copyright 1991 American Institute of Physics.

with density functional theory (and, thus, with experiment) disappears completely and errors arise of 15–20 orders of magnitude in rates. In other words, the observed reasonable agreement of classical theory with experiment in overall order of magnitude of rates is largely fortuitous; if nature had supplied slightly longer ranged potentials, classical theory would fail so badly that it would never be used. The reasons for its qualitative success can be traced to a cancellation of errors. Two critical physical features of nucleation are omitted by classical theory: the surface free energy of a small nucleus should depend on curvature, and the nucleation barrier should vanish at the spinodal (the point where the vapor phase becomes thermodynamically unstable). The first feature should lower the nucleation rate relative to the classical prediction, while the second should increase it. The two errors accidently cancel at some temperature (often within the experimentally accessible region) but together give rise to the systematically incorrect temperature dependence of classical theory.

Binary Condensation

As just described, classical nucleation theory gives qualitatively reasonable but quantitatively incorrect results for the condensation of single-component nonpolar fluids. For the condensation of binary gases, on the other hand, classical theory can give unphysical results, so a theory with a sounder theoretical base such as density functional theory is even more necessary.

Binary nucleation theory has long been plagued by problems of thermodynamic inconsistency. As Wilemski[5] and others have pointed out, straightforward extensions of one-component classical theory to binary or multicomponent mixtures can violate the Gibbs–Duhem relations. It is possible, though, to construct generalizations of classical theory that satisfy these relations; the simplest of such is the revised classical theory of Wilemski himself, in which the bulk and surface compositions of the nucleus are permitted to vary independently. However, even this

improved classical theory can violate other thermodynamic relations.

To see this, note that Kashchiev and I have proven the nucleation theorem,[6] a relationship between the effect of pressure (or more directly, chemical potential) on the free energy of the critical nucleus and its size and composition:

$$(\partial \Delta \Omega^* / \partial \mu_{o,i})_T = -\Delta n_i^*$$

Here, $\mu_{o,i}$ is the chemical potential of component i in the background phase (here, the mixed vapor) and Δn_i^* is the number of molecules of i in the critical nucleus. This relation, which we derived by methods of small-system thermodynamics and thus holds under quite general conditions, allows experimental measurement of the composition of critical nuclei. (Kashchiev[7] had earlier given an intuitive derivation based on classical nucleation theory, and Viisanen et al.[8] gave a statistical mechanical derivation.) The chemical potential is readily varied at constant temperature for a gas mixture by changing the partial pressure of each component separately while holding the temperature and the other partial pressures fixed. The variation of the logarithm of the nucleation rate with partial pressure (the quantity directly measured experimentally) can then be related to the variation of the nucleation prefactor and of the free energy barrier:

$$(\partial kT \ln J / \partial \mu_{o,i})_T = (\partial kT \ln J_o / \partial \mu_{o,i})_T - (\partial \Delta \Omega^* / \partial \mu_{o,i})_T$$

The first term on the right side is small and can be estimated,[6] allowing experimental determination of the second term and thus of the number of molecules of each type i in the critical nucleus, Δn_i^*.

The procedure just described tests predictions of the size and composition of the critical nucleus as well as its rate of formation. It also highlights one of the problems with revised classical theory for binary systems. For certain mixtures, especially ones in which the liquid phase shows substantial surface enrichment of one component, the revised classical theory predicts that the nucleation rate can decrease as the partial pressure of one of the components in the gas mixture increases; equivalently, the vapor phase activity of the second component increases as that of the first increases at constant nucleation rate (see Figure 3). The nucleation theorem shows that this prediction is unphysical because it would correspond to a negative number of molecules of that component in the critical nucleus. Density functional theory,[9] on the other hand, is fully consistent with the nucleation theorem and also gives more information, such as the density profile of the two components present in the critical nucleus. Surface enrichment in small droplets can thus be elucidated for a variety of systems.

Ternary Nucleation and Amphiphilic Molecules

It is straightforward to extend experimental nucleation measurements, the nucleation theorem, and density functional theory to ternary and higher order mixtures. Particularly interesting results have been obtained for
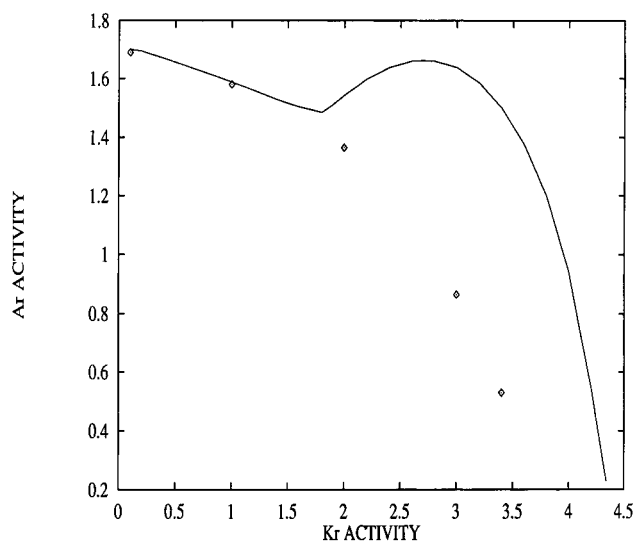
FIGURE 3. Activity plot showing gas-phase activities of the two components for a constant nucleation rate of 1 cm^{-3} s^{-1}. The classical theory (solid line) shows an unphysical range with positive slope, whereas density functional theory (diamonds) is consistent with the thermodynamic constraints of the nucleation theorem. Reprinted with permission from ref 9. Copyright 1995 American Institute of Physics.

ternary mixtures in which two incompatible components are brought together by a third amphiphilic component. Viisanen and Strey[10] studied ternary mixtures of water, butanol, and nonane. Water and nonane are immiscible and a gas mixture of the two nucleates to the liquid with the two components essentially ignoring each other; critical nuclei of pure water lead to a liquid water phase or those of pure nonane lead to liquid nonane even starting from a gas mixture. When butanol is present, the behavior changes dramatically, however, because the hydrocarbon and the hydroxyl end groups on the alcohol molecules allow them to interact effectively with both nonane and water. By inserting themselves at a nonane–water interface and lowering the surface tension, butanol molecules permit nonane and water to be present simultaneously in droplets. Their role is that of a surfactant, a typical characteristic of such amphiphilic molecules. The experiments of Viisanen and Strey took advantage of the nucleation theorem to measure nucleation rates as a function of the three partial pressures at constant temperature; they showed that, over a certain range of gas-phase compositions, all three components are present in the critical nucleus.

Although the authors of the experimental work suspected that the butanol molecules lay at the interface between regions of water and nonane in their critical nuclei, the microscopic structure of the droplets was not accessible to experimental measurement. Our density functional calculation of a model ternary mixture sheds light on the problem.[11] We modeled the system using Lennard-Jones potentials, with an additonal orientation-dependent interaction so that one end of the amphiphile (butanol) interacts more favorably with water and the other end with nonane. The potential parameters were fit to observed bulk thermodynamic behavior of the binary
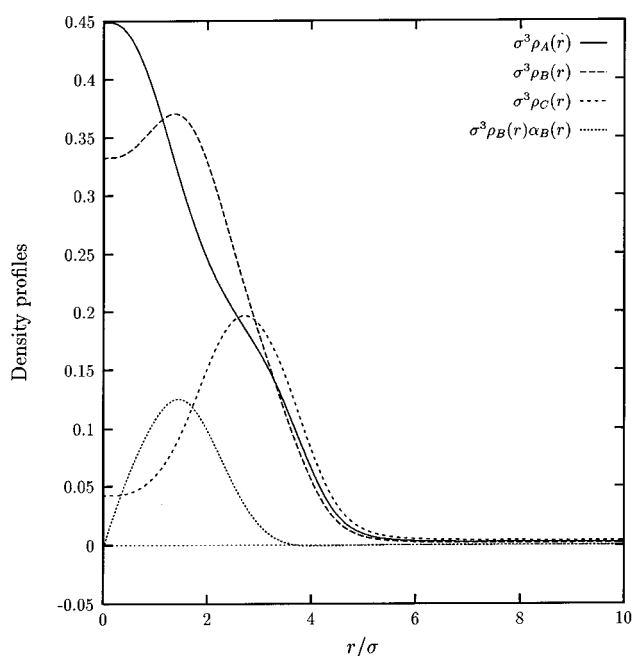

FIGURE 4. Density profiles for the three components of a ternary mixture in the critical nucleus. The solid line represents the water-like component, the long dashed line butanol, and the short dashed line nonane. The dotted line represents the orientational distribution of the butanol; its positive values reflect the hydroxyl group pointing toward the water. Reprinted with permission from ref 11. Copyright 1997 American Institute of Physics.

mixtures, and calculation confirms that in the binary nonane–water mixtures the two components do not interact significantly during the nucleation process. The composition of critical ternary nuclei was quite close to that observed experimentally, however, and the structure of these nuclei is consistent with the qualitative expectation of the earlier work. Figure 4 shows a critical nucleus with "water" at the center, a layer of "butanol" at the interface with the "hydroxyl" end pointing inward, and "nonane" on the outside of the droplet. Such a critical nucleus will grow to become a macroscopic liquid droplet of almost pure nonane under these conditions. The composition of the critical nucleus (which includes a significant amount of water and butanol) is entirely different from that of the eventual bulk phase. The density functional theory reveals a crucial feature absent in classical nucleation theory.

Cavitation

The gas-to-liquid nucleation just described takes place via the formation and growth of molecular clusters of increasing size. The reverse process of liquid-to-gas nucleation occurs via the assembling of voids into a cavity (or bubble) that is large enough that it can lower its free energy by continuing to grow. A liquid can be brought into a metastable state by superheating it above its normal boiling point until bubbles form explosively or by exerting a negative pressure on it until it pulls apart. Superheating often brings a liquid into the critical region, a portion of phase space in which a mean field approach such as

density functional theory is less reliable. I therefore focus instead on the negative pressure domain. The fact that a liquid can sustain a small negative pressure means that, like a solid, it has a measurable tensile strength. Pulling on a liquid puts it under a state of tension, and when the negative pressure exerted becomes large enough, it will break and pull apart; this process is referred to as cavitation and is caused also by strong shear.

The classical nucleation theory of cavitation parallels that of condensation. The critical bubble is a void of radius R (if the coexisting gas pressure is low, the bubble will be almost empty). Once again a free energy per unit volume favors the formation of the new (gaseous) phase and a surface tension disfavors it. The free energy barrier $\Delta\Omega^*$ has the same form as that given before. Bubbles with radii larger than the critical radius R^* will tend to grow, and those that are smaller will shrink.

The nonclassical (density functional) approach, on the other hand, gives completely different results for the two transitions, even though the method of calculation is parallel. The primary reason is an asymmetry in the underlying thermodynamics: the spinodal is much closer to the phase coexistence curve on the liquid side than on the gas side. (This feature is not captured by simple lattice models of gases and liquids that have hole–particle symmetry.) As a result, the spinodal exerts a much larger influence on nucleation under experimentally realizable conditions and the classical theory fails completely. Our calculations[4] yield cavitation rates 15–20 orders of magnitude greater than classical even for realistic Lennard-Jones potentials (recall that for condensation this only took place when the range of the potential was artificially extended). This should translate into a measurably smaller tensile strength for the liquid.

Such a prediction is unfortunately difficult to verify. Liquids do indeed show lower tensile strengths than expected classically, but this is usually due to impurities that catalyze heterogeneous nucleation. A liquid cannot be cleaned of such impurities to the extent possible with a gas, and thus, it is difficult to reach the range of purity where the prediction could be tested. One promising material is liquid helium, which can be purified to an extraordinary extent at cryogenic temperatures. Here quantum effects come into play, however. We have extended the density functional approach to a quantum mechanical theory for liquid ^{3}He, and predict smaller tensile strengths than from classical nucleation theory for this material as well;[12] experiments are not yet available.

By turning to the cavitation of binary liquid mixtures, we can make some predictions that are experimentally verifiable and that resolve some earlier paradoxes. Consider, in particular, cases in which a relatively volatile gas (such as nitrogen or hydrogen) is dissolved in a less volatile liquid (such as water). Such a mixture can be brought into a metastable state in a third way (in addition to the superheating and negative pressures already described): by supersaturating the liquid with an excess of dissolved gas. This is done by carrying out gas-generating reactions in liquids and measuring the con-
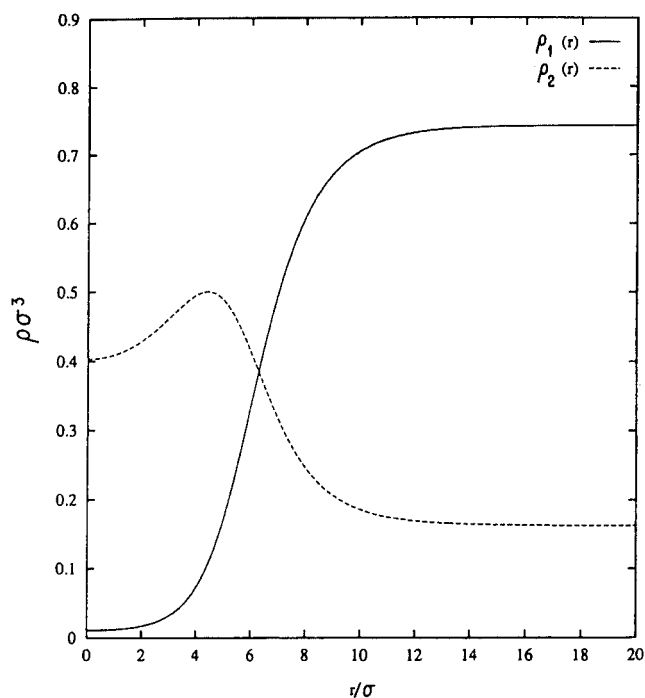

FIGURE 5. Density profiles for a critical bubble of "hydrogen" (dashed line) in "water" (solid line). The high density at the center suggests liquid–liquid phase separation rather than gas bubble formation in the critical nucleus. Reprinted with permission from ref 14. Copyright 1995 American Institute of Physics.

centration at which the (kinetic, not thermodynamic) limit of supersaturation is reached.[13] For nitrogen dissolved in water the expected temperature dependence results: bubble nucleation becomes faster at higher temperatures. For hydrogen, on the other hand, the outcome is surprising: bubble nucleation becomes slower as the temperature is raised. Surely high temperatures should favor gas formation; why is this result found?

Our density functional calculations[14] provide an explanation for this behavior. We modeled Lennard-Jones mixtures in which the relative volatility of the two components sets the strengths of the attractive forces between their molecules. When these strengths are reasonably close to each other (as in the nitrogen/water case) the nucleation of bubbles is faster at high temperatures. When the relative volatility becomes more extreme (as in the hydrogen/water case), the reverse temperature dependence emerges, in agreement with experiment. An examination of the density profile in the critical nucleus shows the qualititative origin of this change (Figure 5). The critical nucleus is not a gas bubble surrounded by liquid, but rather a nearly liquidlike bubble of hydrogen surrounded by liquid water. In other words, the crucial nucleation step in this case is a liquid–liquid phase separation more than a liquid–gas transition. Because liquid–liquid phase separation is thermodynamically favored at low temperature, the increase in nucleation rates under these conditions is now understandable. As the hydrogen bubble grows, its density drops, so by the time it becomes visible to the experimentalist, it looks like an ordinary gas bubble. Here again (as in the ternary

condensation discussed earlier) the critical nucleus is completely different from the eventual stable phase that forms, and classical theory fails entirely. Binary cavitation is a two-variable problem in which both density and composition change during the transition; for hydrogen in water, the composition change takes place first (leading to the critical nucleus) before the subsequent lowering of the density to form a recognizable gas bubble.

Nucleation of Crystals from the Melt

The liquid-to-solid transition is more complex than transitions between the gas and liquid state because it involves a change in symmetry (the appearance of periodic structure) as well as density. The average density of a periodic crystal can be represented[15] as a Fourier expansion using reciprocal lattice vectors k_i:

$$\rho(r) = \rho_l[1 + \mu_o + \sum_i \mu_i \exp(ik_i \cdot r)]$$

In this equation, ρ_l is the liquid density and μ_o is the average density change on freezing. The parameters μ_i are amplitudes that describe the periodic structure in the crystal; they are zero in the liquid. The transition is thus characterized by an infinite set of order parameters $\{\mu_i\}$ instead of the single parameter (the average density) characterizing the gas−liquid transition.

During nucleation and growth, a small crystallite is surrounded by liquid. This can be modeled by letting the order parameters μ_i depend on radial distance r from the center of the crystallite.[16] Defining the critical nucleus again as the saddle point in this (now infinite) function space gives a set of coupled equations to solve for the structure and free energy of the critical nucleus. In practice, reduced level descriptions are used.[17] It is a reasonable approximation to take the crystal to be harmonic (Gaussian) even near its melting point. In this case, all higher order structural parameters μ_i are related to the lowest order μ_1 and a two-order parameter description including the average density change μ_o and a structural parameter μ_1 results. Interestingly, the two do not follow each other directly during the transition. The first step in crystallization involves structuring (μ_1 changes at fixed density μ_o) and only later does the average density change.[16] This makes physical sense because a liquid is difficult to compress, but once periodic order appears, its molecules can be packed more closely together.

The density functional nucleation theory can be compared with the corresponding classical theory and, in most cases, gives significantly lower nucleation rates. The liquid−solid transition differs from the gas−liquid in that there is no evidence in the former case for a spinodal at which the nucleation barrier vanishes. Instead, there is sometimes a glass transition where nucleation slows down for kinetic, not thermodynamic, reasons. There is also considerable asymmetry in the behavior of undercooled liquids and superheated crystals. Not only is there a spinodal in the high temperature solid, but it appears unusually close to the equilibrium melting point (often only tens of degrees above). This has a large effect on
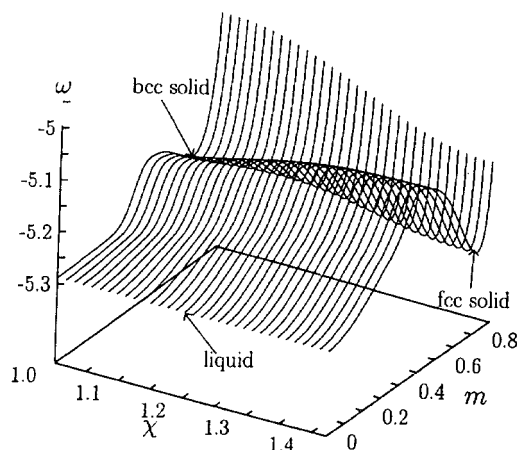

FIGURE 6. Free energy per unit volume for a uniform system intermediate between liquid, fcc solid, and metastable bcc solid. Symmetry and structure vary along the two axes. Reprinted with permission from ref 19. Copyright 1996 American Institute of Physics.

nucleation rates and prevents significant superheating of crystals. Experimentally, solids are difficult to superheat, but this is generally due more to the presence of free surfaces or defects where melting can be initiated.

The approach described so far assumes that the crystal symmetry is known. In some cases, one or more metastable solid phases may be close enough in free energy to the stable phase that they can affect the phase transition. Such is the case in the crystallization of argon-like Lennard-Jones fluids, where computer simulations[18] show substantial body-centered-cubic (bcc) ordering in the interface between the liquid and the stable face-centered-cubic (fcc) crystal. To investigate this possibility using density functional theory, we used the fact that a bcc lattice can be continuously converted into an fcc lattice via the Bain transformation.[19] Our calculations allowed the structural order parameter μ_1 to change continuously from zero to finite values (describing a partially crystalline material) and the Bain transformation parameter χ to change from 1 to 1.414 (describing a crystal intermediate between bcc and fcc). For simplicity, we omitted the effect of the small average density change μ_o. The resulting free energy surface (Figure 6) shows a metastable bcc crystalline phase not far above the stable fcc phase.[19]

We then used the free energy functional in this calculation to study crystal-melt free energies and the properties of critical nuclei. The results are striking and confirm the picture first seen in computer simulations. Instead of passing directly from fcc crystal to liquid (changing μ_1 at fixed χ), which might seem the simplest path to follow, the equilibrium interface follows a trajectory in which a bcc region inserts itself between stable liquid and crystal (Figure 7). The metastable bcc phase induces a saddle point in the free energy surface near $\chi = 1$ (clearly visible in Figure 6), and the minimum free energy interface passes close to that saddle point. The consequence for nucleation is significant: a small critical nucleus will have largely bcc character at its center and will only evolve into a stable fcc crystal as it grows larger. Once again, the
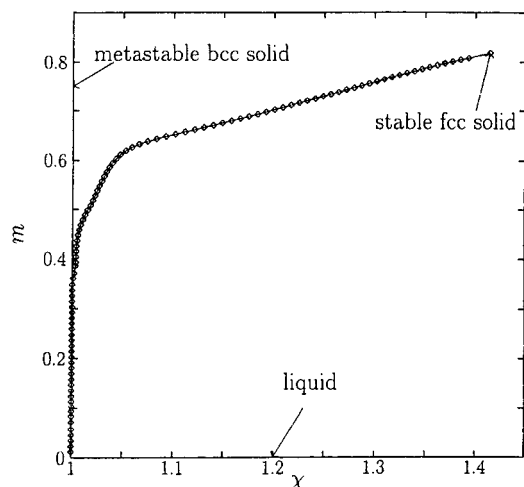
FIGURE 7. Variation of the order parameters m (μ_1) and χ through the planar crystal–melt interface, as they depend parametrically on position z. The symmetry of the lattice changes from fcc to bcc before m approaches the liquid value. Reprinted with permission from ref 19. Copyright 1996 American Institute of Physics.

critical nucleus differs significantly from the eventual stable phase.

Concluding Remarks

An underlying theme of this research is the demonstration that the properties of a critical nucleus can differ significantly from those of the stable bulk phase that eventually forms. This is especially true when two or more order parameters are coupled together (composition and average density for binary gas–liquid transitions, or structure and symmetry for crystallization). In these cases, one of the order parameters can dominate the pathway to the critical nucleus with the other evolving later in the growth process.

Extensions to other first-order phase transitions are underway, one of the most interesting being crystallization of binary fluids in which structure and composition both play a role. One application will be to metal alloy crystallization. Rapid solidification methods can cause metastable solid solutions to form, a kinetically dominated process in which the free energy of different types of critical nuclei is essential. A second application is to protein crystallization from aqueous solution in which protein concentration and crystal structure evolve together

but not necessarily at the same rate. Recent simulations[20] have suggested the crucial role played by aggregation (concentration fluctuations), suggesting that protein crystal nucleation is strongly affected by the types of curved pathways seen also (Figure 7) in the crystallization of simple fluids. A density functional approach should shed light on these and many other problems.

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