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# Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies

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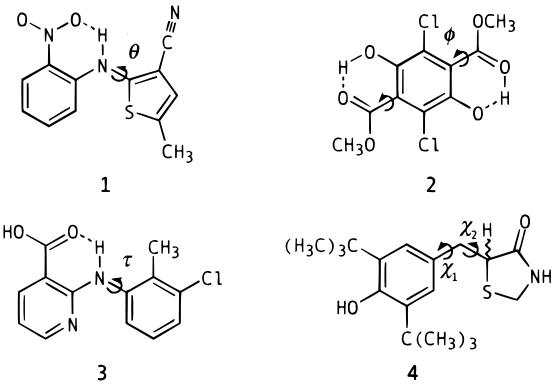
**Abstract:**

**Two effects of conformational flexibility on crystallization, namely conformational polymorphism and reduction of crystallization tendency, are discussed using examples from the literature and our own studies. The preferred molecular conformations observed in several polymorphic systems are correlated with the nature of the forces present in the crystals. The reduction of crystallization tendency for conformationally flexible molecules arises from the presence of multiple conformers in the crystallizing media and the need for certain molecules to crystallize in high-energy conformations. Despite their peculiarities, the control of crystallization of conformationally flexible molecules should begin with traditional approaches applicable to most crystallization situations. However, special techniques, including conformational mimicry, solvent-mediated self-assembly, and templated growth, have been devised to introduce molecular-level control to the crystallization process.**

## I. Introduction

Crystallization can be envisioned as a multistep process in which molecules first associate into pre-nucleation aggregates (molecular clusters whose structure resembles that of the mature crystal),[1] pre-nucleation aggregates then assemble into crystal nuclei, and crystal nuclei finally grow into mature crystals. Conformational flexibility introduces two potential complications to the crystallization process. First, a greater number of structural options are available for crystallization, giving rise to polymorphs that differ not only in the mode of packing but also in molecular conformation (*conformational polymorphism*).[2] This phenomenon is illustrated in Figure 1 for a system with two competing pathways originating from different conformers and leading to different mature crystals. Second, the tendency of crystallization may be significantly reduced by conformational flexibility. Since flexible molecules exist in solutions or melts as mixtures of energetically similar conformers, the process of crystallization must select the "right" conformers from among the "wrong" ones, a difficulty not encountered by rigid molecules and analogous to that faced by the crystallization of enantiomers from a racemate.[3]

***Scheme 1***




We discuss in this work these two phenomena, using examples from the literature and our own studies. With respect to conformational polymorphism, we focus on the effects of different crystal forces and their interplay on molecular conformation in several polymorphic systems (**1**−**4**) (Scheme 1). The effect of conformational flexibility on crystallization tendency is discussed using alditols and carbohydrates as examples. We end with a discussion of strategies for dealing with the crystallization of conformationally flexible molecules.

## II. Conformational Polymorphism

Conformational polymorphism arises when multiple molecular conformations can be stabilized in the solid state.[2] The energy limit within which conformers can be stabilized by crystal forces is typically placed at ~2 kcal/mol above the most stable conformer, although a much higher limit (8 kcal/mol) has recently been proposed.[4] The types of conformers within this energy limit are diverse—single-bond rotamers, conformers related by ring inversion, conformers generated by inversion about an $sp^3$ N, etc.—all of which may be in dynamic equilibrium in a crystallizing medium. While conformational polymorphs are possible when multiple energetically accessible conformations exist, one might expect the probability of observing conformational polymorphs to increase as the energy difference between conformers decreases. These energetic principles are illustrated by a series of *N*-acylbenzamides, which can adopt four planar conformations, namely *cis*−*cis*, *cis*−*trans*, *trans*−*cis*, and *trans*−*trans* (designated in terms of the

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(1) Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 4610; Weissbuch, I.; Kuzmenko, I.; Vaida, M.; Zait, S.; Leiserowitz, L.; Lahav, M. *Chem. Mater.* **1994**, *6*, 1258.

(2) Bernstein, J. Conformational Polymorphism. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987. Conformationally flexible molecules can also produce crystals in which different conformers exist in the *same* unit cell. This phenomenon will not be discussed here.

(3) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions;* Krieger Publishing Company: Malabar, Florida, 1991.

(4) Buttar, D.; Charlton, M. H.; Docherty, R.; Starbuck J. *J. Chem. Soc., Perkin Trans 2* **1998**, 763.

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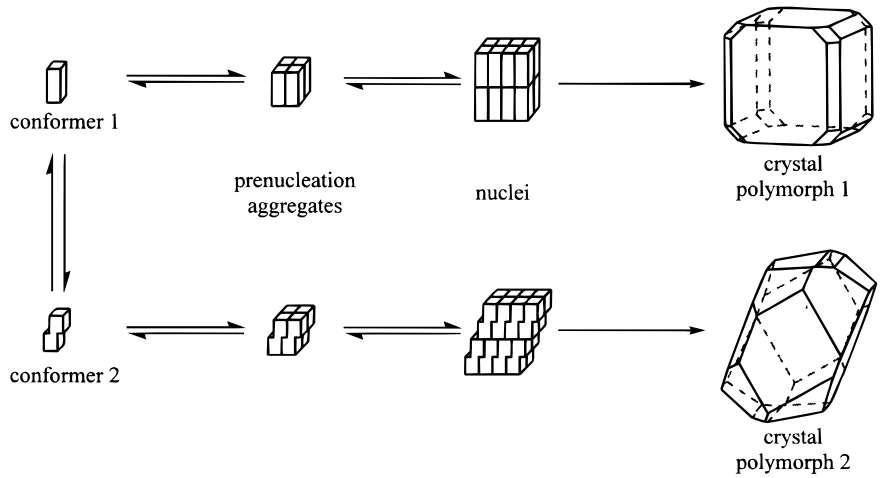
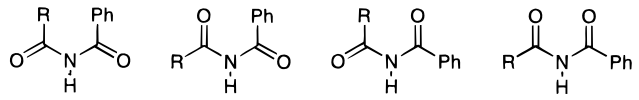



***Figure 1.*** **An illustration of the crystallization of conformationally flexible molecules.**

***Scheme 2***




carbonyl O and amino H positions about the C−N bonds) (Scheme 2). Of these, only the lowest-energy *cis*−*trans* and *trans*−*trans* forms have been observed in the solid state, and conformational polymorphism has been observed only when the energy difference between the two lowest-energy conformers is small.[5]

From a thermodynamic viewpoint, the conformers that crystallize are those that can assemble in a favorable way to minimize the system's free energy ($G = H - TS$). The energy term (effectively $H$) typically dominates at low temperatures and favors high-density structures with tight binding. The entropy term ($TS$), on the other hand, becomes more important at higher temperatures and favors structures that are more open or contain disorder (e.g., plastic crystals[6]). From a molecular viewpoint, the analysis of crystal energies recognizes different types of intermolecular forces, that is, ionic, van der Waals (vdW), dipole−dipole, hydrogen bonding, etc. These forces differ in their strength and orientational requirements. For example, the two isotropic forces, ionic and vdW, are considered the cause for the close-packing behavior. Hydrogen bonding, on the other hand, is highly directional and can lead to structures with low packing efficiency (e.g., resorcinol[7]). Dipole−dipole interactions, of course, favor the parallel or antiparallel alignment of dipoles.

To the extent that one type of force dominates crystal energy, which conformers are likely to crystallize may be anticipated on the basis of the nature of the intermolecular interaction. For example, if crystal energy is determined primarily by van der Waals forces, the conformers selected should be the ones that optimize close packing. If dipole−dipole interactions dominate crystal energy, high-dipole conformers should be favored. Hydrogen-bonded crystals may feature high-energy conformers to satisfy orientational requirements imposed by certain "motifs" (dimers, chains, sheets, etc.). However, if several types of forces exist, with conflicting conformational requirements, the prediction of preferred crystal conformers is more difficult.

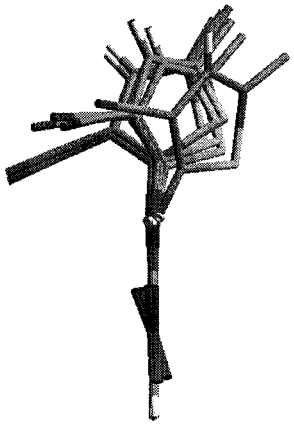


***Figure 2.*** **Crystal conformers of 1. The methyl hydrogens have been omitted for clarity.**

Compound **1** has been crystallized in a surprising number of solvent-free polymorphs (at least six), which are predominantly vdW-bonded crystals.[8] These polymorphs differ both in the mode of packing and in molecular conformation. The polymorphs vary in color from red to orange to yellow, corresponding to increasing torsion of the thiophene ring, $\theta$, and a decrease in the delocalization of the $\pi$ system, as shown in Figure 2. The crystallization of **1** displays a tendency toward more planar and higher dipole conformers. The solution conformers of **1**, in comparison, are predominantly perpendicular and have lower dipole moments.

The conformational preferences in crystals displayed by **1** are also observed in the crystallization of several derivatives of **1**,[9] $C_6$-substituted 6-(4-(dimethylamino)phenyl)fulvenes,[10] and 2-{[3-(trifluoromethyl)-phenyl]amino}benzoic acid (Fig-

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(6) Aston, J. G. Plastic Crystals. In *Physical Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Interscience Publishers: New York, 1963.
(7) Yoshino, M.; Takahashi, K.; Okuda, Y.; Yoshizawa, T.; Fukushima, N.; Naoki, M. *J. Phys. Chem. A* **1999**, *103*, 2775.
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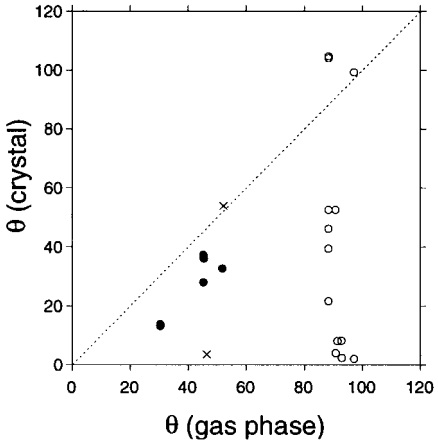


***Figure 3.*** **Comparison of gas phase and crystal torsion angles. Key: (○) 1 and derivatives of 1; (●) 6-(4-(dimethylamino)-phenyl)fulvenes; (×) 2-{[3-(trifluoromethyl)-phenyl]amino}-benzoic acid.**

ure 3). These molecules are analogous in that they all contain two relatively rigid planar fragments that are linked by a single bond (C−N or C−C). For the non-fulvene molecules, one fragment is "locked" by an intramolecular hydrogen bond (see the structure of **1**). The trend displayed in Figure 3 is that upon crystallization, the two-ring systems tend to be more coplanar in comparison to gas-phase geometries. One explanation for this trend is that planar molecules provide a more favorable packing geometry. In the case of **1** and its derivatives, the more planar conformers in crystals also have higher dipole moments, which provides another source of stabilization through dipole−dipole interactions.

Conformational polymorphism can also result from the different demands of inter- and intramolecular hydrogen bonding. This effect is seen clearly when a molecule exists in one conformation in the gas phase to satisfy intramolecular hydrogen bonding but adopts another, higher-energy conformation in the crystalline state to satisfy intermolecular hydrogen bonding. An example showing this delicate balance is 3,6-dichloro-2,5-dihydroxyterephthalate (**2**),[11] in which the molecules in three crystal forms differ in the angle between the planes of the ester and phenyl groups ($\phi$) in order to participate in dramatically different hydrogen-bonding patterns, as shown in Figure 4. In the most stable Y polymorph, intramolecular OH···O═C bonds fix the molecule in a planar conformation ($\phi \approx 0$), but the molecules can still participate in weak bifurcated intermolecular H-bonds between the −OH and neighboring carbonyl oxygens. The W form has its ester groups nearly perpendicular to the phenyl plane, allowing the carbonyl and hydroxyl groups to form only intermolecular H-bonds. The LY form has its ester groups rotated about 40° out of the phenyl plane, and contains inter- and intramolecular hydrogen bonds of less than optimal geometry.

Although hydrogen bonding affects the choice of conformers, the effect is by no means deterministic. For example,

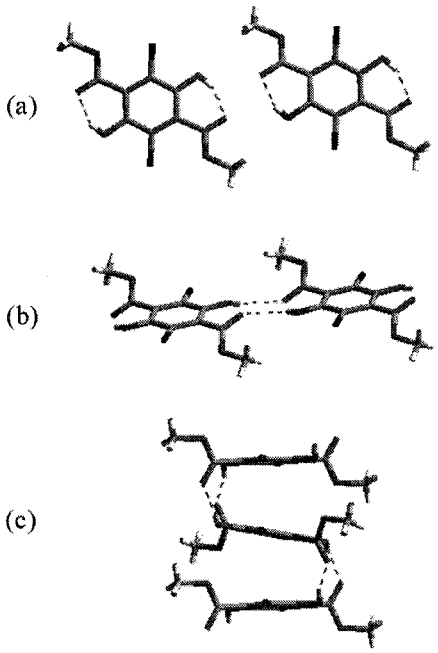


***Figure 4.*** **Hydrogen-bonding interactions in conformational polymorphs of 2. (a) form Y, (b) form LY, and (c) form W.**

D-mannitol adopts the same conformation (extended zigzag) in its three known polymorphs and in D,L-mannitol, all of which differ in intermolecular hydrogen bonding.[12] On the other hand, [2-(2-methyl-3-chloroanilino)nicotinic acid](**3**)[13] adopts significantly different conformations in two of its three polymorphs (III and IV) that have similar hydrogen bonding. Forms I, III, and IV all possess an intramolecular NH···O═C hydrogen bond but differ in the torsion about the phenyl ring ($\tau$). In form I, the phenyl ring is twisted ($\tau$ = 111.9°), allowing for strong intermolecular OH···N(pyridyl) hydrogen bonds, which are more stabilizing than the commonly seen carboxylic acid dimer arrangements found in the less stable III and IV. Although forms III and IV have similar hydrogen bonding, they differ by the amount of twist of the phenyl ring ($\tau$ = 22.2° in III and 0.6° in IV). These examples underscore the difficulty of attributing preferred conformations in crystals to single sources.

The conformational flexibility of tazofelone, **4**, allows the molecule to change conformation in response to different packing requirements in racemic and chiral crystals.[14] In both racemic compound polymorphs, each enantiomer adopts its lowest-energy conformation and two opposite enantiomers form a hydrogen-bonded dimer (Figure 5). Since a similar amide dimer cannot form between conformers of the same chirality due to significant steric interactions, **4** adopts high energy (+2 and +5 kcal/mol for two independent molecules), low-dipole conformers in the enantiomorph that can be stabilized by different, but efficient, hydrogen bonding and crystal packing. Although a variety of intermolecular forces may account for the stabilization of the +2 kcal/mol conformer, hydrogen-bonding interactions are likely to be

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(13) Takasuka, M.; Nakai, H.; Shiro, M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1061. Form II is zwitterionic and is not included in this discussion.
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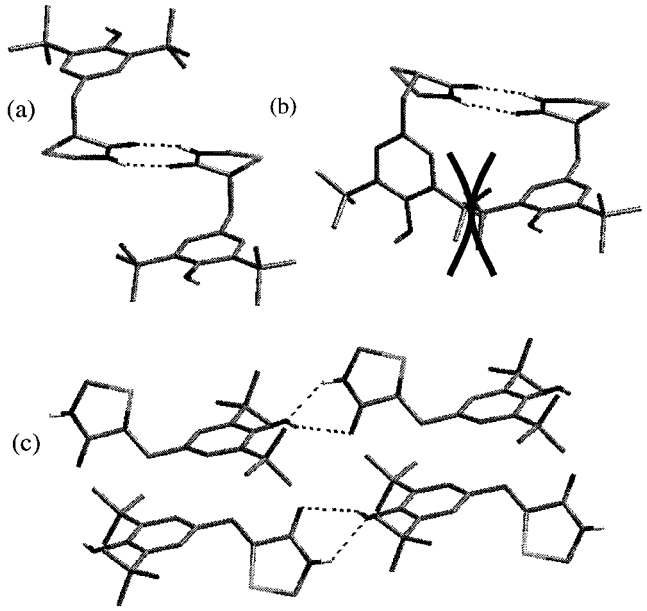


***Figure 5.*** **Hydrogen-bonding aggregates of 4. (a) Hydrogen-bonded racemic dimer observed in polymorphic racemates, (b) hypothetical homochiral dimer, (c) hydrogen-bonded heterodimers formed by two crystallographically inequivalent conformers in the enantiomorph. The C−H hydrogen atoms have been omitted for clarity. The heavy curved lines in (b) indicate the congested structure produced by the packing of homochiral dimers.**

needed to stabilize the +5 kcal/mol conformer. Despite the comparably efficient hydrogen bonding and crystal packing in the enantiomorph, thermodynamic measurements indicate that the enantiomorph has higher energy (by 3 kcal/mol) and free energy (by 1 kcal/mol) than the racemic compound. It is therefore impossible for the enantiomers of **4** to spontaneously resolve from a racemic solution.

In summary, conformational flexibility of organic molecules introduces more structural options accessible by crystallization. For systems in which one type of intermolecular force dominates, the choice of conformers may be anticipated to some extent from the nature and interplay of crystal forces. In general, however, it is practically impossible to predict which conformers will crystallize. To complicate the issue further, a greater number of potential structures for crystallization does not translate to a greater ease of crystallization for conformationally flexible molecules. In fact, the opposite may be true, as is discussed in the next section. When a molecule fails to crystallize, either because of the absence or abundance of crystallization options, there are other means of solidification, for example, as amorphous solids or mixed crystals with solvent molecules.

## III. Effect of Conformational Flexibility on Crystallization Tendency

The effect of conformational flexibility on crystallization can be appreciated from a consideration of Figure 1. Since multiple conformers (1, 2, etc.) exist in solution, the "right" conformer (1) that gives a desired crystal, say Polymorph 1, is "diluted", which in turn reduces the degree of supersaturation and the tendency of crystallization. If the "right" conformer actually is of high energy in solution, crystallization will slow even more in proportion to the unfavorable Boltzmann population factor. After crystallization begins, the solution must be "restocked" with the crystallizing conformer, at a rate which will depend on the barrier of conformer conversion and temperature. It is easy to imagine that an unfavorable combination of these factors will lead to significantly decreased crystallization tendency of conformationally flexible molecules.

The effect just described can be viewed in reverse as an effect on the stability of crystals of conformationally flexible molecules. The presence of other conformers in solution (or melt) has the same effect as impurities in that they cause a depression of melting or dissolution temperatures. Thermodynamically, the presence of other conformers stabilizes the solution (or melt), thus shifting the dissolution or melting equilibrium in favor of the solution (or melt).

Alditols (sugar alcohols) are unbranched polyols, $HOCH_2(CHOH)_nCH_2OH$, which feature multiple single bonds and extensive hydrogen bonding. Naturally occurring alditols derive their stereochemistry from the closely related carbohydrates. Besides displaying polymorphism (e.g., mannitol,[15] sorbitol,[16,17] dulcitol[18,19]), hydrate formation (e.g., mannitol[20] and sorbitol[21]), and conformational polymorphism (e.g., sorbitol,[17] iditol[22,23]), alditols exhibit strikingly different tendencies to crystallize, even between isomers whose stereochemistry differs at only one carbon. For example, among the C6 series, mannitol and galactitol crystallize easily, whereas sorbitol and iditol crystallize extremely slowly; among the C5 series, xylitol crystallizes with difficulty[24] and has a "disappearing polymorph",[25] whereas the other members crystallize more easily.

The conformational flexibility of alditol carbon chains is evident from a variety of straight and bent geometries observed in crystals. The correlation between conformation and configuration is summarized elegantly by Jeffrey and Kim's rule.[12] This rule, based on the avoidance of 1−3 parallel C−O interactions, implies that certain alditols (e.g., mannitol) assume extended zigzags as the "natural" solution or melt conformation, while others (e.g., sorbitol) take on

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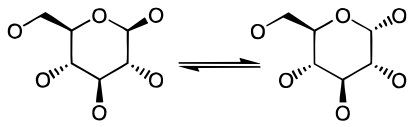
***Scheme 3***




"sickle" or bent-chain conformations. This rule summarizes a body of crystallographic data (with only one exception to date involving sorbitol[17]) and is substantiated by a series of solution NMR studies.[26−28]

From the standpoint of molecular conformation, several factors may contribute to the different crystallization tendencies of alditols. First, there may be an intrinsic difference between straight and bent-chain conformers as crystal building units, a hypothesis testable by crystal modeling. Second, the potential energy surface of bent-chain alditols may be highly "degenerate", in that several ways of bending the carbon chain exist, which may produce many energetically comparable conformers. Finally, some crystal conformers may have high energy and thus low concentration in solution. Therefore, for an "average" molecule in solution, crystallization requires a major conformational change.[29]

A standard conformational analysis has been carried out to test the latter two hypotheses.[30] The preliminary results show that for those alditols whose crystals contain straight-chain conformers such as mannitol, galactitol, and arabitol, the lowest-energy conformers in solution are the same straight-chain conformers. On the other hand, for the slow-crystallizing alditols such as sorbitol, iditol, and xylitol, the lowest-energy conformers are generally different (e.g., *gauche* rather than *anti*) from those observed in crystals. These results argue for a conformational cause that may contribute to the different crystallization tendencies of alditols.

The crystallization of carbohydrates (glucose, sucrose, lactose, etc.) has similar features to the alditols. These molecules exist in solution as mixtures of anomers (configurational isomers). In the same way conformational equilibrium affects crystallization tendency, so should configurational equilibrium. For the monosaccharide D-glucose, the equilibrium between α- and β-anomers is shown in Scheme 3.

At equilibrium, the solution contains 64% β-anomer (more stable) and 36% α-anomer (less stable), both of which can produce crystals (α as a monohydrate and an anhydrate and β as an anhydrate).[31] Despite the greater stability of the β-anomer, the Merck Index reports "below 50 °C, α-D-glucose hydrate is the stable cryst form, above 50 °C the anhydr form is obtained and at still higher temps β-D-glucose is formed."[32] Boje et al.[33] studied the rate of crystallization of D-galactose, a stereoisomer of D-glucose, as a function of the anomer equilibrium, the relative stability of mature crystals, and solution-mediated polymorphic transformation. Similar to D-glucose, the β-anomer of D-galactose is more stable in solution ($\beta/\alpha \approx 2/1$ at equilibrium), yet the crystal of the α-anomer is more stable.

For the disaccharide lactose, the equilibrium anomer composition is 37% α and 63% β in aqueous solutions.[34] An α-monohydrate normally crystallizes from water and a β-anhydrate precipitates above 93.5 °C.[32] By spray-drying a solution prepared with a commercial anhydrous lactose (20% α), Schmitt et al. obtained an amorphous solid containing 24% α, which crystallized in humid atmosphere into a mixture of α-monohydrate and β-anhydrate (29% α).[35] In this example, the change in anomer composition is small (5%) during crystallization, perhaps because of the slow rate of anomer conversion in the amorphous solid. Consequently, the crystallization of one anomer is independent of the other, and both crystallize. This feature is in contrast with the outcome of lactose crystallization from solutions. Because the anomer conversion is rapid in solutions, the nucleation of one anomer can convert all molecules into crystals of that anomer.

## IV. Strategies for Controlling the Crystallization of Conformationally Flexible Molecules

The crystallization of polymorphs can be difficult to control, even in systems whose crystallization processes seem well-understood. Polymorphs can disappear and reappear,[25,36] sometimes with significant economic ramifications. With increased crystallization options and reduced crystallization tendencies, conformationally flexible molecules can present even more challenges. In this section, we discuss strategies for controlling the crystallization process. With the aid of the "crystallization flowchart" (Figure 1), we consider how one can influence each step of the crystallization process. For convenience, we proceed in the opposite direction of the "flowchart", beginning with mature crystals.

The relative thermodynamic stability of polymorphs is described by an equilibrium phase diagram, with concentration, temperature, or pressure as variables. A free energy vs temperature phase diagram, for example, describes whether the stability order between polymorphs changes with temperature (enantiotropic) or not (monotropic).[37−39] If phase equilibrium is maintained during crystallization(usually not so in practice), the most stable polymorph will be obtained. Since thermodynamic arguments are independent of molec-

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ular details, "equilibrium crystallization" strategies apply to all types of polymorphs (conformational, configurational, tautomeric, etc.).

If metastable polymorphs precipitate initially, the more stable polymorphs can be obtained through polymorphic transformation. The E-to-B conversion in stearic acid, for example, involves a conformational change from a straight carbon chain to one in which the C1−C3 conformation is *gauche*.[40] Polymorphic conversions can be mediated by melt, solution, or interface.[41] Solid-state phase transformations, which include thermal and mechanical annealing, tend to disrupt the crystal structure, oftentimes producing crystals with poor mechanical properties. If the transformation involves releasing solvent to the environment, caking of the material may also result during storage. Cardew and Davey developed a theoretical framework for investigating solvent-mediated transformations in terms of dissolution kinetics of one phase and growth of a second phase.[42]

At the nucleation-growth stage of crystallization (Figure 1), an often cited effect relevant to controlling polymorphism is Ostwald's law of stages,[43] which states that at high supersaturation, the first form to nucleate is the most soluble (the least stable). This form then transforms to the next most soluble form through a process of dissolution and recrystallization, and so on until the least soluble (thermodynamically most stable) form remains. A practical implication of Ostwald's law would be that by manipulating the level of supersaturation, different polymorphs can be isolated. Despite its successes, this law is not infallible. For example, Ostwald's law is observed in the crystallization of sulfathiazole polymorphs from acetone−$CHCl_3$ and in water, but only the most stable polymorph could be isolated from *n*-propanol at any supersaturation level.[44] This is perhaps not surprising since the crystallization outcome is affected by many parameters, including solvent, cooling and stirring rates, temperature, pressure, and impurities.

Seeding a crystallizing medium with mature crystals eliminates the need for a normal nucleation step. Seeding is essential for materials that are difficult to crystallize; for example, crystalline sorbitol ($\gamma$ form) is obtained commercially from a seeded melt.[45,46] Seed crystals have also been used to induce crystallization of cimetidine from solution at different supersaturation levels.[47] Even for crystals that are not exceedingly difficult to nucleate, seeding is a common practice. Indeed, once a polymorph has been obtained for the first time, subsequent crystallization becomes easier with seeding.

Unfortunately, seeding is not always deliberate, or wholly effective. "Unintentional" seeding can occur when contaminants are present which promote nucleation.[25] Ritanovir is

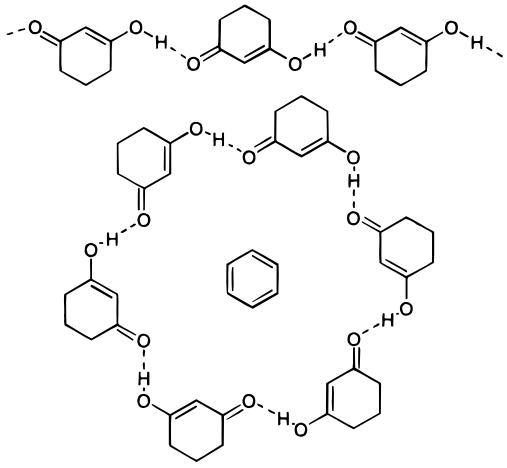

***Figure 6.*** **Different hydrogen-bonded units of 1,3-cyclohexanedione as a result of crystallization from polar solvents (top) and benzene (bottom).**

an extreme case of the "hazards of unwanted seeding".[48] A metastable phase of theophylline can promote the nucleation of another, stable monohydrate crystal.[49] In the case of lactose crystallization from an amorphous solid (see section III), seeding with crystals of one anomer is not likely to cause complete crystallization in that crystal form because of the slow rate of anomer conversion.

"Tailor-made" nucleation inhibitors (small-molecule and polymeric) have been used to induce the resolution of enantiomers by crystallization.[50] The underlying principle is to stabilize or destabilize pre-nucleation aggregates of a specific polymorph. This approach has been extended to selectively precipitate metastable polymorphs by kinetic control.[51] Similarly, Davey et al. advanced the idea of conformational mimicry for controlling the polymorphism of conformationally flexible molecules.[52] Using rigid additives that mimic the molecular conformation in the stable $\beta$ polymorph of L-glutamic acid, they were able to selectively inhibit its appearance and hence crystallize the metastable $\alpha$ structure.

Solvents provide another means to influence crystallization outcomes. An example that illustrates this principle is the crystallization of 1,3-cyclohexanedione (CHD), even though this example involves a solvate. Etter et al.[53] found that, depending on solvents, the enol tautomer of CHD self-assembles into stereoisomeric hydrogen-bonded infinite chains (Figure 6, top) or hexameric rings, called cyclamers


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(Figure 6, bottom), in the solid state. The crystals of infinite chains were isolated from polar solvents, while a 6:1 CHD/benzene solvate featuring the cyclamer unit was obtained from benzene. Because the benzene has the same symmetry and size as the cyclamer cavity, the guest molecules presumably stabilize the pre-nucleation aggregates. The solvent-dependent appearance of sulfathiazole polymorphs has also been explained on the basis of supramolecular aggregation that precedes nucleation.[54] Gavezzotti has used molecular dynamics calculations to simulate solvent and kinetic effects on molecular aggregation.[55] The solvent effect on crystallization has also been interpreted in the light of inhibiting nucleation or retarding crystal growth. In this respect, the phenomenon is analogous to controlling crystal morphology through additives and solvents.[56]

Epitaxy is another route to controlling crystal nucleation. Ward and co-workers[57] found that selective nucleation can be achieved when there is a geometric match between the interfacial angles of low-energy ledges of an organic crystal substrate and those of the pre-nucleation aggregate. This technique, termed ledge-directed epitaxy, has been used to selectively grow oriented crystals of an unstable polymorph of an organic charge-transfer salt on a cleaved succinic acid substrate.[58] In this case, one set of interfacial angles of the unstable polymorph uniquely matched the angle between the ledge planes of the substrate.

In addition to ledge-directed mechanism, two-dimensional epitaxy (between substrate and overlayer) can be used to effect selective nucleation. For example, using cleaved pimelic acid crystals as the substrate, we have found that oriented crystals of an unstable polymorph of **1** could be grown by a 2-dimensional epitaxial mechanism.[59] In this case, the substrate terrace must be large enough to cause an epitaxial match, or the crystals will not nucleate. We also observed that a new unstable polymorph nucleated on succinic acid substrates, which had not been obtained from solutions. While epitaxial approaches show great promise for controlling polymorphism, this field is still very much in its infancy.

## V. Conclusions

The crystallization of conformationally flexible molecules has two potential complications not encountered by rigid molecules, namely, conformational polymorphism and reduced crystallization tendency. We have examined several examples for which the conformational choice in crystals can be explained on the basis of the nature and interplay of crystal forces. However, the general prediction of crystal conformation and polymorphism is extremely difficult for conformationally flexible molecules. The existence of multiple conformers is identified as an underlying cause for reduced crystallization tendencies. Given these potential problems, the crystallization of conformationally flexible molecules should be approached with greater caution and with attention to each stage of the crystallization process. In addition to "traditional" techniques (e.g., control through thermodynamics and seeding), techniques devised to control pre-nucleation aggregates may be explored.

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