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# Polymorphism − A Perspective

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## Introduction

*Perspective* − "a particular evaluation of a situation or facts, especially from one person's point of view" − "a measured or objective assessment of a situation, giving all elements their comparative point of view".[1]

The continuing success and increasing impact of *Crystal Growth & Design* in its first decade is due in large measure to the editorial leadership of the journal, but no doubt it has also benefited from the increasing interest and activity in research on polymorphism in molecular crystals in all of its ramifications. There has been an exponential increase in the number of publications exploring and exploiting the phenomenon of polymorphism in particular and crystal forms in general. A comprehensive review of the subject is beyond the scope of this *Perspective*, so in concert with the definition of the term in the epigraph I will try to give a view of where we are and some of the directions we might be headed. In particular, I will attempt to give "a measured or objective assessment of a situation, giving all elements their comparative point of view", but the reader must remember that after all, as also appears in the definition, this *Perspective* is written "from one person's point of view", and thus necessarily reflects personal scientific bias.

## Definitions and Terminology

The launching of *Crystal Growth & Design* was nearly coincidental with the publication of *Polymorphism in Molecular Crystals*[2] (hereafter cited as [PMC*nn*−*nn*] for specific page numbers). As noted in the preface to the latter, my intent was to provide an introduction and entry into the field for those encountering it for the first time, as well as to provide a basic body of literature that could be used as a starting point for keeping track of subsequent developments by suitable citation searches. In keeping with that spirit, and that of a *Perspective*, most of the discussion here will relate to issues and developments in the past decade.

That period has witnessed a continuing debate about the terminology and nomenclature of multiple crystal forms.[3−7] Time and experience have apparently not diluted the general agreement with McCrone's definition of polymorphism in molecular crystals[PMC2−4] vide infra, although some alternatives have been offered.[7] However, the natural tendency of scientists to categorize and to pigeonhole phenomena has led to a number of definitions of related phenomena that are misleading at best and simply incorrect at worst.

Perhaps the centerpiece of this interchange has been *pseudopolymorphism*[PMC4−6] that prompted an exchange of letters in this journal. The self-styled "polemic" was initiated by Seddon[3] and I was one of the later joining disputants.[5] In spite of the fact that the term has been included in CrystEngWiki ("a service provided by CrystEngCommunity, hosted by the UK's Royal Society of Chemistry") [http://prospect.rsc.org/wiki/rsc/index.php?title=CrystEngWiki:About] and defined there as "When different crystal types are the result of hydration or solvation, the phenomenon is called pseudopolymorphism", it is mistaken English usage and a scientific misnomer. In response to my objection to the use of this term, apparently first coined by McCrone[8] and subsequently adopted by Bryn[9] to encompass all solvates and hydrates, there appeared a rejoinder advocating continued use of the term − only because it is apparently part of the *lingua franca* (i.e., "...this widely accepted term").[6]

Language is an aid to science only if we define our terms precisely and unambiguously; it is inappropriate and misleading to propagate inaccurate, indeed incorrect, terminology. To repeat, in short, the conclusion of my earlier missive: "*Pseudo* means *false*. Appending "pseudo" before another noun is an abdication of the responsibility of naming. It is a failure to invent a proper name. Solvates and hydrates are not false anything, least of all polymorphs (by any accepted definition); moreover, any of those solvates and hydrates can be polymorphic, which would require their absurd description as polymorphs of pseudopolymorphs. Again, the existing literature cannot be corrected, but the future literature need not be polluted or corrupted with such imprecise, confusing, erroneous language." See, for example, the discussion on the pseudoasymmetric carbon atom and the confusion engendered by this "infelicitous term."[10]

Furthermore, pseudopolymorphism is regressive with respect to the history of chemistry nomenclature. Liebig labored at C/H analyses with his *Kaliapparat* and pan balances he designed in order to differentiate discriminate compounds with different chemical compositions. From this we gained the science of organic chemistry and *isomers*, a term qualified later only when models of bonding required discriminating *constitutional* isomers and *stereo*isomers. In science, we add language to distinguish, not to confuse. *Pseudopolymorphism* convolves that set of things with similar structures and different compositions and that set of things with very different structures and identical compositions.


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In a 2008 paper entitled "Polymorphism: The Same and Not Quite the Same",[7] Desiraju commented on many of the idiosyncrasies of the world of multiple crystal forms, the variety of compositions and structures observed, and the conceptual problems in defining the various situations encountered and the nomenclature to describe them. These conundrums are not unique to crystal forms; they exist in all branches of chemistry. As I noted earlier,[5] using the chemical bond as an example: in order to properly conceptualize them, we tend to make our definitions and our descriptions in terms of often idealized models. We then can attribute some or all of the idealized characteristics to any particular (often nonideal) situation. Much of chemistry – often the most interesting chemistry, because it does not fit the definitions precisely – deals with understanding the sources of the differences from the idealized situations. It is simply not necessary, nor is it particularly informative, to have a definition or a nomenclature for every imaginable situation. However, the same author seems to be somewhat uncomfortable with the term *pseudopolymorphism*. In the abstract of a 2003 paper he coauthored "Five New Pseudopolymorphs of *sym*-Trinitrobenzene" appears the following statement: "This study indicates that the use of terms such as *solvate*, *pseudopolymorph*, *donor–acceptor complex*, and *molecular complex* is a subjective matter, and also that a better definition for the term *pseudopolymorph* may be needed, especially because it occurs frequently in the pharmaceutical literature."[11] There may be some strength in numbers, but the fact that the term "occurs frequently in the literature" does not make it correct or incorrect. The question is simply whether it is a definition that incisively divides a set of things and is linguistically and scientifically appropriate. To quote the late Jerry Donohue in another context, "It isn't".[12]

I simply do not agree that there is a "need for the term 'false polymorphism' or *pseudopolymorphism*", which it is claimed arises, for instance, in the difficulties of describing crystals with more than one component. What is the difficulty? Just say that it has more than one component. The dilemma, determining whether two materials are polymorphic, can be resolved by McCrone's simple test of whether they have identical melts. Materials of different composition will not meet that criterion; they are not polymorphic (nor isomorphous) and therefore not pseudopolymorphic. If the relative amount of solvent or guest varies, then simply call it a variable solvate.[13,14] or a host with a variable guest. Both of these are simple, clear descriptions, requiring no further amplification.

I also see no reason to restrict polymorphism to a single compound. Why, for instance, can co-crystals not be polymorphic (vide infra)? Surely among molecular complexes (lately reincarnated as co-crystals), there are numerous examples of polymorphs as defined above[PMC189–197] that meet McCrone's criteria. If the composition varies, then clearly they do not meet the criterion of having identical melts and they are not polymorphs; they are something else.

Other hitchhikers on the nomenclature bandwagon should no longer be carried. For instance, *structural polymorphism*[15] is simply redundant and belongs in the etymological trash heap. Likewise *synthon polymorphism*[16] and *packing polymorphs*.[17] And what criteria must a compound meet in order to be classified as a *pharmaceutical polymorph*?[18] Must it be a pharmaceutically active ingredient? Do excipients count? What if the compound is taken off the market for some reason? Does it no longer qualify as a *pharmaceutical polymorph*? To quote Stahly,[19] "There is really no reason to classify organic compounds as 'pharmaceutical' or 'non-pharmaceutical', in discussing solid properties. Compounds used in the pharmaceutical industry are quite structurally varied; there is not any specific chemical attribute that renders them pharmaceutically active or warrants the term *pharmaceutical polymorph*."[20]

On the other hand, there certainly are situations where a new term is helpful in recognizing and even describing a particular previously unobserved phenomenon. An example is the recently coined *isotopomeric polymorphism*,[21] describing a change in crystal structure upon changing the isotopic identity of one or more of the atoms in a molecule. While seemingly an isolated incident when initially discovered, at least one other example has been reported.[22] There will undoubtedly be many others given the incredible sensititivity of molecular crystal structure to the positions of hydrogen atoms.[23] In a related development, the influence of the isotopic distribution of the solvent on the polymorphic outcome of the crystallization of glycine from aqueous solutions has also been observed.[24]

Perhaps somewhere in between these extremes of appropriate and nonappropriate definitions is the case of *tautomeric polymorphism*,[25] particularly of omeprazole. In keeping with the spirit of the McCrone definition alluded to earlier, the appropriate questions to ask would be essentially: (1) Are the crystal structures different? (2) Do they give the same melt? The answers to both are somewhat ambiguous. Bhatt and Desiraju obtained five different forms with varying ratios of two tautomers. Three forms have been patented, distinguishable by their solid-state properties. Do they all give the same composition of tautomers in the melt? As the authors point out, this may be a matter of time, until equilibrium is reached; that also may be a complicating factor. The problem seems closely related dynamic isomerism, also discussed by McCrone.[8,PMC6]

This actually brings us back to the question of polymorphism in molecular crystals. McCrone's definition first requires establishing the concept of molecularity, and in those cases the definition works very well. Even though McCrone's definition is still very useful, the last half century has led to a vastly expanded view of solids, which flaunts this concept wonderfully, so that even molecularity is an inherently fuzzy concept. For instance, are molecular solids limited to neutral molecules? Are metal organic frameworks molecular solids? At what point is a solid no longer *molecular*?

In the end, on the issue of nomenclature I would prefer pragmatism to dogmatism.[26] What excites and motivates many of us about chemistry is the infinite variability that is possible and often observed. That variability defies precise definitions in many cases. As noted above, we use definitions to define essentially ideal cases in order to create a conceptual framework, and we then describe any particular situation as exhibiting or embodying features from more than one of those ideal situations. The example I gave earlier was that of the chemical bond – in many cases described as a covalent bond with a certain amount of polarity or ionic character. All the terms are clear and the meaning is clear. This is the language of chemistry and we should use that same language in the realm of multiple crystal forms. When a particular situation defies a precise description on the basis of our definitional framework that does not necessary warrant the creation of a new descriptive term. The perfectly acceptable alternative for special situations is to describe it as it is; it does not necessarily

**Table 1. Statistics[a] on Multiple Crystal Forms from "Disinterested"* and "Interested"‡ Sources**

| database | total number of entries | (monomorphic) % | (polymorphs) % | (hydrates) % | (solvates) % |
|---|---|---|---|---|---|
| *Merck Index 13th ed. (2001) | 10,250 | (10,160) | | | |
| *Cambridge Structural Database (November 2008) | 456,637 | | (16,035) | (119,107) | |
| *Beilstein (2009) | 11,000,000 | 70.4[b] | 3.5 | 26.1 | |
| ‡Agrochemicals | 686 | 99.85 | | | |
| ‡*Pharmacopoeia Europa* 5.8 | 960 drug compounds | 78 | 18.8 | 42 | 2.2 |
| | | 36 | 41 | 34 | 18 |

[a] Data from U. Griesser,[33] except for entry from Cambridge Structural Database. [b] All the rest. These entries do not necessarily sum to 100%, since there are many cases for which there are solvates and/or hydrates and/or polymorphs for a single compound.

require an inclusive moniker. Let tautomeric polymorphism "pass and be forgotten".[27−29]

In short, as one of my colleagues often reminds me, "words have meaning" and we should exercise care and avoid flippancy.

### Propensity to Formation of Multiple Crystal Forms

How common is the appearance of multiple crystal forms (polymorphs, solvates, and hydrates) in molecular crystals? Even neophytes would no doubt encounter the widely quoted assessments by two of the historically most prominent scholars in the field of polymorphism:

> It is at least this author's opinion that *every compound* has different polymorphic forms and that, in general, the number of forms known for each compound is proportional to the time and money spent in research on that compound. (italics in original)
>
> Walter McCrone[8]

> Probably every substance is potentially polymorphic. The only question is whether it is possible to adjust the external conditions in such a way that polymorphism can be realized or not.
>
> Maria Kuhnert-Brandstätter[30]

Clearly such statements from two of the doyens in the field might lead one to expect to find polymorphs or multiple crystal forms for any compound. The accumulated facts and experience leave one a bit less sanguine. First of all, two extremely common compounds that have been crystallized repeatedly and in huge quantities have never shown any evidence of polymorphism: sucrose and naphthalene. The widely used analgesic ibuprofen, developed in the early 1960s has annual production of ~15,000 tons, and until very recently had never exhibited any evidence of polymorphism. The caveat here is that the frame of reference is that the vast majority of these crystallizations have been carried out under "normal" conditions − atmospheric pressure and close to ambient temperature or up to the boiling points of various solvents employed. As the case of ibuprofen demonstrates, a wider exploration of phase space can reveal the existence of other polymorphic forms. A second form was obtained by specific recrystallization of the supercooled liquid, from which a protocol was developed to reproducibly obtain that form.[31] The structure of phase II, determined by powder diffraction methods, was recently reported.[32]

What is the reality? Statistics on crystal forms are not easy to determine. The choice of the database for the statistical study in essence biases the result. There are many reports (or hints) of multiple crystal forms in the primary literature that are not included in information recorded in databases. Claimed examples of polymorphism may turn out not to be so and vice versa. The results of the statistical survey may actually be dependent on the intent of the survey. This is not meant to be a criticism, but simply a statement of fact. One may distinguish, for instance, between a statistics based on "disinterested sources" and "interested sources". Some examples from both categories appear in Table 1.

From these data, it is clearly not possible to affirm either of the two quotations above. The entries for "Agrochemicals" and the *Pharmacopoeia Europa* might be considered to provide some support for these claims, but in the end in both cases more entries do *not* exhibit polymorphism than those that do, and in no case are more than half of the cases polymorphs, hydrates, or solvates.

At the other extreme, it is informative to examine the statistics from an "interested" source. Stahly[19] summarized the results on 245 compounds that had been specifically *screened* by SSCI Aptuit, Inc. in the search for multiple crystal forms. Even on the basis of an intentional and concerted experimental search, 18% of the compounds did not exhibit multiple crystal forms, although some of those did exhibit noncrystalline forms. It might be pointed out here that these data, and those of Tischler,[34] apparently suggest that salts tend to form more hydrates than neutral compounds, while polymorphism was more common for nonsalts than for salts. In any event, none of these statistical analyses truly fulfill the prophecies of the two "giants" of the field,[35] and it is clear that even when actively sought by some of the most experienced practitioners in the field, true polymorphs (as defined above) are found in barely 50% of the compounds studied.

### The Experimental Search for Polymorphs

Crystallization from solution is one of the first laboratory skills that chemists acquire, and applying variations to the conventional methods has been the traditional strategy in the search for polymorphs. However, the increasing recognition of the desire, indeed the need, to explore crystal form space as thoroughly as possible in the search for improved materials and/or because of intellectual property considerations has led to the development of a dazzling panoply of new techniques for growing crystals, with the aim of obtaining new forms of crystals. A number of excellent reviews of these techniques have appeared recently, and offer the potential for developing exciting strategies for searching for new forms.[36] It is illustrative to list some of the traditional methods for growing crystals along with those that have been developed recently.

**Table 2. Percentage of Forms from Polymorph Screening[a]**

| | all compounds [count (%)] | salts [count (%)] | nonsalts [count (%)] |
|---|---|---|---|
| multiple forms[b] | 220 (89) | 86 (91) | 116 (91) |
| multiple crystalline forms[c] | 200 (82) | 77 (81) | 105 (82) |
| polymorphs[d] | 118 (48) | 37 (39) | 71 (55) |
| hydrates | 94 (38) | 46 (48) | 38 (30) |
| solvates | 78 (32) | 34 (36) | 36 (28) |
| noncrystalline | 118 (48) | 51 (54) | 55 (43) |
| total compounds | 245 | 95 | 128 |

[a] Reproduced from ref 19, with permission. Copyright 2007 American Chemical Society. [b] Crystalline polymorph, hydrate, and solvates plus noncrystalline forms. [c] Crystalline polymorphs, hydrates, and solvates. [d] Crystalline polymorphs.

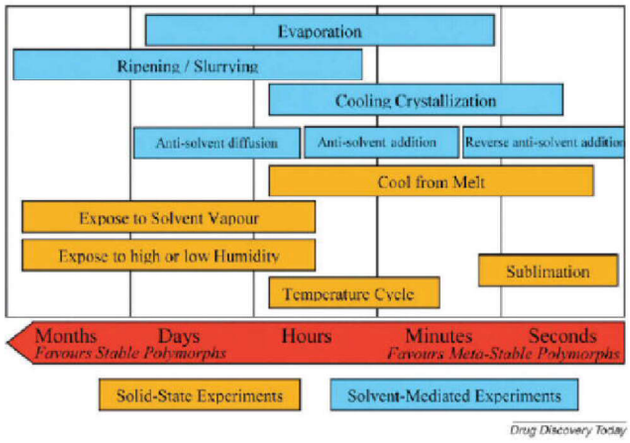



**Figure 1.** Time frames for various crystallization techniques (from ref 36, with permission. Copyright 2008 Elsevier).

Traditional solution crystallizations generally allow for variation in the following parameters:

Solution crystallization, solvent(s) (including solvent mixtures), temperature, stirring, cooling rate, seeding, antisolvent, slurrying

Llanas and Goodman's useful chart summarizes the time scales of solution crystallization techniques as well as the qualitative relationship between the stability of the form obtained and the time required to obtain those forms. Many pharmaceutical companies seek to identify and then develop the most stable form of an active pharmaceutical ingredient (API),[37] but there are sometimes reasons, for instance material handling properties or intellectual property issues, to identify and occasionally use less stable forms, provided they can be stabilized to prevent conversion to the stable form.[38,39]

Other conventional (although not as widely used) methods of crystallization (with typical variable parameters) include the following:

Sublimation (pressure, temperature gradient), crystallization from melt (temperature program), freeze drying, spray drying

Some (but by no means all) of the additional methods of crystallization that have been added to the armory of crystallization tools:[36]

High throughput (solution) crystallizations, confinement crystallizations (capillary, contact line, nano), electrochemical crystallizations, gel crystallizations, vapor diffusion crystallizations, use of ("tailor made") additives, use of templates (polymers, inert surfaces, etc.), mechanical grinding (cocrystals), solvent drop grinding (cocrystals),

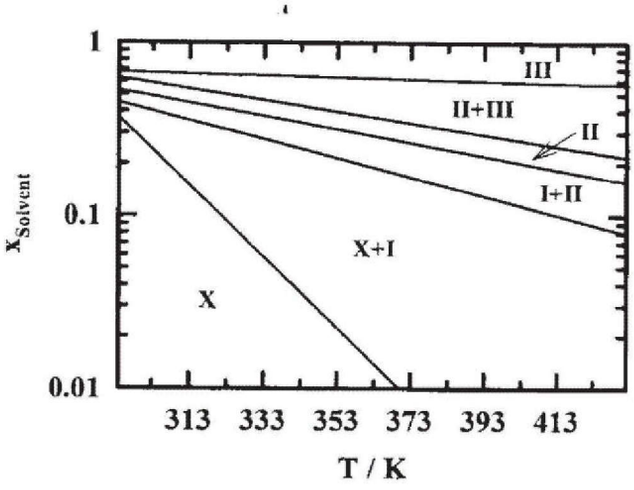



**Figure 2.** Demonstration of control over polymorphic form obtained through crystallization via supercritical $CO_2$ an anticancer quinazoline derivative. Forms I–III were known prior to the experiment. Form X was discovered in the course of the experiment (from ref 42). Form II was most prized.

microporous membranes, sonocrystallizations, light field induced control of crystallization.[40]

In addition, there have been some notable developments that warrant attention and further development and exploitation. Many of these are techniques that were designed to gain control over the crystallization process. It is important to establish that control even in the exploratory stage for crystal forms, since it can greatly aid in scale up and can play a role in preventing the appearance of undesired forms or the disappearance of the desired form somewhere down line, even beyond launch of a product.

One technique that promises a fairly high degree of control over the polymorphic form obtained is crystallization by supercritical fluids – in particular supercritical $CO_2$. For instance, Bouchard et al.[41] demonstrated that they could obtain $\beta$-glycine exclusively by control of the conditions of supercritical $CO_2$ crystallization. One potential advantage of this technique is that it is engineering based, offering considerable control over most crystallization conditions.

This degree of control is demonstrated by the sample of an anticancer quinazoline derivative studied by Kordikowski and York.[42] The compound exhibited five polymorphs, of which the difficult to obtain metastable Form II was desired. The variation of the conditions revealed a small processing window for Form II that was achievable with the added benefit of particle size control. Also in the course of determining the conditions for obtaining the various polymorphs, a new metastable Form X was discovered, which was not obtained by conventional crystallizations.

## Which Polymorph Will We Obtain? Some Comments about $Z'$, and a "Crystal on the Way"

Many chemical crystallographers have been fascinated by the phenomenon of $Z' > 1$ – more than one molecule in the asymmetric unit – and the explanations for its appearance and its meaning have generated considerable debate, with Steed and Desiraju among the principal protagonists.[43,44] Desiraju has contended that all the reasons suggested for the existence of structures with $Z' > 1$ can be attributed to metastable forms obtained under kinetic (i.e., nonequilibrium)

conditions. The implication of this postulate is that if a structure, or a number of structures, are determined to have $Z' > 1$ they must be metastable forms and there exists, or will exist (if it has not yet been prepared) a more stable form with $Z' = 1$ or lower. Such postulates indeed generate discussion, new theories, and in the best cases definitive experiments (I am inclined to include "computer experiments" in this category). However, as the adage goes, "Theory guides; experiment decides", and until there is a body of experimental evidence to *prove* that the higher Z′ structures of a polymorphic system are all (or almost always all − we should always allow for the possibility of exceptions) of higher energy than the $Z' = 1$ structures it seems prudent to reserve judgment on this issue. Brock and Duncan[45] in their study of alcohols with $Z' > 1$ concluded that packing (i.e., space filling) considerations better account for the $Z' > 1$ than energetic or crystallization conditions. Moreover, we exhaustively studied benzidine[46] and found only four polymorphs of with $Z' = 4.5, 3, 1.5$, and 4.5. In addition to our own numerous crystallizations (many in the attempts to prepare co-crystals), the system has been studied intensively by hot stage methods by two previous groups[47,48] with no evidence for an additional lower energy form (with or without $Z' = 1$). Similarly, for cholesterol, another "classic" molecule first studied by Bernal, two monoclinic $P1$ forms have been reported, one with 16 molecules in the asymmetric unit,[49] and the second with 8 molecules in the symmetric unit.[50] However, we are certainly aware of the caveat noted by Revel and Ricard, "But not to be able to find something is no proof of its nonexistence."[51] While the failure to obtain a form with $Z' = 1$ is certainly no proof of its nonexistence, until such a form is found, this case along with numerous other examples[144] argues against the kinetic and thermodynamic rationale for the preference for $Z' = 1$.

It has been argued that crystal structures with high $Z' > 1$ should be considered as a "crystal on the way".[44] While intuitively this notion may have some appeal, it defies the very essence of a crystal structure. Upon determining a crystal structure, we have become accustomed to producing an ORTEP diagram of "the molecule" and a packing diagram to portray "the crystal structure". For many current practitioners of crystallography and users of crystallographic data, the routine generation of these diagrams apparently belies the fact they represent the space average and time average of $\sim 10^{17}$ unit cells, all of which must be essentially identical − or nearly so on the atomic scale − in order for the diffraction experiment to be at all viable. That is, it is precisely a *crystal structure* from which we generate those pictures. It is not on the way to anything; it is already a crystal structure. Otherwise, we could never have done the experiment to determine that structure. However, if the intention is to describe such a crystal structure with $Z' > 1$ as one structure at a local minimum on the multidimensional potential energy surface on the reaction coordinate toward a proposed (or supposed) structure with $Z' = 1$ (presumably, according to this model at the global minimum), then it might be possible to consider this concept as a working hypothesis. Such a notion harkens back to the classic studies of Bürgi and Dunitz on reaction pathways from structures in the CSD.[52] There may be other crystal structures, but they need not per force be on the same reaction coordinate along which the $Z' > 1$ structure crystallized. This is not to deny that it could be the case, but it must be *proven experimentally* before the concept of "a crystal on the way", even in this limited context, can be seriously considered.

## The Crucial Role of Nucleation

The process of crystallization is generally considered to involve two steps − nucleation, followed by crystal growth. Scanning probe microscopies have provided a great deal of insight and understanding into the structural and kinetic aspects of the second step. Of course, once the growth process has begun the structure of the crystal form has essentially been determined. In most cases, that will determine which polymorph results from the process. However, if the first form is indeed metastable, there may be a subsequent change to a more stable form even during the crystallization process, either as a solid → solid transition, or via a solvent mediated transformation, for example, as observed in the case of benzamide.[53,54] Upon cooling an aqueous solution, this compound, arguably the first polymorphic molecular compound, initially studied by Liebig and Wohler,[55] a metastable form appears first and subsequently transforms in situ to the stable form, both with $Z' > 1$.

Recent work has shown that we may have to reconsider the simple, and perhaps naïve, notion that once a crystal form nucleates that form will continue to grow. The concept was at least part of the basis for rationalizing the existence of concomitant polymorphs:[53,56] they nucleate essentially simultaneously and the growth rates are sufficiently similar so that they coexist in the time frame of the crystallization. In the case of benzamide, the transformation to the stable form continues at the expense of the metastable form, but there is a period of time when both may be observed simultaneously − hence concomitant. Some recent molecular dynamics calculations, albeit on simpler systems, suggested the possibility of the cross-nucleation of a metastable polymorph on the stable polymorph.[57] Moreover, Yu and co-workers have demonstrated that such cross-nucleation can occur in the quintessential polymorphic ROY system[58,59] and has also shown that for L-glutamic acid the polymorph that nucleated in the early stages of crystallization was capable of nucleating another, faster-growing polymorph.[60] He concluded that the selective crystallization of a polymorph depends not only on the initial nucleation but also on the cross-nucleation between polymorphs and the relative growth rates of polymorphs.

Clearly, the understanding and control of nucleation is one of the most challenging aspects of current polymorphism research, and recently there has been increasing activity and some impressive experiments in the efforts to develop and control the nucleation step, which of course is the ultimate means of controlling which polymorph is obtained. For example, Meyerson and colleagues[61] have used nonphotochemical laser-induced nucleation on aqueous solutions of urea, and the technique was recently applied for the selective crystallization of α- and γ-glycine.[62]

The debate over the nature of the nucleation of glycine demonstrates some of the questions that need to be resolved.[63] One question intimately related to the nucleation is whether the dominant form of glycine in solution is the cyclic $R_2^2(10)$ dimer (analogous to the $R_2^2(8)$ cyclic dimers in benzoic acid) or monomers − in other words, what is the basic synthon (tecton). In the 1990s, evidence argued in favor of dimers in glycine solution.[64−70] However, Yu et al. have recently carried out freezing point depression and diffusion measurements of supersaturated aqueous solutions of glycine, and both were consistent with the fact that the solutions are mainly (but not exclusively) monomeric glycine.[63] Moreover, the fact that the diffusion of glycine does not slow as the solution ages contradicts

previous models for the formation of dimers. As Yu et al. conclude, their finding "...brings into question the idea of long-lived hydrogen-bonded cyclic dimers as the predominant solution species serving as units of crystal growth. The substantially different rates of nucleation and crystal growth of polymorphs in the same liquid remain a deserving problem for understanding crystallization in polymorphic systems."

It is also important that Yu et al. do not conclude the exclusive presence of monomers but rather a dominant concentration. That notion is consistent with the idea of an equilibrium between the monomer and the dimer, the latter in a number of possible geometric relations, as well as other possible low oligomeric clusters. This concept of multiple competing clusters in equilibrium was earlier promoted by Etter[71,72] and Weissbuch et al.[73] The notion is that the final crystal structure(s) must per force reflect the state or states of aggregations in solution. If there are a number of these aggregates in equilibrium then nucleation and subsequent crystal growth drive that particular equilibrium – or a small number of equilibria in the case of concomitant polymorphs – to the product phase or phases. For instance, in the case of dimorphic tetrolic acid, Davey and co-workers used FTIR spectroscopy to demonstrate the relationship between the hydrogen-bonded motifs in the concentrated solutions of tetrolic acid and those in the resulting crystallized solid.[74] Such studies can aid in the understanding of the relationship between solution and solid state interactions during crystallization and can be used to identify potential new crystal phases. The interactions between various hydrogen-bonded clusters and a number of solvents also provided additional insight into this system.[75] This model has recently been the subject of additional elegant experimental studies.[76,77] The increasing number and sophistication of experimental studies augmented by computational models augur well for probing the details of the initial stages of crystallization.

Together these models suggest a hierarchy of clustering from individual molecules through dimers, trimers, etc. to aggregates to the critical mass of a nucleus and subsequent crystal formation. That is the (perhaps simplistic) model for crystal growth, and there is still a tremendous amount to be learned about the nature and role of each kind of assembly in the ultimate production of various crystal forms of a molecular moiety.

Can we learn anything about the production of polymorphs from melting or dissolution – the reverse process of crystallization? If we invoke dimers, trimers, and other synthonic structures in saturated solutions as precursors to or building blocks of the ultimate crystal structure, then for how long do those clusters persist upon melting? Do they persist in a solution that is not supersaturated? (No shades of homeopathy here!) In essence, we are asking if the solution state has any memory, in terms of the molecular assemblages that constituted the crystal structure from which was derived. This concept of "memory effect" is quite widely used in polymer crystallizations, where conceptually it is easier to understand how some structural feature(s) of the covalently bonded polymer persist in the liquid phase and can determine the structure of the subsequent crystalline material. Indeed, one might even consider this a seeding phenomenon on the molecular scale.

In the spirit of a *Perspective*, I would like to pursue this idea of clustering or aggregation from the opposite direction, that is, starting from melting or dissolution. We tend to imagine the liquid state, and more so solutions of molecules, as random distributions of individual molecules. But how do we generally determine if a solid has melted or dissolved? In normal laboratory practice, we view the liquid with the naked eye, and when we no longer can see any solid particles we determine that the solid has dissolved or melted. And what is the limit on the size of particle we can normally see with the naked eye? Approximately 0.05–0.1 mm. A dimensionally isotropic cube-shaped crystal of this dimension weighs about $10^{-6}$ g and for an organic compound of molecular weight of ~1000 such a crystal could contain approximately $10^{14}$ molecules. Even crystals many orders of magnitude smaller contain many more molecules than the minimum considered necessary to comprise a crystal growth nucleus.[78] So, on dissolution, for how long do these "super nuclei" persist? Can they influence the subsequent crystallization? Can they act as seeds for the subsequent crystallization from the same liquid or solution? There is little or no direct discussion of this issue in the literature.

There are, however, studies that obliquely address these questions. First, an (unpublished)[79] example from our own work. Around 1995, Jan-Olav Henck and I wanted to try to prepare the metastable polymorph of benzophenone. This form had been reported in Groth's marvelous compendium[84] as melting at ~24–26 °C, while the stable form melts at ~48 °C. Numerous attempts failed to produce the metastable form, which we then began to view as a disappearing polymorph.[85] In near frustration, we went back to Groth for the original references, one of which turned out to be a 1910 Ph.D. thesis from the University of Marburg,[86] which, upon obtaining a photocopy, was entirely on the polymorphism of benzophenone! Here (in translation by Henck) is Schaeling's understated description of his efforts to prepare the metastable form:

> Here in brief are some remarks about working with the metastable modification. It requires some practice. We observed that the metastable benzophenone we obtained from the melt heated to a high temperature could be induced to yield crystals of the stable form only by introducing seeds of the stable form.

In fact, Schaeling had heated the melt in a sealed ampule to 230 °C for 10 days and quenched it in liquid nitrogen in order to obtain the metastable form. Apparently, in Schaeling's hands shorter times and lower temperatures were not sufficient. Henck carried out a similar experiment, heating to about the same temperature for four days and quenching in dry ice/acetone, yielding crystals of the metastable form on the first attempt. Note that both our experiment and Schaeling's experiment started with the stable form.

What is one plausible explanation of this experiment? Although the stable form appeared to have melted at 47 °C, even well above this temperature, clusters reminiscent of the original stable form persisted for days. The prolonged heating was necessary to destroy the remnants (i.e., "memory") of the original structure. The metastable form could be obtained by quenching (i.e., kinetically), and after the extended period the stable form could only be obtained by seeding – additional evidence for destruction of the remnants of the original structure, the "memory" of the original structure. In fact, Hammond et al.[87] have recently addressed this question by computationally examining the energetic stability and conformational variability of small molecular precursor clusters for the two forms. The calculations yielded very similar energetic stability for the two small clusters, but the stable form became more stable for clusters exceeding four molecules.

This observation is not inconsistent with the notion that the extended heating process above the melting point is required to destroy the larger clusters favoring the stable form, in order to energetically allow the metastable form to develop from the smaller clusters. Zeng et al.[88] have recently noted similar phenomena (and used the same nomenclature) with respect to the formation of tetrahydrofuran clathrate hydrate crystals.

In solution, the situation is obviously more complicated due to the effects of dilution, which should in the limit of infinite dilution lead to total destruction of any assemblages of molecules. However, many, if not most, recrystallizations are carried out by preparing supersaturated solutions and these could easily retain assemblages of molecules from the starting solid materials – the last "dissolved" solids. Boldyreva has cited some relevant evidence from the recent literature.[89] As often is the case in competitive polymorph crystallizations, intentional (and presumably unintentional) seeding is an important factor. However, aging of solutions apparently also plays a role in determining the polymorph obtained. For example, pure $\beta$-glycine was obtained by antisolvent precipitation from acetic acid solutions by addition of acetone, only if the glycine solution was sufficiently aged; otherwise, impurities of other polymorphs ($\alpha$- and $\gamma$-) were present in the precipitated sample.[90−92]

There is additional evidence that the clusters present in glycine solutions vary depending on which polymorph was dissolved and that these clusters evolve temporally.[93] Atomic force microscopy (AFM) studies have shown that dimers present in the crystals of $\alpha$-glycine are preserved on dissolution.[94] With regard to the reverse process of the retention of basic molecular assemblages in the eventual crystal form, Gavezzotti has demonstrated by computer simulations that clusters of molecules existing in a molecular crystal are preserved long after dissolution,[95] while Hamad et al. have shown by molecular dynamics calculations that they are present even as transient species.[96] Additional molecular dynamics simulations indicate that the rate of dissolution of $\alpha$-glycine seed crystals in highly supersaturated solutions proceeds at a progressively slower rate, also suggesting the role of time and residual assemblages in the determination of the polymorph obtained.[97]

Admittedly, although the facts on these issues are accumulating, the *interpretation* much of the above is in the nature of speculation. However, an understanding of these phenomena, whether manifestations of a solution or melt memory effect, is required to gain control over the polymorphic form(s) obtained from a crystallization.

In almost every field, there are certain systems that become the paradigm for modeling, testing, and understanding a particular phenomenon. In chemistry, these molecules or molecular systems are chosen because they are generally simple, inexpensive, can be studied under relatively mild conditions, and clearly exhibit the property or properties of interest. The (often hidden) message is that any acceptable model or theory for the particular phenomenon must be applicable to that quintessential system. The reader may have already noted that many examples cited above refer to glycine, whose polymorphic behavior was first studied by the legendary J. D. Bernal[98] in 1931. This *Perspective* is not the appropriate forum for a complete review of all of the studies of the crystallization of glycine and its polymorphic behavior. Useful summaries have been given by Boldyreva[89] and Huang and colleagues[63] and demonstrate the variety of techniques that have been applied to study and control the form obtained. However, a few noteworthy developments are given here.

Perhaps because of the intense interest in the trimorphic glycine system one aspect that has been studied recently more than for others is that of nucleation. Some of the questions we would like to be able to answer include: what is the critical size or how many molecules constitute a nucleus? How many different nuclei coexist in a dynamic equilibrium situation? What are the structures of those nuclei? How long does any particular nucleus persist? How similar is the structure of the nucleus to the final crystal structure? How may we promote or inhibit the existence of any particular nucleus? etc. Again, some of those questions have been addressed specifically for glycine.

One thing that is frequently overlooked in my view is the "critical nucleation that occurs after nucleation". By this, I mean that for crystals to grow at reasonable rates at low supersaturations where we typically work in solutions, crystals must nucleate growth spirals or other emergent structures. Otherwise, the germs that form in solution will not be productive. We know virtually nothing about how growth spirals nucleate at the molecular level.

Myerson and colleagues have studied the effects of laser induced nucleation under various conditions,[40,99−101] as well as the influence of confined crystallization,[102] while Davey et al. have studied the crystallization from emulsions, microemulsions, and lamellar phases.[103] Growth from neutral solutions has been investigated,[104] as well as the influence of pH, salt formation, and ionic strength.[105] The crystallization behavior was studied on a pilot/industrial scale using a WWDJ batch crystallizer[106] and spray drying.[107]

The design and use of "tailor-made" additives is now a well-established strategy in influencing both the form and the habit of a crystallization,[108,109] and has been recently expanded, for instance, to demonstrate the possibility of controlling the outcome of a polymorphic *salt* system.[110] While these have generally been designed to selectively *inhibit* crystal growth in a particular direction, recent independent experiments by two groups (in a combined publication) on $\alpha$- and $\gamma$-glycine (with malonic and DL-aspartic acid) led to selective inhibition in the $\alpha$ case, but surprisingly led to *acceleration* of the growth of the $\gamma$ form.[111]

### Are Two (or More) Crystal Structures True Polymorphs?

As the search for new polymorphs has become more sophisticated, the question of proving success in obtaining a new polymorph has become increasingly critical. Are they the "same" or "not the same", "different" or "not different"?[112,113] The question may not always be one limited to scientific interest or curiosity, but it may also have considerable intellectual property ramifications (*vide infra*). There has been a flurry of activity in this area, with the development of a number of tools for comparing structures that are purportedly different polymorphs – or purportedly not different.

Two recent examples suffice to demonstrate the point. The first was a paper by Vujovic and Nassimbeni,[114] actually posing the question in the title: "Methyl Paraben – A New Polymorph?" and supposedly answering in the affirmative in the body of the paper. Threlfall and Gelbrich[115] answered the same question in the title to their paper "The Crystal Structure of Methyl Paraben at 118 K Does Not Represent a New Polymorph". What was the basis for this conclusion? Threlfall and Gelbrich make a prescient statement that defines the

conundrum: "...one can get a change of structure without a change of phase but not a change of phase without a change of structure. The existence of distinct phases will normally be recognized either by a phase transition or by structural and property changes greatly in excess of those brought about by normal temperature expansion." They have used the Xpac program[116] to demonstrate that the packing in the two structures described by Vujovic and Nassimbeni "is identical", in accord with error criteria defined by previous authors;[117,118] hence, they conclude that Vujovic and Nassimbeni's two structures are not polymorphs.

The second, perhaps more notorious, example is that of aspirin. In the 1960s and 1970s, there was a great deal of interest in the possibility of polymorphism in aspirin[119] with the conclusion that the evidence was not sufficient to establish the existence of an additional crystal form. In 2005, a group attempting to prepare co-crystals of aspirin reported the apparent serendipitous discovery of a second polymorph.[120] Subsequent characterization indicated that the X-ray powder diffraction pattern could be matched with one calculated from an earlier computed structure based on lattice energy calculations.[121] This finding was questioned by Bond et al. stating initially on the basis of their own experimental evidence that "it is not possible to determine if there is a second form of aspirin in the samples obtained by [Vishweshwar et al.]"[122] and then reaching the conclusion that "the [Vishweshwar et al.] crystal, like several other aspirin crystals described in this paper, is an intergrowth of two 'polymorphic' domains".[123] In the next-to-last paragraph of this paper, the authors raised several important questions, including whether these two situations should be legitimately described as polymorphs. Similar phenomena had been discussed on a number of previous occasions,[124−127] and have been described as "composite crystals" by Coppens et al.[128] Then, of course, there is the possibility of mixed crystals with the same "structure" and composition (same melts) having different symmetries. Are they the same or different polymorphs? The question regarding aspirin is still open.

To answer the question posed at the heading of this section, we need to be able to determine if they are different crystal structures of the same material. Two approaches for that have been presented in the preceding paragraphs. Traditionally this has been done by examining the X-ray powder diffraction patterns of two or more samples and deciding if they are the same or different. In cases where the structural differences are subtle, making that distinction might be quite difficult, and if the judgment is made (as it often is) by a simple visual comparison of X-ray powder diffraction patterns, then it may be subject to considerable bias and/or error. Even a program for calculating the match between two powder patterns will not give a perfect match, so it is necessary to make a decision on the significance of the correlation (or lack thereof) between two or more powder patterns.[129]

What we require are additional objective and quantitative tools to determine if two or more crystal structures are polymorphs. Fortunately, the past decade has witnessed the development of some of those tools.

As in many aspects of molecular chemical crystallography, the Cambridge Crystallographic Data Centre was among the leaders in this effort. Over the years there were quite a few compounds for which multiple crystal structures had been determined. Some of these turned out to be polymorphs, while others were improved structures, structures determined at different temperatures, etc., and the plethora of structural entries for a single compound led to confusion on which were unique polymorphs, and indeed which was the "best", that is, the standard for each polymorphic structure of that compound. This situation was sorted out by Motherwell and van de Streek.[130] They automatically identified and compared 35 000 pairs of crystal structures of the same chemical compound. A total of 7300 pairs of polymorphs were identified, of which 154 previously were unknown or unrecognized. Subsequently, for any particular compound each group of unique structures was scanned to determine the best determination for each structure.[131] The software developed in the course of this study can be used to reliably compare a newly prepared crystal with a standard structure to determine if one has obtained a new polymorph of a compound for which there is an entry in the CSD.

A number of other approaches have been used to test for structural uniqueness. We have already mentioned the similarity index of Gelbrich and Hursthouse in connection with the paraben case. Gavezzotti has used his OPiX program[132] to calculate the distribution of molecule−molecule energies in the packing coordination sphere of a reference molecule, in combination with the more traditional crystallographic cell reductions and powder patterns. For each crystal structure in an ostensible polymorphic system, the program calculates the distances between centers of mass of pairs of molecules and the intermolecular energy associated with each pair, obtained by summing over the pair wise atom−atom energy contributions between the two molecules. A plot of the intermolecular energy as a function of the center-to-center distance is then prepared. The result is a profile of the energetic environment of an individual molecule in the crystal structure. The working assumption for the purposes of identifying polymorphs (or lack thereof) is that the energetic environment of a molecule is unique for a particular crystal structure (i.e., single polymorph); thus, the coincidence of points for two potential polymorphs on such a plot indicates that two structures are essentially identical and not polymorphs, whereas different distributions are very strong indications of polymorphic structures.

An example of the use of this method to determine the existence of polymorphism in 3-amino-5-(4-pyridyl)-1,2-dihydro-pyrid-2-one. Figure 3 reveals the complete overlap of DUVZOJ[133] and DUVZOJ03,[134] while DUVZOJ01[133] is clearly different from the other two. Further details on this and a number of other examples may be found in ref 135.

A very powerful technique for comparing structures for the purpose of determining if two (or more) structures are polymorphic utilizes the Hirshfeld surfaces, originally conceptualized in the 1970s by Hirshfeld[138] and developed during the past decade by Spackman and his colleagues.[139] The derivation of the Hirshfeld surface, and the various ways of representing it are described in the previous references. Briefly, the Hirshfeld surface of a molecule in a crystal is constructed by partitioning space in the crystal into regions where the electron distribution of a sum of spherical atoms for the molecule (the *promolecule*) dominates the corresponding sum over the crystal (the *procrystal*). The Hirshfeld surface is then defined in a crystal as that region around a molecule where $w(\mathbf{r}) \geq 0.5$, that is the region where the promolecule contribution to the procrystal electron density exceeds that from all other molecules in the crystal. These representations have been incorporated into a user-friendly software package *CrystalExplorer*[140] that is readily available on the web. For the purposes of

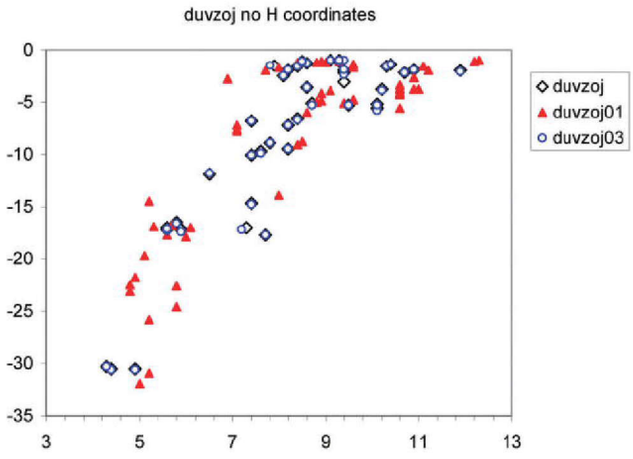



**Figure 3.** A typical example of a distance/energy plot. The horizontal axis is the distance between molecular centers of mass (Å); the vertical axis is molecule−molecule interaction energy calculated by the 6-exp UNI atom−atom potential function.[136,137] The intermolecular energies for the structures with refcodes DUVZOJ and DUVZOJ03 are clustered, indicating that they are the same form, while those for DUVZOJ01 exhibit a different distribution, indicating a different polymorphic structure (from ref 135, with permission).

comparing crystal structures and identifying polymorphs the Hirshfeld surfaces, and in particular the two-dimensional "molecular fingerprint" associated with it specifically developed by Spackman,[139] allow one to analyze in detail the intermolecular interactions. But more importantly for establishing the existence or absence of polymorphism for a set of structures the visual comparison of fingerprints is quick, straightforward, and noncontroversial, even when differences in structures are quite small.[141] The fingerprint is a standard graphical two-dimensional map that indicates the distribution of the interactions for a single molecule in the structure and is perhaps the most useful tool for comparing polymorphs. It is also possible to easily derive a raft of quantitative data for the comparison of specific interactions, the contribution to the overall packing energy, dipole moments, etc.[142]

Spackman and his colleagues recognized the potential for comparing polymorphic substances using the Hirshfeld representations,[143] and as examples of the utility of this tool have presented detailed analyses of a number of classic polymorphic systems including dichlorobenzene, terephthalic acid, tetrathiafulvalene and ROY, along with guidelines on the interpretation of the fingerprint plots.[144]

The utility of this very powerful tool is best demonstrated with an example that also indicates the complementarity of the methods of examining the energetic and the electronic surroundings of a molecule. It also raises another aspect of polymorphic structures that has become of increasing interest and activity − namely, structures with $Z' > 1$.[139] In the early days of single crystal crystallography − into the late 1960s, before the development of direct methods for structure solution − the determination that $Z' > 1$ for a structure essentially relegated it to the crystallographic graveyard, since there were very limited means for solving such structures.[145] Structures with $Z' > 1$ are now solved routinely − perhaps in some cases too routinely, as we shall see.

In our examination of a number polymorphic structures with at least one form with $Z' > 1$, we note the structures of 4,4-diphenyl-2,5-cyclohexanedione (**I**) (refcode HEYHUO),

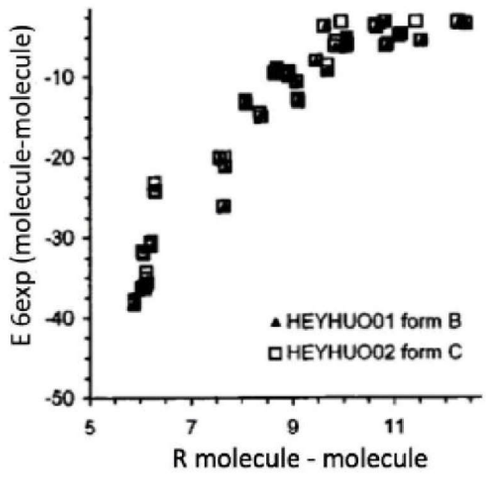
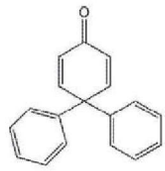



**Figure 4.** $R/E$ (distance−energy) plots for Form B of HEYHUO01 ($Z' = 4$) and Form C HEYHUO02 ($Z' = 12$) (from ref 135, with permission).

which is reported to crystallize in four crystal forms, A, B, C, D.[148]



**I**

Of special interest was the fact that two of these forms, B and C, crystallize in the same space group $P\bar{1}$ with $Z' = 4$ and $Z' = 12$, respectively. These structures were also discussed in a recent review of conformational polymorphism.[149] The $R/E$ plots are given in Figure 4.

It is clear that there is near perfect overlap between the points indicating that they are not polymorphs. The examination of the Hirshfeld surfaces for the structures (Figure 5) readily demonstrates the power of this tool. A visual inspection reveals that the two molecules D clearly have different fingerprints and they in turn differ from that of Form A. Hence, the two are clearly different polymorphs. The differences among the four molecules in Form B are readily apparent, and they also clearly differ from the three molecules in Forms A and D.

Form C has been claimed to contain $Z' = 12$, in itself an unusual phenomenon, but in principle, of course, possible. First, we can compare the fingerprints of the 12 "independent" molecules. Even a casual visual inspection readily reveals the following coincidences (according to numbering of molecule as published):

$$1 = 2 = 3$$

$$4 = 5 = 6$$

$$8 = 9 = 12$$

$$7 = 10 = 11$$

Thus there are four different triplets of molecules with identical surroundings, which means there are only four crystallographically independent molecules in the asymmetric unit ($Z' = 4$) for this structure. That could still constitute

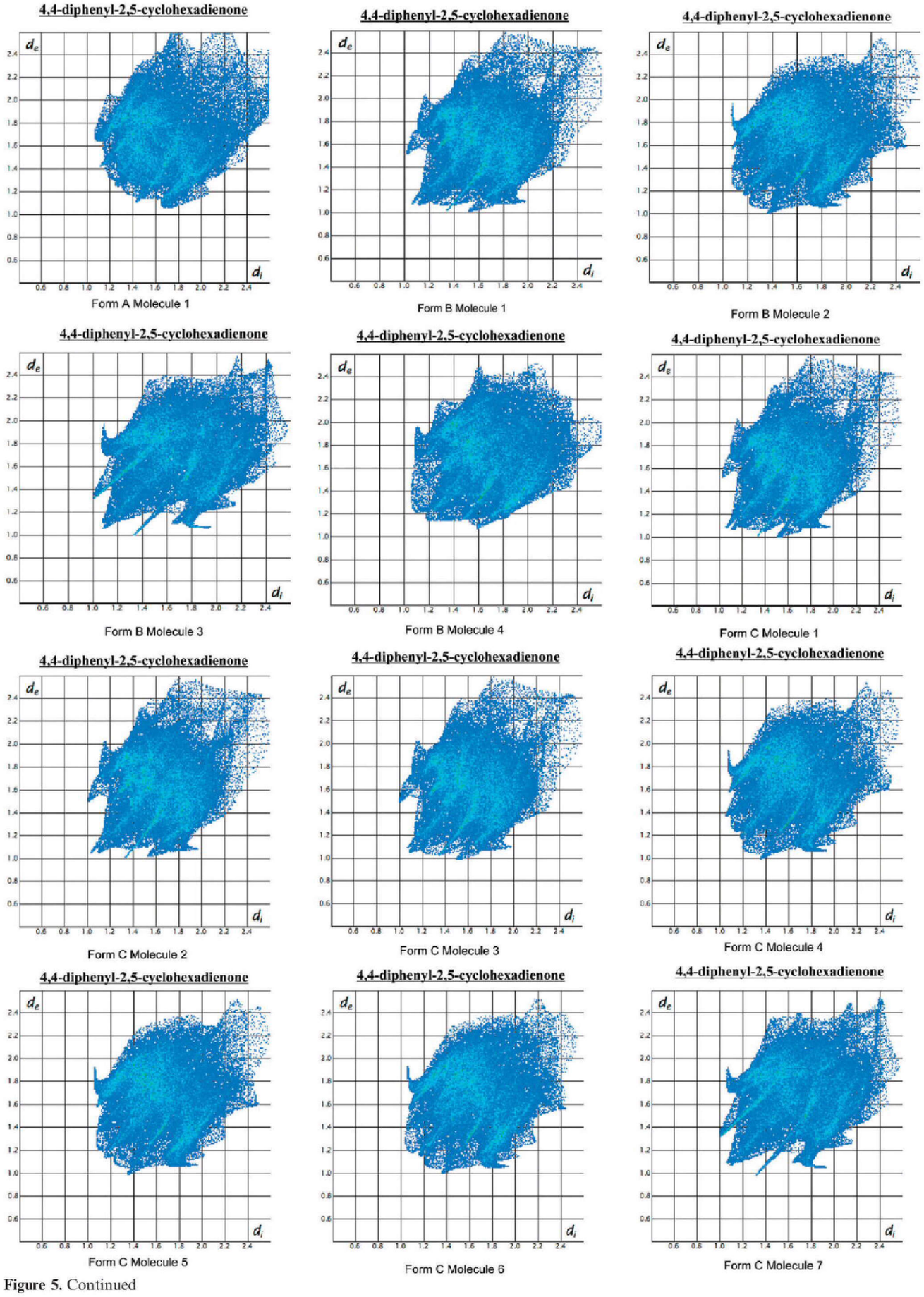



**Figure 5.** Continued

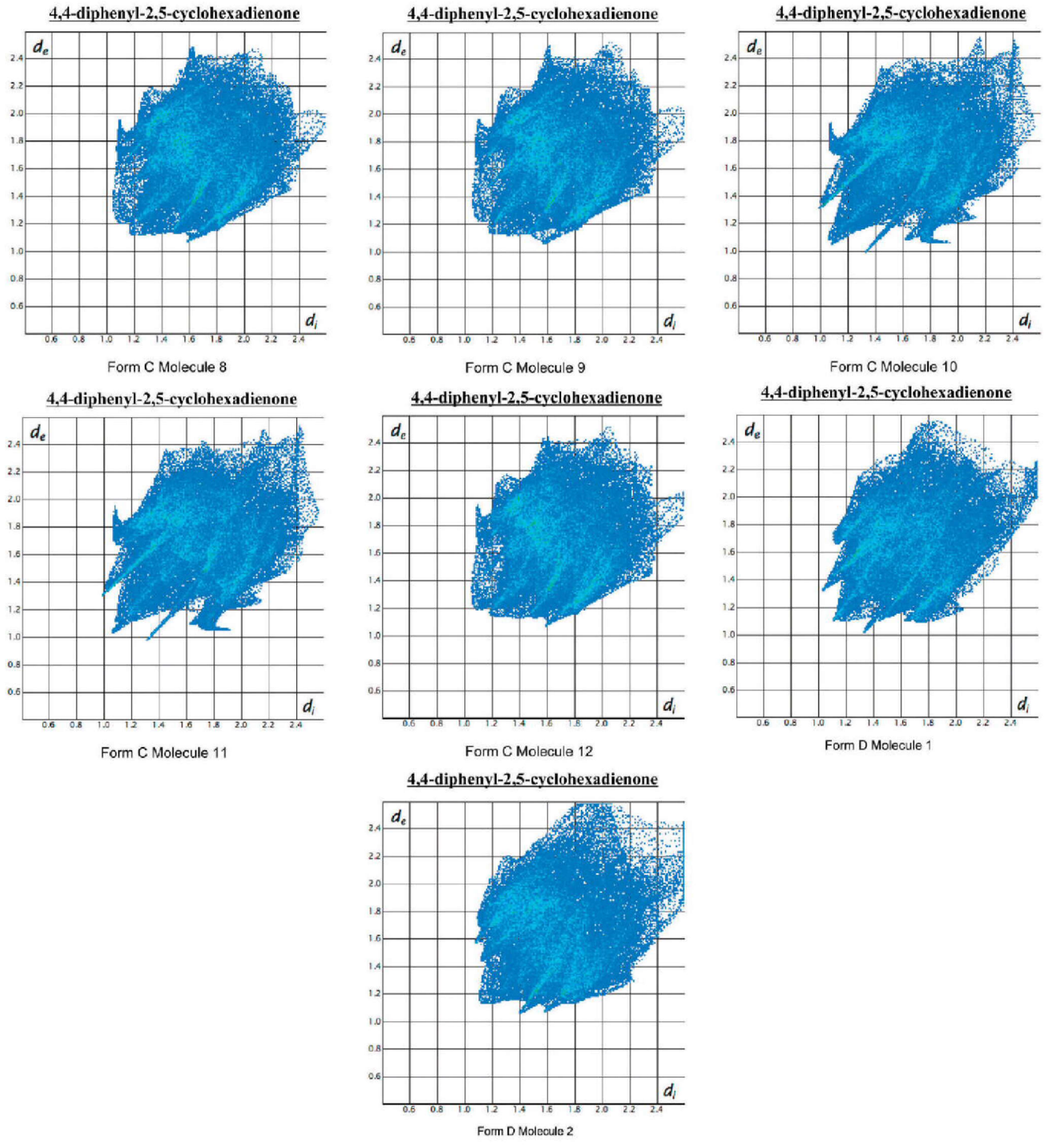



**Figure 5.** Hirshfeld fingerprint plots for the 19 presumably crystallographically independent molecules in the four crystal structures of 4,4-diphenyl-2,5-cyclohexanedione. Each fingerprint is labeled according to the polymorph (A, B, C, D) and the number of the molecule in the asymmetric unit as in the original publication. Top row: Form A ($Z' = 1$) and Form D ($Z' = 2$). Second row: Form B ($Z' = 4$). Rows 3−5, Form C ($Z' = 12$). See text for subsequent comparison.

another polymorph. But is this structure equivalent to Form B? Examination of the fingerprint of molecule C1, for instance, reveals identity with molecule B1, and similarly the fingerprints of C4 = B2, C7 = B3, and C8 = B4. These results graphically and quite dramatically confirm the earlier conclusions based on the $R/E$ plots and the powder diffraction data[132] that Forms B and C are indeed one and the same. Thus this trimorphic (not tetramorphic) system exhibits not 19, but seven crystallographically different molecules. This example clearly and unequivocally demonstrates the actual identity of crystal forms that had been reported as different polymorphs.

There is no reason to be limited to one method for evaluating polymorphism. One of the motivations for the computational study of reported structures with large or unusual $Z'$ values was to authenticate the unusual situation in benzidine noted above. If these methods are to be reliable, they should

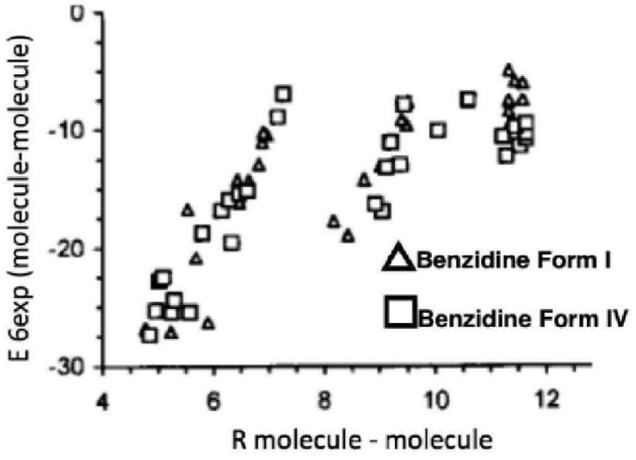



**Figure 6.** $R/E$ (distance−energy) plots for the two polymorphs of benzidine with $Z' = 4.5$ (from ref 135, with permission).

reinforce and confirm, rather than contradict, each other. We also examined two of the four polymorphic structures of benzidine[46] whose genuine identity as polymorphs was suspect since they both contained $Z' = 4.5$, a very rare occurrence for any molecular crystal.[150] Calculation of the $R/E$ landscape (Figure 6) indicated that those two structures were indeed different.

The power and simplicity of the Hirshfeld fingerprints in distinguishing polymorphs and crystallographically independent molecules is clearly demonstrated in this system (Figure 7). The plots for the 15 crystallographically independent molecules in the four structures can be readily seen to be unambiguously different, reflecting a different crystallographic environment for each.

There may be instances where a quantitative measure of the degree of similarity or difference may be desirable. The fact that the identical two-dimensional grid is used for every fingerprint plot allows the calculation of a similarity index between whole molecular structures.[151]

The ideal test of the identity or difference of crystal structures is a comparison of the experimental X-ray powder diffraction patterns, which do not depend on the choice of cell constants. The difficulties in doing so involve, first and foremost, obtaining pure samples of each of the crystal forms. Even then experimental powder patterns can be fraught with many errors.[152] A simple and rapid alternative is to calculate the powder pattern from the solved structures [now simply done in the Mercury Suite of the software for the CSD]. These contain any errors generated in solving and refining the structures, which generally influence the intensity rather than the $2\theta$ values of the diffraction peaks. Nevertheless, comparison of the powder patterns is highly recommended when there is a question of the existence polymorphism. This approach was adopted in the study of Eniluracil, in which different samples exhibited different degrees of disorder. Price et al. pointed out that this result is due to the results of the refinements for different crystals, which could lead to the mistaken identity of polymorphism rather than different degrees of disorder in a single structure, as demonstrated above.[153] Here again the decision may be a matter of degree. If one of the structures is ordered and another disordered, then by that simple fact they are different. Do the powder patterns differ sufficiently to correspond to experimentally significant different cell constants? In fact, in discussing the $Z' = 12$ case we also discussed the crystallographic and experimental factors that could have led to such a model.[135]

## Some Myths on Factors That Increase the Occurrence of Polymorphism − or Do Not

The role of intuition in chemical research should not be underestimated. Hunches drive our curiosity, and the pursuit of that curiosity is often the key to discovery, even if the basis of that hunch was weak or even unfounded. But intuition is not necessarily based on facts, and it should not be confused with facts. There seem to be a number of myths in the realm of research on crystal forms; they may inspire creative research, but they remain myths, not facts. They remain myths because there is no research, at least to the best of my knowledge, to justify the assumptions made. Since every molecule presents a new situation regarding the possibility of crystal forms, the research required to justify or even prove these assumptions can only lead to statistical conclusions, and the *probability* of obtaining a certain result on the next system to be investigated. Those probabilities are also guidelines − indeed they may be very useful guidelines when considering the alternatives − but guidelines nevertheless. Guidelines provide us with information on what to *try*, and suggest what the result might be, not what it will be.

What are some of these unfounded myths (not necessarily in order of importance)? The first is that conformationally flexible molecules tend to form polymorphs more than those that have few degrees of conformational freedom. Again, intuitively such a working *assumption* is quite reasonable. However, there is no statistical analysis on which to base that assumption. In fact, it is virtually impossible to carry out such a statistical analysis, because in order to be valid it would have to include compounds that do not form multiple crystal forms − or more correctly, have *not yet* been found to exhibit multiple crystal forms. Since the literature contains fewer and fewer examples of failed experiments, we are generally not even aware of those cases in which a search for multiple crystal forms was unsuccessful. Even if we try to develop some generalizations based on intuition rather than fact, it is the nature of chemistry in general, and crystal chemistry in particular, that we can almost always find exceptions to those generalizations. Two common materials demonstrate the point: sucrose is a flexible molecule that has been crystallized countless times under an almost endless variety of conditions, and no more than one crystal form has even been reported; on the other hand, *p*-dichlorobenzene, a rigid molecule, is known to have three polymorphic forms.[154]

The second shibboleth is that the tendency to form multiple crystal forms increases with the number of hydrogen bonding functionalities. Again, this *possibility* may exist and again it seems intuitively reasonable, but no research raises this possibility to *fact*. That does not prevent us from using it as a *working assumption*, but it cannot be used to predict, guarantee, or justify the result of any particular experiment or set of experiments. The results of such experiments may be explained by the fact that different crystal forms exhibit different hydrogen bonding schemes, but by the same token they may exhibit the same hydrogen bonding schemes and differ in other packing features. That is, different polymorphs may *result in* different hydrogen bonding schemes, but one cannot necessarily conclude that they exist *because of* the possibility of a variety of different hydrogen bonding schemes. The connection between cause and effect has to be proven.

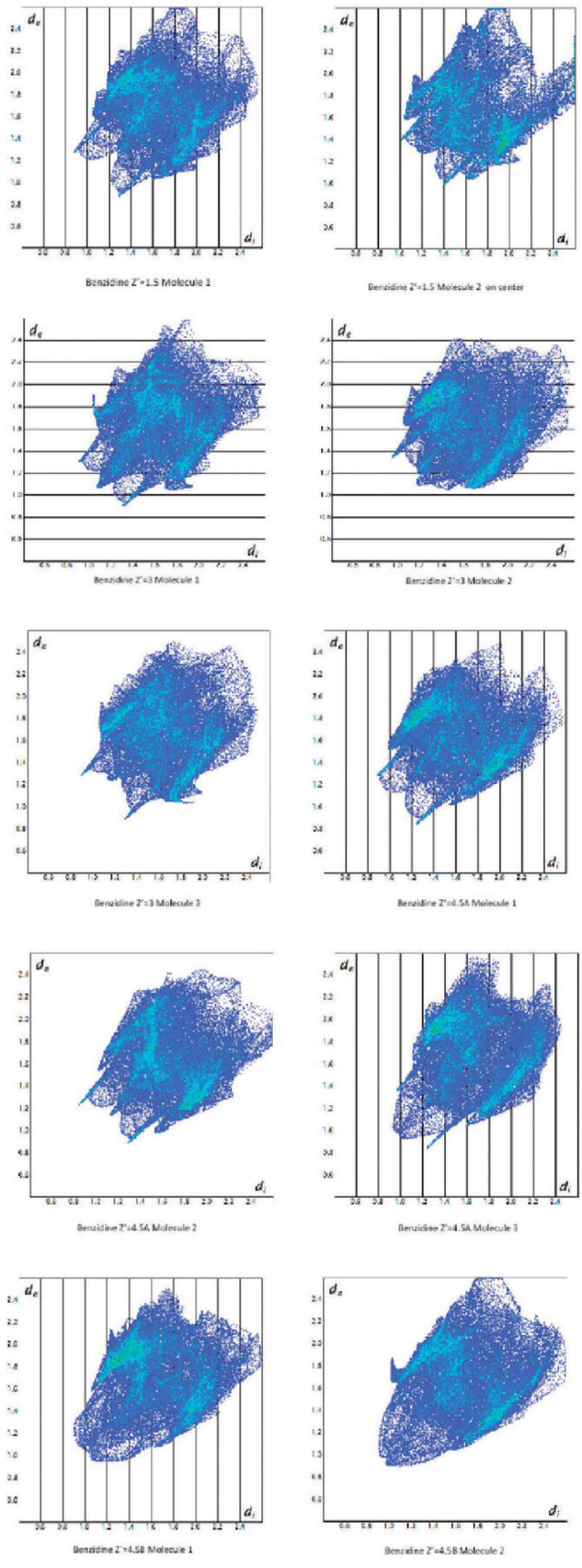



**Figure 7.** Continued

That proof is indeed a very difficult challenge when it comes to demonstrating *why* a particular crystal form appears (e.g., the role of all the thermodynamic and kinetic factors), as opposed to simply describing or characterizing a crystal form that appeared (e.g., detailing the crystal structure).

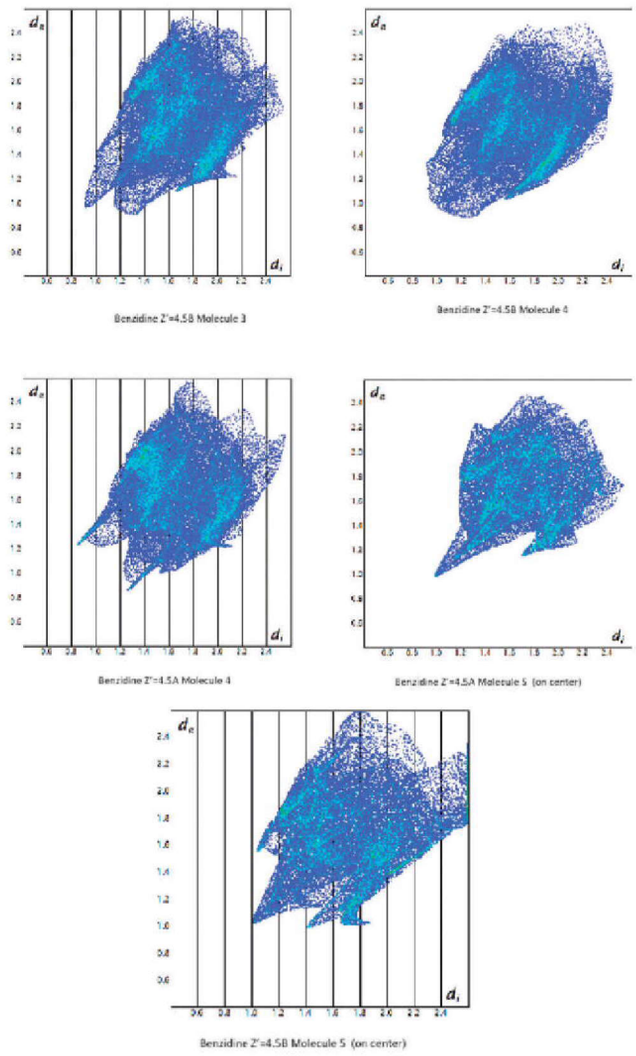
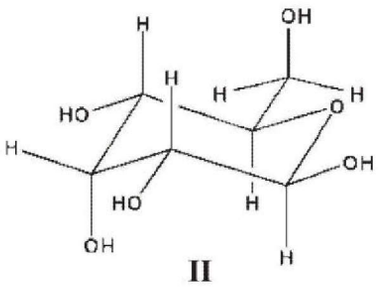



**Figure 7.** Hirshfeld fingerprint plots for the 15 different molecules in the four polymorphs of benzidine. The molecular numbering is the same as that given in the original publication.[46]

An example of the complexity of such assumptions may be found in the recently reported pair of $\beta$-D-allose (**II**) structures, obviously rich in hydrogen bonds. The *primary* hydrogen-bonding pattern in the metastable form is the same as in the stable form, with both exhibiting stacked hydrogen bonded columns of molecules in the short axis (~4.9 Å) direction. In what may be considered the tertiary structure these columns are linked differently, but in terms of the fundamental hydrogen bonded synthons, the building blocks are the same.[155] This phenomenon of common hydrogen bond motifs among polymorphs has been noted by others.[156] The $\beta$-D-allose structure is also an example of the increasingly important contribution that structure solution from powder diffraction data is playing in the characterization of polymorphs. Perhaps contrary to Ostwald's Rule – historically at least – the structure of the less stable form was reported 20 years after that of the stable form,[157] although there was indeed evidence of the former's existence 30 years prior.[158] Experiments to grow single crystals of the less stable form were not successful, but the high degree of crystallinity of the powder permitted the

structure solution and refinement from laboratory X-ray data, even though the sample was contaminated by the stable form. This is simply an example of the increasing sophistication and potential of structure solution from powder data – a tool that should be increasingly employed in polymorphic studies. Unfortunately for its immediate potential, the number of practitioners of this technique is still quite limited, although access to suitable data (laboratory and synchrotron) is rapidly increasing.




II

In the case of hydrogen bonding, there have been some significant recent attempts to go beyond intuition and provide a knowledge-based (from the CSD) model of hydrogen-bonding propensity in organic crystals.[159] As the authors note,

> This [knowledge based] approach has a potential application in identifying both likely and stable and metastable crystalline forms of relevance to drug development in the pharmaceutical industry. Whilst polymorph prediction techniques are widely used, the LHP [logit hydrogen-bonding propensity model developed by the authors] model is knowledge-based and is not restricted by the computational issues of polymorph prediction, and as such may form a valuable precursor to polymorph screening.

Note again, while the method may provide very valuable guidelines and insights into what one might reasonably expect, the only ultimate proof is in the execution of experimental screening and the structural characterization of the solid forms obtained.

A third unproven, but again perhaps intuitively plausible assumption is that co-crystals would tend to exhibit fewer instances of polymorphism than single component crystals. Presumably, such an assumption is consistent with our intuitive notions of the role of entropy: it does seem reasonable to assume that a variety of crystal structures is much less likely for a two (or more) component system than for a one component system.[160] Again, no *proof* is offered for this assertion. In fact the comparative dearth of co-crystal structures may have justified a prejudice that is just now being undermined.[161−163]

While serendipity continues to play a role in the discovery of new crystal forms, and likely will continue to do so for the foreseeable future, an increasing number of crystal forms are being discovered by systematic screens, often employing many the new techniques noted above. When applied to co-crystals, such techniques have no less potential for success in generating polymorphs. Thus, while much of the armory of co-crystallization (e.g., solution crystal growth, slurry conversion, melt crystallization, high-throughput polymorph screening with the CRYSTALMAX technology, mechanical grinding, and slurry conversion experiments) had been applied to two iconic co-crystals, carbamazepine/saccharin and carbamazepine/nicotinamide, none of these methods had yielded more than one crystal form until Matzger et al. produced a second form of each by polymer heteronucleation.[154]

## Where Are We on the Road to Predicting Polymorphs?

Arguably the most succinct (and most memorable) response in the chemical literature was Gavezzotti's "No!" to the question in his title: "Can crystal structures be predicted?"[165] That was 16 years ago, and it was in part prompted by the launch of a program package entitled the "Polymorph Predictor". In the interim, Dunitz addressed the same question with a slightly more measured "The one-word answer to the title question is still "No", although at certain levels of discussion a "Maybe", or even a conditional "Yes", may be entertained as possible responses."[166]

In a 2011 *Perspective* (retrospective?) article on polymorphism, I would be remiss if I did not address this issue. First, I believe that a bit of historical perspective is helpful to recall where we have come from. The idea of solving crystal structures computationally was first promoted by Kitaigorodskii, in the 1950s in a now classic book.[167] In addition to promoting the atom...atom potential functions now widely employed for calculations, he shows photographs of the "crystal packer", mechanical ball and stick models with conformational flexibility that were built to seek the best way that these molecules could pack together. An early pioneer in lattice energy calculations was the late Don Williams whose "PCK65" program[168] was used to solve some crystal structures[169] in the days that preceded the universal use of direct methods. Williams continued to develop those methods, and his atom... atom potentials are still widely used.[170,171] Over the years, a relatively small cadre of dedicated practitioners has been developing and refining a variety of computational strategies and techniques and indeed significant progress has been made. In addition to continuing reports in the literature, the field has been blessed by the initiative of the Cambridge Crystallographic Data Centre which organizes an open series of competitive "blind tests" to monitor progress in the field.[172]

Very considerable and impressive progress has been made in the computation of crystal structures, and these computational tools are playing an increasingly important role in many aspects of chemical crystallography and crystal engineering. As one of the early users of "PCK65" I can certainly appreciate that progress. However as noted below, we are still quite a way from the ultimately desired situation where we can input any molecular formula into a computer and generate the crystal structures (including the polymorphs and solvates) that that compound will exhibit. That, of course, is the goal. For instance, the rules of the blind test still define a limited – albeit expanding – subset of all possibilities of the crystal structures to be computed (e.g., space group, $Z'$, salt formation, solvation (including hydration), and expected polymorphs of the various combinations – ideally with a recipe for preparing them). Until there is no longer any need to define that subset the problem has not been solved.[173]

Having said that, I think it is important to note here some of the recent noteworthy landmarks in the development of computational tools for studying crystal structures. Sally Price's recent overview[23] presents an excellent snapshot of the current strategies, problems, and challenges. An important landmark was achieved in the latest (published) blind test.[174] Although many groups had limited or no success, one group (Neumann) did compute the correct structure for all four of the test molecules, using dispersion-corrected DFT

calculations to generate reference data for tailoring a force field to each molecule under consideration, which is then used with a Monte Carlo parallel tempering algorithm to generate crystal structures and the calculation of lattice energies and energy derivatives.[176,177] The method is very CPU intensive. For instance, in a recent study which led to the prediction of a third energetically accessible polymorph of paracetamol.[177] including all 230 space groups and $Z' = 1,2$. The major portion of the calculations took 3 weeks on a 256 core Opteron cluster with 2 Gb of memory per core, a clock rate of 2 GHz, and an InfiniPath network. These kinds of computing and time resources are not yet widely available, but the potential has been demonstrated. The predicted third form of paracetamol has not yet been prepared, and remains an experimental challenge.

There has been some other recent important progress in this area. For instance, Graeme Day and his colleagues at Cambridge have been expanding the field in terms of the size/complexity of molecules that we can now be studied. Progress in treating flexible molecules was demonstrated in a study of the α-amino acids,[179] while the structures of two-component crystals of fairly flexible molecules were predicted under blind test conditions including pseudoracemic amino acid (two-component) complexes,[180] and the methods have been extended to organic framework structures and inclusion complexes.[181]

## Polymorphs (Crystal Forms) and Patents

The connection between multiple crystal forms and patents was hardly an issue 40 years ago; it is not even raised in Haleblian and McCrone's landmark 1969 review of polymorphism in pharmaceuticals.[182] However, a number of high profile patent litigations of pharmaceuticals and an increasing number of applications for patents on crystal forms have radically changed that situation.[183] The connection between crystal forms and patents is increasingly cited as a rationale for searching for and characterizing crystal forms.[18,19,36,122,184,185] This *Perspective* is certainly not intended to provide any legal advice, but it is useful to remind ourselves briefly of the connection between polymorphs and patents.[186]

In principle, patents are granted for inventions and give the grantee exclusive rights over that invention – that is, the right to prevent others from making it, using it, or selling it. Two of the fundamental criteria for the granting of a patent are that the invention must be *novel* and it must be *nonobvious* to the hypothetical person "skilled in the art" – someone with competence but without imagination. Novelty and obviousness are terms that are debated in virtually every legal confrontation on crystal forms. As I pointed out earlier,[PMC241] by definition, essentially every new crystal form is novel. Furthermore, for any compound it is not obvious – and not possible to predict – how many different crystal forms can be prepared, how to prepare any, as yet unknown, crystal forms, or to predict the properties of any, as yet unknown, crystal forms. It is virtually impossible to provide specifics beyond that general statement since every compound is a new situation and every legal jurisdiction has its own rules, regulations, legal framework, and case law, but the novelty and nonobviousness of crystal forms mean that virtually every new crystal form is potentially a patentable entity.

Having said that, it is important to recall here that there is a distinction between what is "obvious" and "obvious to try", and different legal jurisdictions may treat these two very differently. Dealing with these two concepts can raise some fundamental scientific issues and legitimate scientific differences of opinion. For instance, if a known (i.e., published or patented) crystal form was obtained by crystallization from methanol, would it be obvious to someone "skilled in the art" to try to crystallize it from ethanol? If the results were the same the crystal form, is that obvious? If it were different, is that obvious? As an example of this dilemma from the scientific point of view is our experience with *p*′-methylchalcone.[187] This compound was studied in detail by Weygand in 1929 who reported finding no less than 13 different forms.[188] Once the stable room temperature form has been obtained, it is extremely difficult to obtain any of the other forms. The compound is prepared by a simple condensation reaction between an aldehyde and a ketone. In Beer Sheva, Jan-Olav Henck prepared one of the metastable forms directly from the reaction vessel (without recrystallization) with methanol as the solvent. He then varied the temperature over three values (20 °C, 4 °C, −13 °C) and with two other solvents, ethanol and isopropanol, for a total of nine different conditions, obtaining four of the metastable polymorphs. For one skilled in the art is the experiment obvious to try? Is the result obvious? I will leave it to the reader to ponder these questions.

This issue of patentability brings us full circle to the beginning of this *Perspective* and the discussion of nomenclature. In many jurisdictions, patent applicants are free to define their inventions to a large extent as they see fit; it does not necessarily have to neatly fit into some earlier defined category. As Shakespeare's Juliet said, "What's in a name? That which we call a rose [b]y any other name would smell as sweet." In fact, most patentees do not deviate from the standard terminology. The point is that if a crystal form has never been prepared before and its existence and/or its preparation are nonobvious it is potentially patentable as a novel, nonobvious new material – no matter what nomenclature is used to describe it.

I noted above the progress that crystallography has made in the course of my own career. That progress was reflected in a recent "Opinion" piece in the RSC's *Chemistry World* by science commentator Philip Ball.[189] Headlined as "welcom-[ing] the age of automated chemical crystallography" it seemed to augur the death knell for our discipline. But two-thirds of the way through the column, Ball reminds his readers, "It is true that actually making crystals for the sample chamber is still a black art". The discipline of solving crystal structures has indeed advanced beyond anything most of us could have imagined 50 years ago, but crystals in the crystallographic sample chamber do not differ from crystals anywhere else – there is still a great deal of black art (art, not magic!) and I might add skill, experience, and chemical intuition in making them. As the preceding pages testify, in spite of the great progress that has been made in making and understanding crystals and crystal structures, there remain vast areas to be explored about them and their properties – that is, chemical crystallography – especially with regard to polymorphism, the specific topic of this *Perspective*, before we can claim that we understand and can control the phenomenon. Obtaining new crystal forms, whether by systematic search or by serendipity, is an adventure into the crystallographic unknown, and preparing or recognizing a new crystal form is undeniably a chemical invention.

In that light, it is fitting to close this topic with a quote from John Milton:

> The invention all admired, and each how he
> To be the inventor missed; so easy it seemed
> Once found, which yet unfound all would have thought
> Impossible;
> *Paradise Lost* (1667), Book VI

**Acknowledgment.** I am greatly indebted to many valued colleagues and friends who shared their results (in some cases prior to publication) and their views with me in the preparation of this manuscript. I count myself particularly fortunate that they are too numerous to name individually here. The choice of topics to include and works to cite in an article of this sort is a selective process and therefore naturally biased. The difficulty is not what to include; it is in what not to include, since there is an incredible body of very creative and very exciting science going on in this field of polymorphism research. In spite of this apologia, there are five people who deserve special mention. Mark Spackman at the University of Western Australia (UAW) was a consummate professional and personal host during a number of extended visits to Perth this year where much of this content was "hatched". The Institute of Advanced Study at the UAW provided an extremely congenial atmosphere, facilities, and generous support with two separate appointments initially as a Gledden Fellow and later as a Professor-at-Large. As ever, Jan-Olav Henck of SSCI-Aptuit provided extremely good counsel and enthusiasm, and Ulrich Griesser from the University of Innsbruck was there with a key piece of data or reference seemingly within minutes of receiving an email from me. I am most grateful to Bart Kahr, Jan-Olav Henck, and Christer Aakeröy for critical reading of early versions of the manuscript. Referees also made some helpful and valuable suggestions that are greatly appreciated.

**Note Added in Proof.** The original Hirshfeld paper contains the conceptualization of separating the *promolelcule* from the *procrystal*. The translation of those concepts into the extremely useful graphic representations and their interpretation was the work of the Spackman group, who named them in honor and in memory of Fred Hirshfeld.

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(27) "The Whiffenpoofs Song", based on a tune written by Tod Galloway and adapted with lyrics by Meade Minnigeode.
(28) In principle, one might make similar arguments with regard to *conformational polymorphism*. In PMC155−168 and elsewhere, we clearly noted that in order to establish the existence of conformational polymorphism, one must determine the significantly different conformations of the molecules in the different crystal structures. That criterion may appear to be arbitrary, but the experimental determination of the crystal structure provides one with experimental errors that set the limits for the statistical significance of similarities and differences in conformational parameters. This question may be answered (or debated) quantitatively in any particular instance. The case of the proposed "tautomeric polymorphism" requires a somewhat arbitrary assignment of valency to various atoms in the molecular structure.
(29) *Historical Footnote.* A referee has noted that this *Perspective* on polymorphism lacks any direct reference to *disappearing polymorphs*.[81] The paper describing this phenomenon justifies the use of this term, whose genesis is of some historical interest. In the late 1960s, I was interested in the conformation and electronic spectra of benzylideneaniline (BA), the "hybrid" of azobenzene and stilbene. Unknown to me was that BA and some derivatives were the subject of Hans-Beat Bürgi's Ph.D. thesis under the direction of Jack Dunitz. In 1968, they published a paper that included a report of the cell constants of a dimethyl derivative of BA. Early in 1973, we repeated that work using oscillation and Weissenberg photos and verified the reported cell constants and space group. After a hiatus of about 8 months, attempts to obtain that material again failed, but resulted in the discovery of two new polymorphs. Following almost two years of frustration, only by carrying out the synthesis in a new lab with virgin glassware and a "new" student was the original material obtained. In the late 1980s Prof. Dunitz had a similar experience with *p'*-methyl chalcone, a substance that had been reported by Weygand in the 1920s to have 13 polymorphs. In part as the result

of our experience with these systems, Dunitz and I were recruited as expert witnesses in a patent infringement trial on ranitidine hydrochloride.[PMC-Chapter 10] As part of our involvement in that litigation, we collected other literature examples of known and characterized polymorphic forms that had become difficult to prepare under conditions that had previously routinely yielded them. With the realization that there were a number of well documented cases with similar circumstances, we felt that the topic was of sufficient interest to the chemical community and jointly authored the 1995 *Accounts of Chemical Research* paper on "Disappearing Polymorphs".

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(129) I do not mean to disparage the value or importance of this kind of thinking and decision-making. In fact, it is very much the *modus operandi* of much of chemistry: we are asked or expected to compare our results with those in the literature or a previous experiment. The match is never complete in every detail, but we have been taught by experience how to make a judgment if two (or more) things are equivalent or not, and it is the nature of our science that we usually do get it right.
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(145) *Historical Footnote.* Perhaps a demonstration of one of the most remarkable exceptions was the solution of the isostructural crystal structures of *trans*-stilbene[146] and *trans*-azobenzene[147] by J. M. Robertson in Glasgow in the 1930s. These molecules crystallize in space group $P2_1/a$ and $Z = 4$. This would seem to be the "normal" situation for these centrosymmetric molecules, but the asymmetric unit is composed of the crystallographically independent halves of two molecules, each lying on a crystallographic center of symmetry. The structures were solved in two-dimensional projection. Electron densities were calculated by hand. Among Robertson's many students were Jack Dunitz, Sidney Abrahams, James Trotter, Michael Rossman, J. C. Speakman, and Iain C. Paul.
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(173) *Historical Footnote*. At the risk of being accused of setting the barrier too high, I think it is informative to provide a bit of historical perspective here. Today, the experimental *determination* of a crystal structure has essentially reached the demanding stage I outlined for the computational effort to *predict* crystal structure. When I arrived as a postdoc in Ken Trueblood's laboratory at UCLA in 1967, every crystallography laboratory had its own collection of separate, often barely linked, programs (e.g., data collection, data reduction, Patterson calculation, Fourier transforms, printing of Fourier maps, geometry calculation, least-squares, etc.) Carroll Johnson's ORTEP was published in 1965 (originally without hidden line removal−which was done with Tip-ex) Programs were run on campus-wide mainframe computers on punched cards, usually with one card per reflection. There were no generally available direct methods programs, and the light atom noncentrosymmetric problem was still in a state that we routinely "closeted" as not solvable structures in space groups $P2_1$ and $P2_12_12_1$ that did not contain a heavy atom (for possible solution by Patterson methods). The first edition of Stout and Jensen (which appeared in 1968) had a chapter entitled "Trial and Error Methods" for structure solution. A Ph.D thesis in crystallography could − and did − contain (only) the solution of one or two crystal structures. As a personal note, during that period one of Ken's graduate students, Michael Crisp, and I used Willams' PCK65 program to solve and refine the structure of [2.2]-*meta,para*-cyclophane (a rigid molecule prepared by Don Cram's group) with manually collected single crystal diffractometer data. Because of the rather severe strain in the molecule, there was an "extraordinarily long" exocyclic C−C bond length of 1.64 Å, and since that exceeded all known values (in spite of repeated unsuccessful efforts to find the source of some error), we felt that it was not publishable. In 1987, the structure was published with Crisp as a coauthor using automated diffractometer data at two temperatures.[175] *Grosso modo* our structure was correct, but there was disorder in space group $P2_12_12_1$ with $Z' = 2$ and a phase change to *Pbam* at 316 K that we had not detected, so Ken's caution in not publishing was justified. In short, it is helpful to have some perspective on how things develop in science in ways that we cannot even imagine.
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