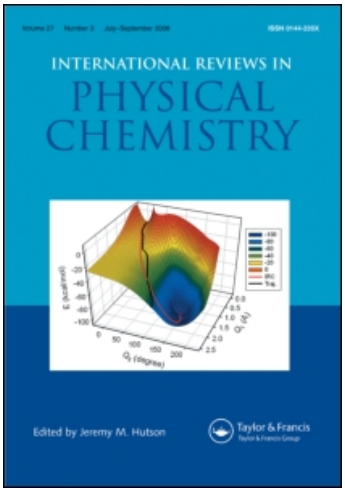

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Computational prediction of organic crystal structures and polymorphism

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Computational prediction of organic crystal structures and polymorphism

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The development of a robust manufacturing process for solid organic materials, such as pharmaceuticals, can be complicated when the molecules crystallize in different solid forms, including polymorphs. The diverse challenges to computational chemistry in computing the relative thermodynamic stability of different potential crystal structures for a range of organic molecules are outlined. Once the crystal structures which are thermodynamically feasible have been obtained, then comparison with the experimentally known polymorphs can provide interesting insights into crystallization behaviour. Although the computational prediction of polymorphism requires modelling the kinetic factors that can influence crystallization, the computational prediction of the crystal energy landscape is already a valuable complement to experimental searches for polymorphs.

Keywords: organic solid state; lattice energy; polymorphism

Contents

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1. Introduction

Organic crystal structure prediction was originally seen as the challenge of being able to predict the crystal structure of an organic molecule, given only the chemical diagram. The practical utility of such a computational methodology was to determine whether a molecule would form a solid with the desired technological properties, prior to its synthesis. For example, would a molecule with a high non-linear optical coefficient pack in a non-centrosymmetric space group and so retain that property in the solid, or would an energetic molecule pack sufficiently densely to make an effective explosive? Progress towards this objective has been reviewed in a most effective manner by the international blind tests of crystal structure prediction organized by the Cambridge Crystallographic Data Centre (CCDC). In these blind tests, all groups actively developing an approach to organic crystal structure prediction were sent the molecular diagrams shown in Figure 1, and asked to submit three predictions of the crystal structure (i.e. spacegroup, cell dimensions and atomic fractional coordinates) by a deadline. The accounts of the meetings held after each challenge [1–4] provide an excellent review of the methods being seriously pursued as well as valuable collective conclusions. As Figure 1 shows, there was a considerable breakthrough in the current test [4], in that all structures were correctly predicted by more than one group as the most thermodynamically stable crystal found in an extensive search. The final relative energies were either evaluated by a van der Waals empirically corrected periodic electronic structure optimization [5], or by a lattice energy minimization based on an anisotropic atom–atom intermolecular potential [6,7].

It could be too hastily concluded from the success of this recent test, that reviewing the methodologies used for predicting organic crystal structures would be describing a nearly mature field. However, this is far from the case because of the prevalence of polymorphism: the ability of a molecule to adopt more than one crystal structure. Polymorphism has complicated the interpretation of the blind test results from the first, as four groups successfully predicted a metastable crystal structure of I, which was obtained by the first crystallization, and none predicted the structure found in all subsequent experiments. In the second blind test, so many groups predicted structures with alternative

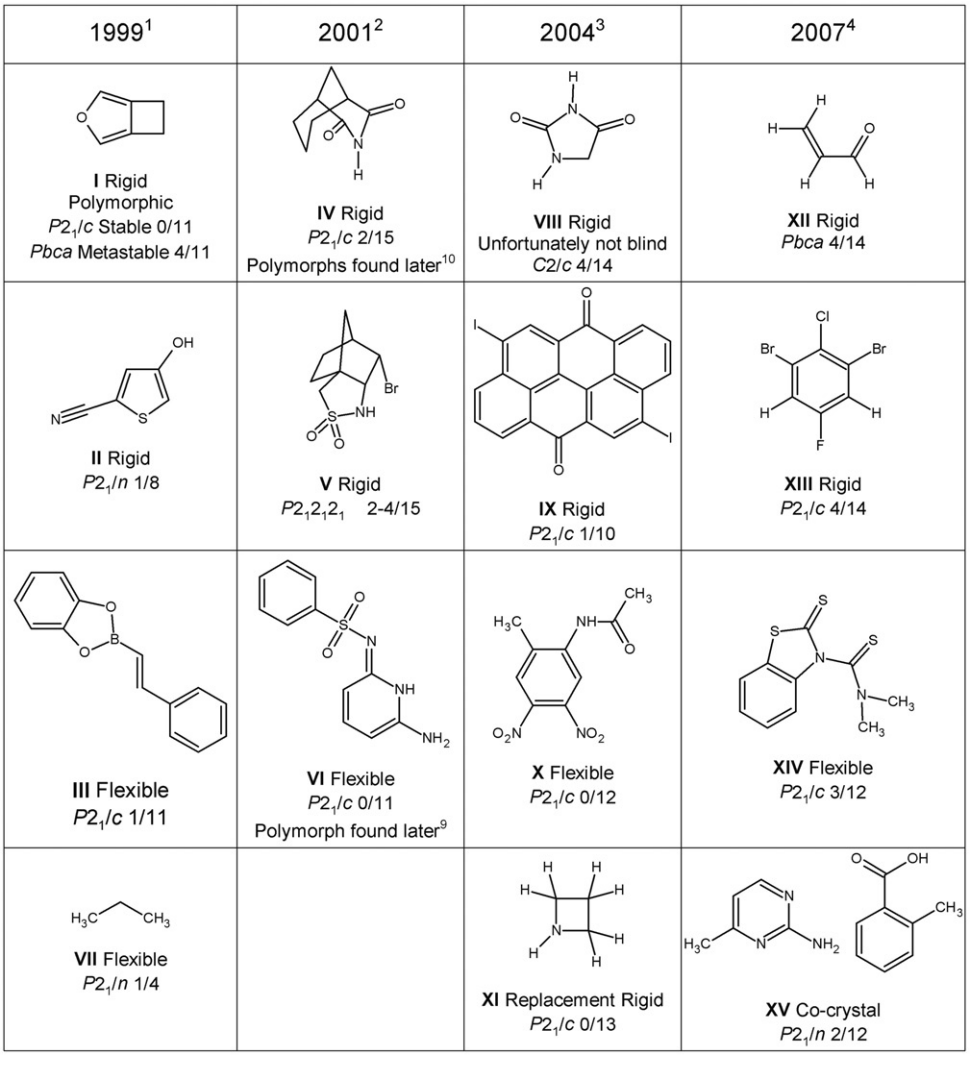

Figure 1. The success rates for predicting the crystal structures of the molecules given only the chemical diagram, in the Cambridge Crystallographic Data Centre's blind tests of crystal structure prediction. x/y indicates that there were x correct predictions, as judged by a reasonable overlay of the 15 molecule coordination sphere, from the y participating groups who each submitted three predictions [8]. Reproduced by permission of the PCCP Owner Societies.

hydrogen bonding motifs for IV and VI that the participants invited [2] experimentalists to search for such polymorphs. These were indeed found: for VI a probably more thermodynamically stable polymorph with the anticipated distinct hydrogen bonding motif [9], and for IV a closely related polymorph and a plastic crystalline phase which led [10] to the rationalization of why the anticipated polymorph could not be found. Thus the success of the 2007 blind test also suggests that the target crystal structures were, fortunately, all the most thermodynamically stable polymorphs, at least at the

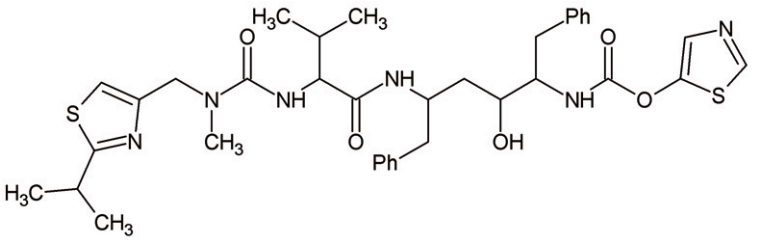

Figure 2. Chemical diagram of ritonavir.

crystallization temperature and down to the nominal 0 K assumed by most of the computational models.

Establishing the most thermodynamically stable polymorph over all practically important ranges of conditions found in manufacture, storage and use, is a major concern in the pharmaceutical and other speciality chemical industries [11–13]. The quality control implications are huge, since the physical properties can change dramatically with polymorph. Hence, pharmaceuticals are only licensed for manufacture in a specified solid form, as a change of polymorph could change the dissolution rates and general bioavailability of the pharmaceutical product. The problem of finding the most thermodynamically stable form is compounded by a tendency [14], known as Ostwald's law [15], for the first crystallization from melt or solution to yield a metastable form. There can be major problems in generating the most stable polymorph, most notoriously for ritonavir [16] (Figure 2), when the most stable polymorph first appeared two years into the production of this anti-HIV treatment, resulting in Abbott's inability to produce the licensed product and requiring urgent reformulation. Thus, there are now many companies, as well as research divisions in the major pharmaceutical laboratories, devoted to solid form development, seeking the most stable polymorph of the most desirable solid form (including salts, hydrates and co-crystals) that can be controllably produced for marketing. The output from such screens is more in accord [17] with McCrone's provocative comment [18] in 1965 that 'the number of forms known for a given compound is proportional to the time and energy spent in research on that compound' than there being only one crystal structure. However, there are very different estimates of the proportion of molecules exhibiting polymorphism [19], with definition and advances in scientific methods of characterization playing a role. A solid form screening company recently reported [17] polymorphs for 50% of the compounds studied, and multiple solid forms for 90%. This is in stark contrast to the Cambridge Structural Database [20] only containing two or more good quality crystal structures for 1% of its compounds [21]. There are obviously significant sociological influences on research endeavours into the organic solid state. Hence, it is perhaps also worth mentioning that an experiment in crystal structure prediction by popular vote [22], carried out at an International Union of Crystallography meeting, showed that crystallographers were unable to pick out the correct crystal structure from a small set of computed low energy structures.

Once the first crystals of a more thermodynamically stable polymorph have been obtained, they can then be used to seed crystallization experiments to produce it more readily. Hence, any method of generating new polymorphs [23] is potentially useful,

however impractical for production. In some cases the problems of preventing seeding leads to the phenomenon of disappearing polymorphs [24,25]: the inability to recrystallize a polymorph by a recipe that appeared perfectly reproducible [26] prior to the discovery of a new, more stable form. (Other cases of disappearing polymorphs are associated with changes in the impurity profiles in the crystallization [27].) Hence, despite the development of a wide range of automated polymorph screening systems [28,29], it is still not possible to experimentally cover all possible crystallization conditions that might possibly produce a new polymorph.

Polymorphism shows that kinetic factors can lead to practically important crystal structures that are not the most thermodynamically stable form. The computational prediction of the crystal energy landscape (the structures and relative energies of all thermodynamically feasible crystal structures) is a valuable complement to experimental polymorph screening [8]. It has the potential to provide either reassurance that the most thermodynamically stable and all practically important polymorphs are known, or provide structures to be targeted in an experimental search. More fundamentally, contrasting the thermodynamically feasible crystal structures with those observed can provide insight into the many factors that influence the process of crystallization.

Hence this review will concentrate on the recent developments of methods of calculating the relative stability of organic crystals, both observed and computationally predicted to be thermodynamically competitive. One of the first lessons learnt from the development of crystal structure prediction was that there are often many lattice energy minima within an energy range of order of $10\,\mathrm{kJ\,mol^{-1}}$ of the global minimum, and there are usually far more thermodynamically plausible structures than known polymorphs. This review aims to complement the international blind test papers [1–4], which provide a more complete account of the approaches that have been used. These include methods [30–32] which use experimental information from other crystal structures in the Cambridge Structural Database [33] to predict which of the structures predicted with an admittedly crude relative energy model are most plausible. In addition to surveying the progress in applying better levels of theory to calculating the relative energies of organic crystal structures, some illustrations of the way in which the computed crystal energy landscape have complemented experimental polymorphism studies, and vice versa, for the molecules in Figure 3, will be mentioned. However, the emerging picture of the potential complexities of the organic solid state mean that the use of computed crystal energy landscapes to understand solid form diversity is in its infancy, with various serendipitous findings making it a fascinating field.

2. Computing the thermodynamically most stable structures

2.1. *Searching for crystal structures*

A first challenge in crystal structure prediction is to search through a sufficient range of crystal structures, in terms of the space groups that are considered and the number of molecules in the asymmetric unit cell (Z'). The evaluation of the relative strengths of the many different search methods is an important outcome from the blind tests [34], though even here, the target crystal structures have been limited to 'common space groups' and $Z' = 1$ or occasionally 2. There is an increasing number of reported organic crystal structures with $Z' > 1$, and a proportion of these can be seen as 'fossil relics' [35] or

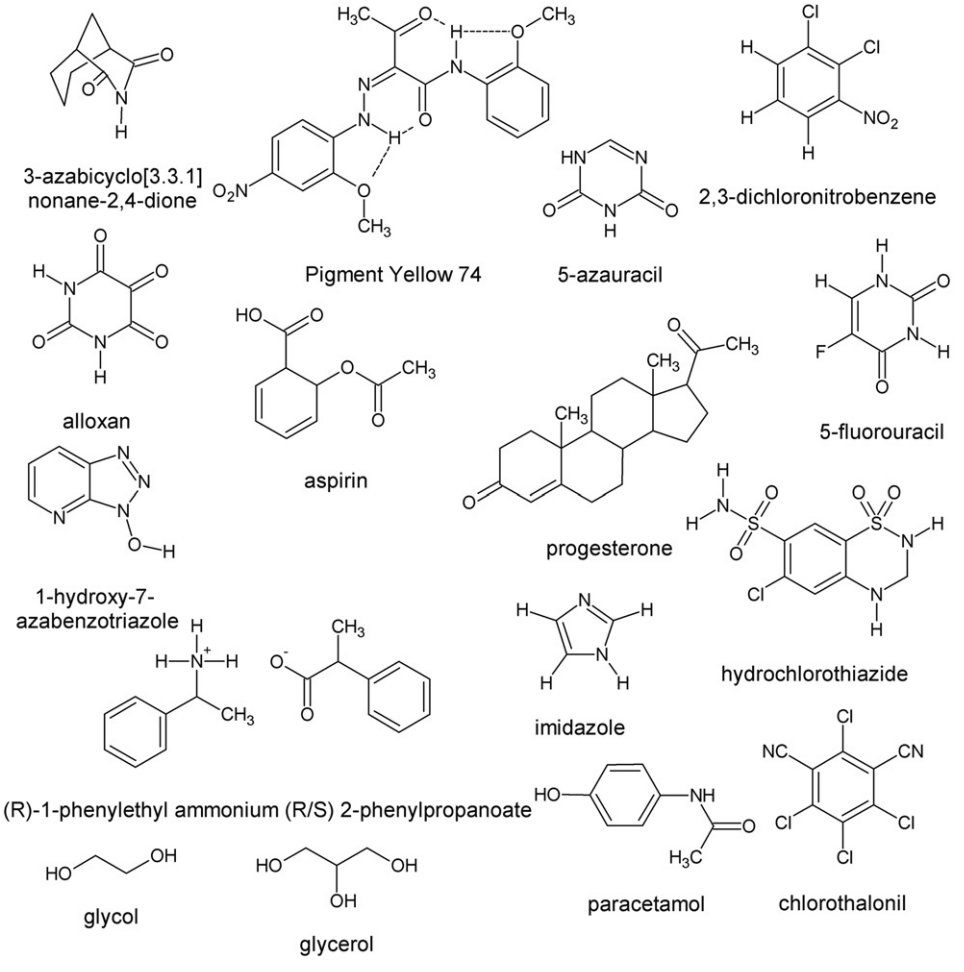

Figure 3. Chemical diagrams for some of the molecules whose crystal energy landscapes are mentioned in this article.

'arrested crystallization' [36] as they closely approximate [37] a more stable polymorph with $Z' = 1$. However, there are examples [37] where the most stable polymorph is $Z' > 1$ and has a hydrogen bonding motif that could not be achieved with $Z' = 1$, such as form II of 7-fluoroisatin [38]. The search problem for $Z' = 2$ is effectively equivalent to that for mono-hydrates or 1:1 co-crystals, diasteromeric salts or other solids where there are two molecular entities whose relative position in the unit cell increases the number of variables in the search. Thus, as the range of application of crystal structure prediction methods increases, so does the number of structures whose relative energies need considering. To illustrate, most of the searches discussed in this review have been performed using MOLPAK [39], where for each rigid conformation of the molecule, a systematic search for dense packings (considering $\sim 19^3$ pseudo-hard sphere packings) in each of up to 52 common coordination types (covering 26 of the most commonly observed spacegroups)

typically generates around three thousand structures which are reasonably close packed as starting points for the lattice energy minimization. For more extensive searches, Crystal Predictor [40,41] uses Sobol sequences to do a complete search over a specified range of flexible torsion angles as well as spacegroups and lattice variables, using a look up table of intramolecular energies, and typically covers at least several hundred thousand structures. The lattice energy minima always have to be clustered to remove equivalent structures. Further calculations, including more accurate re-evaluation of the energies, can then be performed on the most promising candidates. Thus, crystal structure prediction is certainly a problem where computer science can assist in making the calculations feasible. [42,43].

2.2. *Evaluation of intermolecular lattice energy*

The first selection of the most stable static crystal structures is usually done on the basis of the intermolecular lattice energy U_{inter} for rigid molecules. For flexible molecules, the total lattice energy, $E_{\text{latt}} = U_{\text{inter}} + \Delta E_{\text{intra}}$ is used, which includes the energy penalty ΔE_{intra} for the molecular distortion from the most stable conformer that occurs to improve the intermolecular interactions. Very recently, periodic electronic structure methods, which avoid this division into inter- and intramolecular energies have been applied to organic crystal structure prediction. The challenges and successes provided by these three approaches will first be reviewed, before discussing the progress towards evaluating the differences in free energy between the structures.

2.2.1. *Empirical model intermolecular potentials*

The relative stability of crystals of rigid molecules can be evaluated from the intermolecular lattice energy, U_{inter}, a static, nominally 0 K energy, which crudely approximates the heat of sublimation of the crystal [44]. This is usually evaluated from a model intermolecular pair potential, summed over the infinite perfect lattice [45]. The most widely used [7] model potentials are transferable, isotropic atom–atom models, which have been empirically fitted to crystal structures and heats of sublimation. Whilst a carefully parameterized *exp-6* functional form [46,47] gives a very worthwhile compromise between computational cheapness and accuracy, there are two sets of empirically fitted repulsion–dispersion potentials, which are often used in conjunction with an electrostatic model that has been derived from the *ab initio* charge density of the molecule. One set, FIT [48–51], uses parameters derived in the 1980s for C, H, N, O, F, Cl, and was extended to hydrogen-bonding molecules by the introduction of separate polar hydrogen parameters [52]. The more recent reparameterization by Williams [53,54] has a larger range of atomic types and an explicit shifting of the hydrogen interaction site from the nucleus. In these parameterizations, it was often found necessary to add non-nuclear sites to the point charge electrostatic model. Greater realism in the electrostatic forces is achieved by using the sets of atomic charges, dipoles, quadrupoles, etc., obtained by a Distributed Multipole Analysis [55,56] of the *ab initio* charge density. Representing the anisotropy in the electrostatic forces arising from lone pair and π electrons is critical in evaluating the relative stability of crystals that differ subtly in the geometries of their hydrogen bonding and π–π stacking arrangements. Indeed, crystal structure prediction studies have been successful in accounting for observed crystal structures which lack expected hydrogen

bonds to certain acceptors [57], including alloxan, which despite being purely composed of C=O and N–H groups does not have any conventional hydrogen bonds in its crystal structure. The improvement of a distributed multipole model over atomic point charges obtained by fitting [58] to the electrostatic potential generated by the same density, has been quantified by a study contrasting the crystal structure prediction results [59] of 50 rigid organic C, H, N, O molecules (60 observed crystal structures), with the change in the electrostatic model. This found that the use of distributed multipoles gave a significant improvement over the point charges from the same charge density, increasing the number of observed crystal structures being predicted to be at or within 0.5 kJ mol^{-1} of the global minimum to more than 50%.

This type of empirically-based repulsion–dispersion model has proved to be a useful approach to predicting the crystal structures of rigid organic molecules when combined with an *ab initio* based electrostatic model. However, whilst it is useful for seeing what types of structures are plausible, the energy ordering is often unreliable and needs to be improved. For example, the prediction of more stable structures for 5-fluorouracil did inspire a careful polymorph screen that found [60] the structure predicted at the global minimum, form II, by crystallization from dry nitromethane. However, thermal measurements of the heats of fusion and melting points of the polymorphs showed that this new form was probably not the thermodynamically most stable.

2.2.2. *Towards non-empirical* ab initio *based model intermolecular potentials*

Thus, providing more accurate model potentials for crystal structure prediction is a major driving force for the development of more accurate model intermolecular potentials. Indeed targeting the known structure to be the global minimum has been used as a criterion for the empirical fitting of force-fields [61–63]. However, more confidence can be placed in the predicted structures if the model potential is non-empirical and derived using the theory of intermolecular forces [64]. The general approach is to write the analytic intermolecular potential in an atom–atom form, with different functional forms used to model the short-range and long-range forces. The parameters of the long-range forces, which include the electrostatic, induction and dispersion forces, are derived from the *ab initio* molecular properties, calculated in distributed form. The parameters of the short range potential are derived through the intermediate step of fitting the short-range energies, which include the exchange-repulsion and penetration energies, to a density overlap model. By subsequently partitioning the molecular densities into atomic contributions, the short-range potential can be written in atom–atom form. This sequence of steps has the advantage of allowing us to assess the required form of the anisotropy and also whether distinct atomic types are required for the same element in different environments. Increasingly sophisticated intermolecular perturbation theory calculations for the exchange-repulsion and other short range terms can then be used to calculate a reasonable number of points on the intermolecular potential energy surface. These points are then used to fit a very limited number of constants of proportionality between the overlap and short range potential, and generally validate the approach. For example, an early success of the overlap model was to derive [65] a non-empirical atom–atom potential for oxalic acid which was capable of modelling both polymorphs satisfactorily. The key point here was the use of separate parameters for the two types of oxygen in the carboxylic

group, because the oxalic acid polymorphs sample different intermolecular contacts from most carboxylic acid crystal structures [66].

The use of a non-empirical, model intermolecular potential specifically derived for chlorothalonil [67], with an anisotropic atom–atom repulsion model obtained from the overlap model, was notably successful in rationalizing its complex solid state, where so far three polymorphs have been characterized. The global minimum corresponded to the most stable form, two low energy sheet structures rationalized the disordered form 2, two others appeared as constituents of the $Z'=3$ structure of form 3. Thus the five lowest energy structures found in the search, within an energy range of $1.25\,\mathrm{kJ\,mol^{-1}}$, were useful in understanding the powder X-ray diffraction data, and helped rationalize a complex solid state that, in this case, could be validated by single crystal data.

A transferable potential of the chlorobenzenes was developed [68], using the overlap model to determine that a set of anisotropic repulsion parameters for only two types of carbon (bonded to chlorine or hydrogen), chlorine and hydrogen would give reasonable accuracy. Transferable C_6 coefficients were derived from various atomic polarizability schemes, and the ability to reproduce the twelve known crystal structures of ten chlorobenzenes well was used to discriminate between the dispersion models: the only use made of experimental data in deriving the potential. The electrostatic forces were calculated using the distributed multipoles of the molecule's charge distribution. The resulting potential satisfactorily reproduced the available phonon and mechanical property data. Moreover, a search for possible crystal structures of *p*-dichlorobenzene gave the three polymorphic forms as the 2nd, 3rd, and 4th most stable structures, lattice energies within $0.2\,\mathrm{kJ\,mol^{-1}}$ of each other and all within $0.6\,\mathrm{kJ\,mol^{-1}}$ of the global minimum. The unobserved structure at the global minimum was a combination of the packings in the α and β forms, and the attachment energy model predicted that it would grow more slowly than these polymorphs. The predictive value of this almost non-empirical model was demonstrated later by its ability to reproduce the structure of the low temperature polymorph of 1,2,4,5-tetrachlorobenzene [69] and also show that the sheet structures of the two closely related polymorphs were thermodynamically more stable than the alternative herringbone packings.

Over the past few years there have been several developments in the theory of intermolecular forces [64] that considerably improve the prospects for obtaining even more accurate *ab initio* derived potentials. Firstly, it is now possible to obtain accurate distributed polarizability models and hence distributed dispersion models [64,70–73]. Indeed, now that very accurate damped isotropic or anisotropic $C_n(n=6,8,10,12)$ dispersion models can be parameterized from high quality wavefunctions using CamCASP [74], crystal structure modelling programs, such as DMACRYS (the successor to DMAREL [75,76]), need to be adapted to use these terms. More vitally, it is now possible to obtain more accurate short-range intermolecular energies corresponding to correlated wavefunctions by using symmetry adapted perturbation theory based on density functional theory SAPT(DFT) [64,77,78]. The CamCASP program suite is now capable of generating model intermolecular potentials in an anisotropic atom–atom form for quite a range of molecules. This was recently demonstrated [79] for $C_6Br_2ClFH_2$, when a model potential that was derived purely from *ab initio* calculations was able to predict the known crystal structure as the global minimum under the CCDC blind test conditions (Figure 1) [4].

2.2.3. *Semi-classical density sums 'Pixel' approach*

An alternative approach to evaluating the relative energies of organic crystal structures, based on the *ab initio* monomer charge density, is the semi-classical density sums SCDS-Pixel method [80]. This uses numerical integration over a crystal structure in which the molecules are represented by the *ab initio* charge density of the isolated molecule. The electrostatic term is therefore exact [81], the short range repulsion is derived by assuming the overlap model, and the induction and dispersion energies by distributing atomic polarizabilities over the pixels of charge density for that atom [82]. This method has proved very successful in re-ranking the energies of the low energy crystal structures found on crystal energy landscapes generated using simple model potentials [83]. However, it has had even more impact on the understanding of crystal packing [84,85], by dissecting the lattice energy into various contributions and into the interactions between pairs of molecules in van der Waals contact in the crystal. There are examples where the interaction between pairs of molecules in close contact are overall barely attractive, warning [86] against the over-interpretation of individual atom–atom contacts (weak hydrogen bonds, etc.) as playing a major role in determining the crystal structure. Apart from emphasizing the role of the dispersion in determining crystal packing, the SCDS-Pixel analyses have also shown that the induction energy is significant in many organic crystals.

2.2.4. *Including induction in organic crystal modelling*

Recent developments to provide realistic distributed atomic polarizability tensors for organic molecules [70,71] open up the possibility of including the induction energy explicitly in lattice energy minimization. The close contacts within crystal structures, particularly in hydrogen bonds, require the induction energy to be damped [71]. Also the incremental field due to the induced moments is sufficient that it is necessary to iterate the induced moments to consistency. The modelling of these two opposing effects has been validated by calculations on dimers in comparison with SAPT(DFT) estimates of the induction energy [71]. The likely magnitude of the induction contribution to the lattice energy has also been investigated, by calculating the induced moments in a molecule in the centre of a large cluster, extending at least 15 Å, representing the crystal. Two methods have been compared [87]: the use of distributed polarizabilities on the central molecule within the field arising from the distributed multipoles, and *ab initio* calculation on the central molecule within the field of the corresponding potential derived charges. In both cases the induced moments are iterated to self-consistency in the cluster then used to evaluate the induction contribution in the full periodic crystal using DMACRYS. The consistency between the two rather different methods is reassuring, and the implementation of dipolar polarizability tensors into DMACRYS to allow lattice energy minimization including the induction term is in progress.

The comparison of the relative induction energy contributions to the lattice energies of a range of known and hypothetical crystal structures shows that it can provide valuable reordering of lattice energies, particularly between different hydrogen bonding motifs. The prediction that carbamazepine has a more stable structure with a hydrogen bonded catemer motif than the hydrogen bonded dimer motif in its known polymorphs has stimulated an extensive automated screen to search for such a polymorph. This was not found, though the extensive coverage of 66 solvents and five different types of

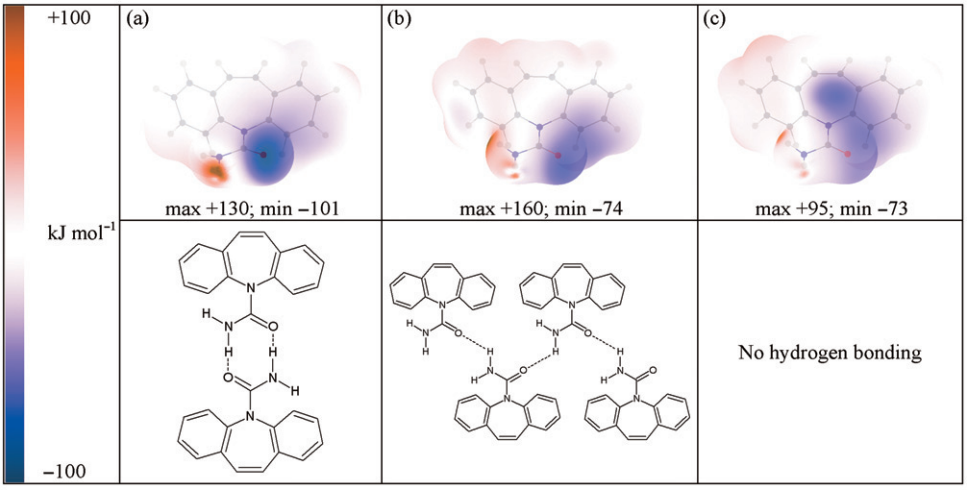

Figure 4. The electrostatic potential due to the induced moments arising from the polarization of carbamazepine in (a) the most stable polymorph, form III, which forms amide dimers (b) the hypothetical structure which forms catemeric hydrogen bonds and is observed in solid solution with dihydrocarbamazepine (c) a low energy structure which does not contain any conventional hydrogen bonds, but whose lattice energy is within 13 kJ mol^{-1} of the global minimum. The induced moments are calculated as described in reference [87] for the computationally consistent crystal structures (am7, cc12 and ab41) and the resulting additional electrostatic potential displayed on the van der Waals surface, using ORIENT4.6. The maximum and minimum potential values on this surface are given in kJ mol^{-1}.

crystallization protocols (temperature, cooling rate, agitation rate) led [88] to the discovery of three new solvates (in addition to three of the four known polymorphs and five known solvates), and further analysis of this data to a further three new solvates [89]. Although improving the quality of the wavefunction used for the DMA [87] and allowing flexibility in the amide group to adjust the positions of the protons [90,91] all improve the relative stability of the most stable known polymorph to an unobserved catemer structure, it is the relative induction energy that most strongly suggests that form III is the most thermodynamically stable. This is demonstrated in Figure 4, which displays [92] the change in the electrostatic potential around the molecule caused by its polarization within three crystal structures. However, understanding why a catemer structure is not observed as a metastable polymorph remains intriguing [93] given that carbamazepine does form the catemer motif in a solid solution with dihydrocarbamazepine [94].

2.3. *Flexibility, adding the intramolecular energy penalty*

2.3.1. *The 'monomer + model' intermolecular potential approach*

The crystal structure prediction of conformationally flexible molecules poses an additional challenge, as there are many examples of conformational polymorphism [11] where each polymorph has a distinct conformation in the crystal structure. The current top system for the number of coexisting polymorphs of known structure [95] is nicknamed ROY because

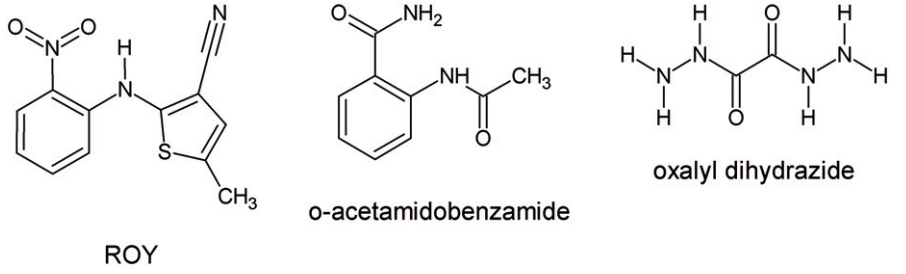

Figure 5. Molecules with challenging conformational polymorphism: ROY (5-methyl-2-(2-nitrophenylamino)-thiophene-3-carbonitrile), o-acetamidobenzamide and oxalyl dihydrazide.

of the Red–Orange–Yellow spectrum of colours caused by the change in conformation, as well as diverse morphologies, observed in the original six polymorphs [96]. In such polymorphs, the energy penalty ΔE_{intra} from changing the molecular conformation from the most stable 'gas phase' conformation (assumed to be the *ab initio* minimum energy structure) is compensated for by the increased stability of the intermolecular lattice energy. Hence, neglecting thermal effects, we need to consider the relative crystal energies, $E_{\text{latt}} = \Delta E_{\text{intra}} + U_{\text{inter}}$. This is clearly very sensitive to the balance between the model for the inter and intramolecular forces. Although there have been many successful crystal structure predictions with atomistic force-fields of the type used in biomolecular modelling [97], it is also clear that for many pharmaceutical molecules, the balance of forces in a particular force-field may lead to gross changes in the molecular conformation when the experimental crystal structure is energy minimized [98] and hence be obviously unsuitable for predictive work. Aspirin provided an early demonstration of more subtle errors: an early force-field study predicted the possibility of a polymorph with a planar conformation [99]. However, this force-field gives a planar conformer for the molecule in isolation, unlike *ab initio* studies which show that the observed non-planar conformation in the crystal approximates a local minimum in the conformational energy. A crystal structure prediction study [100] using the two lowest B3LYP/6-31G(d,p) gas phase optimized minima as rigid (plus three planar transition state structures) found three structures a few kJ mol^{-1} more stable than the others. One was based on the most stable isolated molecule structure, and was stabilized by an unusual hydrogen bonding motif, which seemed unlikely to readily form in solution. The local minimum in the conformational energy ($\Delta E_{\text{intra}} = 3.5$ kJ mol^{-1}) produced two crystal structures [100], containing the usual carboxylic acid dimer hydrogen bonding motif within the same sheets, which were stacked in different ways. One corresponded to the known structure of aspirin. The other structure was very susceptible to shear, and so was dismissed as unlikely to be formed. However, this alternative structure was later found in crystals of aspirin produced in an attempt to co-crystallize aspirin with levetiracetam [101]. This illustrates the complementary problems of being sure all polymorphs are found experimentally and explaining why a number of thermodynamically feasible structures are not observed.

The "*monomer + model*" approach of combining *ab initio* intramolecular energies for isolated molecules (ΔE_{intra}) with carefully developed model intermolecular potentials (U_{inter}) was demonstrated to be successful for the relative energies of crystal structures of

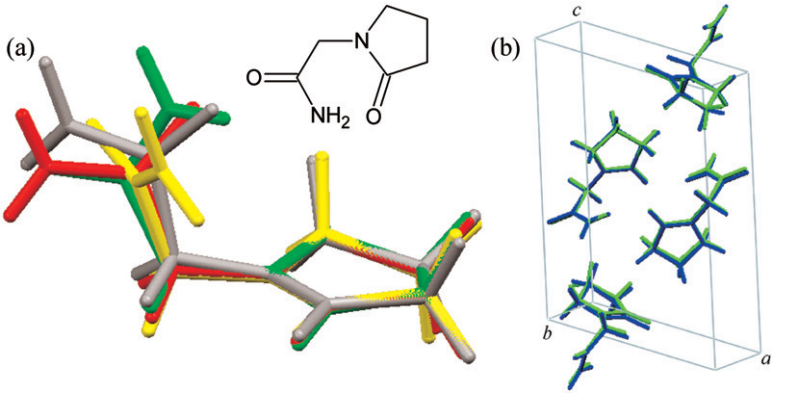

Figure 6. The conformational polymorphism of the nootropic drug piracetam (a) An overlay of the *ab initio* gas-phase optimized conformer (yellow) with the observed conformers in form I (major component of the disordered structure in red), form II (grey)(form III and the new high pressure form V also have this conformation) and form IV (green). (b) Observed unit-cell contents of form IV (green) with the structure predicted in an informal blind test (blue) overlaid [104].

glycol and glycerol [102]. The challenge is to implement this for larger organic molecules. The use of multiple rigid conformations in separate rigid body searches can be very effective when there are only a small number of conformations to consider, as illustrated by the successful blind prediction of a new polymorph of 1-hydroxy-7-azabenzotriazole [103] by considering 19 orientations of the hydroxyl group. Careful consideration needs to be given to the conformational flexibility of any molecule, to ensure that a search is carried out with any type of conformation whose conformational energy penalty might be compensated for by stabilizing the intermolecular lattice energy. Whilst considering all low energy conformational minima is an obvious starting point, this may not be sufficient: in piracetam, the gas phase minimum has a poor internal hydrogen bond which is not observed in any of the three polymorphs known at the time (Figure 6). A systematic search [104] over the two most flexible torsion angles found various conformations where the intermolecular hydrogen-bonds more than compensated for the loss of the intramolecular contact. This approach of scanning to see the conformations that resulted in a low (stabilizing) E_{latt}, and then interactively refining the search by smaller increments in the main and amide proton torsion angles, correctly identified the two ordered conformational polymorphs as low energy. This study was then given more impetus, and the technique validated, by the challenge to predict a new conformational polymorph that had been discovered [105] by crystallization under high pressure. The lowest E_{latt} structure with a substantially different conformation from published polymorphs proved [104] to be an excellent match for the newly discovered polymorph, as shown in Figure 6. Since then, another polymorph has been found at high pressure [106], but it appears that this form V transforms both physically and computationally to form II at ambient pressure [107]. This emphasizes the desirability of being able to explore the crystal energy landscape as a function of pressure.

Whilst all methods for crystal structure prediction of flexible molecules need to ensure that all regions of conformational space are considered [40], the use of multiple rigid

conformers can result in many structures that are sufficiently closely related that they would correspond to the same minimum if the flexible torsion angles were optimized in response to the crystal packing forces. This is achieved by DMAflex [90], a procedure that performs a simplex minimization of E_{latt}, by combining minimization of the intermolecular lattice energy, U_{inter}, by DMACRYS for each conformation whose energy penalty, $\Delta E_{\mathrm{intra}}$, is calculated using GAUSSIAN [108]. For each change in the specified torsion angles, the corresponding distributed multipoles [55] are evaluated by using GDMA [109] to analyse the GAUSSIAN charge density and used within DMACRYS, i.e. the procedure models the conformation dependence of the electrostatic forces. This approach has been validated for its ability to reproduce a range of crystal structures of molecules with a limited number of flexible torsion angles [90]. More importantly, the change in the relative energies of (R)-1-phenylethylammonium (R/S)-2-phenylpropanoate structures found in rigid body searches produced [110] using DMAflex, predicted the structures and relative energies of the three diastereomeric salts (the RR-salt is polymorphic) in far better agreement with experiment. Apart from its use to refine the structures and relative energies for obviously conformationally flexible molecules, the lattice energy is quite sensitive to the position of hydrogen bonding protons, and so DMAflex refinements of proton positions can lead to improvements in relative energies.

The DMAflex procedure is very computationally expensive, and a quicker variant that looks up $\Delta E_{\mathrm{intra}}$ from a tabulated *ab initio* conformational energy surface (in the region of each minimum) and analytically rotates the multipoles to represent each new conformation is under development [111]. The principle use of such a procedure is in conjunction with the Crystal Predictor [40] search methodology, which also uses the computed $\Delta E_{\mathrm{intra}}$ surface, to improve the modelling of the electrostatic contribution to the lattice energy from an atomic point charge model.

2.3.2. *Electronic structure modelling*

An extreme case of conformational polymorphism, which served as an early warning of the problems of determining the energy range of conformations to be considered in crystal structure prediction [112], is o-acetamidobenzamide (Figure 5) because the transformation from the α to the β polymorph involves the breaking of an intramolecular hydrogen bond to form an additional intermolecular hydrogen bond [113]. There is a large gas phase conformational energy difference, of the order of 40 kJ mol^{-1} between the two molecular structures in isolation, which is only adequately modelled as balanced by the intermolecular lattice energy difference when the differential induction energy is taken into account [114]. The general stability of the intramolecular hydrogen-bond and yet poor packing of this molecular conformation within its crystal structure is evidenced by the molecule adopting the α form conformation in a wide range of solvated structures [115].

This fairly extreme case of needing to model both inter- and intramolecular hydrogen bonding equally accurately suggests that modelling all interactions at the electronic structure level should be more effective than the '*monomer + model*' approach. The ability to optimize all the atomic positions and the cell parameters simultaneously is clearly very attractive, as it avoids the DMAflex requirement to choose which molecular torsions and angles are explicitly varied whilst all other conformation degrees of freedom are determined by a constrained isolated molecule *ab initio* optimization. Recently there have been many developments in periodic *ab initio* codes. The advantages of the scaling of

density functional methods with number of electrons in the unit cell over wavefunction approaches, such as periodic post-HF calculations, means that such approaches have started to be used for crystal structure prediction of organic systems [116,117]. The case of o-acetabenzamide, and the five recently published polymorphs of oxalyl dihydrazide [118] (Figure 5, where the α form has more classical intermolecular hydrogen bonds than the β, γ, δ and ε forms with strained intramolecular hydrogen bonds), provided a good test of these methods. Unfortunately, none of the three standard hybrid and non-hybrid functionals used with a 6-311G(d,p) atom-centred basis set methods with CRYSTAL06 [119] nor the three functionals using plane wave basis set calculations with CASTEP [120] were capable of energy minimizing all seven crystal structures to give even reasonable agreement with experiment [114]. The hydrogen-bonding motifs were well reproduced, but there was generally considerable expansion in the cell directions which are determined by the dispersion forces. The absolute crystal energies (derived by subtracting the isolated molecule energies calculated by the same method, after the atom-centred basis set calculations had been corrected for basis set superposition error), were generally such poor underestimates of the expected heats of sublimation, that no confidence could be placed in the relative energies. This was in marked contrast to the consistency found for the molecular energies and ΔE_{intra} values. Thus, the generally acknowledged weakness of current density functional methods in reproducing the long range dispersion, prevents these non-empirical electronic structure methods from adequately modelling organic crystal structures.

Various methods of correcting this inadequacy for organic crystal structures, by adding the dispersion to the density functional energy, have been proposed [121–123]. For example, the GRACE package [124] combines a DFT evaluation using VASP [125] (with standard projector-augmented wave potentials and the PW91 exchange-correlation functional) with an atom–atom pairwise C_6/R^6 correction, using atomic C_6 coefficients, which is smoothly damped by a functional form which was determined for organics containing C, H, O, N, Cl and S by fitting to a wide range of known crystal structures [5]. This method has given very good relative energies in crystal structure searches for a range of small organics [5] and predicted all four targets in the 2007 international blind test as the most stable [4,126]. This methodology also passes the severe test of modelling the structures and giving plausible absolute and relative crystal energies for the o-acetamidobenzamide and oxalyl dihydrazide polymorphs [114]. Thus such empirically dispersion-corrected DFT methods are very promising for providing more accurate relative energies at the last stage of a crystal structure prediction search, at least for smaller molecules and unit cells with current computational resources.

2.4. *Free energy*

The polymorphs of practical importance are those which can exist over the range of temperature and pressure conditions that may be encountered in use, production and storage of the materials around the world. Polymorphs are often enantiotropically related, i.e. the thermodynamically more stable polymorph changes at some temperature below the melting points. However, this transition is often not observed within the solid, and even when it is, is almost invariably a first order transition with considerable sample-dependent hysteresis, even for very closely related polymorphs such as those of

1,2,4,5-tetrachlorobenzene [69]. Polymorphs can be monotropically related, i.e. some are always metastable throughout the temperature range. The relative stability of polymorphs at a given temperature can be established by allowing solution mediated transformations (slurrying the two forms over a long period) and the enantiotropic or monotropic relationship deduced from various empirical rules, such as the heat of fusion or heat of transition rule, which are based on varying qualities of assumptions. Thus a method of computing the relative free energies of the polymorphs (and other energetically competitive structures) as a function of temperature is a highly desirable target for computational chemistry because the experimental validation over the range of different types of organic crystal is so difficult. Harmonic-approximation, rigid-body estimates for pairs of polymorphs have shown that lattice-vibrational entropy differences are seldom, if ever, large enough to equal or exceed the enthalpy differences at room temperature [127]. Hence the evaluation of E_{latt} is generally a good first approximation to the relative stability. However, when the predicted differences in E_{latt} are small, consideration of the entropy difference can reorder the different structures significantly.

The harmonic approximation to estimate the lattice frequencies, and hence the lattice vibrational contributions to the entropy, has the computational efficiency to be applied to hundreds of low energy crystal structures. Including the coupling between the low frequency intramolecular modes of flexible molecules with the intermolecular lattice modes, is clearly even more demanding of the balance between the inter- and intramolecular forces than the relative energies: lattice entropy effects have been explored with force-fields for glycol and glycerol [128], but obtaining realistic lattice frequencies for flexible pharmaceutical molecules is a very stringent test for atomistic force-fields. Rigid-body lattice dynamics methods have been used to calculate zone centre ($k = 0$) frequencies for naphthalene, pyrazine, imidazole and α-glycine using a variety of model potentials, including distributed multipole electrostatic models [129]. This demonstrated a correlation between the accuracy of the potential and the errors in the frequencies of modes involving deformations of different intermolecular contacts, emphasizing the need for realistic potentials. Similarly the computed elastic constants are very sensitive to the anisotropy in the intermolecular forces in many hydrogen bonded crystal structures [130]. Using the elastic constants to estimate the contribution of the acoustic modes to the thermal energy, in conjunction with the phonon modes, allows the estimation of the Helmholtz free energy as a function of temperature [131]. We routinely calculate this estimate of the thermal energy, as well as the zero-point vibrational energy, for the low energy crystal structures: as expected, these contributions generally only reorder the relative energies of structures that are close in energy but very different in packing. For example, a hydrogen bonded sheet structure may have low frequency modes for relative motions of the sheets that entropically stabilize the structure at higher temperatures relative to those structures with hydrogen bonding in all three directions.

The interplay between the different types of bonding in an organic crystal limits the validity of the rigid-body and harmonic approximation in different ways. A molecular dynamics study of crystalline imidazole (with hydrogen bonding chains) and 5-azauracil (which has hydrogen bonding sheets), with the same rigid-molecule and distributed multipole based model potential, carried out using DL_MUTLI [132,133] was analysed for its phonon frequencies. The results compared well with the use of the harmonic approximation [134], with frequencies differing by less than 5 cm^{-1} for imidazole at 100 K

and 20 cm^{-1} for 5-azauracil at 310 K. However there was no obvious correlation of the errors in the harmonic approximation with the type of intermolecular contacts being deformed in a given mode. Thus, for reasonably rigid molecules, the harmonic approximation can give useful estimates of phonon energies. It is also proving useful in assigning modes in low temperature terahertz spectroscopy, for molecules such as carbamazepine [135], an evolving experimental methodology for characterizing polymorphs.

A major limitation of the harmonic approximation is that it will not show when a lattice energy minimum is not a free energy minimum. It has been noted that many low energy structures prove unstable in a short molecular dynamics simulation shake-up [136]. The ability for a known crystal structure to remain stable in a Molecular Dynamics simulation is also seen as quite a severe test of the model potential: an isotropic model specifically derived for imidazole failed this test [137] which has been used to test the transferability of potentials for energetic materials such as 2,4,6-trinitrotoluene [138]. However, if the potential is adequate to reproduce the known structures, the Molecular Dynamics simulation can show that some of the static lattice energy minima are thermally unstable: for example approximately a quarter of the 66 low energy crystal structures predicted for 5-fluorouracil [60] proved thermally unstable in a careful free energy minimization [139] using the same distributed multipole based model potential. There are cases where the lattice energy minimum will have a lower symmetry than the experimental structure, as the latter is a thermal average over the symmetry related minima. This caused problems in the interpretation of the blind test results for azetidine (Figure 1, XI), when various participants found a $Z' = 4$ structure which closely approximated the experimental $Z' = 2$ structure, which was a transition state between minima. This can indicate the likelihood of genuine phase transitions: MD simulations [140] of cyclopentane reproduced the phase transition between the ordered low temperature phase III, and the rotationally disordered high temperature phase I in good agreement with experiment. It also gave insight into the complex intermediate phase II, seen both experimentally in the range 118–134 K [140] and in the simulations between 125 and 127 K, as being a rotationally disordered phase that sampled a smaller subset of the many almost equi-energetic predicted static structures.

Ideally, crystal structure prediction should just locate the structures that are free energy minima under practically accessible conditions. The method of metadynamics seeks to explore the free energy surface to locate all minima. Very promising results were obtained for benzene [141] where such a study only located seven free energy minima which could be associated with the seven known phases. Application of this methodology [139] to the known and predicted low energy structures of 5-fluorouracil show that the methodology needs further development for cases where the intermolecular interactions produce a variety of free energy barrier types between minima: the metadynamics method only produced transitions between small subsets of structures which had the same hydrogen-bonding motif. It is clear that establishing the range of plausible crystal structures by static crystal energy minimization and an adequate model for the inter- and intramolecular forces is an essential prerequisite to developing more powerful methods of considering the free energy surface.

2.5. *Summary of thermodynamic methods of calculation*

The early (1995) discovery [142] that there were thousands of possible crystal structures for six monosaccharides within 10 kcal mol^{-1} led to systematic improvements to *ab initio* based model potentials [143] and consideration of free energy [128] based on glycol and glycerol. This theoretically based '*monomer + model*' approach, including the free energies, eventually led to five of six monosacharides being found as the global minimum [144]. This series of studies, and others mentioned above, clearly indicate that improving the theoretical basis of the evaluation of the relative stability of the crystal structures leads to more observed polymorphs being either the most stable or within a few kJ mol^{-1}. However, highly accurate expensive calculations will often not always be necessary: Pigment Yellow 74 has the known structure as 12 kJ mol^{-1} more stable than any other possibility [145], and it is so plausible that the close packing and polar interactions could not be satisfied in any other way, that this structure could be clearly predicted by quite crude models.

It is the specific molecule that determines whether it has one simple crystal structure that is uniquely favourable and will not be polymorphic, or whether it has many approximately thermodynamically equivalent structures so that calculating their relative energy ordering is very demanding. This was demonstrated by a combined experimental and computational study of five isomers of dichloronitrobenzene [146]. The 2,3 isomer is readily predicted [146] as the global minimum in the lattice energy (for all isomers), by a simple MOLPAK search using the *ab initio* optimized molecular conformation. However, although the predictions for 2,4-dichloronitrobenzene were almost as clear, it was found [146] to adopt a $Z' = 2$ structure with the two molecules having significantly different changes in the nitro group torsion angle. Thus, although it is possible to estimate from the degree of flexibility, functional groups and size of the molecule, whether it is possible to calculate the relative energies with worthwhile accuracy, you need to do a crystal structure prediction search before you can assess whether this accuracy is sufficient to determine the most stable structure.

3. Thermodynamic stability relative to what?

The preceding discussion has assumed that predicting organic crystal structures is a matter of evaluating the relative thermodynamic stability of the crystals relative to the molecules in the gas phase. However, organic crystals are rarely formed from gas phase molecules: many decompose prior to sublimation. There are also competing reactions with kinetic barriers. Before considering briefly the kinetic factors that are usually invoked in discussing polymorphism, I would like to raise a few other issues that illustrate the problems in defining the thermodynamic driving forces which determine how molecules crystallize.

3.1. *Chiral molecules and diasteromeric salts*

Chirally pure molecules often [147] adopt crystal structures which are not the most thermodynamically stable relative to infinitely separated molecules. For example, a crystal structure of racemic progesterone is predicted [148] to be more stable than the known polymorphs, but this crystal structure could only be formed by mixing the naturally

occurring chiral steroid with its synthetic mirror image. (This internal validation [148] of a prediction was an unusual and costly crystallization experiment!) There is such a huge conformational barrier to changing chirality at sp^3 carbon atoms, that crystal structure prediction work can be restricted to chiral spacegroups and be used to study chiral separation by the formation of diastereomeric salts. Adding an enantiomerically pure acid to a mixture of enantiomers of a base can result in chiral separation by crystallization if the solubility difference between the resulting salts is sufficiently different. Current methods appear capable of establishing whether the solubility difference, as approximated by the lattice energy difference, is sufficiently large for a given acid that it is worth testing to provide an effective chiral resolution process [149]. However, accurate free energies are required to quantitatively predict the resolution efficiency.

3.2. *Tautomers*

A different question of what base-line to take arises for the crystal structure prediction of molecules capable of forming tautomers. (Tautomeric conversion rates also pose a problem in defining polymorphism [19] in terms of different crystal structures that give an identical solution.) Figure 7 shows the lattice energy landscapes for two tautomers of

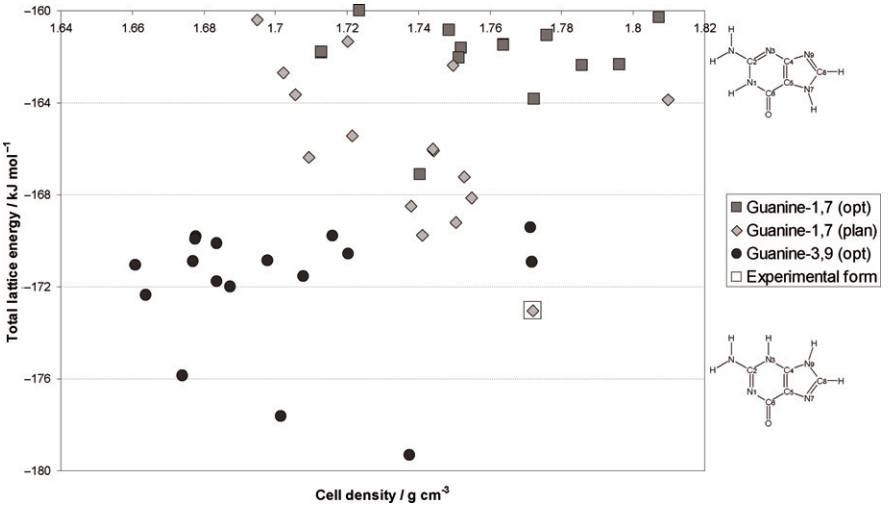

Figure 7. Partial lattice energy landscapes for guanine showing the sensitivity to tautomer and conformation for the (1,7) tautomer found in anhydrous guanine and the (3,9) tautomer found in the monohydrate crystal. Each symbol represents a low energy crystal structure which is a minimum in the total lattice energy, $E_{\mathrm{latt}} = U_{\mathrm{inter}} + \Delta E_{\mathrm{intra}}$ relative to the specified tautomer in the gas phase, with U_{inter} calculated using a distributed multipole electrostatic model of the MP2 6-31G(d,p) wavefunction and the FIT empirical model potential, and $\Delta E_{\mathrm{intra}} = 3.1\,\mathrm{kJ\,mol^{-1}}$ [150] for the NH_2 constrained planar molecular conformation (plan) used in addition to the MP2 6-31G(d,p) optimized conformation (opt) for the (1,7) tautomer. Only structures within $10\,\mathrm{kJ\,mol^{-1}}$ of the global minimum for the (3,9) tautomer for this optimized molecular structure have been shown for clarity. The open square denotes the minimum calculated starting from the experimental structure with the same computational model.

guanine, with the lattice energy being defined relative to that tautomer in the gas phase. The (3,9) tautomer has a crystal with the lowest lattice energy, but this tautomer is significantly less stable [151] than the (1,7) tautomer in the gas phase, by over 70 kJ mol^{-1}. The most stable crystal structure for the (1,7) tautomer corresponds closely to the recently determined crystal structure of guanine [152], which is thermodynamically consistent. However, we should note that the (3,9) tautomer is found in the monohydrate structure, and is so stabilized by hydration that it, and not the (1,7) tautomer, exists in aqueous solution [151]. Since the structure of anhydrous guanine was determined from very small crystals obtained in an attempted solvothermal synthesis of a potassium complex using guanine and solid potassium in dry ethanol, the tautomeric equilibrium involved in the crystallization is not obvious. Since fish grow scales containing the anhydrous form of guanine [153], there are clearly many issues to be addressed to understand its crystal growth! The challenge to computational chemistry to predict the crystal structures of guanine thus includes determining the relative energies of the many possible tautomers of guanine [151] and estimating the barrier to planarization of the amine [150] sufficiently accurately relative to the intermolecular lattice energies.

3.3. *Formation of multi-component crystals*

The issue of thermodynamic driving forces for crystallization can be complex when there is competition between different crystalline forms of the molecule, with some containing additional components. There are reported successes in predicting monohydrates [154,155], solvates [156], diastereomeric salts [110,149] and co-crystals (e.g. Figure 1 XV [4,126]) which show that the increased search problem in considering the relative orientation of two molecules in the asymmetric unit [154] can be tackled successfully. However, these studies aimed to predict a known multi-component crystal structure, rather than whether it can form in preference to crystallizing as pure components. Assuming that this requires the multi-component form to be thermodynamically more stable than its components, such predictions are a stringent test of the computational model for the relative crystal energies. Predicting the possible existence of co-crystals, such as the 1:1 carbamazepine-aspirin cocrystal [101] would be extremely worthwhile, because the pharmaceuticals industry is interested in producing co-crystals [157] of active ingredients that allow beneficial formulations. However, even when a co-crystal appears on the ternary phase diagram for its component molecules and the solvent, it will not be formed by solvent evaporation if the two components differ so much in solubility that one crystallizes out preferentially [158]. We could test whether a co-crystal is more thermodynamically stable than its components, in principle, by predicting the lowest energy possible for the cocrystal, and comparing it with those of the pure components. There have been a few studies comparing the lattice energy of two component (1:1) crystals with the sum of lattice energies of the separate components, a series of monohydrates [155], and co-crystals of succinic acid and aminobenzoic acid [159]. The thermodynamic driving force in favour of formation of the two component crystal is often not markedly greater than the uncertainty in the calculations due to the molecular flexibility, intermolecular potential and entropic effects.

This section illustrates that conformational and tautomeric equilibria, and competing crystallization products are amongst the many factors that influence crystallization.

Although predicting the relative thermodynamic stability of different observed and hypothetical solid forms of a given organic molecule is challenging, it is very worthwhile because of the experimental problems in finding all possible solid forms [23]. When there are more thermodynamically feasible crystal structures than known polymorphs, it is important to understand the factors that determine which crystal structures are found.

4. Towards deciphering kinetic factors

The kinetics of molecular association, nucleation and growth, relative to transformation rates to more stable forms, will determine which of the crystal structures on the crystal energy landscape are observed. Entire reviews could be written on computational studies of the kinetics involved in each step, and such work is beginning to be applied to organic solids. However, I would like to conclude by mentioning how the computed lattice energy landscapes of the thermodynamically feasible crystal structures have shown the potential of computational chemistry to complement work in this area.

4.1. *Molecular association*

When there is strong association of the molecules into certain hydrogen bonded dimers, or other motifs, in a solvent, then it is highly probable that this will be reflected in the polymorph that crystallizes, provided it can do so in a thermodynamically feasible crystal structure. FTIR [160] and NMR [161] studies have demonstrated that initial aggregation in solution correlates with certain polymorphic forms, though in other cases the solute–solute interactions detected in solution have a more limited relationship [162]. Certainly, the solvent can have a major effect: in the case of 5-fluorouracil, Molecular Dynamics [163] showed that water so strongly hydrates the N–H and C = O groups of 5-fluorouracil that the initial aggregation of two molecules in water is usually through a close contact between the hydrophobic F atoms, as seen in form I. Even when one N–H···O=C bond is formed between two 5-fluorouracil molecules, the hydrating water is not readily displaced to allow the formation of the second hydrogen bond, though this would readily form in the gas phase or in dry nitromethane giving the doubly hydrogen bonded ribbon seen in form II, the novel polymorph [60] found by crystallizing from this solvent.

4.1.1. *Solvate formation*

It might be expected that solvates would form when there was a particularly strong association of the molecule with the solvent, making it difficult for the solvent to be expelled from a nucleating cluster. However, other solvates have structures [164] in which the solvent appears to be filling the space between the preferred solute motifs. The latter appears to be the case for 5-fluorocytosine where all the low energy computed structures contained [165] the same hydrogen bonded ribbon motif that was simultaneously discovered in the two polymorphs and four stable solvates. In contrast, the diverse range of doubly hydrogen bonded dimer motifs in the low energy structures of hydrochlorothiazide [166] correlates with those found in the two polymorphs and five of the solvates, but in a further two solvates, the hydrochlorothiazide hydrogen bonds to the solvent. Thus, whilst even establishing the range of solvates that can be found for some molecules is

challenging [89,164]), and desolvation of crystalline solvates is a route to finding polymorphs, some ideas about the propensity and likely motifs in solvates can come from analysing the structures on the lattice energy landscape.

4.1.2. *Nucleation*

It is possible that the thermodynamically stable crystal structure may have difficulty in nucleating. For example, the long delay before the appearance of the more stable conformational polymorph of ritonavir [16] (Figure 2) reflects the difficulty of its nucleation. A 99 : 1 ratio of conformations in solution, even at elevated temperatures, indicates a significant barrier to the conversion of molecules to the crystal conformation. However, after the first crystallization of form II, probably through heterogeneous nucleation by a degradation product [16], seeds of the new structure existed and facilitated nucleation to the extent of requiring reformulation of the pharmaceutical.

Many discoveries of new polymorphs appear associated with forcing molecules into conformations and associations that might not otherwise occur and stabilizing specific types of nuclei, either accidentally or deliberately, as in crystallization in the presence of polymers [167], templating surfaces [168] or capillary confinement [169]. For example, the polymorphic outcome of glycine has been shown to be dependent on a huge range of variables, including whether the crystallization occurs in the bulk or in the thin film on the walls of the vessel [170].

It will be a long time before nucleation is sufficiently well understood to be able to select which low energy structures are kinetically preferred because of their nucleation rate. However, some inferences are possible. An experimental search for the most commonly predicted [2] polymorph of 3-azabicyclo [3.3.1] nonane-2,4-dione (Figure 1), containing doubly hydrogen-bonded dimers, was unsuccessful [10]. However, the observation of a plastic phase suggested that the assumption that the barrier to rearranging the hydrogen bonds was sufficient to allow the formation of polymorphs was not valid in this case. This was confirmed by simulations of the approach of a third molecule breaking one of the two hydrogen bonds in a dimer, implying that the rearrangement of any dimer motifs to the catemer would be sufficiently facile that a nucleus of dimers was very unlikely [10]. Experimentally studying nucleation is challenging, but central to understanding polymorphism [171], as the role of solvent, interfaces, and other nucleation inhibitors and promoters is often critical [172]. (Nucleation promoters and inhibitors can be tailor-made additives for control of the crystallization, but may be synthetic impurities [27].) At least knowing the thermodynamically feasible crystal structures gives insight into what crystal structures could potentially be formed, if they could be made to nucleate.

4.2. *Crystal growth rate*

The relative rate of growth of different crystallites is also a key issue in determining which crystal structures will be observed. A simple model for estimating the relative growth rate from the vapour of different polymorphs [173,174] is based on comparing the morphologies predicted by the attachment energy model. Since this model assumes that the growth rate of a given face is proportional to the attachment energy, the proportionality can be extended to different polymorphs. In some cases this comparison

can indicate a kinetic advantage of certain low energy structures [68,174] and indicate which faces may have difficulty in growing [173]. However, the effects of solvent, impurities and additives on organic crystal growth is so complex, that the prediction of morphologies is another challenging area where computational chemistry could aid the development of industrial processes [175].

There are strong indications that having related crystal structures very closely clustered around the global minimum in the lattice energy is showing a propensity for growth problems and disordered structures. For example, if structures with the same (hydrogen-bonded) sheet stacked in different ways that are very close in energy, this implies a small energy penalty for a stacking error. This has been exemplified by aspirin, where the lattice energy landscape [100] has two stackings of the same sheet as almost equi-energetic near the global minimum, one corresponds to the usual aspirin structure and the other to the recently discovered metastable polymorph [101]. A careful X-ray study of a single crystal of aspirin [176] has recently shown 'polymorphic domains' of regions of form I intergrown with regions of form II. Similarly, form 2 of chlorothalonil is a disordered sheet structure [67] that is far more plausibly a stacking or domain disorder of the two different low energy sheet structures found on the crystal energy landscape than disorder in the positions of the Cl and CN groups within the sheets. The crystal structure of 5-chlorouracil has a disorder that can be rationalized as growth errors in the interdigitation of the non-polar ribbons in either a parallel or anti-parallel mode to form the sheets, since there are a range of nearly equi-energetic crystal structures which are very similar apart from the significant distinction between C=O and C−H, which defines the polar and non-polar ribbons [177]. Two different methods of preparation of carbonic acid give distinct amorphous states which transform into the two polymorphs, as shown by correlation of their FTIR spectra [178]. This appears consistent with each method of preparation favouring a different conformation of carbonic acid, as two low energy conformations have such a large number of low energy crystal structures of almost the same energy, that initial growth in an amorphous state seems highly likely. Thus, considering the range of low energy motifs on a crystal energy landscape can give insights into the possibilities of growth errors, which could result in disorder or various types of complex crystallization behaviour. Such sensitivity to crystallization conditions makes designing a process that provides crystalline samples with reproducible properties rather challenging!

5. Crystal energy landscapes

The computation of the crystal energy landscape for an organic molecule, i.e. the free energy surface that includes all the thermodynamically feasible crystal structures, presents a significant challenge to computational chemistry, because organic crystal structures involve a range of forces from covalent bonds, through hydrogen and other strong directional intermolecular interactions, to the weak dispersive forces. However, it is a worthwhile objective because of its potential value [8] in solid form development, to either confirm that all practically important polymorphs are known, provide targets for polymorph screening to find the more thermodynamically stable forms, or indicate possible types of disorder. It is also the first step towards determining whether polymorphism is possible and complements the many different experimental studies on

understanding nucleation, crystal growth, morphology and the many other fields relevant to understanding the organic solid state.

We are still a long way from being able to calculate our ideal crystal energy landscapes. However, in many cases high accuracy is not necessary to provide some insight and contribute to a multi-disciplinary understanding of the organic solid state. The uses of these landscapes to help solve crystal structures from X-ray powder data [179], confirm the feasibility of structures when evidence of new polymorphs is found (which has already occurred for paracetamol [173,180] aspirin [101] and piracetam [104]) as well as provide the structures for refinement of their relative energies by better theoretical methods. We are therefore building up a database [181] of the computed low energy crystal structures which currently holds structures for about a hundred molecules. For many of these low energy crystal structures, the database also holds second derivative properties (rigid-body estimates of their elastic constants, $k=0$ frequencies, and derived free energies) and morphological properties (attachment energies, morphologies and relative vapour growth rates). There is much more to be done, but this database provides a starting point for investigating the diversity of the crystal energy landscapes and developing computer modelling as an aid to the control and prediction of the organic solid state.

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