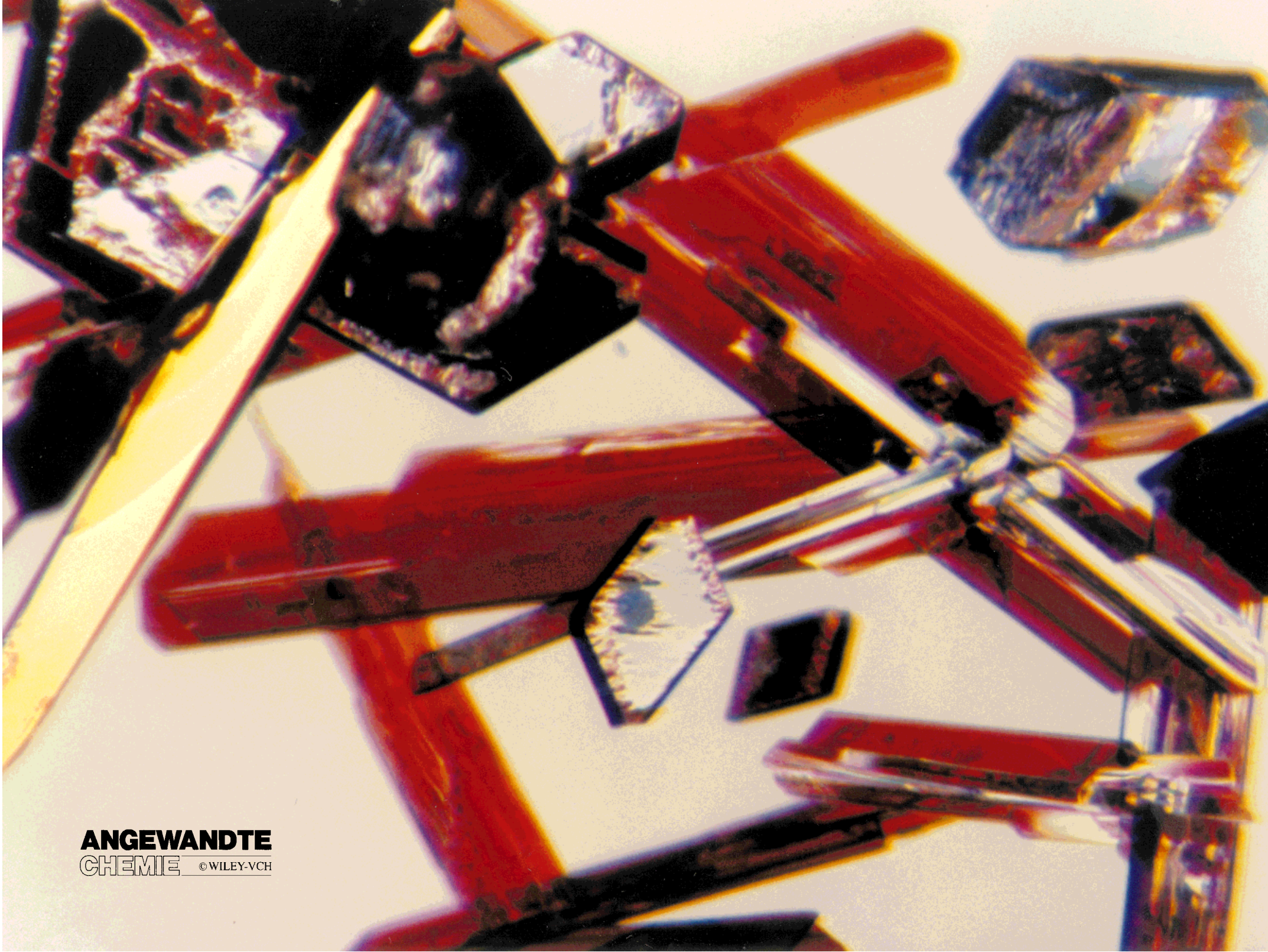

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Concomitant Polymorphs

Joel Bernstein,* Roger J. Davey, and Jan-Olav Henck

Chemists who encounter polymorphism for the first time are often unaware of its existence and baffled by its manifestations. Experimental problems might include, for example, variable or diffuse melting point, crystal batches with inconsistent physical properties (electrical or thermal conductivity, filtering, drying, flow, tabletting, dissolution), or two (or more) different colored or different shaped crystals in the same batch of (chemically) "pure" material. These problems arise because the conditions of the particular crystallization have led to the production of a number of polymorphs, which are present in the crystallizing medium or vessel at the time the crystals are harvested. The fact that polymorphs of a substance can appear concomitantly has long been recognized but rarely noted or studied. Is the phenomenon of concomitant polymorphs a curse or a blessing? It can be both. It is a curse for the chemist seeking a pure substance and a robust procedure to repeatedly and consistently produce the pure material, and the existence of concomitant polymorphs corrupts that procedure. It is a blessing, however, because (the recognition of) the existence of polymorphs in general, and concomitant polymorphs in particular, can provide the information and the opportunity to gain control over the crystallization process, and to achieve the desired specificity and robustness. An understanding of the competing thermodynamic and kinetic factors that govern the crystallization of polymorphs in general, or of a particular substance in particular, facilitates the control over the production of the desired polymorph, to the exclusion of undesired ones. Such control has important implications in a variety of industrial applications, of which pharmaceutical production and formulation is but one important example. This review covers the factors that govern competitive polymorphic crystallization and the rationale behind concomitantly crystallizing polymorphs, followed by a survey of concomitant polymorphs of a variety of chemical systems and a variety of crystallization procedures and conditions.

Keywords: concomitant polymorphs · crystallization · kinetics · polymorphism · thermodynamics

You can observe a lot just by watching.
Yogi Berra

1. Introduction

Even the title of this paper[1] requires close examination: are we referring to a description of the phenomenon of polymorphs that crystallize simultaneously or is this meant to be a practitioner's recipe for obtaining two or more polymorphs at the same time? The intent is the former, but in describing the phenomenon we certainly can provide hints on how one might accomplish the crystallization of polymorphs, if that were the desired experimental goal.

A polymorph has been defined as "a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state".[2] Different polymorphs have different structures and hence, in effect, each is a unique material with its own physical and chemical properties. Every student learns early on that crystallization is one of the principal methods of purification, and indeed most industrial processes that lead to solid products rely on this technique almost exclusively to prepare active materials which meet the regulatory and market demands of reproducibility and purity. In a polymorphic system, crystallization can result in the production of more than one material, in fact a mixture of materials; hence a knowledge of the processes that govern nucleation, crystal growth, and phase transformation in these systems is essential, on the one hand, for process control and, on the other hand, to ensure that maximum data and understanding are generated from experiments. This review

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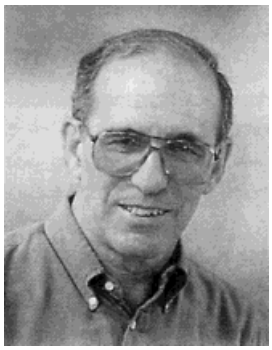
deals with a particular phenomenon which is not widely recognized but is associated with crystallization in polymorphic systems—namely that of concomitant crystallization of polymorphic crystal forms. We shall show that this is of particular relevance on two counts. First, from a scientific point of view, experiments that simultaneously yield crystals of different polymorphic structures potentially offer both structural and thermodynamic information not available when only one phase crystallizes. Second, from a commercial perspective, process conditions that result in concomitant crystallization are to be strenuously avoided since they lead to variable materials that do not meet prescribed specifications. We will address a number of questions related to this phenomenon:

1) Why do different polymorphs crystallize concomitantly?
2) How can concomitant polymorphic crystallization be achieved or avoided?
3) What information can be obtained by the observation and study of such systems?
4) What use can be made of such information?
5) What examples of concomitant polymorphs are available?

Although in the course of addressing these questions a number of examples will be given in demonstration, this paper is not intended to be exhaustive or comprehensive. It is meant to provide an introduction and an entry to a generally unrecognized phenomenon which, when properly recognized and studied, can provide useful information for a variety of disciplines.

2. Why do Polymorphs Crystallize Concomitantly?—The Qualitative Picture

Crystallization is a remarkable process that brings approximately 10^{20} molecules or ions into an essentially ordered array, and results in the same structure—or limited number of structures, in the case of polymorphism—for every crystal, in every laboratory, and, in principle, every time it is done. There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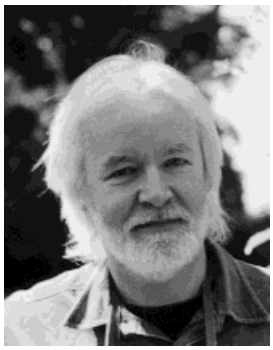
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Joel Bernstein was born in Cleveland, Ohio, in 1941. After obtaining a BA degree at Cornell University, he earned a PhD degree in physical chemistry at Yale University for research on the solid-state spectroscopy of organic compounds. Following two-year postdoctoral stints in X-ray crystallography with the late Ken Trueblood at UCLA and in organic solid-state chemistry with the late Gerhardt Schmidt at the Weizmann Institute of Science in Rehovoth, Israel, he joined the faculty of the newly established Ben-Gurion University of the Negev, where he is now Professor of Chemistry. His research interests center on the organic solid state, with particular emphasis on understanding and utilizing polymorphism, structure–property relationships, hydrogen-bonding patterns and graph sets, and organic conducting materials. His career has been punctuated by visiting professorships at the University of Illinois, Cornell University, and the University of Minnesota, and as a visiting scientist at the Cambridge Crystallographic Data Centre.

Roger Davey graduated as a chemist from Bristol University. He earned a PhD degree on crystal-habit modification with Professor J. W. Mullin at University College London and spent four years studying the growth of molecular crystals at the ETH in Zurich, Switzerland. He then joined ICI at their Corporate Laboratory in Cheshire where he became a Company Research Associate, eventually transferring to ZENECA's Process Studies Group at Huddersfield. He joined UMIST in 1995 and now holds the Chair in Molecular Engineering in the Department of Chemical Engineering and leads the Department's activities in the area of colloids, crystals, and interfaces. His research interests in solid-state and surface chemistry form the basis for a range of activities in crystallization, precipitation, phase transitions, and the design of surface-active molecules.

Jan-Olav Henck obtained his Diplom in chemistry from the Universität Essen (Germany) in 1993. During the experimental work on his master thesis on phase transitions of drug substances under pressure, at the pharmaceutical division of Bayer AG in Wuppertal-Elberfeld (Germany), he came in contact with the topic of polymorphism of drug substances. For further studies in this research field he moved to the University of Innsbruck (Austria), where he received his PhD degree at the Institute of Pharmacognosy with Prof. Dr. Artur Burger in 1996. His thesis on conformational polymorphism of n-butyl-substituted drug substances was awarded the State Capitol Prize from the city of Innsbruck for scientific research at the University of Innsbruck. During 1996–1997 he was an Alexander von Humboldt Foundation Postdoctoral Fellow (Feodor Lynen Program) with Prof. Joel Bernstein at the Ben-Gurion University of the Negev in Israel.

are exceptions, but it is these characteristics of the crystallization process that make it so attractive as a purification technique. As generations of chemists have learned, it is possible to define experimentally for any substance the solvent, temperature, rate of evaporation or cooling, and other conditions under which a material will crystallize.[6] This has been termed the *occurrence domain*.[7] This domain exists for any substance, but rarely, if ever, are its contents completely known. The contents of the occurrence domain for any material—in the present context, any polymorph—are not necessarily unique. In regions in which there is overlap of domains, one may expect that two or more polymorphs would crystallize under essentially identical conditions, thus leading to the phenomenon discussed in this review.

3. Polymorphism—Some Fundamentals

Like most chemical processes, crystallization in polymorphic systems is governed by a combination of thermodynamic and kinetic factors. We shall see in this and the following Section that it is in fact the interplay between thermodynamics and kinetics that makes concomitant crystallization possible. This section deals with the essentials of the thermodynamic processes involved. More detailed accounts may be found elsewhere.[8–13]

3.1. Thermodynamic and Kinetic Stability Amongst Polymorphs

Thermodynamic theory tells us that crystallization must result in an overall decrease in the free energy of the system. This means that, in general, the crystal structures that appear will be those with the greater (negative) lattice (free) energies. In polymorphic systems there are evidently a number of possible structures with similar lattice energies.

This drive towards free energy minimization will be balanced, as in all chemical changes, by the kinetic tendency of the system to crystallize as quickly as possible to relieve the imposed supersaturation. From the molecular point of view, the process of crystallization is one of supramolecular assembly in which the building blocks of the crystal assemble through the utilization of molecular recognition forces involving an array of intermolecular interactions as well as stereochemical packing constraints. If some structures are able to form more quickly than others then the system may, in the short term, settle for less than the maximum energy decrease, providing such a situation can be achieved at speed. A secondary transformation to a lower energy state can take place later.

The distinction between thermodynamic and kinetic influences is often demonstrated using the example of the graphite and diamond forms of carbon. The former is the thermodynamically preferred crystalline form, but kinetic factors (in particular, a high activation barrier) make the rate of transformation from diamond to graphite infinitely slow.[14]

3.1.1. Energy versus Temperature Diagrams

The energy versus temperature (E/T) diagram was introduced into crystallography by Buerger[15] in 1951 without application to any specific example. The theoretical derivation and practical application of this diagram have been described and discussed by Burger and Ramberger[11, 12] and by Grunenberg et al.[13] For simplicity we will limit the discussion to two polymorphic solids, although the extension to a larger number is based on the same principles.

The relative stability of two polymorphs depends on their free energies, the more stable polymorph having a lower free energy. The Gibbs free energy of a substance is expressed as Equation (1), where G and H are clearly functions of temperature and this variation may be plotted for one possible relationship between the two polymorphs and the melt (liquid) as in Figure 1. Such diagrams contain a great deal of information in a compact form, and provide a visual and readily interpretable summary of the often complex relationships among polymorphs.

$$G = H - TS \quad (1)$$

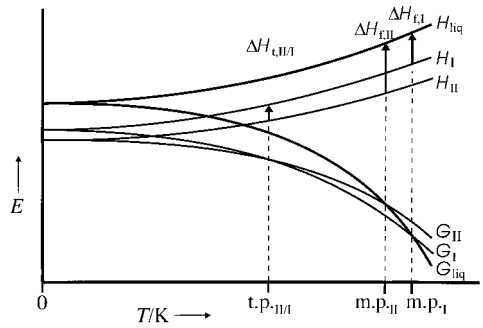


Figure 1. Energy versus temperature (E/T) diagram of a dimorphic system. G is the Gibbs free energy and H is the enthalpy. The Roman numerals indicate the two polymorphs; m.p. is the melting point and t.p.$_{II/I}$ is the transition point between the two polymorphs. This diagram represents the situation for an enantiotropic system, in which form II is the stable form below the transition point. (Reprinted from ref. [13] with permission.)

At absolute zero, TS vanishes so that the enthalpy is equal to the Gibbs free energy. As a consequence, at absolute zero, the most stable polymorphic modification should have the lowest Gibbs free energy. As mentioned above, at absolute zero the entropy term will play a role which may differ for the two polymorphs so that the free energy as a function of the temperature follows a different trajectory for the two polymorphs, as represented by the G_I and G_{II} curves in Figure 1. The two curves cross at the thermodynamic transition point t.p.$_{II/I}$, but since the enthalpy of II is lower than that of I, a quantity of energy $\Delta H_{t,II/I}$ is required to be input for the phase transition, which must be endothermic for the transition above t.p. and exothermic below t.p. for the situation that is depicted in Figure 1. The endothermic solid-to-liquid transitions at the melting points may be understood in the same way, with $\Delta H_{f,I}$ and $\Delta H_{f,II}$ denoting the respective enthalpies of fusion. Figure 1 represents an *enantiotropic* situation, since

t.p.$_{II/I}$ lies at a temperature below the melting points for the two polymorphs.

The *monotropic* situation is represented in Figure 2. In this case, there is no transition point below the melting points of the two polymorphs. The phenomenological manifestation of enantiotropism is that there can be a reversible transition from one phase to another without going through the gas or liquid phase. If the thermodynamic relationship is one of monotropism the two modifications are not interconvertible.[16] In the context of simultaneously crystallizing polymorphs, the thermodynamic aspects are clear. First, only at thermodynamic transition points can two forms have the same stability and hence coexist as mixtures at equilibrium. At any other temperature there will be a thermodynamic tendency to transform to the more stable structure. This implies that mixtures of polymorphs will have limited lifetimes, except at the thermodynamic transition point, with transformation kinetics playing a role in those lifetimes.

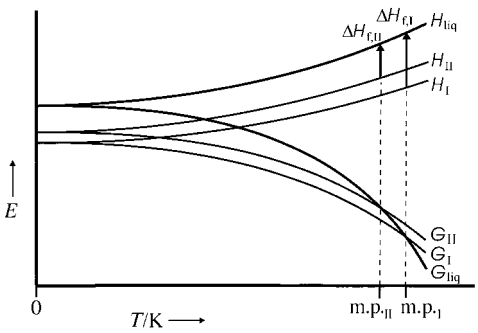


Figure 2. The E/T diagram of a monotropic dimorphic system. All symbols have the same meaning as in Figure 1. (Reprinted from ref. [13] with permission.)

3.1.2. *Vapor Pressure versus Temperature Diagram*

Another common representation of phase relationships is the pressure versus temperature (p/T) diagram. Figure 3 shows prototypical p/T plots for the enantiotropic and monotropic cases. These are best understood by traversing along various curves, which represent equilibrium situations between two phases. The liq./v. line in the high-temperature region of Figure 3a is the boiling point curve for the (common) melt of the two polymorphs. Moving to lower temperatures along that line, one encounters the II/v. line, which is the sublimation curve for form II. The intersection is the melting point for form II. Under thermodynamic conditions form II would crystallize out at this point and the solid part of the II/v. line would govern the behavior. However, if kinetic conditions prevail (for example, if the temperature is lowered rapidly) the system may proceed along the broken liq./v. line to the intersection with the I/v. line, at which point form I would crystallize. Continuing downward along the solid part of the II/v. curve, the crossing point with the I/v. sublimation curve is the transition point between the two polymorphic phases. Once again, if thermodynamic conditions prevail, form II will transform to form I. Under kinetic conditions form II may continue to exist (even indefinitely in some cases) along the II/v. sublimation curve. Figure 3a represents the enantiotropic case because the transition point between the two phases is found at a temperature below the melting point of form II, while Figure 3b represents the monotropic situation, in which the transition point is above the melting points of both forms.

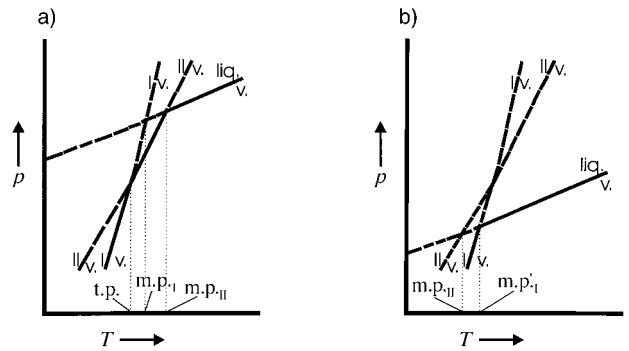


Figure 3. Pressure *versus* temperature plots: I/v. and II/v. represent sublimation curves, liq.v. is the boiling point curve. Broken lines represent regions which are thermodynamically unstable or inaccessible. a) Enantiotropic system; b) monotropic system. The labeling corresponds to that of Figures 1 and 2 to indicate that form I is stable at room temperature, which is below the transition point in the enantiotropic case. (Adapted from ref. [2] with permission.)

3.2. Some Practical Aspects of Relative Stabilities of Polymorphs

Knowledge of the enantiotropic or monotropic nature of the relationship between polymorphs can be used to steer crystallization processes to obtain a desired polymorph at the exclusion of an undesired one. For a dimorphic system there are four possibilities:

1) The thermodynamically stable form in a monotropic system: no transformation can take place to another form, and no precautions need be taken to preserve that form or to prevent a transformation.
2) The thermodynamically stable form in an enantiotropic system: precautions must be taken to maintain the thermodynamic conditions (temperature, pressure, relative humidity, etc.) at which the G curve for the desired polymorph is below that for the undesired one.
3) The thermodynamically metastable form in a monotropic system: a kinetically controlled transformation may take place to the undesired thermodynamically stable form. To prevent such a transformation it may be necessary to employ drastic conditions to reduce kinetic effects (e.g. very low temperatures, very dry conditions, storage in the dark).
4) The thermodynamically metastable form in an enantiotropic system: the information for obtaining and maintaining this form is essentially found in the E/T diagram.

Therefore, it is of practical importance (e.g. preformulation studies of a drug substance[10, 13]) to determine whether a system of concomitant polymorphs is monotropic or enantiotropic to enable the choice of and control over the desired

polymorphic form. The combination of experience with polymorphic systems and the accumulation of sufficient thermodynamic and structural data have permitted the development of some useful "rules" for determining the relative positions of the G and H isobars, as well as the enantiotropic or monotropic nature of the relationship between polymorphs.[11–13]

3.2.1. Heat-of-Transition Rule[11]

If an endothermic phase transition is observed at a particular temperature, this experimental transition temperature lies above the thermodynamic transition temperature. An endothermic phase transition is observed if two modifications are enantiotropically related and is represented in the E/T diagram by the intersection point of the G isobars of two modifications. If the phase transition is exothermic, there is no thermodynamic transition point below the experimentally observed transition temperature. This is generally observed if two modifications are monotropically related. Exceptions to this rule were discussed by Burger and Ramberger.[12]

3.2.2. Entropy-of-Fusion Rule

The entropy of fusion is easily accessible by means of differential scanning calorimetry (DSC), since the enthalpy of fusion and the melting point of a crystal can be obtained in one experiment ($\Delta H_f/T_f = \Delta S_f$). At the melting point, the difference between the Gibbs free energy of a modification and its melt is zero. If a modification with the higher melting point has the lower entropy of fusion, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower entropy of fusion.[13]

3.2.3. Enthalpy-of-Sublimation Rule

The enthalpy of sublimation of a particular crystal form is the sum of its enthalpy of fusion and enthalpy of vaporization. The latter is identical for all polymorphs of a compound. Therefore the enthalpy of transition for the transformation of one modification into another is the same as the difference in their enthalpies of sublimation[9] and their enthalpies of fusion. Thus, if the modification with the higher melting point has the lower enthalpy of sublimation, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower enthalpy of fusion.

3.2.4. Density Rule[11]

If a particular modification exhibits a lower density than another one at ambient conditions, then it may be assumed that, at absolute zero, this form is thermodynamically metastable. The energetically most favorable packing of molecules in a crystal has the strongest interactions between the molecules and hence the greatest density. The best possible packing also corresponds to thermodynamic stability. This energetically favorable modification requires more energy than any other modification to melt. At absolute zero, the form with the greatest density is thermodynamically stable. This approximation assumes that there is no great variation in the density of solids over a wide range of temperature. The two modifications are monotropically related if the higher melting modification shows the higher density. Otherwise they are enantiotropically related. Exceptions to this rule (e.g. resorcinol[17] or acetazolamide[18]) are discussed by Burger and Ramberger.[11]

3.2.5. Heat-Capacity Rule[13]

If the higher melting modification shows a higher heat capacity at a given temperature than another modification, these two crystal forms are enantiotropically related. Otherwise the two modifications are monotropically related.

3.2.6. Solubility and Dissolution Rates

In addition to differences in melting points, heats of fusion, entropies of fusion, densities, heat capacities, and virtually every chemical and physical property, different modifications can also exhibit different solubilities and dissolution rates. Since the solubility is directly proportional to the free energy of a modification, determination of solubility curves is the most reliable method of assessing the relative free energies of polymorphs. The difference in solubility of two polymorphs is a direct measure of the ΔG between them. It is important to note that although the absolute solubility (and hence the dissolution rate) of a polymorph will be solvent dependent, the relative solubility of different forms will not depend on the solvent used.

As discussed in Sections 4 and 5, the situations in which polymorphs concomitantly crystallize are determined by the experimental conditions in relation to both the free energy–temperature relationships and the relative kinetic factors. These situations may arise either because specific thermodynamic conditions prevail or because the kinetic processes have equivalent rates. In thermodynamic terms we have seen that polymorphs can only exist in true equilibrium at the thermodynamic transition temperature (where the G curves cross). The chance of carrying out a crystallization precisely at such a temperature must be small, with the inevitable conclusion that kinetics play at least some role in the overall process. The final consequence of this, of course, is that a system of concomitantly crystallizing polymorphs will be subject to change in the direction that favors the formation of the most stable structure. If the crystals have grown from and remain in contact with solution, the most likely route for this transformation is via the solution by dissolution and recrystallization.[2, 19] If the crystals have formed from the melt or vapor phase or have been isolated from their mother phase, solid-state transformation is possible.[20] Either way, keen observation is vital to recognize the phenomenon, as discussed in Section 5.

4. Why do Polymorphs Appear Together?—Kinetic Factors

The starting point for a discussion of the kinetic factors is the traditional energy–reaction coordinate diagram in Figure 4. This shows G_0, the free energy per mole of a solute in a supersaturated fluid which transforms by crystallization into one of two crystalline products, I or II, in which II is the more stable ($G_I > G_{II}$). Associated with each reaction pathway is a transition state and an activation free energy which is implicated in the relative rates of formation of the two structures. Unlike a chemical reaction, crystallization is complicated by the nature of the activated state since it is not a simple bi- or trimolecular complex as would be expected for a process in which a covalent bond is formed; rather it relates to a collection of self-assembled molecules with not only a precise packing arrangement but which also exist as a new separate solid phase.

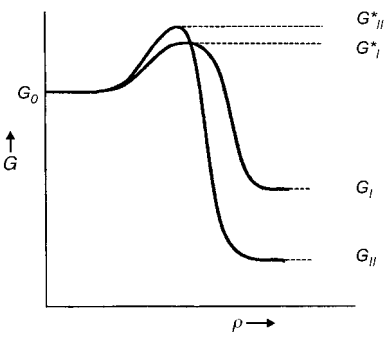


Figure 4. Schematic representation of the reaction coordinate ρ for crystallization in a dimorphic system to show the activated barriers for the formation of polymorphs I and II.

It is the existence of the phase boundary that complicates matters since this is associated with an increase in free energy of the system which must be offset by the overall loss of free energy. For this reason the magnitudes of the activated barriers are dependent on the size (i.e., the surface-to-volume ratio of the new phase) of the supramolecular assembly (crystal nucleus). This was recognized in 1939 by Volmer in his development of the kinetic theory of nucleation from homogeneous solutions which remains our best guide today.[21]

One of the key outcomes of this theory is the concept of critical size which an assembly of molecules must have in order to be stabilized by further growth. The higher the operating level of supersaturation, the smaller this size is (typically a few tens of molecules). In Figure 4, the supersaturation with respect to I is simply $G_0 - G_I$ and is lower than $G_0 - G_{II}$ for structure II. However, it can now be seen that if the critical size is lower for I than for II for a particular solution composition then the activation free energy for nucleation is lower and kinetics will favor form I. Ultimately form I will have to transform to form II, a process that we discuss later. Overall we can say that the probability that a particular form i will appear is given by Equation (2) in which

$$P(i) = f(\Delta G, R) \quad (2)$$

ΔG is the free energy for forming the ith polymorph and R is the rate of some kinetic process associated with the formation of a crystal by molecular aggregation. Thus, for example, if we follow the above reasoning we could equate the rate process with J, the rate of nucleation of the form. If all polymorphs had the same rates of nucleation then their appearance probability would be dominated by the relative free energies of the possible crystal structures.

The rates of nucleation as expressed by the classical expression of Volmer are related to various thermodynamic and physical properties of the system such as bulk and surface free energy (γ), temperature (T), degree of supersaturation (σ), solubility (hidden in the preexponential factor A_n) which will not be the same for each structure but will correctly reflect the balance between changes in bulk and surface free energies during nucleation. This is seen in Equation (3), which relates the rate of nucleation to the above parameters (ν is the molecular volume).

$$J = A_n \exp(-16\pi\gamma^3\nu^2/3\kappa^3T^3\sigma^2) \quad (3)$$

From this analysis it can be seen that the tradeoff between kinetics and thermodynamics is not at all obvious. Consider a monotropic, dimorphic system (for simplicity) whose solubility diagram is shown schematically in Figure 5. It is quite clear that for the occurrence given by solution compositions and temperatures that lie between the form I and II solubility curves, only polymorph II can crystallize. However, the outcome of an isothermal crystallization that follows the crystallization pathway indicated by the vector in Figure 5 is not so obvious since the initial solution is now supersaturated with respect to both polymorphic structures, with thermodynamics favoring form II and kinetics form I.

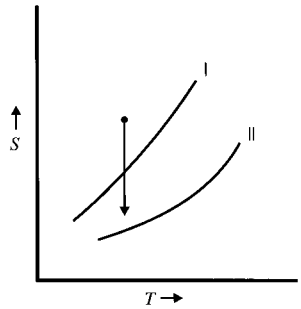


Figure 5. Schematic solubility diagram for a dimorphic system (polymorphs I and II) showing a hypothetical crystallization pathway at constant temperature.

Experimentally, the reality of this overall scenario of kinetic versus thermodynamic control was known long before the development of nucleation theory and is encompassed by Ostwald in his Rule of Stages in 1897.[22, 23] The German scientific literature between 1870 and 1914 contains many examples from organic and inorganic chemistry in which crystallization from melts and solutions yields an initial metastable form which is ultimately replaced by a stable structure, and Ostwald was led to conclude that "when leaving a metastable state, a given chemical system does not seek out the most stable state, rather the nearest metastable one that can be reached without loss of free energy".[24] Figure 6 shows an example of Ostwald's rule for potassium nitrate. It shows a group of rhombic (β form) crystals in contact with their mother liquor and their solution-mediated conversion to the more stable needle morphology (α form) by means of dissolution and recrystallization.

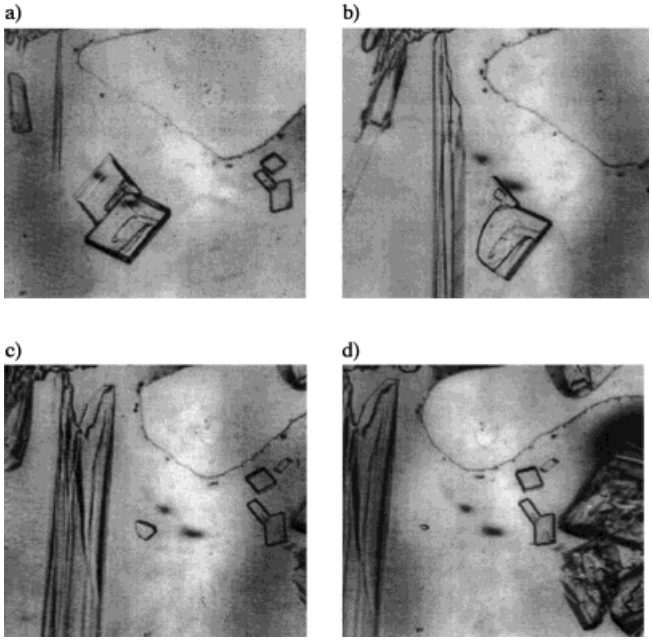


Figure 6. Time-lapse micrographs (×50) of the crystallization of potassium nitrate from aqueous solution at room temperature. a) After 1 min, showing well formed rhombs and a single needle (upper left quadrant); b) after 5 min—note the rounded edges of the rhombs due to dissolution and the enlargement of the needle; c) and d) after 10 and 15 min—note the further dissolution of the rhombs and growth of the needle.

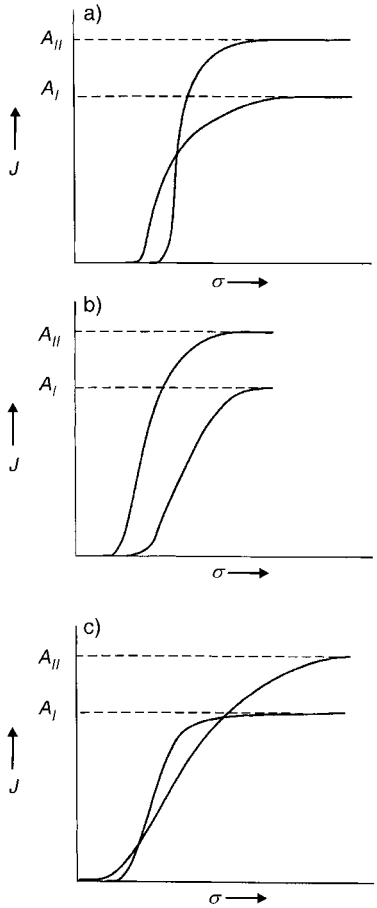


Figure 7. The rates of nucleation as functions of supersaturation for the dimorphic system defined in Figure 5. The three diagrams a, b, and c represent the three possible solutions for the simultaneous nucleation of two polymorphs each of which follows a rate equation of the form of Equation (3). Note that solutions a and c both allow for simultaneous nucleation of the forms at supersaturation levels corresponding to the crossover of the curves.

Of course this conclusion is significantly flawed: when a crystallization experiment yields only a single form there is no way of knowing whether it contradicts the rule or whether the material is simply not polymorphic. There is no way of answering this question. However, a sufficient number of cases of successively crystallizing polymorphic forms have been observed to warrant consideration of the principles behind Ostwald's rule as guidelines for understanding the phenomenon.

By making use of Volmer's equations, some attempts have been made by Becker and Doering, Stranski and Totomanov, and Davey to explain the rule in kinetic terms.[25] In doing so it becomes apparent that the situation is by no means as clear cut as Ostwald might have led us to believe. Figure 7 shows the three possible simultaneous solutions of the nucleation equations which indicate that, by careful control of the occurrence domain, there may be conditions in which the nucleation rates of the two forms are equal and hence their appearance probabilities are nearly equal. Under such conditions we might expect the polymorphs to crystallize concomitantly.

5. How Can Concomitant Polymorphs be Recognized?

Most cases of concomitant polymorphs have been recognized visually simply by a combination of curiosity, thoroughness, and keen observation. In the first years following the discovery of polymorphism by Mitscherlich in 1822,[26] the principal method of the study of crystals was observation and measurement on the microscope, particularly the polarizing microscope, and the measurement of interfacial angles on an appropriate goniometer. Differences in habit are indicative (but not necessarily conclusive) evidence of polymorphism, which could be confirmed by physical measurements such as index of refraction, melting behavior (including, of course, the melting point itself) and others. Groth's landmark compilation of such data contains many examples of polymorphism.[27] He was apparently also intrigued by the instances of concomitant crystallization of polymorphs, and compiled a list of examples in his book on chemical crystallography in 1904.[28]

With the emergence of X-ray diffraction and the development of more sophisticated methods of analysis, the discovery of concomitant polymorphs should have become more frequent—provided one is aware of the phenomenon. Even a variable melting point may be a sign of concomitant polymorphs since mixtures of different polymorphic composition can result from the crystallization, but also a peak on a DSC scan, or a broadening or doubling of lines in a solid-state IR or solid-state NMR spectrum may be signs for the existence of concomitant polymorphs. Still, probably the best

method for discovering them is careful thermomicroscopic examination on the hot-stage polarizing microscope,[29, 30] and three examples of the facility with which concomitant polymorphs may be observed on the hot-stage polarizing microscope are given in Figure 8.

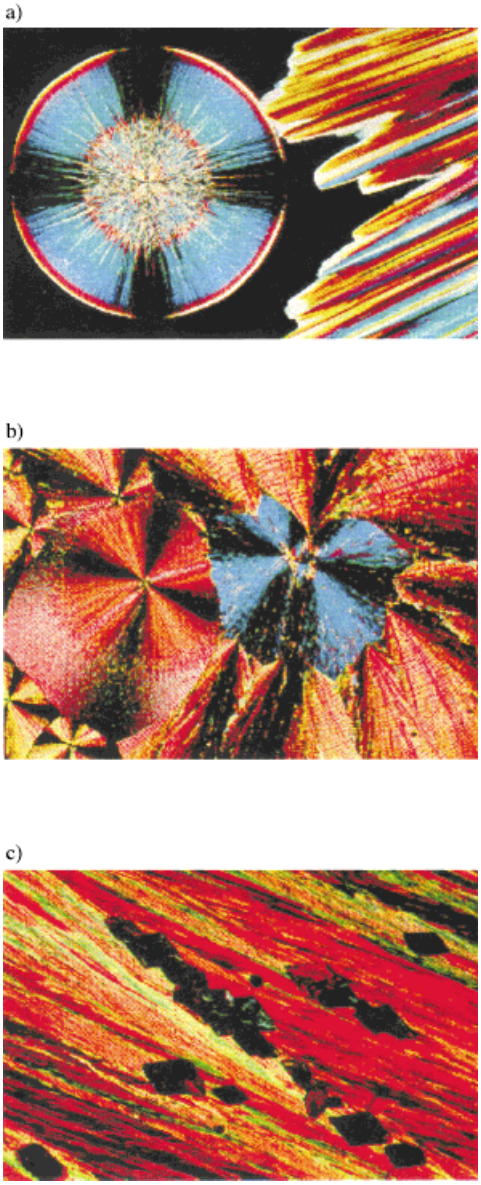


Figure 8. Cocrystallizing polymorphs as observed on the hot-stage microscope. a) Two crystal modifications of phenobarbital; b) three crystal modifications of nicotinamide; c) growth of the stable (diamond-shaped) crystals of sulfethidole from the unstable form. (Reprinted from ref. [30] with permission.)

6. What Are Concomitant Polymorphs Good For?

Polymorphs are of general interest because they represent special situations for the study of structure–property relations in systems with limited numbers of variables. They are also of interest since they provide unique data on the factors that govern molecular packing. Finally they are, as pointed out earlier, of extreme interest to those involved in the large-scale preparation of solid forms of specialty chemical and pharmaceutical materials.

Thus, if concomitant crystallization occurs, it offers the crystallographer the chance to maximize the data from a single crystallization experiment. It offers the formulation chemist the chance to measure physical properties and hence to select the structure that best matches the needs of the product. It gives the process chemist and chemical engineer a choice of which morphology might separate more effectively and also a warning that the process will have to be robust if a single polymorph is to be consistently isolated. For these reasons we believe that chemists should be aware of this phenomenon and maximize the information it offers.

Finally, we comment that since concomitant polymorphs are very nearly energetically equivalent structures, they provide excellent and demanding benchmarks for the validation of lattice energy programs[31] and so-called "polymorph predictor" programs.[32, 33] The programs and the force fields employed in those programs must reproduce the near equivalency of the crystal energetics, even if the absolute lattice energy is not reproduced or even not known.[34]

7. Examples of Concomitant Polymorphs

Apart from the above-mentioned section in Groth's book we are not aware of any other attempt to collect and document examples of concomitant polymorphs. It is a daunting, perhaps even impossible task to systematically extract additional instances from the literature.[35] Most examples given here were taken from our own experience, from chance encounters of descriptions of crystal growth procedures in the experimental sections of papers in the literature[24] or from responses to appeals by the authors at scientific meetings for testimonial cases from colleagues. One of the objects of this paper is to increase awareness of the phenomenon so it can become a keyword for indexing and abstracting, to enable future workers to take advantage of the useful information to be extracted from situations in which polymorphs crystallize concomitantly.

7.1. The Earliest Reported Concomitant Polymorphs

The first recognized example of a polymorphic organic substance was also an example with concomitant polymorphs. In 1832 Wöhler and Liebig described the dimorphism of benzamide.[36] They synthesized the material for the first time and initially found a melting point of 115 °C (later called modification II).[37] Reexamination led to a melting point of 128 °C (modification I). The lower melting modification crystallizes in featherlike needles while the higher melting modification shows blocks (Figure 9). It is of interest that if a hot saturated aqueous solution of benzamide is allowed to cool rapidly, one is able to observe by microscopy that the two modifications crystallize concomitantly, and in accord with Ostwald's rule. With increasing time the blocks of modification I grow at the expense of the feathery needles.

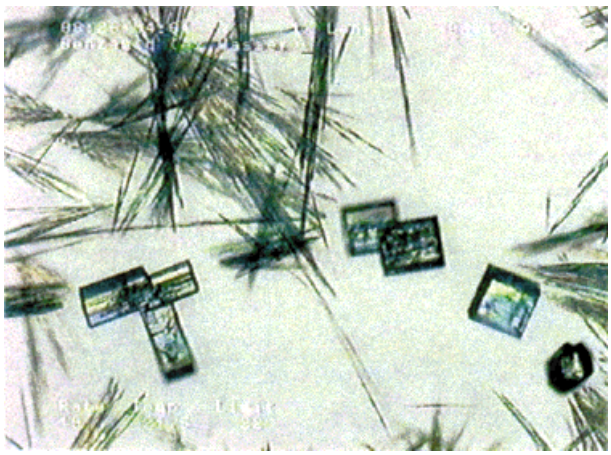
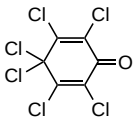


Figure 9. Photograph of the two forms of benzamide growing in aqueous solution. Form I are the blocklike crystals which grow at the expense of the featherlike needles of the less stable form II.

7.2. Groth's Collection

As noted above, Groth was apparently the first to collect a number of cases of the phenomenon of concomitant polymorphism from the literature until roughly the turn of the 20th century.[28] He noted that concomitant crystallization can occur for an enantiotropic system such as sulfur as well as in a monotropic dimorphous material such as "hexachloro-keto-dihydrobenzene, C_6Cl_6O" (**1**). He characterized the phenomenon as a "peculiarity" which is "analogous to the…indifference towards direct transformation" between polymorphic forms.



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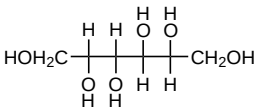

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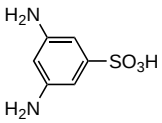

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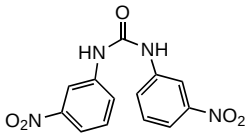

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Groth presents examples across a wide range of compound types, but what appears to be common among these examples is that keen observation was combined with considerable time and effort to study and characterize the compounds. Among the inorganic examples cited by Groth are telluric acid (H_6TeO_6),[38] ammonium fluorosilicate $(NH_4)_2SiF_6$,[39] sodium beryllium fluoride (Na_2BeF_4),[40] rubidium dichromate ($Rb_2Cr_2O_7$),[41] and ammonium paratungstate $(NH_4)_{10}W_{12}O_{41} \cdot H_2O$,[42] while the organic examples include mannitol $C_6H_{14}O_6$ (**2**),[43, 44] *m*-diaminobenzenesulfonic acid ($C_6H_3(NH_2)_2SO_3H$) (**3**),[45] and di-*m*-nitro-*s*-diphenylcarbamide $CO(NHC_6H_4NO_2)_2$ (**4**).[46] An organometallic salt exhibiting the phenomenon is dimethylammonium chloroplatinate $[\{NH_2(CH_3)_2\}_2PtCl_6]$.[47]

7.3. *m*-Nitrophenol: 120 Years of History

In spite of their generally keen powers of observation, the giants of 19th and early 20th century chemical microscopy and morphology certainly could have been aided by modern technology in the discovery of concomitant polymorphs. *m*-Nitrophenol is a case in point. The description of the material appears in Groth's book.[48] The two melting points quoted by Groth, 96 °C[49] and 93 °C,[50] and the description of the crystals might have suggested that the phase was not pure but the difference was within the acceptable range for different determinations. Groth himself had determined the interfacial angles in 1875, and Barker[51, 52] and Steinmetz[50] obtained similar results, with no hint of polymorphism.

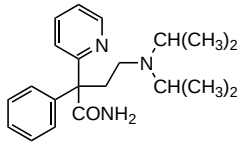
In 1934 Davis and Hartshorne[53, 54] determined indices of refraction as a technique for the identification of organic solids, including *m*-nitrophenol. They did note "occasional individuals (of crystals) with more or less rhombic outlines" amid monoclinic prismatic crystals (m.p. 96 °C) from water and benzene.

In 1972 Shigorin and Shipulo[55] reported that the compound exhibited a strong second harmonic generation (SHG), an effect known to require a non-centrosymmetric space group,[56] but Groth's morphological description indicated a centrosymmetric space group. In an attempt to resolve this discrepancy, Pandarese et al. carried out the crystal structure determination of the material described by Groth and others on crystals grown from the melt and from benzene.[57] The crystals were indeed centrosymmetric, in the common space group $P2_1/n$.

With the dilemma not resolved, they carefully reexamined many individual crystals from the benzene-grown batch, and discovered that approximately 20% belonged to the non-centrosymmetric orthorhombic space group $P2_12_12_1$, thus explaining the source of the SHG. A method for purifying *m*-nitrophenol and growing single crystals was developed by Wojack and Marqueton in 1989[58] and the structure of the orthorhombic form was published in 1996.[59]

7.4. Similar and Dissimilar Solubilities

One example from our own collection of concomitant polymorphs from solution is the dimorphic drug substance disopyramide **5**. Crystallization from *n*-hexane at 25 °C led to both modifications simultaneously. Gunning et al.[60] have described the solubility behavior and dissolution rates of two modifications of this material. They found no significant differences in the solubilities and the dissolution rates of the crystal forms at 37 °C. No thermodynamic or structural studies have been published until now.



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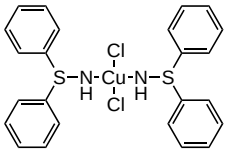
We prepared single crystals of the two forms, determined their thermodynamic properties, and solved their structures, which will be published in a separate contribution. The two crystal forms are enantiotropically related with a t.p. at about

40 °C. Modification II (m.p. 86 °C) crystallizes in rough blocks, while modification I (m.p. 96 °C) shows a needlelike habit. This example shows that similar solubilities and dissolution rates favor concomitant crystallization of different modifications.

The recent report of work on a neutral copper complex reveals some possible additional features of concomitant crystallization. Kelly et al.[61] prepared blue crystals of **6**, which precipitate from "reasonably concentrated (acetonitrile) solutions" with square-planar coordination geometry around the copper center (Figure 10). When the precipitate was filtered off and the remaining mother liquor treated with diethyl ether, followed by cooling in a freezer, concomitant crystallization of the blue crystals with green crystals occurred, in which the molecular structure exhibits pseudotetrahedral coordination geometry around the copper center.



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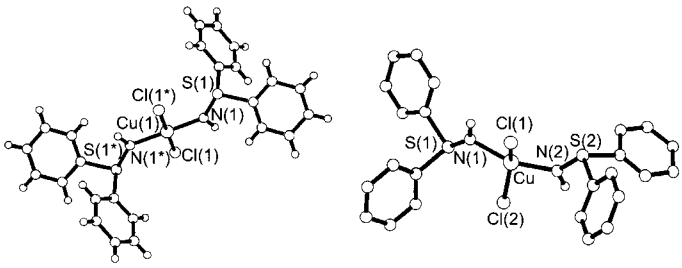


Figure 10. Molecular structure of the concomitant polymorphs of **6**. Left: the square-planar geometry found in the blue crystals. Right: The pseudotetragonal geometry found in the green crystals. (Reprinted from ref. [61] with permission.)

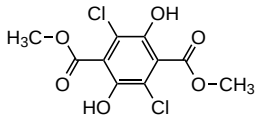
There is ample evidence that this also is a genuine case of polymorphism. The blue square-planar form can be dissolved to obtain the green tetrahedral one; indeed the authors state that the two form intergrowths, which apparently grow coincidentally. The green form is obtained only from dilute solutions, and once it is obtained the blue form cannot be regenerated. The sequence of events and the experimental conditions are compatible with Ostwald's Rule of Stages: the slight thermodynamic preference for the green form over the blue one (at least in dilute solutions—the melting points are essentially identical) and the phenomenon of "disappearing polymorphs".[62] Once seeds of the (even slightly) preferred green form are present in the immediate environment, the blue form cannot be obtained.

7.5. Trimorphic Concomitant Crystallization

The "diphenylcarbamide" **4** is, in fact, a urea derivative, and was recently studied by Etter et al. for apparently entirely different reasons.[63] As a symmetrically substituted urea derivative it was expected to exhibit a tendency to form polar chains,[64] while the substituents may be considered derivatives of *m*-nitroaniline and therefore might exhibit the known tendency of such compounds to avoid a centrosymmetric structure.[56, 65] However, it is the concomitant trimorphic crystallization behavior of this compound, which was extensively studied almost a century ago, that is of interest here.

The three reported forms are α, yellow prismatic needles; β, white needles; and γ, yellow tablets. Upon crystallization from 95 % ethanol in the range 30–75 °C, the α and β forms always crystallize concomitantly, even in the presence of seeds of one form. The relative amounts can be regulated by varying the temperature; α is preferred at higher temperatures. Upon evaporation of the mother liquid at "the ordinary temperature (13 °C)" γ crystallizes out alone; warming the same mother liquor leads also to some crystals of β; at 40 °C γ no longer appears, but small amounts of α appear. The authors conclude that on the basis of the experiments with 95 % alcoholic solutions, γ is the stable form at room temperature (considerably lower than room temperature today), and with increasing temperature, β and then α are the stable forms. However, this behavior may be modified by solvent. This is clearly a rich system with a very delicate balance between the relative stabilities of the three forms, as well as the kinetic factors that govern their appearance.

There are other examples of trimorphic concomitant crystallizations, generally recognized by differences in color. One, also originating in the early literature,[66] but on which a great deal of work has subsequently been done is methyl 2,5-hydroxy-3,6-dichloroterephthalate (**7**). The white and yellow forms were reported by Hantzsch in 1916[66] and studied by Byrn et at. in 1972,[67] but it was not until a thorough study was undertaken in 1989 that a third light yellow form was discovered by Dunitz and co-workers.[68] As the latter authors point out, visual observation during heating often reveals changes that are not detected by instrumental analytical methods, and it was this observation that led to the discovery of the previously undetected form.



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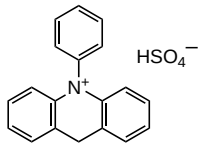
Crystallization of the dibromo derivative of **7** from concentrated ethanolic solutions yields first polymorphic modification I, which transforms over a period of a week to a second modification II, upon which small crystals of the first form adhere. Crystals of both modifications are recognizable and separable by their morphology and color: the first are colorless blocks or plates, while the second are colorless on some faces and light violet on others.[69]

The term coined by Hantzsch[70] for polymorphs that exhibit different colors is *chromoisomerism*, recently discussed in historical perspective by Kahr and co-workers.[71] An example given by Kahr, which is also one of concomitant polymorphs, is that of 9-phenylacridinium hydrogen sulfate (**8**) which yields equal masses of red and green forms from acetonitrile/DMSO (10/1). The physical basis for the color difference remains an enigma.



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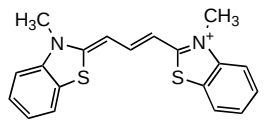
7.6. Concomitant Crystallization of Multicomponent Systems

Concomitant crystallization is not limited to single component systems. For the remarkable cyanine/oxonol system (**9**/**10**) at least fourteen different polymorphs or solvates have been identified.[72] Two of these, a gold and a red form (each containing a molecule of $CHCl_3$ solvent per 1:1 complex, and



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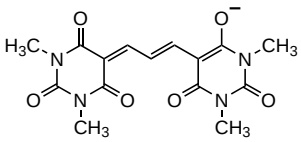

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hence true polymorphs) crystallize concomitantly and have been structurally characterized.[72] Three of these polymorphs are shown in Figure 11. Despite the fact that both of these dyes are known to be individually self-aggregating,[73] the two

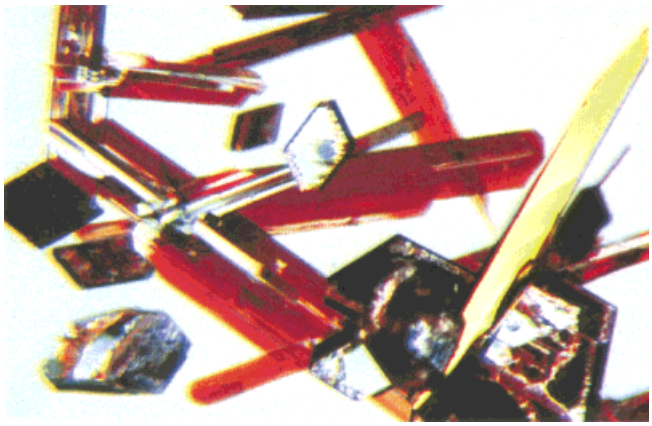
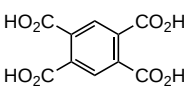


Figure 11. Three of the concomitant polymorphs of the cyanine/oxonol dyes **9** and **10**. The gold (by reflection; otherwise red by transmission) and red forms mentioned in the text are easily distinguishable. The third form is purple, normally diamond shaped as on the middle right, but many of these crystals are undergoing conversion, as indicated by varying degrees of mottled surfaces.

structures exhibit mixed stacks, with very significant differences in the relative orientation of neighboring molecules along the stack (Figure 12): in the case of the gold structure the molecular long axes are oriented nearly perpendicular to each other, while in the red polymorph the molecular long axes are very nearly parallel. Recently Bonafede and Ward have shown how edge-directed epitaxy on single crystal succinic acid substrates may be used for the selective nucleation and growth of the less stable red polymorph.[74]

The often serendipitous nature of the discovery of concomitant polymorphs is illustrated by another recent example of a two-component system, pyromellitic acid (**11**) and 2,4,6-trimethylpyridine (**12**).[75] The first polymorph (A) was



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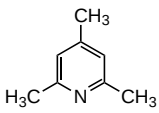

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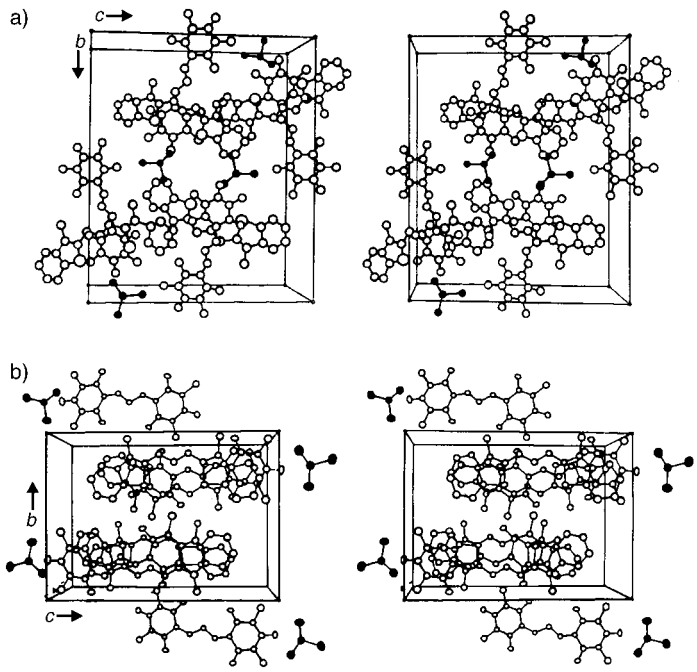
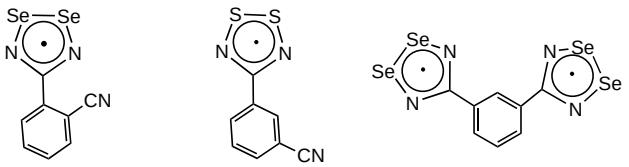


Figure 12. Stereoviews of the unit cells of the gold (a) and red (b) forms of the salt of **9** and **10**. a) View along [100] of the entire cell. Chloroform molecules of solvation (shaded black in the figure) fill (010) planes of the structure, providing stabilization by hydrogen-bond interaction with the oxonol dye. b) [100] view of the entire cell of the red form. Chloroform molecules represented in a similar manner. Both figures are viewed down the stack axis and indicate the relative orientation of cation and anion which is one feature of the overall packing. (Reprinted from ref. [72] with permission.)

obtained by the reaction of **11** with four equivalents of **12** in a methanolic solution. When **12** was used as the solvent, a second polymorph (B) crystallized in fifteen minutes. Form A was found to have crystallized as well in the same reaction vessel after about 24 hours. These two polymorphs are not readily distinguishable by their morphology. However, the authors point out that the experimental evidence indicates that form B is the kinetically controlled one, while form A is the thermodynamically preferred one.

7.7. Concomitant Crystallization by Sublimation

Concomitant crystallization is by no means limited to crystallization from solution, nor to preservation of constant molecular conformation. As noted in Section 3.1.2, the classic p/T phase diagram for two solid phases (Figure 3) of one material exhibits two lines corresponding to the solid/vapor equilibrium for each of two polymorphs. At any one temperature one would expect the two polymorphs to have different vapor pressures. This, in fact, is the basis for purification of solids by sublimation. Nevertheless there are examples where the two have nearly equal vapor pressures at a particular temperature and cosublime. For instance, the two compounds **13** and **14** both yield two phases upon vacuum sublimation.[76] For **13** slow sublimation at 140 °C and 0.1 Torr led to a mixture of a "few feathery needles" (m.p. 192–193 °C) among the main product of "lustrous coppery blocks" (m.p. 220–223 °C),



13 **14** **15**

which could be separated manually for further characterization. Compound **14** was also purified/crystallized by vacuum sublimation (120 °C, 10^{-2} Torr) to yield manually separable deep red needles (α phase, m.p. 157–160 °C) and blocks (β phase 165–168 °C). The crystal structure determinations of the two phases of **14** indicated significantly different molecular geometry (Figure 13), a cofacial dimer in the α phase, and a *trans* antarafacial dimer in the β phase.[77]

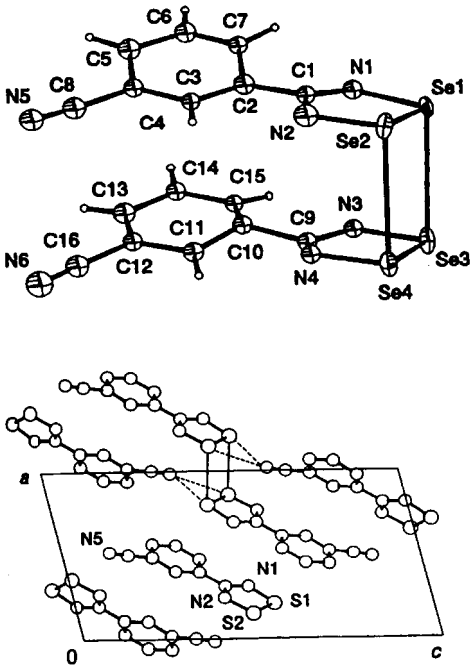
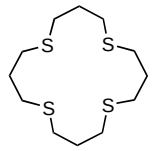


Figure 13. Molecular geometry in the two polymorphs of the dimers of **14** obtained by sublimation. Top: α phase, cofacial dimer; bottom: β phase, antarafacial dimer. (Reprinted from ref. [76] with permission.)

Another example of cosublimed phases is the compound **15** for which it appears that the sublimation conditions were systematically varied in an attempt to obtain a second polymorph.[78] The α form was initially prepared as a single phase of golden needles by slow sublimation over several weeks at 10^{-6} Torr during which the sample was heated to 180 °C and the cold finger was maintained at 100 °C. Raising the pressure to 10^{-1}–10^{-2} Torr and increasing the sample temperature to 220 °C, with a cold finger in the range 120–140 °C also led to the same α-phase needles, but they were accompanied by blocks of an additional β phase. The two can be separated manually. Clearly, the authors moved along the solid/vapor line of the α phase towards the intersection with the solid/vapor line of the β phase (see Figure 3).

7.8. Concomitant Crystallization by Solvent Diffusion

Concomitant crystallization has also been reported from solvent diffusion crystallization, which means that the concomitant forms have very similar solubilities in the same *mixture* of solvents—under the same thermodynamic and kinetic conditions. Such is the case for 1,5,9,13-tetrathiacyclohexadecane (**16**).[79] The material is reported to be trimorphic; all three forms crystallize in polar space groups [needles, $Pbc2_1$ (α); plates, $P2_1$ (β); and twinned, apparently $Fdd2$ (γ)]. The α and β forms are obtained simultaneously at ambient temperature by diffusion of hexane into dichloromethane solutions of **16**. Lowering the temperature to −130 °C for the same diffusion process leads exclusively to the γ form. The forms that crystallize concomitantly have unusual, but similar molecular conformations. Not surprising for the phenomenon observed, in particular for the α and β forms, the three melting points (59.5–60.2 (α), 57.8–59.0 (β), 60.0–60.9 °C (γ)) are very similar, and the authors used the technique of mixed melting points to verify the existence of the three polymorphs.



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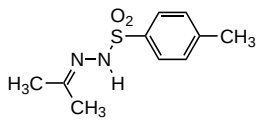
7.9. Concomitant Crystallization of Conformational Polymorphs

One of the definitions of polymorphism[2, 5, 80] requires that all polymorphic structures of a material dissolve, melt, or vaporize to give the same species or equilibrium mixture of species. If this is accepted as a definition, the time necessary for equilibrium to be achieved becomes an issue, as well as the temperature of the dissolution, melting, or vaporization process. Clearly, years is too long to meet this criterion, but are hours or days too long? The question is still open. Nevertheless, a number of cases of concomitant polymorphs demonstrate the principles.

Gleason and co-workers[81] recently reported the crystallization of two *conformational polymorphs*[82] of acetone tosylhydrazone (**17**). A triclinic form and a monoclinic form are obtained from anhydrous ethanol, sometimes together. If the crystallizing solution is allowed to evaporate completely, only the monoclinic form is obtained, which suggests that it is the thermodynamically preferred form at room temperature. This is consistent with Ostwald's Rule of Stages[22] and McCrone's test for relative stability of polymorphs:[2] the more stable polymorph will grow at the expense of the less stable one. The crystal structure determination indicates that the conformations differ by ≈15° about the S–C exocyclic bond. In this case, the solution has an equilibrium mixture of (at least) these two molecular conformations. Lattice energy calculations (Cerius2)[83] are consistent with this observation, and indicate that the triclinic polymorph is more stable than the monoclinic form by about 1 kcal mol^{-1}.



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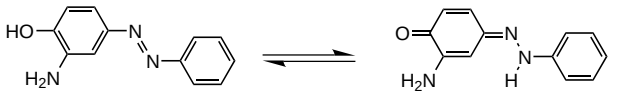
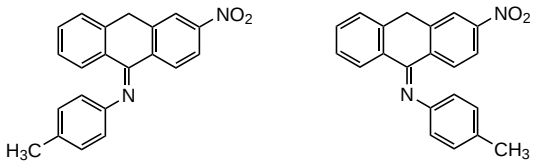
Another issue in the definition of polymorphs is that of *tautomerism*. An example of the crystallizing tautomeric structures of 2-amino-3-hydroxy-6-phenylazopyridine (**18**) has been reported by Desiraju,[84] **18a** being the "low temperature" form as lustrous blue needles and red **18b** being the



18a **18b**

"high temperature" form, both with melting points of 181–182 °C. They were obtained simultaneously from recrystallization of the crude synthetic product from ethanol, but the relative amounts varied from batch to batch in subsequent crystallizations when concentration and temperature were varied. The high temperature form was always obtained; the amount of low temperature form varied with the crystallization conditions. The tautomeric separation clearly takes place upon crystallization. To complete the picture and to make this, arguably, a case of polymorphism, it must be shown that the blue and red crystals dissolve to yield the same equilibrium mixture.

A case of concomitant crystallization which involves *configurational isomerism* has been reported by Matthews et al.[85] which again called into question the definition of polymorphism. The benzophenone anil **19** can exist in two configurational isomers, designated *E* and *Z*. The material has been shown to be trimorphic: a yellow form (triclinic, $P\bar{1}$, $Z=6$, m.p. 91 °C) and an orange form (triclinic, $P\bar{1}$, $Z=4$, m.p. 78–80 °C) often crystallizing from ethanol or benzene/diethyl ether at 0 °C. The third form (monoclinic $P2_1/c$, $Z=4$, m.p. 91 °C) is obtained from ethanol at room temperature.



(*E*)–**19** (*Z*)–**19**

In the first polymorph, all molecules exhibit the *Z* configuration. In the second, concomitant polymorph all molecules are in the *E* configuration. The third polymorph also contains molecules with *E* configuration. The conformations of the molecules in the second and third polymorphs differ slightly, which suggests that they might qualify as conformational polymorphs.[82]

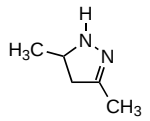
But should the first two structures be considered as properly belonging to a polymorphic system? Again, we can revert to McCrone's tests.[2] As Matthews et al. point out, these configurational isomers can interconvert at rates which vary by up to 10^{14}. If they interconvert quickly (i.e., on the order of hours) then they will give the same equilibrium mixture and may properly be called polymorphs according to the McCrone definition.

McCrone suggests some additional tests.[2] Two crystals of the same compound suspected of being polymorphic are placed side by side on a microscope slide in a mutually suitable solvent. If they are polymorphs of different thermodynamic stability the more stable one will grow at the expense of the less stable one. While it is not clear how soluble the polymorphs of **19** are in Nujol, when both the *E*-containing polymorphs were allowed to stand in Nujol for a few days the result was a conversion to the *Z*-containing polymorph. On the basis of the available evidence this does seem to be a case of polymorphism, in spite of the original authors' preference to avoid the use of the term.

7.10. Concomitant Crystallization of Racemates and Enantiomers

Another issue in the definition of polymorphs deals with racemic mixtures versus enantiomerically pure crystals or conglomerates.[2, 5, 80] In principle, enantiomerically pure crystals are different from racemic ones, but if they racemize quickly in solution and/or spontaneously resolve upon crystallization, it is still debatable whether these are to be considered polymorphic substances. Sironi and co-workers[86] have recently characterized a concomitantly crystallized system that incorporates and illustrates many of these features, and in addition, provides an example of a substance in which the synthetic approach to the material apparently plays a role in determining which polymorph is initially obtained.

The molecule under study was $[Pd\{(dmpz)_2(Hdmpz)_2\}_2]$ (**20**). The material is trimorphic. The reaction mixture yields mostly (90 %) the monoclinic (*C2/c*, racemic) α phase, the remainder being the triclinic ($P\bar{1}$, racemic) γ phase. The latter can be removed by recrystallization from 1,2-dichloroethane, which suggests that it is the more soluble and hence less stable polymorph in that solvent. Sironi and co-workers found that mixtures of various amounts of α and γ polymorphs could be obtained by varying the solvent and precipitation temperature (−70 °C to +50 °C), with α preferred at higher temperatures, consistent with the earlier observation of relative stabilities. Pure polymorph γ may be obtained by a different synthetic route, which, with an excess of 3,5-dimethylpyrazole, leads to an approximately 50:50 mixture of polymorphs α and γ. This system thus also represents a case in which the polymorph obtained, or the polymorphic mixture obtained, depends on the synthetic route to the desired material. It is probably more correct to state that as usual, the polymorph or polymorphic mixture depends on the crystallization conditions, and these will clearly differ in the solvent/reagent/product compositions that result from different synthetic conditions and routes.[87]



Hdmpz

The tetragonal (*I*422, chiral) β "polymorph" is obtained quantitatively by a solid–liquid synthesis. The product is a conglomerate of enantiomeric crystals, which the authors claim does not transform into the α phase because of the impossibility of a solid–solid transformation. Dissolution of the β phase in 1,2-dichloroethane and subsequent evaporation quantitatively restores a mixture of α and γ forms. Despite the

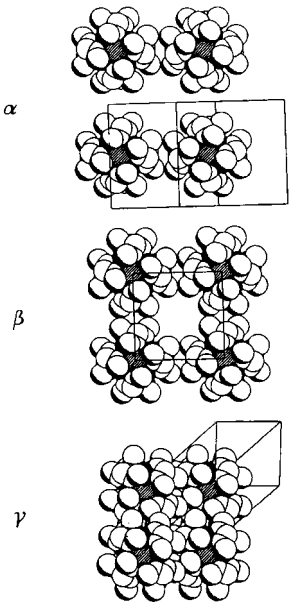


Figure 14. Packing of the $[Pd(dmpz)_2(Hdmpz)_2]_2$ (**20**) molecules in the three polymorphs, viewed approximately down the pseudo-fourfold axis. (Reprinted from ref. [86] with permission.)

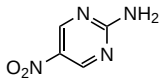
different space groups, the gross features of the packing modes are very similar, the molecules being arranged about a pseudo (α, γ) or real (β) fourfold axis (Figure 14). Such a view of the crystal structure is consistent with observations of Gavezzotti and Desiraju[91] and Braga and Grepioni[92] on the general similarities of packing features and coordination numbers of organic and organometallic compounds.

7.11. Concomitant Crystallization and Crystal Engineering

The growing interest in crystal engineering is certain to lead to more recognized cases of concomitant polymorphs. Indeed, if crystal engineering can be considered as control over the design and preparation of desired crystal structures then the phenomenon of polymorphism—and concomitantly crystallizing polymorphs—is antithetical to such an approach.[93] One popular strategy in crystal engineering is to build up structures from systems of two molecular components between which the intermolecular interactions are well defined, usually by the potential formation of hydrogen bonds.[94]

A recent example from this realm of chemistry, which again illustrates the role of the synthetic route in determining the generation of polymorphic structures comes from the work of Biradha and Zaworotko on **11** and **12** (see Section 7.6).

Another attempt at crystal engineering led to a remarkable number of concomitant crystallized materials. Aakeroy et al. dissolved **21** and **22** in a 1:1 ratio in butanol. Upon slow evaporation they obtained *five* crystalline materials, three polymorphs of **21** (thick, diamond-shaped plates, white needles and colorless blocks)[95] and yellow platelike crystals of **22** along with yellow/colorless dichroic blocks of a monohydrate of **22**. Only keen observation could be responsible for the discovery and characterization of all five crystalline materials in this mixture.



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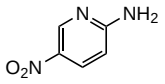

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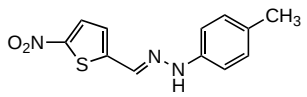
One practical mission-driven aspect of crystal engineering is the attempt to design and prepare nonlinear optical materials. This goal has led to the variation of crystallization conditions in the search for crystals of potential SHG materials, and has resulted in the discovery of polymorphic systems,[96] as well as the development of a number of strategies for obtaining structures with the required symmetry properties.[97] Recently Pan et al. reported many crystallization studies on **23**, which is at least trimorphic, the three modifications being easily recognized by habit and color: form I, red greenish plates ($P2_1/n$); form II, red orange prisms ($Pna2_1$); form III, black needles ($P2_1/n$). Hence only form II is SHG active. Solvent evaporation or controlled lowering of the temperature lead to form I from all solvents used, but rapid cooling of highly supersaturated solutions of protonic solvents (e.g. methanol or ethanol) sometimes led to concomitant crystallization of forms II and III. The crystal structures of these three modifications could also be distinguished by the nature of the intermolecular interactions dominating them.[98]



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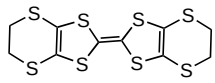
7.12. Organic Conductors and Magnets

It is not surprising that quite a few examples of concomitant polymorphs are found amongst the compounds and salts of potential use as organic conductors and magnetic materials. Considerable effort is generally expended in growing crystals and fine tuning conditions for obtaining crystals of sufficient quality for further structural and physical characterization. Thus a wide variety of crystallizing conditions are often tested and many individual crystals from a single crystallization might be subjected to structural and physical characterization.[99] These are favorable circumstances for the preparation and recognition of polymorphism and concomitant polymorphs.

7.12.1. Organic Conductors by Electrocrystallization

Perhaps most prominent of these materials are the organic conducting and superconducting salts based on so-called ethylenedithio ("ET") compounds, in which bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF; **24**) is the donor (cation in the salt), generally in a 2:1 ratio with the acceptor (anion in the salt).[100a]

One of the most widely studied of these salts is $(ET)_2I_3$, for which at least 14 different phases have been reported, [100] although the α and β phases tend to dominate.[101] Most of the 2:1 salts are obtained by electrochemical crystallization which affords additional degrees of freedom of crystallization conditions compared to "conventional" crystallization: voltage, current density, counterion (for the salt anion), supporting electrolyte, electrode materials, and so on. So, for $(ET)_2I_3$ for instance, it has been shown that the α phase is the kinetically favored product (>90%) under conditions of high current density and a small amount of water or oxidant in the crystallization medium. Under more nearly equilibrium conditions (i.e., much lower



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current density) and dry solvent (tetrahydrofuran), pure β phase can be obtained, which suggests that it is the thermodynamically preferred form. Intermediate conditions apparently lead to concomitant crystallization of the two forms.[100]

When the crystallization is carried out as an oxidation of ET in tetrahydrofuran with a mixture of $(n\text{-}C_4H_9)_4NI_3$ and $(n\text{-}C_4H_9)_4NAuI_2$ (16/1 w/w) with an intermediate current to that described above, the α form is the main product, concomitantly crystallized with small amounts of θ and κ polymorphs.[102] The authors note the difficulty in identifying the three forms on the basis of crystal shape alone, and the three were characterized by a combination of X-ray diffraction and other physical measurements.

Two distinct superconducting κ phases (labeled κ_H and κ_L) are obtained simultaneously in the electrocrystallization of the salt of ET with the anion $[Cu(CF_3)_4]^-$ in 1,1,2-trichloroethane.[103] After four days black needles of the κ_H form appeared on the anode, and within a week black plates of the κ_L form appeared amongst the needles (Figure 15). Both salts are, in fact, solvates of $(ET)Cu(CF_3)_4$, with κ_L containing one molecule per salt formula unit, and κ_H containing slightly less than one molecule per salt formula unit. The authors note that the growth of the plates apparently inhibits the growth of the needles, which after 14 days amounted to approximately 5% by weight of the product. These results were reproducible. The addition of 10% ethanol to the electrolyte solution led to a slight increase in crystal quality in some experiments, but otherwise did not alter the results. ET also forms a concomitant dimorphic salt with $Pt(CN)_4$, with the stoichiometry $(ET)_4Pt(CN)_4$; the two forms are designated α and β.[104, 105]

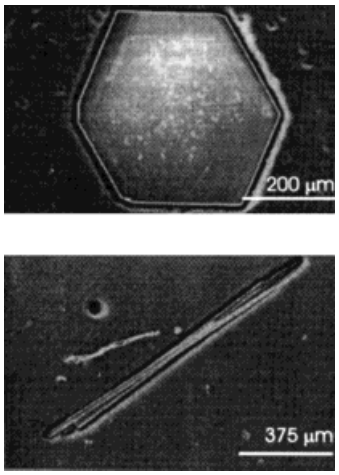
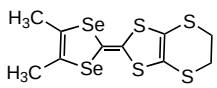


Figure 15. Photograph of the two κ phases of $(ET)_2Cu(CF_3)_4$. (Reprinted from ref. [103] with permission.)

In another example that involves similar materials, the dimethyl ethylenedithio donor is DMET **25** and the acceptor is $AuBr_2$ to form both rhombs and platelike crystals of $(DMET)_2AuBr_2$;[106, 107] no further information on crystallization conditions, color, habit, and so on are given. The crystal structure and temperature-dependent resistivities differ significantly for the two polymorphs.



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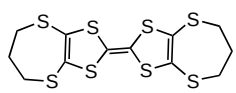

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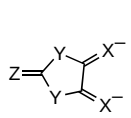
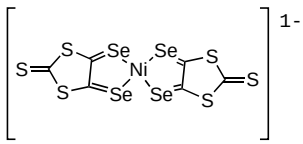


27: X,Y,Z = S,Se



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Montgomery et al.[108] have shown that, in systems in which attempts were made to prepare alloys of β-$(ET)_2I_3$ with β-$(PT)_2I_3$ (PT = **26**, a propylenethio donor), they apparently obtained "single crystals" of $(ET)_2I_3$ which were in fact mixtures of the α and β forms. The phenomenon in this system was initially detected and then confirmed by ESR spectroscopy, which was subsequently used to develop a quantitative procedure for the determination of the polymorphic composition of such "mixed single crystals". There are other scattered reports in the literature of this phenomenon,[109] which has been termed "composite crystals" and has been discussed in detail by Coppens et al.[110]

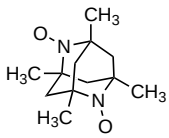
Another widely studied series of conducting organic salts is based on the ligand **27**. In the case where X = Se, Y = Z = S, known as dsit, the organometallic monovalent anion **28** can be formed with Ni^{III} to give a dimorphic salt with composition $(Bu_4N)_2[Ni(dsit)_2]_2$.[111] Concomitant crystallization of the α and β forms was noted upon recrystallization of the crude material, the α form being chunky blocks, while the β form crystallizes as needles. Slow evaporation of a solution prepared by dissolution of both forms leads to the α form, which suggests that it is the more stable form.

7.12.2. Organic Conductors by Interdiffusion

Interdiffusion of saturated solutions (as opposed to electrocrystallization) is another method for obtaining crystals of potentially conducting salts. In most of the preparations of $TTF[Pd(dmit)_2]_2$ (dmit: **27**, X = Y = Z = S) by diffusion of $(TTF)_3(BF_4)_2$ and $(nBu_4N)[Pd(dmit)_2]$, mainly black shiny needles of the α phase were obtained. However, some experiments yielded, in addition, a so-called α' phase (due to its structural similarity to the α phase, but different electrical behavior), and occasionally it was possible to separate a third δ phase of plate-shaped crystals from the batch.[112–114]

7.12.3. Organic Magnetic Materials

The significant increase in interest and activity in the design, preparation, and study of organic magnetic materials has led to the discovery of a number of polymorphic systems.[116, 117] One of the few purely organic materials shown to undergo a well-characterized ferromagnetic transition is the azaadamantane derivative **29**.[118] The material is dimorphic, and both forms appear simultaneously by evaporation of a diethyl ether solution at room temperature. The authors note that they have not succeeded in determining the conditions for selectively crystallizing either form.



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The structures of the α and β forms are shown in Figure 16. It can be seen that there is indeed a subtle difference in the environment of the oxygen atom on which the unpaired electrons are formally located, and in other intermolecular interactions, but the concomitant crystallization suggests that

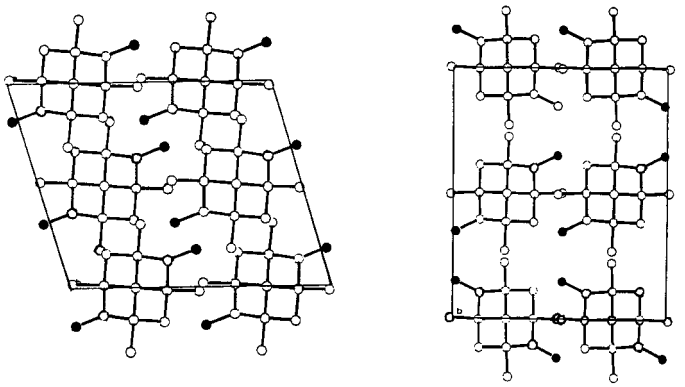
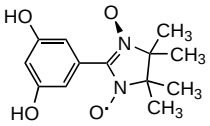


Figure 16. Representation of the packing of the two forms of **29**. Oxygen atoms are denoted by solid circles. Left: the monoclinic α form; right: the orthorhombic β form. (Reprinted from ref. [118] with permission.)

the energetic consequences of the sum of these differences are very small.

This lack of control over the polymorph obtained is in contrast to the dimorphic system HQNN **30**. Sugawara et al. reported in a preliminary communication[119] that the bluish-purple blocks of the α phase could be obtained above 4 °C and the needle-shaped β phase can be crystallized below 0 °C. In addition, they add that "both crystals can be obtained selectively by using a seed crystal at room temperature". In a later publication[120] it was noted that the α phase was obtained in a refrigerator, "(≈4 °C) under a nitrogen atmosphere" while the β form was obtained from a solution "stored in a freezer (≈ −10 °C)".



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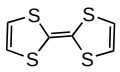
Legros and Valade reported the concomitant (α and γ) forms of **31** and **32**. The crystals are obtained from the slow interdiffusion of saturated solutions of $(TTF)_3(BF_4)_2$ and



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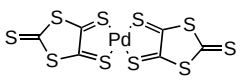

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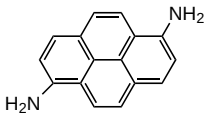
$(n\mathrm{Bu}_4\mathrm{N})[\mathrm{Pd(dmit)}_2]$.[112] The α form is the main product as shiny black needles, with some platelets of the γ phase usually present. Occasionally, a so-called α' phase is also obtained in this crystallization procedure. The α and γ forms have very different crystal structures and correspondingly different electrical behavior. The former are built up of segregated stacks of donor and acceptor molecules and undergoes a metal–semiconductor transition. The latter has stacks of dimers of **32**, and exhibits metallic behavior in the range 120–300 K.

A recent study on the system of 1,6-diaminopyrene (**33**) and chloranil (**34**) is edifying with regard to the connection between structure and electrical conductivity. Compound **33** is a relatively strong donor that was an early subject of study as a component of potential electrically conducting complexes,[121, 122] and quite a few complexes of this donor were prepared.[123, 124] The complex of **33** with **34** was investigated in



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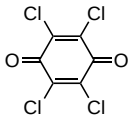

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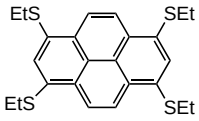

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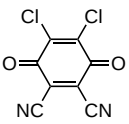

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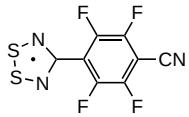
detail recently[124, 125] with results that indicate both the utility and some of the limitations of studies of polymorphic systems. The 1:1 complex is polymorphic, with a dark brown α form and a green β form. Both may be obtained *simultaneously* from benzene solution by both slow cooling and "prolonged" slow evaporation.[124] Under cooling or grinding, the resistivity of the α form is reduced by eight orders of magnitude, with no detectable structural changes by X-ray crystallography.

Modification of the substituents on the pyrene donor and the benzoquinone acceptor leads to the 1:1 complex of **35** with **36**, which was studied by Lee et al.[126] Slow evaporation of an equimolar mixture of the compounds in dichloromethane led to a mixture of black crystals; the α phase were "branchy" microcrystals and the β phase were large platelets.

7.12.4. Free Radicals by Sublimation

The recently reported 1,2,3,5-dithiadiazolyl radical **37** is the first to retain its paramagnetic behavior in the solid state.[127, 128] It also provides another example of concomitant crystallization by sublimation. Large black blocks of the α phase may be obtained pure by very rapid vacuum sublimation at 120 °C and 10^{-2} Torr. The long, plastically deformable needles or small red blocks of the β phase are prepared at the same pressure and 80–100 °C, with the crystals collecting just above the level of the oil bath or heating tape of the source vessel (i.e., small temperature gradient).[129] The two phases appear simultaneously under vacuum in a sublimation tube subjected to a temperature gradient. The difference in color of the latter two types of β crystals is most likely a size effect, the larger crystals being opaque and hence reflecting.



37

7.13. Concomitant Crystallization of Proteins

In view of the many experiments carried out on the crystallization of proteins and subsequently refinement of the conditions to maximize crystal size and quality for X-ray structure determination, it is not surprising that examples of concomitant crystallization are found among proteins. Wang and co-workers reported the simultaneous crystallization of three polymorphs of a m-class glutathione S-transferase from

rat liver[130] (Figure 17). Day and McPherson reported crystallization of two crystalline forms in stages in accord with Ostwald's Rule for cytochrome c from *Valida membranaefaciens*[131] (Figure 18). In every case of crystallization they obtained arrays of thin triclinic plates (Figure 18a), some of which grew up to 0.5 mm along the largest physical dimension (Figure 18b). In some cases, some of these dissolved (in accord with Ostwald's Rule of Stages) to give rectangular prisms (Figure 18c), which turned out to be orthorhombic.

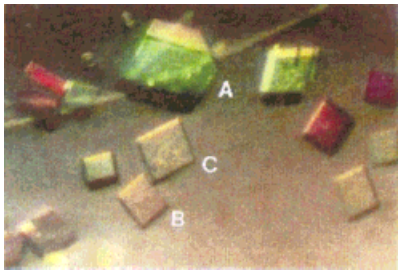


Figure 17. Photograph of cocrystallizing forms of rat liver glutathione S-transferase. The three forms are labeled. (Reprinted from ref. [130] with permission.)

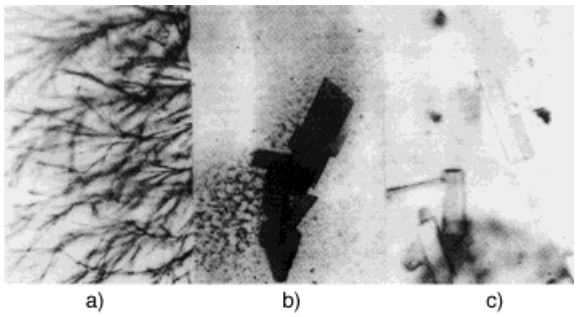
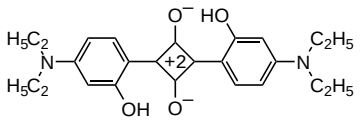


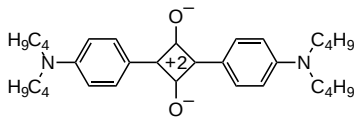
Figure 18. Example of the stagelike growth in cytochrome c from *Valida membranaefaciens*. a) Treelike arrays of small triclinic crystals. b) Triclinic crystals, which are frequently seen to dissolve at the expense of the orthorhombic prism (c). (Reprinted from ref. [131] with permission.)

8. A Structural Approach to Concomitant Crystallization

Up to this point this account of instances of concomitant polymorphs has been phenomenological. We have discussed the thermodynamic and kinetic crystallization of polymorphs. There is still the question of whether any insight can be gained from the study of the crystal structures of concomitantly crystallized polymorphs. A qualitative attempt was made to see if details of the crystal structures may provide clues to the reasons for concomitant crystallization. The squarylium dye **38** crystallizes from dichloromethane in a triclinic violet form and a monoclinic green form.[132] The cell constants (Table 1) do not suggest any similarity of the structures. However, a projection on the molecular plane which includes two neighboring molecules (Figure 19) indicates that the stacking of the planar molecules is virtually identical in the two structures. In both cases the two molecules are related by a lattice translation: in the triclinic structure it is along the *c* axis and in the monoclinic structure along the *b* axis. Although the



38



39

Table 1. Crystallographic cell constants for the two polymorphic forms of **38**.

	Triclinic	Monoclinic
a [Å]	11.911	15.72
b [Å]	7.401	7.283
c [Å]	6.501	9.591
α [°]	92.78	90
β [°]	111.9	106.11
γ [°]	98.08	90
space group	$P\bar{1}$	$P2_1/c$

views appear the same to the eye, the vertical separation between planes differs (3.40 Å vs 3.86 Å), which is a manifestation of the different axial lengths involved. The similarity of these diagrams strongly suggests that the stacking

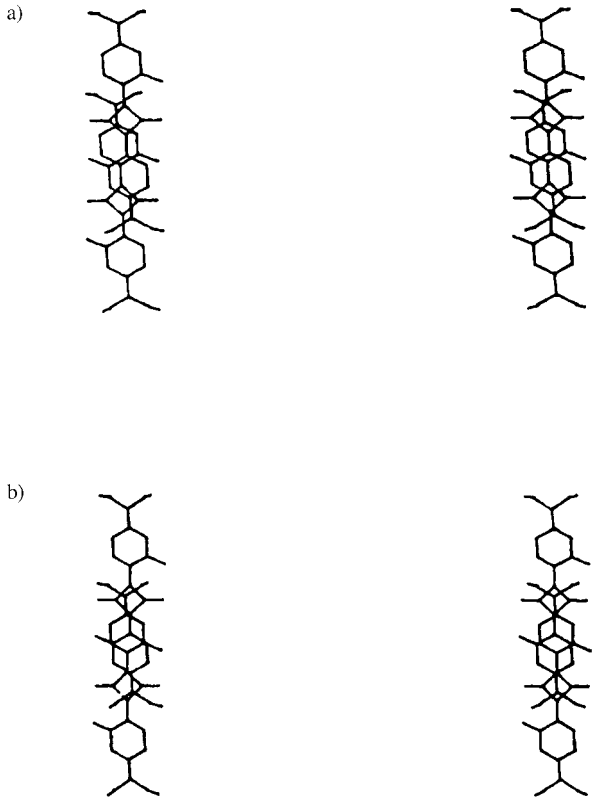


Figure 19. Stereoviews of the overlap of translationally related molecules in the two structures of **38**. In both cases the view is on the plane of the reference molecule. a) Triclinic structure, *c*-axis translation; b) monoclinic structure, *b*-axis translation. (Reprinted from ref. [132] with permission.)

is the dominant influence in the crystal growth process for both—hence the concomitant crystallization. The crystal structures differ, of course, in that stacks are related by translation in the triclinic structure and by a screw axis in the monoclinic one, as shown in Figure 20, but the fact that these phases crystallize concomitantly would be consistent with the assumption that energetically, at least, these interstack interactions contribute in a less significant way than those within the stack.

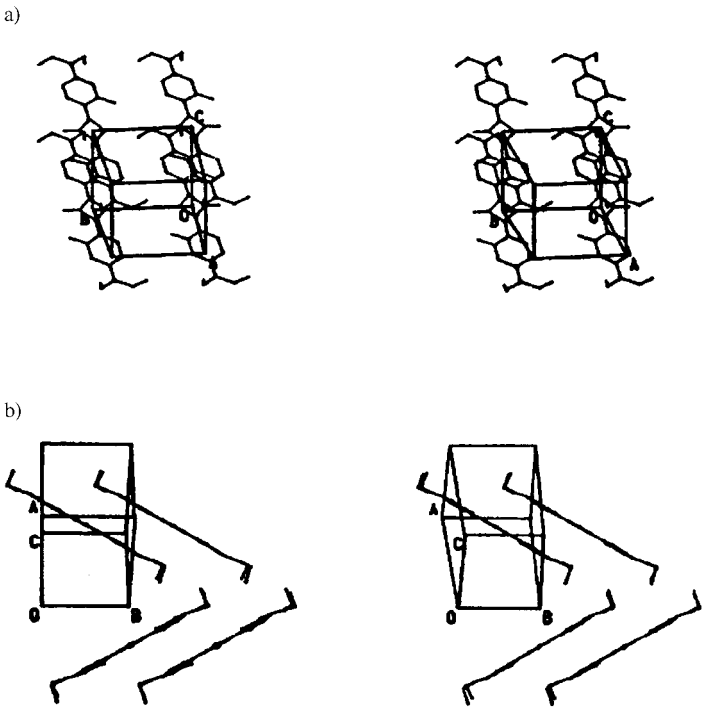


Figure 20. Stereoviews showing the relationship between the stacks shown in Figure 19 for **38**. a) Triclinic structure, translational relationship. b) Monoclinic structure, screw-axis relationship. (Reprinted from ref. [132] with permission.)

It is of interest to note that another similar squarylium dye **39** has also been shown to concomitantly crystallize in a green monoclinic phase and a purple triclinic phase.[133] The structure has been reported for the former, but crystals of the latter were not of sufficient quality to determine the crystal structure. The monoclinic phase crystallizes in space group $P2_1/c$ with cell constants $a = 9.046$, $b = 19.615$, $c = 9.055$ Å, $\beta = 116.1°$, which precludes any molecular overlap of the type seen in Figure 19 for **38**. The crystal structures of **38** and **39** are significantly different so that the similarity in the colors of the polymorphs of the two compounds appears to be entirely coincidental, albeit unusual.[115]

9. Summary and Outlook

Sironi and co-workers have described the current situation of the discovery of polymorphs in general and of concomitantly crystallizing polymorphs in particular:[86] "Normally, after a good-looking single crystal is randomly picked out of a bunch of crystals, or more frequently, from a complex mixture containing also (morphologically) amorphous, microcrystalline or powdered material, no scattering measurements characterizing the nature of the bulk are routinely performed, thus overlooking the possibility of finding [the] coexistence of different crystalline phases of the same composition in the same sample."

Sironi and co-workers advocate the use of fast (≈30 min) diffraction patterns as a "routine control of reaction products". We have no argument with this: any suitable technique could and should be used. We still prefer the initial careful optical examination with the polarizing, and preferably, hot-stage microscope. Very little material is required, the method is usually non-destructive, and a great deal can be learned with a very small investment in time and money.

We have described a phenomenon that can be useful in the investigation of solid materials, and in understanding the relative crystal energetics of polymorphic materials. In general no sophisticated technique or instrumentation is required to detect concomitant polymorphs. All that is necessary is the willingness to observe crystalline samples carefully, the awareness that such samples may contain more than one polymorphic modification, and the understanding that such a situation can provide a great deal more information than one polymorphic modification can yield. We hope that this awareness will stimulate those dealing with crystallizations and with crystals to look a little closer at the batch of crystals before moving on to further study or relegating them to storage, and to describe the associated crystallizing procedures, crystal habits, color, and so on in more detail than is the common practice today.[134]

As the awareness of polymorphism has grown, there has been increasing effort to understand the phenomenon and to gain control over the crystallization process in order to selectively obtain a desired polymorph or suppress the growth of an undesired one. Historically, this was done by a combination of trial and error, intuition, serendipity, varying solvents, temperature,[2, 18] and occasionally additives.[135] The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization.[136–139]

Although the phenomenon of concomitant crystallization has a long history, many of our examples have been taken from the very recent literature. This is not totally by accident. The relative ease with which crystal structures can be solved compared, say, to a generation ago has facilitated the structural investigation of crystals per se. However, a large proportion of the papers cited have been authored by what might be called practitioners of the organic solid state who, through training and experience, tend to benefit from an awareness of polymorphism and an interest in polymorphic systems. It is hoped that this review will promote that awareness throughout the general chemical community.

We are grateful to many enthusiastic colleagues who responded to our call for examples of concomitant polymorphs and to subsequent follow-ups for details. Many of the examples presented here benefited from some extra effort or assistance

from them. Helpful discussions with Dr. Nick Blagden are appreciated. Special thanks to R. Goddard for permission to describe his independent results on the preparation of the second form of tetrathiafulvalene. We also wish to thank the Alexander von Humboldt Foundation for a postdoctoral fellowship to J.-O.H., the Academic Study Group (London) for a travel grant to R.J.D. to Israel, and an Austria–Israel Cultural and Scientific Exchange Program for J.B. to travel to Innsbruck and J.-O.H. to travel to Beer Sheva. The warm hospitality and availability of resources of the Cambridge Crystallographic Data Centre during a sabbatical leave of J.B. are greatly appreciated.

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[1] This phrase has been chosen with some consideration, and a number of other options were available. Our intention is to refer to polymorphs that are observed in the crystallization medium, usually simultaneously, although we do not rule out the possibility that they occur in stages, a later modification replacing an earlier one. This is compatible with the choice of "concomitant", which is defined as "accompanying, or happening together". Another possibility was "cocrystallizing", but this term is already in use with reference to the formation of solid solutions of enantiomers and also in the formation of crystalline complexes of two or more molecules, usually as a result of hydrogen bonding. Other options (with definitions) included concurrent (happening together), concrescent (the growing together of related parts), convergent (becoming similar or identical), simultaneously crystallizing (crystallizing at the same time). None of these portrayed more aptly than "concomitant" the phenomenon we wish to describe here.

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[34] For a critical evaluation of these procedures, see S. L. Price in *Implication of Molecular and Materials Structure for New Technologies* (Eds.: J. A. K. Howard, F. H. Allen, G. P. Shields), NATO Science Series E: Applied Sciences, Kluwer Academic, Dordrecht, **1999**, pp. 315–320.

[35] Part of the difficulty in searching and interpreting the literature on polymorphic behavior of materials is due to the inconsistent labeling of polymorphs. In many cases, the inconsistency arises from lack of an accepted standard notation. However, often, and perhaps more important, it is due to the lack of various authors' awareness of previous work or lack of attempts to reconcile their own work with earlier studies. While many polymorphic minerals and inorganic compounds actually have different names (e.g., calcite, aragonite, and vaterite for calcium carbonate or rutile, brookite, and anatase for titanium oxide) this has not been the practice for molecular crystals, which have been labeled with Arabic (1, 2, 3,…) or Roman (I, II, III,…) numerals, lower or upper case Latin (a, b, c,… or A, B, C,…) or lower case Greek (α, β, γ,…) letters, or by names descriptive of properties (red form, low-temperature polymorph, metastable modification, etc.). As Threlfall has pointed out, arbitrary systems for naming polymorphs should be discouraged to avoid confusion as regards the number and identity of polymorphs for any compound.[5] Those based on relative stability or order of melting point do not allow for the discovery of forms with intermediate values; also small differences in stability or melting point might lead to different order and different labeling by different workers. McCrone[2] proposed the use of Roman numerals for the polymorphs in the order of their discovery, with the numeral I specifying the most stable form at room temperature. By Ostwald's Rule[22, 23] the order of discovery should in general follow the order of stability. McCrone also supported the suggestion by the Koflers that the Roman numeral be succeeded by the melting point in parentheses. In fact, the successors of the Koflers at the Innsbruck school have attempted to follow this practice,[11, 30] although in general it has not been widely adopted by others. In view

of the body of literature already extant and the questions surrounding the definition of a polymorph, it is clearly not practical to define strict rules for labeling polymorphs. The Kofler method has some obvious advantages, since the melting point identifier may eliminate some questions of identity; hence its use should be encouraged. The important point for those studying polymorphic systems is to be fully aware of previous work, to try to identify the correspondence between their own polymorphic discoveries and those of earlier workers, and to avoid flippancy in the use of nomenclature in the naming of truly new polymorphs. In this review we have carried over the nomenclature adopted by the original workers.

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