Nucleation of Crystals from Solution

Mechanisms of precipitation are fundamental to analytical and physiological processes.

Alan G. Walton

Cloud condensation, photography, polymer crystallization, metal solidification, bubble formation, and bone growth are but a few isolated examples of nucleation phenomena, in that each represents the birth of one phase from another. Historically, the theory underlying vapor condensation was the first to receive experimental verification. Although substantially the same theoretical principles were believed applicable to the more complicated crystal formation process, it has only been relatively recently that correlation between theory and practice has been achieved in this latter area.

Some of the practical difficulties arising in the study of crystal nucleation from solution are concerned with the elucidation of the relative roles of crystallization, dissolution, and agglomeration in the overall precipitation scheme. For these and other reasons the mechanism of the primary processes in precipitation from solution is to some extent obscured, and as a consequence the interpretation of experimental data has often been contradictory. Many investigators have agreed about the qualitative description of events, but there is continuing disagreement concerning quantitative measurements. Even so, the mechanism of the nucleation process is now being elucidated as a result of studies in several branches of physics and mathematics. Several excellent reviews of the principles of nucleation theory are available (*1*); some of the main points are restated here to show the fundamental aspects of nucleation and the crucial observations directly relating to the process.

Cluster Formation

The interaction between ions and between molecules which leads to cluster formation and eventually to the evolution of crystals has been likened to a chemical reaction. In the chemical reaction the activation energy is a barrier which must be surmounted before products may be formed; similarly, the energy barrier to nucleation must be overcome before crystallization can occur. One result of this energy barrier is the necessary creation of some degree of supersaturation before spontaneous crystallization will occur.

In solutions at normal temperature the molecules or ions of solute are in constant motion and consequently are often within the sphere of influence of another molecule or ion. Hence groups of molecules or ions are always present when the solute is present in any, other than trivial, concentration. There is, though, at the onset, a distinct difference between the behavior of ions and that of molecules. Because of their ionic charge, ions tend to associate with neutral or oppositely charged groups, whereas uncharged molecules do not suffer this restriction.

Prior to nucleation there is continuous formation and dissolution of ionic or molecular clusters in equilibrium with all other clusters. If the concentration of solute ions or molecules is large enough the clusters become sufficiently large to become consolidated into small crystallites, whereupon the supposedly irreversible crystal growth ensues.

The largest cluster which may exist before spontaneous crystallization is usually referred to as the critical cluster, so that in terms of molecular aggregation the process may be represented as follows:

$$\begin{aligned}
&A + A \rightleftarrows A_2\\
&A_2 + A \rightleftarrows A_3\\
&A_{x-1} + A \rightleftarrows A_x \text{ (critical cluster)}\\
&A_x + A \xrightarrow{\text{Nucleation}} A_{x+1}\\
&A_{x+1} + A \rightarrow \text{crystal growth}
\end{aligned}$$

Factors Affecting Nucleation

The formulation and refinement of nucleation theory have become mathematically complex, and considerable controversy exists over the applicability of such theory. However, it is possible to understand several of the problems by a very elementary exposition as follows.

If the critical cluster is regarded as the smallest possible crystallite and the largest ionic cluster, then this cluster must be in metastable equilibrium with its surroundings. This means that very small crystallites must be more soluble than larger crystals.

Until very recently the theoretical support for the increase of solubility with decrease in crystal size was based, by analogy, on the so-called Gibbs-Kelvin equation, which related the vapor pressure of small drops to the radius of curvature of the drop. It is, though, apparent that crystals do not in general have curved surfaces, and therefore the analogy might be inapplicable. C. A. Johnson (*2*) has now shown theoretically that faceted crystals do show increased solubility with decrease in size, and this has consequently strengthened the formulation of the nucleation theory for crystals.

The relation then, which is appropriate to the unstrained cubic crystal of size larger than about 100 Å, is

$$\log_{10} a/a_0 = 4v\bar{\gamma}/2.303nkTx \qquad (1)$$

where a is the solubility of a crystal of cube side length x, a_0 the theoretical solubility of an infinitely large crystal, v the molecular volume, n the number of ions per molecule ($n = 1$ for molecular crystals), and $\bar{\gamma}$ is the interfacial energy of the crystal, a parameter which will require further consideration later.

In that nucleation and crystal growth are spontaneous processes which lower the energy of the growing particle (the system receives the energy in the form of heat) and the nucleation process has to overcome an activation energy, the critical cluster is the cluster with maximum (Gibbs free) energy. A physical expression of this energy barrier is the supersaturation which is attained before nucleation and crystal growth ensue.

The activation energy barrier ($\Delta G'$) may be represented by three parameters which always come to attention in nucleation studies; these are the crit-

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The author is assistant professor of chemistry at Case Institute of Technology, Cleveland 6, Ohio.

ical supersaturation ratio, s' (concentration of precipitant at the onset of nucleation divided by the solubility), the reaction temperature T, and the interfacial energy $\bar{\gamma}$, related as follows:

$$\Delta G' = 32\bar{\gamma}^3 v^2/(2.303nkT \log_{10} s')^2 \quad (2)$$

The rate of formation (J) of nuclei may be represented very approximately by

$$J = A \exp(-\Delta G/kT) \quad (3)$$

where A is a factor related to the efficiency of ion (or molecular) collisions and k is the Boltzmann constant. For simplicity J is often defined as equal to one nucleus per second when $\Delta G = \Delta G'$.

Thus the factors controlling nucleation are the interfacial energy, the temperature, and the collision frequency efficiency, and these parameters result in a characteristic critical supersaturation.

Criticisms and Improvements

Early experimental observations on water vapor condensation made by Volmer and Flood (*3*) were in good agreement with the above theory (Volmer's); unfortunately this agreement is now believed to have resulted from a rather remarkable coincidence which deserves further comment.

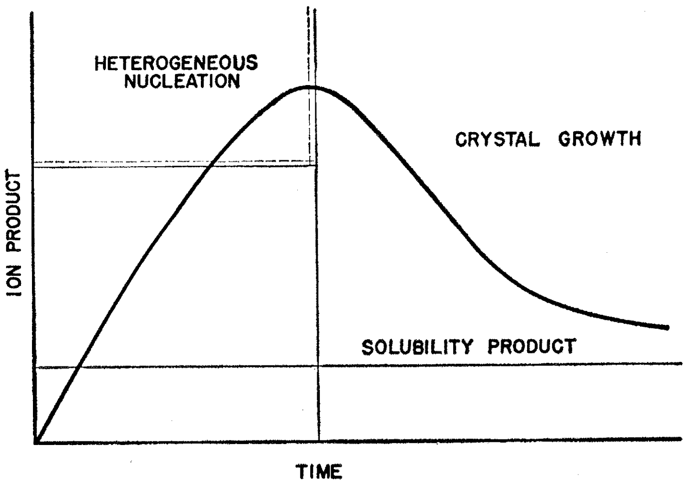
The original theory was based on several—now considered not entirely valid—approximations. First, the equation originally formulated depended on equilibrium thermodynamics, but actually the situation is dynamic or "nonequilibrium." This problem was studied by Becker and Döring (*4*), who used kinetic arguments, and by Zeldovich (*5*), who determined a nonequilibrium factor. These authors found that the general form of the Volmer equation remained valid but that small correction factors should be included. Second, there have been considerable misgivings about the applicability of the Gibbs-Kelvin equation (Eq. 2) to small clusters of molecules. Work by Tolman (*6*) and others showed that there was good reason for this doubt, since the surface tension (on a thermodynamic basis) decreased sharply for clusters smaller than 20 Å in diameter. However, later work by Benson and Shuttleworth (*7*) and Sundquist and Oriani (*8*), based on a consideration of atomic interactions, showed that the use of the bulk surface tension was accurate to within a few percent even for very small clusters. The most telling blow, however, came with recent developments (*9*) which show that various contributions to the energy barrier had been ignored in the early treatment and that, consequently, the measured energy barrier was too low. It seems likely, now, that Volmer and Flood's experiments were hampered by stray sources of charge (ions and other sources, or by experimentally induced error) which apparently lowered the energy barrier. Basically the Volmer-Becker-Döring theory of nucleation is, despite modifications, believed to be valid, and it is the point of this article to show how crystal nucleation may be represented by this type of approach.

Interfacial Energy

Before proceeding to the experimental evidence in support or otherwise of the modified Volmer equation as applied to crystal nucleation, it is worthwhile to examine specific differences between the nucleation of drops from vapor and of crystals from solution.

First, for ionic crystals the collision efficiency between ions is limited by the net charge on the cluster. Other direct modifications of the equations accounting for molecular volume and those for interfacial energy replacing surface tension must also be made. The term interfacial energy (energy required to form the interface) is to be preferred to interfacial tension because of the thermodynamic derivation and, although these terms have often been used interchangeably, the surface tension and surface energy of a solid cannot be equivalent because surface strain must be considered here also.

It is not at all clear how the interfacial energy of small crystals is related to that for an infinite crystal surface, but it might be argued that the changes of interfacial energy with crystal size will be of the same order as the change of surface free energy with crystal size. The surface free energy or energy required to form the surface of a crystal in vacuo may be calculated from theory. We have made some calculations of this type for various crystals including KCl (*10*), $BaSO_4$, $SrSO_4$, $PbSO_4$, and $CaSO_4$ (*11*). Apparently, if relaxation effects are not taken into account, the surface energy of smallest



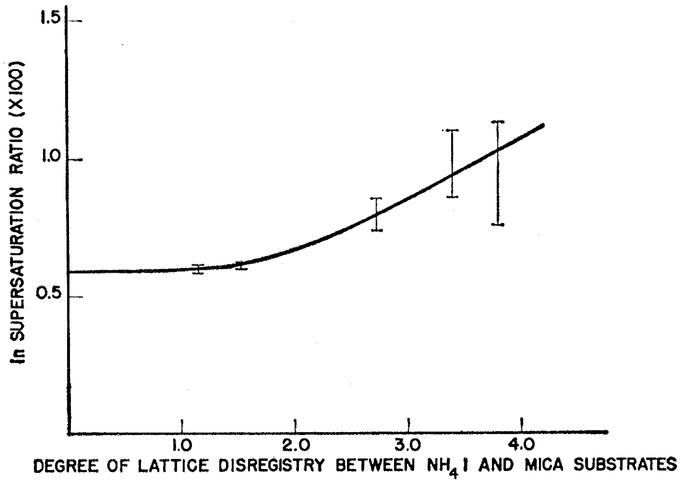


Fig. 1 (left). The change of ion product with time, for precipitation from homogeneous solution. Fig. 2 (right). Maximum stable supersaturation as a function of lattice matching between ammonium iodide crystals nucleated upon various natural and synthetic micas (after Newkirk and Turnbull, *20*).

clusters is about 80 percent higher than that for an infinite surface (at least in the case of cubic and orthorhombic crystals). This calculated increase is due to edge and corner effects and also to the long-range effect of electrostatic forces. If, however, relaxation effects are taken into account, the small clusters would probably have only slightly higher surface energy than the infinite surface.

To a first approximation then, the value for the interfacial energy of a small cluster of ions would appear similar to that for the infinite surface, if, of course, the cluster lattice is not internally solvated. Since the nucleation of ionic crystals will take place in such a manner that the interfacial energy is a minimum, the possibility of a net charge on the nucleating species should not be overlooked.

Experimental Evidence

The basic theory for the nucleation of crystals from solution has been known for many years, and it may therefore seem strange that real progress in relating the experimental to the theoretical process has been made only recently.

To establish the validity of the theory it is necessary to show that the Gibbs-Kelvin equation, Eq. 1, is applicable to the experimental observations and also that the nucleation process involves a critical supersaturation which leads to reasonable values for the interfacial energy.

Many workers have attempted to determine the solubility of small crystals in order to ascertain whether the smaller crystals show enhanced solubility as predicted by the Gibbs-Kelvin equation. Although some success was achieved, it was not until recently that Enüstün and Turkevich (*12*) were able to demonstrate convincingly that increased solubility does occur with small particles. Their calculated value of $\bar{\gamma}$ for the interface between strontium sulfate and water is 84 ± 8 erg/cm^2.

One of the features of a Volmer-type equation (Eq. 3) that is particularly important in the study of nucleation phenomena is its prediction of a nucleation rate which is very critically dependent upon supersaturation. The rate of nucleation is negligible until a fairly well-defined supersaturation (the critical supersaturation) occurs. At supersaturations greater than this, the nucleation rate is rapid, and usually the supersaturation will then collapse as a result of nucleation and crystal-growth processes. The critical supersaturation is the most important parameter in Eq. 3 since it can be measured directly by experiment. The only other unknown ($\bar{\gamma}$, the interfacial energy) can then be calculated, at least approximately.

The test of the Volmer-type nucleation equations has, however, proved frustrating. It is easily shown that a test tube full of saturated (soluble) electrolyte solution may be supercooled before the onset of sudden, massive nucleation and growth, and it has seemed reasonable to suppose that the supersaturation attained in this process could be related to the interfacial energy of the electrolyte by using the nucleation equations of the form of Eq. 2 and Eq. 3. Unfortunately the results from this type of calculation ($\bar{\gamma} = 0.1$–2.0 erg/cm^2) are not in accord with reasonable expectations for this parameter. Electrolytes generally have a surface energy greater than 100 erg/cm^2, and the interfacial energy between solid and solution should be greater than 30 erg/cm^2. The reason for this anomaly was not immediately obvious.

Nucleation of crystals from solution cannot be observed directly, and it has been (and still is) necessary to infer the nucleation mechanism from examination of the physical characteristics of the precipitated phase. This can, however, be extremely difficult since the role of the competing crystal growth and that of coalescence of crystals must be separated from the nucleation process.

If two reactants are mixed and an insoluble precipitate is formed, and if each nucleus grows to one precipitate particle, then from Eq. 2 the rate of nucleation and hence the number of particles produced should increase greatly with increase in reactant concentration. Although some increase is usually observed, there have been several cases (*13*) where virtually no increase in the number of precipitate particles is detectable over a considerable range of concentration. These anomalies have been attributed to two possible causes. Either the precipitating phase had coalesced, in which case the final number of particles could not be identified with the nucleation process, or, possibly, the macroscopic thermodynamic treatment was not applicable, if very small clusters of ions or molecules were involved in the germinating process.

This second line of reasoning seemed to indicate that some other approach to the theory of the nucleation process might be more valuable. In the late 1940's and early 1950's Christiansen and Nielsen (*14*) proposed that reacting ions do form clusters, but that the precipitation rate (R) could be better expressed in terms of the primary ion concentration c by

$$R = k_1 c^p \qquad (4)$$

where p is the number of ions in the critical cluster.

They argued that provided the precipitated phase becomes visible when $c \sim c_0$ then the induction time λ could be related to c by

$$\lambda^{-1} = k_2 c_0^{\,p-1} \qquad (5)$$

In the early 1950's several sparingly soluble salts were shown to follow this type of relation with p in the range 2 to 6, and a considerable amount of effort was devoted to working on this hypothesis (*15*). However, it now seems probable that it is heterogeneous nucleation that initiates precipitation in such systems, and it does not appear that Eq. 4 accurately relates to the real nucleation process.

Precipitation from Homogeneous Solution

Concurrently with the advent of the Christiansen and Nielsen theory, La-Mer and co-workers developed the method known as "precipitation from homogeneous solution" for producing monodisperse sulfur sols, and applied nucleation concepts to this method (*16*). Typically a supersaturation of the precipitating phase is created by a controlled chemical reaction of the type

$$\mathrm{AB} \rightarrow \mathrm{A} + \mathrm{B}$$
$$\mathrm{A} + \mathrm{C} \rightarrow \mathrm{AC}\downarrow$$

Eventually the supersaturation becomes large enough for the onset of nucleation and crystal growth, and these in turn cause supersaturation to disappear (Fig. 1). Some values obtained for the maximum stable supersaturation ratio by this method are as follows (*16–18*): AgCl, 1.7; $SrSO_4$, 10; $BaSO_4$, 32; $PbCrO_4$, 45.

The advantages in producing uniform precipitates by this method are well known, and under these controlled conditions removal of impurities led to higher critical supersaturations. Nucleation must therefore be essentially heterogeneous and not homogeneous as required by the Volmer concept approach. At last then there was a clue to the reason for the failure of the theory to correspond with experimental observation.

Heterogeneous Nucleation

Just as certain catalysts promote chemical reactions, other catalysts promote nucleation processes. The vital step takes place on the surface of the substrate, and the energy barrier is reduced. Having arrived at this stage it must be admitted that there is often no clue to the nature of the impurity that initiates the precipitation of crystals from solution. The catalyzing impurities probably come from any, or all, of the solvent, the reactants, or the walls of the reaction vessel. Silicates are generally believed to be among the main initiators; one is reminded of the scraping of test tube walls to initiate crystallization. Certain organic crystals are often more difficult to nucleate than inorganic crystals, and because of such difficulty specific catalysts may often be required for efficient nucleation.

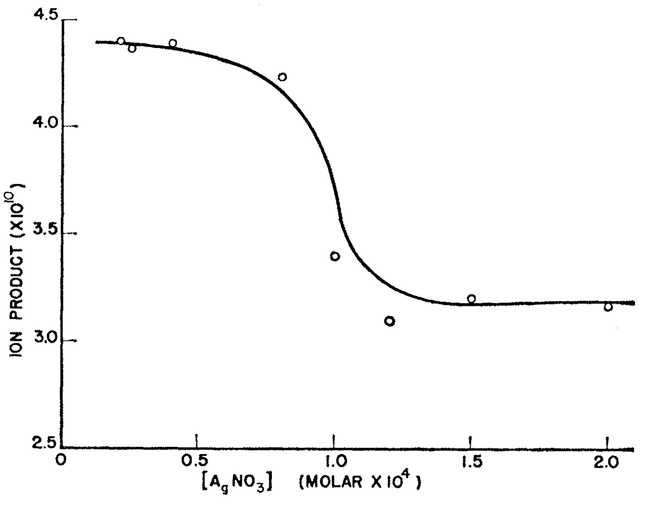
Nucleation of vapor drops on surfaces has been described by Volmer in terms of the contact angle θ as

$$\Delta G_{\mathrm{het}} = \Delta G_{\mathrm{hom}}[(2 + \cos\theta)(1 - \cos\theta)^2]/4$$

where ΔG_{het} is the activation energy of heterogeneous nucleation and ΔG_{hom} that for homogeneous nucleation.

In extending this work to the deposition of one crystal upon another, Turnbull and Vonnegut (*19*) have described the process in relation to the strain developed in the initial layers of the precipitating crystal lying adjacent to the substrate surface. Newkirk and Turnbull (*20*) have investigated the nucleation of ammonium iodide upon various mica substrates, and, in accordance with the Turnbull theory, the nucleating ability of the mica substrates was dependent upon the degree of lattice mismatch between substrate and ammonium iodide. It has previously been noted that the degree of supersaturation is the physical effect which relates to the submicroscopic nucleation processes, and in Fig. 2 is reproduced the data obtained by Newkirk and Turnbull showing supersaturation as a function of "disregistry" (degree of mismatching) between ammonium iodide and substrate.

A method of examining heterogeneous nucleation by small particles is to choose nucleating agents which are better than naturally occurring impurities. A good example of such a process is the formation of ice crystals in supercooled water. Normally nucleation occurs upon dispersed impurity particles but many model substrates may be found which are more efficient nucleating agents. Some of these are given in Table 1. Although the concepts of lattice matching between substrate and depositing crystal lead qualitatively to agreement between theory and experiment, quantitatively agreement has proved to be elusive. There is currently some doubt that nucleation can be effectively phrased in terms of lattice parameters (*21*), and some recent work has directed attention toward specific atomic interactions in interface regions (*22*).



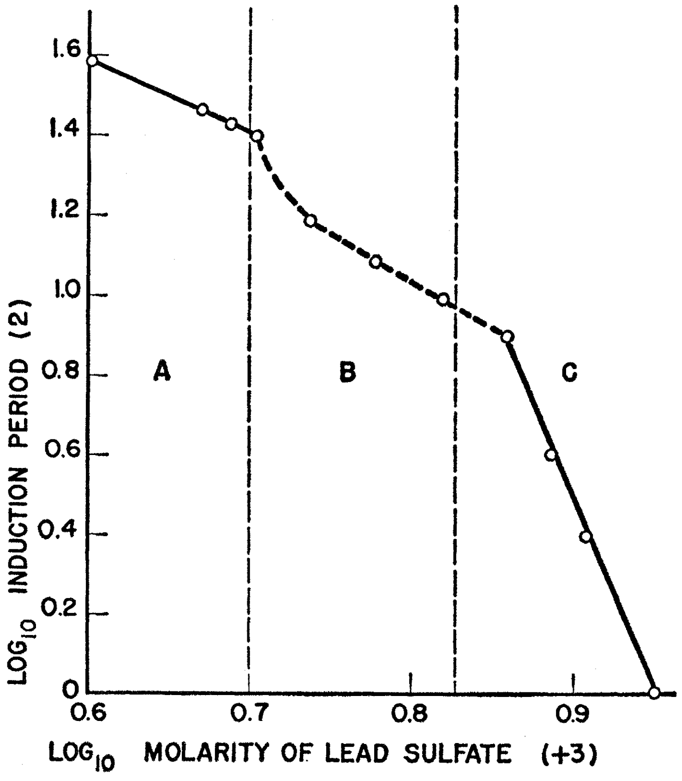


Fig. 3 (above). The critical ion product is shown as a function of the initial silver ion concentration for the precipitation of silver chloride from homogeneous solution. Zero point of charge occurs at $|Ag^+| \sim 10^{-4}$ molar (after Black, Insley, and Parfitt, *25*). Fig. 4 (right). The induction period before onset of precipitation is shown as a function of initial lead sulfate concentration. In section *A* the particles are compact and increase in size with increase in lead sulfate concentration. A similar increase in size is observed in section *B* but there is evidence of dendritic growth. In sections *A* and *B* nucleation is probably entirely heterogeneous. In section *C* homogeneous nucleation probably competes with crystal growth, and particle size decreases with increase in concentration (after Kolthoff and van't Riet, *30*).

Ancillary Nucleation

An interesting offshoot of ice nucleation studies is an effect which I shall call ancillary nucleation. If, for example, silver iodide particles are used to seed clouds so that ice or eventually rain is precipitated, it turns out that there are produced many more ice particles or water droplets than there were silver iodide nuclei added. This strange effect may also be familiar to the organic chemist who is accustomed to seeding supersaturated solutions with one or two crystals of solute and hence producing a host of precipitated crystals. A recent study of this effect by Melia and Moffitt (*23*) has shown that in stirred solutions inorganic seed crystals are also generating a considerable number of nuclei. They found that the number of new nuclei produced by seed crystals of potassium chloride seed was a function both of the stirring rate and of the degree of supercooling. Although this type of heterogeneous nucleation is not fully understood, it appears that two major mechanisms are possible: either nuclei formed on the seed surface are washed into the bulk of solution and hence act as new nuclei, or small dendritic crystals growing on the seed surface may fracture and again act as new nuclei.

One other form of heterogeneous nucleation which will not be considered in detail here concerns the formation of clusters on a crystal surface which lead to growth of that crystal (*24*). This form of nucleation, known as surface or secondary nucleation, is often considered two-dimensional. The kinetics of crystal-growth are, however, outside the scope of this article.

Nucleation in Analytical Chemistry

In most precipitation reactions in analytical chemistry, steps cannot be taken to remove all impurities or to use model substrates. However, useful information relating to the nucleation process may still be obtained, some examples being as follows.

The stoichiometry and chemical structure of an initiating nucleus will in general be dependent upon the local environment. Ionic crystal nuclei may well be charged species since a net charge lowers the energy of nucleus formation. Changes in structure of the nucleus, whether it be a homogeneous nucleus or supported on a substrate (impurity or model) are reflected by changes in the maximum stable supersaturation of the depositing material which can be attained. In support of these assertions we may look for (i) changes brought about by change of solvent environment affecting the interfacial energy, and (ii) structure changes effected by the ionic environment.

Table 1. Critical degrees of water supercooling in the presence of powdered substrates.

Substrate	Critical supercooling (°C)
Teflon	> 16
Benzophenone	> 16
Thallium iodide	6.2
Lead iodide	4.1
Silver iodide	2.5
Silver chloride	4.5
Mercuric sulfide	5.6
Cadmium sulfide	6.5

In the first category Collins and Leineweber (*18*) have found that the maximum supersaturation ratio (S_c) for the precipitation of barium sulfate from aqueous solution may be raised from about 32 to 58 by addition of glycerol.

Changes in the composition of the nucleus might be obtained if the relative concentrations of the ions in the bulk of solution are varied widely. In this connection Black *et al.* (*25*) studied the precipitation of silver chloride from solution and found (Fig. 3) a change in critical supersaturation at a concentration of silver ion corresponding approximately to the macroscopic zero point of charge. That is, crystals nucleating and growing from solutions in which the silver ion concentration is kept less than $10^{-4}M$ are negatively charged, and those growing from solutions consistently more concentrated than $10^{-4}M$ in silver ions are positively charged. Whether or not this analogy can be carried back to the nucleation stage is debatable, but the evidence does point to some fundamental change in the initiating nucleus.

In the second set of data (*26*), obtained in my own laboratory, I have looked for a change of critical supersaturation in the precipitation of calcium phosphate from solutions of various hydrogen ion concentrations. This process is particularly important in the understanding of bone formation in that hydroxyapatite (bone mineral) is the stable form of calcium phosphate at the *p*H of serum. We have found that the maximum stable supersaturation in terms of the solubility of dicalcium phosphate remains independent of acid concentration up to *p*H 6.3. Above this *p*H the supersaturation is constant in terms of the solubility of the metastable octocalcium phosphate which then undergoes conversion to hydroxyapatite. Thus nucleation studies yield valuable information in quite complicated physiological systems. Other biophysical processes which involve nucleation of crystals from solution are gallstone formation (cholesterol), kidney stone formation (calcium oxalate and uric acid), and urate crystallization (as in some forms of arthritis).

Turning from precipitation from homogeneous solution to precipitation by direct mixing, we find that predominantly the same features exist. Although the initial supersaturation is unlikely to be uniform, heterogeneous nucleation again plays an important part in the overall scheme.

The formation of crystal nuclei from solution most often is, then, dependent upon the presence of foreign nuclei. I should perhaps differentiate between inorganic crystals, where heterogeneous nucleation is predominant, and organic crystals, where there is still some doubt regarding the initiation mechanism. It is true that seeding of organic solution induces crystallization, but crops of organic crystals may commonly be harvested from the mother liquor without apparently diminishing the rate of formation of new ones. Although this phenomenon may be due to fragmentation of crystals which leads to new nuclei, there does seem a strong possibility that homogeneous and not heterogeneous nucleation is the initiating process. This also seems reasonable if we realize that impurities in most solutions are likely to be inorganic and not particularly suitable as nucleation catalysts for organic materials.

Homogeneous Nucleation

Thus, since heterogeneous nucleation appears to be the most common and widespread form of initiating precipitation, it is not unnatural to ask whether homogeneous nucleation ever occurs in inorganic crystal formation. As mentioned previously it is not possible to remove all impurity particles from solution by any known technique, but the drop-condensation method devised by Vonnegut (*27*) has partially circumvented this difficulty. The principle is as follows. If a solution possesses some 10^5 impurity particles per milliliter and 1 ml of solution is broken up into more than 10^5 drops, then some of the drops do not contain impurity particles, and measurements upon these drops will avoid the influence of impurity particles. The difficulties of this technique are clearly the problems of producing drops that are small enough and of detecting crystallization within these drops. Some success with fairly soluble materials has been achieved with this method; for example, White (*28*) has investigated the homogeneous nucleation of ammonium nitrate and obtained a value of 45 erg/cm^2 for the interfacial energy, seeming support for the validity of the experimental technique. Again, analytical precipitation is carried out under less controlled conditions, where reactants are mixed directly, and the only data at hand are the initial concentrations and the final morphology of the precipitate. I believe that under these conditions, also, homogeneous nucleation does occur and that a meaningful interpretation may be made. The reasoning is as follows.

If the initial supersaturation is large enough, the homogeneous nucleation process should become energetically favorable, and it then will start to compete with the heterogeneous process. Since the number of heterogeneous nuclei (impurities) is limited to those which have in some way been introduced into the system, one would expect the heterogeneous nucleation process to be characterized by a final number of precipitate particles (if all nuclei grow) which is invariant or which changes only slowly with reactant concentration.

In the homogeneous process an extremely large increase of particle numbers with concentration of reactants should be observed. For any chance of homogeneous nucleation to occur it is necessary to use direct mixing of reactants or some form of quenching which gives rise to a large initial supersaturation. Nielsen (*29*) was the first to elucidate this type of phenomenon in the early 1960's but, as often happens, there had been uninterpreted data available in the earlier literature which could also have been interpreted in a similar manner. Nielsen found that when barium sulfate was precipitated by direct mixing of solutions containing barium and sulfate ions there was a sudden and dramatic increase in the number of precipitate particles produced when the supersaturation ratio (supersaturation divided by solubility) was of the order of 1000. The fact that this change occurs seems indisputable since published data obtained by a number of techniques by different workers confirms the effect. Using the value for the supersaturation required for this critical change in nucleation and the Volmer equation, Nielsen deduced that the interfacial energy of barium sulfate against water is approximately 120 erg/cm^2, which seems to be a very reasonable value.

Table 2. Interfacial energies (against water) calculated from nucleation data.

Material	$\bar{\gamma}$ (erg/cm^2)	Ref.
$BaSO_4$	123	*31*
$SrSO_4$	86	*31*
$PbSO_4$	79	*31*
$PbCO_3$	112	*31*
$SrCO_3$	92	*31*
Ag_2SO_4	65	*32*
CH_3COOAg	47	*32*
$(NH_2)CH_2COOH$ (glycine)	29	*35*

I have referred to the period after mixing two reactants, before a precipitate appears, as the induction time. Nielsen interprets this induction period as a direct function of the nucleation rate whether it be homogeneous or heterogeneous. I prefer to think of the induction period as more representative of a growth process combined with a nucleation phenomenon, and would like to amplify the importance of the growth mechanism by referring to the work of Kolthoff and van't Riet (*30*). The physical appearance of precipitate particles is very much determined by the supersaturation from which they were precipitated. Particles produced from low supersaturations are usually compact in shape because the total interfacial energy is required to be at a minimum. At higher supersaturations the rate of growth becomes so rapid that the heat which is liberated by the new phase cannot easily be dissipated. Consequently dendritic growth (snowflake type) occurs such that the surface area of the growing particle tends to a maximum, thus enabling the crystal to evolve the heat to its surroundings. At still higher supersaturations, if homogeneous nucleation occurs then it will superimpose its effect upon the growth mechanism. Figure 4 shows the Kolthoff and van't Riet's results for lead sulfate nucleation and growth, in which they observed the relation between induction times, supersaturation, and crystal form. There are clearly three sections corresponding to the three areas of supersaturation just mentioned.

Subsequent experimentation based upon the outlined relation between homogeneous and heterogeneous nucleation has enabled interfacial energies to be established for a number of crystals against water (*31*). Some of the data are summarized in Table 2. In connection with the calculated values of the interfacial energy between crystal and solution it is interesting that the silver chloride nucleus is apparently influenced by the ratio of silver to chloride ion in solution, the maximum interfacial energy corresponding to the zero point charge (*32*). There seems therefore to be a strong resemblance between the homogeneous and heterogeneous nucleation of silver chloride, in that the nucleus adjusts to its solvent environment.

The difficulties in interpreting data relating to the nucleation of crystals from solution are not inconsiderable. The processes of nucleation, crystal growth, and coalescence are generally competing. Ostwald ripening, that is, the growth of large particles at the expense of smaller ones, may also add confusion to analysis of the formation process. However, much of the data presented has been obtained from elementary laboratory techniques, and refinements will no doubt render further progress.

Techniques

The techniques available for such studies may broadly be divided into three categories. The aforementioned drop condensation method has had only limited use owing to the uncertainties accompanying complete removal of impurities. Furthermore, should the drops be very small and the salt be a sparingly soluble one, the crystallites formed within its drops are too small to detect *in situ*.

For heterogeneous nucleation processes there is a wide scope for experimental studies of the type pioneered by Newkirk and Turnbull, since extensive data is available concerning the compatability of crystals with model substrates (*33*). In analytical systems it is likely that only qualitative deductions can be made when relating maximum stable supersaturations to heterogeneous nucleation. Suitable data required for a study of homogeneous nucleation are provided by an analysis of the number of precipitated particles produced by a wide range of initial supersaturation.

Quench methods, in which the product is removed from solution and examined by some form of microscopy, are rather tedious, and difficulties arise concerning the accurate estimation of the number of particles. Measurements may be made *in situ* by conductivity, by light scattering, or by some form of particle-counting unit. All three readily detect the onset of precipitation, but only the last can yield really valuable information. The reason is that precipitates are often heterodisperse, that is, the particles vary in size. Since no convenient and reliable method has yet been devised for assessing the size distribution of inorganic particles from light scattering data, the most useful instrument for determining simultaneously the size-distribution and number of particles is the Coulter counter. This instrument is designed not only for detecting and counting particles as small as 2000 Å in diameter, but also for continuously monitoring particle numbers and size distributions.

In summary, we are beginning to learn a little about the nature of the primary nucleus in crystal formation from solution. The best estimates show that the homogeneous nucleus of ionic materials consists of between 10 and 100 ions and the heterogeneous nucleus, ten or fewer ions (*34*). Data for the formation of organic crystals from solution are sparse, but the initial nuclei are probably of the same order of size as ionic crystals. Exceptions may however be noted in organic systems where large molecules (polymers, and others) do not undergo the same critical phenomena as might be predicted from the classical (Volmer) nucleation concept. This is probably due to the fact that only a few (sometimes two or three) molecules are present in the initiating nucleus.

More data are clearly required before any really systematic conclusions may be reached, and many exciting areas of chemistry and biophysics remain unstudied in this respect.

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