RSC Publishing Faraday Discussions

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Journal:	*Faraday Discussions*
Manuscript ID:	FD-ART-04-2015-000042
Article Type:	Paper
Date Submitted by the Author:	27-Apr-2015
Complete List of Authors:	Myerson, Allan; Massachusetts Institute of Technology, Chemical l Engineering

FD Nucleation Concluding Remarks

Allan S. Myerson

Massachusetts Institute of Technology - Chemical l Engineering

77 Massacusetts Avenue 66-568 , Cambridge, Massachusetts 02139

United States

Abstract

Crystallization from solution is a crucial process used in the manufacture of a wide variety of materials. The first step in the crystallization process in the birth of a new crystalline phase which is known as nucleation. Nucleation plays a key role in determining the results of any crystallization process with respect to the size, shape and crystal form obtained. Classical nucleation theory does not adequately explain the crystal nucleation process. Work described in the literature and at the Faraday Discussion describe more complex nucleation mechanism which are generally known as two step nucleation models. In addition as most nucleation is influenced by dust dirt and container surfaces, the importance of heterogeneous nucleation and the use of templates to accelerate nucleation and influence crystal form are promising methods for the study and control of nucleation. It is also clear from the Faraday discussion that interest in this topic has grown and new and novel experimental and modeling approaches are being used for the study of crystal nucleation from solution.

A. Introduction and Motivation

Crystallization from solution is used in the manufacture of a wide variety of materials in the chemical, pharmaceutical and food industry. The goal of the crystallization process is the production of a material with the desired purity and process yield while obtaining crystals of the desired size, shape, and crystal form. In a crystallization process a solution containing the species to be crystallized undergoes a change of state so as to form a supersaturated solution in which crystals will nucleate and then grow. Nucleation plays a decisive role in determining the crystal form and size distribution. Thus, improved of control of crystallization cannot be

achieved without understanding the fundamentals of nucleation. However, our understanding of the nucleation process is still developing and no accurate description of the process exists.

All theories and descriptions of the nucleation of crystals postulate the existence of molecule clusters (or concentration fluctuations). In 1988 I gave a lecture at Gordon Conference on Crystal Growth (Colby Sawyer College, New Hampshire) which was entitled "Structure of Supersaturated Solutions". At the beginning of the lecture I asked a series of questions about pre-nucleation clusters which are listed below:

1. Do clusters they exist?
2. What is their size and size distribution?
3. What is the structure of the cluster—lattice arrangement, amorphous or something intermediate?
4. Are the clusters solvated?
5. How do the clusters become crystalline nuclei?

While there is a fairly general consensus that clusters exist (Question 1), the presentations and discussions at the conference indicate that we are still asking Questions 2-5 and that these issues are under study using both experimental and computational methods.

B. Nucleation Theory: Classical and Two Step Models

Classical nucleation theory (CNT) is the most widely used theory which describes the nucleation process. CNT was derived for the condensation of a vapour but is applied to the nucleation of crystalline solids from solution.

The thermodynamic description of this process was developed by Gibbs, who defined the free energy change required for cluster formation (ΔG) as sum of the free energy change for the phase transformation (ΔG_v) and the free energy change for the formation of a surface (ΔG_s). The first describes the spontaneous tendency of a supersaturated solution to change from solution to the more stable solid state resulting in a negative value for ΔG_v. The introduction of a solid/liquid interface increases the free energy by an amount proportional to the surface area of the cluster. The growth of clusters is thus a competition between a decrease in ΔG_v, which favours growth, and an increase in ΔG_s, which favours dissolution resulting in the classic free energy diagram for nucleation and the concept of the critical size as shown in Figure 1.

CNT has a number of major assumptions (1) but I would like to focus on the assumption which relates to the crystalline state. CNT models clusters as spherical droplets having uniform interior densities and sharp interfaces with the density of the droplet independent of size and equal to the macroscopic density of the bulk condensed phase. For crystallization from solution, this assumption requires that the molecular arrangement in a cluster is identical to that of the crystal produced.

Given the wide range of molecules which form crystal nuclei from solution (ionic species, organic molecular crystals, proteins) which form lattice structures with varying degrees of symmetry, this assumption at best cannot describe nucleation of all crystalline materials and at worst is incorrect in virtually all cases involving the formation of crystalline nuclei from solution.

The flaws of CNT when applied to nucleation of crystals from solution has led to theories which postulate more complex routes to nucleation. These routes are generally referred to as two-step

nucleation, but actually encompass a number of potential mechanisms (2,3). A general description of these models involves a clustering step in which the molecules are not in the lattice structure of the final crystalline solid followed by a rearrangement step into an ordered crystalline structure as shown in Figure 2. The organization step is proposed as the rate-determining step, which is consistent with the observation that the nucleation from solution takes longer time as the complexity of molecules increases since it would be more difficult for more complex molecules to arrange themselves in the appropriate lattice structures due to their high degree of conformational flexibility. In addition, the existence isolated site and channel hydrates whose structures are stabilized by solvent molecules requires the active involvement of solvent molecules in the nucleation process further complicating the mechanism.

In discussing work done related to the two step nucleation mechanism, it is convenient to divide the studies into three groups based on the types of compounds studied. These group are organic molecular crystals, inorganic (ionic) crystals and protein crystals.

Experimental evidence of a two- step nucleation mechanism of organic molecular crystals was provided through a phenomenon known as non-photochemical laser induced nucleation (NPLIN) (4, 5). Supersaturated solutions of small organic molecules exposed to the laser nucleate much faster compared with control solutions. In addition, polymorphs of glycine can be preferentially nucleated by changing the polarization state of the laser. Linear and circularly light appears to influence in the alignment of the molecular building blocks of the two polymorphs. NPLIN appears to work through rearrangement of clusters which are not yet in the correct lattice structure thus increasing the rate of the second step in the two step process.

Studies of protein nucleation indicate that the first step in the nucleation process is the formation of a dense protein liquid droplets. Crystalline nuclei then form within these droplets. This has been demonstrated for a variety of protein systems (6, 7). The size of these dense liquid protein clusters varies from varies from ten to several hundred nanometers and thus are experimentally observable. They have low volume fractions (0.1%) and extended lifetimes.

While a variety of inorganic systems have been examined experimentally, calcium carbonate has been extensively studied because of its importance in biologic systems (8, 9). Novel experimental studies using Cryo-Transmission Electron Microscopy (Cryo-TEM) and Scanning Electron Microscopy (SEM) (8, 9) have reported liquid like precursors which have been described as liquid like and amorphous. Further experimental studies have provided evidence for stable CaCO3 clusters with diameters as large as 2 nm. The authors suggest that these large clusters coalesce and then rearrange to form nuclei.

The studies discussed as well as the work presented at this meeting demonstrate the complexity of the nucleation process as well as the significant progress made in attempting to elucidate nucleation mechanisms.

C. Heterogeneous Nucleation

Heterogeneous nucleation refers to nucleation which is influenced by the presence of dust, dirt or container surfaces. Generally these decrease the nucleation induction time at a given

supersaturation. Virtually all experiments which involve studies of nucleation and crystallization involve heterogeneous nucleation (except for methods as levitated droplets and isolated droplets in microfluidic devices).

Surfaces can influence nucleation by through epitaxy where the molecules in a cluster near the surface are ordered by the surface into their lattice structure. One way this can be done is through the use of a crystalline substrate which provides a lattice match to the crystallizing species (10). This has be shown to both reduce nucleation induction time and allow control of the polymorph nucleated. Functional group chemistry can also be used to reduce nucleation induction time and control polymorphism. The use of Self Assembled Monolayers (SAMs) can be used to alter the crystallographic plane nucleated on a surface as well as influence the polymorph obtained (11). The ability to functionalize a surface with the desired properties and their highly ordered structure makes self-assembled monolayers attractive templates for nucleation. Amorphous polymer surfaces can also be used a heterogeneous nucleating agents and can reduce induction time and influence the polymorph obtained. Recent work in our laboratory has demonstrated that polymers imprinted with angular nanopores can further enhance nucleation through angular matching of the nanopore angles to the angles between major crystallographic planes of the crystalline material (12, 13).

Heterogeneous nucleation complicates nucleation studies as care must be made in developing appropriate repeatable experimental techniques. In addition, the stochastic nature of the nucleation process requires that a statistically significant number of experiments be performed.

Computational Studies

In addition to experiment, computational studies can aid in our understanding of the crystal nucleation process. The difficulty in applying molecular simulations to the nucleation process is large time scale and the large number of molecules involved making the simulations very long and computationally expensive. In addition, models used must be accurate enough to model real systems. A number of groups are developing methods to attempt to address the problem of time scale by developing novel sampling methods (14-16). Computational methods generally can be categorized as biased and unbiased. Biased methods use functions which are assumed to be governing parameters of the nucleation process. The difficulty of biased methods is whether the functions used are correct. Unbiased methods sample a system without imposing collective variable or limiting their motion however limit the complexity of the problem that can be studied. Improved computational methods and faster computing should continue to aid in the development of computational methods.

Conclusion

The study of crystalline nucleation has increased dramatically in recent years. In addition, new experimental methods and improved instrumentation has greatly improved our ability to probe this complex phenomenon. Computational methods are also improving through new methods and faster computers and can add to our understanding of the nucleation process. The quality of the work presented at the meeting including excellent posters along with the robust discussions make me optimistic about future advances in our understanding of this complex problem. I would like to thank the Scientific Committee and the RSC for their excellent work in organizing and running this meeting.

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Figure 1. Free energy diagram for nucleation

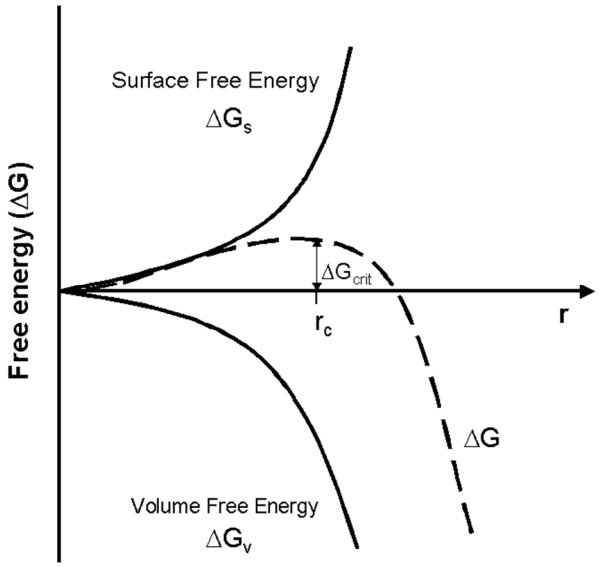

Figure 2. Classical vs. Two Step Nucleation Models