

Chemistry and Crystal Growth

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Dedicated to Professor Hanns Thomas Arend on the occasion of his 70th birthday

Single-crystal materials, along with other forms of condensed matter (ceramics, polymers, liquid crystals, etc.) are fundamental to modern technology. The basic research and production of new materials with "tailored" solid-state physical properties therefore necessitate not only chemical synthesis but also the production of single crystals of a partic-

ular morphology (either bulk or thin layer crystals) and well-defined crystal defects (doping). In this review, an attempt is made to broaden the traditional synthetic concept of chemistry to the process of single-crystal synthesis. The methods of the resulting approach, which takes into account the specific properties of solid materials, are dis-

cussed and illustrated by experimental set-ups for the solution of a range of problems in chemical crystallization. Also included is recent work on the growing of single crystals of high-temperature superconductors, organic nonlinear optical compounds, and proteins.

1. Introduction

Solve et Coagula!^[1]

1.1. Chemistry and Crystal Growth: The Evolution and Significance of Crystallization

The endeavor to transform liquid and gaseous substances into the solid, pure state, thereby immobilizing them (coagulation), permeates the whole of chemistry, from the early uncertain attempts of the alchemists^[1, 2] to present day methods of purification and crystal growth (Fig. 1).^[3, 4] Coagulation, in the modern sense, means the bonding of atoms, ions, and molecules to form supramolecular solid-state structures.^[5] Therefore, the formation of crystal nuclei of molecular substances would seem to be an ideal case of molecular self-organization,^[6] in which the generation of a multiplicity of system-determined morphological forms can be interpreted, for example, within the framework of pattern formation theory.^[7]

In the course of the development of chemistry, chemists have been primarily concerned with the synthesis of low molecular weight and macromolecular substances and the building up of extended solid-state structures, basically by molecular accretion. This led to the fact that "crystal nucleation and growth

... remained virtual areas of darkness on the map of the chemical knowledge".^[8] Somewhat belatedly, great interest in supramolecular chemistry became apparent very recently. This has been strongly motivated, for example, by the development of functional solid materials (for molecular electronics,^[9] for sensors,^[10] and for applications based on their mechanical and other properties^[11]). Traditionally, however, the physical properties of single-crystal materials (e.g., cooperative phenomena such as magnetism,^[12] ferroelectricity,^[13] or superconductivity,^[14] etc) did not occupy the center of interest. In this context Lüttringhaus commented:^[15] "The more chemistry expanded, the more the chemist concerned himself with chemical reactions, and the less with the state of his substances. In particular, he entrusted the study of crystals to crystallographers or structural physicists."

When the anisotropy of physical phenomena in single crystals was discovered, the peculiarities of their physical properties, however, became a topic of physics. The Neumann Principle enabled an increasing number of properties represented by tensors to be qualitatively classified by point symmetry groups.^[16] The direction of solid-state physics had been pointed towards the "high tech" age by important discoveries including the technologies of high frequencies, semiconductors, magnetic storage, and lasers, and by the physics of solid phases characterized by nonlinear properties. This could not have been contemplated without experiments with increasingly complex single crystals. The necessary crystal growth technique had taken its place in the field of crystal physics alongside crystallography and experimental mineralogy.

Significantly, the above passage can be found in the introduction to general laboratory practice (crystallization) in Volume 1 of the textbook *Methoden der Organischen Chemie* (Houben-

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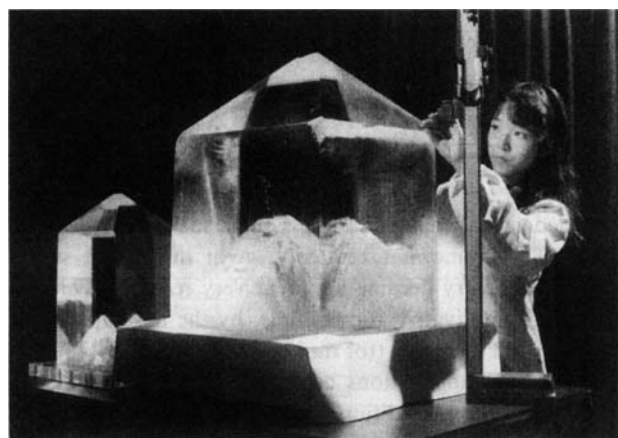
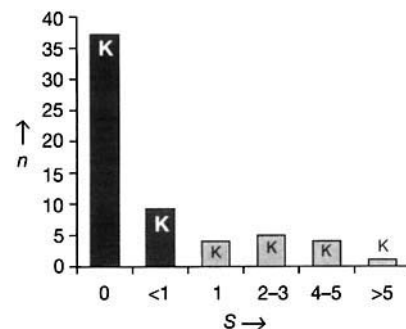


Fig. 1. Crystallization in the course of time. Top: Salt production in the Middle Ages [2c]; evaporation and crystallization of vitriol; bottom: Advanced crystal growth of large, highly pure crystals of KH_2PO_4 for optical frequency doubling [4].

Weyl);^[15] crystallization had not become a theme of modern chemistry. Obviously, crystallization processes have always played an important role in chemistry, and crystallization has been exhaustively described in the older chemical litera-

ture.^[17,18] Nevertheless, crystallization, in the conventional chemical sense, is merely a useful laboratory technique even today, whereas crystal growth in the true sense, that is, the science of producing large single crystals for a particular purpose, is a topic mainly found in the field of physics research. A glance at the many general chemistry textbooks available today reinforces this impression (Scheme 1). On average, the subject of



Scheme 1. References to crystal growth in chemical textbooks: 60 recent general textbooks of organic, inorganic, and physical chemistry were searched for references to crystallization, recrystallization, and crystal growth [19]. The histogram shows the frequency of these references. S = number of pages on crystallization (K); n = number of books: out of approximately 43 000 pages, about 50 pages covered this theme ($c_K \approx 0.12\%$). If the c_K value is compared with the corresponding value of 50 old *organic* chemistry textbooks, the value of c_K today is considerably smaller.

crystallization forms only about 0.1% of the total.^[19] The majority of current chemistry textbooks do not describe it at all, nor do they describe the solid-state properties of the interesting types of materials mentioned above. (The review of well-known chemical journals (1968–1991) gives a similar picture.) Compared with textbooks written 20–40 years ago, the relative amount of space devoted to the special science of crystallization has clearly decreased. One can only assume that the situation with respect to solid-state chemistry could be improved; however, in a recent summary of views on the theme “Is Everything O.K. with Solid-State Chemistry?”^[20] it is stated: “... there is no textbook on solid-state chemistry adequate for modern science...”,^[20] and the reviewer summarizes the results of an opinion poll involving 50 specialists in solid-state chemistry:

“It is high time to recognize that besides classical chemistry, which deals with individual molecules and atoms or ions,



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there exists chemistry where chemical transformation has a collective character. This chemistry cannot be equated with classical chemistry nor extrapolated from it."^[20]

In the case of solid-state chemistry, the collective character of the process which leads to the formation of complex solids is stressed, but, even in this connection, the general importance of processes and mechanisms of crystal growth and their characterization by instrumental analysis have not been mentioned. We have to say, with no exaggeration: solid-state properties (as considered by physics) in association with crystal growth (synthesis of single crystals—as distinct from molecular synthesis or the usual kind of synthesis of solid materials) has not been the concern of chemistry, or has only been on the fringe.

On the other hand, how are developments progressing in the field of materials research (see, for example, the recently founded (1988) journal *Advanced Materials*, VCH, or papers in *Issues and Opportunities in Materials Research*^[21]) whose success depends to a large extent on the contribution from chemical synthesis? The concept of crystal engineering was given an identity after 1945 by von Hippel,^[22] and in its further development (Hahn,^[23] Kitaigorodski,^[24] Arend,^[25] Willet,^[26] F. Hülligér,^[27] Kaldis,^[28] Leiserowitz et al.,^[29] Schmidt,^[30] McBride et al.,^[31] Desiraju,^[32] Etter,^[33] Fagan et al.,^[6] etc.) is to be regarded as a solid-state analogue of "molecular engineering", the well-known system of synthesis. One of the great challenges of modern chemistry thus concerns the reinforcing of ways of thinking about supramolecular structures and developing methods for their construction, in particular the synthesis of single-crystal materials with "tailored" physical properties (see Tables in refs. [3, 34]).

In this context, a new topochemical subject known as nanochemistry^[35] deserves special attention (see, for example, Ozin^[36]). Thus, a series of methods of extremely wide application are available to the modern grower of crystals, enabling the targeted construction of solid-state structures or molecular syntheses, impossible by the classical route. These include (in addition to the possibilities discussed by Ozin,^[36] and the fullerene syntheses) molecular beam epitaxy (MBE),^[37] metal-organic chemical vapor deposition (MOCVD), chemical beam epitaxy (CBE)^[38] CVD, or plasma-assisted deposition techniques, the Langmuir–Blodgett process,^[39] and special applications of topochemistry.^[40] There is also an analogy between the mechanistic concepts of molecular synthesis and controlled crystallization. Kahr et al.^[31], for example, have compared the production of true growth locations of a crystal nucleus with the starting point of a radical chain reaction (see Section 2.1). The term chemospecificity in crystallization corresponds to the selective choice of a particular guest molecule, regiospecificity is shown by alteration of crystal habit, and stereospecificity in the spatial distribution of crystal defects.

Modern achievements in synthetic chemistry such as superconducting oxides,^[41] magnetically-ordered organic or organometallic compounds,^[42] fullerenes and their derivatives,^[43] and organic, strongly nonlinear, optical compounds^[44] are of interest for their distinctive solid-state physical properties. The detailed investigation of these subjects requires well-defined single crystals, and, increasingly, also epitaxial thin films. In general, a detailed investigation of the physical properties of a new substance discovered by classical synthesis is only possible after

single-crystal samples of known real structure have been prepared. Single crystals, epitaxial thin films, and fibers made from an increasingly large number of different compounds are today undeniably a part of the fundamental research into material science and technology. Here, where success largely depends on an interdisciplinary method of thought and work, the elucidation of complex plans of materials research requires the interlinking of chemistry and physics. The modern science of crystal growth is active in the promising areas in which chemistry and physics overlap, that is, where growth processes are investigated, and special methods for producing solid single crystals, epitaxial layers, and fibers with tailored properties are developed.

To quote but one example: "Materials are really the key to new solid-state lasers" (Chai).^[45] Following the first phase of development of solid-state lasers in the 1960s and 1970s, a more vigorous search for other matrix lattices has recently been started,^[46] which, along with high power short wavelength semiconductor laser diodes, has the main aim of producing tunable light sources and "up-conversion" systems.^[47] This involves, for example, the crystal growth of fluorides (LiYF₄, KYF₄, etc.) and oxides (silicates, garnets, etc.) as well as fluoride glasses.^[48]

From today's viewpoint, the basic question for chemists is to what extent chemistry should integrate solid-state properties and single-crystal synthesis as one of its new leitmotifs into research and teaching in the future.

Single crystals play a decisive role not only in the context of complex materials research. Single-crystal X-ray structural analysis still represents the definitive proof of structure for the chemist. The discussion of molecular and other properties depends upon it, especially for a comparison with structures calculated from quantum chemistry.

Based on this outline, two subjects are dealt with in the following sections: 1) an introductory description for the chemist of the basic principles of crystallization and crystal growth from the modern viewpoint (see especially refs. [3, 34, 49]), and 2) a practical discussion of methods which can contribute to progress in mass crystallization (on the laboratory scale), or the production of small single crystals (for structural investigations), and the preparation of larger single crystals (for the investigation of the physics of the solid state).

1.2. From Crystallization to Single-Crystal Growth

Crystallization is one of the most perfect purification operations...^[17b]

In practice, crystallization was, for organic chemistry, one of the most effective methods of purifying substances for a long time, especially for the separation of enantiomers (resolution of racemates). With the development of chromatography and other methods of separation (including chiral stationary phases), crystallization itself lost some importance as a laboratory technique, which must be the main reason why it is not treated at all in the newer textbooks of general chemistry, or at least only briefly, although methods for the preparation of small single crystals or polycrystalline materials, mainly for complete crystal structure analysis by X-ray or neutron diffraction, have remained in use.

The special techniques summarized in Scheme 2, for which crystallization processes were developed or used, have attained importance in chemical research and technology. Industrial crystallization is undoubtedly most important.^[50] Because of

1. Industrial crystallization [50–53]
Sales of a) polycrystalline bulk materials in which each product is estimated to exceed 10^6 t per year, for example, NaCl, urea, sugar, or zeolite Linde A with 10^5 t per year [54]; b) single-crystal production of elements (e.g., Si with no dislocations: 10^4 t per year) [55] and compounds (e.g., cubic stabilized ZrO_2 : 300 t per year) [56]
2. Determination of structures of crystals and molecules (about 8 000 new crystal structures per year)
3. Separation, purification, and purity determination of fine chemicals, pigments, and natural products
4. Racemate separation and determination of absolute configurations [29, 57]
5. Crystallization of macromolecular substances (proteins, polymers) [58, 59]
6. Measurement of physical properties by spectroscopic and other physical methods
7. Biocrystallization (also in the medical field: osteoporosis (see ref. [3]: kidney stones and gall stones)) [60]
8. Synthesis under topochemical control [40, 61] (e.g., cracking catalysts based on zeolites [54])

Scheme 2. Areas where crystallization processes are important in chemical research and technology.

the necessity for quality control of bulk production, as well as a technically feasible user-friendly crystal morphology,^[51, 52] and defined particle size distribution of agglomerates,^[53] the process control system must be based on extensive knowledge of the mechanisms of nucleation and growth for a given hydrodynamic regime and set of surface-active agents (crystal habit modifiers^[62]). In the industrial production of mainly large single crystals with defined real structure, extremely pure starting materials are required on the one hand, and very closely controlled crystal growth technology on the other (Fig. 2).^[2, 4, 55, 63]

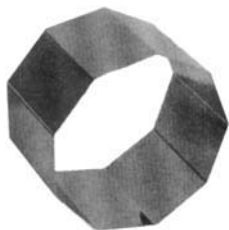
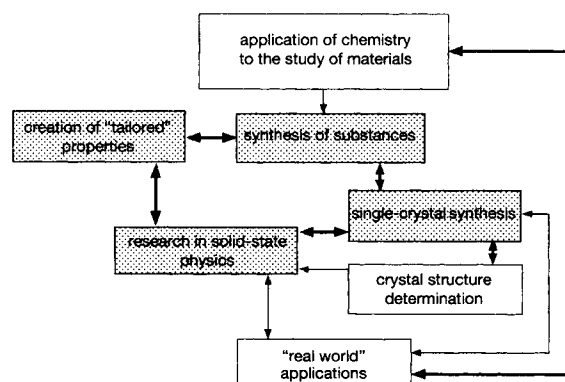


Fig. 2. Special technology ("edge-defined film-fed growth") for the economic production of silicon solar cells. Eight- or nine-sided thin-walled single crystals, several meters long, are obtained from the molten material by crystal pulling [63].

In the laboratory, the elucidation of structure has had to take second place in view of the demand for small single crystals (linear dimensions d less than one mm); about 8000 new crystal structures per year currently result either from the purification of various compounds or the separation of racemates. As a more detailed discussion of all recent relevant fields would go far beyond the scope of this article, the reader is referred to the recent literature on this subject in some cases.

To recapitulate, most types of chemical crystallization can be divided into three classes, which differ in the method used: a) large-scale production of small crystals, b) crystallization of individual single crystals (d less than one mm), and c) growth of single crystals ($1 \text{ mm} \lesssim d \lesssim 1 \text{ m}$). As modern materials research and crystal growth are oriented towards the same stages of the

processes, this classification will be used for the planning of Section 3. That is to say, for newly synthesized compounds, the desired solid-state properties are at first investigated with polycrystalline (for example, ceramic) and small single-crystal samples, and are then optimized (see Scheme 3) by developing specific methods of crystal growth (bulk, thin film, and fiber single crystals). From the viewpoint of materials research, the usual synthetic methods at this point give way to methods of single-crystal growth to achieve the desired solid-state properties.



Scheme 3. Chemistry and crystal growth: interlinking of the processes in materials science including single-crystal synthesis.

In view of the continually increasing number of initially poorly characterized compounds, the question of simple but effective strategies of crystallization arises. A cost estimate ("man-years investments") based on "response theory" (Tiller, 1991)^[49] shows that the implementation of the "black box" assumption (a current view of crystal growth!) leads to an "art-based technology" (crystal growth = a collection of recipes) based on the multidimensional parameter space $j + k$, where j = the number of materials and k = the number of experimental parameters, whereas a "system approach", which always presupposes some sort of prestructuring "clustering", leads to a "science-based technology" (strategies for proceeding with a minimum of experiments). A proposed plan for an intelligently organized laboratory crystallization process is discussed from a practical point of view in Sections 3.2 and 3.3. This contains the exploratory methods of crystallization and the advanced methods of single-crystal growth.

All methods must be termed exploratory when they systematically use a phenomenological approach with a minimum of experimental work, for example, by the deliberate use of self-regulating mechanisms. In many cases, crystals produced in a first stage are used as nuclei in a second stage of advanced crystal growth. The so-called temperature-difference method of solution growth (see Section 3.2) should be regarded as a simple example of a "science-based technology". Here it should be mentioned that H. T. Arend contributed greatly to the research and development work on exploratory strategies of crystallization during the course of his activity as a crystal grower at the Eidgenössische Technische Hochschule (ETH), Zürich.

In the future, the electronic storage and handling of data concerning methods and materials should provide the chemist

with a database, in which the knowledge about crystallization is stored ("computer knowledge base for crystallization"^[64]). A first attempt at this has been in existence since 1990,^[64] and it is to be hoped that its usefulness and shortcomings will become apparent through continual use. However, data systems will certainly not be able to replace the specialist in the foreseeable future. If a problem is too difficult for the crystal growth expert to solve, existing electronic strategies will also fail. "The expert then falls back on his intuition and far more wide background knowledge."^[64] There is another electronic data bank that stores information on the crystallization of biological macromolecules.^[65] This contains data on more than 1000 crystalline forms of over 600 biological macromolecules. The use of this when attempting systematic protein crystallization (e.g. "successive automated grid searches") is discussed by Weber.^[58]

In addition to the electronic media, it should not be forgotten that a rich experience of the solution of crystallization problems exists, for example, in the older organic chemical literature. This can now be extended in a methodical manner.^[15, 18]

This article has so far been aimed at throwing some light on the significance of crystallization in chemistry, and preparing the reader for the specific nature of the later part of the discussion which describes experiments in modern crystal growth. After a general outline of the theory (Section 2), a very practically oriented systematic approach is set out in Section 3. In Section 4, the crystal growth of three classes of materials of topical interest is briefly discussed.

2. Fundamentals of Crystal Growth

2.1. Energetics and Kinetics of Nucleation and Volume Growth

A crystal is nothing but a large molecule.
Van Vleck^[66]

Crystallization leads to the buildup of supraatomic and supramolecular ordered states, whose microscopic real structure and macroscopic morphology are determined by energetic, kinetic, and transport (mass and heat) mechanisms; thus, lattice components are attached. This means that, as a nonequilibrium process of a heterogeneous system ($\Delta G(N \rightarrow C) = G_C - G_N < 0$; C: crystal, N: nutrient phase), the final condition of a macroscopic crystal is the result of a transition process due to a local thermodynamic deviation from equilibrium, $\Delta G(x, y, z; \Delta p, \Delta T, \Delta X_i)$, the removal of the heat of crystallization, the inflow of lattice components, and the outflow of dispersive and other components which are not taken up into the lattice or are only taken up in small amounts.^[49] If the crystal growth takes place at a high or low temperature (or pressure), attention must also be paid to defect equilibria on changing to normal conditions (e.g. Schottky defects^[67]). It is today widely recognized that crystal growth must be regarded as a complex process (Neuhaus^[68]) whose mechanism is divided into stages. This has consequences for the experimental methods of producing single crystals with "tailored" physical properties.

Kinetic effects (in processes involving a large deviation from equilibrium, e.g., in MBE or MOCVD technology^[69]) make

possible the buildup of heteroepitaxial layers,^[70] superlattices, or mechanically strong strained thin films,^[70, 71] and also affect the distribution equilibrium of dopants^[49] and dominate the morphology.^[72] An example of kinetically controlled crystal growth is provided by optically anomalous crystals in which a regular incorporation of foreign components or a disorientation of the lattice components disturbs the symmetry of individual growth sectors.^[31]

Whereas, in the 1960s and 1970s, crystal growth was mainly studied phenomenologically,^[73] during the 1980s the development of new experimental techniques for investigating growth in situ introduced the possibility of "taking a picture" at the atomic/molecular level (transmission electron microscopy (TEM),^[74] reflection high-energy electron diffraction (RHEED), low-energy electron diffraction (LEED),^[75] synchrotron radiation and light scattering experiments at the crystal–nutrient phase interface (CNI),^[76] scanning tunneling microscopy (STM),^[77] and atomic force microscopy (AFM)^[78]). Light scattering experiments have shown that, for example, in a supercooled melt, the growing crystal is surrounded by a partially ordered layer that can be several μm thick, depending on the degree of supercooling.^[76] In situ observations of the properties of metallic clusters (Pt, Au, Pb) in vacuo have been carried out by TEM (video recording).^[79]

Turning now to the theory,^[73] (for historical information, see refs. [2, 34]) the early contributions of Gibbs (1878), Wulff (1895), Volmer (1926), Kossel (1927), Stranski (1928), and others have been fundamentally extended by the discovery of the energetically favorable growth by screw dislocations (Burton, Cabrera, Frank (BCF theory) 1949^[80]), the treatment of morphological stability/instability criteria (Mullins and Sekerka, 1963^[81]) for the crystal–nutrient phase interface, and the incorporation of impurities into the lattice (Burton, Prim, Slichter, 1953^[82]). More recently, Monte Carlo methods,^[83] "molecular modeling", and ab initio simulations (for Si, GaAs, noble gases, etc.)^[84] illustrate space and time aspects of the growth steps at a crystal surface. Also, progress has been made in the calculation of the expected binding energy of macroscopic (*hkl*) surfaces^[85] (for the general consideration of theoretical models, see literature quoted, for example, in ref. [3, 34]).

An understanding of the mechanism of homogeneous nucleation is of fundamental interest.^[53, 86] Starting from the statistically disordered nutrient phase N ($T > T_{\text{equilibrium}}$), the structure-forming self-organization of the components (Fig. 3) takes place in the supercooled or supersaturated state in several stages,^[87] leading to a reaction principle (with a part played by molecular recognition mechanisms) whose elementary steps, infinitely repeated, lead to the "macromolecular" crystal. Homogeneous nucleation and crystal growth can be described in analogy to chemical reactions according to Scheme 4.^[49, 86a] As an illustration of stepwise buildup by nucleation, Figure 3 shows structures calculated from quantum mechanics of associates and clusters ($\text{Na}^+(\text{NaCl})_n$) up to the formation of a "first" NaCl ordered structure of a unit cell (gas phase).^[87a]

In the classical capillary approximation, the transition of small molecular agglomerates to clusters (C) of increasing size leads to the formation of a phase boundary surface (outer surface), for which the cluster formation energy ΔG_C consists of a volume and surface area term. For a nucleus, assumed to be

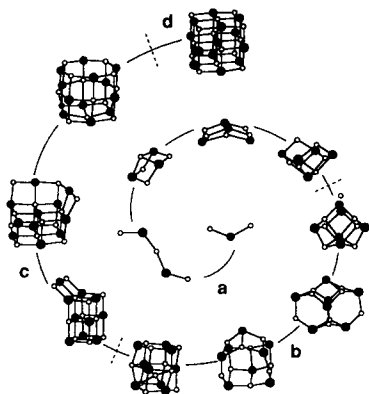


Fig. 3. Quantum-mechanical calculation of the stepwise development of structures leading to the formation of an NaCl lattice cell structure (from ref. [87a] with additions from the author). a) Small aggregates; b) cluster formation; c) transition to an NaCl lattice structure unit; d) first "unit cell".

spherical, in solution, $\Delta G_c^{[53]}$ is described by Equation (a), where the cluster radius r^* [Eq. (b)] represents the critical size, and ΔG_c^* [Eq. (c)] represents the activation energy to overcome the critical size of the nucleus. The molar volume of the cluster is represented by v ; $\sigma = (X - X_0)/X_0$ represents the relative supersaturation,^[88] X_0 represents the equilibrium concentration, γ represents the interface surface energy per unit area, and k_B is the Boltzmann constant.

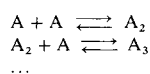
$$\Delta G_c = \Delta G_c(r) = -\frac{4\pi}{3} r^3 [k_B T \ln(\sigma + 1)]/v + 4\pi r^2 \gamma \quad (\text{a})$$

$$r^* = 2v\gamma/[k_B T \ln(\sigma + 1)] \quad (\text{b})$$

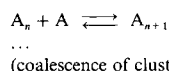
$$\Delta G_c^* = 16\pi v^2 \gamma^3/[3k_B^2 T^2 \ln^2(\sigma + 1)] \quad (\text{c})$$

The transition into growth of macroscopic crystals (Reactions 3 and 4 in Scheme 4) can take place by energy fluctuations in the system; thus, r^* and ΔG_c^* are overcome.

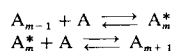
1) Formation of associates from monomer A



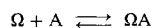
2) Buildup of clusters



3) Formation of critical nucleus A_m^* and its growth



4) Molecular accretion on macroscopic crystal surfaces (Ω)



Scheme 4. Reaction scheme for homogeneous nucleation (see text).

According to Larson et al.,^[89] consideration of surface curvature anisotropy (for example, by the attachment of clusters to macroscopic surfaces) leads to a thermodynamic stabilization of small clusters with $r < r^*$. Therefore, in real systems (in the supersaturated state), there exists a specific distribution of

metastable or stable but subcritical nuclei of varying size r . Since r^* depends on σ , the construction of the first ordered lattice cell does not in general lead to a production of the critical nucleus size. Statistical thermodynamic models confirm the capillary approximation [Eq. (a)] down to cluster sizes of approximately 10–30 atoms/molecules.^[86a] Gas-phase experiments by Volmer et al. have shown that condensed droplets of organic compounds have a diameter of $r^* = 0.8\text{--}1.5$ nm, and $n = 30\text{--}130$ molecules,^[50] which would be expected to be a realistic description of the capillary model. For liquid–solid phase systems, there is some experimental data about the size distribution and concentration of clusters, but a great lack of structural information. The size of clusters in solutions is in the range 1–10 nm, with up to 1000 molecules.^[89]

According to Boltzmann statistics, the number of clusters that exist in the state with ΔG_c^* is proportional to $\exp(-\Delta G_c^*/k_B T)$. The nucleation rate J [$\text{cm}^{-3}\text{s}^{-1}$] therefore follows Arrhenius's Law. This is true when the activation energy for the diffusion is appreciably less than ΔG_c^* , as, for example, for molten materials, in which nucleation takes place just below the liquidus temperature. Including the contribution made by diffusion ΔG_D^* , J (for solutions) is given by Equation (d), in which v_L represents the molar volume of the solvent, and h is Planck's constant.

$$J = \exp(-\Delta G_D^*/k_B T) \exp(-\Delta G_c^*/k_B T) k_B T/hv_L \quad (\text{d})$$

As shown by measurements by Tammann (1898) and others,^[18, 34, 86b] $J(\sigma)$ can show a fairly sharp maximum, where the temperature range for maximum nucleation and that for maximum growth rate do not in general overlap to a great extent. In the crystallization of proteins, one of the main problems can be that conditions for nucleation and those for growth are optimized separately.^[58]

In many systems, nucleation proceeds heterogeneously, as interactions with solid items of equipment or vessel walls reduce activation energy and nucleation temperature. If the critical nucleus size is reached, the continuing process of accretion of materials becomes the growth of macroscopic crystals (in analogy with polymerization reactions), for which various mechanisms can be effective within the CNI.^[34, 73, 86b] Both experimentally and theoretically, the distinction must be made between growth on an atomically rough or smooth (in this case stepped) surface, and growth by means of screw dislocations. The step velocity v and the macroscopically measurable surface growth velocity R (R : linear or nonlinear) are functions of the supersaturation σ , and depend on the transport mechanisms; thus, lattice components are added, and are incorporated into the "kink position" preferentially for energy reasons. In the case of a growth mechanism driven by adsorption onto the growth surface and by screw dislocations (BCF Theory^[80]) the growth rate R of macroscopic faces can be described (in solution) by Equation (e) where k_1 and k_2 represent kinetic, temperature-dependent constants.^[90]

$$R = k_2 \sigma^2 \tanh(\sigma^{-1} k_1/k_2) \quad (\text{e})$$

For small values of σ a parabolic rate relationship would be expected, and for larger values of σ it would be linear

(v is linearly dependent on σ). Detailed measurements^[91] of $R(\sigma)$ and $v(\sigma)$ on, for example, KH_2PO_4 , have shown considerable deviations from the expected parabolic relationship for small values of σ , attributed to the effect of foreign materials. Above a critical supersaturation value σ' , the growth velocity R increases considerably (suppression of growth for a small deviation from equilibrium). This shows once again the importance of prior purification of materials before mechanisms of crystallization can be investigated and interpreted. Because specific impurities are active down to the ppm level, this presents no easy task for preparative and analytical chemistry. This helps to understand why, in some cases, even when seed nuclei are used and the supercooling and/or supersaturation is relatively large ($\Delta T, \sigma$), no crystal growth, or very slow crystal growth is observed. From general experience with solid materials of various types, it can be said that the problems of chemical crystallization are not with the crystal growth, but with the nucleation. This happens in many systems where nucleation takes place at a high degree of supersaturation, so that the volume growth proceeds too quickly. Separate production of seed nuclei for a later crystallization process is therefore to be recommended.

Foreign materials can reduce the rate of accretion, even without adsorption onto growth-active locations. When $k_0 < 1$ (Nernst distribution coefficient $k_0 = X_C/X_N$), the foreign material (including dispersive components) becomes concentrated in the vicinity of the growing faces,^[34] which leads, for example, to a reduction in the liquidus temperature in accordance with the phase diagram of a two-component system (see Section 2.2, Fig. 6, Type I, III). Thus, when the temperature is kept constant (provided that the system is thermally homogeneous), the supercooling ΔT or the supersaturation σ decreases, and the growth proceeds more slowly. It is therefore useful to reduce the thickness of the diffusive matter transfer zone by a suitable flow profile in the nutrient phase, and thorough mixing throughout its volume. Regarding the incorporation of foreign material into the lattice, an increase in the concentration X_C due to kinetic effects is observed. Depending on the growth rate R and the hydrodynamic condition, $k_{\text{kinetic}} > k_0$, and in extreme cases reaches 1, where $X_C \approx X_N$. In analogy to the result of comparable work, the theory of Burton et al. gives the Equation (f),^[82]

$$k_{\text{kinetic}} = k_{\text{CNI}} [k_{\text{CNI}} + (1 - k_{\text{CNI}}) \exp(-R\delta/D)]^{-1} \quad (\text{f})$$

where D denotes the diffusion constant, δ the thickness of the crystal–nutrient interface (CNI), and k_{CNI} the Nernst distribution coefficient in the CNI (approximation: $k_{\text{CNI}} \approx k_0$).

The well-known rule that, in purification by crystallization, the crystallization process must take place slowly is therefore confirmed in one respect. Since too rapid a growth rate can lead to a macroscopic inclusion of nutrient phase, a suitably slow growth rate is always advisable (see earlier comment on nucleation at high σ values).

2.2. Phase Diagrams and a Systematic Classification for General Methods of Crystal Growth

Experimental crystal growth requires exact knowledge of the relevant phase diagram, at least in the region of existence

($\Delta p, \Delta T, \Delta X$) of the primary product to be crystallized. As the necessary thermodynamic data are known in relatively few cases, or their accuracy may be inadequate with respect to the values of p, T, X , limited-range phase diagrams often have to be specially determined under conditions comparable to those to be used in the crystal growth work (containers, purity requirements, time scales,^[92] etc.). (For experimental methods, see ref. [93], and, for data, ref. [94].) In the thermoanalytical investigations, visual observation of the liquefaction and crystallization processes should be included. In this way, information is commonly obtained that may well be irrelevant in pure phase diagram work, but can be very important in crystal growth (existence of small amounts of undissolved solid materials or cloudiness, melt–solution segregation, morphological aspects, color effects during crystal growth, etc.). As an example from high-temperature solution growth, an experimental procedure is briefly described here. This was used as an exploratory technique (see Section 3.2) in the determination of growth conditions for the production of epitaxial layers of $\text{KTa}_{1-x}\text{Nb}_x\text{O}_3$,^[95]

High-melting materials (e.g. ABO_3 perovskites) can be brought into solution by fluxes (that is, lower melting oxides or halides) at much lower temperatures than the melting point of the pure substances, and crystallized.^[96, 97] Here, it is necessary to know at least part of the quasi-binary phase diagram (see Figs. 6, 7). Solution and crystallization processes for temperatures up to about 1200 °C can be investigated in situ by visual observation and/or thermoanalytical measurements by using the system shown schematically in Figure 4. By simultaneously

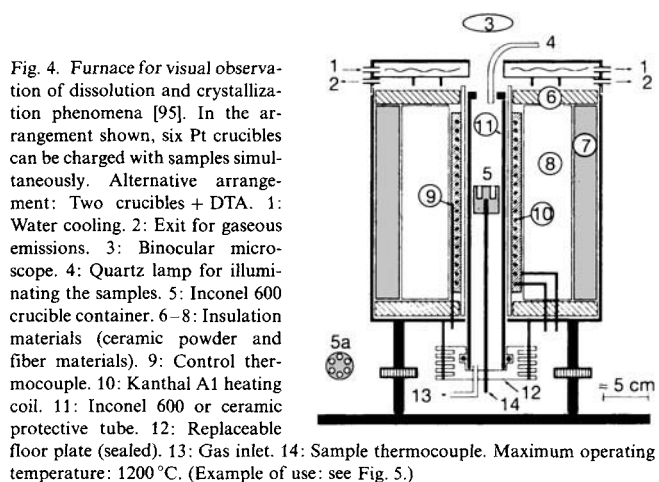


Fig. 4. Furnace for visual observation of dissolution and crystallization phenomena [95]. In the arrangement shown, six Pt crucibles can be charged with samples simultaneously. Alternative arrangement: Two crucibles + DTA. 1: Water cooling. 2: Exit for gaseous emissions. 3: Binocular microscope. 4: Quartz lamp for illuminating the samples. 5: Inconel 600 crucible container. 6–8: Insulation materials (ceramic powder and fiber materials). 9: Control thermocouple. 10: Kanthal A1 heating coil. 11: Inconel 600 or ceramic protective tube. 12: Replaceable floor plate (sealed). 13: Gas inlet. 14: Sample thermocouple. Maximum operating temperature: 1200 °C. (Example of use: see Fig. 5.)

using six platinum crucibles (diameter: 8 mm, $l = 15$ mm) illuminated with a fiber-optical light guide, morphological and chemical information can be obtained and color effects observed. In the case of the $\text{KTa}_{1-x}\text{Nb}_x\text{O}_3$ referred to above, this led to a simple determination of the phase diagram (Type I, see Fig. 6) with potassium fluoride as the solvent. Moreover, useful basic information for the later development of an epitaxial process^[98] was obtained from experiments on KTAO_3 substrates, which were several mm^2 in size. The growth of the $\text{KTa}_{1-x}\text{Nb}_x\text{O}_3$ layers is accompanied by the formation of a strong blue color, noticeable even at the early stage of the growth process (Fig. 5).

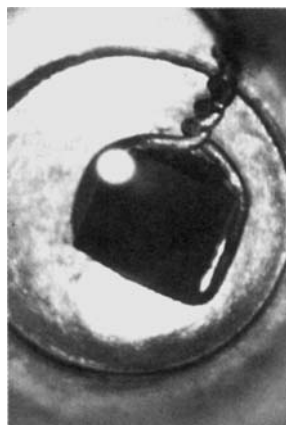


Fig. 5. In situ observation (see furnace in Fig. 4) of epitaxial growth of dark blue $\text{KTa}_{1-x}\text{Nb}_x\text{O}_3$ crystals on a KTaO_3 substrate from KF flux at 920°C after 10 min (110) orientation with macroscopically rough growth surface [95]. Crucible diameter $\varnothing = 8$ mm.

Three phase diagrams (T , X , at constant p) are shown schematically in Figures 6 and 7 to help in understanding the later discussion of the crystal growth of many substances: 1) The

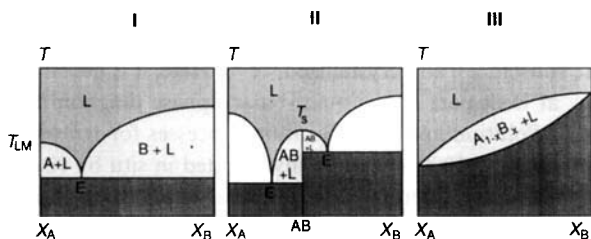


Fig. 6. (T , X) Phase diagram for two-component systems (A/B) as a basis for: solution growth of B (I; see also Fig. 7); the melt growth or flux growth of a congruently melting compound AB (II); the growth of mixed crystals A_{1-x}B_x (III). L: liquid phase, E: eutectic point; T_{LM} , T_S : melting points of solvent and of substance AB, respectively.

two-component system A/B without formation of solid solutions, as a basis for solution growth from dilute or concentrated solution, 2) the melting diagram for crystal growth of a congruently melting compound AB from the pure melt or from the self-fluxing mixture (incongruently melting compounds are usu-

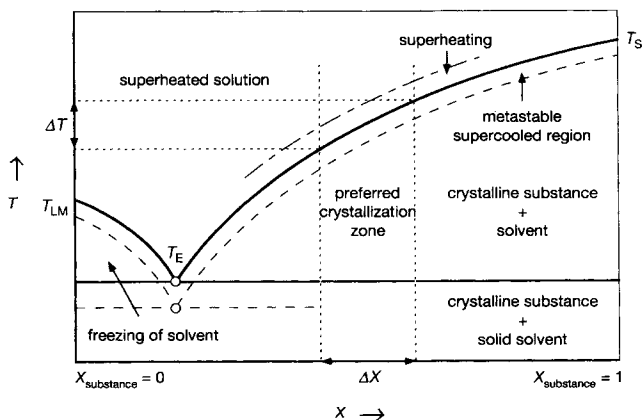


Fig. 7. Phase diagram (T , X) of solution growth, showing optimum crystallization zone (ΔT , ΔX), and metastable region of supersaturation and of superheating. The region of freezing of the solvent is shown on the left of the diagram (see Sections 3.1.1 and 4). T_{LM} , T_S : melting points of solvent and substance S, respectively; T_E : eutectic temperature.

ally obtained from nonstoichiometric melt solutions, that is an excess of one of the components (self-fluxing mixtures)), and 3) the two-component system forming solid solutions A_{1-x}B_x , which requires special techniques for growing macroscopic homogeneous mixed crystals. The diagram illustrating the most commonly used solution growth method (Fig. 7) is discussed in more detail: In the A/B system (no solid solutions), to enable as wide a range of T (largest value of ΔT) on the solubility curve to be utilized practically, the eutectic temperature T_E should be reached at a low concentration of $X_{\text{substance}}$. Below the liquidus curve and adjacent to it, there is a metastable state, such that when this is crossed, spontaneous nucleation takes place. In the metastable region of the phase diagram, the reactions of Scheme 4 take place. These reactions have so far been very little investigated experimentally. A complex array of processes and conditions determine the width (ΔT) of this important zone. These include cooling velocity, hydrodynamic state, concentration of dissolved and undissolved foreign substances, type of solvent and extent of solvation, dwell times, etc. In the case of mass crystallization (see Section 3.1), the attempt should be made to cause nucleation in the system without too large a step beyond the metastable zone. If seed nuclei are used, it is advantageous to superheat the system, and then to keep it always within the metastable zone, so that controlled growth is then possible without the formation of secondary nuclei.

With regard to the classification of crystallization processes to be described later, it should be said that if crystallization is regarded as a phase change of a system of one or more components, this leads to a systematization of the general methods (Laudise,^[99] Arend^[100]). Sections 3 and 4 give more details of individual processes.

2.3. Morphology as a Property

Growth processes lead not only to the formation of the real structure of a crystalline solid (which largely determines its physical properties), but also to the creation of a morphology, which determines the real structure by means of the growth mechanisms of the individual faces, and also creates additional properties. The scale of this effect extends to large three-dimensional crystals with specific crystal habit, two-dimensional epitaxial thin films, one-dimensional fiber crystals or whiskers, and "zero-dimensional" "quantum dots". For about 15 years, methods of two-dimensional crystallization (liquid-phase epitaxy (LPE), MBE, and MOCVD) have enabled functional semiconductor structures to be produced.^[70, 71] Homo- and heteroepitaxy increasingly includes other classes of materials such as oxides (ABO_3 ferroelectric materials,^[98, 101] magneto-optic garnets^[102]), and even organic compounds. Also in the area of three-dimensional crystals, process control of the morphology has become important. The Stephanov process,^[103] for example, enables crystals of sapphire and LiNbO_3 in the form of plates, tubes, and other shapes to be pulled. Silicon single crystals for solar cells have recently been produced with a profile in the form of a thin-walled polygon (see Fig. 2).^[63]

In industrial mass crystallization and general crystal growth, those molecular processes are of interest which lead to the formation of a specific growth morphology. Here, the distinction

must be made between mechanisms for pure substances and those influenced by surface-active [(*hkl*)-specific or site-specific] foreign materials. For pure substances, the morphology is determined by stability/instability criteria in the crystal–nutrient interface (CNI), and is essentially controlled kinetically. Depending on the extent of supersaturation and on the mass and heat flow, polygonal, hopper-shaped, dendritic,^[49] and irregular (even fractal)^[7] growth is observed (Fig. 8).^[72]

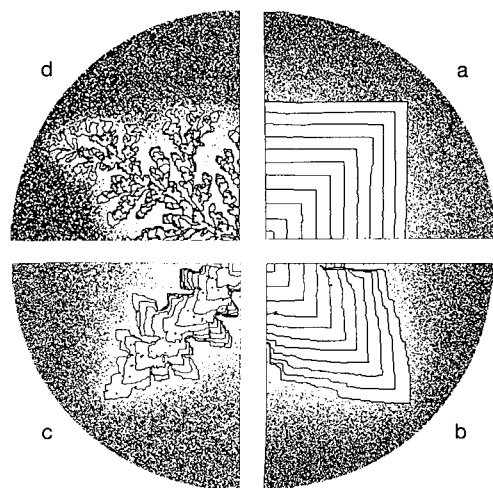


Fig. 8. Monte Carlo simulations of growth in two dimensions as a mathematical function of the driving potential (from [72]). a) Polygonal surface growth, b) transition to hopper-shaped growth, c) dendritic growth, d) irregular growth.

In general, the end morphology of a faceted crystal is determined by the slowest growing faces. The theory of Hartman and Perdok can be used to predict flat crystal surfaces (“periodic bond chains”, so-called PBC vectors;^[104] for new developments see ref. [85]), according to which, the (*hkl*) faces with the lowest energy of attachment of a growth layer show the lowest face growth rate *R*.

Even small concentrations (ppm) of suitable foreign substances can influence growth, for example, by molecular recognition mechanisms, and can retard rapidly growing surfaces. With the synthesis of tailored additives (“habit modifiers”), the formation of a desired crystal habit or form of agglomerates is realized in industrial crystallization,^[52, 62b] enabling the properties of a large number of products in powder form to be controlled (purity, bulk density, dissolution rate, etc.). The activity of foreign substances is deduced experimentally from the form of the function $R(\sigma, X_{\text{foreign substance}})$. Here, it is certain that in situ atomic force microscopy will yield interesting results within the next few years.^[78] As well as the effect of the foreign substance on *R*, the effect on the nucleation rate *J* is of practical as well as theoretical interest. The majority of the well-known crystallization problems in organic synthetic chemistry must to some extent be caused by small or large amounts of mainly unknown foreign substances.

Considerable progress in the understanding of molecular recognition processes achieved during the last decade,^[29, 35] have, according to Davey et al., had the result that “tailor-made additives for the control of specific processes are now a reality”.^[62b]

3. Experimental Methods of Crystallization

Crystal growth is a science and an art. The scientists' role in the crystal growth process is that of an assistant who helps molecules to crystallize. Most molecules, after all, are very good at growing crystals. The scientific challenge is to learn how to intervene in the process in order to improve the final product.
Etter^[105]

Following the classification made in Section 1, the techniques of mass crystallization and of true methods of crystal growth (exploratory and advanced) are treated separately. We shall therefore collate the crystallization techniques described in the chemical literature, briefly discuss them, and hence elucidate the basic principles of the most commonly used process of solution crystallization. The obvious consequences for methods of mass crystallization on the laboratory scale are set out in Sections 3.1 and 3.2. As examples of bulk growth, three crystal growth processes are described in Section 3.3. These are used in materials research into molecular substances for nonlinear optics.

3.1. Mass Crystallization on the Laboratory Scale

The processes listed in Sections 3.1.1–3.1.5 are described in the extensive literature on industrial crystallization^[50, 106] and chemical laboratory practice:^[15, 17, 18]

3.1.1. Crystallization from Solution

Crystallization from solutions has mainly two aims: the isolation of a solid, which was synthesized in solution, and the stepwise purification of a soluble solid. Isolation: Crystallization is achieved by 1. complete, usually rapid (isothermal) evaporation of the solvent (rotary evaporator); 2. partial or complete, usually slow (isothermal) evaporation of the solvent (crystallizing dishes, open to the atmosphere or in a desiccator); 3. slow or rapid reduction of the temperature of a saturated solution (without evaporation); 4. freezing of the solvent; 5. precipitation by the (isothermal) addition of reactive components or solvent components to reduce solubility (addition by diffusion or with stirring); 6. salting out by the (isothermal) addition of a strong electrolyte; 7. spray drying by rapid evaporation of the solvent by pressure reduction (flash evaporation); 8. freeze drying; 9. electrocrystallization; 10. molten salt synthesis (at high temperatures);^[107] 11. hydrothermal synthesis.^[108]

Here, in practice, crystallization is essentially performed more rapidly than with single-crystal growth, the purity of the substances obtained is rather less, and the crystallized material often shows inclusions of solvent. Success depends greatly on the choice of solvent,^[109] and on the nature of the impurities present. Van der Sluis et al.^[110] have used statistical analysis methods to determine which solvent molecules are preferentially included in the crystal lattices of known organic compounds: water to 61%, dichloromethane to 6%, benzene to 5%, methanol to 4%, acetonitrile to 2%, and dimethyl sulfoxide to

0.5%. These figures indicate the proportion of the structures that can include solvent molecules or form solvates. It should also be noted that the concentration and frequency of the inclusions are strongly dependent on the growth conditions (kinetic effects, see Section 2.1), which are usually not discussed in this connection.

Even if the aim of the crystallization is the isolation of a compound, the principle applies that the material should be purified by other methods before crystallization, and analysis for trace elements or molecules for control purposes should be included.

If a compound needs to be purified in a stepwise manner, this can be achieved by crystallization with rejection of mother liquor or by fractional crystallization with reuse of mother liquor.

3.1.2. Crystallization from the Melt

Crystals that form from molten substances can be obtained by zone melting carried out one or more times, by Bridgman techniques or by solidification of a supercooled melt. Whereas solution processes cover almost the entire range of classes of materials, melt crystallization is restricted to those that are thermally stable in the liquid state at their melting point, and where chemically inert vessels are available (a problem with high-temperature superconductors, see Section 4.2). Zone melting has been of great importance for the purification of thermally stable materials for a long time.^[111] Bridgman techniques have been applied in many cases.^[34]

3.1.3. Crystallization from the Gas Phase

Crystals form from the gaseous state by 1. sublimation and desublimation in a vacuum or in a gas flow, 2. chemical transport, 3. reactive deposition from the gas phase (chemical vapor deposition CVD). Quantitative crystallization from the gas phase is usually of limited application due to the low vapor pressure of the component being transported. With semiconductor materials (Si, ZnSe, ZnS, SiC, etc.), CVD is an important process.

3.1.4. Crystallization in the Solid State

Crystals form likewise from solids by 1. recrystallization, 2. devitrification (slow crystallization of supercooled organic and inorganic glasses), 3. reactive solid-state diffusion and ceramic synthesis, 4. sol-gel syntheses of ceramic materials.^[112]

The crystallization of the so-called oils of organic compounds (glassy, high viscosity condensed phases), which is often described as difficult, is here discussed in more detail. The fundamental investigations of Tammann have led to the formulation of rules for the nucleation behavior of organic melts (see Section 2).^[15, 18] According to these, for complex molecular materials, the temperature T_N of the maximum rate of nucleus formation J can be considerably below the temperature T_G of the maximum rate of crystal growth. As exemplified by glycerine, this difference can be as much as 65 K in exceptional cases.^[34] It is generally known that many organic melts that are thermally fairly stable (benzophenone, salol, benzil, etc.) can be strongly

supercooled,^[113] without producing growth nuclei within a reasonably short time. As the nucleation rate J is in general reduced by dissimilar dissolved materials, prior purification and trace analysis are of the greatest importance, and active impurities must be limited to the ppm concentration range. To bring about the crystallization of analytically pure, stable, but difficult to nucleate supercooled melts (see ref. [15], therein Fig. 1, 2), the samples are preferentially heated above the melting point, slowly supercooled (1 K min^{-1} to 1 K h^{-1}), and repeatedly subjected to temperature cycling at temperatures just below the melting point (5–20 K), so that the oily substance does not completely harden in the supercooled region (insufficient diffusion, Eq. (d), Section 2.1). Slow heating and cooling, with periods of constant temperature (hours to days), at various temperatures (induction periods) can be helpful in finding the regions for T_N and T_G , which sometimes do not overlap. For most real systems (material + its surroundings), heterogeneous nucleation is more probable than homogeneous nucleation. Therefore, purification of the melts should only involve the removal of dissolved impurities. The introduction of a matrix with a similar lattice structure can lead to crystallization by heteroepitaxial processes. For other induction possibilities (e.g., by ultrasound), see references [18, 50].

3.1.5. Crystallization by the Formation of Derivatives

Several organic compounds crystallize better 1. as salts (alkali metal or ammonium salts), 2. as hydrochloride, 3. as metal-salt complex, 4. as molecular compounds (diastereomeric reaction partners for racemate separation), or 5. as inclusion compounds.^[114]

3.1.6. Basic Principles of Chemical Crystallization from Solution

Although many methods are available, for most newly synthesized substances, only crystallization from solution (temperature reduction or evaporation) is used. (For a critical review of crystallization from solutions and melts, see Matz.^[50]) The further development of efficient and versatile laboratory methods of solution crystallization that take advantage of established knowledge of nucleation and growth mechanisms are therefore still important for synthetic chemistry.

If one wishes to obtain crystals from solution efficiently, the following points should be taken into consideration:

- 1) Choice of a chemically stable two-component or multicomponent system without formation of solid solutions and with a eutectic temperature T_E for small values of $X_{\text{substance}}$ (see phase diagram in Fig. 7; solvents: see refs. [34, 109]).
- 2) Exclusion of components that inhibit nucleation and growth (which may include solvents).
- 3) Suitable concentration range for crystallization: $\approx 5 \text{ wt\%} \lesssim X_{\text{substance}} \lesssim 30 \text{ wt\%}$ (for systems showing good nucleation properties, superheating for a short period at 5–20 K above saturation temperature is recommended; otherwise not). When growing large single crystals, the $X_{\text{substance}}$ concentration should be as high as possible.
- 4) The optimum nucleation and growth temperatures (in particular for molecular crystals) are usually considerably below

the melting point of the pure material, and considerably above the eutectic temperature or the melting point of the pure solvent.

- 5) After successful nucleation (N) at $T_N < T_G$ (Fig. 7), volume growth (G) should be carried out closer to the saturation temperature (but always within the metastable region) and with increasing depletion of the solution at a temperature that is reduced in a controlled manner with thorough mixing (maintenance of constant supersaturation). The chemical laboratory equipment normally available is not suitable for these operations. A heating bath with programmable temperature is required (see Section 3.2).
- 6) When working with spontaneous nucleation, small amounts of insoluble solids should not be removed for the first crystallization of the compound, as these usually reduce the nucleation threshold. However, for later crystallization, solid particles can lead to macrodefects (inclusions of solution and particles), and are to be avoided.

If careful attention is paid to the complex relationships during crystallization and to systematic working methods, a solution to many difficult problems can be found, sometimes quite quickly. This implies that proficiency in crystallization should always remain a part (preferably increasing) of theoretical and practical chemical education.

This results in the following approach for chemical mass crystallization:

- 1) The first nuclei are prepared by exploratory methods of crystal growth (see Section 3.2).
- 2) Mass crystallization (on the laboratory scale) is carried out by using process control comparable to that used in growing bulk single crystals. This increases the chance (in the sense of Section 1) that the synthetic chemist will, on average, obtain significantly larger crystals than hitherto, and that (in special cases) it will be possible to use these for an initial determination of solid-state physical properties.

By this "trick of the trade", the area of interest and the experimental practice of traditional synthesis may be extended in the direction of single-crystal synthesis and solid-state properties of interesting classes of substances. So-called "exploratory" methods of crystal growth can be of further assistance, as these attempt to give maximum control of the process at minimum cost.

3.2. Exploratory Methods of Crystal Growth

Compared with the major improvements of the last decade in almost all structure-determination steps of X-ray crystallography, crystallization lags behind.

Van der Sluis et al.^[115]

In Section 1 we commented on the significance of crystallization for chemistry. Crystal structure investigations must today be the largest (nonindustrial) consumer of small single crystals. The preparation of suitable samples ($d \approx 0.1-0.3$ mm, as isometric as possible) is therefore becoming more and more the rate-determining step. Initial attempts at designing a versatile set of apparatus for purposeful crystallization are already in existence.^[100, 115, 116]

Exploratory techniques have the advantage that they require relatively simple equipment in the chemical laboratory and that only small amounts of substance are necessary. The process operation has the best possible control of crystallization parameters, preferably self-regulating. During the measurements the solution and crystallization phenomena can be visually observed. The crystals can be removed without mechanical and thermal stress and without serious surface contamination.

With the aim of applicability over as wide a range of substances as possible, the following should be considered:

- 1) Isothermal evaporation (Fig. 9), 2) temperature reduction (also in a gel, Fig. 10), 3) temperature difference methods (Figs. 12, 13), 4) isothermal diffusion (in droplets (Fig. 14a), using membranes (Fig. 14b), in a gel (Fig. 14c), or through a coating), 5) melt growth in capillaries, 6) sublimation/desublimation (evaporation from Knudsen cells, Fig. 17), 7) chemical transport and reactive evaporation, 8) high-temperature solution growth (see Section 2.2, Fig. 4), and 9) hydrothermal solution growth (miniaturized equipment, see Fig. 18).

For methods 1–5, it is necessary to have chambers with temperature control, homogeneous heating, and controlled atmospheres (commercial ovens are not always suitable), which incorporate visual observation by a binocular microscope, and where small crystals can be removed.

The important features of these techniques are illustrated in Figures 9, 10, and 12–19. For example, for controlled isothermal evaporation (Fig. 9), the walls of the vessels should be such that the solutions do not creep up them to a great extent (silanated glass or polytetrafluoroethylene (Teflon) should be used), unless it is intended to use this as an effective method of promoting nucleation. The junction of the walls to the floor should be

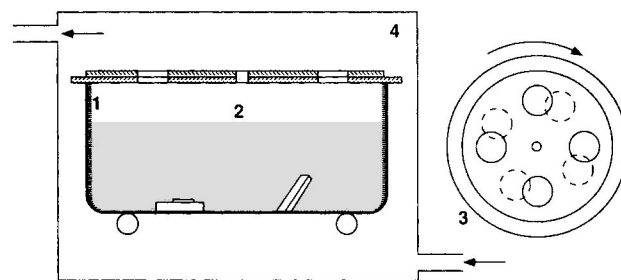


Fig. 9. Crystallization vessel with flat or slightly convex bottom for isothermal evaporation of the solvent. 1: Silanization to prevent creeping of the solution. 2: Supersaturated nutrient phase. 3: Lid with turnplate with apertures for the regulation of evaporation rate. 4: Arrangement in homogeneously heated chamber with through flow of gas and access for observation and removal of samples; $T = \text{constant}$.

gently rounded and it is advantageous when the floor is convex (the vessel being held vertical by standing it on a ring), and the clearance of the loosely fitting lid can be adjusted by a turnplate. A saturated solution of the substance to be crystallized should be prepared in a separate vessel at the evaporation temperature, and, before charging, 5–10 vol% solvent should be added to reduce the concentration below saturation. When the first crystals become visible, the solution is usually too strongly supersaturated, causing rapid growth to start. This should be retarded by a slight increase in temperature (if $\partial X_{\text{substance}}/\partial T > 0$). The

gas flow through the evaporation chamber should be reduced at the same time. It is recommended that the first crystals should be almost completely redissolved in the solution, so that they can then be allowed to grow slowly as has been described. The removal of small crystals ($d \approx 0.1-0.3$ mm) requires great care. A thin-walled capillary can be used with a mechanical means of applying reduced pressure (with fine adjustment), so that the small crystal brings with it a minimal amount of solution. The nutrient phase and the crystal are then ejected into a large volume of preheated liquid in which the crystallized compound is less soluble (only for stable hydrates and solvates). After a small amount of etching of the crystal, it is again picked up and transferred to the absorbent base of a preheated container, which also serves for the removal and slow cooling of the crystal. Meanwhile, the growth of the remaining crystals continues fairly undisturbed. The other crystallization methods also require an equal amount of care. In general, isothermal evaporation is the preferred choice if $\partial X_{\text{substance}}/\partial T < 0$. High-temperature variations of the method are discussed by Elwell et al.^[96] and Wanklyn.^[97]

Crystallization in a gel by reducing the temperature (Fig. 10 right): Crystallization from gels is usually used for sparingly soluble salts, by using counter-current diffusion.^[34, 117, 118] For

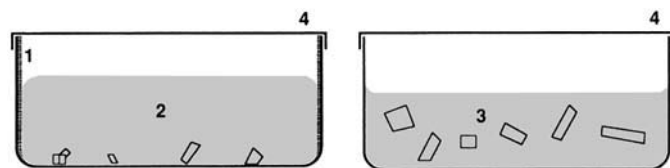


Fig. 10. Crystallization vessels for lowering the temperature of a solution (left) or of a gelled solution (right). 1: Silanization. 2: Solution. 3: Gelled solution (in superheated state). 4: Lid with observation facility (similar to Fig. 9).

substances of normal solubility, an aqueous or ethanolic/aqueous solution can, for example, be gelled in the supersaturated state by adding 5–10 vol% tetramethoxysilane (Arend et al.^[119]) in the superheated state. Nucleation takes place normally in a strongly supercooled state. This is retarded by increasing the temperature, and the process then changes to slow growth of single crystals. The crystallization from gels by reducing the temperature has the advantage that phenomena associated with convection are prevented; thus, growth takes place purely by diffusional matter transfer. If gels are absent, the crystals grow preferentially at the bottom of the vessel and are fed from one direction only. For the same reason, the growing nuclei in a gel tend to be more widely separated (self-regulating mechanism), so that fewer agglomerates are produced. Typical growth times after the induction phase are weeks or months. Small crystals are picked up together with a piece of gel, and then treated in the manner already described. By using flat (closable) dishes and a relatively thin layer of gel, the continued growth of remaining crystals is possible. The gel growth method has recently been used successfully for nonlinear optical organic compounds (Fig. 11).^[120a] This very simple method provides serious competition to the technique of growing molecular substances in space (removal of gravitational convection).^[120b] Also, experiments with gels should be valuable for the investiga-

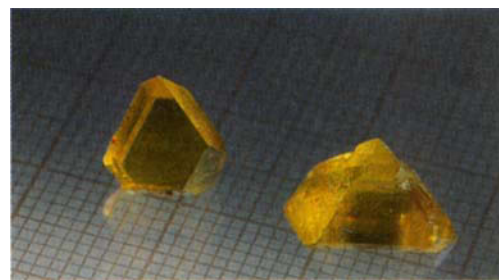


Fig. 11. Solution growth of PNP (B. Brezina, ETH, Zürich): Gel growth by lowering the temperature (left: maximum crystal size $d \approx 1$ cm), and by growth in a solution moving with laminar flow (right: starting from a b platelet seed crystal, the crystal grew preferentially in the direction of the pyroelectrically negative pole ($\Delta T > 0$) of the polar twofold axis; see Fig. 21). Use: measurement of nonlinear optical and electro-optical effects [169].

tion of deviations from the 1:1 distribution of D and L crystals (“chiral symmetry breaking”^[121]) as the mobility of secondary nuclei is here much reduced.

Temperature-difference method (Fig. 12): This system has a wide application spectrum (provided that $5 \lesssim X_{\text{substance}} \lesssim 30$ wt %, $\partial X_{\text{substance}}/\partial T > 0$ ^[122]). The separately saturated solu-

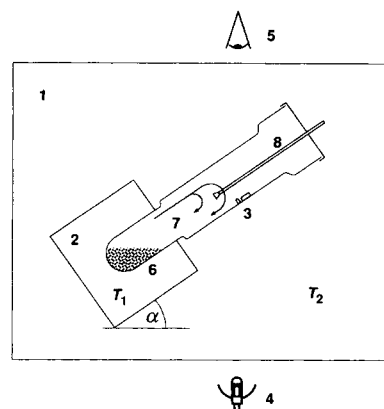


Fig. 12. Crystallization by the temperature-difference (ΔT) process (from [122], modified). Arrangement for the observation of spontaneous crystallization or growth upon nuclei. 1: Thermostatically controlled air bath. 2: T -controlled Al block inclined at angle $\alpha = 10-30^\circ$ ($\Delta T = T_1 - T_2 = 1-5$ K). 3: Glass vessel with rectangular center section [123] and screw lid. 4: Cold light illumination. 5: Observation by binocular microscope. 6: Supply of solid phase. 7: Flow due to thermal convection. 8: Holder for seed crystal (eccentrically mounted) for seed-growth experiments.

tion at T_2 is placed in the glass vessel (with a small excess of solid phase at the bottom), so that, in the temperature gradient $\Delta T = T_1 - T_2 < 1-5$ K, the solution, rising by natural convection, becomes supersaturated, and begins to form nuclei spontaneously (self-regulating mechanism). The central part of the closed vessel should preferably be a smooth rectangular glass vessel (inside dimensions: 12, 15, 23 mm),^[123] so that the faceted growth of the crystals is not disturbed by the curvature of the vessel wall. Two conditions are recommended to give the most favorable crystallization parameters: a) Single-sample operation, as described in Figure 11, while observing with a binocular microscope and slowly increasing ΔT , b) series operation in a crystallization matrix (Fig. 13). Around 50 crystallizing

vessels can be placed in conventionally heated cabinets fitted with the appropriate equipment. As indicated, crystallization can also be carried out by using seed nuclei. The small crystals should be removed in the manner described. Typical crystallization times can be several weeks. As this process operates after reaching a stationary state of constant supersaturation, it can also be used to produce macroscopic homogeneous single crystals of solid solutions.^[122]

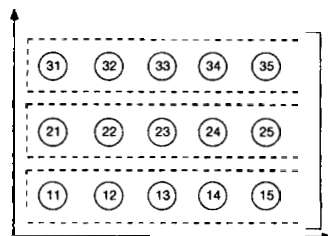


Fig. 13. Crystallization matrix for the determination of optimum growth conditions; on the y axis the temperature difference ΔT is varied and on the x axis the solvent is varied. Series arrangement using sample tubes in a matrix [123] PR_{ij} (i : ΔT , j : solvent) in a heated cabinet [122]. The temperatures of the blocks (shown by dashed lines) are individually

controlled, so that a constant $\Delta T(i)$ with respect to the ambient temperature (i.e. of the heated cabinet) is obtained. The blocks have several holes (numbered) for the sample tubes PR_{ij} . ΔT influences the supersaturation and flow velocity.

Based on many years of experience (Arend, Hulliger) with a wide range of classes of substances, the chance of success of crystallization with the ΔT method is over 90%. It is possible to extend the process to large crystals^[122a] and to the use of high temperatures (approximating to hydrothermal in subcritical pressure ranges).

The isothermal diffusion method (Fig. 14) also has a wide application spectrum, and the "sitting-drop" version of this is reported to be most successful.^[115] Also included here is gel crystallization by counter-current diffusion of two components

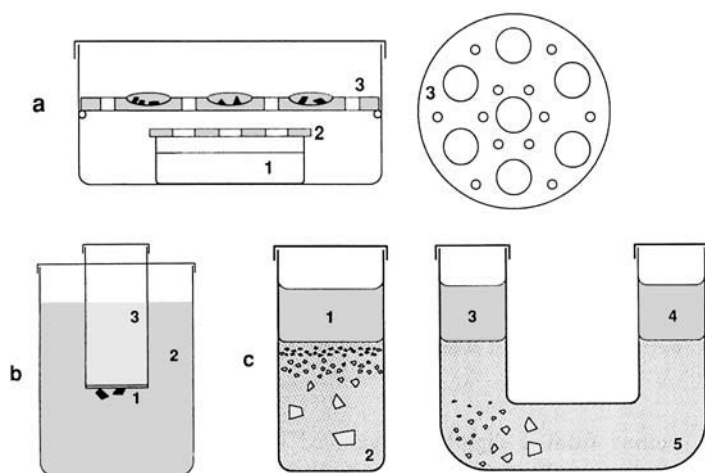


Fig. 14. Crystallization by isothermal diffusion a) "sitting drop" method. 1: Precipitating agent, 2: control of evaporation rate, 3: plate with hollows for receiving the drops (see also commercial products for protein crystallization); b) diffusion through a membrane. 1: Membrane, 2/3: solution/precipitating agent; c) two types of diffusion in the gel (see also [34, 117]): mostly unidirectional diffusion into the gel (left-hand diagram 1: precipitating agent or second component) or counter-current diffusion (right-hand diagram 3, 4: components A and B in solution), 2: gel with crystallizing substance, 5: initially pure gel.

(a slow precipitation reaction), in general using inward diffusion of components that reduce solubility or change pH (substance example:^[124] see Fig. 15). It is also possible to work with the help of a membrane.^[125]



Fig. 15. Gel growth of silver periodate by pH reduction ($AgNO_3$, H_2IO_6 , and sodium silicate gel). Yellow crystals: $Ag_2H_3IO_6$, red-brown crystals (black in photograph): Ag_2IO_5 [124].

Melt growth in capillaries may be used if, for example, only small amounts of material are available. The cylindrical crystallizates formed can be used for X-ray work, either together with the capillary (Lindemann glass) or after etching. A modern application of melt growth in glass capillaries is in the production of nonlinear optical organic fibers (Fig. 16).^[126]

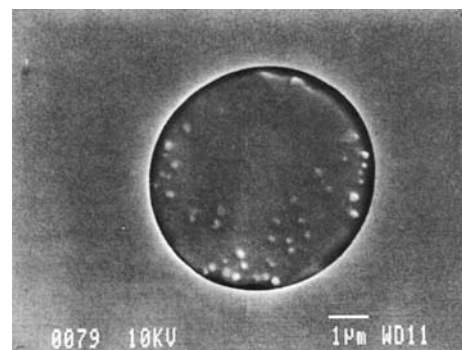


Fig. 16. Modern application of melt growth in glass capillaries. Fiber single crystal of 4-(*N,N*-dimethylamino)-3-acetamidonitrobenzene (DAN). Internal diameter = 6 μm . With DAN fibers, a high efficiency was obtainable in optical frequency doubling experiments (Nd:YAG, 1064 nm) (Kerkoc et al. [126]).

Sublimation and Desublimation (Fig. 17): In addition to the well-known variations of gas-phase crystallization, the technique of controlled evaporation from Knudsen cells should be mentioned here.^[127] This system (Fig. 17) can be used for crystallization by forming derivatives, but particularly for producing macroscopically homogeneous solid solutions (other processes are given in ref. [34] and by Karl^[111]).

Possible processes for crystal growth by using chemical transport reactions are described in the well-known work of Schäfer.^[128]

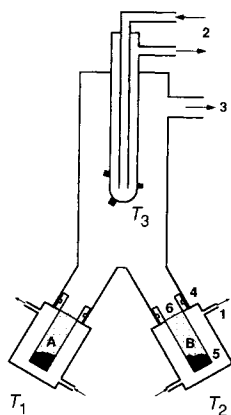


Fig. 17. Growth from the gas phase by controlled evaporation from Knudsen cells [127]. (T_1 , T_2 : cell temperatures, T_3 : temperature of deposition (cold finger). Suitable for the growth of mixed crystals $A_{1-x}B_x$ by separate evaporation of A (T_1) and B (T_2), and for low temperatures (unstable compounds). 1: Inlet or outlet for heating liquid. 2: Connections for coolant. 3: To high vacuum pump with cold trap. 4: Knudsen cells sealed with O-rings. 5: Supply of solid phase. 6: Aperture for controlled evaporation rate at cell pressure $p(T)$.)

The hydrothermal crystallization process involves considerable cost.^[34, 129] Moret has developed a small apparatus for exploratory work (Fig. 18),^[130] which was used in reactive counter-current diffusion experiments for forming single crystals of a series of compounds, including NiFe_2O_4 , KFeF_4 , Te_4O_9 , PbCu_6O_8 , Cu_2I_2 . The construction of autoclaves, in general, is described by Laudise et al.;^[131] the hydrothermal synthesis of inorganic substances by Rabenau.^[108]

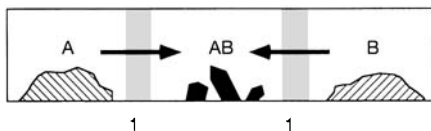


Fig. 18. Schematic diagram of a hydrothermal reactor for the synthesis of AB by counter-current diffusion of the starting materials A and B through a diaphragm (1). Miniaturized, easily operated equipment for the synthesis and single-crystal growth of small crystals is described by Moret [130]. (Reactor dimensions: $l \approx 15$ cm, internal diameter ≈ 0.7 cm; see also [108]).

This discussion of the practical aspects of exploratory crystal growth is deliberately not oriented towards particular classes of substances, but has attempted to propose a developable range of basic equipment whose design must be optimized in individual cases. The classification of processes according to substances is based only on distinctions such as low melting point, high melting point, stability/instability, etc. The substance-based approach, which corresponds more closely with chemical thought, has not proved useful in crystal growth. Chemically unimportant differences in the structure of the molecules or in associated impurities can affect crystal growth disproportionately, and can influence the choice of process decisively. The present approach should provide useful guidelines and should enable crystallization to be carried out by the most adequate means as the *last synthesis step*. It should also lead to an improvement in the reproducibility of crystallization results in the majority of cases.

3.3. Discussion of Modern Methods of Advanced Chemical Crystallization

A fairly complete overview of advanced methods used today can be obtained from the following articles: Gilman (Ed.),^[132] Pamplin (Ed.),^[133] Laudise,^[99] Elwell et al.,^[96] Dryburgh et al.

(Eds.),^[134] Wilke et al.,^[34] Arend et al. (Eds.),^[135] and Hurle et al. (Eds.).^[136]

Three processes will be described in more detail. These are currently used for growing single crystals of nonlinear optical molecular crystals. Their applicability to other classes of compounds depends on specific properties which cannot be discussed in general terms.

3.3.1. Crystallization from Slightly Supercooled Organic Melts

Under certain conditions, the strong tendency of organic melts to supercool (Section 3.1.4) can be successfully used for the synthesis of single crystals of cm^3 dimensions, and for making single crystals that are almost perfect crystallographically. For this, pure materials are required that are sufficiently thermally stable for long periods (days or weeks). These are melted, preferably degassed, superheated (10–20 K), slightly supercooled ($\Delta T \approx 0.1$ –2 K), and can then be crystallized by the complete immersion of a seed crystal. Scheffen-Lauenroth et al. and Klapper^[137] have recently demonstrated the usefulness of this method with salol, benzophenone, and benzil. Using equipment similar to that shown in Figure 19 (left), a strongly nonlinear optical compound (COANP: 2-cyclo-octylamino-5-nitropyridine) could be crystallized (Fig. 19 right).^[138] Crystal

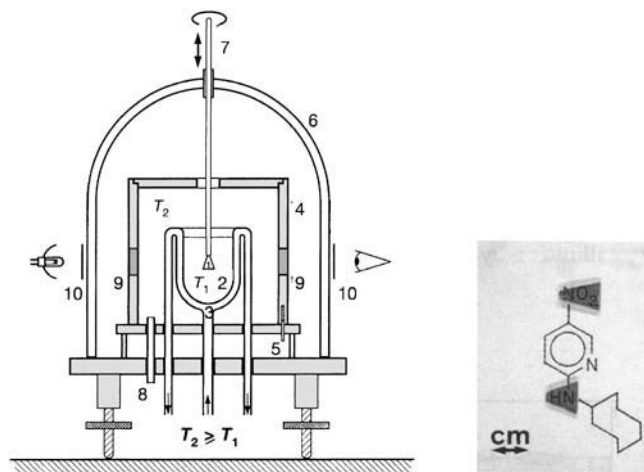


Fig. 19. Left: Crystallization from a supercooled melt (Hulliger et al. [138]). 1: Seed crystal (completely immersed; crystal pulling also possible). 2: Isothermally heated melt. 3: Glass vessel with water cooling. 4: Heating for gas atmosphere. 5: Pt-100 control thermocouple. 6: Vacuum hood. 7: Equipment for moving seed crystal (translation or rotation). 8: Inert gas inlet. 9: Red glass (protection against short wave light). 10: Polarizer, analyzer, and cold light illumination (IR filter not shown). Right: COANP single crystals (1 mm thick platelets) produced by crystal growth from slightly supercooled melts by complete immersion of the seed crystal [138]. Growth time: 1–2 weeks. Application: frequency doubling experiments and measurement of electro-optical effect [169].

pulling from a slightly supercooled melt produced cm^3 -size single crystals of COANP which had not been obtainable by other methods.^[139] Moreover, the same growth method has led to the discovery of the first purely organic photorefractive crystal.^[139, 140] The investigation of the physical state (vitreous state and cluster formation) of supercooled COANP melts is described by Kind et al.^[141] Crystal growth from supercooled melts has at least two important advantages over normal meth-

ods (zone melting and Bridgman techniques)^[34]: The growing crystal is surrounded only by the liquid phase (as well as by the seed holder), and the growth takes place under virtually isothermal conditions.

3.3.2. Crystallization by Isothermal Evaporation with Resaturation

The principle of controlled isothermal evaporation and resaturation has attractive advantages compared with temperature-reduction methods. This method is 1) possible when $\partial X_{\text{substance}}/\partial T \lesssim 0$ and for relatively small values of $X_{\text{substance}}$; 2) single-crystal synthesis is possible when the evaporation temperature is constant and as low as necessary (unstable compounds). Bösch et al.^[142] and Hesse et al.^[143] crystallized alkali metal hyperoxides, peroxides, as well as ozonides from liquid ammonia by this technique. Fuith et al.^[144] discussed the design of the apparatus shown in modified form in Figure 20 (and the growth of, for example, sulfate crystals). This apparatus is also used by the present author for organic compounds.

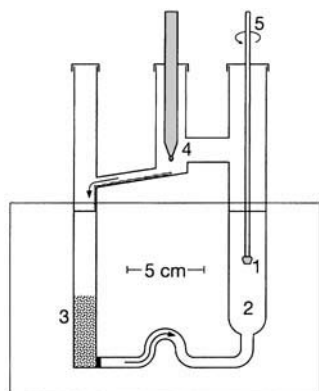


Fig. 20. Crystal growth by isothermal evaporation (arrangement placed in a thermostatically heated water bath) with resaturation (Fuith et al. [144], modified). 1: Seed crystal. 2: Solution with hydrostatic equilibration. 3: Nutrient material. 4: Cold finger (thermostat or Peltier element) for condensation of solvent. 5: Rotational movement of crystal (for relatively rapid growth).

3.3.3. Crystal Growth in Laminar Flow by Lowering the Temperature of a Solution

Convection phenomena or other uncontrolled flow conditions in the nutrient phase can reduce the width of the metastable area of supercooling^[68] and lead to the formation of undesired growing crystal surfaces (defect formation and morphological instabilities).^[91, 145] The hydrodynamic state of the system is more easily controlled by a directed, almost laminar flow over a seed nucleus (stationary or intermittently rotated, Fig. 21). Furthermore, thorough mixing is ensured by the careful selection of the method of propelling the solution. In some cases, growth rate by the solution process is considerably increased at increased flow velocities (several cm s^{-1}). This has been used for the relatively rapid growth of very large crystals of KH_2PO_4 (see Fig. 1).^[146] Also, in cases of strongly anisotropic growth, the directed flow improves deposition on slowly growing surfaces. This should have many small-scale applications. At the present time, the author is crystallizing nonlinear optical compounds, such as 2-(*N*-(*L*)-prolinol)-5-nitropyridine (PNP) (Fig. 11) and 4'-dimethylamino-*N*-methyl-stilbazonium-*p*-tosylate (DAST: one of the strongest electro-optical organic compounds known today) by this method.

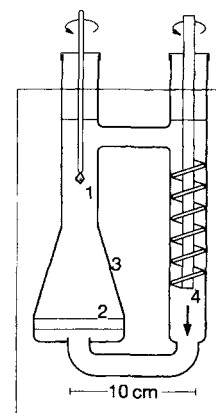


Fig. 21. Crystal growth by lowering the temperature (arrangement placed in a temperature-controlled water bath) under smooth fluid flow: 1: Seed crystal in a zone with almost laminar flow. 2: Diaphragm or glass spheres (disturbance of stream lines). 3: Cone (smoothing and compression of the flow). 4: Propulsion helix (Delrin).

4. Progress in the Single-Crystal Growth of Materials of Topical Interest

4.1. Special Literature Information

A wide-ranging review of developments in the crystal growth of approximately 2000 compounds is available in the latest edition (1988) of the highly regarded standard work of Wilke and Böhm (349-pages index of materials information and literature).^[34] Another compendium will be available in 1993, namely the first handbook of crystal growth, including the newer methods and materials (MBE, MOCVD, superconductors, proteins, etc.).^[136] Current work (e.g., CA selects, "crystal growth", etc.) is reported in the *Journal of Crystal Growth*, which also publishes the reports of the conferences held by the ICCG (International Conferences on Crystal Growth) that take place every 3–4 years. Journals of national speciality groups^[147] may also be of interest, since they publish lists of grown crystals (special materials), and name indexes from time to time.

4.2. High-Temperature Superconductors: Oxocuprates

Up to three or four years ago oxocuprates were a class of chemical compounds no more remarkable than countless others.
Müller-Buschbaum^[148]

With the discovery of the relatively high transition temperature of $\text{La}_{2-x}\text{Ba}_x\text{CuO}_4$,^[149] the superconductivity of several oxides [NbO , SrTiO_3 (doped), LiTi_2O_4 ($T_c = 13.7$ K), $\text{BaPb}_x\text{Bi}_{1-x}\text{O}_3$ ($T_c = 13$ K), known for quite a long time] became the center of interest of solid-state science virtually overnight.^[41, 150] Where is the challenge of growing crystals of this type of material?

It was soon realized that for $\text{La}_{2-x}\text{M}_x\text{CuO}_4$ ($M = \text{Ba}, \text{Sr}$) and the related compounds of Y-Ba-Cu-O, Bi-Ca-Sr-Cu-O, Tl-Ca-Ba-Cu-O, etc., the controlled three- and two-dimensional crystal growth (see Section 2.3) of the oxocuprates requires detailed knowledge of the stability regions (primary crystallization fields) of incongruently melting substances within a pseudo-ternary or pseudo-quaternary phase diagram, including oxygen pressure, so that the pure compounds can be crystallized from

nonstoichiometric melt solutions.^[151a] The determination of phase diagrams and the crystal growth itself are made more difficult by complex reaction equilibria that are established kinetically slowly.^[152] Moreover, the Ba-Cu-O liquid phase has extremely corrosive properties, which require the development of resistant crucible materials:^[153] "Corrosion of the crucible is the most basic problem for crystal growth of the high T_c superconductors" (Changkang^[151a]). The determination of the phase diagram of YBCO has given very variable results (Fig. 22).^[152e] Also, the use of foreign fluxing agents, in analogy to the usual process of flux growth, gives mainly negative results. Watanabe has tested nearly 100 flux compositions at various temperatures,^[154a] and concludes: "The present results suggest that a more extensive and detailed search for a suitable flux may be worthwhile: but there may be no suitable flux"^[154a] (apart from self-fluxing^[154b]).

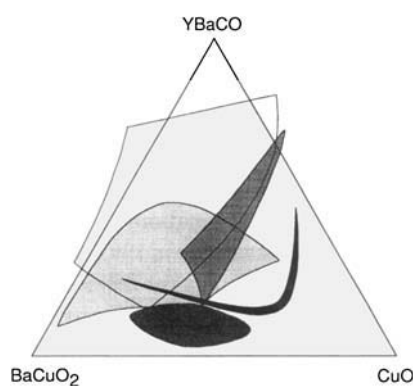


Fig. 22. Graphic design or the key to YBCO crystallization? Primary crystallization fields from the results of several authors (from [152e]).

Nevertheless, mm-size single crystals were occasionally produced. However, the still-awaited breakthrough in oxocuprate crystal growth depends on: 1) the chemical stability of liquid phases towards crucible materials yet to be developed^[151b] (cold crucible processes are conceivable), 2) knowledge of the phase diagram (T, X_i, p) and of the purity of the phases (effects of impurities), 3) the establishment of equilibrium (oxygen pressure) and the homogenization of the liquid phase (mixing, superheating), 4) the control of growth kinetics within the metastable region of supercooling. The solution of the crucible problem is of the greatest importance, and not only from the practical point of view: side reactions disturb the equilibration of the oxocuprate, so that relatively narrow existence and stability regions change continuously during phase diagram or crystal growth work.

Even if all these problems were solved (including problems of phase changes during cooling), large oxocuprate crystals may soon be of minor importance technologically; this does not apply to epitaxial and polycrystalline thin films. In this area, as well as LPE,^[155] gas-phase techniques^[156] have mainly been used, including laser ablation,^[157] RF sputtering,^[158] MBE,^[159] MOCVD, and even sol-gel techniques. This has stimulated developments in the epitaxy of other oxides, for example, in ferroelectricity.^[101] Just as the epitaxy of other materials (semiconductors and magneto-optic garnets) was achieved in a

similar way, a parallel development of substrate crystals is required for thin film growth of oxocuprates.^[160]

The known hurdles in three- and two-dimensional crystal growth of oxocuprates reveal themselves primarily as a chemical problem, and high-temperature and solid-state chemistry will be able to contribute greatly to its solution. In conclusion, it may be mentioned that advances have been made in the last 12 years in the crystal growth of organic superconductors (ambient pressure, $T_c(\text{max}) = 11.4 \text{ K}$).^[161, 162] The future may well have some big surprises in store directly stemming from the merging of these two worlds of chemistry (alkali metal- C_{60}, \dots).^[163] A real challenge for crystal synthesis!

4.3. Nonlinear Optical Molecular Crystals

Special donor-substituted and acceptor-substituted π -electron systems^[44] show optical frequency doubling or an electro-optical effect in crystals. These effects have appreciably higher or comparable values compared with those observed with inorganic substances known for a long time, such as LiNbO_3 ,^[164] KNbO_3 ,^[165] KH_2PO_4 (see Fig. 1).^[4, 166]

During the past 15 years, about 300 more or less strongly hyperpolarizable organic compounds were rediscovered for modern optics. Some of these were modified existing compounds and some were newly synthesized ("molecular and crystal engineering"), and were investigated as single crystals^[44] or Langmuir-Blodgett (LB) films,^[39b, 167] and in the form of poled polymers.^[168] In frequency doubling experiments with the Nd:YAG laser ($\lambda_0 = 1064 \text{ nm}$), for three-^[138, 169] and one-dimensional crystals^[126, 170] (see Figs. 16, 19 right), efficiencies of over 25% producing green light were reached. Reviews of compounds, crystal growth, and optical characteristics have been published by Zyss et al.^[44a] and in reference [171].

In three-dimensional crystal growth, it was necessary to work mainly with solutions (and gels) for stability reasons.^[120] By the method of temperature reduction and isothermal evaporation, cm^3 -sized crystals were produced of MBANP (2-(α -methylbenzylamino)-5-nitropyridine),^[171c] POM (methyl-3-nitro-4-pyridine-1-oxide),^[171a] NPP (N-(4-nitrophenyl)-(L/D)-prolinol),^[171a] PNP,^[172] DAST,^[173] and other compounds. Melt growth was used only infrequently (for example, for *m*-dinitrobenzene, *m*-nitroaniline, methyl-(2,4-dinitrophenyl)-amino-2-propanoate,^[171a] COANP,^[138] and DAN,^[126]), where the best conditions for obtaining the desired optical quality should be provided by slow growth from the homogeneously supercooled melt (see Section 3.3.1).

In analogy to other topical subjects, interest in two-dimensional crystallization is also increasing. With the achievement of growing μm -thick crystal platelets^[174] in a smooth (sometimes wedge-shaped) fissure, development is clearly proceeding in the direction of heteroepitaxy from the gas phase (MBE).^[175]

Faced with the wide variability of organic compounds, the salient question is not what can be achieved but whether the class of materials shows sufficient long-term stability after incorporation into an optical component. It is well known that the optical damage threshold of organic compounds is lower than with oxides or semiconductors. Also, in this field, a further chemically interesting task presents itself, namely, to find hyper-

polarizable systems that are significantly more stable photochemically and thermally than the amino- or hydroxy- and nitro- or cyano-substituted π -electron systems that have been used for a long time. Here, the resulting nonlinearity would be expected to be less, which reduces one of the important advantages compared with oxides. However, for electro-optical use, organic crystals and thin films of significantly more stable compounds should have a chance (a general discussion of application areas is given in [176]). The newly discovered photorefractive effects in organic crystals are even less researched.^[140]

4.4. Protein Crystallization

Many protein crystallographers believe that the growth of protein crystals is much more complicated than the growth of inorganic crystals
Rosenberger^[177]

The fact that it has taken so long to produce proteins whose crystals have sufficiently good diffraction properties (Bernal and Crowfoot, 1934) "... is undoubtedly partly due to prejudice..." (Lüttringhaus^[15]) although the crystallization of hemoglobin was first reported in 1840 (McPherson, historical review).^[178]

From the modern point of view, it is generally accepted that, as regards nucleation and growth behavior, proteins do not differ in principle from lower molecular weight substances.^[58, 179] Some differences arise from the biological origin of the samples and the fact that a protein crystal contains 30–80 vol% combined water. Hence, crystallization is carried out from water ($T \leq 30^\circ\text{C}$), usually after adding a controlled quantity of a precipitating agent [(NH₄)₂SO₄, 2-methyl-2,4-pentandiol, polyethylene glycol, etc.^[65, 180]] so that, for a given total system, the solubility behavior of the protein becomes a critical parameter of the process. When salts are used, the solubility decreases with increasing ionic strength. Although solubility properties have been widely researched, there is still no model that can explain what takes place when the type of precipitating agent or its concentration is changed. According to Sieker,^[180] experiments on 70 proteins produced crystals with a 60% success rate, although crystals of a quality good enough for X-ray structural analysis could be produced from only 70% of the crystallizable samples after further development of the crystallization techniques used.

The main difference in behavior compared with lower molecular weight substances is that a higher degree of supersaturation ($\sigma \approx 5-20$) is often necessary, together with a long induction period (lysozyme: 1–200 days depending on the concentrations of protein and NaCl).^[181] Because of the molar volume, ν^* is approximately 500 times as large for proteins as for lower molecular weight substances. For some years, induction periods have been investigated with dynamic light scattering, leading to conclusions about the diffusion and size of the scattering centers. This method could also be used diagnostically to establish the effectiveness of precipitation agents.^[179]

Work on the growth kinetics of macroscopic protein crystals has led to the conclusion that the rate-determining step depends on processes on the growth surface. The measured growth rates

R are of the order of a few 10^{-3} cm per day. In comparison with typical R values for other solution growth processes, protein crystals do not grow appreciably more slowly. On the other hand, at the molecular level, the mass transfer rate is approximately 10^{-3} times less^[116b] (a recent discussion of growth mechanisms is given by Weber^[58]). One of the remaining problems in the mechanistic investigation lies with the poor reproducibility of the data. Apart from the effects of impurities (including bacteria), this is certainly associated with the slow establishment of complex equilibria (folds and water inclusions, etc.). However, the use of the atomic force microscopy (AFM) method by Durbin et al.^[182] showed that the well-known BCF (see Section 2) mechanism^[80] for low molecular weight materials is in fact also valid for protein crystals.

Experimental methods of protein crystallization have been described by many researchers.^[58, 116b, 179, 180] In analogy to the methods described in Section 3, the following are available: 1. Isothermal diffusion, a) over the gas phase (5–50 μL , "hanging or sitting drop" method—the commonest), b) by using a membrane, c) in a gel ("hanging drop"),^[183] and d) by diffusion across the interface between the protein solution and the precipitant solution, and 2. temperature reduction (rare).

In addition to the literature mentioned previously, four conference reports *Crystal Growth of Biological Macromolecules* (1985, 1987, 1989, 1992) are worthy of note.^[184]

5. Summary and Future Prospects

It has become increasingly evident in the last few years that scientific aspects of crystal growth have attracted the attention of physicists, chemists, metallurgists, ceramists, materials scientists, mineralogists, geologists, as well as a small number of biologists, and that a substantial number of these people regard crystal growth as their special field of competence and interest.^[185]

Although these lines were written 25 years ago, large areas of synthetic chemistry have not yet adopted crystal growth as a possible special method of synthesis for building supramolecular structures with specific physical properties. Nevertheless, the development of a large number of single-crystal materials since the general upsurge in solid-state physics and materials science has shown the way towards the possibility of a chemistry that encompasses both the classical synthesis of new compounds and the formation of single-crystal phases with interesting properties. As well as giving an account of interdisciplinary cooperation and the theoretical side of the science of crystal growth, it seemed to me that the central topic was a discussion of recent developments in the systematic practical solution of crystallization problems. Here, the distinction has been made between exploratory methods, which are as simple and self-regulating as possible, and advanced methods of crystal growth. Crystallization is no longer an "outdated laboratory technique" for the chemist, but a modern and novel method of carrying out chemical syntheses in new areas of materials research.

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