Perspective

Molecular Thermodynamics of Solid-Fluid and Solid-Solid Equilibria

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Introduction

Chemical Engineering as an academic discipline emerged and has matured in parallel with the petroleum and petrochemical industries. A large fraction of the processing in these industries is done in fluid (liquid or gas) phases, and this perhaps accounts for the overwhelming emphasis on fluid-phase processes in chemical engineering curricula. However, processes and products involving solids have always been more important in the chemical process industries than is widely appreciated, and they have arguably received insufficient emphasis in both chemical engineering research and chemical engineering education.

Solids appear across the landscape of chemical engineering. In the oil and gas industries we have petroleum waxes (solid-phase mixtures, mostly of alkanes), and gas hydrates, as well as solid phases of various higher molecular weight hydrocarbons, such as asphaltenes. In the petrochemical industry we encounter solid phases for higher molecular weight organic molecules, and when crystallization is more economical than other separation methods. As the industry moves from commodity chemicals to higher molecular weight specialty chemicals the importance of solid phases increases. Most of the drugs produced by the pharmaceutical industry are prescribed as solids, with drug formulations requiring careful control of properties in the solid state. Beyond these areas we have solid-state organic polymers, inorganic solids (e.g., fertilizers, porous materials for catalysis and separations, as well as materials for electronics applications) and metallurgy. Examples in Bioengineering include protein crystallization and its importance in structural characterization and separations.

The title of this article is partly inspired by the book by Prausnitz et al., "Molecular Thermodynamics of Fluid Phase Equilibria".[3] That book, best known for its influence on the teaching and practice of phase equilibrium thermodynamics for chemical engineers, also features a chapter on solid-fluid equilibria (SFE). One of the achievements of the Prausnitz book is that it builds a link between the physics and chemistry of molecular interactions with the thermodynamic models used by practicing engineers. The purpose of this article is twofold. We describe some concepts about the molecular physics underlying solid phase stability and SFE behavior, in a way that might help engineers think about these systems in a practical context. Additionally, we seek to highlight the importance of solid-fluid systems, and their molecular level understanding, throughout chemical process technologies, describing some key areas where molecular modeling can make a contribution.

In defining the scope of this article we begin with the question: "what is a solid?". In everyday experience solid phases are distinguished from liquids and gases in the first instance by their ability to support a shear stress. In many cases solid phases exhibit long-range three-dimensional (3-D) translational ordering of the molecules that is captured in X-ray diffraction experiments. Loss of this translational order on melting gives rise to the typical first-order character of the solid-fluid phase transition for these crystalline solids, with finite changes in molar enthalpy and molar volume. This distinguishes crystalline solids from glasses and other "amorphous" solids. This discussion is concerned with crystalline solid phases, a restriction that still defines a very wide range of systems. Further distinctions can be made in a traditional way in terms of the major contributions to the solid phase binding energy, e.g., ionic, covalent, metallic or van der Waals interactions (loosely defined for the moment as the interactions between neutral molecules). The perspective guiding this article emerged in modeling solid-fluid phase behavior of organic molecules, a situation where phase stability is determined by van der Waals interactions. The solids of interest here are often referred to as molecular solids or molecular crystals. However, there are features of solid phase stability that have origins transcending traditional classifications of types of solid or types of interactions.

Fundamental Physics of the Solid-Fluid Transition

The modeling of fluid phase equilibrium in chemical engineering thermodynamics using equations of state is the legacy of a physical picture originally developed by van der Waals[4] and now formalized within the context of thermodynamic per-

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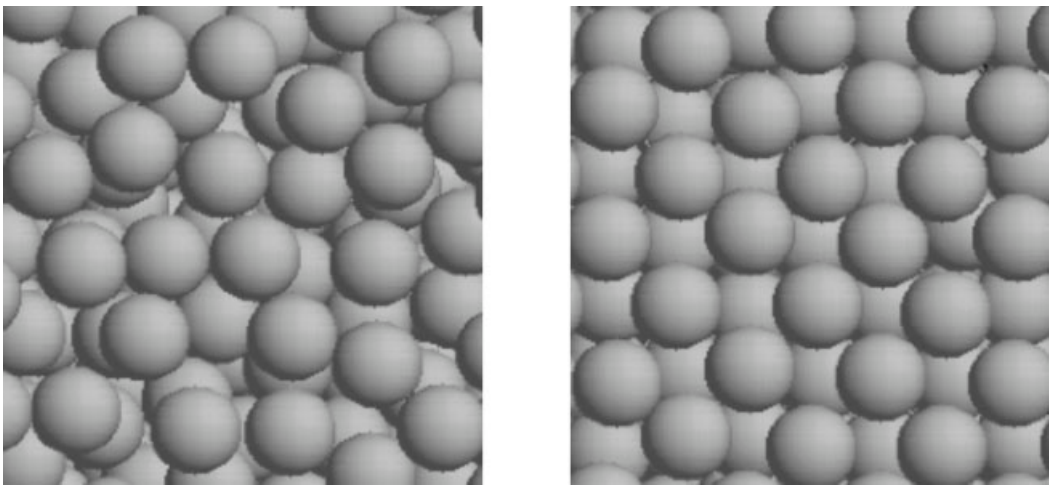

Figure 1. Computer graphics visualizations showing fluid (left), and solid (right) states at the solid-fluid coexistence pressure from Monte Carlo simulations of the hard-sphere system.
The view of the solid is normal to a 100 plane of the fcc crystal.

turbation theory.[5] In this picture the free energy or pressure is a sum of separate contributions from repulsive forces and attractive forces between the molecules. We have

$$P = P_0 - a\rho^2 \; ; \quad A = A_0 - a\rho \tag{1}$$

where P is the pressure, A is the Helmholtz free energy per mole, ρ is the molar density, and a is a parameter proportional to the magnitude of the attractive forces. P_0 and A_0 refer to the system with just repulsive forces. From this point of view the structure of condensed phases is determined by the packing restrictions created by the repulsive forces, while attractive interactions associated with dispersion forces give rise to a structure-independent binding that stabilizes high-density phases at low-pressure. The contribution to the equation of state from the repulsive forces can be modeled rather nicely by that of hard spheres.

Although apparently not anticipated by van der Waals[4] this picture can be extended to include solid phases, as was first described by Longuet-Higgins and Widom.[6] This is made possible by the existence of a solid-fluid transition in the hard sphere system, discovered using molecular simulations,[7] and now experimentally realized in the form of colloidal suspensions.[8] Hard spheres have a low-density fluid phase, and a high-density solid phase. The solid phase adopts cubic close packing with the face-centered cubic (fcc) structure, although this structure has only a slightly lower free energy than the hexagonal close-packed crystal.[5] Figure 1 shows visualizations from Monte Carlo simulations of the coexisting fluid and solid states of hard spheres. Hard spheres provide an excellent geometrical picture of freezing by isothermal compression, and also freezing by isobaric cooling.[5] The relevance of the hard-sphere model in the latter case is not so obvious, but follows from a reinterpretation of the dimensionless pressure (defined as $P\sigma^3/kT$, where σ is the sphere diameter, T is absolute temperature, and k is Boltzmann's constant) used to plot the hard-sphere equation of state as an inverse temperature (defined as $kT/P\sigma^3$). This suggests that freezing by cooling and freezing by compression are physically similar processes. The generalization of the van der Waals picture to solid phases gives a qualitatively satisfactory picture of the phase diagram for simple substances.[5]

Does the van der Waals picture have any value in understanding SFE beyond the realm of spherical molecules? Let us consider the interactions that contribute to the stability of molecular crystals. Broadly speaking we have: short-range repulsion associated with molecular shape (molecular packing), long-range attraction (dispersion forces), classical electrostatic (e.g., dipole-dipole, quadrupole-quadrupole) interactions and strongly directional electrostatic interactions (hydrogen bonds). As noted earlier dispersion forces are only weakly dependent on the structure, and the effects of multipolar interactions can be less significant for large molecules with highly nonspherical shapes, where the shape dominates the configurations. Thus, in the absence of hydrogen bonding we find that the structure of a solid will be significantly determined by how the molecules can be packed together to minimize the short-range repulsive forces, so indeed the van der Waals picture should hold a wider place in our understanding of SFE. This point is illustrated by work on the n-alkanes, where the repulsive force contribution to the free energy was modeled using systems of flexible hard sphere chains.[9]

In fact, these ideas are already evident in the organic crystallography literature in the maximum close packing principle of Kitaigorodsky,[10] summarized as: *the crystal structure of an organic compound will be that which gives the closest packing of the molecules*. We reach the limit of the van der Waals picture when we encounter systems with strongly directional intermolecular forces, such as hydrogen bonds, that can lead to so-called anomalies in SFE behavior (e.g., expansion on freezing).

Molecular Modeling of Solids and SFE

A recent review[5] gives a comprehensive description of molecular modeling approaches to systems with solid phases, and here we just highlight some major themes and developments. Applications of statistical mechanics to solid-fluid systems

include theories yielding approximations to the free energy of solid and fluid phases and molecular simulations by Monte Carlo or molecular dynamics methods. Such methods, especially molecular simulations, have become the tools for a new generation of researchers in molecular thermodynamics.

Four levels of approximation have been used to build theories of solid-phase stability and SFE.[5] The simplest is to assume that the structure is determined by minimizing the intermolecular potential energy for the system. This is the basis of most theoretical structure determinations for molecules encountered in the pharmaceutical industry.[11] The next level of approximation is to introduce thermal fluctuations, based on harmonic motion of the molecules, an approach usually called lattice dynamics, which works well at low-temperatures. The next step beyond lattice dynamics is to include the motion of the molecules in a field created by a static configuration of the other molecules. This is the basis of cell theories, which can work very well for simple models of the intermolecular forces. Prediction of SFE using the aforementioned methods also requires a theory of the fluid phase thermodynamics. The most recently developed theoretical formalism is the classical density functional theory, which treats a solid as a highly inhomogeneous fluid. This has been very widely used for models of spherical molecules, such as hard-spheres, although with only limited success for more complex molecules.

Much new information about solids has come from molecular simulation studies, going back to studies of hard-sphere systems,[7] and this is particularly true for more complex molecules. Three developments in simulation technique have contributed most to progress in this field over the last 20 years. The first is the use of simulation cells that fluctuate in shape in an isobaric ensemble.[12] In this way simulations may explore changes in solid-phase symmetry. The second contribution is Frenkel-Ladd[13] method for calculating the free energy of a solid phase using a reversible path to a classical Einstein crystal. Finally we have the Gibbs-Duhem integration method of Kofke[14] in which molecular simulations are used to trace phase boundaries. More recent developments include phase switch Monte Carlo,[15] which allows a single simulation to sample both fluid and solid phases or multiple solid phase.

Predicting Structures for Molecular Crystals

For molecules that are nonspherical, perhaps with strong electrostatic interactions or internal flexibility, the determination of the stable crystal structure can be a nontrivial problem. The potential energy landscape associated with the possible crystalline configurations of the molecules may be quite complex with many local energy minima. The energy minima correspond to different crystalline structures, frequently referred to as polymorphs.[16] Polymorphs may correspond to solid phases that are thermodynamically stable over some range of temperature and pressure, or they may correspond to metastable states. If the energy barriers surrounding a particular metastable state are sufficiently large, thermal fluctuations large enough to take the system out of that structure will be exceedingly rare events, and such a state would then be "stable" for practical purposes. The metastability of diamond with respect to graphite is a well-known example of this phenomenon (different phases of pure substances are usually called allotropes rather than polymorphs). The statement by McCrone,[17] "*It is at least this author's opinion that every compound has different polymorphic forms, and that, in general, the number of forms known for given compound is proportional to the time and money spent in research on that compound*" is widely quoted in this field.

Understanding the structure of polymorphs, and their stability has special impact in the pharmaceutical industry where drug formulations are required to specify the polymorph of the active pharmacological ingredient (API).[18] Polymorphs may have different physical properties, such as dissolution kinetics, that can impact pharmacological activity. Moreover, polymorphs are separately patentable, a significant component of the intellectual property landscape for pharmaceuticals. Controlling which polymorph is produced in a manufacturing process can sometimes be a major problem, as illustrated by the experience of Abbott Laboratories with its HIV protease inhibitor drug ritonavir.[18]

From a modeling perspective the most straightforward route to identifying polymorphs is energy minimization, based on a classical model of the intermolecular and intramolecular potential energies in the system, as discussed in a recent review by Price.[11] This neglects the effects of thermal fluctuations (or, putting it more loosely, "entropy effects") on the crystal-free energy. There are two components to predicting structures by this approach.[11] The first is the formulation and parameterization of a suitable potential energy model or force field for the system. The second is an energy minimization procedure for which several techniques are used, and some of these will be familiar to chemical engineers who have worked on optimization problems. The polymorph search methods developed by different research groups are often compared using "blind" tests,[11] where predictions are made for a molecule, where the crystal structure, previously unknown, is independently determined by X-ray diffraction.

A full statistical mechanical treatment of solid-phase stability including thermal fluctuations allows the determination of the relative stability of different polymorphs in terms of the free energy rather than just the potential energy.[5] One route to this is provided by the molecular simulation methods discussed earlier. In addition to yielding the free energy molecular simulations reveal whether a polymorph is stable in the presence of the thermal fluctuations typically encountered in such simulations. This may give some indication of how likely it is that a metastable polymorph could be encountered in nature. The main barrier to use of these methods is the high-computational cost of molecular simulations using realistic force fields for complex molecules. Techniques like phase switch Monte Carlo[15] may also be useful for determining stable polymorphs.

Solid-Phase Mixtures

Matsuoka has presented a survey of the known SFE phase diagrams for binary organic mixtures.[1] The six most common types of temperature-composition phase diagram are shown in Figure 2, listed in the order of their frequency of appearance in the survey. Perhaps not surprisingly over 50% of the mixtures studied exhibit eutectic phase diagrams with no solubility

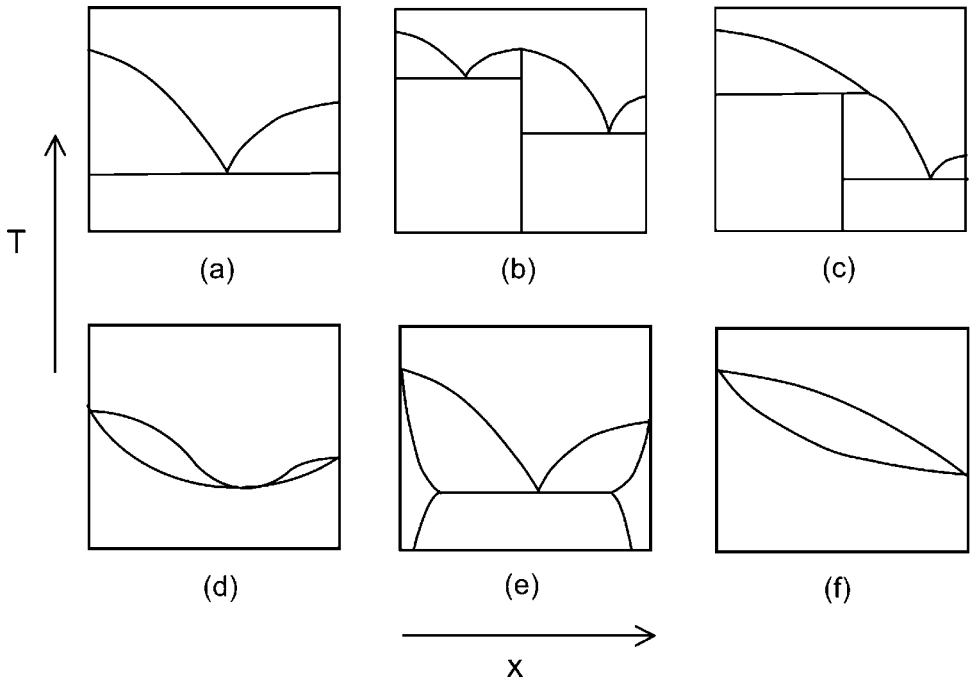

Figure 2. The six most common types of temperature vs. composition SFE phase diagrams for binary mixtures of organic molecules based on a survey by Matsuoka.[1]

The phase diagrams are listed in the sequence based on their frequencies of occurrence in the survey: (a) eutectic phase diagram with no solid-phase miscibility; (b) congruently melting AB compound; (c) AB compound with a peritectic point; (d) minimum melting azeotrope; (e) eutectic phase diagram with partial solid-phase miscibility, and (e) spindle phase diagram indicating ideal solution behavior in the solid phase.

of the components in the solid phase. This reflects the difficulty of packing molecules of different sizes and shapes into a solid-phase mixture with crystalline order. The next most common behavior features an equimolar, congruent melting, solid-phase compound (also known as a cocrystal or substitutionally ordered solid solution). Together the first two types of behavior encompass almost 80% of the systems in the Matsuoka survey. Congruent melting refers to the compound melting into a liquid without a change of composition. Solid-phase compounds with a variety of stoichiometries are of course well known for inorganic solids, whether ionic or covalent, and for metal alloys. Their stability for molecular solids might be viewed as somewhat more remarkable given the relative weakness of the interactions in these systems.

Several researchers have studied SFE for simple molecular models of binary mixtures using hard-sphere[19–21] and Lennard-Jones potentials.[22,23] When additive collision diameters are used binary hard-sphere systems can exhibit five of the six classes of phase diagram shown in Figure 1, and it has been generally viewed as a surprising result that such a simple model can display such a wide range of SFE behavior. What these simple models do not seem to exhibit are solid phase compounds with congruent melting. Vlot and coworkers[22] studied SFE for symmetric Lennard-Jones mixtures with departures from the Lorentz-Berthelot (LB) combining rules, a simple model for mixtures of the enantiomers of a chiral molecule, and discovered that congruent melting can occur when there are departures from the LB combining rules. A study of a model of benzene and hexafluorobenzene[24] has shown that compound stability can arise from a special confluence of electrostatic interactions with molecular packing.

In the pharmaceutical industry API's are frequently chiral molecules, and the enantiomers may have different pharmacological activity, as was demonstrated so tragically in the 1960s in the case of thalidomide. FDA guidelines emphasize "chiral control" in drug formulations, involving issues, such as the enantiomeric composition of the drugs, the pharmacological activity of the individual enantiomers, and the rate of interconversion of the enantiomers under different conditions.[25] A key aspect from an intellectual property perspective is that an API that was originally patented and marketed as a racemic mixture can be subsequently patented and marketed as a single enantiomer. AstraZeneca's proton pump inhibitor drugs Prilosec and Nexium provide a good example. Methods for producing API's as pure enantiomers, either through separation (also called resolution) or asymmetric synthesis, are at a premium in this area. A great majority of racemic mixtures of chiral molecules form solid-phase racemic compounds that are more stable than the pure enantiomer solids,[26] and this complicates separation by crystallization.[27] Recent modeling calculations show how the stability of racemic compounds can arise from molecular packing effects.[28]

Colloidal Solid-Fluid Systems

A remarkable recent development in understanding solid-fluid systems has been the ability to prepare colloidal systems

in which the particles have controlled interactions that on a larger length-scale mimic the behavior of molecular scale systems.[8] These systems can form solid phases that closely resemble their molecular scale counterparts. Hard-sphere colloids are an experimental realization of the hard-sphere model and the solid-fluid phase transition in that model. There is now an extensive research effort in extending this to other types of interactions.[29] Studies of solid-fluid colloidal systems offer a new route to understanding solid-fluid phase transition mechanisms, such as crystal nucleation and, collaterally, a way of testing theoretical predictions. At the same time crystallization of colloidal systems is an important route to the synthesis of materials via 3-D self-assembly.[29]

Packing with Low-Coordination Number: From ice to hydrates to zeolites

When molecular interactions are intrinsically directional, this gives rise to crystal structures with lower coordination number (lower numbers of nearest neighbors for each molecule in the solid), solids with relatively low-density and an increase in the number of stable solid phases. This leads naturally to a discussion of water and the many phases of ice, as well as to natural gas hydrates. There is also a connection between the behavior of water and that of other systems with low-coordination solids, such as zeolites.

There have been an enormous number molecular simulation studies of liquid water over the last 30 years or more, but only recently have there been detailed studies of ice phases and SFE. The work of Vega and coworkers[30] stands out, with their extensive studies of SFE for several intermolecular potential models of water, highlighting the fact that force fields developed in studies of fluid phases may not work so well in solid phases. One of the fascinating features of water-ice equilibrium is the volume expansion on freezing at ambient pressure, and an interesting question to ask is what is the simplest model that might describe this behavior. One approach is to take simple models, such as hard-spheres and impose low-coordination number association interactions upon them and, remarkably, this can indeed describe qualitative features of the ice-water equilibrium.[31]

A recent article in this journal[32] describes the importance of natural gas hydrates in chemical engineering. Hydrates are a key challenge for molecular thermodynamics research, e.g. molecular models of methane/water mixtures need to be able to account for both the stability of structure-1 hydrates with a methane mole fraction approaching 15%, and the very low-solubility of methane in liquid water under ambient conditions. There has been a tendency to view hydrate equilibria as conceptually different from other types of SFE, in part reflecting the influence of the van der Waals and Platteeuw theory,[33] which makes the thermodynamics of hydrates look like an adsorption problem for the gas molecules in the hydrate cages. Current research on methods for calculating the free energies and chemical potentials for hydrates show more clearly how the hydrate equilibrium problem relates to other SFE problems.[34,35]

Strictly speaking inorganic materials lie outside the scope of this article, but one can make interesting parallels between the properties of ice phases or hydrates with those of zeolites. Zeolites are aluminosilicate[36] materials that have well-defined framework structures with channels and cavities large enough to accommodate small organic molecules. They are widely used in catalysis, as well as in adsorption and membrane separations. A remarkable feature of these materials is that more than 150 framework structures can be synthesized. Many of these can be obtained in an all-silica form. These all-silica framework structures are polymorphs of silica, and are presumed to be metastable with respect to the naturally occurring polymorphs (e.g., quartz, cristobalite, etc.,). Calculations using quantum mechanical density functional theory indicate that the polymorphs of silica featuring four-fold coordination of silicon have similar binding energies.[37] These polymorphs differ primarily in the connectivity of the SiO_4 tetrahedra. The picture that emerges is an energy landscape for crystalline silica with many minima with similar energies separated by very large barriers. This is fertile territory for synthesis procedures,[36] based on silica polymerization in the presence of structure directing agents or templates that can take the system into silica energy minima without crossing large energy barriers. This may account for the large number of zeolite frameworks that can be synthesized. We may draw a parallel with the many phases of ice, and how the range of ice structures is expanded even further by the presence of the guest molecules in hydrates. For silica and zeolites the framework binding is so strong that the structure survives removal of the template, which of course is not the case for hydrates.

Crystal Nucleation

While the primary focus of this article is on equilibrium properties, it is also worthwhile to highlight some progress on understanding the kinetics of crystallization that builds directly on the capability of molecular modeling to calculate SFE. In particular molecular simulations now have the potential to revolutionalize our understanding of crystal nucleation. Frenkel and his coworkers[38] have shown how enhanced sampling techniques can be used to study the thermodynamic and structural properties of crystal nuclei formed in homogeneous nucleation from supercooled liquids or supersaturated solutions. These methods permit determination of the Gibbs energy of crystal nuclei as a function of their size, identification of the critical nucleus and the study of its properties.

Application of Frenkel's approach to homogeneous nucleation in hard-sphere systems has yielded results very close to those obtained from experiments on hard-sphere colloids,[38] an achievement that bodes well for future developments in this field. Studies of crystal nucleation for models of simple non-spherical molecules[39] have been used to investigate the validity of the Ostwald rule of stages, which prescribes that crystallization should occur via nucleation of metastable solid phases that lie closer in free energy to the initial state. The methods have also been applied to binary mixtures.[2] Interesting information emerges about the composition of nuclei and the role of compositional differences between the fluid and solid phases in determining the nucleation barriers. For instance, Figure 3 shows a computer graphics visualization of a crystal nucleus formed from an equimolar symmetric mixture of hard spheres where the AB collision diameter is smaller than the pure component diameter. This system exhibits an

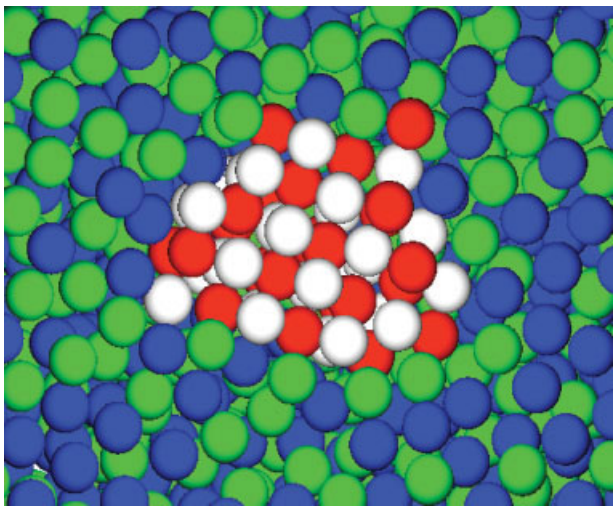

Figure 3. Computer graphics visualization showing a plane cut through a configuration from a Monte Carlo simulation of a crystallizing symmetric nonadditive binary hard-sphere mixture.[2]

The red and white spheres are those in the crystal nucleus and the blue and green spheres are those in the supersaturated mixture. The nucleus has the structure of a CsCl cocrystal. (Picture courtesy of S. Punnathanam.)

equimolar, congruent melting compound and indeed we see that the nucleus in this case has the substitutional order of the cocrystal, which has the CsCl structure.

Outlook

We have sketched some key ideas and concepts in the molecular thermodynamics of solid-fluid systems. This continues to be an area where there is a close link between fundamental science and engineering applications. It will be a fertile area for research for some time to come. Many research problems are deserving of additional attention and, while difficult to solve, promise significant breakthroughs. We highlight a few of these.

The central problem of molecular thermodynamics for systems with solid phases is being able to predict the structure and free energy of solid phases from the intermolecular potential or force field. As we discussed earlier the problem of polymorph prediction, especially for pharmaceuticals has generally focused on energy minimization, and does not include thermal fluctuations. Molecular simulations go beyond this by including fluctuations, even allowing for changes in the unit cell symmetry. On the other hand there is no guarantee that the structure associated with the lowest free energy is found by existing methodologies. This will continue to be a challenge for molecular modeling, as it is in most examples of self-assembly in condensed phase systems. Another problem that will continue to engage researchers in this field is the development of intermolecular potentials. Much more needs to be done in finding force fields that are accurate in both solid and fluid phases.

Cocrystals are an emerging area in pharmaceutical research[40] and an example of a growing research area known as crystal engineering. Predicting the stability of cocrystals for pairs of organic molecules is an especially good challenge for molecular modeling. Previous work discussed previously has focused on determining the phase behavior emerging from particular molecular interactions. This can be done in a qualitative way without detailed modeling of a specific system. Once we are dealing with a specific choice of molecules we have the problem of having a quantitative model for the intermolecular interactions. This is already a difficult — and to a large extent unsolved — problem even for pure systems. For mixtures we have to know the nature of the unlike, or AB, molecular interaction. This returns us to one of the classic problems of solution thermodynamics in chemical engineering: "How can we estimate binary interaction parameters?"

Modeling crystallization processes is an area of both growing interest and growing importance in chemical engineering, but progress is hindered by a generally poor understanding of the nucleation processes involved. We can look forward to significant impact from application of the Monte Carlo simulation techniques for studying crystal nucleation that we have described. Applications can be envisaged in areas ranging from pharmaceuticals to gas hydrates and, ultimately, even to inorganic materials, such as zeolites.

Applying molecular modeling to inorganic solid materials is a very promising area for research, especially in the context of using these methods to predict new materials and their properties. We have seen some commonalities in behavior between silica materials and molecular solids with hydrogen bonds, such as water and hydrates. In the future we can anticipate calculations of solid-state properties and crystal growth from solution that address the detailed chemical structure of the systems.

Acknowledgments

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