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Integrating Novel Examples into Thermodynamics Courses*

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The study of thermodynamics began around the 1820s, stimulated by the practical concerns of improving the efficiency of steam engines. While the principles underlying the conversion of thermal energy to mechanical work are now well established, thermodynamic laws have been applied to interpreting many other natural phenomena ranging from everyday life to cosmology. For contemporary chemical engineering, applications of thermodynamics are not limited to energy balances in flow processes, production of power from heat, or phase-equilibrium calculations for the design of efficient separation processes, as introduced in a typical undergraduate textbook or as encountered in the traditional chemical and petroleum industries. Today, assisted by statistical physics and molecular simulations, thermodynamics remains useful in numerous emerging areas of chemical engineering. To illustrate, this article provides three examples: application of thermodynamics in environmental protection, in the fabrication of nanostructured materials, and in the specification of conditions for protein crystallization. While these applications are significantly different from those introduced in standard undergraduate thermodynamics courses, the thermodynamic principles needed for the development of today's novel technologies are essentially the same as those used for the design of efficient heat engines.

INTRODUCTION

THE SCIENCE of thermodynamics was established about 180 years ago during studies of the efficiency of steam engines and of the equivalence of heat and mechanical work [1]. Application of heat-engine thermodynamics to chemical and phase equilibria was introduced in 1875 by a prominent American scientist, J. Willard Gibbs, who established the foundation of chemical thermodynamics. Before Gibbs, thermodynamics was primarily concerned with heat engines, i.e., the principles governing the conversion of heat to mechanical work and vice versa. Gibbs first recognized the connections between thermodynamics and equilibria in chemical reactions and in distributions of components among different phases. He invented a new thermodynamic function, chemical potential, which represents the driving force for mass transfer, as temperature does for heat conduction. Chemical potential provides an efficient and convenient way to describe the conditions of chemical and phase equilibria. Although Gibbs did not provide the practical relations between chemical potential and system temperature, pressure and composition as required in chemical engineering applications, Gibbs did solve the problems of chemical and phase equilibria in principle.

Thermodynamics has been an important subject in chemical engineering education because it contributes to the central goal of chemical industry: conversion of raw materials, such as crude oil, coal and air, into thousands of products in daily use; for example, plastic materials for computers, nylon in clothing, rubber for automobile tires, fertilizers for agriculture, paint for furniture, paper and ink for books and newspapers, pharmaceuticals, soaps and detergents, computer chips, and many more. Chemical engineering thermodynamics provides quantitative design guidelines that help address two essential questions: how does one select the right reaction conditions to produce the desired products, and how does one design efficient processes for the separation of useful reactants from raw materials or for the separation of desired products from undesired byproducts, and unreacted reactants [2]. Until the advent of modern computers, chemical engineers applied Gibbs' results using thermodynamic tables, graphs and empirical correlations. Now we solve chemical- and phase-equilibrium problems using commercial software such as that by Aspen, developed primarily from semi-empirical equations of state and local-composition models proposed in the period 1950–1975, nearly one hundred years after Gibbs invented the chemical potential.

In the past few decades, the frontiers of chemical engineering are no longer concerned with the design of efficient separation and reaction processes, but with biomedical engineering,

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environmental protection, and materials engineering, as emphasized in many graduate chemical-engineering programs around the country [3]. Unlike applications to traditional chemical-process design, application of thermodynamics in these new areas becomes less apparent and educational materials toward such applications are sparse [4]. Several major universities now offer at least one course on statistical thermodynamics that is oriented toward these new areas but, due to the lack of suitable examples with emphasis toward chemical engineering applications, in these courses statistical thermodynamics tends to be introduced as for students majoring physics or physical chemistry. Chemical engineering students are frequently overexposed to statistical-mechanics theory and to detailed mathematical derivations. Often, illustrative applications are limited to the thermodynamic properties of oversimplified systems (e.g., ideal gas) that are of little interest to chemical engineers. Chemical engineering students want (and need) up-to-date realistic applications.

The purpose of this article is to illustrate some relatively simple applications of thermodynamics in modern technology that can be used in the introductory lecture of advanced undergraduate/graduate thermodynamics courses. Such introduction is necessary because engineering students properly want relevance: they can be motivated to study hard science (thermodynamics) only if they are assured early on that their efforts and struggles will lead to something useful in the not-too-distant future [5]. Engineering students are motivated by giving them very early at least a preliminary notion of where and how particular scientific knowledge can be applied. Besides, the examples introduced here can also be used as 'open-ended' discussion topics or class projects in the senior undergraduate/graduate thermodynamics courses. Because of the complexity of realistic systems, applications of thermodynamics outside of the petrochemical industry require a different type of mindset. 'Open-ended' discussion sessions that focus on conceptual issues rather than algorithmic problem solving make the student more adaptable and appreciate better the broad applications of thermodynamics [6].

Unlike typical examples in standard thermodynamic textbooks, the examples discussed here emphasize applications of thermodynamic concepts to phenomenological analysis of complex, poorly understood systems, or to the design of processes or products [7]. Methods for quantitative calculations in these new areas are under development in numerous current research projects. Exercises on conceptual understanding of thermodynamics and application of thermodynamic analysis in real-world systems are often neglected in conventional thermodynamics courses. Many students fail to assimilate thermodynamic laws into more applied subjects such as biotechnology and advanced materials even though they are required to take a few thermodynamics courses in the curriculum [8].

DEVELOPMENT OF ADDITIVES FOR UTILIZATION OF CO_2

This is an example I often use for my undergraduate thermodynamics courses when I lecture the phase diagram of one-component fluids, after finishing the first and second laws of thermodynamics. The same topic is also used for a discussion session. The development of efficient additives for utilization of carbon dioxide remains an active research topic, but many students are fascinated by how simple thermodynamic analysis could be used to guide experimental design of relevant technology and they are often actively involved when the subject is used as an 'open-ended' discussion.

Although chemical industry has made impressive contributions to modern life and to our economy, many achievements of chemical engineers are not appreciated or even recognized by the public. For example, at social events, I am often asked about my wife's profession. When I mention that she is an engineer at IBM, the immediate response, frequently, is that she must be a software engineer, a computer engineer, or an electrical engineer. However, my wife is one of many chemical engineers working for IBM. Most of us have not given any thought to those who make the silicon wafers, CD/DVD diskettes, computer cases, and polymer films for photolithography, electromagnetic materials for input/output devices, and numerous other essential components in a modern computer. While the contributions of chemical engineering are not well known, our society is fully aware of the contrasting unpleasant aspects of the chemical industry [9]. Regulations concerning air and water pollution become increasingly strict every year.

Air and water pollution in chemical industry is often due to extensive use of organic solvents. These solvents are essential to dissolve solid and gaseous reactants required for chemical reactions. In addition, organic solvents are needed to control mixing, flow, and diffusion properties. Unfortunately, most organic solvents are volatile, flammable, and toxic. To prevent pollution, these organic solvents must be replaced by environmentally benign substitutes. For this purpose, liquid or supercritical carbon dioxide provides a promising alternative. With the exception of global warming, environmentalists have no opposition to CO_2 because it is plentiful in nature; it is non-toxic and non-flammable. Many people enjoy carbonated beverages such as Coca Cola. Indeed, from an environmental point of view, carbon dioxide is almost a perfect solvent except for the greenhouse effect. Nevertheless, even if all solvents in chemical industry were replaced by carbon dioxide, the additional CO_2 released to the atmosphere would be negligible compared to the CO_2 produced by power plants, automobiles, and other combustion sources.

Utilization of CO_2 requires, first, a good understanding of its physiochemical properties that can be best represented by the phase diagram. Figure 1 shows the phase diagram of carbon dioxide. The three lines schematically represent the vapor-liquid, vapor-solid, and solid-liquid coexistence curves, i.e., conditions when two phases are at equilibrium. As required by the Gibbs phase rule, these lines should intercept at a common point called the triple point where the three phases coexist. The vapor-liquid coexistence curve stops at the critical point where vapor and liquid phases are no more distinguishable. Carbon dioxide has a convenient critical temperature (31.1°C) and a relatively moderate critical pressure (7.38 MPa). Near the critical point, the solvent properties of CO_2 change dramatically with only subtle changes of temperature or pressure. At low pressure but not so low temperature, say ambient condition, CO_2 exists as a vapor phase. Lowering the temperature below the triple point pressure will lead to the formation of 'dry ice': i.e., if the solid carbon dioxide is left out in the room, it does not melt the way ordinary ice does; it sublimes. Upon the reduction of temperature above the triple point but below the critical pressure, CO_2 will be liquefied before freezing. The supercritical region is where both temperature and pressure are above the critical values. The supercritical CO_2 has a liquid-like density but a gas-like viscosity and diffusion coefficient.

The potential use of liquid or supercritical CO_2 as an environmentally benign solvent has been recognized for many years. A well-known example is provided by the removal of caffeine from coffee beans. The key advantage of using liquid CO_2 as an extraction solvent is that it is easily removed from the extracted product by simply lowering the pressure: when the pressure is released, it leaves the extracted solute free of CO_2. However, one major problem is that many interesting substances in the chemical industry have very low solubility in liquid or supercritical CO_2. For this reason, its utilization as a solvent is often limited. CO_2 has relatively inert physiochemical properties; it has no electrical dipole moment, a small average polarizability (similar to that of methane). These properties make carbon dioxide a poor solvent for most solutes.

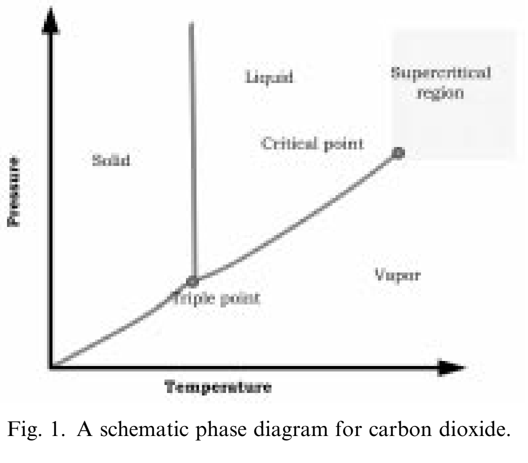

Fig. 1. A schematic phase diagram for carbon dioxide.

At given temperature T and pressure P, the solubility of a liquid or a solid in CO_2 is determined by the Gibbs energy of mixing, ΔG. For a system at constant T and P, the second law of thermodynamics requires that its Gibbs energy reaches a minimum at equilibrium. The Gibbs energy of mixing includes an enthalpic contribution that is related to system energy and volume, ΔH, and an entropic contribution ΔS that is related to the changes in the degrees of freedom of individual molecules:

$$\Delta G = \Delta H - T\Delta S = \Delta U + P\Delta V - T\Delta S \quad (1)$$

where ΔU stands for the internal energy of mixing and ΔV is the change in volume. To form a stable mixture, ΔG must be negative and the total Gibbs energy as a function of the composition shows a minimum. Dissolution of a solute in a solvent is often favored by the entropy of mixing ΔS, because it is positive in most cases. However, the extent of solubility is also heavily influenced by the internal energy of mixing ΔU, which reflects the change in molecular interactions created by the mixing process. (The physical meaning of internal energy is the energy related to the motion and potential of molecules.) Because the attraction among solute molecules in a condensed phase is normally much stronger than that when they are dispersed in compressed CO_2, the change in internal energy, ΔU, is often positive and dominates the right-hand side of Equation (1). This positive contribution to the Gibbs energy of mixing disfavors the dissolution of a condensed solute in CO_2.

Solubility in CO_2 can be enhanced by minimizing the Gibbs energy of mixing. One common way to achieve that is by increasing the pressure because the volume of mixing ΔV is typically negative; an increase in pressure helps raise solubility through the $P\Delta V$ term on the right-hand-side of Equation (1). Besides, because CO_2 is normally more compressible than the condensed solute, isothermal compression enhances van der Waals attraction between the solvent-solute molecules, minimizing the energy lost with dispersing solute molecules. As a result, upon compression, there is a favorable decrease in ΔU. However, very often increasing pressure is not a choice because from an operational point of view, high pressure also means high cost and concerns about safety. A better way to improve solubility might be by adding small amounts of additives, highly soluble in CO_2, that interact favorably with the desired solute molecules. For example, a perfluoroalkane is a good additive for the dissolution of many solutes because it is readily soluble in liquid carbon dioxide while it interacts favorably with many organic molecules [10]. High solubility of fluorinated molecules in CO_2 is related to weak intermolecular attraction and a subsequent low internal energy of mixing. Fluorochemical-containing carbon dioxide is now used in the dry-cleaning industry to replace the conventional solvent, perchloroethylene (often called 'perc'), which is known to be harmful to people because it damages the nervous system, liver and kidney. The advantage of CO_2-based dry cleaning is not only that it is good for environmental reasons; this new technology also provides more efficient cleaning.

Regrettably, fluorochemicals are normally too expensive for large-scale industrial processes. Recently, Beckman and colleagues at the University of Pittsburgh developed CO_2-philic copolymers that are stable in CO_2 but about a hundred times cheaper than fluorochemicals [11]. These copolymers can help CO_2 to dissolve significant amounts of wide varieties of substances, including water and biomacromolecules. This discovery by Beckman and coworkers may remove one of the major hurdles for extensive application of CO_2 in the chemical industry.

The discovery by Beckman *et al.* was motivated by phenomenological thermodynamic analysis. Beckman recognized that, as indicated in Equation (1), the dissolution of a polymer into solvent requires a favorable energy of mixing, i.e., the polymer must exhibit sufficient attraction to the solvent molecules. Because the energy of mixing is positive for most systems with only non-polar interactions, the best way to minimize the energy term in Equation (1) is to identify chemicals that yield zero mixing energy, such as CO_2 themselves. Further, Beckman recognized that solubility can also be enhanced by increasing a positive entropy of mixing, i.e., the polymers in CO_2 have more degrees of freedom than in the condensed state. Entropy represents the freedom of molecules.) To achieve that, the polymer chains should be flexible enough to maximize the number of possible polymer configurations in the solvent. Following these simple thermodynamic considerations, Beckman and coworkers found that copolymers, created by linking polyether (flexible) and polycarbonate groups (essentially CO_2), provide the desired dual roles: the polyether groups provide flexibility while the polycarbonate groups provide favorable attraction with CO_2 molecules. The CO_2-philic copolymers can be chemically bonded to functional groups (e.g., $-NO_2$, $-CN$, $-OH$) that interact favorably with solute molecules of practical interest. These surfactant-like, modified copolymers can then be added to liquid or supercritical CO_2 for increasing the solubility of desired substances in CO_2. Beckman's work indicates that chemical principles, coupled with thermodynamics, can contribute toward the solution of a contemporary problem in environmental technology.

Are there any other ways to increase the solubility? Or can one formulate the problem in a different way? In a senior/graduate thermodynamics class, very often the students may come with out more quantitative analysis based on the thermodynamic equations for vapor/liquid or vapor/solid equilibrium. One may consider the same problem by focusing on the vapor pressure of polymer instead of the Gibbs energy of mixing. Anyway, the answer is wide open to the students. During the discussion, the students are interested in this problem not because they are able to learn new thermodynamics but instead they see that thermodynamics may provide useful insights for solving practical problems.

HARD SPHERES FOR SOFT MATERIALS

I often use this example to illustrate the physical meaning of entropy when I lecture undergraduate thermodynamics and the same example is used in graduate thermodynamics to illustrate its application for materials fabrications, one important aspect of modern chemical engineering.

In recent years, colloidal dispersions have been used extensively in many rapidly advancing areas of material sciences, such as in the fabrication of photonic crystals, catalysts, membranes, and ceramics [12]. Efficient assembly of colloidal particles for materials applications requires theoretical guidelines for controlling colloidal stability and for selecting optimal solution conditions that lead toward useful structures.

The simplest thermodynamic model of colloidal dispersion is given by hard spheres, in which the colloidal particles do not interact except they cannot occupy the same space defined by the particle size. Despite its simplicity, the hard-sphere model provides a fair representation of many practical colloids because the range of interaction between colloidal particles is often much smaller than the particle diameter. Besides, the dispersing medium can be adjusted such that the attraction between colloidal particles can be effectively minimized.

The hard-sphere model has a long history. More than two thousand years ago, Greek philosopher Democritus claimed that the world was made of hard atoms that would never break [13]. Throughout history, much of the research on hard spheres has been concerned with the efficiency of packing, i.e., the arrangement of hard spheres such that they occupy a minimal volume. In one instance, Johannes Kepler attempted to solve the problem using geometry [13]. He argued that the most efficient way to pack uniform hard spheres is by arranging them in a face-centered-cubic (fcc) lattice like that often seen in grocery stores for displaying oranges. Kepler did not prove his conjecture; indeed, a mathematical proof is so difficult that it has remained unsolved for nearly four centuries [14]. Packing of hard spheres was of great interest a few hundred years ago for efficient loading of cannon balls in a warship. Now, material chemists employ hard-sphere-like nanoparticles for the fabrication of nanostructured materials. An excellent example is reported recently by Blanco and coworkers where hard-sphere-like colloids are used to fabricate photonic crystals by self-assembly. (Photonic crystals are analogous to semiconductors; whereas the latter control the flow of electrons, photonic crystals can be used for controlling the propagation of light.) The novel crystal is potentially useful for controlling infrared signals in telecommunications [15].

The self-assembly of colloidal particles for materials applications is essentially the same as the packing of billiard balls. While geometry is useful for solving the packing problem, thermodynamics is essential for modern materials applications to identify stable self-assembled structures from colloidal dispersions. For materials fabrication, a more general question related to Kepler's conjecture is whether a system of nanoparticles is ever crystallized; and if yes, what is the most stable structure? For hard spheres, the first part of this question was answered positively about fifty years ago based on molecular simulations [16] but the second part of the question was solved only recently [17].

In the context of thermodynamics, the search for optimum packing, i.e., the packing of hard spheres, requiring a minimum volume, is equivalent to the identification of a stable structure that gives maximum entropy, or equivalently, minimum Gibbs energy. The second law of thermodynamic requires that at equilibrium, an isolated system (constant volume and energy) has maximum entropy, or equivalently, (at constant temperature and pressure), has a minimum Gibbs energy. For a hard-sphere system, energy is irrelevant because, by definition, there is no interaction between hard spheres except that they cannot overlap. Entropy of a hard-sphere system then, is directly related to the free volume accessible to individual particles.

To identify a fluid-solid transition of hard spheres, we need equations to describe volumetric properties of both the fluid and solid phases. Volumetric properties of a hard-sphere fluid can be represented by the Carnahan-Starling equation of state [18] which relates pressure P to the number density of particles ρ:

$$\frac{P}{\rho kT} = \frac{1+\eta+\eta^2-\eta^3}{(1-\eta)^3} \tag{2}$$

where k is the Boltzmann constant and T is the Kelvin temperature. The packing fraction $\eta = \pi\rho\sigma^3$ represents the fraction of total volume occupied by hard spheres with diameter σ. The volumetric properties of a hard-sphere solid can be represented by the cell model [19]:

$$\frac{P}{\rho kT} = \frac{1}{1-(\eta/\eta_c)^{1/3}} \tag{3}$$

where $\eta_c = \pi\sqrt{2}/6$ is the packing fraction when all spheres are in contact with their immediate neighbors (i.e., close packing). Whereas the Carnahan-Starling equation of state, derived from statistical mechanics, cannot be explained by geometry, the cell model for a crystalline solid is conceptually simple, i.e., all particles are confined within independent, free spaces where each free space is centered around a lattice site. (For calculation of the freezing and melting densities, the classical cell model must be modified by allowing particles to access the free space of neighboring cells. While this modification does not affect the equation of state, it introduces a factor of $-\ln 8$ in the reduced chemical potential.)

Figure 2 shows schematically the pressure P of a hard-sphere fluid and of a hard-sphere fcc crystal. At equilibrium, the fluid and solid phases have the same pressure and the same chemical potential. The chemical potentials for hard-sphere fluid and solid are given by, respectively:

$$\frac{\mu_F}{kT} = \ln(\rho\Lambda^3) + \eta\frac{8-9\eta+3\eta^2}{(1-\eta)^3}$$

$$\frac{\mu_S}{kT} = \ln(\rho\Lambda^3) + \frac{1}{1-(\rho/\rho_c)^{1/3}} - 3\ln[1-(\rho/\rho_c)^{1/3}] - \ln 8$$

where Λ denotes thermal wavelength.

The Carnahan-Starling equation and the cell model predict that at freezing-melting equilibrium, the packing fractions of the fluid and the solid phases are, respectively, 0.492 and 0.555, in close agreement with those from molecular simulation [16].

At first glance, the freezing of hard spheres appears counterintuitive because conventional wisdom tells us that formation of a solid phase requires intermolecular attraction. Indeed, when Alder and Wainwright first reported their simulation results in 1957, many scientists, including a few

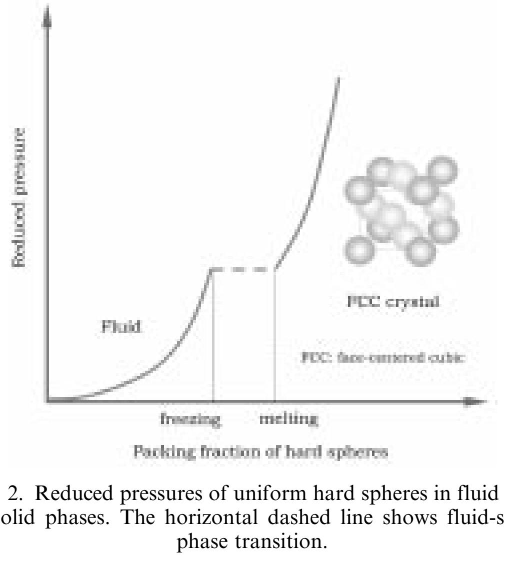

Fig. 2. Reduced pressures of uniform hard spheres in fluid and in solid phases. The horizontal dashed line shows fluid-solid phase transition.

Nobel-Prize laureates in theoretical physics, suspected an error in their calculations. In the absence of attraction, the fluid-to-solid phase transition implies that, at sufficiently high density, hard spheres in an ordered (solid) state have higher entropy than when they are in a disordered (liquid) state. (This comparison applied when fluid and solid have the same density. When a hard-sphere fluid coexists with an fcc crystal with a density higher than that of the fluid, the molar entropy of the fluid phase is higher than that of the solid phase. In that case, the entropy difference is due to the change in density.) This result contradicts the common understanding of entropy that, as a system becomes more ordered the entropy decreases.

To facilitate a quantitative analysis, Fig. 3 compares the entropy of the hard-sphere fluid with that of the hard-sphere solid as calculated from the Carnahan-Starling equation of state and from the cell model. At low packing fraction ($\eta < 0.520$), the entropy in the fluid phase is higher than that in the solid phase, but the opposite is true when $\eta > 0.520$.

Figure 3 indicates that at sufficiently high density, the entropy of hard spheres in the ordered (solid) state is indeed higher than that in the disordered (fluid) state. (Here the fluid and solid are compared at the same particle number density. The fluid is unstable when its entropy is lower than that of the solid.) As an intuitive analogy, imagine a busy parking lot where all the cars are parked at random; gridlock prevails and no car can move. In this scenario, each car has few degrees of freedom. Because entropy provides a measure of the degrees of freedom, the gridlocked system has low entropy. However, for the same number of cars in the same parking lot, every car can move freely if all the cars are in marked parking spaces. Freezing of hard spheres follows the same reasoning: when the density is sufficiently high, each hard sphere has a larger free volume in an fcc lattice compared to that of a random state (fluid) at the same density; subsequently, the crystalline system has a higher entropy. At the fluid-solid coexistence point, the entropy of freezing is about –1.4 J/mol. In this case, the solid phase has lower entropy because the phase transition occurs at constant T and P and it is accompanied by a negative change in molar volume $\Delta v = v^s - v^l < 0$.

This example illustrates that entropy does not necessarily represent 'disorder' or 'randomness' because at the same packing fraction, well-packed hard spheres (ordered in common sense) have entropy larger than that when they are randomly packed. A similar example has been reported, for educational purposes, by Bartell on the freezing of ^{3}He at very low temperatures ($T < 0.2$ K) [1]. Many students like 'freedom' better than 'disorder' or 'randomness' because not only does it represent a more faithful definition but also at the end, they realize entropy can be a good thing!

Although research on the packing of hard spheres has a long history, direct experimental investigations and utilization for practical applications were achieved only a few years ago, by precise control over interaction between colloidal particles. One way to prepare a real hard-sphere system is by a colloidal dispersion of uniform poly(methylmethacrylate) spheres suspended in a mixture of decalin and tetralin. In this colloidal dispersion, van der Waals attraction between colloidal particles is minimized by matching the refractive index of the particles to that of the solvent. The van der Waals (dispersion) attraction between colloidal particles is approximately proportional to $(n_c^2 - n_s^2)^2$ where n_c and n_s stand, respectively, for refractive indices of colloidal particles and solvent.

To minimize the effect of gravity on the phase behavior of colloidal dispersion, this self-assembly of colloidal particles was performed at an expensive laboratory: the US space shuttle Columbia [20]. As predicted by theory and by molecular simulation, hard-sphere-like colloidal dispersions indeed crystallize in outer space when the colloid number density is sufficiently high. Despite its simplicity, the hard-sphere model provides for many essential aspects of colloidal phenomena.

The conceptual part of this example is easily accepted by most undergraduate students. However, a quantitative analysis using the equations of states is more suitable for graduate classes after some basics on statistical mechanics have been introduced.

PROTEIN CRYSTALLIZATION

This example is suitable for senior undergraduate or graduate students after the concept of osmotic equilibrium has been introduced. It illustrates the similarity between the phase diagram of colloids and that for a simple fluid such as argon. Because a large number of chemical engineering students are interested in biotechnology, I use this example also for the introductory lecture to show the application of thermodynamics in

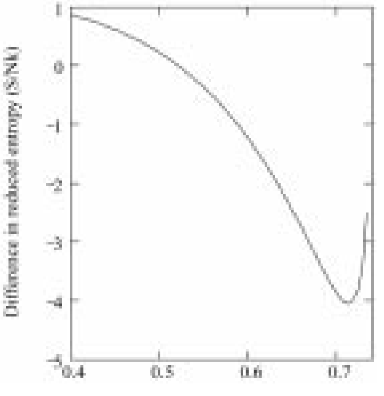

Fig. 3. The difference in reduced entropy (S/Nk) between hard-sphere fluid and solid at the same density as predicted by, respectively, the Carnahan-Starling equation of state and by the cell model.

bioengineering. Even though the concepts are relatively simple, colloidal thermodynamics is unfortunately often neglected in most thermodynamics texts.

A major effort in current biotechnology is to identify the three-dimensional structures of proteins as well as their interactions with other biomacromolecules. These structures are essential for understanding protein functions and rational drug design, i.e., systematic development of effective therapeutic agents. Using X-ray diffraction, the structure of a protein molecule can be obtained but only when the protein is crystallized. Although the experimental procedure for protein crystallization is relatively straightforward, crystallization only occurs under highly specific conditions that depend on numerous experimental parameters, e.g., the chemistry and concentration of additives, temperature and pH. In the absence of information on the phase behavior of protein solutions, protein crystallization requires tedious and time-consuming trial-and-error experiments.

Reliable molecular-thermodynamic models for both protein solutions and crystals are essential for predicting suitable conditions for protein crystallization. As yet, a truly fundamental model does not exist, but thanks to much research on thermodynamic properties of protein solutions, we now have some simple criteria that may significantly reduce the number of crystallization experiments. A so-called 'crystallization window', established by thermodynamic analysis of successful crystallization conditions in protein solutions [21] represents one such criterion.

Figure 4, first reported a few years ago by George and Wilson [21], relates successful crystallization conditions to the osmotic second virial coefficients for about twenty proteins. (The osmotic second virial coefficient is a thermodynamic quantity that is closely related to the interaction potential between dissolved protein molecules. It can be easily measured using standard methods such as membrane osmometry or low-angle light scattering.) A *negative* osmotic second virial coefficient means that the overall interaction between dissolved protein molecules is *attractive*; the more negative this osmotic second virial coefficient is, the stronger the attraction. Figure 4 clearly indicates that crystallization only occurs when there is *moderate* attraction between dissolved protein molecules. If the attraction is too strong, protein molecules aggregate and precipitate from the solution in amorphous form. On the other hand, if the attraction is too weak, protein solubility *is* too high to achieve the super saturation needed to produce the crystal.

While the crystallization window was first established empirically, thermodynamic analysis provides a rational explanation and, more important, useful insights on the phase behavior of protein solutions [22]. Figure 5 shows schematically the phase diagram of a protein solution as observed in experiments and in theoretical calculations [23, 24]. In this figure, the horizontal axis represents protein concentration and the vertical axis represents the reduced second virial coefficient, that is, the osmotic second virial coefficient divided by the protein's molecular volume. The fluid-fluid coexistence curve, shown as the dashed line, exists beneath the freezing and melting lines (represented by the solid lines) and is therefore metastable. This fluid-fluid coexistence curve resembles that for the vapor-liquid equilibrium in a simple fluid such as argon but, unlike argon, it exists underneath the fluid-solid equilibrium lines. This is because the range of attraction between protein molecules is shorter than that between simple molecules. On the left side of the freezing line, a protein solution exists as a stable liquid phase, and on the right side of the melting line, the protein solution becomes a colloidal crystal; in between, the system is unstable.

Using only thermodynamic considerations, a protein solution will crystallize once its concentration exceeds the freezing point. However, due to slow kinetics for crystal formation, a supersaturated protein solution often yields an amorphous phase; the dynamics of phase separation being so

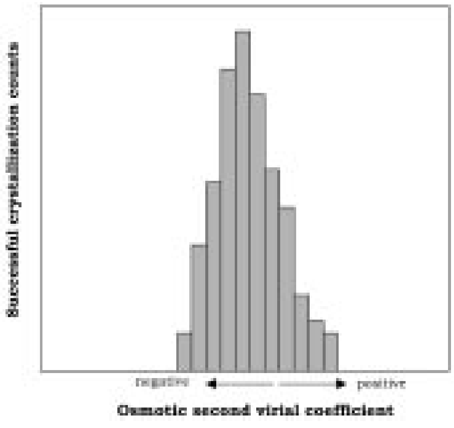

Fig. 4. An empirical correlation between successful crystallization condition and the osmotic second virial coefficient of protein solutions.

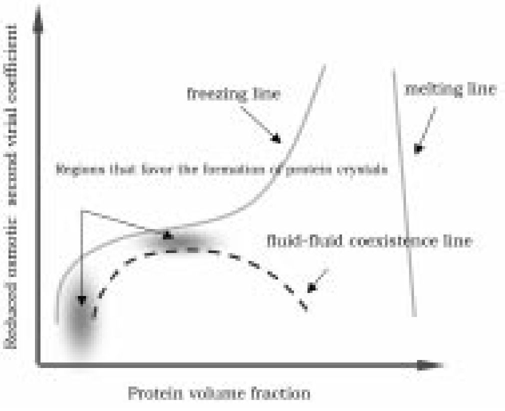

Fig. 5. A generalized phase diagram for protein (colloid) solutions. Shade areas indicate favorable crystallization conditions.

fast that protein molecules do not have sufficient time to orient themselves to form a crystal. While thermodynamics itself cannot predict the dynamics of phase separation, it does suggest that crystallization will be most favorable at two regions, as shown by shaded areas in Figure 5. One region is near the critical point of the metastable fluid-fluid phase transition where the long-range concentration fluctuations favor crystal formation. (Near the critical point of a phase transition, long-range fluctuations mean that the concentrations at different positions in the system are highly correlated; that is, they depend on each other.) The other region is between the freezing line and the fluid-fluid coexistence curve where crystallization proceeds through an intermediate state; a liquid droplet at high protein concentration is formed prior to crystallization. The favorable protein crystallization conditions predicted by thermodynamics have been recently confirmed by experiments [25].

Both experimental and theoretical studies suggest that the phase diagrams of a wide variety of protein solutions and colloidal dispersions may collapse into one *master* diagram when the data are plotted as the reduced osmotic second virial coefficient against dimensionless protein concentration. Such a master phase diagram is valuable to biochemists for identifying favorable experimental conditions to grow protein crystals. Whereas a *master* phase diagram is well known for the vapor-liquid coexistence of one-component simple fluids as suggested by the theory of corresponding states, the similarity of fluid-solid equilibrium for colloidal dispersions and protein solutions was discovered only recently [24].

CONCLUSIONS

Thermodynamics courses have been part of standard undergraduate and graduate curricula in chemical engineering for about 60 years. In recent decades, chemical engineering has expanded into numerous new areas. While the classical topics remain important for chemical engineering education because they are useful for applications in traditional chemical and petrochemical industries, effective education in chemical engineering thermodynamics must also introduce new examples reflecting the recent advances. However, it has been a very difficult task to introduce modern applications of thermodynamics to chemical engineering majors.

The challenge is twofold. First, traditional materials in statistical mechanics and molecular modeling as introduced in physics or chemistry courses are remote from evident applications in chemical engineering. Second, most statistical-mechanical theories and simulation techniques that are directly (or potentially) useful for engineering applications were established only recently. Many, probably most, chemical engineering educators are not familiar with them and those that are have had difficulty in using that familiarity in undergraduate courses. One major reason for this difficulty is the lack of suitable examples. The purpose of this article is to provide chemical engineering students (and educators) up-to-date realistic applications that may be incorporated into lectures or discussions.

Many years ago, Albert Einstein said, 'Thermodynamics is the only physical theory of universal content which I am convinced will never be overthrown, within the framework of applicability and of its basic concepts'. There can be no doubt that thermodynamics will remain useful in chemical engineering, no matter what chemical engineers do in the future. As indicated in the introduction, the history of thermodynamics began with practical concerns related to the generation of mechanical power. Later developments were directed toward applications in production of common chemical products. The examples shown in this article illustrate phenomenological applications of thermodynamics to three new areas in chemical engineering: environmental protection, advanced materials and biochemical engineering. More quantitative application of modern thermodynamics, statistical mechanics in particular, can be found in a recent review by Deem [26].

Einstein also said, 'God is subtle but not malicious'. Because God is subtle, nature is difficult to understand. But how do we know that God is not malicious? Professor John Prausnitz from the University of California at Berkeley, once gave an excellent interpretation of Einstein's uncanny words: 'God is not malicious because he has given us a chance to understand. He has given us thermodynamics'[2].

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