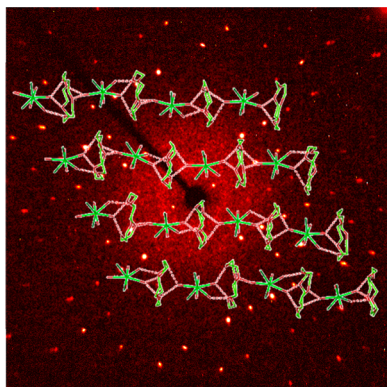


Packing Problems: High Z' Crystal Structures and Their Relationship to Cocrystals, Inclusion Compounds, and Polymorphism

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1. INTRODUCTION

Generally speaking, molecular compounds have a strong tendency to have crystalline order in the solid state. Amorphous materials do exist, of course, but they are rarely the most stable solid form unless they are stabilized by a surface such as that of a polymer or inorganic particle.¹ Understanding, predicting, and controlling the structure of these crystalline materials is a topic of tremendous contemporary importance, not least in the pharmaceuticals and agrichemicals sectors where crystal structure directly affects properties such as solubility, processability, hygroscopicity, chemical and physical stability, and bioavailability. Estimates vary widely; however, the market for solid-state pharmaceuticals is likely to be in excess of US \$1.5 trillion p.a. The need to discover and control the solid form of active pharmaceutical ingredients (APIs) is highlighted by cases such as ritonavir and cefdinir in which newly discovered polymorphs have resulted in considerable processing difficulties, formulation problems, and legal wrangling.² In recent years, the commercial interest in the crystalline solid state has gone beyond single component materials (“homomolecular crystals”) and also encompasses multicomponent systems, generally termed cocrystals.³

Polymorphism in crystals is defined as the ability of a compound to exist in more than one arrangement in the solid state.⁴ Sometimes the same molecule in two different polymorphic forms adopts clearly different conformations (conformational polymorphism⁵); however, even the same conformers can adopt more than one crystal packing arrangement. Typically, the packing arrangement is described by the crystallographic unit cell and the application of the crystallographic symmetry operations of the particular space group of the structure. Thus, in most cases, knowledge of the atomic coordinates of one molecule plus the symmetry of the crystal lattice effectively allows the conceptually infinite 3D structure of the crystal to be derived. For about 9% of crystal structures, however, some chemically identical molecules are not related to one another by crystallographic symmetry and occupy distinct independent positions. An understanding of this awkward subset of crystals is absolutely crucial if we are to ever gain a holistic picture of crystal packing phenomena. Perhaps more interestingly, these “exceptions” to the rule of a single molecular entity being the building block of the crystal have a great deal to tell us about the way in which crystals form and pack.

Why do molecules have an extremely strong tendency to assemble into ordered crystalline structures upon solidifying? After all, when you demolish a house the resulting piles of bricks

Received: October 2, 2014

Published: February 12, 2015

do not spontaneously reassemble into an elegant architectural masterpiece once the demolition crew goes home! Trivially, the answer of course is that, unlike bricks (which require mortar, and human design and engineering to form a house), molecules are attracted to one another, not just weakly attracted, but very strongly and directionally attracted indeed, such that empty space in crystals is almost as rare and elusive as the “Questing Beast” of Arthurian Legend.⁶ It is this mutual attraction of molecules for one another that gives rise to Aristotle’s anthropomorphic adage “horror vacui” or “nature abhors a vacuum”, and lies behind the close-packing principle of Kitaigorodskii.⁷ Admittedly, in recent years, there has been tremendous progress in engineering against this tendency, as in the production of very low density coordination polymer crystals (metal organic frameworks), but even these voids are generally filled with disordered molecules of gas or solvent sequestered from the surroundings.⁸

It has been known since the work of Fyodorov in 1891⁹ that all possible crystal symmetries in three dimensions can be described using exactly 230 crystallographic space groups.¹⁰ In two dimensions there are just 17 “wallpaper groups” (Figure 1),

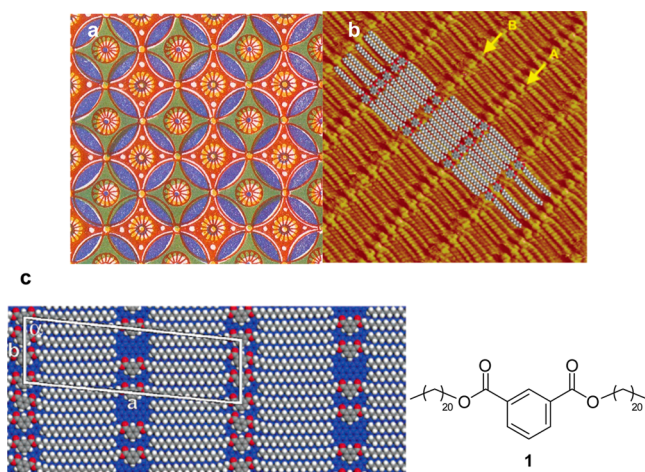


Figure 1. (a) An Egyptian design with wallpaper group $p4m$ (from *The Grammar of Ornament*, Owen Jones, 1856). (b and c) STM image and model of a 2D crystal of diheptacosylisophthalate (**1**) in $p1$ with $Z' = 5$. Column B has two molecules for every three molecules in column A. Reproduced with permission from ref 26. Copyright 2004 American Chemical Society.

which describe, for example, ordered packing on surfaces. The 230 space groups are the only way in which the translational symmetry of a unit cell (including lattice centering) can be uniquely combined with the point group symmetry operations of reflection, rotation and improper rotation, and the screw axis and glide plane symmetry operations to allow an object to fill three-dimensional space in an ordered, periodic manner. Any other packing arrangement such as in incommensurate, quasi-, and composite crystals cannot be described in this way and requires treatment in higher dimensional space¹¹ (superspace groups for up to three additional dimensions have recently been systematically tabulated¹²). Space group symmetry pays no heed to molecular shape and the intrinsic “stickiness” of molecules, and hence the interactions between them. As a result, while we can computationally derive numerous 3D crystal structures for any molecule by simply assuming a conformation and orientation, and applying space group symmetry to the molecular coordinates,¹³ very few of these thousands of possible structures

will be stable in the real world of van der Waals close packing, let alone exhibiting energetically favorable, electrostatic, and directional intermolecular interactions such as hydrogen bonding and dipolar interactions,¹⁴ halogen bonding,¹⁵ π – π and ion– π interactions,¹⁶ secondary bonding,¹⁷ and so on.¹⁸ In the ideal case, only one such structure is stable under reasonably experimentally accessible conditions, and hence we often talk of “the crystal structure” of the substance even though it would be more proper to speak of “a crystal structure” of a given compound. In some cases, a few such structures are sufficiently stable to be observable, and, in combination with accessible nucleation and growth kinetics, they can be isolated and studied. This diversity is the origin of crystal polymorphism.^{5a,19} In some cases, the operation of space group symmetry on a single molecule does not give an accessible, stable packing arrangement. In these cases, a single molecule is no longer a viable building block to form a close-packed, crystalline solid, and we observe the formation of crystals with more complex, multimolecular building blocks (which can be thought of as growth units²⁰). These crystals can be either cocrystals (or multicomponent crystals)^{3b,19d,21} in which two or more different kinds of molecule make up the building block, or structures with more than one symmetry-independent molecule.²² (The term cocrystal here is used broadly to encompass all multicomponent crystalline solids, i.e., cases where both molecular components are solids at room temperature,²³ solvates, hydrates, clathrates, and both stoichiometric and nonstoichiometric lattice inclusion compounds.²⁴) Structures with more than one symmetry-independent molecule can be viewed as having a relationship with cocrystals in the sense that in symmetry terms there is more than one distinct molecular entity in the crystal structure even though, of course, molecules of the same chemical structure are all identical to one another in solution. Indeed the very definition of crystal polymorphism^{4,19a,b} generally relates to substances that are identical in solution but have distinct packing arrangements in the solid state, although slowly interconverting isomers can fall into something of a gray area. However, crystallographically unrelated molecules of the same chemical type can be quite distinct from one another in the solid state because the environment around each symmetry-independent molecule is different, giving rise, for example, to distinct solid-state NMR spectra.^{19b,25}

The number of molecules (or formula units) in the whole unit cell is referred to as Z , and the number of symmetry-independent molecules in a crystal structure as Z' . Crystal structures with $Z' > 1$ represent a possible solution to the problem of packing molecules in three dimensions. Interestingly, even in two-dimensional groups there are known structures with $Z' > 1$ as in the 2D $Z' = 5$ structure of monolayers of compound **1**, Figure 1b,c.²⁶ Interest in crystal structure and the crystallization process, particularly with regard to unusual packing phenomena such as high Z' structures and the formation of cocrystals,^{3,21a,23,27} has enjoyed a surge in interest in the scientific community in recent years, particularly driven by the key importance of understanding organic solid-state materials properties in the pharmaceutical and agrichemicals industries.^{22a,27e,28} In this Review, we present a holistic overview of the recent startling progress in scientific understanding of crystal packing in general, and attempt to place the phenomenon of crystal structures with $Z' > 1$ firmly into context within the contemporary view of crystal packing phenomena. Because there are around 70 000 known organic crystal structures with $Z' > 1$, it is clearly an impossible task to list them all, and examples are included only where they advance the understanding of the general concepts in the field. However, this

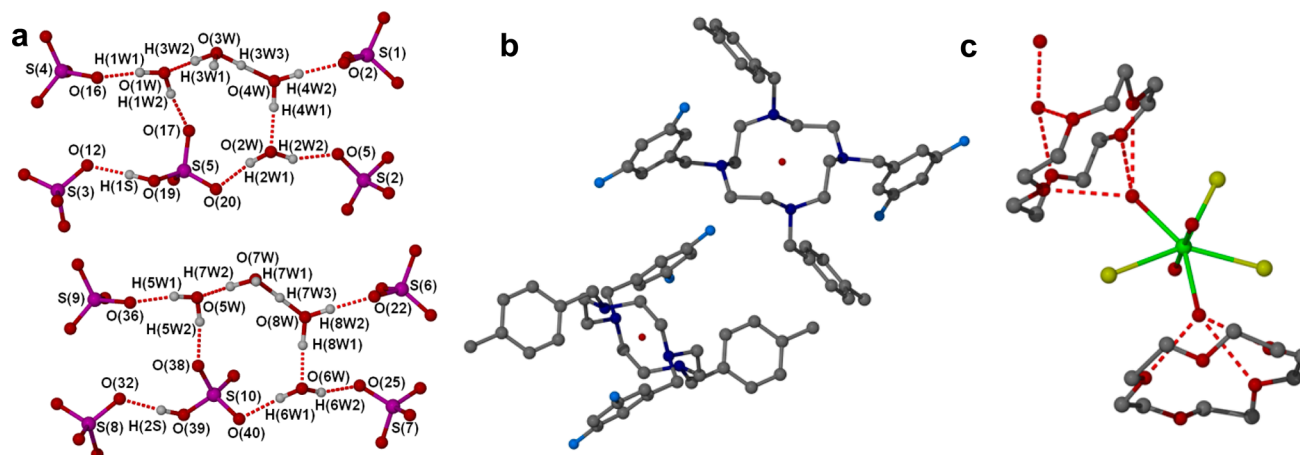


Figure 2. (a) Single-crystal neutron structure of $(\text{H}_2\text{-}o\text{-PDA}^{2+})_8(\text{SO}_4^{2-})_6(\text{HSO}_4^-)_4 \cdot 8\text{H}_2\text{O}$ (**2**) showing the 10 crystallographically independent anions; the anions based on S(5) and S(10) become symmetry-related (the Z' value halves) upon warming above 140 K.³² (b) Unit cell of macrocycle **3** showing the two crystallographically independent molecules related by the inversion centers at the center of each molecule, $Z' = 1$, that is, $1/2 + 1/2$.³⁷ (c) X-ray crystal structure of the salt cocrystal $(\text{H}_5\text{O}_2)[\text{UO}_2\text{Cl}_3(\text{H}_2\text{O})_2] \cdot (15\text{-crown-5})_2$ (**5**). While there are four crystallographically independent entities including two independent crown ethers situated on a mirror plane in space group $Pm\bar{c}n$, the Z' value is 1.³⁹

Review can be read in partnership with the Durham Z' web resource²⁹ (zprime.co.uk), which catalogues every structure with $Z' > 4$. We also limit the present discussion to “small-molecule” structures; however, the concepts in principle may also have some bearing on macromolecular crystallography.

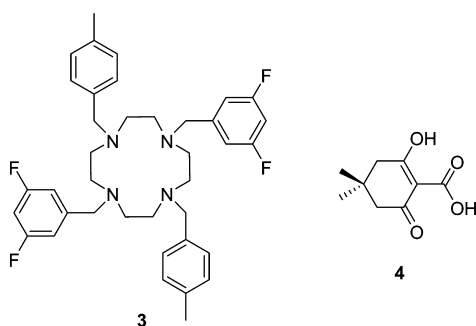
2. DESCRIBING REAL CRYSTALS AND DETERMINING Z'

Researchers in molecular materials chemistry place considerable emphasis on questions of definitions and nomenclature, as exemplified by the discussion surrounding the attempts to defend or render obsolete the term pseudopolymorphism.^{3a,19a,30} Some key terms of use in the study of molecular crystals and the rather interesting concepts that underlie them have been succinctly defined by Barbour and co-workers recently.²⁴ The study of crystals with more than one symmetry independent molecule (and indeed the related fields of cocrystals and polymorphism, in general) has its own nomenclature pitfalls and areas of contention, not least starting with the apparently innocent-seeming parameter Z' itself. Formally Z' is defined as the number of formula units in the crystallographic unit cell divided by the number of independent general positions. This latter number is a direct consequence of space group symmetry and is unambiguous. However, the definition of what constitutes the “formula unit” can be subjective, particularly in multi-component crystals. For example, the mixed sulfate/hydrogen sulfate salt of doubly protonated *o*-phenylenediamine (PDA), of formula $(\text{H}_2\text{-}o\text{-PDA}^{2+})_8(\text{SO}_4^{2-})_6(\text{HSO}_4^-)_4 \cdot 8\text{H}_2\text{O}$ (**2**), crystallizes with 26 independent molecules or ions in the asymmetric unit (the total number of chemical entities in the asymmetric unit has been referred to as Z'' by van Eijck and co-workers³¹) including eight independent *o*-phenylenediammonium cations. This makes the assignment of $Z' = 8$ a logical choice. However, accurate location of the protons by neutron diffraction reveals that despite the large value of Z'' , the value of Z' is formally 2 as the smallest integer formula unit is $(\text{H}_2\text{-}o\text{-PDA}^{2+})_4(\text{SO}_4^{2-})_3(\text{HSO}_4^-)_2 \cdot 4\text{H}_2\text{O}$ (Figure 2a).³² The situation is even more ambiguous for nonstoichiometric solvates and inclusion compounds where the actual contents of the asymmetric unit may not even be fully known.

In addition to issues of definition of the formula unit, it is important to realize that the Z' parameter arises from a mathematical description of real diffraction data and this description may represent an erroneous, approximate, or idealized interpretation of the real experimental situation. An obvious potential flaw is space group misassignment, and there have been many cases where structures in low symmetry space groups such as $P1$ or Cc have been later shown to be adequately described by a higher symmetry model with consequently lowered Z' value.³³ In addition, the model of the diffraction data from which Z' is derived is an average model that assumes a periodic arrangement of identical unit cells. While this is very often an accurate representation of the real crystal, modulations in the molecular packing can make the description ambiguous or approximate. A modulated structure is one in which there are at least two crystallographically independent formula units where small changes in position or orientation would make them crystallographically equivalent and give a smaller unit cell.³⁴ Modulations result in the appearance of satellite reflections between the peaks corresponding to the high symmetry subcell. Increasing the unit cell size and Z' value can account for these satellites and hence result in an ordered high Z' structure, and indeed many high Z' structures are modulated variants of higher symmetry subcells.^{34,35} Modulations are thought to occur when competing noncovalent interactions between nearest and next-nearest neighbors are of comparable importance and a balance needs to be struck between them. However, for more complex, long-range modulations, there may be a progression of increasingly higher order satellite reflections of decreasing intensity, to the point where some may fall below the instrument detection threshold. Indeed the modulation wave (a gradual shift or twist in the crystal packing arrangement) may be completely incommensurate with the 3D unit cell (in other words, there may be no simple integer relationship between the repeat distance between molecules and the repeat distances of the modulation). This kind of situation is exemplified by the structure of the salt quininium (*R*)-mandelate, which can be described by approximate $Z' = 15$ or 18 unit cells but is in reality an incommensurately modulated structure with the modulation arising from competition between intramolecular and intermolecular interactions.^{11b} Incommensurately modulated struc-

tures are very rare in the literature, although this may be because they are often ignored or missed. Modulation is discussed further in section 5.4 in the context of changes of temperature of structures with multiple independent molecules.

Such ambiguous or erroneous cases aside, Z' is usually a simple and reasonably readily determined parameter, and its inclusion within the data archived by the Cambridge Structural Database³⁶ (CSD) has greatly facilitated systematic surveys of crystal structures with $Z' > 1$. Interestingly, the very simplicity of the Z' nomenclature can mask some of the very packing phenomena it is intended to describe. Take structures in which molecules occupy crystallographically distinct special equivalent positions such as the macrocycle 1,7-bis(3,5-difluorobenzyl)-4,10-bis(4-methylbenzyl)-1,4,7,10-tetraazacyclododecane (**3**, CSD refcode BERKAM³⁷) in which there are two symmetry-independent crown ether molecules each situated on a crystallographic inversion center, Figure 2b. Despite the Z' value of 1 (two half molecules), there are two quite distinct, symmetry-independent molecules. Yet more striking is the extremely complicated structure of 4,4'-dimethyl-2-hydroxy-6-oxocyclohexene-1-carboxylic acid (**4**), which exhibits five symmetry-independent half molecules (so, $Z' = 2.5$) in its asymmetric unit, each situated upon a crystallographic mirror plane. The structure is a modulated version of a $Z' = 0.5$ subcell with the modulation involving small rotations of the molecules around axes perpendicular to the mirror plane. These modulations are suggested to be a solution to packing problems involving the oxygen end of the molecule and the thicker methyl region.³⁸ The allocation of Z' value is even more nuanced for the salt cocrystal $(\text{H}_5\text{O}_2)[\text{UO}_2\text{Cl}_3(\text{H}_2\text{O})_2] \cdot (15\text{-crown-5})_2$ (**5**), in which there are also two symmetry-independent crown ether macrocycles, in this case each situated across a crystallographic mirror plane, Figure 2c. However, there is only a single independent oxonium cation and uranyl anion, and hence the proper integer formula unit corresponds to the formula given above, and even though the Z'' value is 4, the Z' of just 1 is representative of the structure.³⁹



The Z'' parameter has perhaps not received as much attention as it deserves. It more fully encompasses the number of independent species required to describe, model, or calculate the structure, and avoids being reduced as a result of formula units of complex stoichiometry, as in the amazing C_{60} calixarene toluene inclusion complex $(\text{calix}[5]\text{arene})_4 \cdot (\text{C}_{60})_5 \cdot (\text{toluene})_2$.⁴⁰ The complex is $Z' = 1$ because the 4:5:2 ratio cannot be divided to give a smaller integer ratio; however, the Z'' value of 11 highlights the complexity of the structure. Similarly, the Z'' value of 4 highlights very nicely the three crystallographically independent *p*-nitrophenol molecules in forms A and C of the 3:1 cocrystal with 2-methylaminopyridine ($Z' = 1$ in each case), Figure 3.⁴¹ There is also a further concomitant polymorph B of this material with $Z' = 2$ and $Z'' = 8$! In addition to Z , Z' , and Z'' , we have

found a further parameter Z^c defined as the number of different types of chemical residue (including ions, solvents, and other molecules) of use in studies on cocrystals.⁴² In accord with the current convention on assignment of Z' to racemate structures, enantiomers are not counted separately in assignment of Z' . It is explicitly possible to search the CSD using *Conquest* software for Z , Z' , and Z^c (up to 12) but not currently Z'' . Note that the frequency survey reported by Nichol and Clegg⁴³ and described as being for Z'' is actually Z^c . This list shows that there are far more structures with more than one type of chemical residue than with $Z' > 1$ reflecting factors such as the occurrence of salt structures with chemically independent cation and anion. Some recent reports on structurally complex cocrystals have begun to explicitly list Z' , Z'' , and Z^c to make the explanation of complex packing phenomena as clear as possible.⁴⁴

This situation seen for **3** arises from the coincidence of molecular symmetry and crystallographic symmetry, which are conflated in the Z' parameter. One way to describe this special situation is some kind of extended Z' description such as $Z' = 1/2 + 1/2$.⁴⁵ Bond has pointed out that a more rigorous approach, however, is to apply the structural class (SC) descriptors developed by Belsky and Zorky.⁴⁶ The SC descriptor for a molecular crystal structure comprises the space group, Z (the number molecules in the unit cell), and a description of the crystallographic site symmetry of all crystallographically distinct molecules. Thus, a $Z' = 1$ structure such as that of **3** or of bis[(μ^2 - σ^2 , η^2 -mesityl)(η^8 -cyclooctatetraene) zirconium(IV)] (CSD code FAWSIF⁴⁷) in the triclinic space group $P\bar{1}$ with two independent molecules situated on crystallographically distinct inversion centers (i.e., half of each molecule crystallographically unique) would be represented as $P\bar{1}, 2(\bar{1}, \bar{1})$. The arguably less informative extended Z' descriptors can be derived by taking the reciprocal of the order of each crystallographic site symmetry group listed within the brackets. The disadvantage of the SC approach is that it is rather difficult to use in comparison to (extended) Z' descriptors, particularly in the case of multi-component crystals, and indeed the surveys published so far have been limited to crystal structures with only one kind of molecule ($Z' = 1$). It also is very much a “molecular” approach and hence does not go as far as addressing the much more nebulous issue of the crystallization of supermolecules, which may have some kind of solution or melt aggregation into a multimolecular growth unit that is carried intact into the crystalline phase as a recognizable supramolecular synthon, as we will discuss in section 5.3.

3. TECHNIQUES USED TO DETERMINE HIGH Z' STRUCTURES

3.1. Diffraction

The vast majority of structural information about crystals with multiple symmetry independent molecules has come from single-crystal X-ray crystallography, and historically the topic of $Z' > 1$ structures has been perhaps regarded as something of a niche curiosity within the single-crystal field.^{22b} The past couple of decades, however, have seen rapid growth of interest in the understanding, prediction, and control of molecular crystal structure, polymorphism, and cocrystal formation, including challenging issues such as high Z' , particularly driven by the pharmaceutical field. Along with growing interest in the topic and advances in instrumental and analytical techniques, there has been increased willingness, opportunity, and ability to integrate information from multiple techniques. This approach has been accompanied by the realization that single-crystal work, with its

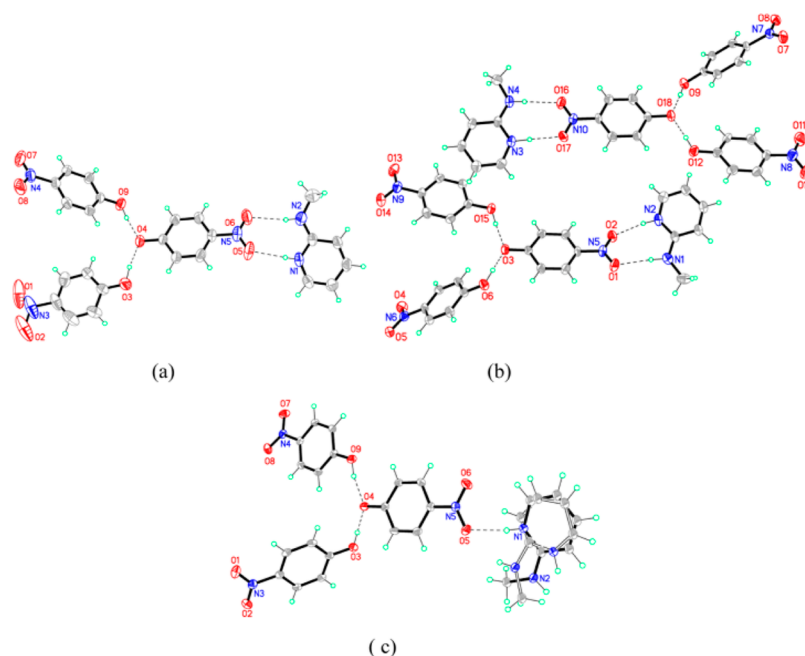


Figure 3. Asymmetric units of the three polymorphs of 1:3 2-methylaminopyridine-*p*-nitrophenol cocrystal showing the three (a and c) or six (b) independent *p*-nitrophenol molecules; the Z' values of 4 or 8 are more informative than $Z' = 1$ or 2. Reproduced with permission from ref 41. Copyright 2014 American Chemical Society.

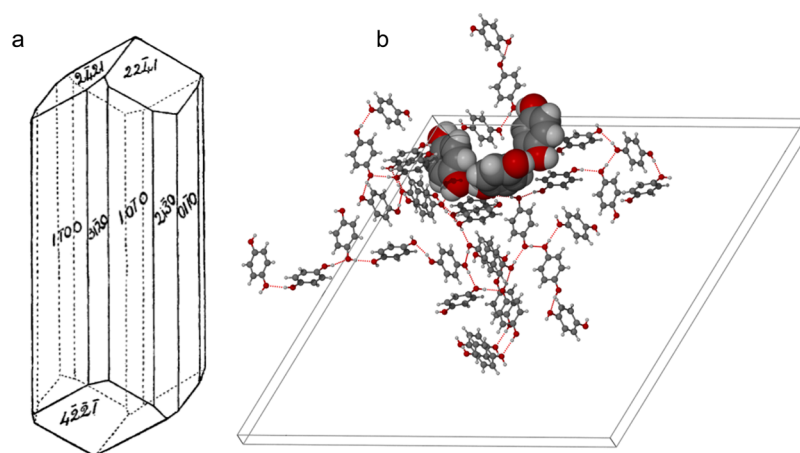


Figure 4. (a) Hand-drawn representation of α -hydroquinone from the original 1926 report. Reproduced with permission from ref 49. Copyright 1926 Royal Society of Chemistry. (b) Crystal structure of α -hydroquinone viewed along the c axis with the $Z' = 3$ asymmetric unit highlighted.⁵¹

emphasis on long-range ordered average structure, is sometimes not the only and even not the best way to fully understand and characterize crystal structure and the technique is very much complemented by solid-state CPMAS NMR spectroscopy, with its ability to probe local structure, X-ray and neutron powder diffraction, infrared and Raman spectroscopy, thermal methods such as DSC, and computational approaches to lattice energy calculation and crystal structure prediction (CSP). Electron crystallography also has significant potential in structurally characterizing small samples; however, for organic compounds radiation damage is a significant issue.⁴⁸

The earliest $Z' > 1$ structure in the CSD is William Augustus Caspari's 1926 determination of the $Z' = 3$ crystal of hexagonal α -hydroquinone with its hexagonal prism morphology hinting at the underlying unit cell symmetry (Figure 4a).⁴⁹ This work was followed in 1927 by the structure of β -hydroquinone.⁵⁰ Caspari was unable to determine the molecular structure by X-ray

diffraction at this early stage but noted that there seemed to be some kind of intermolecular association in the solid state and furthermore that "association of two molecules occurs in several other organic crystals, and the phenomenon may indeed be a somewhat common one". He was right! Caspari's work relied on single-crystal Laue photographs, and he noted that earlier work on the same system had used "the powder-method, which is now known to be of minor utility for the determination of unit cells." Perhaps this statement was not quite so right! Later work in 1980 by Wallwork and Powell showed the actual unit cell of α -hydroquinone to be 3 times larger than the original cell, but it still retained its Z' value of 3, which seems to arise from the need to produce a close-packed structure maintaining both a hydrogen-bonded chain and an edge-to-face π -stacking (Figure 4b).⁵¹ There is still some void space in the crystals that can include guest species, however. In that same year, Ripmeester showed that solid-state NMR spectroscopy could also readily distinguish the

various hydroquinone polymorphs⁵² with the α -polymorph displaying 3 times the number of resonances as the β -analogue.⁵³ Incidentally, the first actual molecular structure determination of a $Z' > 1$ system was the work by J. M. Robertson on *trans*-stilbene in 1937. Robertson solved the structure in two-dimensional projection, calculating electron densities by hand. The crystal comprises two crystallographically independent half molecules sited on crystallographic inversion centers in $P2_1/a$.⁵⁴

The utility of X-ray powder diffraction has moved on considerably since Caspari's time, particularly with the increasingly ready availability of high-resolution synchrotron radiation sources, to the point where not just the determination of unit cell dimensions is routine but also full structure solution and refinement using direct space methods such as Monte Carlo simulated annealing,⁵⁵ genetic algorithms,⁵⁶ or charge flipping⁵⁷ as well as more traditional approaches, in conjunction with Rietveld refinement.⁵⁸ The larger unit cells and increased number of variables needed to describe structures with $Z' > 1$ still present challenges for structure determination from powder diffraction data. However, the 2013 version of the CSD contains some 128 entries determined from powder diffraction data with $Z' > 1$. A striking example is the combined synchrotron and neutron powder diffraction structure of 4-methylpyridine-*N*-oxide.⁵⁹ While the 250 and 100 K phases each have a single crystallographically independent molecule, at 10 K the symmetry lowers to give a $Z' = 8$ structure in which the methyl groups become "frozen" and distinct. The authors propose that this low symmetry structure could explain the four tunneling transitions observed with inelastic neutron scattering, giving rise to different effective potentials for methyl rotors. Structure determination by powder methods is also of vital importance in characterizing products produced mechanochemically⁶⁰ as in the three polymorphs of a capped amino acid, *N*-acetyl-*L*-phenylalanyl- NH_2 . While the α - and β -forms can be produced both mechanochemically and from solution and hence characterized by single-crystal methods, the $Z' = 4$ form is only accessible mechanochemically, and hence the structure was necessarily determined by powder diffraction.⁶¹ Powder diffraction has also been used to fully determine the structures of the two $Z' = 3$ polymorphs of the highly polymorphic phenobarbital,⁶² and four polymorphs of the pesticide dithianon, two of which have $Z' > 1$.⁶³

Comparative powder diffraction patterns can be very useful in distinguishing between genuine cases of polymorphism as opposed to redeterminations or incidences of mistaken unit cell or space group assignment, which can artificially increase the apparent Z' value. An automated comparison of related structures in the CSD has been carried out by Motherwell and van de Streek based on simulated powder diffraction patterns, but with additional provisions to deal with differences in unit-cell volumes caused by temperature or pressure. Their study resulted in the identification of some 154 previously unknown pairs of polymorphs among some 35 000 determinations of pairs of the same compound.⁶⁴ The work has now resulted in a subset of the CSD containing the "best" representative structure of each unique polymorph.⁶⁵

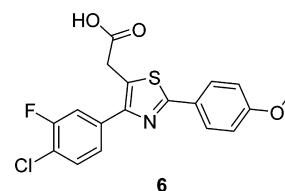
Comparison of X-ray powder diffraction (XRPD) data can be used in conjunction with computational structural comparison to identify genuine cases of polymorphism including different Z' values. The XPac software has been developed to quantify structural similarity between structural subunits⁶⁶ and was used to establish that two proposed polymorphs of methyl paraben are not, in fact, different forms.⁶⁷ The method also established a

curious 2D similarity between the $Z' = 4$ triclinic form I of the anticonvulsant and mood-stabilizing drug carbamazepine and its trigonal form II with $Z' = 1$.⁶⁸ Work aimed at distinguishing distinct polymorphs by Gavezzotti using his OPIX software has looked at the energetic environment of each molecular pair in a crystal structure by summing over the pairwise atom–atom potentials. The work assumes that in a unique polymorph the energetic environment of the same molecule should be distinct from its environment in a different polymorph. Similarly, the energetic environment of symmetry unique molecules within a given structure should also be unique.⁶⁹

Another powerful visualization tool for intermolecular interactions and hence degree of similarity of the molecular environment in a crystal structure is the derivation of the Hirshfeld surface for each crystallographically distinct molecule. The Hirshfeld surface is obtained by deriving a promolecule based on spherical atoms and partitioning the crystal into regions where the space is dominated by the promolecule and regions where it is dominated by all of the other molecules (the procrystal). This information can then be used to derive a fingerprint for each molecule based on its intermolecular interactions. The approach is incorporated within an accessible user interface within the *CrystalExplorer* program.⁷⁰ Both Hirshfeld surface analysis and pairwise energy comparison have been used to show that the triclinic $Z' = 12$ form of 4,4-diphenyl-2,5-cyclohexadienone is equivalent to a $Z' = 4$ form in the same space group.^{19a,71}

3.2. Solid-State NMR Spectroscopy

A hugely important contemporary tool in molecular solid-state chemistry is the use of CPDAS NMR spectroscopy in resolving questions of solid form that can be ambiguous by X-ray means.⁷² A comprehensive example is the comparative solid-state NMR spectra for forms 1 and 2 of the overactive bladder drug {4-(4-chloro-3-fluorophenyl)-2-[4-(methoxy)phenyl]-1,3-thiazol-5-yl} acetic acid (**6**), which have $Z' = 4$ and 1, respectively. The $Z' = 4$ polymorph shows splitting in the ^1H , ^{13}C , ^{15}N , and ^{19}F solid-state NMR spectra, clearly indicating its high Z' nature in space group *Cc* and confirming that there is no crystallographic inversion center, which would imply space group *C2/c* with $Z' = 2$. The $Z' = 4$ and 1 forms are enantiotropically related, with the $Z' = 4$ form being the thermodynamic form below 35 °C.⁷³ Solid-state NMR in conjunction with XRPD is being used increasingly to characterize high Z' systems, particularly in the pharmaceutical field, where suitable single crystals cannot be obtained.⁷⁴



Solid-state NMR spectroscopy is highly sensitive both to molecular structure and to local intermolecular interactions. This means that computational fitting of a model structure to high-quality NMR data can not only assist with the resolution of issues of disorder arising from the long-range average nature of diffraction data, but also can be used as a means of direct structure determination in its own right. This technique is termed NMR crystallography and is complementary to X-ray, neutron, and electron crystallography.²⁵ In 2010 the group of Brown reported the remarkable $Z' = 6$ NMR structure of campho[2,3-*c*]pyrazole (Figure 5a,b) using a combination of

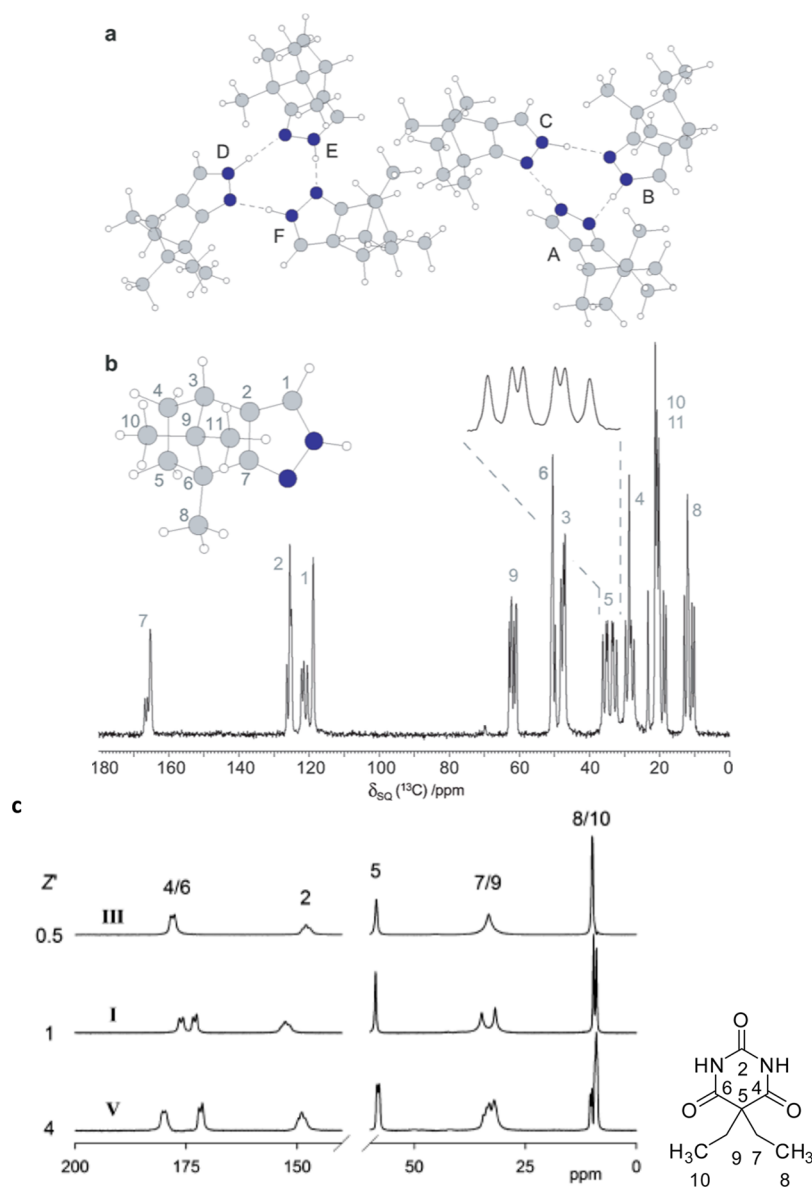


Figure 5. (a) Geometry-optimized crystal structure of campho[2,3-*c*]pyrazole showing the organization of the six independent molecules in the asymmetric unit into two hydrogen-bonded trimers. (b) ^{13}C CPMAS NMR spectrum of campho[2,3-*c*]pyrazole. The six resolved resonances for C5 are shown in an expanded region. Reproduced with permission from ref 75. Copyright 2010 American Chemical Society. (c) ^{13}C CPMAS NMR spectra of barbital (pictured) forms I, III, and V. Reproduced with permission from ref 77. Copyright 2014 American Chemical Society.

high-resolution ^1H – ^{13}C solid-state MAS NMR spectroscopy and chemical-shift calculations based on a Gauge Including Projector Augmented Waves (GIPAW) pseudopotential approach.⁷⁵ This method allowed the individual assignment of chemical shifts for each of the six symmetry independent molecules in the CASTEP geometry-optimized structure to the experimental spectrum. The sensitivity of the NMR spectra to the differences in local environment is demonstrated by the six resonances for carbon atom C5, for example, which are fully resolved, Figure 5. The structure has also been determined by X-ray methods, which were used as a starting point for the geometry optimization.⁷⁶ The sensitivity of solid-state NMR methods to molecular environment is also demonstrated by a recent study on the classic barbital for which the ^{13}C CPMAS spectra of the $Z' = 0.5$, 1, and 4 forms III, I, and V, respectively, are quite distinct (Figure 5c).⁷⁷

Solid-state NMR spectroscopy has also been used in key cases for discriminating disorder or ambiguity in diffraction derived structures. The apparent $Z' = 5$ structure of β -caffeine initially determined by X-ray powder diffraction⁷⁸ was later shown to be a disordered $Z' = 2.5$ structure using a combination of high field solid-state NMR spectroscopy and single-crystal methods.⁷⁹ A recent, fascinating piece of detective work has been the question over the structure of the elusive paracetamol form III (indeed even its very existence was originally doubted). The thermodynamic form I of paracetamol is particularly difficult to compress directly into tablets because the structure is based on puckered hydrogen-bonded sheets of molecules that do not easily slip over each other. There is therefore considerable interest in the structure and properties of other forms of the substance. Solid-state NMR spectroscopy allowed Burley et al.⁸⁰ to establish in 2007 that form II has two crystallographically independent molecules after around quarter of a century of attempts to isolate

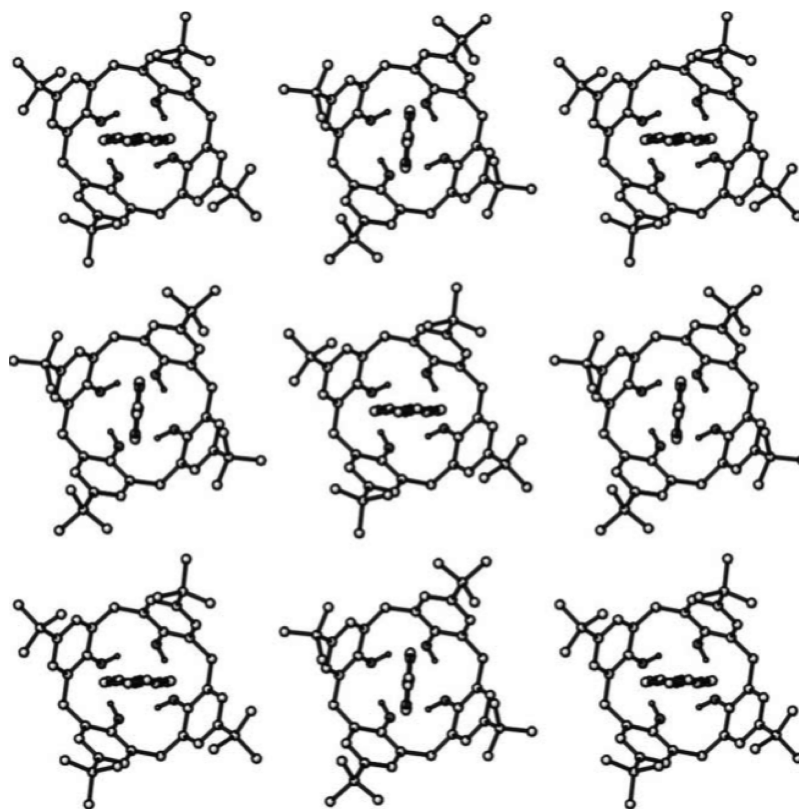


Figure 6. Crystal packing in the $Z' = 1/2 + 1/2$ low temperature phase of *p*-*t*-butylcalix[4]arene-toluene. The 2-fold distorted ordered structure is in agreement with the CPMAS ^{13}C NMR spectrum. Reproduced with permission from ref 88b. Copyright 2006 Royal Society of Chemistry.

the material. These data cast into doubt a number of calculated $Z' = 1$ structures. Even with this information, it proved impossible to index the XRPD pattern for form III, and it was not until 2009 that Perrin et al. used the clear indication that the structure is $Z' = 2$ to solve the structure from XRPD measurements in conjunction with crystal structure calculation using GRACE, a program based on high level dispersion corrected DFT calculations.⁸¹ Other organic $Z' > 1$ structures that have been studied by ^{13}C MAS NMR spectroscopy include *N,N*-dimethylselenobenzamide, which has two polymorphic forms, one of them with $Z' = 2$,⁸² and chlodiazepoxide, which has two polymorphs, both of them with $Z' = 4$ arranged in hydrogen-bonded pairs.⁸³

Perhaps one of the most striking cases of the combined use of solid-state NMR spectroscopy and X-ray crystallography to determine a structure with multiple independent molecules is the case of the toluene clathrate of *p*-*t*-butylcalix[4]arene. The calixarenes are well-known, vase-shaped host molecules with a small molecular cavity suitable for including small guest molecules. The room-temperature X-ray crystal structure of the *p*-*t*-butylcalix[4]arene-toluene clathrate was first reported in 1979 by the Parma group⁸⁴ and has since become something of a classic⁸⁵ as the popularity of the calixarenes has increased dramatically in supramolecular chemistry. The room-temperature structure is in the high symmetry tetragonal space group $P4/n$ with $Z' = 0.25$ implying a 4-fold symmetric calixarene. There is extensive disorder with the toluene situated upon the 4-fold rotation axis with the methyl group pointing down into the calixarene cavity. The *t*-butyl groups and calixarene aromatic rings are also disordered. The structure undergoes a phase transition at 250 K, and in 1998 Arduini et al. (also from Parma) modeled the low temperature structure in terms of twinned

monoclinic components in space group $P112/a$ giving two unique half-calixarenes, $Z' = 1/2 + 1/2$. This determination revealed the fact that the cavity is not fully 4-fold symmetric but adopts a “pinched cone” geometry.⁸⁶ Work by the Atwood and Barbour groups in 2002 confirmed the $P4/n$ room-temperature structure and characterized a 2:1 host:toluene clathrate in $P4/nnc$ with $Z' = 0.25$ by removal of toluene from the 1:1 material as a single-crystal-to-single-crystal transition.⁸⁷ Detailed work by Ripmeester and co-workers on the 1:1 complex, also in 2002, supported by ^{13}C and ^2H solid-state NMR data showed that⁸⁸ lowering the temperature resulted in the appearance of satellite reflections in the X-ray data that proved persistent only when observed with molybdenum radiation, a factor attributed to the average domain size probed by the different radiation sources. The solid-state NMR data indicate that at room temperature the toluene guest rapidly reorients between all possible orientations; however, at low temperature the resonances split, consistent with lowered symmetry, allowing the structure to be determined as monoclinic $P2/c$ with two unique molecules, $Z' = 1/2 + 1/2$ (Figure 6). The NMR data also revealed that some 5% of the guest toluene molecules are inverted with the methyl groups pointing out of the cavity.

3.3. Crystal Structure Calculation

One of the ultimate goals of solid-state chemistry is the ability to predict or computationally calculate the experimental crystal structure(s) of a compound solely from knowledge of its molecular structure. This is an ambitious goal and has not yet been fully realized, although there has been considerable progress toward meeting this ambitious aspiration as described in recent reviews.^{13b,89} The possible occurrence of more than one symmetry unique molecule greatly complicates the crystal

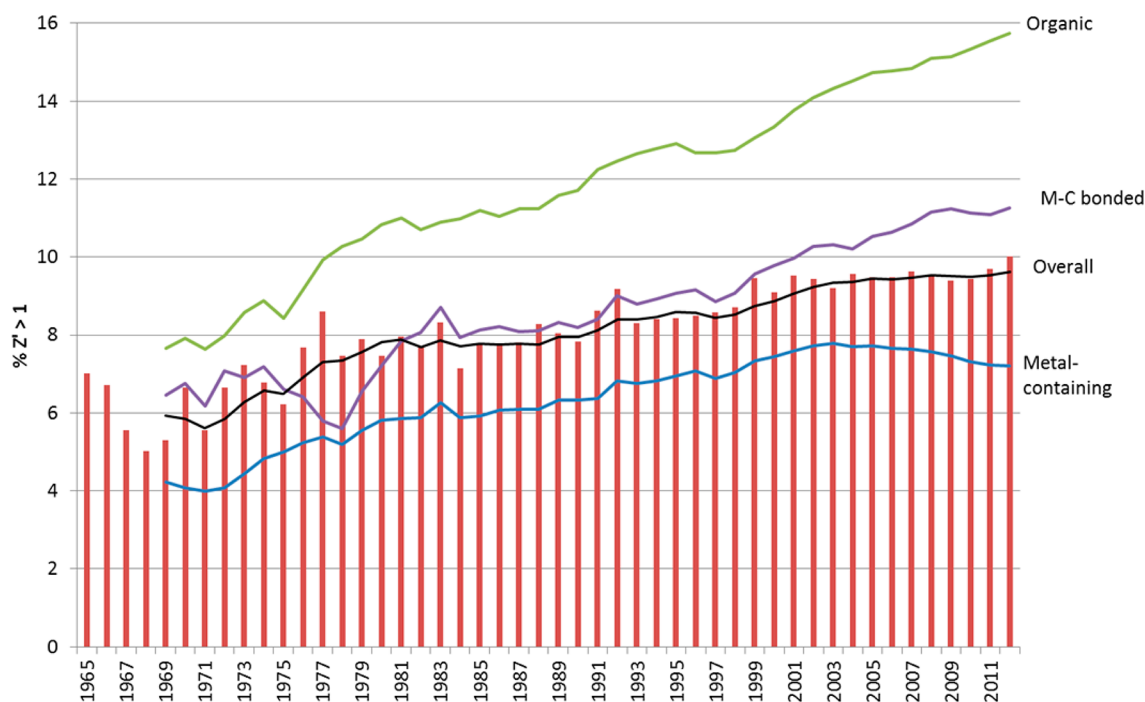


Figure 7. Proportion of structures in the CSD with $Z' > 1$ as a function of year of publication. Structures with $Z' = 0$ are omitted. Five-year rolling averages for various categories of structure are depicted as solid lines. The metal-containing category includes all compounds described in the CSD as “organometallic”, while M–C bonded refers specifically to structures containing a metal–carbon bond. Updated from ref 45b.

structure prediction (CSP) process. Typical CSP methodologies involve optimization of the molecular conformation and then the generation of many thousands of trial crystal structures in all space groups (or at least in all of the commonly occurring ones) by packing the optimized structure in all possible orientations according to space group symmetry. These trial structures are then ranked according to various lattice energy calculations based on either empirical potentials or DFT methods. Observed polymorphs should be among the lowest energy and most dense calculated structures. Clearly the requirement to treat two or more independent molecules in this way, each with three positional and three orientational parameters, dramatically increases the number of possibilities and hence computational resources required.^{31,90} A computational study by Price and co-workers in 2002 explicitly addressed the unusual $Z' = 4$ structure of pyridine and found it to be metastable as compared to over a dozen other candidate structures in terms of its calculated energy ranking even after harmonic phonon estimates of the intermolecular zero point energy and entropy were included.⁹¹ An exhaustive polymorphism screen revealed one other polymorph of perdeuteropyridine with $Z' = 1$; however, this form was also not close to the lowest energy calculated polymorphs. The calculations were revisited in 2011 by van de Streek and Neumann using the dispersion corrected DFT method in GRACE.⁹⁰ This procedure correctly calculated the two known structures as the lowest energy forms and predicted the $Z' = 1$ form as the most stable under high pressure. At ambient pressure, the $Z' = 4$ form is only stable between 215 and 232 K, with the $Z' = 1$ form most stable below 215 K but its nucleation is kinetically hindered. In terms of CSP methodology, the computation only included values of $Z' > 2$ because of the known $Z' = 4$ experimental structure, and searches of structures only with $Z' \leq 2$ are the norm. A 2007 study aimed at predicting the polymorphism of the highly polymorphic phenobarbital correctly reproduced the experimental $Z' = 1$ form, but there

were considerable difficulties with convergence and fully sampling the conformational and packing space, particularly for $Z' = 3$.^{13c}

The state of the art in CSP is benchmarked every few years by means of the blind tests for crystal structure prediction. For the first two sets of blind tests up to 2001, only structures with $Z' = 1$ were considered. This restriction was lifted for the third blind tests but contributed to poor success rates, and as a result in the fourth blind test that concluded in 2007 a specific category of structure with a cocrystal with two independent rigid molecules was included.⁹² The fourth blind test was notable in that the GRACE-VASP program, which is based on ab initio DFT calculations with an empirical dispersion correction, was able to correctly predict all four candidate structures as its number one energy ranked candidates, including the cocrystal structure with two independent molecules.^{13e} The fifth blind test in 2011 specifically allowed for the possibility of $Z' = 2$ structures, although in fact all of the experimental structures were $Z' = 1$, although a hydrate cocrystal was included.⁹³ No predictions were exactly correct for the rather complex, polymorphic hydrate structure, although, excluding H atoms, there were some correct predictions in the top energy ranked structures. The sixth blind test began on first September 2014 and will conclude on 31st August 2015. As well as a cocrystal category, it includes the category “molecules with 4–8 internal degrees of freedom; no more than two molecules in the asymmetric unit, in any space group; 50–60 atoms”; hence predictions on fairly complex molecules must include the possibility of $Z' = 2$. The results will be interesting! Even in cases where calculations do not correctly reproduce the experimental crystal structure, an innovative approach has been adopted by Cruz-Cabeza and co-workers who have related high energy calculated structures containing significant void space to real structures of known multi-component inclusion compounds.⁹⁴ The calculations on hydro-

quinone, for example, were able to reproduce the porous β -form, although they stopped short of the $Z' = 3$ α -form.

4. STATISTICAL TRENDS

4.1. Symmetry and Space Groups

The Cambridge Structural Database (CSD) with its collection of over 700 000 crystal structures⁹⁵ is an enormously powerful resource in teasing out factors that can contribute to interesting crystal packing effects, including the occurrence of multiple symmetry-independent molecules. The Z' parameter is explicitly included in the CSD and in the accompanying resource *CSDSymmetry*, a database derived from the CSD that includes information about molecular and crystal symmetry, and packing.⁹⁶ The CSD Z' value is simply derived from the number of the given formula units in the unit cell (Z) and the unit cell symmetry. There are several thousand cases (albeit a very small proportion of the total) where Z' is given as 0 where the situation is ambiguous or unassigned. Moreover, multiple redeterminations and sociological factors can skew the analysis in selected cases.^{28i,45b} Errors such as missed space group symmetry can also artificially increase Z' as in the 1958 report of the $Z' = 10$ structure of 10-methyl-1,2-benzanthracene⁹⁷ in which the high Z' value ("aggregation factor") was initially implicated in the compound's biological activity, only to be later shown to be a twinning artifact.^{22a,98} Generally, however, the number of errors is sufficiently small that underlying statistical trends are not obscured. The CSD lists structures with Z' values ranging from 1/96 to 32. A detailed analysis by Steiner in 2000 showed that Z' values of 1/2, 1, and 2 make up some 95.3% of the structures, with the proportion with $Z' > 1$ being 8.8%.^{28i,k} Later work by Bond shows this value rising to 10.92% for "homomolecular structures" (i.e., single component, discrete molecules) when all structures with more than one crystallographically distinct molecule are included (i.e., including cases such as $Z' = 1/2 + 1/2$).^{45a} The number of structures with $Z' > 4$ is really quite low (0.07%) to the point where all of the published occurrences are listed on the Durham Z' web resource.²⁹ The proportion of structures $Z' > 1$ is gradually rising over time, with continual improvements in instrumentation that can address increasingly large unit cells in a routine fashion, Figure 7.⁴⁵ Structures with $Z' > 1$ sometimes (although not always⁹⁹) exhibit approximate crystallographic symmetry (pseudosymmetry) with crystallographically independent molecules deviating only a little from exact symmetry. It has been suggested that approximate symmetry elements are present in about 27% of structures with $Z' > 1$.¹⁰⁰ For example, a survey of structures in the chiral (strictly Sohnke) space group $P1$ showed that the rms deviation away from inversion symmetry can be as low as 0.07 Å.^{33b,101} A reliable systematic procedure for matching of two independent groups of atoms in a crystal structure and quantifying differences between them has been developed by Collins et al. and is implemented in the CRYSTALS program.¹⁰² The occurrence of pseudosymmetry can result in erroneous space group assignment by assigning a space group that treats the pseudosymmetry as actual crystallographic symmetry. Lyssenko and co-workers carried out an unusual, detailed electron density distribution study on the energetic cost of missed pseudosymmetry on the structure of trinitropyrazole. The initial report in $C2/c$ with $Z' = 1.5$ was shown to be in error, and the structure is actually pseudosymmetric $P2_1/c$ with $Z' = 3$. The authors calculate that the resulting missing interactions not accounted for in the erroneous determination contribute some 8.9 kcal mol⁻¹.¹⁰³

There have been a number of statistical studies on space group frequency that explicitly address the distribution of Z' values, beginning with the work of Padmaja et al. in 1990,¹⁰⁴ and Wilson in 1991,¹⁰⁵ and these begin to shed considerable light on some of the factors that may give rise to crystals with multiple symmetry independent molecules. Earlier work on space group frequency has been elegantly summarized and extended by Brock in Dunitz in 1994.¹⁰⁶ In particular, they produced an extensive series of tables of space group frequency as a function of Z' . It is clear that structures with $Z' > 1$ are generally found in low symmetry crystal systems, particularly space group $P1$ (with the caveat that missed inversion symmetry in this space group is a common source of error^{33b,101}). Sohnke space groups also have a far higher than average proportion of structures with $Z' > 1$, often exhibiting pseudoinversion symmetry with $Z' = 2$ or 4, for example, $P1$, 45%, $P2_1$, 15%, and $C2$, 9%. The data are anomalous for orthorhombic space groups, however, with the non-Sohnke class exhibiting a slightly higher proportion of multiple independent molecules than the Sohnke class (7.7% as opposed to 6.8%).^{45a}

Care is required in examining space group frequency data, because of the difficulty in separating molecular and crystallographic symmetry effects. For example, space groups involving mirror symmetry such as $Pbcm$ must always involve the mirror plane as a molecular symmetry element, automatically halving the Z' value; mirror planes never relate one adjacent molecule to another in real crystals.¹⁰⁶ As a result, there is an intrinsic bias in raw frequency data in space group tables. Structures in space group $Pmc2_1$ are exclusively composed of crystals with $Z' = 1/2 + 1/2 = 1$, for example.¹⁰⁶ The SC descriptors to a great extent overcome such drawbacks. On the basis of a validated, automated procedure, Bond has derived SC descriptions for some 173 497 single component structures from the November 2007 release of the CSD and analyzed the frequency of occurrence of the various SC descriptors along with their derived extended Z' values.^{45a} Structures with two unique whole molecules in space groups $P\bar{1}$, $P2_1/c$, $P2_1$, and $P2_12_12_1$ are among the top 16 SC (Table 1). Structures that are formally $Z' = 1$ with two independent

Table 1. Summary of the Most Frequent Structural Classes Derived by Bond in 2008^a

structural class (SC)	N	% ^b
$P2_1/c$, $Z = 4$ (1)	53986	31.12
$P\bar{1}$, $Z = 2$ (1)	23226	13.39
$P2_12_12_1$, $Z = 4$ (1)	17306	9.97
$P2_1/c$, $Z = 2$ (1)	8739	5.04
$P2_1$, $Z = 2$ (1)	8728	5.03
$Pbca$, $Z = 8$ (1)	6509	3.75
$C2/c$, $Z = 8$ (1)	5357	3.09
$P\bar{1}$, $Z = 1$ ($\bar{1}$)	5085	2.93
$C2/c$, $Z = 4$ (2)	4755	2.74
$P\bar{1}$, $Z = 4$ (1, 1)	4619	2.66
$P2_1/c$, $Z = 8$ (1, 1)	4503	2.60
$Pna2_1$, $Z = 4$ (1)	2418	1.39
$P2_1$, $Z = 4$ (1, 1)	2345	1.35
$Pnma$, $Z = 4$ (m)	1677	0.97
Cc , $Z = 4$ (1)	1376	0.79
$P2_12_12_1$, $Z = 8$ (1, 1)	1089	0.63
$C2/c$, $Z = 4$ ($\bar{1}$)	1055	0.61
$Pca2_1$, $Z = 4$ (1)	1022	0.59

^aReproduced with permission from ref 45a. Copyright 2008 Royal Society of Chemistry. ^bPercentage of the total 173 497 entries.

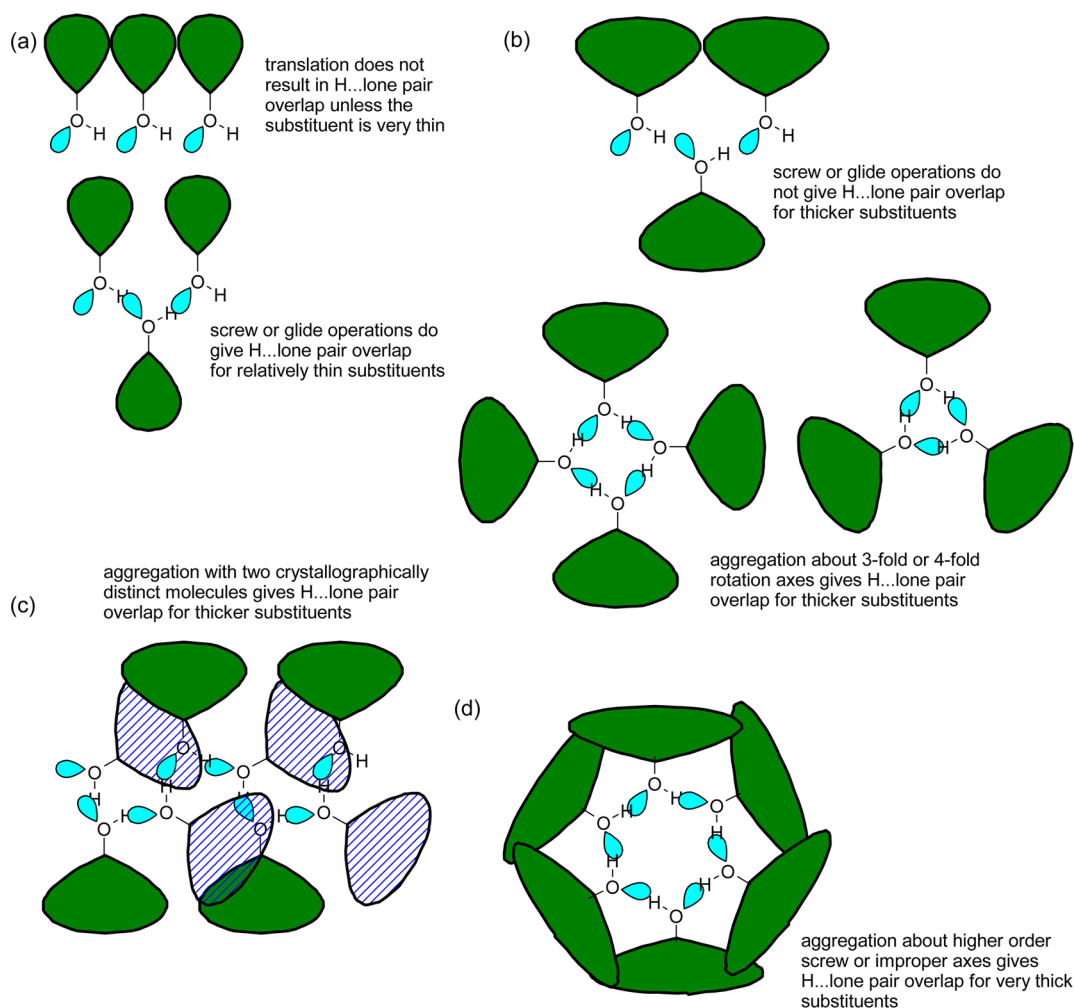


Figure 8. Ways of packing monoalcohols with variable thickness of substituent: (a) thin substituents pack by translation or by 2_1 screw or glide operations, (b) with thicker substituents rings are favored, (c) thicker substituents may also pack with more than one molecule in the asymmetric unit, and (d) very thick substituents result in packing about higher order screw or improper rotation axes.¹⁰⁷ Reproduced with permission from ref 18. Copyright 2009 Wiley-Blackwell.

molecules occupying distinct special equivalent positions are actually rather rare, and overwhelmingly dominated by $P\bar{1}$, $Z = 2(\bar{1}, \bar{1})$, which comprises 0.53% of the total structures. Just 0.18% of the sample is SC $P2_1/c$, $Z = 4(\bar{1}, \bar{1})$. This means that these “false positive” $Z' = 1$ structures do not exert a substantial statistical influence if ignored in a standard *Conquest* search.

4.2. Variations in Z' According to Types of Compound

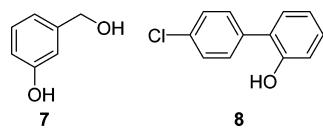
Analysis of the CSD reveals interesting variations according to chemical type. Consideration of the full SC descriptors demonstrates that organic compounds are far more likely to exhibit multiple independent molecules (12.29%) than metal containing structures (9.20%).^{45a} The trend is similar if just the pure Z' values are used instead of the SC (10.8% vs 6.42%).^{28k} Within the class of metal-containing compounds, those with a metal–carbon bond (i.e., organometallics that tend to be more “molecular”) are more likely to exhibit more than one symmetry-independent molecule than coordination compounds and salts.^{45b} Indeed the frequency of $Z' > 1$ for both organic and inorganic salts (ionic compounds) is markedly lower than for neutral molecules at around 6.5%.²⁸ⁱ Resolved chiral substances also exhibit a significantly increased tendency to form low symmetry (high Z') structures,^{28c} whereas hydrates and cocrystals in general (structures with more than one chemically

independent residue in the asymmetric unit, $Z' > 1$) show smaller than average percentages of structures with $Z' > 1$.⁴²

Seminal work by Brock and Duncan in 1994 showed that monoalcohols and monoamines display a significant predisposition to form either very high symmetry structures or high Z' .¹⁰⁷ This study was distinguished by an extremely detailed explanation for the observed trend based on the molecular structures and intermolecular interactions of these compounds. In particular, the dominant $\text{OH}\cdots\text{O}$ hydrogen bonding observed in the alcohols (and $\text{NH}\cdots\text{N}$ interactions in amines) imposes very specific packing requirements. Formation of an $\text{OH}\cdots\text{O}$ hydrogen bond requires the two oxygen atoms to approach to within about 2.8 Å of one another. The resulting packing is then determined largely by the steric properties of the alcohol substituent group. Long “thin” substituents can be related by 2_1 screw axes or by glide planes, or by translation in the case of very thin groups. In the case of bulkier substituents, these symmetry operations do not permit the hydrogen-bonding chain or ring to complete because a third molecule cannot approach closely enough. Similar issues arise from 2-fold rotation axes or inversion centers (Figure 8). Brock and Duncan proposed two solutions to this packing problem, that the asymmetric unit can contain more than one symmetry independent molecule or that the structure

can involve aggregation of molecules around screw or rotation-inversion axes of order 3, 4, or 6, Figure 8. In practice, the proportion of monoalcohol structures with full OH \cdots O hydrogen bonding (as opposed to some OH $\cdots\pi$ or other interactions) that exhibit $Z' > 1$ is very high indeed at 51% as compared to the 8% of the CSD as a whole at the time of the study. The prediction regarding high symmetry space groups was also borne out (32% vs 1%). The work was later extended to vicinal dialcohols, with the $R_2^2(10)$ motif¹⁰⁸ between two diols being the most common and the percentage of $Z' > 1$ being 33%, rising to 45% where the hydrogen-bonded chain is complete or nearly complete.^{28p} Interestingly, the monoalcohol butylated hydroxyanisole can adopt both alternative solutions to these packing problems and forms two polymorphs, one in $P\bar{1}$ with $Z' = 3$ based on hydrogen-bonded double helices, the other based on discrete hexameric assemblies in the high symmetry $R\bar{3}$ with $Z' = 1$.¹⁰⁹

Brock and Duncan's work was followed by a further study by Taylor and Macrae in an early application of the CCDC *Mercury* software, who attempted to produce a systematic description of alcohol packing.¹¹⁰ They found that in general primary monoalcohols give rise to chain structures, while secondary monoalcohols can give chains or rings. Tertiary alcohols are significantly affected by steric factors and tend to form isolated OH \cdots O hydrogen bonding or CH \cdots O and OH $\cdots\pi$ interactions. For dialcohols, chains are much more common unless there is a high degree of steric hindrance on the β -carbon, in which case isolated or intramolecular OH \cdots O interactions are observed. Interestingly, the tendency toward high symmetry or high Z' is not observed for tertiary monoalcohols that form no OH \cdots O hydrogen bonds, but high Z' values are still common when they do. More recent work by Lemmerer and Esterhuysen used a series of methylolphenol derivatives to test the conclusions of Taylor and Macrae and isolated two concomitant polymorphs of 3-methylolphenol (**7**) with $Z' = 2$ and 3. DFT calculations suggested that the polymorph with the lower Z' value is slightly more stable.¹¹¹ Their data confirmed that chains are more common for these dialcohols bearing a primary OH group and also showed that heteromeric hydrogen bonds are prevalent, reflecting the higher acidity of the phenol group despite its greater steric hindrance.



A particularly interesting monoalcohol is the $Z' = 4$ structure of 4-chloro-20-biphenylol (**8**).^{28o} Biphenyl and its derivatives are unusual in that the twisted conformation favored in the gas phase is not found in the solid state, in which optimal intermolecular interactions favor a less awkward planar geometry.¹¹² The *ortho* hydroxyl substituent destabilizes the planar geometry in **8**,

however, and hence the biphenyl unit is twisted. In the $Z' = 4$ structure, the four independent OH groups form a cyclic tetramer without any pseudosymmetry, reflecting the idea that the whole tetramer should be regarded as the building block of the crystal. Brock suggested that poorly packed molecules such as this might represent good candidates for cocrystal formation (see section 7).

It is important to note that Brock's compelling arguments on alcohol crystal packing, which have stood the test of time, are structural arguments based on the feasibility and hence stability of particular packing arrangements in the final crystal. They thus imply that assuming complete OH \cdots O hydrogen bonding is required, the observed high Z' structures are the thermodynamically preferred forms, and it is not necessary to invoke kinetic or nucleation effects to explain the trend. From the alcohol data, Brock and Duncan made the general conclusion that "the existence of surprisingly large numbers of structures with $Z' > 1$ or in high symmetry groups would then constitute evidence for a structure-determining intermolecular interaction".¹⁰⁷ The case of 1,2,3,5-dithiadiazole derivatives is another example identified by Brock of a type of compound adopting high Z' or high symmetry. These systems frequently form dimers that stack via S \cdots S interactions.^{107,113} The data for monoamines were considerably more sparse at the time; however, this trend also seems to be borne out, particularly in a rare case with complete hydrogen-bonded chains as in the striking $Z' = 10$ helical structure of N'' -cyano- N,N -diisopropylguanidine (**9**) reported by Brock in 2005 (Figure 9). The structure is all the more remarkable because the analogous N,N' isomer (one isopropyl group on each nitrogen atom) has a similar hydrogen-bonded chain structure but adopts an unremarkable $Z' = 1$ structure in $P2_1/c$.²⁸ⁿ

Analysis of the CSD by Steiner in 2000 showed a number of other specific chemical classes that are predisposed to crystallize with $Z' > 1$.^{28k} Particularly high incidences of multiple independent molecules were observed for nucleosides and nucleotides (20.8%) and steroids (18.8%), both of which tend to be chiral natural products with relatively large molecular size and both polar and hydrophobic regions. In contrast, metalloporphyrins exhibit only some 3.5% of structures with $Z' > 1$.

There have been other studies that have singled out particular classes of compound with a propensity to form high Z' structures, albeit often without there being a statistically very large number of cases. Tröger's base derivatives seem to exhibit a tendency to crystallize with multiple independent molecules despite the absence of strong, directional intermolecular interactions. This behavior was attributed to a combination of their awkward molecular shape (which is a V-shape useful in the construction of supramolecular host systems) and their chirality.¹¹⁴

The relatively small crown ether 15-crown-5 plays a role in a number of different kinds of high Z' structure. Its bifacial nature as a hydrogen-bond acceptor results in the formation of a

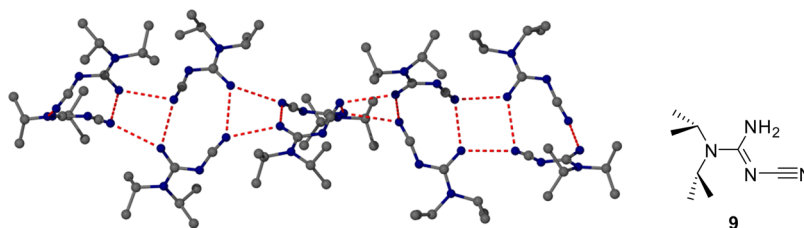


Figure 9. Asymmetric unit of the $Z' = 10$ helical structure of N'' -cyano- N,N -diisopropylguanidine (**9**).²⁸ⁿ

hydrogen-bonded cocrystal with a range of lanthanide and uranyl aquo complexes linked by multiple, highly directional hydrogen-bonding interactions from the coordinated water molecules to the crown ether oxygen atoms. One of the most striking of these structures is the $Z' = 16$, $Z'' = 32$ cocrystal structure of $[\text{UO}_2(\text{OH}_2)_3\text{Cl}_2] \cdot 15\text{-crown-5}$,³⁹ discussed in detail in section 6. As a ligand, 15-crown-5 also forms an interesting range of structures of type $[\text{M}(\text{OH}_2)_2(15\text{-crown-5})](\text{NO}_3)_2$ ($\text{M} = \text{Mg}$, Mn , Fe , Co , Cu , and Zn), which have been extensively investigated by Brock.^{34,115} This system forms no fewer than five related types of crystal structure, all of which have $Z' > 1$, including quite unusual values of 5 and 8. The structures are all based on hydrogen bonding from the aquo ligands to the nitrate anions, as in the manganese example shown in Figure 10, and the

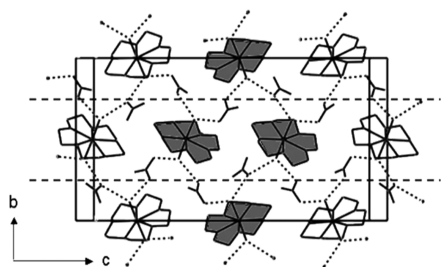


Figure 10. Hydrogen-bonded structure of monoclinic $[\text{Mn}(\text{OH}_2)_2(15\text{-crown-5})](\text{NO}_3)_2$ ($Z' = 3$). The shading distinguishes the 2-fold symmetric conformational enantiomers, which can interconvert in the solid state. The middle three complexes in the middle row are crystallographically independent. Dotted lines indicate glide planes. Reproduced with permission from ref 34. Copyright 2005 American Chemical Society.

rich low symmetry polymorphic behavior fundamentally arises from the conflict between the optimum spacing of different noncovalent interactions, particular $\text{OH} \cdots \text{O}$ hydrogen bonding and space filling requirements. The systems also exhibit considerable temperature dependence and are unusual in that fact that the $[\text{M}(\text{OH}_2)_2(15\text{-crown-5})]^{2+}$ cation is chiral but the enantiomers can readily interconvert in the crystal, further giving rise to the possibility of multiple phases.³⁴

The compound types discussed in this section have been singled out for study by various authors, partly because their interesting characteristics happen to have been noticed, often serendipitously. They are by no means the only classes of compound of interest, and more systematic studies show that many types of compound, particularly those exhibiting strong, directional intermolecular interactions such as hydrogen bonding, halogen bonding, or aurophilic interactions, often in conjunction with properties such as awkward shape or a tendency to adopt particular supramolecular motifs (supramolecular synthons), also show a significant tendency to form high Z' structures. We deal with these cases in a more holistic fashion in section 5.1.

4.3. Lost Opportunities

Another phenomenon that the simple Z' parameter fails to take account of is cases of “wasted” symmetry, particularly molecular inversion symmetry.¹¹⁶ Bond has used the CSD to survey single component crystal structures of compounds possessing molecular inversion but noncentrosymmetric crystallographic site symmetry. Typically this class of compound might, for example, exhibit $Z' = 1$ in a space group such as $P2_1/c$, but had the molecule occupied one of the crystallographic inversion centers

available in the space group, it could have adopted a $Z' = 1/2$ structure. The implication is that the molecular inversion symmetry has been “wasted” and the Z' value is double what it could have been.

In general, molecules with C_i point symmetry adopt a centrosymmetric environment in the crystal (true in 99% of cases),¹¹⁷ although the frequency drops somewhat for molecules with higher symmetry centrosymmetric point groups. Hence, “wasted” inversion symmetry is unusual, and so it is perhaps instructive to examine the factors behind it in the same way as wasted intermolecular symmetry in $Z' > 1$ systems exhibiting pseudosymmetry.¹¹⁸ Taking a chemical structural approach, Bond identified a number of different cases for the lost opportunity to express molecular inversion symmetry in the crystal. A classic example is the ubiquitous class of structures with $Z = 4$, $Z' = 1$ in $P2_1/c$ expressed in structural class form as $P2_1/c$, $Z = 4(1)$, in which the four inversion symmetric molecules in the unit cell form two pairs based on a centrosymmetric supramolecular synthon, and it is the symmetry-related pairs that are situated upon the crystallographic inversion centers. Thus, while the molecules adopt $P2_1/c$, $Z = 4(1)$ with wasted symmetry, the supramolecular pairs can be thought of as adopting SC $P2_1/c$, $Z = 2(1)$. An example is the structure of porphine (PORPIN02¹¹⁹) in which the centrosymmetric porphine molecules form centrosymmetric dimers via π -stacking interactions, Figure 11.

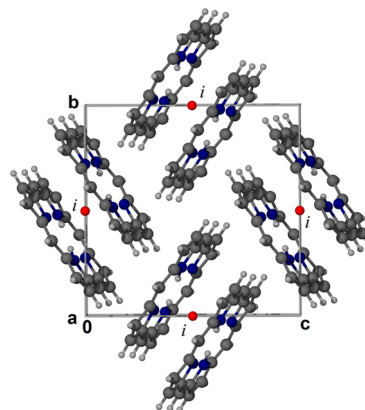


Figure 11. Centrosymmetric dimers of porphine.¹¹⁹ While the molecules pack in $P2_1/c$, $Z = 4(1)$ with $Z' = 1$, apparently wasting their molecular inversion symmetry, each dimer is situated about a crystallographic inversion site (i).¹¹⁶

Other factors responsible for wasted inversion symmetry include formation of layered structures with local symmetry, and structures with crystallographically distinct molecules as in $P2_1/c$, $Z = 6(1, \bar{1})$. Overall the wasted inversion symmetry results from mismatch between the symmetry of some fragment of the structure and the symmetry of the intermolecular interactions between fragments. This mismatch or frustration concept can be naturally extended to rationalize pseudosymmetrical structures with $Z' > 1$ (see section 5.1).

Another interesting “lost opportunity” is the rare case of kryptoracemates¹²⁰ (or “false conglomerates”^{28t}). In general, crystallization of a racemic mixture of two enantiomers of a chiral compound results in a racemic crystal in which the two enantiomers are related to one another by a crystallographic inversion or glide operation. Note that by convention, pairs of enantiomers are considered to be the same molecule in assigning Z' values, even if the enantiomers do not interconvert in solution.

Hence, we do not think of a racemic crystal as a cocrystal. In a few cases (ca. 5–10%),¹²¹ the enantiomers spontaneously resolve to give a mixture of distinct left- and right-handed crystals termed a “conglomerate”.¹²² Indeed Pasteur’s early experiments involving manually separating conglomerates of sodium ammonium tartrate are the first example of deliberate chiral resolution.¹²³ The kryptoracemates are rarer still, representing only some 0.1% of structures. A kryptoracemate, or “hidden racemate”, is an intimate racemic mixture of left- and right-handed molecules (and hence does not rotate plane polarized light in solution) that adopts a chiral crystal packing arrangement in one of the 65 Sohnke (chiral) space groups. Hence, an individual crystal is chiral even though it is made up from a racemic mixture of molecules. In a typical kryptoracemate, a molecule (A) and its enantiomer (A*) adopt crystallographically distinct positions (A and B), and hence the individual left- and right-handed crystals contain either A and B* or A* and B. The situation is summarized in Figure 12.

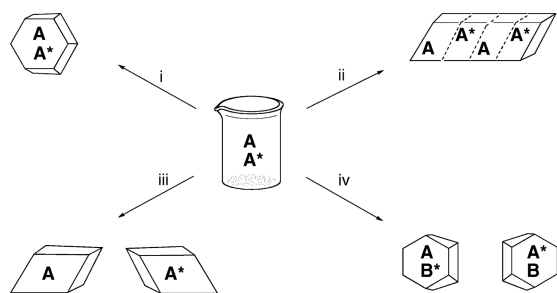
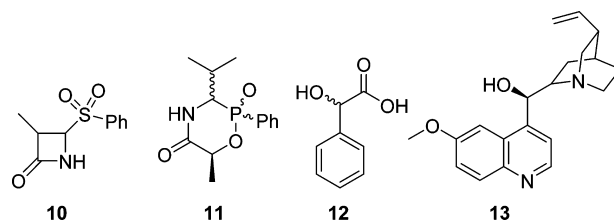


Figure 12. Possible outcomes of allowing a 1:1 racemic solution of A and A* molecules to crystallize. The symbols A and B signify crystallographically independent molecules with the same chirality, and A* and B* are their enantiomers. (i) Formation of a racemic solid containing an intimate mix of A and A* molecules. (ii) Formation of a racemic solid containing domains of both enantiopure A and enantiopure A* molecules. (iii) Formation of a mixture of enantiopure A crystals and enantiopure A* crystals (a conglomerate). (iv) Formation of a kryptoracemate: a mixture of enantiopure A and B* crystals (and containing no A* and B molecules) and enantiopure A* and B crystals (and containing no A and B* molecules). Reproduced with permission from ref 28t. Copyright 2009 American Chemical Society.

In 2010, Fábián and Brock¹²⁰ undertook a comprehensive CSD survey and identified 181 kryptoracemates in the CSD including 13 that crystallize with two crystallographically independent racemic pairs (or four independent molecules) and 11 very strange structures in which there is not a 1:1 ratio between the enantiomers. They also identified a cocrystal based on **10** (ABADUD¹²⁴) comprising a racemic pair of molecules cocrystallized with a closely related derivative in which a CMe₂ group is replaced by a CHMe group. The independent enantiomers in kryptoracemates usually adopt very similar conformations but display little pseudosymmetry. Kryptoracemate formation is closely related to the more general class of compounds that exhibit $Z' = 2$, and several can be understood in terms of formation of optimal hydrogen-bonding interactions. Related to the kryptoracemates is the unusual structure of phosphinanone **11**, which exhibits three independent molecules of a single diastereoisomer of handedness $R_{iPr}S_{Me}S_P$ cocrystallized with one diastereoisomer of configuration $S_{iPr}S_{Me}R_P$.^{28j}

The chiral resolution of organic salts using diastereomeric crystallization with, for example, tartrates is a very well-established technique.^{121,125} While the formation of cocrystals



between different (related) molecules of opposite chirality, so-called quasiracemates, was a useful trick in absolute structure determination before the advent of high precision measurements allowed the widespread use of anomalous dispersion,¹²⁶ examples such as **10** and **11** demonstrate why purification or optical resolution by fractional crystallization is sometimes unexpectedly unsuccessful! Báthori et al. have recently studied the optical resolution of mandelic acid **12** using the cinchona alkaloid quinine (**13**).¹²⁷ Addition of varying mole fractions of R-mandelic acid (X_R) to a solution of a single enantiomer of quinine while maintaining a 1:1 overall quinine:mandelic acid ratio resulted in the selectivity curve shown in Figure 13. Crystal were

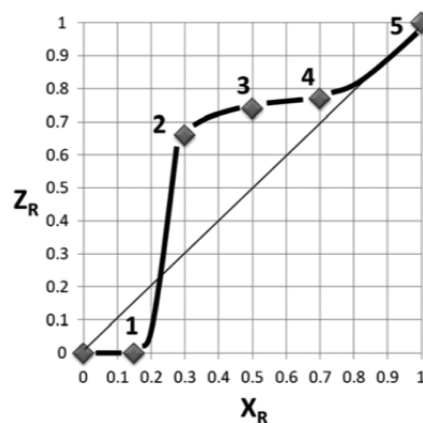


Figure 13. Selectivity curve for the quiniinium mandelate system, Z_R is the mole fraction of R-mandelate in the isolated crystals, while X_R is the mole fraction of R-mandelate added to the 1:1 quiniinium:mandelate crystallization mixture. Reproduced with permission from ref 127. Copyright 2011 Royal Society of Chemistry.

obtained at points 1–5 and characterized by single crystal and powder X-ray diffraction. The ideal resolution is for the mole fraction of the R-mandelate in the isolated crystals to be either 0 or 1 corresponding to complete separation. This is achieved for structure 1, which is a simple $Z' = 1$ salt containing a single mandelate enantiomer (S) even though it is grown from a mixture containing 15% of the R isomer. Interestingly, structure 1 is loosely packed according to Hirshfeld surface analysis and has a rather low density. Structure 5 also, of course, contains a single enantiomer because it was obtained from optically pure R-mandelate. However, these crystals have $Z' = 3$ and are packed with a much higher density (1.340 vs 1.203 g cm^{−3}), in contrast to the usual situation in which high Z' structures have “better interactions” but lower density.¹²⁸ Structures 2–4 are all isomorphous with the $Z' = 3$ structure 5 but contain two R and one S enantiomers giving a Z_R of 67% for 2. Crystals 3 and 4 exhibit disorder of the site containing the S mandelate anion with some R content, raising the actual Z_R values further, but not to 100%. These $Z' = 3$ structures, related to the kryptoracemates, dominate the selectivity profile, substantially complicating attempts to apply the system as a resolution method.

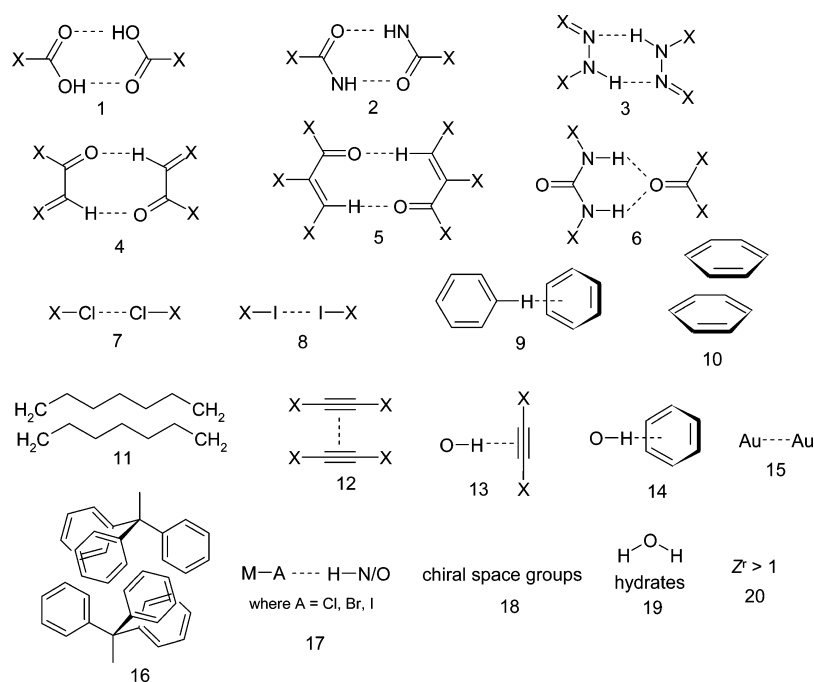


Figure 14. Categories of potentially mutually competing, structure directing factors used to probe the concept of the alleviation of frustration being a factor in the formation of $Z' > 1$ structures: 1–6, supramolecular synthons such as hydrogen-bonded species;¹³⁰ 7–8, halogen–halogen interactions;¹³¹ 9–10, edge-to-face and face-to-face π -stacking interactions;^{16b,132} 11, hydrophobic alkane chain interactions;¹³³ 12, alkyne–alkyne interactions;¹³⁴ 13–14, O–H to alkyne or aryl interactions;¹³⁵ 15, auropilic interactions;¹³⁶ 16, 6-fold phenyl embraces;¹³⁷ 17, hydrogen bonds to metal halides;¹³⁸ 18, compounds crystallizing in chiral (Sohnke) space groups; 19, crystals containing water (hydrates/aqua complexes);¹³⁹ 20, structures with more than one type of chemical residue in the asymmetric unit ($Z' > 1$),⁴² such as cocrystals. Adapted with permission from ref 28c. Copyright 2008 American Chemical Society.

4.4. Concluding Remarks

In general, the explanation of quite why all of the statistical trends in (lack of) crystal symmetry summarized in this section exist remains the subject of considerable debate, while lending itself to some degree of explanation on a case-by-case basis. Indeed, in a recent large-scale automated geometric and energetic comparison of $Z' = 1$ and $Z' = 2$, Gavezzotti concluded that apart from trends such as the common occurrence of pseudosymmetry, few generalities could be made and “each case may be a story in itself”.^{28u} Chemical factors such as the types of intermolecular interaction and the sterics of their packing may well play a part, and indeed this argument is quite well developed for the monoalcohols.¹⁰⁷ Perhaps the existence of multiple components in ionic systems presents additional “freedom” to pack more symmetrically? The inability of resolved chiral compounds to crystallize in non-Sohnke space groups is also a likely factor. Sociological aspects such as the differing crystallization habits of workers in different fields of chemistry may even be relevant.^{45b} It has long been our opinion that $Z' > 1$ “exceptions” to the vast majority of crystal structures crystallizing with a single symmetry independent fragment have something to tell us about the general way in which molecular solids crystallize.^{22b} While other workers have tried to come up with a single, all-encompassing explanation of this behavior,^{28e} we believe that the simple Z' number is a “catch-all” consequence of a range of interesting crystallization factors that have their origins in a wide and distinct set of structural and packing effects, nucleation and precrystallization solution speciation influences, and lattice entropy and dynamics. All of these factors can have a consequence on the observed crystal packing arrangement and hence Z' value. They also impact on the hugely topical areas of polymorphism and the formation of solvates and cocrystals. Some attempts to tease-out

some of these underlying factors are described in the next section with a key focus on a detailed examination of the chemical structure of the components and their mutual interactions.

5. ORIGINS OF CRYSTALS WITH $Z' > 1$

5.1. Structural, Packing, and Crystallization Influences

A key concept that has been raised very frequently in attempting to explain the origins of crystals with multiple symmetry-independent molecules is the idea of there being some kind of conflict or frustration in any putative or real $Z' = 1$ structure that can be resolved, or at least an optimal balance of interactions achieved, by adoption of a high Z' crystal packing arrangement. In other words, a single environment in the crystal cannot allow the molecule to form optimum interactions with all of its neighbors. This kind of explanation is relevant in the context of the high Z' structures of monoalcohols and in modulated structures, for example.^{34,107} In the case of alcohols, the need to simultaneously optimize short $\text{OH}\cdots\text{O}$ interactions and close pack the alcohol substituents results in a conflict that cannot be optimally accommodated in the otherwise common $Z' = 1$ structure in a low symmetry space group. The conflict is resolved either by very high symmetry or by adoption of a $Z' > 1$ structure.

A simple way of visualizing a favorable supramolecular interaction between molecules is as a “supramolecular synthon”,¹²⁹ and the field of crystal engineering has progressed considerably by using such commonly observed interaction motifs as design elements in producing loosely predictable (or readily rationalized) crystal structures. Taking a supramolecular synthon-based approach, we attempted to go beyond surveys of particular classes of molecule (alcohol, nucleoside, 15-crown-5, etc.) and, from a careful consideration of the chemical structure

of the molecules involved in a crystal, identify potential cases of conflicted crystal packing and hence high Z' crystal structure. If a supramolecular synthon represents the kind of interaction that should be optimal in a stable crystal, then conflict between two or more synthons, or with a supramolecular synthon and another packing factor such as close packing, other directional interactions, or properties such as chirality, may mean that a high Z' structure gives the optimal balance. This concept was probed using a statistical analysis of the proportion of $Z' > 1$ structures in the CSD for 20 well-represented categories of compound both by themselves and in combination with one another. These categories were chosen somewhat arbitrarily based on experience and precedent, and are shown in Figure 14.^{28c}

The centrosymmetric dimer synthon categories 1–5 are generally well represented in the CSD; all show significantly above average tendencies toward the formation of $Z' > 1$ structures with between 10% and 19% of entries having high Z' as compared to 8.8% for the database as a whole. This immediately suggests that the dimeric unit is a building block and invites speculation about solution preassociation (section 5.3) and/or the frustration between the optimal interactions in the dimer and the packing of one dimer with adjacent pairs. Other directional interactions such as urea α -tape type hydrogen bonding (category 6) also show a slightly elevated proportion of $Z' > 1$ structures (10%), as do structures based on relatively weakly directional interactions such as halogen...halogen interactions (category 7 and 8) and aromatic stacking (categories 9 and 10). $\text{OH}\cdots\pi$ interactions (types 14 and 15) both show increased Z' , and the effect is particularly marked for auropophilic interactions^{136c} (category 15, 20.1%). In general, however, for all of these classes, structures with $Z' > 1$ are still a distinct minority, and we cannot look to a single type of interaction alone as a reliable indicator of a structural predisposition toward crystal packing with multiple symmetry formula units. Indeed, there are some classes that show a lower than average tendency to give $Z' > 1$ such as 6-fold phenyl embrace structures (which may exhibit significant molecular symmetry, lowering the value of Z') and hydrogen bonds to metal halides (categories 16, 17). It is also clear that cocrystals in general have a significantly reduced tendency to form high Z' structures (entries 19 and 20), which is discussed further in section 7.

The key hypothesis to this work was that the competing demands of more than one factor may lead to high Z' structure as a means to optimize competing symmetry-incompatible interactions and hence alleviate the frustration between the two. An example of an additional frustrating factor is the combination of a centrosymmetric motif such as categories 1–5 with molecular chirality (category 18) because two homochiral molecules cannot be related to one another by inversion symmetry. This simplistic case is an obvious example of where both molecules in the dimer should therefore be crystallographically independent. This simple prediction proves to be correct with the percent $Z' > 1$ for structures that have both one of synthons 1–5 and crystallize in a chiral space group (category 18) being very high indeed (between 33% and 100%, with most synthons being well above 50%). This kind of marked jump in the incidence of $Z' > 1$ suggests a significant casual explanation, discussed in more detail below.

Other frustrated combinations also require an increase in the number of symmetry independent molecules to produce an optimum structure. Crystals containing both a carboxylic acid dimer and an amide dimer (synthons 1 and 2), for example, form

$Z' > 1$ structures in the majority of cases (52.9%). In general, structures with combined, frustrating factors show increased Z' such as the combination of alkyne stacking with edge-to-face π -interactions (categories 12 and 9, 26.3%) and edge-to-face π -interactions and $\text{OH}\cdots\pi$ interactions (categories 9 and 13, 41.7%). Auropophilic interactions in combination with most other factors also show a marked effect.

The particular issue of the frustration between chirality and centrosymmetric dimer formation was examined closely in a related study for the centrosymmetric synthons A–E shown in Figure 15. The carboxylic acids (synthon A) and amides

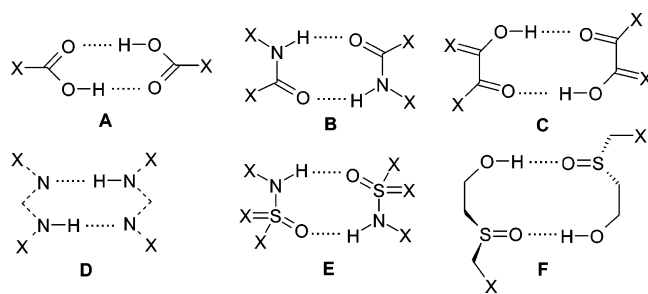


Figure 15. Centrosymmetric hydrogen-bonded dimer synthons (X = non-hydrogen atom, dotted lines indicate hydrogen bonds, dashed bonds indicate any bond type).^{28j,141}

(synthon B) proved to be by far the most well represented and resolved chiral compounds forming these motifs crystallized with $Z' > 1$ in a remarkable 63.2% and 60.4% of cases, respectively. These data confirm an earlier study on chiral carboxylic acids by Sorensen and Larsen.¹⁴⁰ Similar results were subsequently found by Lodochnikova et al., who identified six occurrences of a further 12-membered ring synthon F exhibiting similar behavior, all with $Z' = 2$, and coined the term “crystallization-induced diastereomerization” to describe their findings.¹⁴¹ What is interesting about the chiral carboxylic acid and chiral amide dimers is not so much that there is an extremely high proportion of $Z' > 1$ structures, but that this proportion is not 100%. After all, it is symmetrically impossible to relate two homochiral molecules by inversion symmetry, so what is happening with the remaining 35–40% of structures that are still $Z' = 1$? The answer is that all of these remaining structures fall into three distinct, easily understood groups. The majority of the exceptions are either bifunctional molecules in which the dimer is formed by crystallographically distinct functional groups that are part of the same molecule (these structures represent examples of “wasted symmetry”, section 3.3) or they have more than one kind of molecule ($Z'' > 1$) and the dimer is formed between chemically different molecules (as in quasiracemates¹²⁶). Both of these cases therefore obey the general rule because they do have more than one crystallographically distinct carboxylic acid group despite a Z' of 1. Most interesting are the 12 structures with $Z' = 1$ out of 174 structures that do only contain one symmetry independent carboxylic acid group. All of these structures are in space group C_2 , and the dimer is situated on a crystallographic 2-fold rotation axis. Proper rotations do not invert chirality, but they do represent a relatively inefficient packing mode (screw axes are generally preferred over rotations^{7,104,105b,106}). Exactly the same issues occur for the amide dimers, and hence we can predict that the occurrence of multiple independent molecules is a preferred option as compared to crystallographic symmetry such as 2-fold rotation that results in inefficient packing.

An interesting cocrystal variation of this phenomenon was discovered in the structures of 1:1 nicotinamide-ibuprofen cocrystals by Berry et al. in 2008. The structure of the racemic *R/S*-ibuprofen cocrystal is $Z' = 2$, $Z'' = 4$ and comprises a pseudocentrosymmetric pair of nicotinamide molecules hydrogen bonding to the ibuprofen. The crystal of the *S*-enantiomer is almost isostructural except that there are now two unique pseudocentrosymmetric pairs, $Z' = 4$, $Z'' = 8$. The racemic structure adopts a polar space group $Pna2_1$ with segregated *R* and *S* tapes, while only the *S* tape is retained in the homochiral version, Figure 16. The crystals were obtained both from solution and from the melt with no evidence of polymorphism.¹⁴²

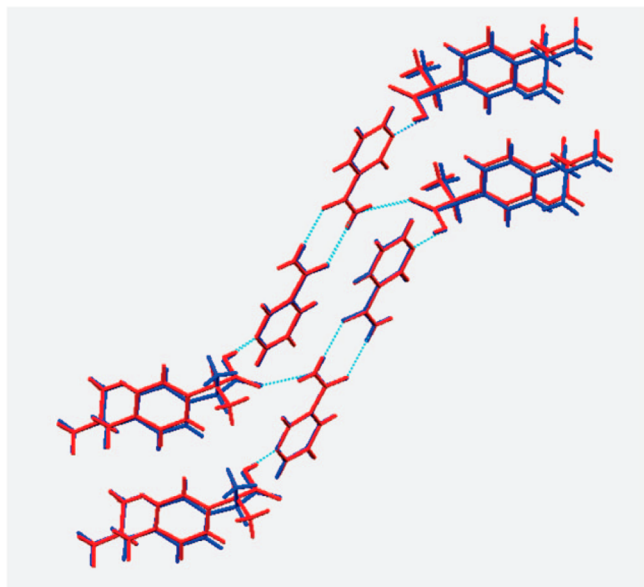


Figure 16. Comparison of the hydrogen-bonding motifs in the nicotinamide-ibuprofen cocrystals (blue *R/S*, red *S*). Reproduced with permission from ref 142. Copyright 2008 American Chemical Society.

The packing of a series of closely related chiral palladium(II) amine complexes with a tendency to form centrosymmetric synthon **14** (Figure 17) was examined by Calmuschi and Englert in 2005, who crystal engineered a variety of quasiracemate cocrystals.¹²⁶ Their work establishes inter alia that there can be other exceptions to the formation of $Z' > 1$ structures of chiral pseudocentrosymmetric dimers. The racemic form of the Pd(II) complex ($R = \text{CH}_3$) shown in Figure 17 crystallizes with $Z' = 1$ in $C2/c$. Quasiracemate formation to give 1:1 cocrystals with complexes bearing two different *R* groups gives the same packing pattern in the subgroup $C2$ with one crystallographically independent molecule of each type. However, the structures of the pure homochiral compounds are also $Z' = 1$ in $P2_12_12_1$. While these homochiral structures have a similar hydrogen-bonding pattern, the centrosymmetric dimer is not the dominant factor, and an $\text{NH}\cdots\text{Cl}$ hydrogen-bonded helical chain of 2_1 symmetry is formed instead.

In another example of the need to optimize supramolecular synthons, Babu and Nangia have argued that a Z' value of more than 1 is needed to pack the carboxylic acid–pyridine trimer motif (Figure 18) in small rigid molecules, in the absence of 3-

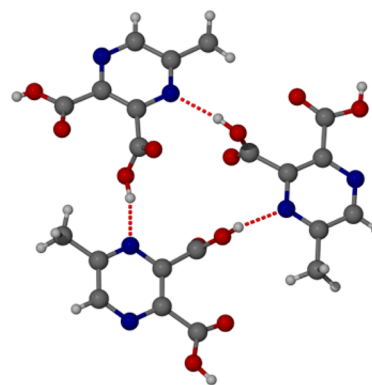


Figure 18. $Z' = 3$ asymmetric unit based on the carboxylic acid–pyridine trimer synthon.^{28h}

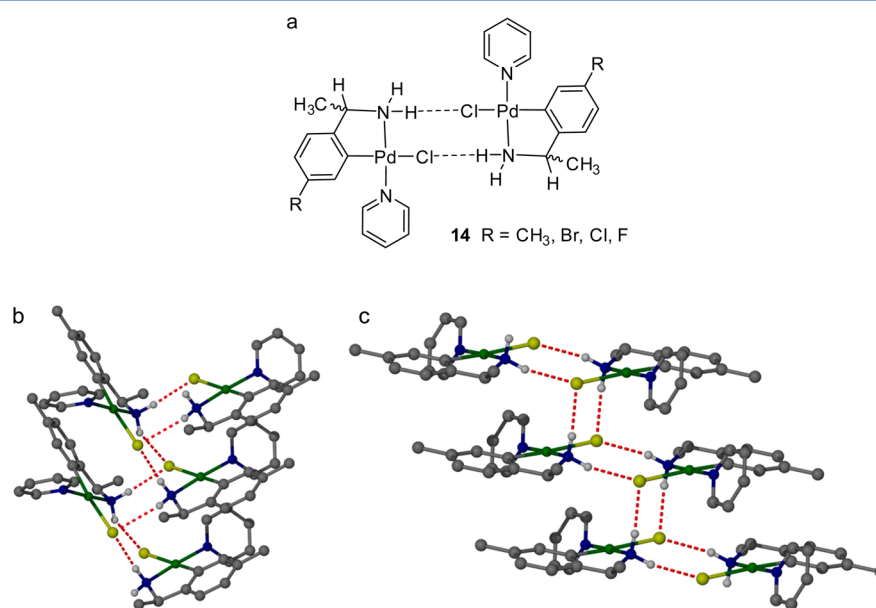


Figure 17. (a) Centrosymmetric dimer synthon **14**.¹²⁶ (b) Hydrogen-bonded helical chain synthon in the structure of the homochiral methyl derivative. (c) Centrosymmetric dimer chains in the racemic analogue.

fold molecular symmetry. While 3-fold packing is possible with $Z' = 1$, they argue that pendant groups would be required to fill the resulting voids in the structures.^{28h} Increased incidence of high Z' was also noted recently for a series of thioamide dimer structures in comparison to their amide analogues and was attributed to “packing challenges associated with the size mismatch between the sulfur atom and the carbon and nitrogen atoms in the dimers”.¹⁴³

5.2. Effect of Molecular Size, Shape, and Flexibility

A study by Gavezzotti in 2008 compared the molecular and energetic properties of two thoroughly curated, error-free data sets for compounds containing only C, H, N, O, S, and F atoms retrieved from the CSD.^{28u} One set, Z1, contained only structures with $Z' = 1$, while the Z2 set contained only $Z' = 2$ structures. The data showed consistently that the molecules in the Z2 set were, on average, slightly smaller in terms of molecular volume than the Z1 set, although average density, packing coefficient, and lattice energy per atom proved to be identical. The size effect was suggested to perhaps arise from a social bias with crystallographers preferring smaller molecules when attempting to determine more challenging $Z' > 1$ structures. The Z2 sample contained a high percentage of alcohol groups, consistent with the earlier work of Brock.¹⁰⁷ Space group analysis showed that the Z2 sample crystallized in a higher percentage of $P1$, $P2_1$, and $P\bar{1}$, and a lower percent in $P2_1/c$ and $P2_12_1$ (with the former being subgroups of the latter). Perhaps the most interesting aspect of the study is that a comparison of the energetics of molecular pairs in the Z1 and Z2 sets showed that for the Z2 set the most strongly bound pair exhibits a higher interaction energy than in the Z1 set, and this pair is generally the asymmetric pair. However, the contribution to the total lattice energy from the asymmetric pair ranged very widely from 10–70% of the total. It was suggested that pairs representing a high total may represent cases where the pair arises from kinetic trapping, particularly in cases where one partner in the asymmetric unit pair is less stable in terms of both intermolecular and intramolecular interaction energy. In contrast, pairs contributing relatively little to the total were suggested to be legitimately stable structures. This range of energies points to there being no single explanation of the phenomena caught up in the $Z' > 1$ umbrella with a full examination of the chemical nature of the compounds in the structure on a case by case basis being perhaps required.

Analysis for the presence of pseudosymmetry showed that 83% of compounds in the Z2 sample showed some kind of pseudosymmetry with a (relatively generous) tolerance of $0.5 \text{ \AA atom}^{-1}$, and it was concluded that “symmetry is a powerful enhancer of aggregation stability.”^{28u} The fact that homomolecular structures tend toward being symmetrical is clear; however, it is quite difficult to disentangle cause and consequence. Because the molecules themselves are chemically identical and we know that donors tend to pair with acceptors or bumps with hollows in real crystals,¹⁰⁶ it is difficult to imagine why the packing should be anything other than symmetrical, which, of course, is why the presence of multiple independent fragments in the asymmetric unit is such a tantalizing puzzle.

In 2011, we also analyzed the size and shape distribution across the whole CSD as a function of Z' , and included subsets of bioactive molecules and molecules that have known cocrystals.^{27e} This work, which also included structures with $Z' > 2$, found that compounds that crystallize with $Z' > 1$ are in general smaller (by around 50 \AA^3 on average) than those forming $Z' = 1$

structures in agreement with Gavezzotti's study. In addition, the same trend is observed among $Z' = 1$ homomolecular structures of molecules that are known to form cocrystals. This finding argues against the social bias suggestion and implies that the size difference is a real phenomenon. Moreover, it is highly statistically significant not just in terms of mean value but as a distribution.^{27e,28u} High Z' structures and cocrystal formers also prove to be significantly less flexible (with ca. two fewer rotatable bonds on average) than molecules that crystallize with $Z' = 1$.^{27e} Interestingly, the idea of high Z' structures arising from the possibility of many different possible conformations of a flexible molecule has been postulated by several authors, and examples are described in section 6.¹⁴⁴ This hypothesis does seem at odds with the statistical observation that high Z' structures have fewer rotatable bonds.^{27e} Indeed particular care is needed to ensure that minor apparent differences are not over interpreted as being different conformers as in the case of 4,4-diphenyl-2,5-cyclohexadienone discussed in section 3. This compound was thought to possess a total of 19 different conformers between the four polymorphs including the erroneous triclinic $Z' = 12$ form.¹⁴⁵ Careful subsequent examination of Hirshfeld molecular fingerprint plots, however, later revealed that the $Z' = 12$ form is equivalent to the $Z' = 4$ form in the same space group, and hence the system exhibits just seven different conformers across three polymorphs.^{19a,71}

Our 2011 study also considered the question of high Z' structures arising as a consequence of awkward molecular shape. This concept had been used in the deliberate design of “wheel-and-axle” type cocrystals,¹⁴⁶ and interestingly wheel-and-axle host systems have recently been shown to adopt structures with $Z' > 1$ as an alternative to guest inclusion.¹⁴⁷ As a measure of “awkwardness”, two molecular shape parameters were examined: the ratio of the molecular volume to the solvent accessible surface area (v/aa where a smaller value represents a more awkward molecule) and the difference between the volume of a hypothetical box where the dimensions map out the boundaries of the molecule and the actual molecular volume ($v-v$; molecules fitting the box well and hence having a small value should be of a less awkward shape). By both measures, molecules in the CSD as a whole crystallizing with $Z' > 1$ are more awkward than those crystallizing with $Z' = 1$. Analysis of homomolecular ($Z' = 1$) parent structures of cocrystal forming molecules proved that these compounds are more awkward still. This was interpreted to mean that small, rigid molecules are rather more likely to have difficulty packing with optimum 3D interactions, and this packing problem can be resolved by forming unsymmetrical interactions or including a second type of chemical residue. This conclusion also seems at odds with the speculation that some very high Z' structures may arise from the existence of many slightly different conformers;¹⁴⁴ however, if there is any kind of molecular flexibility, it is statistically unlikely that in a very high Z' structure the conformation of all of the molecules will be the same, and hence it may be that the observation of many slightly difference conformations is a consequence rather than a cause of high Z' behavior. Indeed it was shown in the work of Sona and Gautham back in 1992 that in structures with $Z' = 2$, both molecules generally have very similar conformations.¹⁴⁸ However, there are significant exceptions as in the $Z' = 4$ structure of 2,3-dinitrobenzoic acid in which the four independent molecules display no pseudosymmetry because they are all of different conformation. Interestingly, in this example, force field calculations indicate that it is not the

ubiquitous hydrogen-bonded dimer that dominates the packing energy but rather $\pi\cdots\pi$ stacking and $\text{O}_{\text{nitro}}\cdots\pi$ interactions.⁹⁹

A detailed analysis of the relationship of crystal packing with molecular shape has recently been undertaken by Motherwell,¹⁴⁹ however, this work addressed only structures with a single crystallographically independent molecule. However, related work by Pidcock explicitly looked at the effect of molecular shape and packing pattern on $Z' = 2$ structures by employing a “box model” in which the molecular structure is approximated by long, medium, and short dimensions.^{28v} The analysis showed a very similar distribution of packing pattern for both $Z' = 1$ and $Z' = 2$ structures implying that the fundamental rules governing the spatial relationship of molecules are independent of whether they exhibit crystallographic symmetry. However, the $Z' = 2$ structures have more freedom to adopt low surface area packing patterns for a given molecular volume. In general, the strongest intermolecular interactions are found between the largest faces of the independent molecules implying that molecules are fitting together to minimize surface area and emphasizing the importance of molecular shape. The fact that the higher Z' set is somewhat more effective at doing this underlines the fact that it is the molecular chemical nature of intermolecular interactions that drives crystal packing, and not the anthropomorphically imposed restraint of symmetry.

Finally, in a recent fascinating study on soft, porous crystals comprising covalent cages of the type shown in Figure 19,

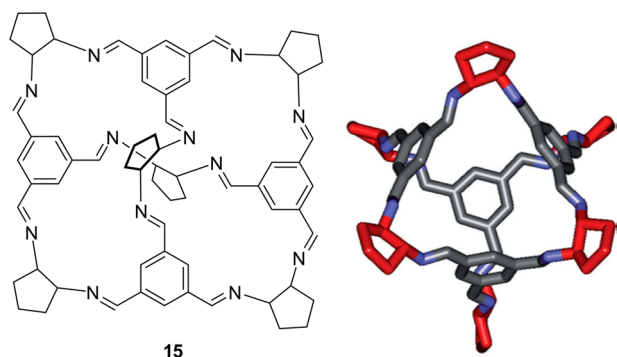


Figure 19. Covalent cage **15** resulting in unique gas sorption properties linked to the formation of shape-frustrated $Z' = 3$ structure. Reproduced with permission from ref 150. Copyright 2011 Wiley-VCH.

Cooper and co-workers have shown that the awkward shape of the cyclopentane derivative (**15**) results in a $Z' = 1$ to $Z' = 3$ transition upon desolvation of the initially formed methanol cocrystal **15**·9MeOH to alleviate steric frustration. The smaller bridging groups in the other derivatives do not result in lowered symmetry on desolvation. The presence of symmetry-independent cages in the empty, porous structure results in unique stepped gas sorption behavior, never before observed for a molecular crystal. This report is one of the first examples of a key materials property being linked to the $Z' > 1$ structure of the substance.¹⁵⁰

5.3. Melts, Mechanochemistry, Sublimation, and Solution – What Is the Growth Unit?

The directional interactions between particular chemical functionalities in conjunction with molecular size and shape, and the requirement to form close-packed structure with optimal intermolecular interactions, are all intrinsic properties of the molecules that are assembled into a crystal structure. Their influence (or otherwise) on the formation of structures with

multiple symmetry-independent molecules should play a part no matter how the crystal is grown. In other words, they relate primarily to the thermodynamic stability of the final structure. In contrast, the circumstances under which a crystal is formed, the crystallization conditions, may also have a significant bearing on the crystallization outcome and hence the solid form obtained. Crystallization is a self-assembly process that occurs in a variety of media (solution, melt, gas-phase sublimation, or mechano-chemically in the solid state) under highly nonequilibrium conditions, with factors such as the degree of supersaturation stabilizing the unfavorable interface between growing crystal nucleus and fluid phase.¹⁵¹ There are two ways in which crystallization conditions may have a bearing. It may be that under the prevailing crystal growth conditions the assembly or growth of the nucleus of a metastable polymorph is favored, resulting in a metastable solid form that can subsequently be transformed into the thermodynamic phase over time or by changes in temperature, pressure, etc. This is the basis for Ostwald's rule of stages, which states that in a polymorphic system it is likely to be the most metastable form that crystallizes first, with increasingly stable forms appearing over time, particularly as the degree of supersaturation (and hence interfacial stabilization) diminishes, for example.¹⁵² More speculatively, the crystallization conditions may also favor some kind of fluid phase assembly that passes intact into the crystal structure. This view has been suggested by Kuleshova et al., who state that loss of symmetry when a crystal is formed from strongly associated aggregates rather than from isolated molecules results from “small displacements of the fragments with respect to one another to form close packing.”¹⁰⁰ These displacements may also explain the occurrence of pseudosymmetry in $Z' > 1$ structures. Structures based on this preformed “growth unit” may or may not possess a mechanism to transform into a different, more stable structure. The observation that high Z' structures often possess “better interactions” (shorter, straighter hydrogen bonds, for example) but can exhibit lower density has stimulated a conception that high Z' structure may thus arise from discrete preassociated aggregates and may be less stable than a putative (or real) $Z' = 1$ thermodynamic form. The structural arguments put forth for monalcohols in section 4.2 and regarding frustration in section 5.1, coupled with the fact that a considerable number of $Z' > 1$ forms are in fact the most thermodynamically stable polymorphs (as has been convincingly demonstrated for napafenac, for example^{28r}), mean that this crystallization-conditions-based argument cannot be true in all cases,^{28e,45b} however, it may well be true in some cases, and in this section we look at how crystallization conditions can influence the Z' value.

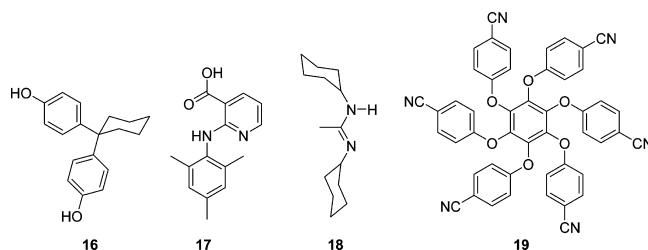
This focus on conditions is effectively a consideration of nucleation and growth effects, as distinct from effects relating to the stability of the final crystal. Nucleation is an extremely poorly understood phenomenon. Classical nucleation theory describes the association of a few molecules (tens to hundreds) to form an unstable precritical nucleus in which the unstable fluid interface is stabilized by a supersaturation gradient. Once this precritical nucleus grows to a certain critical size, growth becomes thermodynamically downhill in free energy terms as the stable molecules fully packed in the volume of the growing crystal begin to dominate over the unstable surface molecules. This simplistic picture (which can overestimate nucleation rate by up to 10 orders of magnitude¹⁵¹) neglects many features of real systems, and recent advances have modified this classical picture considerably. Two-step nucleation describes nucleation as

occurring in a transient metastable, dense liquid phase bearing little resemblance to the final crystal structure.¹⁵³ Nucleation via a solution to crystal spinoidal (defined as a phase boundary in which the nucleation barrier disappears and the rate of generation of a new phase is limited only by cluster growth kinetics) also allows nucleation to be far more quantitatively modeled.¹⁵¹ Aside from primary nucleation, Bernstein has also pointed out how little is known about what he terms the “critical nucleation that occurs after nucleation”,^{19a} the formation of emergent structures such as growth spirals necessary for crystals to grow under the kinds of supersaturations found in real systems. While there is some very interesting information on crystal growth and polymorphic transformation processes coming from high-resolution AFM, for example,¹⁵⁴ the current understanding of nucleation phenomena is a long way from being able to predict structural characteristics such as the occurrence of symmetry independent molecules. However, we can look empirically at the structural outcome of varying crystallization conditions.

In 2006, the Nangia group noticed that melt crystallization of 1,1-bis(4-hydroxyphenyl)cyclohexane (**16**) resulted in a metastable polymorph with $Z' = 2$, while sublimation resulted in the thermodynamically stable form with $Z' = 1$.¹⁵⁵ Similar results were obtained by us in 2002 on the two forms of Ph_3GeH , which crystallizes in a metastable $Z' = 2$ form from the melt but gives the stable $Z' = 1$ form upon warming or from solution.¹⁵⁶ Melt and sublimation crystallization are particularly important techniques if the formation of cocrystals or solvates is to be avoided, especially in the case of awkwardly shaped molecules with a tendency to form inclusion compounds. Because cocrystal structures display a significantly reduced tendency to exhibit multiple independent molecules, it follows that eliminating the possibility of cocrystal formation may result in an enhanced tendency to give high Z' (see section 7 for further discussion). The Nangia group undertook a systematic survey of crystals prepared by melt and sublimation methods and showed that the incidence of $Z' > 1$ structures is higher for crystals prepared by both sublimation and melting methods with the preference being quite dramatic for $Z' \geq 3$. For example, 13 structures out of 334 formed $Z' \geq 3$ by sublimation (3.89%), while the number was 6 out of 83 (7.23%) from a melt phase. This compares to 1.24% for the CSD average for organic compounds prepared in conventional ways such as solution crystallization. Nangia and co-workers attributed this difference to the formation of gas-phase clusters upon condensation. The high effective concentration of the melt phase may also be a significant factor. They noted that slower cooling of sublimed samples allowed time for the thermodynamic $Z' = 1$ form to be produced. In the case of triphenyl germane, we similarly suggested the formation of preassociated 6-fold phenyl embraces in the melt giving the $Z' = 2$ form, which transformed to the $Z' = 1$ form that benefits from long-range dipolar interactions in the crystal.¹⁵⁶

Another interesting example is the well-studied carbamazepine, which exhibits three polymorphs with $Z' = 1$ grown from solution, while the $Z' = 4$ form I is obtained from the melt.¹⁵⁷ The recently discovered carbamazepine form V is grown epitaxially from solution on dihydrocarbamazepine and is also a $Z' = 1$ structure.¹⁵⁸ However, an exhaustive polymorph screen of 2-(mesitylamino)nicotinic acid (**17**) showed that the $Z' = 2$ form I, which is obtained from the melt and by sublimation, is in fact the thermodynamically stable form and is the product of heating or subliming the $Z' = 1$ forms II and III.¹⁵⁹ Form I is not obtained by grinding the other forms in a nonpolar solvent but results easily

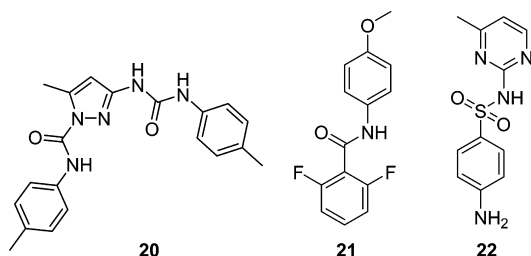
from liquid assisted grinding together with a drop of a polar solvent. Similarly, the helical $Z' = 6$ structure of (*E*)-*N,N'*-dicyclohexylacetamidine (**18**) was obtained from sublimation as part of the experiments aimed at metal organic chemical vapor deposition synthesis. It is tempting to link the sublimation synthesis with the high Z' structure; however, the authors were unable to find any alternative lower Z' polymorph and concluded that the molecule exhibits packing difficulties because of its irregular and non-self-complementary molecular shape, a number of molecular conformations of similar energy, and “frustration between close packing of the cyclohexyl groups of the chains and the N–H...N intermolecular interactions.”¹⁶⁰ Barbour and co-workers have explored the idea of nonsolution crystallization of a well-known inclusion-compound forming hexahost (**19**) and isolated a total of four polymorphs from the melt, two with $Z' = 0.5$ and two exhibiting “wasted symmetry” with $Z' = 1$. Interestingly, they concluded that one of the $Z' = 1$ polymorphs is the most stable despite it not possessing the lowest Z' value.¹⁶¹



A key question in considering whether fluid phase aggregation has any role to play in the polymorphic outcome of the crystallization process is whether intermolecular interactions in the liquid or gas precursor phase are sufficiently strong or long-lasting to result in meaningful concentrations of the aggregate species. Techniques for measuring intermolecular interactions are well established, for example, using NMR spectroscopy, isothermal titration calorimetry, spectrophotometry, etc.¹⁶² In solution, equilibrium association constants for hydrogen-bonded species, for example, can indeed be quite significant, and appreciable concentrations of species such as hydrogen-bonded dimers can be readily detected. Importantly, crystallization does not occur at equilibrium, however, but in a supersaturated regime (or in the case of the melt, at very high effective concentration at the point of phase transition), and as a result there is a stabilization of any kind of intermolecular association by the supersaturation gradient. Hence, even relatively weak intermolecular interactions may well be significant. In his entertaining perspective, Bernstein recounts the anecdote of his own initially unsuccessful attempts to isolate the low melting metastable polymorph of benzophenone.^{19a} In desperation, the 1910 Ph.D. thesis of Schaeling was consulted, which revealed the need to heat molten sample at 230 °C for 10 days followed by quench cooling in liquid nitrogen. Periods of less than 10 days were insufficient. The implication is that it takes this very long period of time to break up seeds or aggregates of the competing stable form. Certainly work on isomorphic seeding of phenobarbital melts has shown that the melt phase is highly susceptible to the influence of pre-existing aggregates such as secondary or heteronuclei.¹⁶³

A simple illustration of the role of solution speciation comes from the polymorphism of 2,6-dihydroxybenzoic acid, which crystallizes as a hydrogen-bonded dimer containing form from the relatively nonpolar solvent toluene, and as a catemer from

chloroform. It is suggested that the relatively polar chloroform inhibits dimer formation, and indeed toluene solutions are found to be dimer rich.¹⁶⁴ Similarly, the “Janus” molecule **20** crystallizes in an “open” form based on the urea α -tape motif from methanol, whereas from chloroform a very different closed conformational polymorph with an intramolecular hydrogen bond is isolated.¹⁶⁵



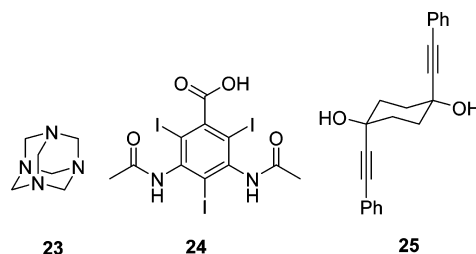
The analogy between solution-phase association and crystal structure has been probed by Hunter and co-workers who used ¹H NMR contact induced shifts over a wide concentration range to derive the solution structure of amides **21** and **22** and their self-association constants. The solution structures matched the hydrogen-bonded dimers observed in the solid state with rmsd values of 0.3–0.44 Å, suggesting that the NMR data give an indication of the kinds of aggregates that may be present in solution pre-nucleation. For **22**, for example, self-association constants are quite modest at 16 M⁻¹ in acetonitrile and 3 M⁻¹ in acetone, giving rise to a nevertheless significant maximum percentage bound of 32% and 20%, respectively, at the concentrations studied. More recently, a detailed study on the solution association of tolfenamic acid has shown that conformational change in solution of the tolfenamic acid molecules is a prerequisite for their dimerization to strengthen intermolecular interactions, and this factor has a bearing on the polymorphic outcome.¹⁶⁶

In conditions slightly closer to real crystallization, Davey and co-workers have used small-angle neutron scattering coupled with empirical potential structure refinement (EPSR) to examine the structure of supersaturated methanolic solutions of benzoic acid.¹⁶⁷ In the crystalline state, benzoic acid can adopt either a hydrogen-bonded dimer or an infinite chain motif. The neutron data in solution suggest that the carboxylate group interacts with a total of two methanol molecules and one other benzoic acid group in a chain-like fashion. In total, each molecule is surrounded by nine methanol molecules and five benzoic acid molecules in a micelle-like structure, although the hydrogen-bonded dimer motif is absent. Clearly the progression from this solvated cluster to a crystal requires considerable rearrangement accompanied by desolvation. Such a process is somewhat reminiscent of two-step nucleation theory.¹⁵³ Analogous neutron scattering studies on hexamethylene tetramine (**23**) give rise to correlations between the molecules of **23** that resemble the pure body-centered cubic solid, while the water interactions with **23** resemble the hexahydrate.¹⁶⁸

Davy and co-workers have also used synchrotron in situ SAXS and WAXS to study the formation of pre-nucleation aggregates in sunflower seed oil, benzamide melts, *p*-azoxyanisole melts, and supersaturated aqueous solutions of urea, sucrose, and citric acid. The aqueous solutions showed no evidence of long-range ordering prior to the appearance of crystals, which the authors point out is consistent with the “accepted stochastic nature of the nucleation process from solution media in which critically sized domains of structure form from a disordered liquid state.” Their data do not rule out the presence of local order in a small volume

of a separate phase. In contrast, the single component melts provided evidence for the appearance of short-lived metastable crystalline and liquid crystalline states indicating precrystalline molecular assembly. This allowed the characterization of a new highly metastable form of benzamide and also showed that liquid crystal ordering for *p*-azoxyanisole is an essential precursor to the formation of a metastable crystal structure.¹⁶⁹

Work in our own group has resulted in the isolation of crystals of three DMSO solvates of the imaging agent diatrizoic acid (**24**). As the DTA:DMSO ratio decreases from 4:1 to 2:1 to 1:1, the structures show a progression from interactions from the carboxylic acid and amide groups purely to DMSO oxygen atoms to increasing association between the DTA molecules themselves. The strongest interaction to solvent (that from the carboxylic acid) is retained in all of the solvates. This leads to speculation that intermolecular association may be guided initially by weaker interactions, while more strongly interacting functional groups remain solvated until a relatively late stage in the desolvation process.¹⁷⁰



Desiraju and co-workers have singled out the polymorphism of pentafluorophenol as an indication of the appearance of a metastable high Z' structure as a result of solution aggregation factors. The $Z' = 3$ polymorph exhibits a very unusual discrete hydrogen-bonded trimeric chain terminated by OH...F interactions. It is only obtained by freezing the liquid in the presence of pentafluoroaniline and is calculated to be significantly less stable than the $Z' = 1$ infinite chain structure that is obtained from the pure liquid. There is no evidence that the $Z' = 3$ structure converts into the $Z' = 1$ structure, and so it is a candidate for a “fossil relic” of the nucleation process. However, a seeding role or formation of a solid solution with the aniline cannot be ruled out and complicates the interpretation of this unusual structure.¹⁷¹ In the same work, the authors also considered the diol **25**, which exists as two polymorphs with $Z' = 2$ and 8. The high Z' form crystallizes directly from the melt and transforms irreversibly to the low Z' form, suggesting that the high Z' form may be a step on the way to the low Z' form. No even more symmetric $Z' = 1$ form has been discovered. A search of the CSD revealed 17 other pairs of polymorphs with the lower Z' structure having the lower energy in 11 cases, the energies being the same in two cases, and the high Z' structure being the more stable in four cases.

Work on the relationship between solution speciation and nucleation, and its relevance to crystal structure remains highly challenging and is beyond the scope of the present work to review in detail. The current state of the art has been recently reviewed by Davey et al.^{20,172}

5.4. Effect of Temperature and Pressure

In a very elegant paper, Johnstone et al. have taken a holistic view of the thermodynamics of the phase behavior of a solid.^{28a} They point out that the overall free energy of the system (G) is given by eq 1, where U is the internal energy, P is the pressure, V is the

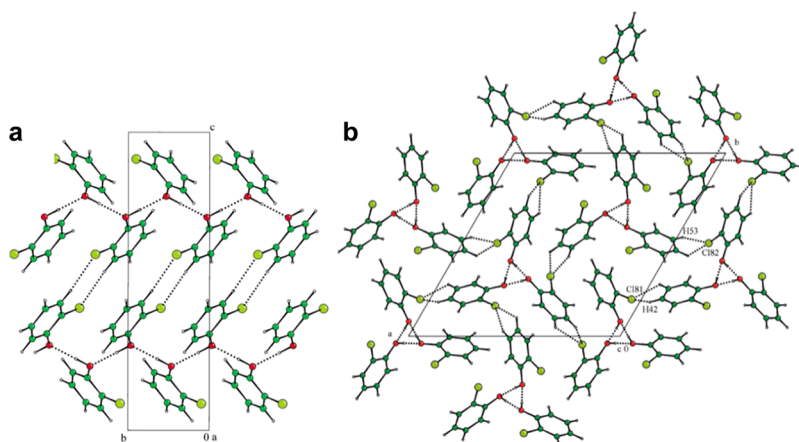


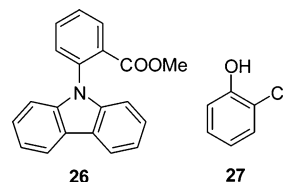
Figure 20. Crystal structures of 2-chlorophenol at (a) 0.12 GPa ($Z' = 1$) and (b) ambient pressure ($Z' = 3$). The application of pressure has changed the steric effect of the chlorophenyl substituent from a large group to a small group. Reproduced with permission from ref 174. Copyright 2005 American Chemical Society.

volume, T is the thermodynamic temperature, and S is the entropy.

$$G = U + PV - TS \quad (1)$$

The internal energy contains contributions from the molecular conformational energy and the crystal packing. The PV term implies that changes in pressure may affect the volume of the system and hence the molecular volume and packing coefficient, while change in temperature will affect the relative importance of the entropic contribution. Within the context of high Z' crystal structures, at low pressures small differences in the molecular conformation and hence molecular volume as well as rather “loose” packing that optimizes intermolecular interactions can be accommodated. As the pressure increases, however, the overall density of the packing becomes dominant, and hence application of pressure (particularly the kinds of very high pressure accessible in a diamond anvil cell¹⁷³) should select conformers that are consistent with efficient packing and are more similar to one another, reducing Z' . Johnstone and co-workers tested this hypothesis using the $Z' = 8$ structure of methyl 2-(carbazol-9-yl)benzoate (**26**). Compound **26** adopts a range of slightly different conformations at 150 K within 6 kJ mol^{−1} of one another in energy. Raising the pressure to 4.9 GPa resulted in a compressed form of the ambient pressure structure, which involves pseudosymmetric molecular pairs; however, at 5.3 GPa the material undergoes a fully reversible phase transition to a $Z' = 2$ form with formerly pseudo- 2_1 symmetry becoming an actual space group symmetry element. Overall, however, the high pressure solid form is quite different. The molecular conformational energy in the new form is considerably less stable than the ambient pressure form; however, the phase is more efficiently packed even allowing for the effect of increased pressure. Upon lowering the pressure, the molecules “spring back” to the original form. The pressure-induced phase change is thus fully reversible. The authors argue that this system demonstrates that high Z' structures can represent a genuinely thermodynamically favorable crystalline form.^{28a} Change in pressure also affects the polymorphic form of 2-chlorophenol (**27**), which adopts a $Z' = 3$ form under ambient pressure and low temperature but transforms to a $Z' = 1$ form at 0.12 GPa and room temperature. This result is interesting from the point of view of the high incidence of $Z' > 1$ structures of monoalcohols, and it is suggested that the application of pressure transforms the behavior of the chlorophenyl group from a large group to a

small group, allowing 2_1 symmetric packing instead of the formation of a 3_2 helix, Figure 20. The observed crystal structures were correctly calculated as being the most stable using an empirical potential crystal structure prediction method, and hence it seems likely that the high Z' structure is the most stable at ambient pressure.¹⁷⁴



In an elegant comparison, Ridout and Probert have recently used in situ crystallization to obtain both low temperature and high pressure polymorphs of the secondary monoalcohol isopropanol, a common laboratory solvent.¹⁷⁵ The low temperature form adopts a 3-fold helical packing arrangement with $Z' = 3$ and relatively linear hydrogen bonds, while the $Z' = 4$ structure at 11.2 kbar comprises discrete hydrogen-bonded octamers with more bent OH...O angles (Figure 21). The work of Taylor and Macrae¹¹⁰ showed that hydrogen-bonded chains and rings are more or less equally likely for secondary alcohols, and this trend is certainly represented in the two structures. The low

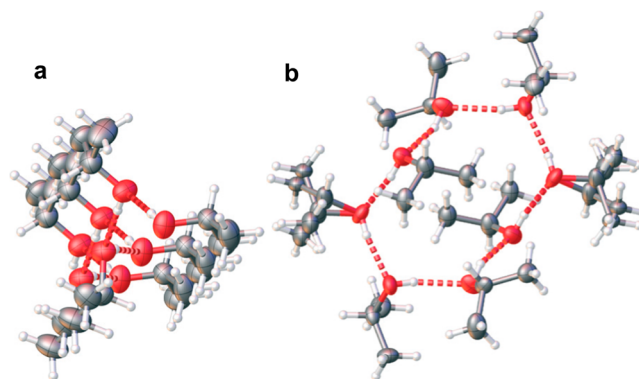


Figure 21. Crystal packing in isopropanol: (a) 3-fold helical packing in the $Z' = 3$ low temperature structure, and (b) a discrete octamer in the high pressure structure. Reproduced with permission from ref 175. Copyright 2014 Royal Society of Chemistry.

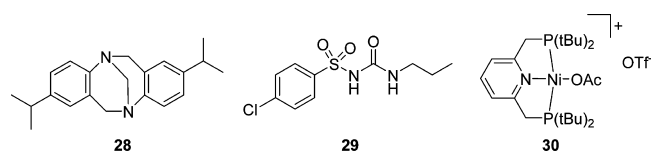
temperature form adopts a rather low density of 0.958 g cm^{-3} , while the high pressure form is more densely packed (1.131 g cm^{-3} , bearing in mind that density increases significantly for most high pressure structures). The effect of pressure would seem to favor the more efficiently packed polymorph with less optimal hydrogen bonds. However, in this case, there is no drive toward increased symmetry, nor any change in space group (both are $P2_1/c$).

Even without conventional strong hydrogen bonds, the interactions of the $\text{C}\equiv\text{C}-\text{H}$ unit in phenylacetylene coupled with crystal packing requirements can generate high Z' structures. The $Z' = 2.5$ and 6 α - and γ -forms are produced by slow, and rapid cooling, respectively,¹⁷⁶ and both involve $\text{C}\equiv\text{C}-\text{H}\cdots\pi$ interactions with the alkyne triple bond π -electron density, in combination with alkyne $\text{CH}\cdots\pi_{\text{aromatic}}$ interactions.¹⁷⁷ The β -polymorph is produced at high pressure and is an ordered version of the α -form with very similar packing but an increased c unit cell axis that allows enough space for a single disordered molecule in the α -form to be replaced by two ordered molecules related by an inversion center.¹⁷⁸

The effect of changing temperature on a crystal is studied far more frequently than changing pressure for practical experimental reasons.¹⁷³ In thermodynamic terms, changes in temperature affect the relative weighting of the entropy component of the free energy. Increasing temperature may also provide sufficient thermal energy to irreversibly transform a metastable polymorph in a monotropic system into the most thermodynamically stable polymorph.¹⁷⁹ Of course in an enantiotropic pair of polymorphs the order of stability switches at a particular transition temperature.⁴ In the context of metastable crystals, we have described notional metastable polymorphs that do not readily transform into a (perhaps undiscovered) thermodynamic form, as a “fossil relic” of the fastest growing crystal nucleus.^{22b,45b} To us at least, this is an appealing piece of language because it implies that such a crystal is in some sense trapped in a state derived from its formation conditions as a result of either some kind of solution or melt aggregation or some stability or structure of the precritical crystal nucleus. Such strong kinetic trapping is one possible factor in the formation of metastable polymorphs, which might show strong directional intermolecular interactions without being as burdened by the increasing importance of close packing as the nucleus, and ultimately crystal, grows larger. It has been pointed out that because little is known about the structure of the crystallization nucleus, this kind of term is almost impossible to confirm or refute,^{22a} a view we have considerable sympathy with. Certainly the existence of many pairs of polymorphs with high and low Z' values in which the higher Z' structure is the most stable automatically implies that this kind of hypothetical locked

memory of some precrystallization state is by no means the only explanation of the observation of multiple independent molecules in the asymmetric unit, but it is one of many explanations that not only warrant consideration but may be relevant in some particular crystals.^{28e,45b} In an interesting insight into this issue, Nichol and Clegg compared the incidence of $Z' > 1$ in synchrotron structures with those determined by neutron radiation.^{28d} They postulated that because of the accessibility and relative intensity of the two different radiation sources, synchrotron structure determination is often undertaken on poor quality crystals that are in some sense “incompletely crystallized”, while neutron studies tend to occur on slowly grown, high-quality samples. Indeed the synchrotron data set showed a significantly higher percent of $Z' > 1$ of 13.5% as compared to 5.1% for neutron data. The sample size is small, however (less than 0.25% of the CSD), and other sociological reasons and sample environment issues are difficult to control, not least the fact that neutron studies are always undertaken on known unit cells and hence known Z' , and are sufficiently challenging and costly that researchers may well shy away from determinations involving two independent molecules. Interestingly, the synchrotron percentage drops to 8.2% for metal-containing structures (a drop reflecting the trend in the CSD as a whole), while the neutron percentage remains essentially constant, perhaps reflecting the high incidence of metal hydride structures¹⁸⁰ studied with this technique. Nichol and Clegg along with Desiraju^{28d,e} talk of high Z' structures as being in some sense “a crystal on the way” or “incompletely crystallized”. Bernstein has disagreed with this description and points out that it “defies the very essence of a crystal structure.”^{19a} Without concurring, Bernstein rephrases this notion of the hypothesis of metastability of $Z' > 1$ structures as their being a “structure at a local minimum on the multidimensional potential energy surface on the reaction coordinate towards a proposed (or supposed) structure with $Z' = 1$.” The IUCr online dictionary of crystallography states that “[a] material is a crystal if it has essentially a sharp diffraction pattern.”¹⁸¹ In this sense, high Z' structures are just as completely crystallized as their $Z' = 1$ analogues.

In many cases, high Z' structures may be described as a modulated variant of a lower Z' parent structure, and this phenomenon is responsible for the experience, relatively familiar



to many crystallographers, of additional satellite reflections appearing on cooling a sample. Tröger's base derivative (**28**), for

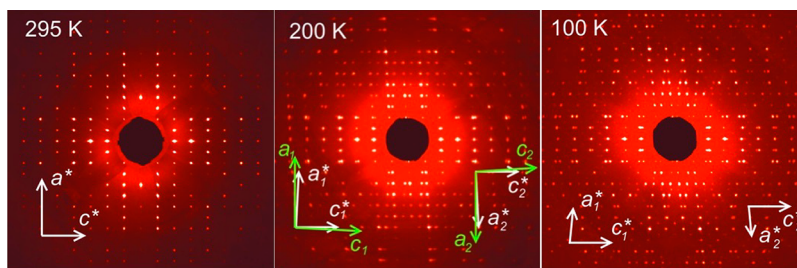


Figure 22. Reciprocal layers $h0l$ of the crystal of chloropropamide at three temperatures, corresponding to the β -, β^{II} -, and β^{III} -forms. Reproduced with permission from ref 182. Copyright 2011 International Union of Crystallography.

example, undergoes a $Z' = 1$ to $Z' = 3$ phase transition on cooling below 130 K. The high temperature structure contains contacts between the disordered iso-propyl groups that are apparently sterically unfeasible as a result of dynamic disorder. The $Z' = 3$ low temperature form may be regarded as a modulation of this parent structure in which the disorder is frozen out, becoming synchronized between different layers of the structure.¹¹⁴ The phase transition is sharp and fully reversible. Calculations with the UNI force field establish that the high Z' form has the most stable lattice energy and the energy difference is offset by the larger $d(\Delta S)/dT$ of the $Z' = 1$ structure as the temperature increases in this enantiotropic pair.

A similar situation is encountered for metastable β -chloropropamide (**29**), which exhibits a cascade of phase changes from $Z' = 1$ to 2 (257 K) and from 2 to 4 (125–150 K), Figure 22.¹⁸² The increasing Z' value is associated with changes in the conformation of the propyl chains in just one-quarter of the molecules in the second phase change. This is the flexible part of the highly hydrogen-bonded chain structure. Interestingly, the change in the unit cell volume is continuous even through the phase transitions, indicating that specific and directional interactions are important in determining stability as well as simply bulk density. Yet more striking is the transition from $Z' = 1$ to $Z' = 6$ in the nickel pincer complex **30**. Upon cooling to around 210 K, the length of the c axis increases 6-fold, and the density and packing coefficient increase. The authors argue that this better packing in the high Z' structure argues against metastability, and the transition is fully reversible.^{28b} It is also suggested that the $Z' = 1$ high temperature structure is an average structure that does not fully account for all of the disorder in the system.

In some cases, the modulation of a structure can be extremely complicated, giving rise to an extended series of satellite reflections. In such cases, the description of the crystal in terms of an increasingly high Z' unit cell may not be the best approximation of the true situation, which may be incommensurately modulated. In such cases, a superspace refinement describing a long-range modulation of a higher symmetry local structure can be the best description.^{11a,183} Because the local environment of each molecule is slightly different across a large number of subcells, such incommensurate cases are closely related to high Z' structures in which the modulation is commensurate. A recently reported example is the structure of 2-chloro-benzo-1,3,2-dithiarsole (**31**), which can be solved and adequately refined in space group $P\bar{1}$ with $Z' = 17$. However, the structure is better described as being incommensurately modulated with the orientation of the C_6S_2 plane varying smoothly, but not in a direction in which the molecules are in contact (Figure 23). The origin of the modulation is thought to be the drive to balance intermolecular interactions, particularly of type $As\cdots Cl$, within and between ribbons.¹⁸⁴

The structure of the hydrogen-bonded cocrystal $[Ni(MeCN)(H_2O)_2(NO_3)_2] \cdot 15\text{-crown-5} \cdot MeCN$ exhibits a remarkable sequence of four phases. The disordered high temperature form I is $Z' = 1/2$ and is stable from room temperature to around 240 K. Below 230 K, the disorder is resolved in the $Z' = 1$ form III, consistent with the frequently observed increase in Z' on cooling. The Z value further doubles to 2 in form IV, which occurs below 145 K. Between forms I and III, in the narrow 238–232 K window an incommensurately modulated form II occurs. The structure seems to bear similarities to both forms I and III. Flash-cooling from room temperature to 90 K gives a metastable material that can be described as being a commensurate $Z' = 5$

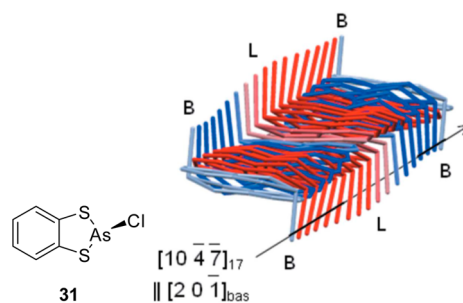


Figure 23. Pattern of small displacements found in the modulated structure of **31**. Reproduced with permission from ref 184. Copyright 2013 International Union of Crystallography.

form that is similar to the structure of phase II.¹⁸⁵ A related example $[Ni(H_2O)_6](NO_3)_2 \cdot 15\text{-crown-5} \cdot 2H_2O$ also passes through a high Z' , likely incommensurate, intermediate phase.^{35a} These structures point to a mechanism of phase transformation in which groups of atoms are required to change their relative position in a nonsimple way.¹⁸⁵ These compounds are further examples of the tendency for [15]-crown-5 complexes to exhibit complex low symmetry crystal packing behavior.¹⁸⁶

While a transition from dynamic behavior to an ordered, modulated structure is a clear way in which Z' can increase, this is by no means the only situation. The interesting $Z' = 12$ structure of 4-ethynyl- N,N -dimethylaniline (**32**) exhibits a reversible, single-crystal to single-crystal, phase transition at around 123 K between two different $Z' = 12$ forms. The reversibility of the phase transition, coupled with the fact that the same solid form is obtained from a variety of crystallization methods including solution and sublimation, implies that the observed enantiotropic pair represents the thermodynamically stable forms of the compound. Both structures exhibit considerable pseudosymmetry; however, the high Z' value appears to arise from the need to pack the molecules closely while retaining the structure-determining alkyne $\equiv CH\cdots C\equiv C$ and $\equiv CH\cdots\pi$ hydrogen bonding along with edge-to-face π -interactions, which give rise to discrete dodecamers in both forms (Figure 24). Indeed a search of the CSD revealed that compounds with terminal alkynyl ($-C\equiv CH$) groups have an enhanced tendency to form high Z' structures (16.0%) as compared both to the CSD as a whole and particularly to those with an internal triple bond (8.7%).¹⁸⁷ The effect is clear in the structures of the three polymorphs of phenylacetylene, for example, which exhibit $Z' = 2.5$, 3, and 6, and the $Z' = 3$ structure of a fluorinated derivative.¹⁷⁷ The origin of the temperature-dependent phase change is unclear in 4-ethynyl- N,N -dimethylaniline; however, it was suggested that the “extensive delocalization provides an entire surface suitable for accepting H-bonds with little preference for what part of the surface is involved”, and that these “simply shift in going from one polymorph to the other.”

As well as increasing on cooling, or remaining the same, Z' can also decrease on cooling, suggesting that some dynamic effect is responsible for lowering the symmetry in the high temperature form. In an extensive survey of polymorphic crystals in which at least one polymorph of a given substance exhibits $Z' > 1$, Bernstein, Dunitz, and Gavezzotti noted that for significantly different (nonmodulated) polymorphs, the polymorph stable at high temperature is likely to have the higher Z' value and that the polymorph obtained may be cooling rate dependent.^{22a} This phenomenon is observed for trimethyltin hydroxide, which changes from 32 to just 1 independent tin atoms upon cooling.

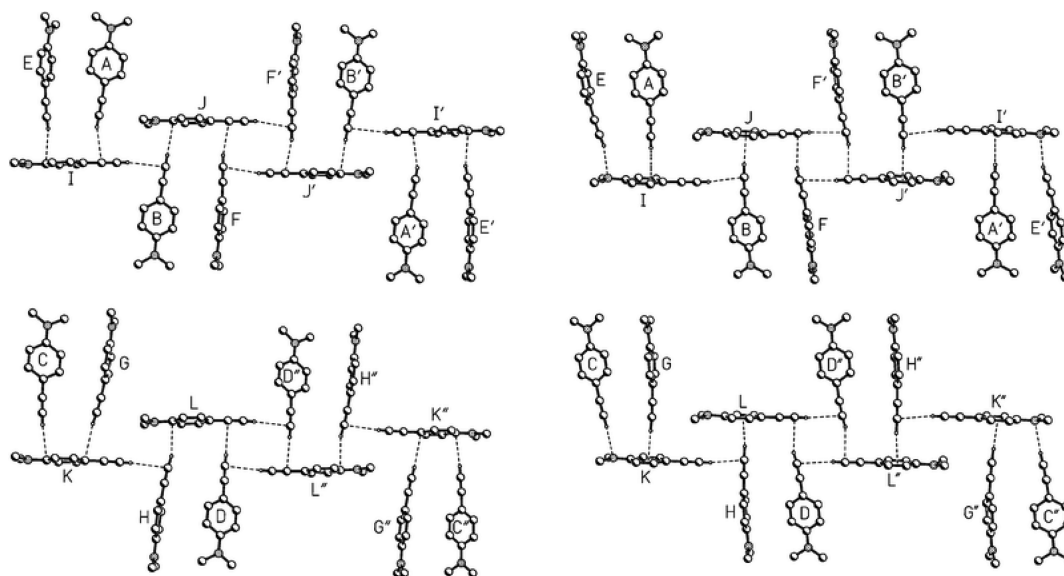


Figure 24. Discrete dodecamers in both polymorphs of 4-ethynyl-*N,N*-dimethylaniline (32). Reproduced with permission from ref 187. Copyright 2006 Royal Society of Chemistry.

This complex case is described in detail in section 7. Another interesting example is the antidepressant drug substance venlafaxine hydrochloride for which a new $Z' = 2$ polymorph (form 6) has recently been obtained by heating the $Z' = 1$ form 2 to 190 °C using a hot stage microscope.¹⁸⁸ The way in which this solid form is obtained has interesting implications for drug polymorph screening because many high throughput screening methods focus on modifying solution crystallization conditions, while methodology for computational structure prediction is relatively poorly developed for $Z' > 1$ structures.³¹ It was concluded that form 6 is the thermodynamically most stable form of the substance. The energy-temperature diagram for venlafaxine hydrochloride is shown in Figure 25, which implies an enantiotropic relationship between the high melting form 6 and forms 1 and 2; however, the formation of form 6 is irreversible upon cooling to room temperature, suggesting a very large back interconversion barrier. This late appearance of the thermodynamic form is consistent with Ostwald's rule of

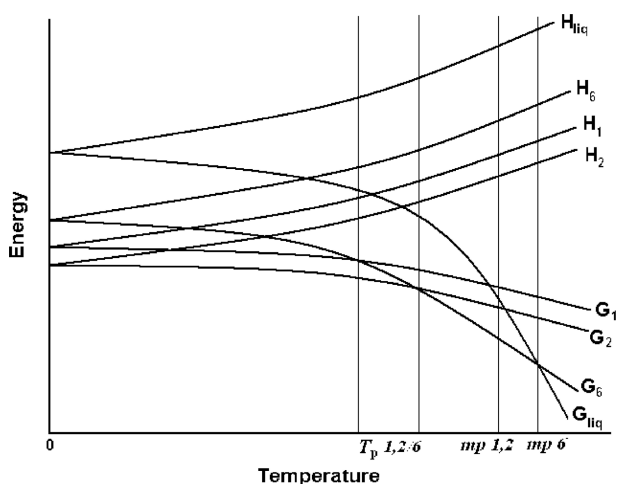


Figure 25. Energy versus temperature diagram for venlafaxine hydrochloride forms 1, 2 ($Z' = 1$) and 6 ($Z' = 2$). Reproduced with permission from ref 188. Copyright 2007 American Chemical Society.

stages.^{152,189} The stability of form 6 was rationalized as arising from a transition from parallel ladders to a 2D brick wall structure resulting in a more compact arrangement of hydrophobic layers with considerable interlocking.

6. THE VERY HIGHEST Z' STRUCTURES

There is something intrinsically fascinating about structures with extremely large Z' values, because of both the technical difficulty in solving and refining them and the immediate speculation they engender as to why they have such dissymmetric packing arrangements. The February 2014 version of the Cambridge Structural Database (CSD)⁹⁵ shows only 55 unique structures with $Z' \geq 10$, only 39 of which have full 3D coordinates, are not polymeric, and are not recorded as having any "errors" (numbers updated from ref 190), and not all of these structures withstand detailed scrutiny.²⁹ Indeed in 2005 Brock and co-workers listed only nine structures with $Z' \geq 10$ that seemed to be reliable,²⁸ⁿ although this number has grown significantly since then. The small subset of structures that crystallize with very large Z' values represent the most extreme examples of the $Z' > 1$ phenomenon, and examination of the chemical and crystallographic details of these compounds in particular could lead to new insights into crystal packing and crystal growth phenomena.⁹¹

Our own interest in the field began with the observation of the striking trigonal diffraction pattern of the $Z' = 16$, $Z'' = 32$ cocrystal $[\text{UO}_2(\text{OH}_2)_3\text{Cl}_2] \cdot 15\text{-crown-5}$ (33) back in the summer of 1997, shortly after taking delivery of one of the then relatively new CCD diffractometers.³⁹ The presence of the heavy uranium atoms distinctly assisted with the solution and refinement of this challenging structure, which adopts space group $P3_2$ with a unit cell volume of over 23 000 Å³, a structure that we would very likely not have attempted to determine on a point detector system. While the asymmetric unit is a 4×4 array (Figure 26a) and hence suggests that it may be a pseudosymmetric or modulated version of a higher symmetry structure, a detailed analysis revealed that the orientation of the components and the hydrogen-bonding distances from the aqua ligands to the crown ether oxygen atoms are all quite unique. This observation is consistent with the general view that high Z' structures tend to be of lower density but have shorter ("better") intermolecular

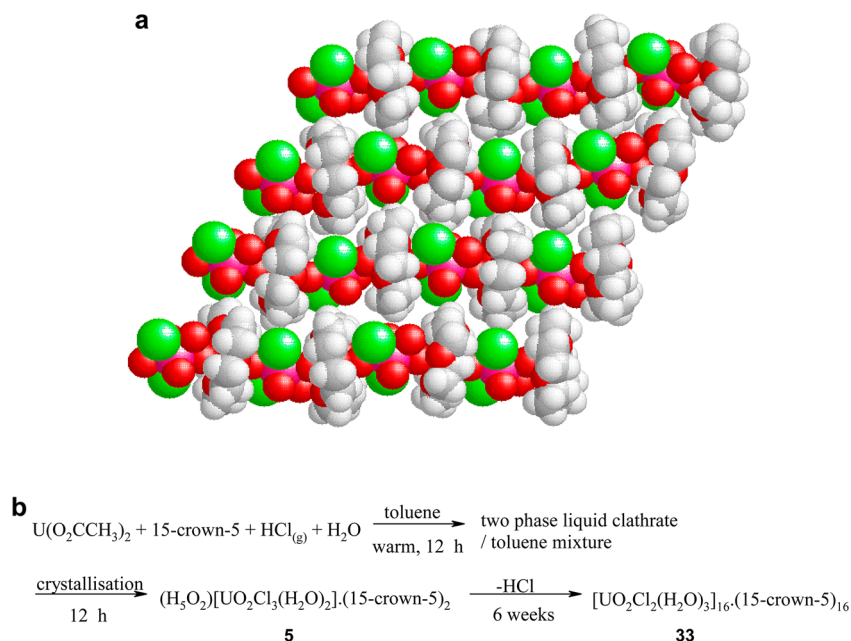


Figure 26. (a) Asymmetric unit of the $Z' = 16$, $Z'' = 32$ cocrystal $[\text{UO}_2\text{Cl}_2(\text{H}_2\text{O})_3] \cdot 15\text{-crown-5}$ (**33**).³⁹ (b) Crystallization procedure for **33** via **5**.

directional interactions such as hydrogen bonds.^{28e,128} As a result, we rationalized the $Z' = 16$ structure as arising for structural reasons related to the optimization of the multiple hydrogen-bonding interactions along the hydrogen-bond polymeric chain and the dissymmetric nature of the 15-crown-5 hydrogen-bond acceptor. Indeed it turned out that other metal aqua complex cocrystals with 15-crown-5 also display high Z' behavior such as the $Z' = 4$ structure of $[\text{Er}(\text{NO}_3)_3(\text{H}_2\text{O})_3] \cdot (15\text{-crown-5}) \cdot \text{H}_2\text{O}$.¹⁸⁶ Despite this structural explanation, however, a particularly intriguing aspect of the structure of **33** is its preparation, which involved the very slow loss of HCl from the precursor oxonium complex **5** over a period of 6 weeks within a liquid clathrate medium (Figure 26b). Had this very gradual crystallization process allowed the structure to form optimal interactions of low symmetry?

Compound **33** is one of a total of just nine unique $Z' = 16$ structures in the CSD as of February 2014. Perhaps the most studied are the structures of cholesterol and cholesterol monohydrate.¹⁹¹ As a monoalcohol with a bulky, asymmetric, lipophilic steroidal substituent, cholesterol is typical of the class of monoalcohols identified by Brock and Duncan as being particularly susceptible to the adoption of either very high symmetry space groups or high Z' packing arrangements depending on the substituent groups.¹⁰⁷ The explanation of these special packing considerations lies in the tendency of the OH groups to form rings or chains in which the short $\text{O} \cdots \text{O}$ separation of around 2.8 Å must be accommodated by the steric demands of the substituents. Cholesterol also forms several other related polymorphs with $Z' = 8$, and the structures exhibit considerable pseudosymmetry, which has been the subject of detailed analysis.¹⁹¹

Another $Z' = 16$ structure is the sodium salt of saccharin “dihydrate”, relatively recently reported by both the groups of Desiraju and Naumov.¹⁹² The $Z' = 16$ designation strictly only applies to the sodium and saccharin anion portion of the structure. The structure comprises “regular” and “irregular” regions held together by hydrogen bonds and $\text{Na} \cdots \text{O}$ interactions. The asymmetric unit contains 16 saccarinates (15 ordered and 1 disordered over two sites), 16 sodium ions (13

ordered and 3 disordered over two sites each), and 30 water molecules. A total of 26 water molecules are ordered, while the remaining four water molecules are disordered over two sites each. The challenges in this structure meant that it was not determined for 125 years following its isolation, even though it is a bulk commercial product. The low symmetry of the asymmetric unit led Desiraju’s group to propose the system as a model for the nucleation process, although it is a fully periodic, infinite crystalline solid.^{192a} The parallel work by the Naumov group showed that the full $P2_1/n$ ($Z = 64$, $Z' = 16$) structure can be described as an “occupational and displacive modulation” of an idealized $C2/m$ ($Z = 8$, $Z' = 1$) structure. The modulation was attributed to structural misfit between the components.^{192b}

In a 2012 report, Görbitz and co-workers determined the $Z' = 16$ structure of the amino acid *l*-tryptophan for the first time (VIXQOK).¹⁹³ The fact that this well-known compound had resisted structural characterization for so long is perhaps because of its low symmetry crystal packing arrangement. The crystal is a conformational isomorph with two groups of eight molecules exhibiting either *gauche* or *trans* side-chain orientations. The structure comes somewhat close to having hexagonal symmetry and has a packing arrangement similar to that of the analogous racemate, with a lower density and longer hydrogen bonds suggesting it to be less efficiently packed. This lower density is in accordance with Wallach’s rule,¹²² which states that racemic crystals tend to be denser than their chiral counterparts. Interestingly, the structure determination was based on a single sample with an unusual rhombohedral prismatic habit, unrepresentative of the usual thin flake morphology. Both prisms and flakes result from very slow evaporation of acetonitrile solutions and are apparently the same polymorph according to XRPD measurements. The low symmetry packing was attributed to extended pseudosymmetry and the occurrence of two independent types of hydrophobic interfaces in the crystal. No evidence was found for a possible modulated description.

As an aside, a fascinating critical study by Brock, Schweizer, and Dunitz in 1991 showed that Wallach’s original 1895 observation does indeed hold true on average, but only for

enantiomeric pairs that can be resolved (albeit with many exceptions where the racemate is the less dense of the pair). There is no difference in density for chiral crystals and achiral polymorphs that are achiral in solution or rapidly interconvert. Even for resolvable enantiomers, there is a statistical bias because less stable racemates may never be isolated and studied. Brock et al. also note a kinetic factor contributing to the rarity of conglomerate formation because small amounts of the “wrong” enantiomer may inhibit the crystallization of chiral crystals, but not racemates.¹²² A much more recent 2012 study by Dunitz and Gavezzotti based on a comparison of chiral and racemic proteogenic amino acids states that Wallach’s rule does not apply.¹⁹⁴ The data and calculations also suggest that racemates are marginally more stable but that stability increases with decreasing density as a result of improved hydrogen-bonding interactions. On a structural level, the authors also note that the racemates tend to form strong hydrogen-bonded dimers, while chiral crystals are held together by screw-symmetric ribbons.

Other $Z' = 16$ structures include tricarbonyl[$((1-4-\eta^4)-6\text{-exo-cyano-2-(phenylsulfonyl)-1,3-cyclohexadiene})\text{iron}$], although unfortunately no 3D coordinates are available.¹⁹⁵ The structure is in $P1$, and the molecule contains no obvious strongly interacting chemical functionality. Unfortunately, the remarkable crystallography is not discussed in the paper. The $Z' = 16$ structure of 2,2-aziridine-dicarboxamide¹⁹⁶ is one of two polymorphs, the other in the high symmetry tetragonal space group $P4_12_12$ with $Z' = 4$. The $Z' = 16$ structure is apparently a case of space group assignment error in $P1$ and has subsequently been redetermined in $P1$ with $Z' = 8$.¹⁹⁷ Even with this correction both polymorphs are high Z' structures, a factor that may be linked to their planar hydrogen-bonded sheet structure. The monoclinic ϵ -polymorph of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexa-azatetracyclo-(5.5.0.03,1105,9)dodecane is also reported to have a Z' of 16;¹⁹⁸ however, no coordinates are available in the CSD, and the unit cell length of 102 Å invites careful scrutiny.

The structure of the organopalladium complex $\text{rac-[PdCl-(C}_6\text{H}_3\text{-4-OMe-CHMeNH}_2\text{)(py)]}$ (UNADOD) was understandably reported in 2011 under the title of “one of the most complex “small molecule structures” ever reported”.^{144b} The 16 independent molecules all differ in minor conformational respects. Interestingly, the compound also forms a solvate with acetonitrile with a less remarkable Z' value of 2. The existence of high Z' forms and low Z' solvates/cocrystals is a recurring theme, and the two extremes represent alternative solutions to the molecular packing problem (section 7).⁴² The authors also point out that the existence of a number of conformations of similar energy and the quasiracemic nature of the material may also be contributing factors (however, see section 5.2, which points out the high Z' structures tend to be formed by more rigid molecules).

Sixteen is by no means the largest Z' value in the CSD, and there are two well-determined structures with $Z' = 18$. The structure of $(\text{bis}(\text{tris}(t\text{-butoxy)silyloxy})\text{boryloxy})\text{-bis}(\eta^5\text{-cyclopentadienyl})\text{-methyl-zirconium}$ (HUVLAL) was reported by the Tilley group in 2003.^{144a} The value of 18 suggests that the structure is unlikely to exhibit pseudosymmetry, and indeed each molecule in the asymmetric unit has a unique conformation or orientation, rather like $\text{rac-[PdCl(C}_6\text{H}_3\text{-4-OMe-CHMeNH}_2\text{)(py)]}$. Interestingly, this is another case where the high Z' crystals were produced by very slow crystallization over several weeks, in this case at -30°C . The ϵ -polymorph of the energetic materials precursor picryl bromide (ZZZVXQ06) also exhibits $Z' = 18$ and is one of five polymorphs of the material, all of them with Z'

values of three or more.¹⁹⁹ All of the structures have a common “triad” motif, consisting of $\text{C-H}\cdots\text{O}$ hydrogen bonds and $\text{N-O}\cdots\text{Br}$ dipole-induced interactions. The differences between the polymorphs come down to the orientation of sheet-to-sheet alignments. Interestingly, all five polymorphs were isolated concomitantly from the same vial provided by the Naval Surface Warfare Center,¹⁹⁹ and subsequent attempts to repeat the crystallization have only resulted in the $Z' = 3$ α -form, suggesting perhaps a role of impurities in influencing polymorphic outcome, as has been observed for Ph_3GeCl .²⁰⁰

The remarkable $Z' = 20$ structure of $N'-(2-(4\text{-bromophenyl})-2\text{-vinylcyclobutylidene})-4\text{-methylbenzenesulfonylhydrazide}$ (VUJBAE) is in space group $P1$; however, the compound is a resolved chiral substance with the crystallographic work aimed at establishing absolute configuration so a space group error seems unlikely.²⁰¹ The original paper, which is focused on catalysis, offers no comment on the structural chemistry. Inspection of the structure shows that the sulfonamide groups are linked together by an eight-membered hydrogen-bonded ring that is twisted slightly out of planarity by steric demands and by the formation of a bifurcated donor interaction to an additional molecule, Figure 27. There are also a number of $\text{CH}\cdots\pi$ interactions and

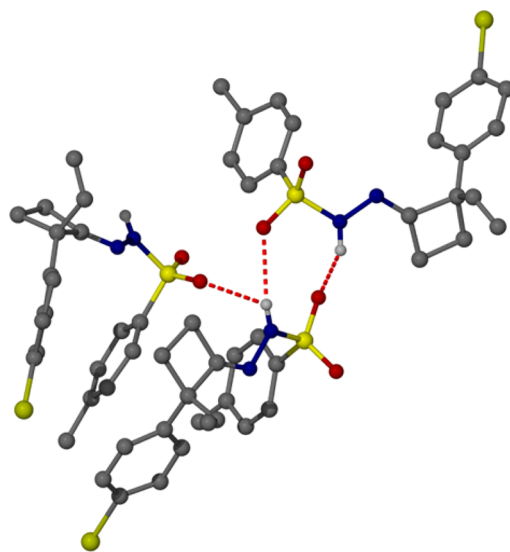


Figure 27. (a) Bifurcated hydrogen bonding in the $Z' = 20$ structure of $N'-(2-(4\text{-bromophenyl})-2\text{-vinylcyclobutylidene})-4\text{-methylbenzenesulfonylhydrazide}$.²⁰¹

some disorder of the vinyl group. Very minor conformational variations suggest that like many other high Z' structures, the optimization of hydrogen bonding and close-packing considerations is a starting point to explain the very high Z' value.

For the other reported determinations in the CSD with Z' values beyond 18, there are issues with several structures including the highest reported value of 32 for trimethyltin hydroxide, as discussed in detail below. The $Z' = 19$ assignment for poly((S),(R)-5-methyl-1-heptene) refers to the number of covalent monomer units in a covalent polymer chain. The $Z' = 20.5$ structure of (1 R ,6 R ,10 R ,11 S ,12 R)-6-acetoxy-10,12,16-trihydroxydolaballa-3 Z ,7 E -diene (BEWZEI) is flagged in the CSD as having suspected errors in the unit cell and Z' value, and there appears to be a typographical error in the original paper,²⁰² and the true Z' value is 2 or perhaps 1.5.^{144a}

The organometallic complex $(\eta^2, \eta^2\text{-cyclo-octa-1,5-diene})\text{-(}(S\text{)-2-(1,1-diphenylethyl)-4-(2-(bis(2-methylphenyl)-$

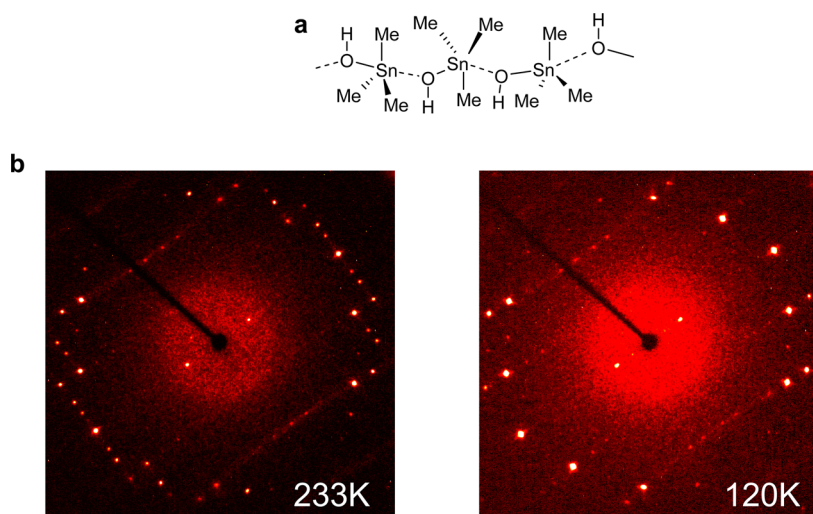


Figure 28. (a) Structure of SnMe_3OH in the solid state; (b) rotation photographs of Me_3SnOH at 233 and 120 K showing disappearance of satellite peaks and collapse of the $Z' = 32/4$ structure to the $P2_1/c$ $Z' = 1$ form. Reproduced with permission from ref 190. Copyright 2011 American Chemical Society.

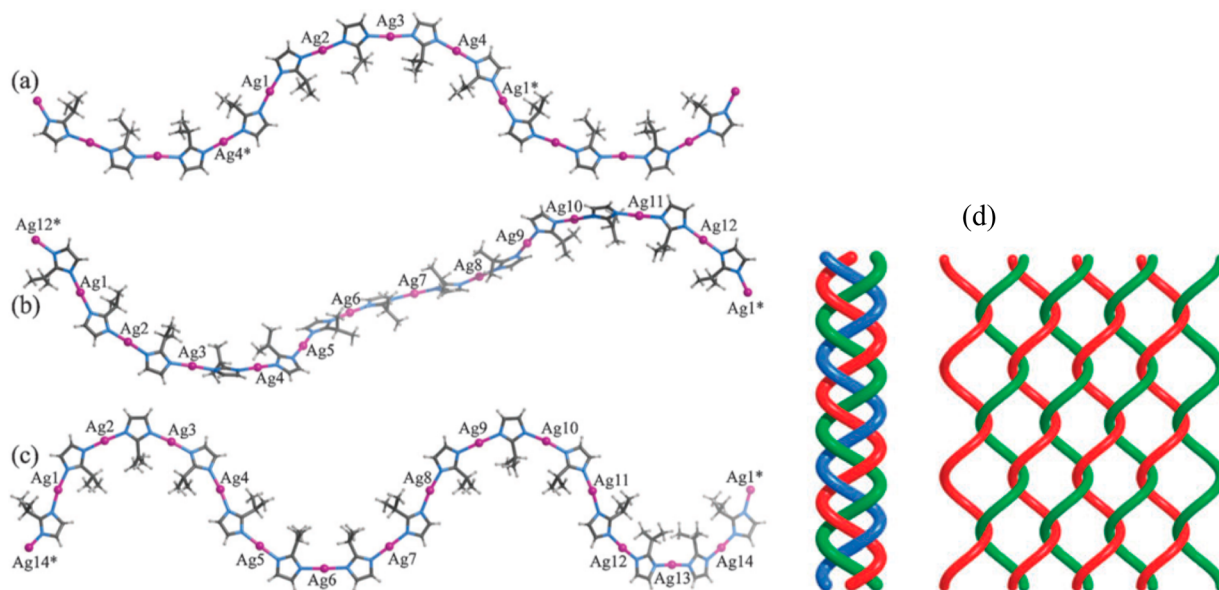


Figure 29. Structures of the three interwoven isomers of silver(I) isopropylimidazolate with 4, 12, and 14 independent $\text{Ag}(\text{I})$ units, respectively, resulting in (d) quintuple helical or chicken wire patterns in the case of (b) and (c), respectively. Reproduced with permission from ref 208. Copyright 2011 Royal Society of Chemistry.

phosphino)ethyl)oxazoline-*N,P*)-iridium tetrakis(3,5-bis-(trifluoromethyl)phenyl)borate (IDOSID) is reported to have a Z' value of 24.²⁰³ The structure is not discussed in the original publication, but the authors report²⁰⁴ that the unit cell can be reduced to a higher symmetry $Z' = 1$ subcell. This description does not account for some relatively weak interlayer reflections that give rise to the much higher Z' supercell, and it is likely that the structure is an incommensurately modulated version of the high symmetry structure.

The largest reported value of Z' in the CSD is the $Z' = 32$ structure of trimethyltin hydroxide, CSD refcode TMESNH. This apparently simple compound was structurally characterized in 1965.²⁰⁵ It is actually a polymer with five-coordinate $\text{Sn}(\text{IV})$ centers linked by hydroxyl bridges, and the reported Z' value refers to the number of independent “ Me_3SnOH ” monomer units (Figure 28a). The structure may also be described by a

much smaller subcell; however, the subcell does not account for an interesting 8_3 helical superstructure arising from short $\text{Sn}\cdots\text{O}$ interactions, which gives rise to supercell reflections (Figure 28b), and the analysis of this challenging system back in 1965 is extremely impressive. The structure was redetermined in 2004 at 150 K and found to exhibit a relatively routine orthorhombic structure in space group $P2_12_12_1$ with $Z' = 1$, reported as a private communication in the CSD.²⁰⁶ In 2003, we also found a $P2_1/c$ $Z' = 1$ form at 120 K.^{22b} The compound's status as the small molecule Z' world record holder prompted us to reinvestigate its solid-state chemistry in 2011.¹⁹⁰ This work elucidated the 3D structures of the $Z' = 32$ and $Z' = 1$ $P2_1/c$ forms and demonstrated them to be an enantiotropic pair with a transition onset temperature of 176 K. Sublimation of the sample produced evidence for a further metastable form, which could not be isolated and may be related to the $P2_12_12_1$ polymorph. The high

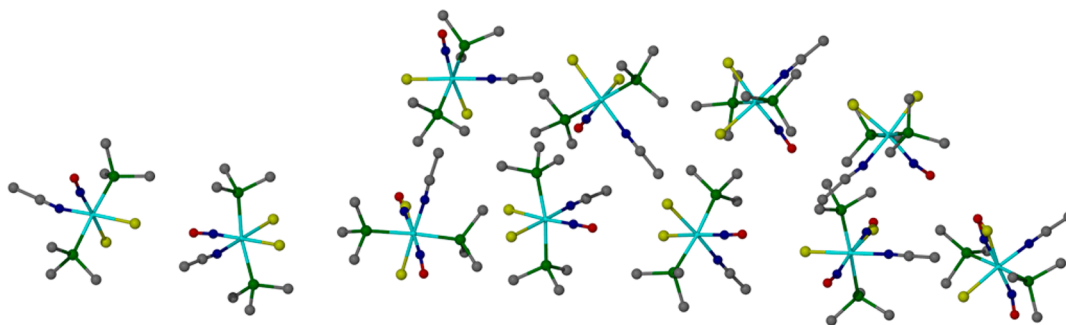


Figure 30. $Z' = 11$ asymmetric unit of $\text{ReCl}_2(\text{NCMe})(\text{NO})(\text{PMe}_3)_2$; the structure lacks significant, directional intermolecular interactions.²¹⁰

temperature form exhibits four crystallographically independent polymeric strands, and hence a designation of $Z' = 4$ may be more appropriate, although this is subjective, partially depending on the evidence for the retention of the polymeric structure in solution.²⁰⁷ The high Z' structure appears to allow better interchain packing, and it is interesting that the higher Z' structure is the most stable form at room temperature consistent with the observations of Bernstein, Dunitz, and Gavezzotti across a series of polymorphic pairs with differing Z' values.^{22a} The enantiotropic transition between high and low Z' polymorphs suggests that an explanation for the high Z' behavior may well lie in a consideration of the polymer chain mutual relative movements rather than static packing concepts such as synthon frustration^{28c} or factors relating to fluid phase speciation and their influence on crystal nucleation processes.^{28e,45b}

Like trimethyl tin hydroxide, another set of compounds that is hard to classify in terms of Z' is an impressive series of interwoven coordination polymers based on silver(I) isopropylimidazolate, all of formula $[\text{Ag}(\text{ipim})]$. Depending on the crystallization conditions, three isomeric coordination polymers have been isolated with either sinusoidal chain, quintuple helix, or a chicken-wire structure (Figure 29). The compounds adopt space groups $P2_1/n$, $P\bar{1}$, or $Pna2_1$, with 4, 12, or 14 independent “Ag(ipim)” units, respectively. The original publication regards the whole asymmetric unit as being unique and assigns $Z' = 1$; however, the situation is clearly analogous to SnMe_3OH with the multiple independent Ag(I) ions arising from the complex geometry of the chain structure and the way in which it fills space in the crystal. In turn, the interesting structure of the polymer derives from the steric bulk of the isopropyl substituents as compared to the flat imidazole region of the ligand, resulting in a wedge shape and hence twisting of the chain.²⁰⁸ Similar effects are also seen for Ag(I) methylsulfanylterpyridines in which “frustration” between weak coordinate interactions and π -stacking results in very complex multimetallic spirals.²⁰⁹

While not as numerically imposing as the rest of the high Z' behemoths discussed in this section, the well-defined $Z' = 11$ structure of $\text{ReCl}_2(\text{NCMe})(\text{NO})(\text{PMe}_3)_2$ reported by Berke and co-workers in 2000 is perhaps one of the most puzzling (Figure 30).²¹⁰ The prime number Z' value argues against the presence of pseudosymmetry. Moreover, the molecules are not linked by strongly directional intermolecular interactions, and the high Z' was attributed to the optimization of an extensive network of weak CH hydrogen bonds from the methyl groups of the acetonitrile ligands to the coordinated chloride and nitrosyl ligands.

The structure of the 4-methylpyrazolate complex of gold(I) (MUTLAO) also has a surprising number of independent molecules and represents a case where the Z' number fails to do

the structure justice. The structure has a total of some 45 crystallographically unique gold(I) centers arranged into planar trimers with significant $\text{Au}\cdots\text{Au}$ interactions, with each pair of gold(I) center bridged by a 4-methylpyrazolato anion (Figure 31). There are 15 crystallographically unique trimers with their

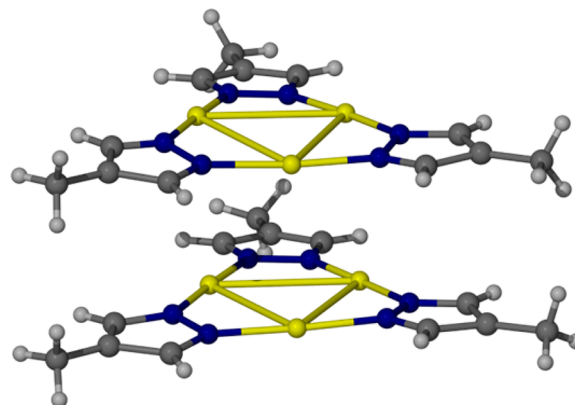


Figure 31. Two of the 15 independent $[\{\text{Au}(\mu\text{-4-Me-pyrazolato})\}_3]$ complexes in the formally $Z' = 1$ asymmetric unit of MUTLAO; the structure is linked by aurophilic interactions, and the anomalous Z' assignment arises because of the presence of a small number of solvent molecules.²¹¹

packing dictated by further interplanar $\text{Au}\cdots\text{Au}$ interactions and the intercalation of the methyl substituents within the concave groove of adjacent trimers to give offset stacks arranged not quite orthogonally. On the basis of reasonable aurophilic interactions, five gold trimers form independent units, while two exist as dimers of trimers. An additional eight trimers (with symmetry equivalents) constitute a 16-membered aggregate of trimers. In this way, fairly close packing of the structure is achieved, with small lattice voids being occupied by a number of solvent molecules, a molecule of hexane, dichloromethane, methanol, and two water molecules for every 15 trimeric complexes. The hexane is disordered. This unusual stoichiometry leads to a formal Z' value of just 1; however, a $Z' = 15$ assignment has considerable justification and is arguably more useful.²¹¹

7. RELATIONSHIP TO COCRYSTALS

A cocrystal is a crystal containing two or more types of molecule that are chemically as well as crystallographically distinct. The term cocrystal is a topical and contentious one. A useful summary of the various definitions of the term cocrystal has been collated by Lemmerer.^{28s} In this Review, we use the term cocrystal to encompass all kinds of multicomponent molecular crystal including solvates, host–guest compounds, and both stoichiometric

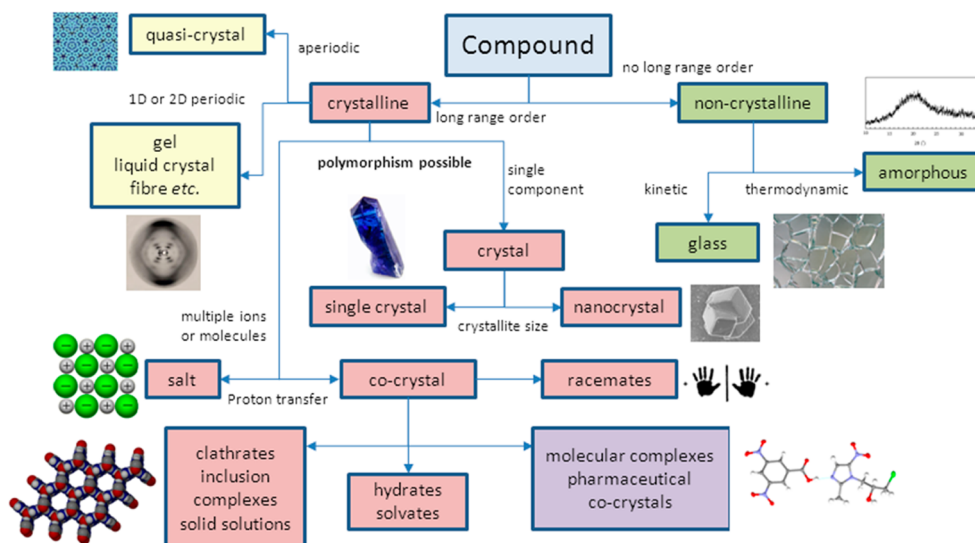


Figure 32. Classification of solid forms. Reproduced with permission from ref 21b. Copyright 2013 Elsevier.

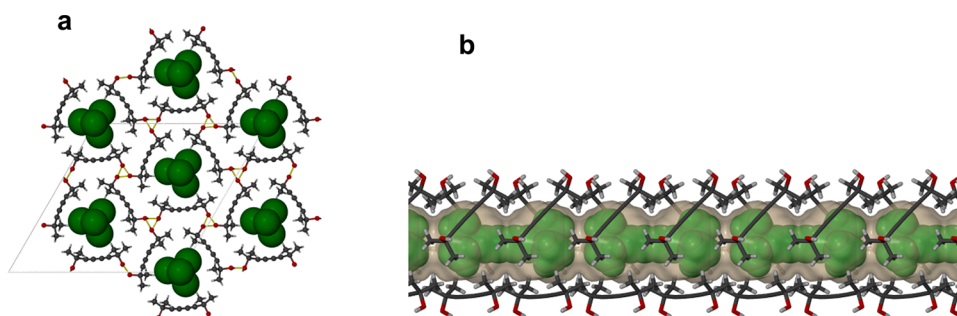


Figure 33. Channel inclusion compounds of diol **34** with either (a) CCl_4 or (b) the host molecule itself as guests.²¹³

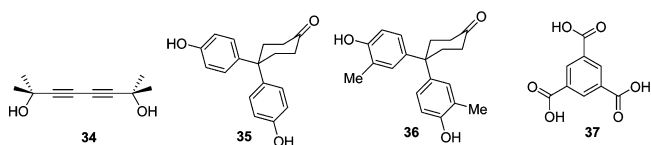
metric and nonstoichiometric lattice inclusion compounds, rather than narrowing it to refer only to stoichiometric mixtures of molecules that are solids at room temperature (Figure 32).^{21b,23b,24,212} There is a clear conceptual analogy between the formation of cocrystals and homomolecular structures with $Z' > 1$. A crystal structure with $Z' > 1$ involves two or more molecules that are chemically identical in fluid phases but occupy crystallographically distinct sites and as a result have distinct properties such as solid-state NMR spectra, for example. To be clear, in no way are homomolecular high Z' crystals a subset of cocrystals. Homomolecular high Z' crystals are comprised of only a single chemical component (although there can also be high Z' cocrystals, of course, as in the structure of **33**); cocrystals have more than one chemical component. However, the study of high Z' structures and cocrystals or solid state, multicomponent molecular compounds^{3a} is not completely orthogonal. In this Review, we seek to tease out the points of similarity where the two types of interesting solid structure can cross-inform one another.

Cocrystal formation is linked to factors such as awkward molecular shape, mismatch in the hydrogen-bond donor/acceptor propensity, or the filling of intrinsic voids in the crystal packing arrangement.^{3b} This concept lies behind the whole field of solid-state host–guest chemistry and solvate formation in which lattice voids in a poorly packed structure are filled by a second type of molecule. Poorly packed pure compounds can be identified by their low melting points and low packing efficiencies, and hence the lower the melting/freezing point of

a pure compound in a binary phase diagram, the more likely its freezing point depression curve is to occur below the melting curve of a possible cocrystal.^{28o} An illustrative example is the bowl-shaped calix[4]arenes discussed in section 3, which have void space in the middle of the molecule that is of the right size to incorporate small solvent molecules such as toluene.⁸⁴ As a result, calixarenes have a strong predilection for cocrystal formation as a result of their awkward shape, which precludes close packing.

If we regard structures with $Z' > 1$ as being related to cocrystals in the sense that there is more than one distinct molecule in the solid state at least (but of course the independent molecules happen to be chemically identical), then there is considerable common ground in the origins of both homomolecular high Z' structures and heteromolecular cocrystals. The key “missing link” between $Z' > 1$ and cocrystal formation was reported by the Barbour group in 2006.²¹³ They showed that the dialkyne host molecule **34** can form a well-defined series of channel host guest cocrystals of 3:1 stoichiometry with included guests such as benzene and tetrachloromethane. Hydrogen bonding between the alcohol functionalities results in a 3-fold symmetrical hydrogen-bonded chain on the channel exterior while the cocrystallized guest occupies the void space inside the channel, Figure 33. Interestingly, if the host molecule is crystallized by sublimation under vacuum, then a homomolecular crystal with the curious Z' value of 1.167 is obtained. The key point is that the host framework in the homomolecular $Z' > 1$ material is isostructural with the cocrystal host guest compounds and has

the same hydrogen-bonded channel arrangement of the host diol. The Barbour group used the word “isoskeletal” to describe this arrangement. The origin of the Z' value of 1.167 lies in the fact that in the homomolecular crystal the host channel is occupied by a further molecule of diol **34**. The crystal can thus be regarded as being of well-defined stoichiometry (*host-34*)₆·(*guest-34*). The existence of the cocrystal structures with their convergent channel and divergent guests allows the assignment of clear host and guest roles to the crystallographically independent molecules of the diol in the homomolecular structure. This factor makes this self-included system quite distinct from trivially describing all $Z' > 1$ structures as being in some sense “self-included”, and clearly implies that the origin of the $Z' > 1$ behavior in this instance is the formation of a void space in the channel host skeleton structure of **34**, which is filled by the only available guest that happens to be chemically identical to the host.



While this system is the only truly self-included structure reported to date, there are other examples of the occurrence of crystallographically independent but chemically identical molecules occurring as a result of their adoption of host and guest roles in a crystal structure, analogous to cocrystals, and the idea of self-inclusion has been raised in a number of different contexts.²¹⁴ Aitipamula et al. have described the $Z' = 2$ structures of 4,4-bis(4-hydroxyphenyl)cyclohexanone (**35**) and 4,4-bis(3-methyl-4-hydroxyphenyl)cyclohexanone (**36**), which differ only in the presence of methyl substituents on the latter.^{214b} In both structures, the two independent molecules adopt different roles, with the structure of **35** being described as a self-host–guest structure and **36** exhibiting interpenetration of nonidentical networks. In both cases, the requirement of close packing an open hydrogen-bonded network is suggested as the root cause of the presence of multiple independent molecules, and hence the structures represent a solution to the frustration between strong directional intermolecular interactions and close packing.^{28c} Another example is the structure of trimesic acid (**37**) 5/6 hydrate, which involves a host framework comprising layers of trimesic acid and water molecules that form a channel that includes further crystallographically distinct unsolvated trimesic acid.²¹⁵ This guest trimesic acid can be replaced with other guests such as picric acid to give a ternary cocrystal of trimesic acid, picric acid, and water. The distinct host and guest roles fully explain the $Z' = 12$ structure and the strange 5/6 stoichiometry in this fully ordered, stoichiometric structure. The crystal asymmetric unit is actually $(37 \cdot \text{H}_2\text{O})_{10} \cdot (37)_2$ with a face-to-face **37** dimer guest spanning five hydrated host layers, Figure 34. Another striking trimesic acid ternary cocrystal system has been reported recently, of stoichiometry $(37)_2(t\text{-butylamine})_5(\text{methanol})_3$, which forms three distinct polymorphs. While the Z' value is just 1 in each case, the authors point out that there are a total of 10 independent molecules in the asymmetric unit, $Z'' = 10$, which is very rare for a polymorphic system.⁶³

In the case of very labile interactions, it can be somewhat arbitrary as to whether a sample is regarded as a homomolecular high Z' structure or a cocrystal. This dilemma is highlighted by an unusual structure comprising several copper(I) chloro com-

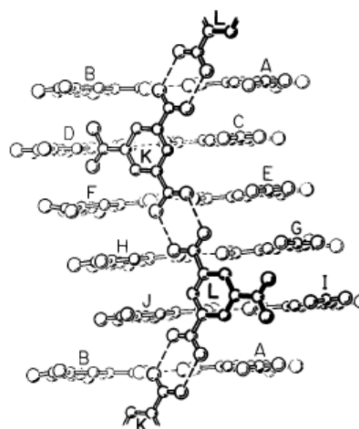


Figure 34. Offset layer packing in $(37 \cdot \text{H}_2\text{O})_{10} \cdot (37)_2$. Trimesic acid molecules A–J form the host framework, while K and L are the crystallographically independent guests. Reproduced with permission from ref 215. Copyright 1977 International Union of Crystallography.

plexes of ligand **38**, which have a basic repeat unit of formula “ $\text{Cu}(\text{38})_2\text{Cl}$ ”. The asymmetric unit of this structure possesses four crystallographically independent “ $\text{Cu}(\text{38})_2\text{Cl}$ ” units that in some cases are linked by weak $\text{Cu} \cdots \text{Cl}$ or $\text{Cu} \cdots \text{S}$ interactions, which are labile in solution. Formally, these weak interactions are coordinate bonds, and hence the crystal (Figure 35) is best defined as comprising two monomers $[\text{Cu}(\text{38})_2\text{Cl}]$, two S-bridged dimers $[\{\text{Cu}(\text{38})(\mu\text{-38})\text{Cl}\}_2]$, and one Cl-bridged dimer $[\{\text{Cu}(\text{38})_2(\mu\text{-Cl})\}_2]$, giving a ternary cocrystal with a very complicated formula unit of $2[\text{Cu}(\text{38})_2\text{Cl}] \cdot 2[\{\text{Cu}(\text{38})(\mu\text{-38})\text{Cl}\}_2] \cdot [\{\text{Cu}(\text{38})_2(\mu\text{-Cl})\}_2]$ with $Z' = 0.5$ in $P2_1/c$. If we regard the labile coordinate bonds to the Cu(I) center as being crystal packing interactions, however (although it is unknown whether the “ $\text{Cu}(\text{38})_2\text{Cl}$ ” units are dissociated in solution), then we can describe the crystal as a homomolecular $Z' = 4$ crystal of the complex $[\text{Cu}(\text{38})_2\text{Cl}]$.²¹⁶ This type of ambiguity is evident in a cocrystal of another isomeric pair of copper(I) complexes $[\{\text{Cu}(\text{PTU})(\mu\text{-PTU})\text{Cl}\}_2]$ and $[\{\text{Cu}(\text{PTU})_2(\mu\text{-Cl})\}_2]$ (PTU = *N*-phenyl-*N'*-2-propenylthiourea).²¹⁷ There are two crystallographically independent dimeric coordination complexes, but because they are also chemically distinct in terms of the identity of the bridging atoms, the CSD⁹⁵ assign $Z' = 0.5$ (each dimer sits on an inversion center, refcode SOGZAP), while the original authors assign $Z' = 2$.²¹⁷

It has been suggested by Brock that compounds with high Z' might represent good candidates for cocrystal formation (a phenomenon that is otherwise rare).^{28o} We have attempted to explore whether more generally there is a relationship between the tendency of a molecule to form cocrystals and its tendency to adopt $Z' > 1$ structures, and to use this insight in a predictive fashion. Statistical analysis comparing known cocrystals with structures of the homomolecular ($Z' = 1$) “parent” phase of the cocrystal forming molecule showed that some 17.7% of homomolecular parent structures adopt $Z' > 1$ as compared to the CSD average for organic molecules of 11.5%. Focusing on drug-like compounds with the CSD tag “bioactive” showed that only 4.8% of homomolecular $Z' = 1$ bioactive parent compounds also form cocrystal “children”, as compared to known cocrystals for 7.1% of compounds crystallizing with $Z' > 1$. The implication is clear; compounds crystallizing in homomolecular structures with $Z' > 1$ also have a strong tendency to form cocrystals. Hence, there is a general tendency for particular molecules that may have difficulty forming symmetrical 3D arrays (perhaps

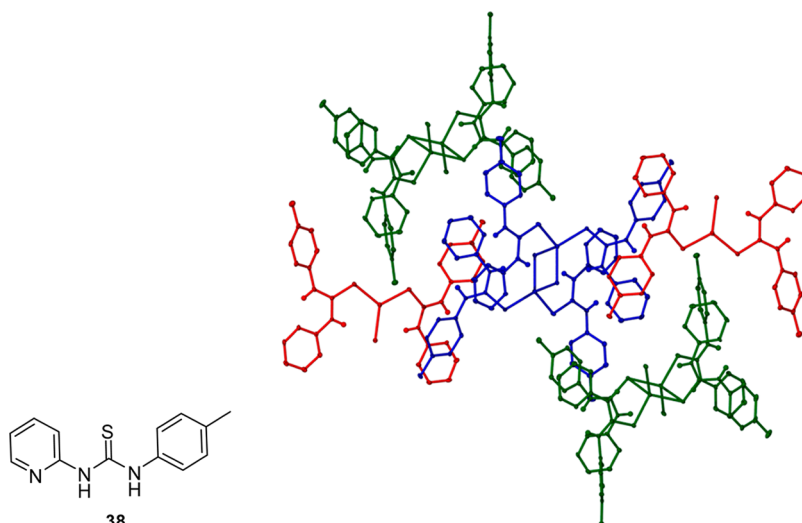


Figure 35. Formula unit (two asymmetric units) in $2[\text{Cu}(\text{38})_2\text{Cl}]\cdot 2[\{\text{Cu}(\text{38})(\mu\text{-L})\text{Cl}\}_2]\cdot [\{\text{Cu}(\text{38})_2(\mu\text{-Cl})\}_2]$. Reproduced with permission from ref 216. Copyright 2007 American Chemical Society.

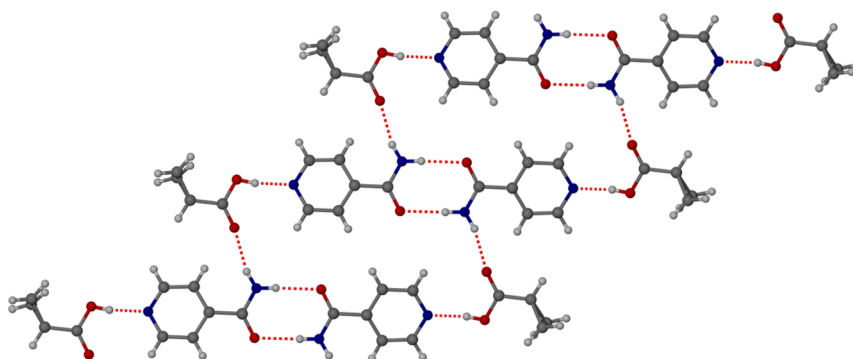


Figure 36. One of six of the independent layers (three symmetry equivalent strands shown) in the $Z' = 12$, $Z'' = 24$ cocrystal of cyclopropanecarboxylic acid with isonicotinamide.^{28s}

because they possess an awkward shape or mismatched hydrogen-bonding functionality) to solve this packing problem by including a second crystallographically independent molecule of whatever chemical nature.⁴² As an example, the $Z' = 3$ structure of the antibacterial ornidazole was identified for further study because it is high Z' but did not at the time have any known cocrystals. Its high Z' parent (homomolecular) structure suggests that cocrystal formation should be favored, and indeed careful consideration of the hydrogen-bond acceptor properties of the molecule allowed the deliberate crystallization of the 1:1 cocrystal with 3,5-dinitrobenzoic acid. At the same time, a hydrate structure was also independently reported.²¹⁸ A CSD search also identified a number of “orphans”, cocrystals without a known homomolecular parent structure. Two were selected for further study on the basis of their ready availability, 2,3,4-trihydroxybenzophenone hydrate and a cocrystal of 6-phenyl-3(2*H*)-pyridazinone with acetic acid. A careful solvent screen allowed the crystallization of the homomolecular parent structures, which, as predicted, adopt $Z' > 1$ structures with $Z' = 2$ and 3, respectively, apparently as a result of synthon frustration.⁴² These results suggest that statistical trends can indeed be used to engineer homomolecular crystals with $Z' > 1$. While the statistical trends are relatively weak in this case and clearly other factors also influence the Z' value of cocrystal homomolecular parent structures, it is telling (or perhaps highly

fortuitous!) that both of the orphans examined did indeed produce new $Z' > 1$ forms.⁴²

Thinking back to the cavity-containing calixarenes, one possible explanation for some molecules showing a particular tendency to form unsymmetrical $Z' > 1$ or multicomponent structures might just be that they simply have some kind of “awkward” shape. This intuitively appealing idea is fully consistent with the close-packing concepts first laid down by Kitaigorodskii⁷ but is quite difficult to test in practice. As discussed in section 5.2, molecules that form $Z' > 1$ structures tend to be smaller and more rigid than those that can pack more symmetrically.^{27e} A statistical CSD survey of homomolecular structures of compounds known to form cocrystals (“parents”) shows that cocrystal-formers are, on average, also much smaller and less flexible than molecules in the CSD as a whole, and indeed are even smaller and less flexible than molecules crystallizing with $Z' > 1$. Hence, both cocrystal formation and the occurrence of multiple symmetry-independent molecules are linked to small, rigid, awkwardly shaped molecules that have more conformational constraints on their crystal packing requirements. We also should note that formation of a $Z' > 1$ structure or the formation of a cocrystal do not represent two mutually orthogonal outcomes to issues of packing problems, as the $Z' = 16$ cocrystal of $[\text{UO}_2\text{Cl}_2(\text{H}_2\text{O})_3]\cdot 15\text{-crown-5}$ (33) demonstrates (section 5). The issue is highlighted by the $Z' = 12$ stoichiometric cocrystal structure of cyclopropanecarboxylic acid

with isonicotinamide (Figure 36). Cyclopropanecarboxylic acid is the smallest and most rigid acid used in a cocrystal study performed by Lemmerer and Fernandes in 2012, and the cocrystal exhibits both acid pyridine and amide–amide supramolecular synthons suggesting possible frustration between the two (section 5.1). However, the very strength of these associations means that they are likely to persist in solution, and hence the transfer of solution phase aggregates to the solid state was also suggested to be a factor.²⁸⁸ It is noteworthy, however, that the $Z' = 12$ structure was also obtained by liquid assisted grinding experiments. It may also be the case that because each independent unit represents a layer of the 2D sheet structure, the origins of the high Z' behavior relate to the optimal packing of layers in the third dimension caused by the need to interdigitate the “bumps” of the cyclopropyl groups.

8. INTERESTING TOPOLOGIES

The fascinating $Z' = 1.167$ structure of **34** is an example of a small but special class of $Z' > 1$ compounds that exhibit multiple independent molecules for fairly readily understood reasons that arise from their interesting topology or structure, rather than for purely crystallographic reasons. An obvious example is the astonishing bis[2]catenane (CSD refcode DIGMUC, shown in Figure 37), which exhibits two crystallography independent

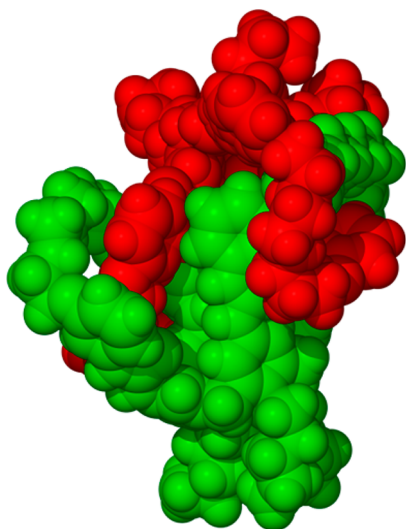
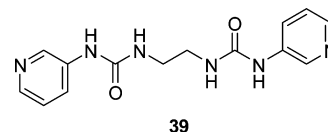


Figure 37. Two crystallographically independent molecules inextricably linked in the bis[2]catenane structure DIGMUC.²¹⁹

molecules. In fact, the two unique molecules form part of a mechanically interlocked structure that cannot fall apart in solution, and hence the mechanically bonded bimolecular unit is better regarded as the “molecule” and certainly as the crystal growth unit.²¹⁹ The steric properties of the mechanically bonded catenane structure mean that it does not exhibit any symmetry, and hence none is expressed in the crystal structure. This is an extreme case of the suggestion that a strong solution association (unbreakable in this case under ambient conditions) can be carried through into the crystal packing arrangement. This example illustrates the need to view a $Z' > 1$ structure in chemical context. Unusual self-assembled topologies involving more labile interactions can also result in crystallographic asymmetry because different molecules are playing different topological roles. The ligand **39** forms an arrangement with three crystallographically independent ligands (albeit with formally

$Z' = 1$) as its AgNO_3 complex as a result of the three unique coordination networks that contort to give a Borromean weave pattern.²²⁰ It is worth noting that structures that are interpenetrated²²¹ or with complex topologies do not necessarily result in multiple crystallographically independent molecules, as the 11-fold interpenetrated diamondoid structure of tetrakis[4-(3-hydroxyphenyl)phenyl]methane·2benzoquinone, which has a Z' value of just 0.25 with the fascinating interpenetrated complexity being fully compatible with space group symmetry in the high symmetry space group $I4_1/a$.²²² An online list of all known interpenetrated structures current to 2005 is published by Batten.^{221,223}



9. CONCLUSIONS AND OUTLOOK

While the Z' number is (usually) easily derived, easily understood, and often correlates directly with the picture of a structure we see on a computer display, it can be somewhat misleading and its assignment somewhat arbitrary. Equally it is difficult to replace Z' with something better that is as useful. The Structural Class descriptors are more rigorous, contain more information, and capture more cases of symmetry independent molecules, particularly instances such as $Z' = 1/2 + 1/2 = 1$. The SC descriptors are also difficult to understand and apply, and not possible to search for in the current CSD software. Moreover, the general phenomenon of intermolecular interactions in crystals that cannot be described by conventional space group symmetry is much more extensive than structures with $Z' > 1$ or $Z' = 1/2 + 1/2$. In real crystals, a proper understanding of molecular packing and of intermolecular interactions that cannot be described by conventional space group symmetry operations must also encompass factors such as “wasted” molecular symmetry, incommensurately modulated structures, some kinds of disorder, and inclusion phenomena, in other words, all of the complicated issues that affect real molecular crystals formed under real world crystallization conditions. This means that the phenomenon is much more widespread than the roughly 9% of structures with $Z' > 1$ in the CSD would imply. It is also growing as instrumentation advances and the ability of solid-state chemists to study complex systems improves.

Where are we in the quest to understand these challenging crystals? The answer to this question is essentially the same as the state of the art in understanding polymorphism and cocrystal formation. Indeed in this Review we have tried to show that crystal structures with “noncrystallographic” packing are a particularly interesting subset of crystals with a conceptual foot in both camps. It is certainly now possible to computationally calculate crystal structures. Unfortunately, the calculated results are sometimes not the same as the experimental structures (or at least the experimental structure is not the lowest in terms of calculated energy), and the calculations predict a lot of structures that are not observed experimentally.^{13b,69,93} In terms of structures with $Z' > 1$ and related crystals, the computational difficulties are magnified considerably.³¹ However, ultimately, the solution to the “continuing scandal”²²⁴ of our inability to predict crystal structure from molecular structure will lie in CSP approaches, and in the coming decades it will be very interesting

to observe progress in this field, particularly as it increasingly addresses special cases such as high Z' .

Meanwhile, we have to recognize that the Z' number (and related descriptions such as the SC descriptors and superspace groups) is a composite description that has its roots in a number of different real phenomena. If we want a “single explanation”, then that single explanation is simply that real crystals are not perfect and that conventional crystallography is an idealized description of nonideal molecular solids. The single explanation of high Z' structures as being universally metastable^{28e} is simply not true in many cases, although there are certainly some metastable polymorphs (probably a majority) where the $Z' > 1$ form is indeed less stable than the $Z' = 1$ form, where both are known. There are also very many cases where a higher Z' structure has been shown to be more stable than a $Z' = 1$ polymorph.^{28a,e,114,159,187} High Z' crystals are also not “on the way” or incompletely crystallized;^{28d,e} they are fully crystalline, periodic ordered structures.^{19a} It is just that some of the intermolecular interactions in them are not compatible with the space group symmetry. Perhaps the real question is why should so many crystal structures be based on a single molecule as the symmetry-independent unit? The answer seems to us that there is a huge difference between the strength of a covalent bond and the strength of an intermolecular interaction such as a hydrogen bond. The crystallization process represents an emergent outcome of all of the possible interactions that could occur between atoms under the ambient conditions. Covalent bonds do not break under the conditions most molecular crystals form, and hence the molecular covalent bonded structure is not “on the table” in terms of its susceptibility to change as part of the crystallization process. The molecular structure hence passes intact into the crystal. If the molecule possesses point group symmetry, then this symmetry can often be described by space group symmetry, and we get a structure with $Z' < 1$. However, sometimes this molecular symmetry is “wasted”¹¹⁶ to optimize another part of the structure. If the molecule possesses no symmetry, then we get $Z' = 1$ as being the basic building block, although sometimes the “intermolecular symmetry” is wasted to optimize the crystal as a whole leading to $Z' > 1$. It is also conceivable that very strong intermolecular bonds such as those in hydrogen-bonded dimeric pairs behave as if they are covalent bonds on the time scale and supersaturation level of the crystallization process, and hence a multimolecular growth unit is transferred intact into the crystal. Because in a pure substance all of the molecules are the same as one another, there is a fair chance that this growth unit will be symmetrical (a centrosymmetric dimer, for example); however, the symmetry of the growth unit may also be wasted or sacrificed if it conflicts with the optimization of intergrowth unit interactions.

A great deal of insight into what types of intermolecular interactions determine the structure of a crystal and perhaps hence its Z' value has been obtained in recent years by statistical surveys of the tremendous resource of the CSD. These insights rely on a subsequent case-by-case examination of the supra-molecular chemistry of the crystals. They represent rationalizations and are at best only weakly predictive. However, on aggregate they point to a strong chemical structural explanation for the occurrence of many high Z' crystals. Statistical surveys of course are limited by the social bias of the data and can be influenced by errors in structure determination. However, the errors are random, and the data sets are now extremely large. Moreover, the statistical data are often a clue to in-depth examination at the molecular level rather than an end in

themselves. On the basis of the statistical surveys, structural data, calculations, and opinions of many workers now interested in the field, we can list the following factors as being significant or suspected contributors to the formation of multiple symmetry independent molecules in a crystal.

- Awkward molecular shape^{27e,28u} (perhaps also leading to inclusion complex/cocrystal formation or even self-inclusion). Molecules forming high Z' structures are also more likely than $Z' = 1$ systems to form cocrystals, and, conversely, observation of a cocrystal suggests that a high Z' structure is more likely than average for the homomolecular parent.⁴²
- Small, rigid molecules. High Z' systems are based, on average, on molecules that are some 50 Å³ smaller and with two fewer rotatable bonds. Cocrystal formers are even smaller and even less flexible. This statistical trend argues against the notion that high Z' structure arise from the possibility of multiple molecular conformations. While minor conformational variations are often observed in symmetry independent molecules, it is highly statistically unlikely that they would be identical given that they are in a different solid-state environment.^{27e,28u}
- Resolved chirality (which limits the number of available symmetry operations).^{28c,j}
- Strong directional intermolecular interactions, to some extent alone, but more often in conjunction with a competing such interaction or with other packing factors. The competing demands of more than one synthon may lead to high Z' structure as a means to optimize competing symmetry-incompatible interactions and hence alleviate the frustration between the two.^{28c}
- There is no “driving force” toward $Z' = 1$ or inherent preference for symmetry. If the optimal interactions are for a $Z' > 1$ crystal with an intermolecular interaction that is not coincident with crystallographic symmetry, then this interaction will form. The fact that the molecular chemical nature of intermolecular interactions drives crystal packing, and not the anthropomorphically imposed restraint of symmetry, is exemplified by the greater stability of symmetry-independent pairs in $Z' = 2$ structures.^{28v}
- Real molecules have bumps and hollows.^{106,112} The most stable crystals are those where intermolecular interactions are maximized and hence exhibit close packing with minimal free space.⁷ This will tend to favor symmetric arrangements, and because the molecules themselves are chemically identical and we know that donors tend to pair with acceptors or bumps with hollows in real crystals,¹⁰⁶ it is difficult to imagine why the packing should be anything other than symmetrical. However, symmetry does not have an energy component and can be sacrificed if particular directional interactions are especially stabilizing and hence dominant.
- A structure with multiple independent molecules is a more common outcome as compared to crystallographic symmetry such as 2-fold rotation that results in inefficient packing.^{28j}
- Crystallization factors, particularly those that generate extremely high supersaturation or involve rapid increases in supersaturation gradient (such as melt crystallization or sublimation onto a cold finger), may trap metastable phases incorporating fluid phase aggregates.¹⁵⁵

- Solution phase aggregation or conformational preference may be translated into a crystal to give a metastable phase or conformer with a particular dominant discrete interaction. Speculatively such solution factors could even dominate nucleation to the point where a putative (or calculated) more symmetric structure is not observed under accessible conditions. Energy calculations that indicate a particular dominant pairwise interaction give a clue as to systems where this may be the case.^{28u}

The past 15 years has seen crystal structures with multiple symmetry independent molecules pass from being regarded as crystallographic curios, to being a particularly interesting, challenging, and informative subset of crystal structures that as “exceptions to the rule” shed considerable light onto the hugely topical fields of polymorphism and cocrystal formation, of which they are an integral part. The growth in both the incidence and the interest in high Z' structures has been stimulated by improving instrumentation and complementary information from a range of techniques including single crystal and powder X-ray and neutron diffraction, solid-state NMR spectroscopy, computational energy calculations, DSC, and hot stage microscopy. A detailed examination of the supramolecular chemistry of these fascinating systems has revealed a wealth of knowledge concerning intermolecular interactions in the solid state, and this chemical approach is complementary to statistical surveys and computational crystal structure calculation. The future will doubtless continue to remove the veils from the mysteries of crystal packing in general and from these fascinating structures in particular.

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Notes

The authors declare no competing financial interest.

Biographies



Kirsty M. Steed (née Anderson) (left) obtained her B.Sc. (1999) and Ph.D. (2002) from Bristol University under the supervision of Prof. A. G. Orpen. She then moved to Cambridge to work for the Royal Society of Chemistry as their Crystallographic Data Editor for four years before returning to academia as a Research Associate with Prof. Jonathan Steed at Durham University in 2006. During her postdoctoral studies she was awarded the Cambridge Crystallographic Data Centre Younger Scientist Prize in 2008. In 2010 she left Durham University to pursue a career in

Research Administration at Newcastle University, where she was employed as administrator for the eFutures academic network before her move to the Science, Agriculture and Engineering Faculty Research Team in 2013. She maintains a keen interest in all things crystallographic and was delighted to be able to contribute to this Review despite her move to the dark side.

Jonathan W. Steed (right) pictured on was born in London, UK in 1969. He obtained his B.Sc. (1990) and Ph.D. (1993) degrees at University College London, working on organometallic chemistry. Between 1993 and 1995 he was a NATO postdoctoral fellow at the University of Alabama and University of Missouri–Columbia. In 1995 he was appointed as a Lecturer at Kings College London, and in 2004 he joined Durham University where he is currently Professor of Inorganic Chemistry. Steed is coauthor and editor of a number of books including *Supramolecular Chemistry* (2000 and 2009) and around 300 research papers. He is the recipient of the RSC Meldola Medal (1998), Durham's Vice Chancellor's Award for Excellence in Postgraduate Teaching (2006), the Bob Hay Lectureship (2008), and the RSC Corday-Morgan Prize (2010). His interests are in organic solid state and pharmaceutical materials chemistry, supramolecular gels, and crystal engineering. He was very pleased to persuade long-time research collaborator Kirsty Anderson to marry him in 2014.

ACKNOWLEDGMENTS

We are very grateful for the assistance of the Cambridge Crystallographic Data Center for their help and advice with the searches used in our work on the high Z' phenomenon. We also appreciate the thoughts and personal communications of many colleagues over the years. We would like to thank the EPSRC for funding.

DEDICATION

This work is dedicated to the memory of our collaborator André E. Goeta.

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