Predictions of Crystal Packings for Uracil, 6-Azauracil, and Allopurinol: The Interplay between Hydrogen Bonding and Close Packing

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An approach to predicting molecular crystal structures, based on systematically searching for densely packed structures within common organic crystal coordination types, followed by lattice energy minimization, has been applied to three planar heterocycles with multiple hydrogen bond donors and acceptors, namely, 6-azauracil, uracil, and allopurinol. The dominant electrostatic contribution to the lattice energies was calculated from an *ab initio* based distributed multipole model of the molecular charge density, providing more confidence that the potential extrapolates correctly to hypothetical crystal structures than is possible with empirical potentials. In all cases, the experimentally observed structure was found, corresponding to the global minimum in the lattice energy. Most of the different possible combinations of hydrogen bonds were found to be able to pack in low-energy crystal structures, with several unknown structures within the energy range associated with possible polymorphism. This raises the question as to what factors, in addition to static lattice energy, need to be considered to predict which crystal structures could be found experimentally.

1. Introduction

A method of predicting the crystal structures of organic molecules, prior to synthesis, would be a useful tool in the design of new nonlinear optical or energetic materials or any other material where the crystal packing has a major influence on the property of interest. Reliable predictions of whether an existing molecular solid could crystallize in another structure would have major implications for patent protection and processing design. However, these are but pragmatic illustrations of the need to understand the fundamental processes that determine the crystal structures of organic molecules and the phenomenon of polymorphism.

Any computational scheme for predicting molecular crystal structures has to include a method of simulation: a method of generating sufficient hypothetical structures as starting points for this simulation method to be reasonably confident that the most stable crystal structure will be found; and a model for the forces which bind the molecules together to form the crystal. Current methods of crystal structure prediction are based on the assumption that the observed crystal structure will correspond to the global minimum in the lattice energy, with any competitive local minima being possible polymorphs. This is a valid starting point, with the neglect of any kinetic, solvent, or temperature effects on the crystallization process being a practical necessity for a computationally tractable method.

Various methods of screening the multidimensional potential energy surface of possible crystal structures have been proposed recently. One method, in the commercial package Polymorph Predictor, is based[1] on a Monte Carlo-simulated annealing method of locating clusters of minima in the lattice energy and so in principle is only restricted by the assumed number of molecules in the unit cell. Other methods are based on systematic searches of the most common space groups for organic molecules. PROMET[2] looks for nuclei with a favorable interaction energy where the molecules are related by suitable crystal symmetry elements to build up hypothetical 3D structures for energy minimization and has been successful for a range of hydrocarbons. MOLPAK[3] systematically searches for promising starting points for energy minimization within common coordination environments in common space groups, the selection criterion being the density of the structure. This criterion is particularly relevant to the design of energetic materials and was successfully applied to a range of nitro compounds. Close packing is also used as the initial criterion in the alternative approach of the program ICE9.[4] Other ideas for predicting molecular crystal structures have appeared in the recent literature. Perlstein[5] has used a Monte Carlo approach to build up favorable one-dimensional motifs using the systematics of the 1D-packing problem, then two dimensional-packing motifs, an approach which shows promise for generating the full three-dimensional structure. A systematic energy-based search, within the constraints of the space group $P2_12_12_1$, was used to predict the crystal structures of six monosaccharides.[6] Alternatively, an energy-based minimization from randomly orientated molecules in expanded cubic unit cells (body-centered for $Z = 2$ and face-centered for $Z = 4$) has been reported as successful for urea and benzene in a preliminary communication.[7] Although all of these methods are sufficiently recent that their capabilities have only been reported for a limited range of molecules, it is clear that their relative effectiveness will depend on the shape, symmetry, and nature of the intermolecular interactions of the molecule and whether a statistically unusual (e.g., high-symmetry, multiple independent molecules per unit cell) structure can be adopted.

The model intermolecular potential is an important component in the search for possible crystal structures. All of these methods can only find the minimum in the lattice energy which corresponds to the minimum obtained starting from the experimental structure. If the model potential does not produce a minimum acceptably close to the experimental structure (if known, or those of related molecules if unknown) then the whole exercise is meaningless. Additionally, the interpretation of other local minima requires confidence that the model potential correctly extrapolates to these hypothetical crystal structures. The empirical model potentials, which have been used in

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previous crystal structure prediction studies, can be checked for reasonably satisfying the first requirement, but the confidence that can be placed in the relative lattice energies of hypothetical structures is limited by the assumed functional form. Ideally, the model potential should be derived either by fitting to a complete (*ab initio*) potential energy surface or as a sum of rigorously derived models for the various contributions, where the anisotropic atom−atom form and the parameters for each term are derived separately, usually from the charge distribution of the molecules. Such potentials are not yet available for organic molecules, although considerable progress has been made toward this goal for smaller polyatomics.[8] As a first step in this direction, we have recently investigated the use of realistic *ab initio* based distributed multipole models for the electrostatic forces in crystal structure modeling.[9] The representation of the molecular charge distribution by sets of multipoles (charge, dipole, quadrupole, octupole, and hexadecapole) on each atomic site, derived by a distributed multipole analysis (DMA)[10] of an *ab initio* wave function, ensures that the accuracy of the electrostatic forces outside the molecule is limited mainly by the quality of the wave function. The combination of such an electrostatic model, with an empirical 6-exp repulsion−dispersion potential, has been shown to give a minimum in the lattice energy reasonably close to the experimental room temperature structure for a wide range of rigid polar organic molecules, including amide, amine, aromatic, heterocyclic, and nitro groups, whose crystal packing is sensitive to the electrostatic model.[9] This potential scheme has the advantage that the electrostatic contribution to the lattice energy will be predicted equally accurately for hypothetical structures and is theoretically well-justified, overcoming a problem that has been frequently beset crystal structure prediction studies.[1,4]

A second approach to crystal structure prediction has been the development of empirical observations about crystal structures, on the basis of the large number of existing structures, which give qualitative guidance as to the intermolecular motifs and properties that are likely to be found. These range from the rule that the packing efficiency should be in the range 65%−77%[11] to detailed information on the most probable directionality of various hydrogen bonds or other interactions.[12] Certainly, hydrogen bonds appear to dominate the crystal structures of molecules capable of forming such bonds—the lack of hydrogen bonds in the crystal structure of alloxan[13] being a notable exception to the general rule that all good proton donors and acceptors are used in hydrogen bonding.[14] The geometric requirements of hydrogen bonds could be expected to significantly reduce the number of possible crystal structures that also obey the close packing criterion, which should make such structures relatively easy to predict.

In this paper, we investigate the ability of a scheme, on the basis of the use of MOLPAK[3] for searching and distributed multipoles for the intermolecular forces, to predict the crystal structures of uracil, 6-azauracil, and allopurinol. As shown in Figure 1, all three molecules are planar, and therefore can be reasonably close packed in a wide range of structures, but the intermolecular forces will strongly favor hydrogen-bonded structures. The multiple hydrogen donors and acceptors allow a range of hydrogen-bonding motifs. Therefore, the hypothetical crystal structures should provide some evidence as to the interplay between hydrogen bonding and close packing in determining crystal structures. The use of an *ab initio* based anisotropic atom−atom model for the electrostatic interaction is an important feature of the study, as the electrostatic term generally dominates the orientation dependence of the hydrogen bonding and $\pi-\pi$ interactions of such molecules,[15] and the anisotropy arising from the lone pair and π electron density makes a significant contribution. The improved confidence in the relative lattice energies of the hypothetical structures provides greater insight into the use of static lattice energies as a criterion for predicting molecular crystal structures.

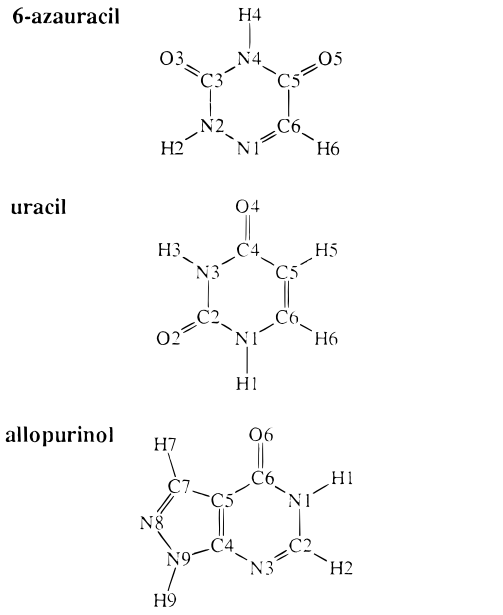

Figure 1. The molecular structure and atom numbering of 6-azauracil, uracil, and allopurinol.

2. Methods

The methodology that we have developed is based on the use of MOLPAK to systematically search specific packing types for dense structures, followed by an accurate evaluation of the lattice energy of the hypothetical densely packed structures. A large number of these structures are then relaxed to find the nearest minimum in the lattice energy.

The structures of the molecules 6-azauracil,[16] uracil,[17] and allopurinol[18] were taken from the experimental room temperature X-ray crystal structures, with the H atom positions corrected to give standard[19] bond lengths of 1.08 Å for C−H and 1.01 Å for N−H. These molecular structures were assumed to be rigid. Each structure was used as a probe in a MOLPAK search for close-packed structures, using the standard MOLPAK program and procedure.[3] For 20 different molecular coordination geometries of molecular crystals with one molecule in the asymmetric unit, the cell volume is evaluated as a function of the orientation of the central molecule by bringing up the coordinating molecules in the defined symmetry relationship until they are in van der Waals contact. This is defined by a pseudorepulsion potential. We used the standard MOLPAK repulsion potential parameters, using the same repulsion for polar hydrogen atoms bonded to nitrogen as had originally been developed for hydrogens bonded to oxygen. The use of a smaller effective van der Waals radius for hydrogen atoms which may be involved in hydrogen bonds than those bonded to carbon was found essential for reasonable starting structures, consistent with the empirical van der Waals separations. However, no attempt to refine the other MOLPAK parameters was made despite the use of different types of molecules, so, for example, we were using parameters derived for nitrogen in nitro groups to determine the effective radius of heterocyclic nitrogens.

The MOLPAK program was used to find the cell volume for each coordination type for 10° increments in the variable Eulerian rotational angles of the central molecule (search probe),

thus considering $19^3 = 6859$ hypothetical structures when each Eulerian angle varies between $-90°$ and $+90°$ to cover all unique orientations. The 25 most densely packed structures were then refined to within 2° in the rotations and considered as hypothetical structures. The version of MOLPAK used considered 20 molecular coordination geometries, covering the space groups $P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $C2/c$, $P2_12_12_1$, $Pca2_1$, $Pna2_1$, and $Pbca$. Most space groups are represented by more than one molecular coordination type, with different symmetry relationships along the different axes for the 14 molecules in the coordination sphere, as established[3] from an analysis of the common coordination environments of organic molecules in the Cambridge Structural Database.[20] The choice of trial molecules was constrained so that the crystal structures had one molecule per asymmetric unit and were in space groups that were handled by MOLPAK, namely, $P2_12_12_1$ for azauracil, $P2_1/a$ for uracil, and $P2_1/c$ for allopurinol, but the degree to which these structures approximated any of the idealized coordination types was not considered.

This procedure generated 25 close packed hypothetical structures in each of the 20 molecular coordination geometries, providing 500 possible starting points for lattice energy minimization. At this point, we departed from the procedure used by Holden *et al.*[3] to take advantage of our ability to evaluate the dominant electrostatic component of the lattice energy, and thus the total energy, accurately. This was done at each structure, using an interface to the program DMAREL.[21] The model for the electrostatic contribution to the lattice energy was evaluated using all terms in the multipole expansion up to R^{-5} from the sets of atomic charges, dipoles, quadrupole, octupole, and hexadecapole tensor moments which represented the molecular charge distribution. These had been obtained by a distributed multipole analysis (DMA)[10] of the SCF *ab initio* wave function of each isolated molecule, calculated using a 6-31G** basis set[22] within the program CADPAC.[23] The multipole moments were scaled by a factor of 0.9 to approximately allow for the neglect of electron correlation in the wavefunction.[24,25] All other contributions to the intermolecular potential were assumed to be represented by an empirical 6-exp atom−atom potential of the form

$$U = \sum_{ik} U_{ik} = \sum_{ik} A_{\mathrm{LK}} \exp(-B_{\mathrm{LK}} R_{ik}) - C_{\mathrm{LK}}/R^6_{ik}$$

where atoms i and k are of types L and K (C, N, O, H, or H_p), respectively. The parameters for C, H, and N were taken from empirical fits to the crystal structures of a variety azahydrocarbons[26] and for O from compatible fits to a group of oxohydrocarbons.[27] The polar hydrogen $H_p(-N)$ parameters were taken from the $O\cdots H_p$ potential fitted to intermolecular perturbation theory calculations of the exchange−repulsion, penetration and dispersion interaction between formamide and formaldehyde in the $N-H\cdots O{=}C$ hydrogen-bonding region.[28] The heteroatomic parameters were fixed using the traditional combining rules

$$A_{\mathrm{LK}} = (A_{\mathrm{LL}} A_{\mathrm{KK}})^{1/2}, \quad B_{\mathrm{LK}} = {}^1/_2(B_{\mathrm{LL}} + B_{\mathrm{KK}}), \quad C_{\mathrm{LK}} = (C_{\mathrm{LL}} C_{\mathrm{KK}})^{1/2}$$

This model potential has been shown to reproduce the crystal structures of these three heterocycles and a variety of similar molecules, within the errors that may be associated with a static lattice energy minimization calculation.[9] It also provides reasonable estimates of the lattice energies across the database of compounds, within the large experimental and theoretical uncertainties with comparing the lattice energy with the experimental heats of sublimation.[29] However, since the electrostatic contribution to the calculated lattice energy is always large (76% azauracil, 83% uracil, and 78% allopurinol with the scaling factor of 0.9^2), possible variations in the effect of the quality of the wave function will have a significant effect on the absolute values of the lattice energy.

It became clear in the initial studies that the 25 minimizations within each molecular coordination geometry converged to a much smaller number of minima. Since the lattice minimizations typically took 0.25 h or more each on a Silicon Graphics Power Challenge, it was worthwhile selecting a smaller number of hypothetical structures to be minimized. Thus, the lattice energies at the 20×25 MOLPAK-generated structures were used to select which should be used as starting structures for full lattice energy minimization. The lowest energy structures within each coordination type for the four most common space groups $P2_1/c$, $P2_12_12_1$, $P\bar{1}$, and $P2_1$ (90 structures) were minimized, plus all other initial structures in the other space groups whose initial energies were below a low-energy cutoff. (Only the results obtained in this restricted search are reported in section 3, unless otherwise indicated.) The parameters of the restricted search (10 and the energy cutoffs) are somewhat arbitrary, but seemed likely to produce the majority of low-energy minima that would be found from all 500 minimizations. However, it obviously does increase the risk, already inherent in the use of MOLPAK and consideration of only the 25 densest structures, that some low-energy structures will not be found.

The lattice energy minimizations were carried out using the standard procedure in DMAREL,[21] which is based on a Newton−Raphson procedure and makes limited use of the second derivative matrix. The minimization is based on a Cartesian representation of the crystal structure, and so does not enforce space group symmetry. The cell angles and lengths and the three rotations and three translations of each molecule in the unit cell are optimized independently.

Many initial structures relaxed to identical minima, and the minima almost always maintained the initial crystallographic symmetry. However, there were clusters of minima which differed little in lattice energy and in cell volume per molecule but had different cell parameters. These were first investigated for exact or approximate equivalence (e.g., different cell settings or approximate symmetries) on the basis of the matrix of intermolecular distances using the program NIPMAT.[30] For an N atom molecule in a crystal structure, NIPMAT calculates the $N \times N$ matrix of the deviation of shortest intermolecular contact R_{ij} between atoms i and j from the sum of the van der Waals radii r_i and r_j,

$$d_{ij} = \mathrm{R}_{ij} - (r_i + r_j)$$

The van der Waals radii used are those due to Bondi,[31] with all hydrogen atoms having the same radius of 1.2 Å. This has the advantage that, when the matrix is displayed as a gray scale, the hydrogen bonds are particularly obvious as the intermolecular contacts that are most significantly shorter than the sum of the conventional van der Waals radii. This analysis was useful in detecting the use of different hydrogen bonds in the various low-energy structures. Graphical techniques had to be used to determine structural differences in hydrogen-bonded networks involving the same types of hydrogen bonds, though the existence of structural differences was apparent from the differences in the NIPMAT matrix for other contacts. The analytical transformations between equivalent sets of cell parameters were carried out using the program and algorithms of Le Page.[32]

TABLE 1: Predicted Structures for 6-Azauracil

space group and MOLPAK structure[a]	exptl $P2_12_12_1$	min[b] $P2_12_12_1$	$P2_12_12_1$ AQ11[b]	$P2_12_12_1$ AZ9[c]	$Pna2_1$ BD22	$P\bar{1}$ AB19	$C2/c$ DD18	$P2_1/c$ AI12	$Pca2_1$ AY5	$Pbca$ CB7	$P2_1$ AF15	$P2_1/c$ AM19	$P2_1$ AH1	$P2_1/c$ AM12	$P2_1/c$ AM10
energy/kJ mol^{-1}	−92.60	−96.11	−96.2	−97.0	−94.4	−95.9	−94.8	−95.0	−88.2	−96.8	−96.0	−87.9	−82.3	−82.9	−86.8
a/Å	4.875	5.17	5.17	5.10	17.36	6.73	7.34	9.51	19.93	10.07	4.96	3.94	5.72	3.81	5.54
b/Å	17.611	17.09	17.09	17.37	5.09	4.98	6.73	6.79	3.60	12.44	4.95	11.29	11.63	10.47	11.68
c/Å	5.022	4.96	4.96	4.97	5.00	9.10	18.04	7.04	6.10	6.87	9.05	10.31	3.66	11.25	7.29
α/deg	90.0	90.0	90.0	90.0	90.0	75.2	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0
β/deg	90.0	90.0	90.0	90.0	90.0	100.1	77.5	103.0	90.0	90.0	100.0	75.9	109.9	94.5	107.3
γ/deg	90.0	90.0	90.0	90.0	90.0	132.9	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0
volume/Z/Å^3	107.8	109.4	109.4	109.9	110.5	108.0	108.7	110.7	109.6	107.6	109.3	111.0	114.3	111.8	112.6
N2H2···O3/Å	1.89	1.99	1.99	1.98	1.99	2.08	2.15	2.13	2.14						2.11
N2H2···O5/Å												2.10	2.33	1.97	2.40
N2H2···N1/Å									2.37	2.15	2.12				
N4H4···O3/Å										2.01				2.07	
N4H4···O5/Å	1.84	1.99	1.99	2.02	1.96	1.95	1.94	1.91	2.13		1.97				
N4H4···N1/Å												2.01	1.91		1.94

[a] Each structure is designated by one of the MOLPAK starting structures which resulted in this minimum. [b] The lattice energy minimum structure (min), found starting from the experimental structure (exptl), is compared with the equivalent structures found by the crystal structure prediction procedure. The lowest energy structure for each space group with a minimum within about 10 kJ/mol of the global minimum are then given, with those with the same hydrogen-bonding pattern as the observed structure first. Other minima with different hydrogen bonds are in the last section. The short (N)H···O/N distances are given for each structure. The latter energies are summed to 15 Å, with this limit applying to atom−atom distances for the repulsion-dispersion energies and molecular center separation for the anisotropic multipole−multipole interactions. The charge−charge, charge−dipole, and dipole−dipole contributions to the lattice energies are evaluated by Ewald summation. [c] Equivalent structure reported.

However, a major objective was to establish whether this crystal structure prediction process had generated the observed crystal structure, and whether this corresponded to the global minimum in the lattice energy. This was done by comparing the minima generated with the minimum in the lattice energy obtained using the experimental structure as the starting point and the same model potential.

3. Results

3.1. 6-Azauracil, $P2_12_12_1$, $Z = 4$. Azauracil has two distinct hydrogen bond donors (N2H2 and N4H4) alternating with the two carbonyl (C3O3 and C5O5) and N1 hydrogen bond acceptors (Figure 1), giving six possible combinations of hydrogen bond donors and acceptors. The experimental structure has N2H2···O3 and N4H4···O5 hydrogen bonds of almost equal length. Each molecule is joined to four others by two unique hydrogen bonds N4H4···O5 and N2H2···O3. The molecules are related by screw axes and do not form sheets. The overlap between parallel pyrimidine rings is minimal, with a carbonyl group close to the ring system. The competition between the different types of hydrogen bonds made this an attractive molecule to study, despite being relatively poorly reproduced by static minimization with the model potential. As shown in Table 1, the minimum energy structure obtained by minimizing from the lattice energy shows an root mean square (rms) error of 4% in the cell lengths relative to the experiment, the worst result for such a heterocycle within the data set tested.[9]

The MOLPAK procedure generated 500 initial structures, with lattice energies ranging from −33 kJ/mol to −87 kJ/mol (i.e., just within 10 kJ/mol of the global minimum). A cutoff of −80 kJ/mol on the initial energy resulted in some minimizations being performed from $C2/c$(9), $Pca2_1$(3), $Pna2_1$(5), and $Pbca$(11) structures. The results of the 118 lattice energy minimizations are displayed in Figure 2, which shows a large number of minimum energy crystal structures within 10 kJ/mol of the global minimum. The cell parameters of the lowest energy minimum in each space group are in Table 1. The minimum found starting from the experimental structure was also found from several MOLPAK-generated starting structures

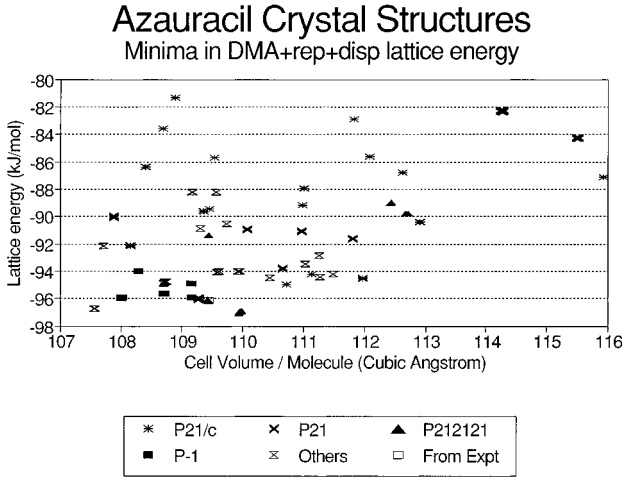

Figure 2. Energy/volume plot of the crystal structures of 6-azauracil which correspond to minima in the lattice energy, denoted according to space group.

such as AQ11. However, two marginally lower energy structures (<0.9 kJ/mol) were also found, denoted by one of the corresponding MOLPAK starting structures, AZ9 and CB7. The AZ9 global minimum structure is extremely similar to both the experimental structure and corresponding minimum and actually has a smaller rms difference in the cell lengths (2.8%) from the experimental structure than the corresponding minimum. The NIPMAT diagrams are identical. Figure 3 confirms that the minimum energy structure found from the experimental structure and AZ9 superimpose very well, being related by a slight rotation of the molecule. It seems likely that both minima and the experimental structure would correspond to the same dynamic structure for the librating room temperature crystal structure. This implies that the structures are equivalent, and the differences are mainly an artifact of the static simulation model.

There is considerable variation in the many other structures which are local minima in the lattice energy. The close intermolecular contacts between the polar hydrogen atoms and the hydrogen bond acceptors are given in Table 1, showing the

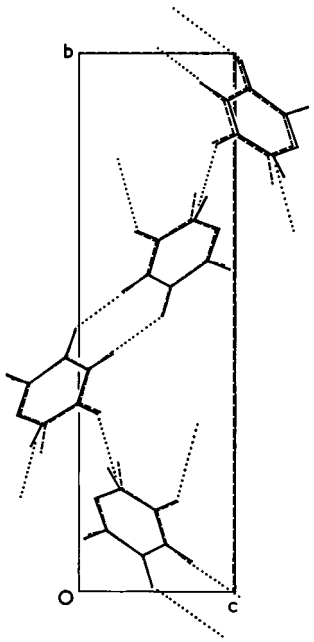

Figure 3. A comparison of the lattice energy minima obtained starting from the experimental structure of 6-azauracil (bold) and the global lattice energy minimum AZ9 (dashed), as projected onto the *bc* plane. The pair of hydrogen bonds that appear to be parallel actually bond to superimposed molecules.

differing "hydrogen bonds" that occur in these structures. The term is used loosely for any intermolecular interaction where a proton bonded to a nitrogen is close to a nitrogen or oxygen acceptor (i.e., a distance criterion for the term hydrogen bond). Thus, the hydrogen bonds vary in their linearity (of NH···O/N) and planarity (whether the H···N/O vector is in the plane of the N−H donor). Several structures with the same hydrogen bonds as the experimental structure have very different arrangements and are only slightly less favourable in energy. One ($Pna2_1$ (BD22)) has each molecule hydrogen bonded to four others, but with N4H4 approaching O5 from the opposite side than in the experimental structure. Two virtually identical $P\bar{1}$ structures, AB19 and AB15 (which is very close to the minimum obtained from experiment in Figure 2), involve molecules being joined by antiparallel pairs of hydrogen bonds, an N2H2···O3 pair to one neighbor, and an N4H4···O5 pair to another. A sheet structure, $C2/c$ (DD18), involves two molecules being joined by an antiparallel pair of N4H4···O5 hydrogen bonds, with elongated N2H2···O3 cross-linking. The N2H2···O3 hydrogen bonds are also long and distorted from linearity in the sheet structure $P2_1/c$ (AI12). The N4H4···O3 hydrogen bond in the $Pca2_1$ (AY5) structure is so non-coplanar that H4 is also within 2.37 Å of N1 of another molecule.

Another interesting feature of these results is the number of minima with different hydrogen bonds that are also close in energy. The complex *Pbca* structure CB7 has essentially the same lattice energy as the observed structure, and yet involves two chemically different hydrogen bonds, N2H2···N1 and N4H4···O3, both of which are slightly elongated (2.15 and 2.01 Å) and significantly nonlinear (136° and 154°) and far from coplanar. This is the densest structure found, and so the dispersion energy will partly offset the reduction in electrostatic energy from the nonideality of the hydrogen bonds. A $P2_1$ structure (AF15), also with distorted antiparallel N2H2···N1 pairs of hydrogen bonds and more ideal N4H4···O5 bonds, is only negligibly higher in energy. This shows that the experimental adoption of a crystal structure with N−H···O hydrogen bonds does not imply that N1 is a significantly weaker acceptor, though it does not pack with idealized hydrogen bonds. It raises

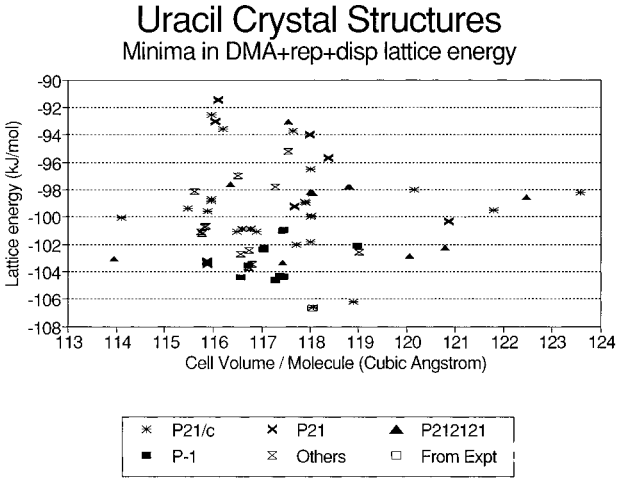

Figure 4. Energy/volume plot of the crystal structures of uracil which correspond to minima in the lattice energy, denoted according to space group. The two structures which resulted from the 10 AH ($P2_1$) minimizations have been omitted, as they had significantly higher energy (−77.5 kJ/mol at a molecular volume of 127.1 Å^3 and −78.0 kJ/mol at 126.2 Å^3). The additional energy minimum AM18 (see Table 2) has been included.

the question as to why the $P2_12_12_1$ structure is found experimentally in preference to the *Pbca*, $P2_1$, or $P\bar{1}$ structures with different hydrogen-bonding networks.

A fourth hydrogen bonding pattern is more marginally within the energy range associated with possible polymorphs (around 10 kJ/mol) with two rather different structures, $P2_1/c$ (AM19) and $P2_1$ (AH1), with N2H2···O5 and N_4H_4···N1 close contacts. The remaining two possible combinations of the proton donors with acceptors have been located in the $P2_1/c$ space group (AM12 and AM10) within 15 kJ/mol of the global minimum, both involving non-coplanar hydrogen bonds.

Thus, the different hydrogen bonding combinations possible for azauracil all seem capable of packing with translational symmetry, though not necessarily with idealized hydrogen-bonding geometries. However, the net loss in electrostatic lattice energy with these distortions is often fairly small.

3.2. Uracil, $P2_1/a$, $Z = 4$. The nucleic acid base uracil has two hydrogen bond donors (N1H1 and N3H3) and two acceptor (C2O2 and C4O4), whose properties are expected to differ as N3H3 is between both C═O groups and C2O2 between both NH groups in the aromatic ring. The observed crystal structure has C4O4 hydrogen bonded to both NH groups, with an antiparallel pair of N3H3···O4 bonds to one molecule, and N1H1···O4 bonds to two neighbors. C2O2 is near to, but not in particularly close contact with, the two protons bonded to carbon, forming planes of molecules. The stacking of these layers produces relatively little overlap of the molecules.

The hypothetical structures generated by MOLPAK varied in lattice energy between −45 and −93 kJ/mol, with the vast majority being within 40 kJ/mol of the global minimum. A cutoff on the initial energy of −85 kJ/mol for the less common space groups resulted in six minimizations in $Pna2_1$, 6 in $Pca2_1$, and 5 in $C2/c$. The results of these 107 minimizations are shown in Figure 4, which shows all the many resulting minima within 15 kJ/mol. The global minimum in the restricted search (AM9) was essentially the same as the minimum found starting from the experimental structure, within the limits of static minimization, differing by only 0.5 kJ/mol in the lattice energy and 0.9 Å^3 in the cell volume per molecule. This is confirmed by comparing the transformed cells (Table 2), structures, and the NIPMAT diagrams of the intermolecular distances. However, minimization from one of the middling energy (−73 kJ/mol)

TABLE 2: Predicted Crystal Structures for Uracil

space group and MOLPAK structure	exptl $P2_1/a$	min[a] $P2_1/a$	min[a] $P2_1/c$	$P2_1/c$ *AM18*[b]	$P2_1/c$ *AM9*	$P\bar{1}$ CA2	$C2/c$ DC4	$P2_12_12_1$ AQ20	$Pca2_1$ AY13	$P2_1$ AF17	$Pna2_1$ BF18	$Pna2_1$ AV16	$P\bar{1}$ AB3
energy/ kJ mol^{-1}	−102.3	−106.7		−106.6	−106.2	−104.6	−103.7	−103.3	−101.2	−103.5	−102.7	−102.5	−102.3
a/Å	11.938	12.17	3.70	3.70	3.72	6.63	12.64	7.00	21.49	5.12	5.26	11.14	4.09
b/Å	12.376	12.66	12.66	12.66	12.80	3.77	3.73	10.87	3.74	4.74	20.50	10.97	5.66
c/Å	3.655	3.70	10.10	10.10	10.05	10.19	19.90	6.18	5.77	10.37	4.32	3.89	10.51
α/deg	90.0	90.0	90.0	90.0	90.0	77.0	90.0	90.0	90.0	90.0	90.0	90.0	103.4
β/deg	120.9	124.0	93.4	93.4	95.2	100.8	83.3	90.0	90.0	102.8	90.0	90.0	98.6
γ/deg	90.0	90.0	90.0	90.0	90.0	107.7	90.0	90.0	90.0	90.0	90.0	90.0	85.8
volume/*Z*/Å^3	115.8	118.0		118.1	118.9	117.3	116.7	117.4	115.8	115.9	116.5	119.0	117.1
N1H1···O2/Å						2.15	2.16	1.94	2.09	2.37	2.40		1.96
N1H1···O4/Å	1.86	2.03		2.03	2.03	2.34	2.32			2.51	2.53	1.99	
N3H3···O2/Å						1.99	1.99	1.93	2.04	1.91	1.92	1.97	
N3H3···O4/Å	1.86	1.97		1.97	1.95								1.93

[a] The lattice energy minimum structure (min), found starting from the experimental structure (exptl), is compared with the equivalent structure found by the crystal structure prediction procedure. The next section gives the lowest energy structure for each space group with a minimum within about 10 kJ/mol of the global minimum. Other minima with different hydrogen bonds are in the last section. The short (N)H···O/N distances are given for each structure. The lattice energies are summed to 15 Å. [b] AM18 corresponds to the 18th in energy, 13th in volume ranking MOLPAK initial structure. The lowest energy structure obtained by using just the 10 lowest energy initial structures was AM9.

and density MOLPAK initial structures (AM18) gave a better, virtually exact, reproduction of the minimum found starting from the experimental structure.

The experimental structure is only a few kJ/mol lower in energy than other structures with alternative hydrogen bonds. There are various structures based on both N2H2 and N4H4 forming hydrogen bonds to the O2, with the protons of C5H5 and C6H6 near O4, the opposite way around to the experimental structure. A $P2_12_12_1$ structure (AQ20) has O2 linked to the N3H3 of one neighbor and N1H1 of the next, so that each molecule is bonded to two others by an unlike pair of hydrogen bonds, forming chains. C5H5, C6H6, and C4O4 form the edges of the bands, and the H···O distances suggest that these stabilize the structures. A $Pca2_1$ structure (AY13) retains one of these pairs of hydrogen bonds, so that each molecule is hydrogen bonded to three others. Two structures where each molecule is hydrogen bonded to two neighbors, one by a pair of antiparallel N1H1···O2 bonds and the other by an antiparallel pair of N3H3···O2 bonds, are formed in $P\bar{1}$ (CA2) and $C2/c$ (DC4). These hydrogen bonded ribbons allow H1 to be fairly close (2.3 Å) to O4. These structures are only about 2 kJ/mol less stable than the observed structure.

The other two hydrogen-bonding possibilities also have lattice energies within the range associated with possible polymorphs. A $Pna2_1$ structure, AV16, with N1H1···O4 and N3H3···O2 hydrogen bonds, has almost the same energy as a $P\bar{1}$ structure (AB3) with N3H3···O4 and N1H1···O2 hydrogen bonds, both being about 4 kJ/mol less stable than the global minimum. AV16 involves sufficient relative tilt of the molecules that all four hydrogen bonds are to different molecules. AB3 has simple hydrogen-bonded chains involving antiparallel pairs of N1H1···O2 and N3H3···O4 hydrogen bonds to neighboring molecules. Other more complicated structures, $P2_1$ (AF17) and $Pna2_1$ (BF18), are formed with conventional N3H3···O2 hydrogen bonds and very distorted elongated interactions between H1 and both O2 and O4.

Thus, in the case of uracil, as azauracil, the molecule is able to adopt a variety of hydrogen-bonding motifs within the energy differences generally associated with polymorphism. The motifs differ in that the experimental one involves hydrogen bonds in sheets, whereas most of the others involve hydrogen-bonded chains.

3.3. Allopurinol, $P2_1/c$, $Z = 4$. Allopurinol, which is used in the treatment of gout, has a potential hydrogen bond donor and a nitrogen acceptor on each ring (N1H1 and N3 in the six-membered ring, N8 and N9H9 in the five-membered ring), plus a carbonyl acceptor C6O6. The experimental crystal structure is based on sheets of molecules in which each molecule is surrounded by six molecules in the plane. Each molecule has two N1H1···N8 bonds to two other molecules forming chains which are linked by the two N9H9···N3 hydrogen bonds to one neighbor. The other three molecules in the plane are only indirectly linked by the hydrogen-bonding network, though two have van der Waals contacts between the O6 and H2C2. There is relatively little overlap of the molecules in the stacked sheets.

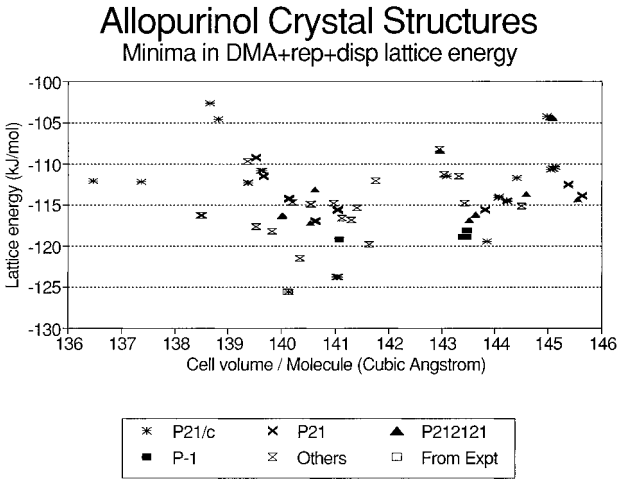

Figure 5. Energy/volume plot of the crystal structures of allopurinol which correspond to minima in the lattice energy, denoted according to space group. The additional energy minimum AM15 (see Table 3) has been included.

The hypothetical structures generated by MOLPAK had lattice energies which were predominantly between −70 and −108 kJ/mol, but there were several less favorable structures and one with a positive lattice energy (+41 kJ/mol for one of the less dense $C2/c$ structures), which may reflect the more complex shape of the double-ring system. An energy cutoff on the initial energies of −100 kJ/mol for the less common space groups resulted in two minimizations in $P1$, 12 in $Pna2_1$, 14 in $Pca2_1$, and five in $C2/c$, giving a total of 123 minimizations. There is also a somewhat larger spread in the energies and volumes of the many lattice energy minima, displayed in

TABLE 3: Predicted Crystal Structures for Allopurinol

space group and MOLPAK structure	exptl $P2_1/c$	min $P2_1/c$[a]	$P2_1/c$ AM15[b]	$P2_1/c$ AM5	$Pna2_1$ AV2	$P2_12_12_1$ AQ15	$Pbca$ CB21	$P\bar{1}$ AB19	$P2_1$ AF4	$P1$ AA19	$Pca2_1$ BH3	$Pca2_1$ AY10
energy/kJ mol^{-1}	−122.1	−125.5	−125.6	−123.8	−121.5	−117.2	−114.9	−119.2	−117.0	−115.3	−116.3	−115.0
a/Å	3.683	3.70	3.70	3.65	12.67	14.63	14.12	8.02	3.81	7.44	25.85	14.78
b/Å	14.685	14.69	14.69	10.92	11.69	11.01	11.60	5.51	5.64	5.96	3.75	4.17
c/Å	10.318	10.35	10.35	14.61	3.79	3.49	6.86	9.74	13.09	3.67	5.72	9.38
α/deg	90.0	90.0	90.0	90.0	90.0	90.0	90.0	107.7	90.0	84.5	90.0	90.0
β/deg	97.47	95.4	95.4	104.1	90.0	90.0	90.0	125.4	91.8	66.4	90.0	90.0
γ/deg	90.0	90.0	90.0	90.0	90.0	90.0	90.0	53.7	90.0	103.9	90.0	90.0
volume/Z/Å^3	138.3	140.1	140.1	141.0	140.3	140.5	140.5	141.1	140.6	141.4	138.5	144.5
N1H1···N3/Å												
N1H1···N8/Å	1.90	1.91	1.91	1.89	1.93	1.90	2.28			2.16		1.98
N1H1···O6/Å								1.95	1.94		1.98	
N9H9···N3/Å	1.90	1.93	1.93	1.94	1.95	2.16	2.21	1.93				
N9H9···N8/Å									1.97		1.97	
N9H9···O6/Å							2.33			1.98		1.98

[a] The lattice energy minimum structure (min), found starting from the experimental structure (exptl), is compared with the equivalent structure found by the crystal structure prediction procedure. The lowest energy structure for each space group with a minimum within about 10 kJ/mol of the global minimum is then given, with those with the same hydrogen-bonding pattern as the observed structure first. Other minima with different hydrogen bonds are in the last section. The short (N)H···O/N distances are given for each structure. The lattice energies are summed to 15 Å. [b] AM15 corresponds to the 24th in energy, 3rd in volume ranking MOLPAK initial structure. An equivalent structure to the one obtained on minimization is reported. The lowest energy structure obtained using just the lowest 10 structures is AM5.

Figure 5, which has a larger scale. Nevertheless, there are still many alternative structures within 10 kJ/mol of the global minimum.

The global minimum found (AM15) is essentially identical to the minimum found starting from the experimental structure, differing by only 0.01 kJ/mol in energy (Table 3). However, this minimum was found from the third densest, but was only the 24th most energetically favorable (−79 kJ/mol) of the 25 initial MOLPAK starting geometries. The lowest energy structure found using only the ten lowest initial energies, AM5, has the same hydrogen-bonding pattern and very similar nearest-neighbor contacts, but the relative tilt between molecules linked by the chains of N1H1···N8 bonds is significant. Thus, only the full search would have correctly predicted the observed sheet structure.

A variety of other crystal structures were found as shown in Table 3. Other variants on the experimental structure were found in $P2_12_12_1$ (AQ15) and $Pbca$ (CB21) in which the antiparallel N9H9···N3 bonds deviated considerably from the plane of the molecule, allowing long (2.3 Å in CB21) to very long (2.7 Å in AQ15) hydrogen bonds to form between N9H9 and O6. In $Pna2_1$ (AV2), a structure within 4 kJ/mol of the global minimum, there are the same types of hydrogen bonds, but each molecule is hydrogen bonded to four others.

There is quite a variety of different hydrogen-bonding patterns within about 10 kJ/mol of the global minimum. The most favorable alternative hydrogen bonding pattern is shown in the $P\bar{1}$ (AB1) structure, which has chains of molecules, with each molecule hydrogen bonded by a pair of N9H9···N3 hydrogen bonds on one side and a pair of N1H1···O6 hydrogen bonds on the other. Structures where each molecule is hydrogen bonded to four others by N1H1···O6 and N9H9···N8 hydrogen bonds were found in $P2_1$ (AF4) and in $Pca2_1$ (BH3) and by N1H1···N8 and N9H9···O6 in $P1$ (AA19) and $Pca2_1$ (AY10).

Although a wide range of alternative structures with different hydrogen bond pairings were found, it is notable that none were found with hydrogen bonds between N1H1 and N3. Calculations with the same model potential on the gas phase dimer suggest that this is not intrinsic to the hydrogen bond. All six possible doubly hydrogen-bonded dimers involving the three neighboring acceptor/donor pairs N1H1/O6, N9H9/N8, and N9H9/N3 (see Figure 1) were found as stable minima with energies ranging from −60 kJ/mol for the dimer with two antiparallel N1H1···O6 to −39 for the dimer with two N9H9···N8 hydrogen bonds. Thus the existence of a dimer structure with N1H1···N3 and N9H9···O6 hydrogen bonds toward the bottom of this range (−44 kJ/mol) suggests that the absence of N1H1···N3 hydrogen bond in the crystal structures may be due to the difficulty of packing the irregularly shaped dimer that would result within the low-Z structures examined.

4. Conclusions

The main conclusion of this paper is that using close-packing criteria, refined by lattice energy minimization, to search the common space groups for organic molecules, is successful in finding the molecular crystal structure adopted by hydrogen bonding heterocycles, as exemplified by uracil, 6-azauracil, and allopurinol. The structures found by searching for dense packings, using a pseudo-repulsive potential developed for different molecules, are sufficiently good starting points for the lattice energy minimization to locate the experimental structure. The simplified repulsion potential in the MOLPAK search was not optimized for these structures, and the cell volume consistently expanded by over 10% during the lattice energy minimization. However, this crude starting point was suitable for the minimization process to be successful, justifying the decision not to refine the MOLPAK parameters. It is worth noting that the packing search generated relatively low-energy structures, with only a few exceptions in the case of allopurinol, implying that structures with strongly unfavorable electrostatic forces, as might be expected if hydrogen bond acceptor atoms were in close contact, are generally not well packed. Thus there does not seem to be any major conflict between close packing and hydrogen bonding in determining crystal structures for these molecules.

The most notable feature of the results is the plethora of alternative structures whose lattice energies are close to those of the observed structure and the global minimum. More structures would certainly be found if further space groups and structures with other than one molecule in the asymmetric unit could be considered, and if more minimizations had been carried out in the space groups considered. However, sufficient low-energy structures have been located by this fairly restricted

search to illustrate the problem of polymorph prediction and the range of hydrogen bonding motifs that can give low-energy structures. No method is guaranteed to find the experimental structure, and indeed, the difficulty of an *a priori* molecular crystal structure prediction will depend on the molecule, crystal symmetry, and force field as well as the method used. Nevertheless, this approach of a MOLPAK search followed by lattice energy minimizations with a realistic model potential appears promising compared with other proposed methods.[1,2,4] Minimization of the 25 lowest volume MOLPAK initial structures in the experimental space group reproduced the minimum found from the experimental structure for all three molecules. The more restricted search of only the 10 lowest energy initial structures found the observed hydrogen-bonding network, and only in the case of allopurinol was extension to the full 25 minimizations necessary to find the experimental structure within the errors of static minimization.

The classification of the hypothetical structures, let alone their interpretation in terms of potential polymorphs, is far from clear cut, though three main types of relationships have been observed. First, there are clusters of structures which are essentially the same, where the minor differences of a few percent in cell lengths can be attributed to the use of a static minimization model. (Indeed, the number of such structures found would be dependent on the details of the minimization procedure.) These structures are so closely related that they would all be on the same trajectory of a librating molecule in a realistic room temperature simulation of the structure.

The second relationship is where the structures have very similar nearest-neighbor contacts with similar hydrogen bonds and other strong interactions. The energies of such structures would be very similar, and the NIPMAT matrices would be virtually identical, with only a few intermolecular distances, which were 1 Å or so greater than van der Waals contact differing between the two structures. Nevertheless, the longer range symmetry is different. An example would be the hypothetical uracil structures which were based on the same hydrogen-bonding bands within different space groups. In this case, further detailed examination would be required to establish whether there is a pathway for their interconversion with a low-energy barrier. The gray area between these two types of structure relationship is related to the question as to how dissimilar two structures need to be to be experimentally observable as two distinct polymorphs, which will depend on the potential energy surface in the crystal. An algorithm that would reliably cluster static molecular crystal structures into groups that would be distinct at room temperature is clearly needed for molecular crystal structure prediction.

The third relationship is that the two structures are definitely so distinct, with very different nearest-neighbor contacts, that they would undoubtedly be experimentally classified as different polymorphs. The hypothetical structures with different hydrogen bonding patterns fall into this class.

Thus, the most interesting result to emerge from this study is that for all three molecules there are hypothetical structures, with different sets of hydrogen bonds, which are within 10 kJ/mol in lattice energy of the observed structure. Almost all the different possible combinations of hydrogen bond donors and acceptors have been found in low-energy structures for uracil and 6-azauracil, whereas in the case of allopurinol, only one possible hydrogen bond appears not to form in simple crystal structures. These hypothetical structures are in common space groups with one molecule per asymmetric unit and 8, 4, 2, or 1 molecules per unit cell, and they seem to be plausible structures. This implies that, at least for these three molecules, the orientational demands for the electrostatic stabilization associated with hydrogen bonds can be relatively easily associated with the translational packing requirements of molecular crystals. This will not always be the case, as demonstrated by the lack of N1H1···N3 hydrogen bonds in allopurinol crystal structures and the non-hydrogen-bonded structure of alloxan being an estimated 5 kJ/mol more stable than hypothetical hydrogen-bonded structures.[33] Thus, the consideration of hydrogen-bonding motifs and their packing requirements eliminates some possibilities, but it still often results in a wide variety of possible crystal structures and may miss some structures stabilized by other interactions.

The use of an accurate model for the distance and orientation dependence of the electrostatic forces, the dominant contribution to the hydrogen bond energy, confirms that the energy differences between different possible crystal packings can be very small. Other crystal structure prediction studies have also noted that there are other plausible crystal structures very close in energy to the observed structure:[1,3,4] Gavezzotti[2] showed for several hydrocarbons that it is possible to construct a large number of crystal structures whose lattice energies differ by less than 10%. He has also shown graphically the large number of possible minimum energy structures within the estimated energy difference of the two known polymorphs for 7-dimethylaminocyclopenta[*c*]coumarin.[34] The attempted prediction of the crystal structures of six monosaccharides[6] resulted in of the order of 1000 possible structures within 10 kcal/mol of the global minimum, showing that the directional properties of the five hydrogen bonds can be easily accommodated in many different ways. The great conformational flexibility of the sugars, particularly the hydroxyl groups, and the low directionality in the intermolecular forces in hydrocarbons and the nonpolar coumarin are likely to increase the number of possible crystal structures. The current study has used rigid molecules with strongly directional bonding interactions and still finds several hypothetical crystal structures for each system within 10 kJ/mol of the global minimum. It seems certain that it is not uncommon for there to be alternative molecular crystal structures within a few kcal/mol of the global minimum. Further refinements of the model potential, such as the inclusion of polarization/charge transfer effects or the use of a more accurate charge distribution instead of an approximate scaling factor, may alter the lattice energies somewhat, but this would not alter the relative energies sufficiently to make all the hypothetical structures energetically unfeasible. Since known polymorphs are expected to differ by up to a few kcal/mol, many of the hypothetical structures have to be considered as energetically possible structures.

Hence genuine structure prediction requires further work to establish which energetically possible structures are likely to be found experimentally. Although the global lattice energy minimum did correspond to the known structure for 6-azauracil, uracil, and allopurinol, within the limits of static minimization, this criterion cannot infallibly predict the most probable crystal structure when the energy differences are small to negligible (as in the case of 6-azauracil). Although uracil, 6-azauracil, and allopurinol may be polymorphic, no alternative structures have been sufficiently well characterized to appear in the Cambridge Structural Database. How can we establish whether further experimental effort would result in some of the hypothetical structures being found?

A fuller thermodynamic treatment might increase the energy differences at finite temperatures, though Gavezzotti and Filippini[35] estimated that including the vibrational entropy did not affect the relative stabilities of known polymorphic structures.

A consideration of the kinetics of crystallization and the effects of the environment, such as solvent, may be more effective. Some types of crystal structures will form more stable nuclei or have an advantageous morphology. Establishing how to effectively predict which of the energetically possible structures are most likely to be formed experimentally, under which conditions, will require a distillation of the next most dominant fundamental effect in the crystallization process. Such studies will almost certainly start from this type of search for the energetically plausible structures. Analysis of the range of hypothetical structures for a given molecule may reveal empirically whether certain structural types, for example, sheet as opposed to chain structures of similar energy, are more likely to form good crystals. Thus, the efficient search for minima in the accurately calculated static lattice energy will only predict the molecular crystal structure in some cases. In others, such as the heterocycles considered here, it will just be the first step to a genuine prediction of which structures could be found as polymorphs. Such a goal will require considerable experimental and theoretical work to improve our understanding of the crystallization process.[36]

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