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Computed Crystal Energy Landscapes for Understanding and Predicting Organic Crystal Structures and Polymorphism

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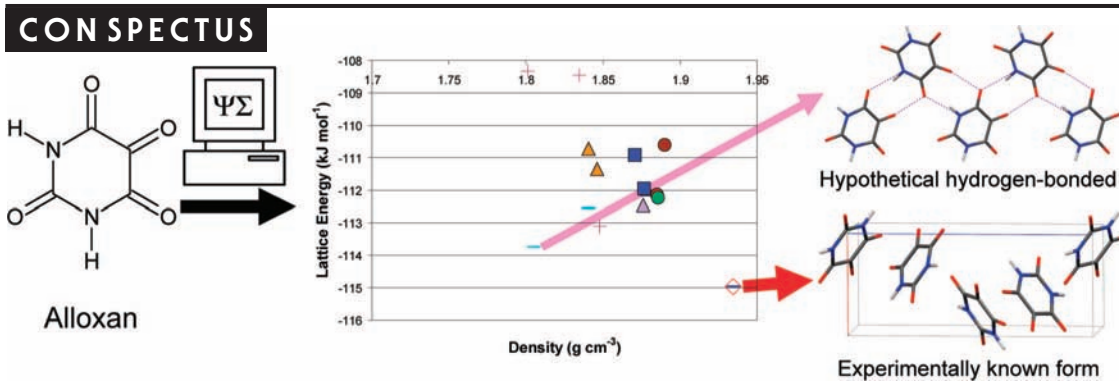

The phenomenon of polymorphism, the ability of a molecule to adopt more than one crystal structure, is a well-established property of crystalline solids. The possible variations in physical properties between polymorphs make the reliable reproduction of a crystalline form essential for all research using organic materials, as well as quality control in manufacture. Thus, the last two decades have seen both an increase in interest in polymorphism and the availability of the computer power needed to make the computational prediction of organic crystal structures a practical possibility.

In the past decade, researchers have made considerable improvements in the theoretical basis for calculating the sets of structures that are within the energy range of possible polymorphism, called crystal energy landscapes. It is common to find that a molecule has a wide variety of ways of packing with lattice energy within a few kilojoules per mole of the most stable structure. However, as we develop methods to search for and characterize "all" solid forms, it is also now usual for polymorphs and solvates to be found. Thus, the computed crystal energy landscape reflects and to an increasing extent "predicts" the emerging complexity of the solid state observed for many organic molecules. This Account will discuss the ways in which the calculation of the crystal energy landscape of a molecule can be used as a complementary technique to solid form screening for polymorphs.

Current methods can predict the known crystal structure, even under "blind test" conditions, but such successes are generally restricted to those structures that are the most stable over a wide range of thermodynamic conditions. The other low-energy structures can be alternative polymorphs, which have sometimes been found in later experimental studies. Examining the computed structures reveals the various compromises between close packing, hydrogen bonding, and $\pi-\pi$ stacking that can result in energetically feasible structures. Indeed, we have observed that systems with many almost equi-energetic structures that contain a common interchangeable motif correlate with a tendency to disorder and problems with control of the crystallization product. Thus, contrasting the computed crystal energy landscape with the known crystal structures of a given molecule provides a valuable complement to solid form screening, and the examination of the low-energy structures often leads to a rationalization of the forms found.

1. Introduction

The forces between all the molecules involved in a crystallization process will determine the resulting crystal structure, but how do we understand crystallization well enough to form a computational model for predicting this structure? A few decades ago,

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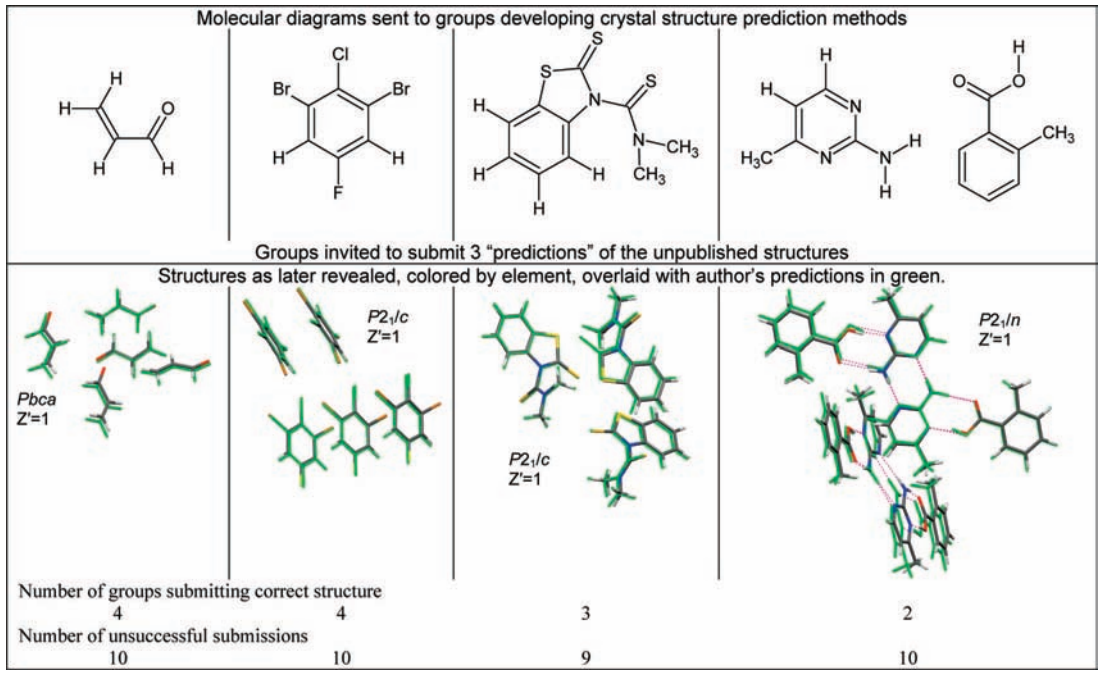

FIGURE 1. The recent blind test of crystal structure prediction organized by the Cambridge Crystallographic Data Centre.[7]

most organic crystal structures were determined to confirm the molecular structure. The difficulty in growing crystals adequate for single-crystal X-ray diffraction meant that the structure of the first suitable crystal obtained became regarded as *the* crystal structure. The phenomenon of polymorphism,[1] the ability of a molecule to adopt more than one crystal structure, although well established, was largely forgotten, until polymorphism became a major issue for the pharmaceutical industry. The possible variations in physical properties between polymorphs make the reliable reproduction of a crystalline form essential for all research using organic materials, as well as quality control in manufacture. Thus, the last two decades have seen both an increase in computer power to make the computational prediction of organic crystal structures a practical possibility and the re-emergence of the study of polymorphism. We are still debating the proportion of molecules that exhibit polymorphism, which depends on the definition of degree of difference and the practical importance of the different polymorphs. However, only a few percent of the molecules in the Cambridge Structural Database[2] have two or more polymorphs well-determined,[3] whereas the estimates from one solid form screening company actively looking for polymorphs has 50% showing polymorphism and 90% having multiple solid forms (including solvates and amorphous forms).[4] The practical difficulty in ensuring experimentally that all practically important polymorphs are known, when so many novel crystallization techniques have been shown to influence the polymorphic outcome,[5] limits the assessment of whether a computational method of crystal structure prediction is successful. However, it makes a predictive technique very valuable for avoiding the major problems that occur when a new polymorph appears late in the industrial process. We have found that combining the development of computational methods of crystal structure prediction with experimental screening and characterization of the crystals of the molecule reveals many insights into the crystallization process. This Account will discuss the ways in which the calculation of the thermodynamically feasible crystal structures, namely, the crystal energy landscape of a molecule,[6] can be used as a complementary technique to solid form screening.

2. Crystal Structure Prediction for Design

The original challenge of organic crystal structure prediction was to be able to predict the crystal structure of a molecule prior to its synthesis. This is a tool for aiding the design of new organic materials with specific properties, for example, to avoid the effort of synthesizing a molecule with a high nonlinear optical coefficient if it would pack in a centrosymmetric and hence inactive crystal or a molecule that cannot crystallize sufficiently densely to be an effective explosive. The community's ability to predict the first determined crystal structure of a molecule has been tested by four international blind tests of crystal structure prediction, starting in 1999, which showed a significant advance this year[7] (Figure 1). One group successfully predicted all four target molecules,[8] and all structures were correctly predicted by at least two different

approaches to evaluating the relative energy of the crystals, which used the electron density distribution of the specific molecule.

The empirically dispersion-corrected density functional method that predicted all four blind test crystal structures as the global minimum in lattice energy had similar success for five out of six small organic test cases.[9] The second, more widely applicable approach models the electrostatic forces arising from lone pairs and π electrons by a distributed multipole model obtained by analyzing the *ab initio* molecular charge density to ensure that the directionality of the hydrogen bonding and $\pi-\pi$ stacking is well-represented. This was tested in a larger survey of fifty rigid carbon-, hydrogen-, nitrogen-, and oxygen-containing organic molecules, which found half of the 62 known crystal structures at or within 0.5 kJ mol^{-1} of the global minimum with nearly 70% having five or fewer unobserved structures lower in energy. The more accurately we model the relative crystal energies, using the developments in the theory of intermolecular forces,[10] the greater the confidence that the structures within the energy range of possible polymorphs (a debatable quantity, on order of 10 kJ mol^{-1}) correspond to thermodynamically feasible polymorphs.

3. Insights from Other Low-Energy Computed Structures

It is rare for there to be one crystal structure that is significantly more stable than any other possibility, just as crystal engineering struggles[11] to design a crystal structure in all three dimensions without solvent or interpenetration ensuring that it satisfies the close-packed principle. However, in general, examining the low-energy crystal structures shows the range of different compromises between the different intermolecular interactions that are favorable: close packing, hydrogen bonds, $\pi-\pi$ interactions. These generally reflect the principles of crystal engineering, for example, that hydrogen bonds are formed wherever possible, but it does sometimes show that not all hydrogen bond acceptors can be used in a close-packed, low-energy crystal structure.[12] For example, the observations that alloxan does not have any conventional length hydrogen bonds, despite being totally comprised of C=O and N−H groups, is explained by the observed structure being somewhat more stable than those based on the expected hydrogen bonding motifs.[13] Thus alloxan is only a problem structure if you focus on hydrogen bonding rather than balance all the intermolecular forces,[14] which computers can do rather more readily than humans. Thus, computing the crystal energy landscape is a valuable enhancement

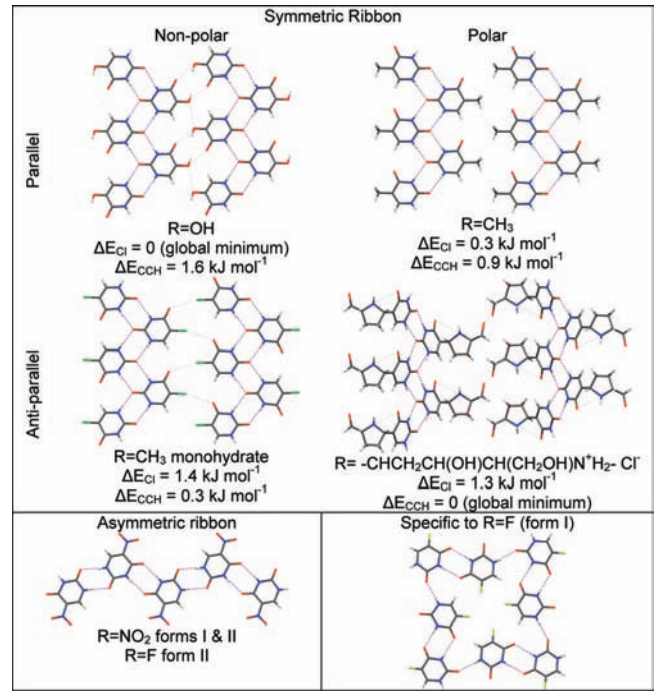

FIGURE 2. Hydrogen-bonding motifs observed in some 5-substituted uracils. The four symmetric ribbon motifs, which are only distinguished by the C6−H and C4=O positions, are very close in energy for R = Cl,[15] and R = CCH,[18] as shown by their lattice energies relative to the global minimum (ΔE), accounting for the observed disorder.

to the qualitative interpretation of experimental crystal structures or even surveys of crystal structures in the Cambridge Structural Database. For example, the symmetric ribbon motif (Figure 2) is the most prevalent multiple hydrogen bonding motif[15] between 5-subsituted uracils, and it appears on the crystal energy landscape of all ten examples studied. However, all also have alternative uracil motifs, such as the asymmetric ribbon and others specifically using the 5-substituent functionality. Overall, these demonstrate that any substituent will affect the relative energies of crystal structures with different uracil···uracil motifs, and the prevalence of the symmetric ribbon just reflects its ability to accommodate, by varying the interdigitation and undulation of the ribbons, a wider variety of functional groups than other motifs (Figure 2).

The variation in the packing of the low-energy structures, such as hydrogen bond motifs, gives insight into the formation of solvates and cocrystals. The crystal energy landscape of 5-fluorocytosine[16] shows many structures, but all the lower energy ones are based on the same hydrogen-bonding ribbon (Figure 3a) giving a clear picture of a preferred mode of association into a ribbon that does not have one optimal way of packing with itself. Following these predictions, two polymorphs and three solvates were characterized, in addition to the known monohydrate, which all contained this ribbon. In

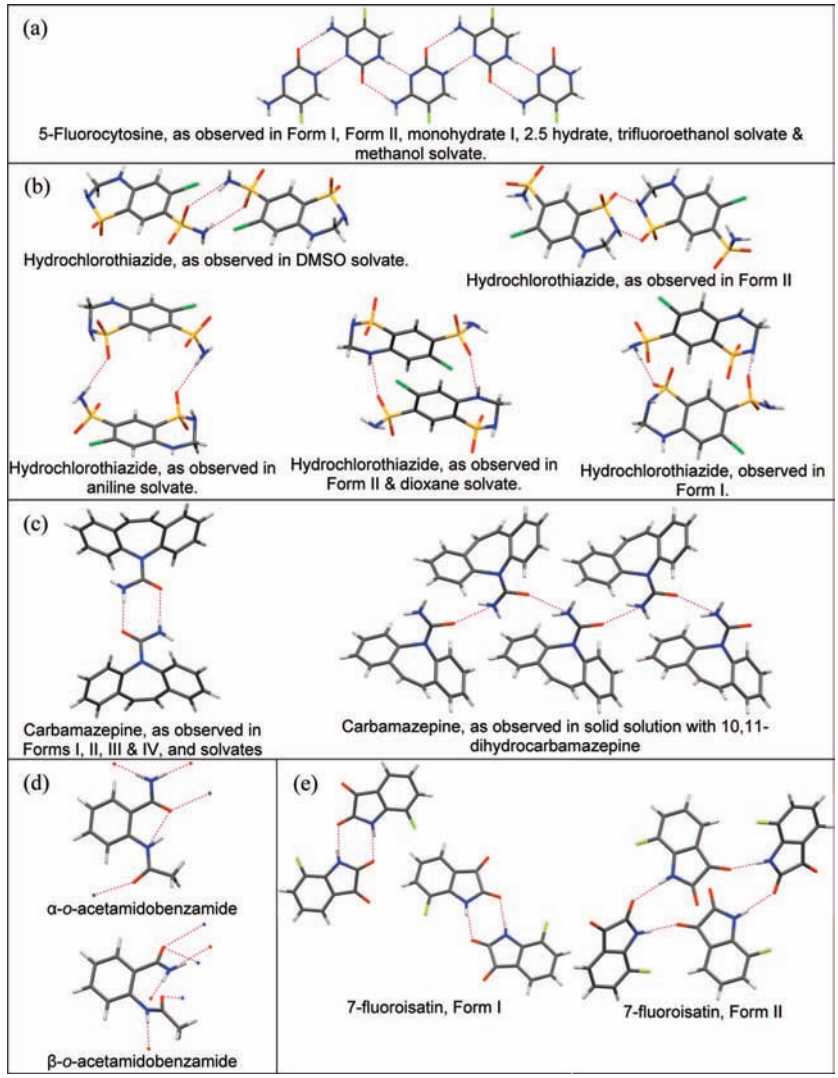

FIGURE 3. Multiple hydrogen-bonding motifs observed in the crystal energy landscape and known polymorphs and solvates of (a) 5-fluorocytosine, (b) hydrochlorothiazide, (c) carbamazepine, (d) *o*-acetamidobenzamide, and (e) 7-fluoroisatin.

contrast, hydrochlorothiazide has no preferred form of self-association as indicated by the crystal energy landscape[17] having structures with over a dozen different ways in which two molecules associate through two hydrogen bonds. Figure 3b shows those dimer motifs that are observed in the multiple crystalline forms.

The range and types of energetically feasible crystal structures are very specific to the individual molecule. For example, the known crystal structure of 2,3-dichloronitrobenzene is clearly predicted[19] to be the most stable; that is, it has a good way of packing with itself. This particular crystal structure prediction methodology is not, however, capable of predicting the crystal structure of all other chloro- and nitro- substituted benzenes, because the other isomers find different, less stable compromises between the various N═O···Cl and stacking interactions, with the only commonality being a lack of Cl···Cl van der Waals close contacts. This leads to 2,4-dichloronitrobenzene adopting[19] a crystal structure with two different torsional distortions of the nitro group in the unit cell, which could not be predicted by a rigid molecule search confined to structures with one molecule in the asymmetric unit. Similarly, a change in chirality will change the possible motifs: the observed crystal structure of (*R*)-1-phenylammonium (*S*)-2-phenylactetate is readily predicted[20] as the most stable, with a particular hydrogen-bonded ladder that appears in all the low-energy structures, but the salt obtained by inverting one chiral center has a range of packing motifs, depending on the exact conformation, and is polymorphic.

Hence, although it is possible to assess from the functional groups and degree of conformational flexibility of a molecule which methods of evaluating the crystal energy are sufficiently accurate to ensure that the observed structures fall within the energy range of polymorphism, it is the molecule itself that determines the number of such structures. When the

energy differences between the most stable structures are small, then advancing from computing what types of motifs are energetically feasible (i.e., providing the crystal energy landscape) to predicting which structures will actually be observed requires a more sophisticated approach that is emerging from combining experimental and theoretical studies.

4. Ideal Crystal Energy Landscapes versus Current Methods

The observation of polymorphism clearly demonstrates that there are kinetic factors that result in metastable crystal structures, which may not transform to the most thermodynamically stable form over a significant period. For example, a new polymorph of 5-fluorouracil that corresponded to the global minimum in the lattice energy[21] could only be crystallized from dry nitromethane. This can be rationalized by Molecular Dynamics simulations showing that this doubly hydrogen-bonded asymmetric ribbon motif (Figure 2) does not readily form when water hydrates the uracil moiety promoting the close F···F contacts seen in the form I motif (Figure 2).[22] However, metastable polymorphs are going to correspond to low-energy local minima, and hence the problem of understanding and predicting polymorphism reduces to determining, which free energy minima can be kinetically accessed and trapped.

Ideally, to distinguish between thermodynamically stable and kinetically produced, apparently stable structures, we would wish to calculate a realistic crystal energy landscape locating the minima in the free energy at the temperatures and pressures under which crystallization takes place. This represents quite a challenge to computational chemistry. Most crystal structure prediction methods are based on the static lattice energy, which approximates the 0 K relative stability. This lattice energy landscape is usually adequate for seeing which crystal structures are thermodynamically feasible (e.g., within $\sim$10 kJ mol^{-1} of the most stable), because differences in the thermal contributions (entropy, zero-point energy, etc.) generally do not exceed a few kilojoules per mole at room temperature between either real[23] or hypothetical structures. Hence, the increasing practice is to add an estimate of dynamical contributions to the free energy,[24] for example, based on rigid body harmonic estimates of the infrared, Raman, and terahertz phonon frequencies[25] and elastic constants,[26] which can reorder the relative energies with temperature. However, such calculations cannot indicate when the motions within a crystal become sufficiently large that it transforms into another structure (i.e., is thermally unstable), which requires Molecular Dynamics simulations of the crystals. This may have a large influence on the number of structures that are free energy minima. A metadynamics study on benzene[27] found only seven free energy minima that could be correlated to the known phases, despite there being orders of magnitude more lattice energy minima. In contrast, only a quarter of the nearly 70 lattice energy minima for 5-fluoruracil within 5 kJ mol^{-1} of the global minimum proved to be thermally unstable in room-temperature simulations.[28] These contrasting results correlate with the ability of benzene to undergo rotation and phase transformations in the solid state, whereas the two polymorphs of 5-fluoruracil do not undergo a solid state transformation prior to melting,[21] and the molecule is seen in a variety of different hydrogen-bonded chains (Figure 2) in its nine crystalline forms, including a symmetric ribbon in the trifluoroethanol solvate.[15]

The ease of dynamic motion within the crystal is very important in determining the structures seen experimentally, in a way that should be reflected in the free energy crystal landscape. The lattice energy landscape of cyclopentane has the observed ordered form as marginally the most stable, but there are so many other lattice energy minima within a small energy range that it is not surprising that it transforms (both experimentally and in simulations) to a high-symmetry rotationally disordered phase, with an intermediate phase that corresponds to a different subset of the low-energy structures being sampled in the thermal motions.[29] Thus, the calculation of lattice energy landscapes can act as a valuable preliminary to Molecular Dynamics studies of the effect of temperature on organic crystals[28,30] to establish the difficulties in transforming from a metastable to the most thermodynamically stable crystal structure. However, the barriers to rearrangement during nucleation and growth are probably more fundamental in determining which lattice energy minima can be trapped as metastable polymorphs. The cyclic imide 3-azabicyclo[3.3.1]nonane-2,4-dione (Figure 4) was expected to be polymorphic because most participants in the 2001 blind test predicted a doubly hydrogen-bonded dimer-based crystal structure to be more stable than the observed catemer structure. However, an extensive experimental search only found other catemer-based structures and a plastic phase. This led to an explanation (Figure 4) of why there was an unusually small barrier to rearranging the hydrogen bonding to the slightly more stable structure.[31]

The computational method required for the relative order of stability of the thermodynamically feasible structures to be reasonably correct is very dependent on the molecule. Almost all widely applicable methods of evaluating lattice energies

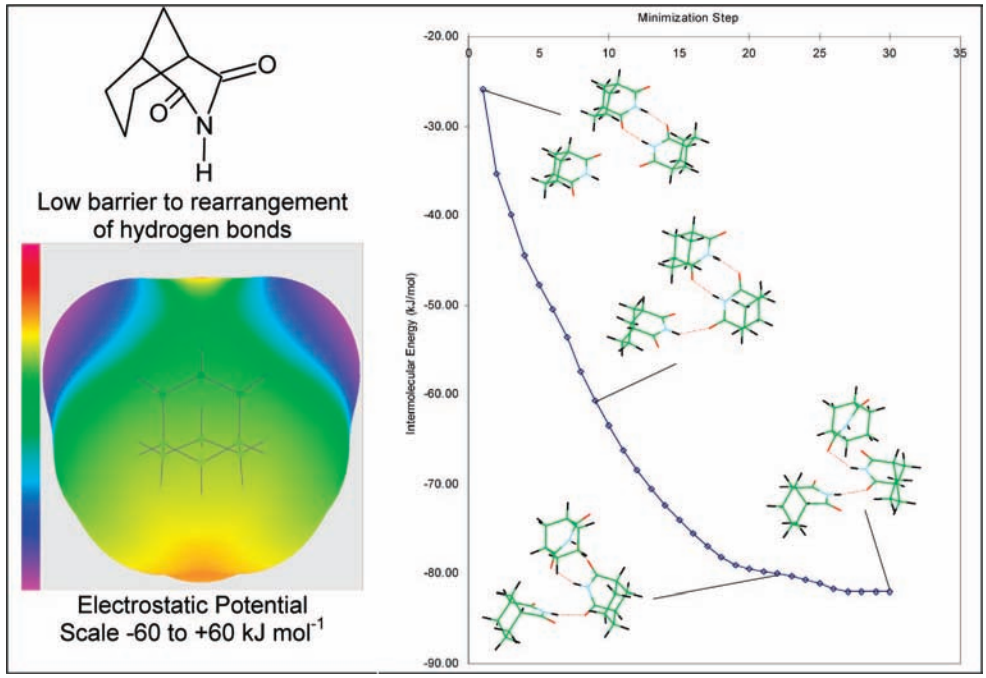

FIGURE 4. A molecule with two different hydrogen-bonding motifs on the lattice energy landscape, which was expected to lead to polymorphism.[31] However, energy minimizations of small clusters (e.g., right) show that the barrier for the molecule rearranging its hydrogen-bonding motif to the marginally more stable chain structure during association appears to be so low as to prevent trapping of a dimer-based polymorph. This is consistent with the displayed electrostatic potential on the water-accessible surface of the almost spherical molecule.

have some component that has been empirically fitted to experimental organic crystal structures, whether in the model of the intermolecular forces or for the missing dispersion contribution in electronic structure methods, so chemical insight has to be used in extrapolating between different molecules. For example, in most organic structures, the conformational energy penalty paid by molecular distortions to improve the intermolecular packing can be reasonably evaluated by *ab initio* calculations on the isolated molecule.[32] However, when the polymorphs differ in the number of intramolecular and intermolecular hydrogen bonds, as in *o*-acetamidobenzamide (Figure 3d), obtaining a plausible energy difference is a significant challenge to these and most solid-state electronic structure modeling methods.[33] The future prospects for more reliable model intermolecular potentials, specific to the molecule, are bright, and indeed, a model potential[34] for $C_6Br_2ClFH_2$ derived purely from the theory of intermolecular forces without any experimental input was capable of predicting the crystal structure under blind test conditions (Figure 1). Even models for the induction energy, the additional stabilization from the distortion of the molecular charge density by the field of the surrounding molecules, can now be determined in a theoretically well-founded manner.[35] However, providing sufficiently accurate evaluations of the relative free energies of pharmaceutical and other organic materials remains a major challenge to the field of computational chemistry.

5. Interpretation of Crystal Energy Landscapes

In the future, we will be able to search through the complete range of crystal structures and evaluate their energies accurately as a function of temperature and pressure to obtain the crystal energy landscape, the structures and relative energies of the crystal structures within a plausible energy range of possible polymorphism of the global minimum. How would we interpret the results,[6] such as those shown in Figure 5?

The simplest outcome is to have one ordered crystal structure calculated to be sufficiently more stable than any others, over the range of practically obtainable thermodynamic conditions, that it provides valuable confirmation that polymorphism is highly unlikely. Such "monomorphic" crystal energy landscapes will only occur when the packing in all three directions is unusually well-defined, as found for Pigment Yellow-74.[36] If the lattice energy gap (ΔE shown in Figure 5a) is insufficient to thermodynamically rule out possible polymorphs but the structures are related with small barriers to transformation to the most stable form, then conversion in the solid or during nucleation and growth will be sufficiently

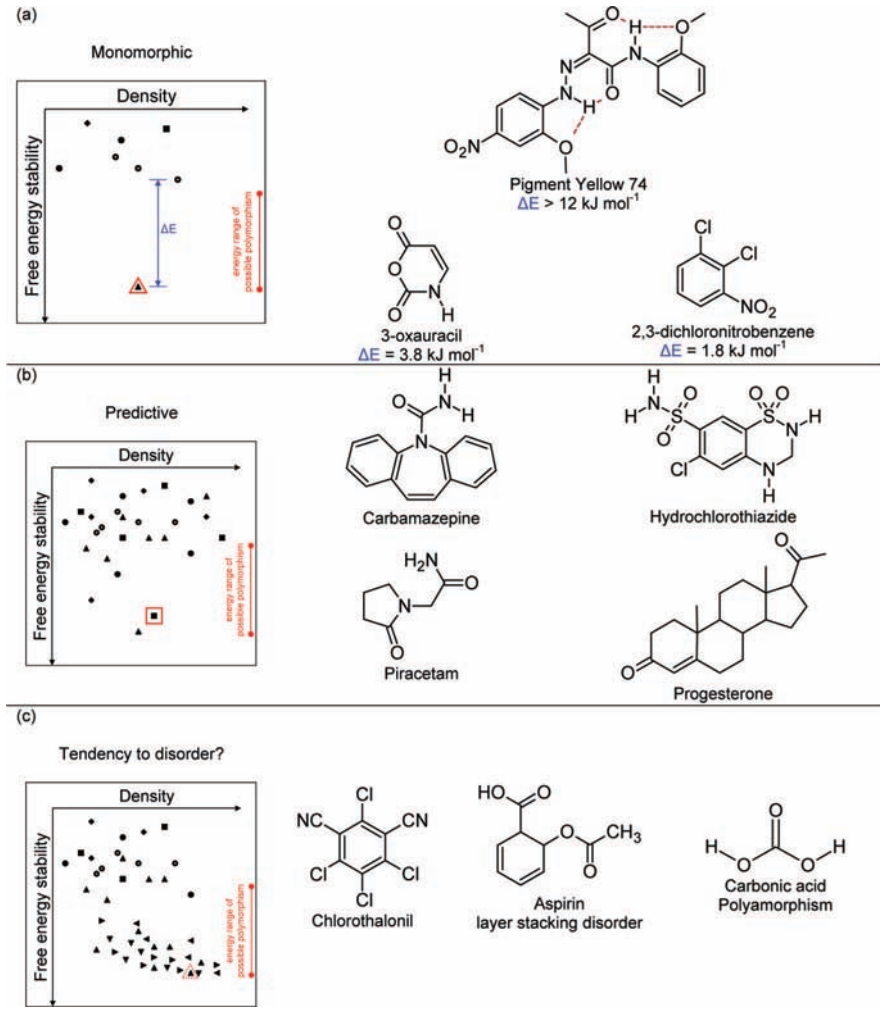

FIGURE 5. Idealized types of crystal energy landscapes and some examples of molecules mentioned in the text that exhibit this behavior.

facile that practically important metastable polymorphs are unlikely. In such cases, as exemplified by oxauracil,[37] the calculation of the energy landscape can provide confirmation of a conclusion of monomorphism from a simple screen of crystallization conditions.

An energy landscape of the "predictive" type (Figure 5b) shows that there is an unknown structure that is more stable than the known polymorph. For a molecule of industrial importance, it would be vital to find this polymorph or risk it appearing unexpectedly and disrupting the production process. A huge range of novel methods of crystallization have been proposed and shown to be effective in finding new polymorphs in certain cases.[5] Knowing the structure would allow the choice of appropriate methods, such as crystallization on templating surfaces or additives. One example resulted from the prediction that a hydrogen-bonded chain structure was more stable than the known dimer-based polymorphs of carbamazepine. Although the new polymorph was not found in extensive crystallization screening[38] and improved calculations show that the known form III is probably the most stable structure,[35] catemers of carbamazepine were found in a solid solution with dihydrocarbamazepine.[39] We cannot rule out the discovery of a catemer-based polymorph. Indeed, for many 5-uracils (Figure 2), it appears[15] that the small range of crystallization conditions that could be easily applied to crystallize these highly insoluble materials limits the number of polymorphs found.

Problems with crystal growth seem to be associated with another type of energy landscape (Figure 5c), where there are related structures within a small energy range. If these are different stackings of the same sheet, then the energy penalty for stacking errors is very small, and polytypism or disorder seems likely. This is exemplified by the high-symmetry disordered form 2 of chlorothalonil[40] being more readily described as disorder in the stacking of the ordered sheets (found in two equi-energetic structures on the lattice energy landscape) than disorder within the sheets. Similarly, the two predicted equi-energetic stackings of aspirin[41] correlate with either two pol-

ymorphs[42] or polymorphic domains.[43] The demonstration that eniluracil has many almost equi-energetic structures (Figure 2), which would be the same if we do not distinguish between the uracils C═O and C−H, accounts for single crystal structures showing variability in the disorder, and accounts for the difficulties in producing a reliable production process.[18] When the crystal energy landscape shows that there are many different ways of molecules associating that are similar in energy, it seems likely that there will be considerable problems in forming ordered nuclei and crystals, that is, the molecules can join the growing solid form in a variety of ways, potentially forming different structural regions. Such a crystal energy landscape suggests that self-association into a crystal will be more difficult than when the intermolecular forces strongly favor the correct alignment. For example, the observation[44] that different methods of producing carbonic acid produce different amorphous forms that evolve into the different polymorphs correlates with two conformers both having a wide range of crystal structures of approximately the same energy.

6. Outlook

Now that we have computed approximate crystal energy landscapes for over 100 small organic molecules, it is clear that they form a useful complement to experimental studies, providing insight into the range of alternative structures but also raising questions about how to control crystallization. There have been cases, such as piracetam[45] and 1-hydroxy-7-azabenzotriazole,[46] where we have been challenged to predict the structure of a newly discovered polymorph and have been able to send a few structures to the experimental group, which included the correct one. In other cases, a polymorph found after the computational study had been published was found to match a predicted structure around the global minimum. In the case of aspirin, the new polymorph had been dismissed[41] as rather too susceptible to shear, and for alloxan the form[47] below 35 K is a better match to the global minimum in the lattice energy landscape than to the thermally averaged, high-temperature, higher symmetry form.[12]

More practically, the simulated X-ray powder patterns of the structures on the crystal energy landscape can be compared with those obtained from new polymorphs when crystals suitable for single-crystal X-ray diffraction cannot be obtained. This led to a suggested structure for form III of paracetamol[48,49] and a solution of the structure of adenine,[50] which was independently verified by single-crystal diffraction. Automating such comparisons is difficult because of the shifting of the peaks caused by the anisotropic thermal expansion, as well as the errors in the cell dimensions of the lattice energy minima. This is particularly demanding when there are many closely related structures with similar powder patterns on the crystal energy landscape, which could be the reason for the crystal growth problems that make this characterization technique essential. Nonetheless, just seeing the range of possible packings can be helpful to the expert in solving structures.

Another potential practical application is in the design of crystallization processes to resolve chirally pure products. Should, unusually, the crystal energy landscape have chiral structures lower in energy than racemates, there will be spontaneous resolution. More typically, progesterone was predicted to have a racemic structure that was more stable than the two lowest energy chiral structures, corresponding to the polymorphs of the natural product. This prediction was verified[51] by the unusual experiment of mixing the synthetic mirror image, *ent*-progesterone, with the natural product. One strategy for chiral purification is to form a diastereomeric salt by crystallizing with a chirally pure acid or base. If there is a large difference in the energies of the most stable of the two diastereomeric salts, then there will be effective resolution.[20] Studies[52] of a family of three R-phenyl carboxylates as "resolving agents" for 1-phenyl ammonium clearly show that obtaining a quantitative estimate for the effectiveness of a resolving agent requires free energy calculations.

The recent extensions of crystal structure prediction methods to more than one molecule in the asymmetric unit cell allows prediction of the structures of not only diastereomeric salts but also cocrystals (Figure 1), solvates,[53] and other fixed stoichiometry multicomponent systems, as well as the prediction of structures with unusual packing motifs (Figure 3e) such as most stable polymorph (II) of 7-fluoroisatin.[54] However, predicting whether the solvate or cocrystal will be formed in preference to the pure compounds can be very demanding of the relative accuracy of the three crystal energies, even assuming that it is thermodynamically determined.[55]

Thus, computing the crystal energy landscape and contrasting the packing motifs can provide valuable insight into the possible solid-state forms for a given molecule. The accuracy of the currently computed energies needs improvement before we can confidently rank the structures in order of thermodynamic stability at accessible conditions. However, crystallization does not always produce the most thermodynamically stable structure, so the calculations give insights into the possibility of polymorphism. Considerably more complementary theoretical and experimental work is required in

order to understand the factors that control crystallization and so be able to confidently predict which polymorphs will be observed and the conditions under which they will be found. However, the approximations to the true crystal energy landscapes are worth archiving for future improvements in computational chemistry and to help understand the causes of polymorphism.

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BIOGRAPHICAL INFORMATION

Sarah (Sally) L. Price studied Natural Sciences at Cambridge University, where she also obtained a Ph.D. in 1980 in Theoretical Chemistry on modelling intermolecular forces. After a year at University of Chicago, she returned to Cambridge for postdoctoral work and a Royal Society University Research Fellowship. She moved to a lectureship at University College London, where she was promoted to a chair in 2000. She is married with two children.

FOOTNOTES

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