The Prediction, Morphology, and Mechanical Properties of the Polymorphs of Paracetamol

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Abstract: The analgesic drug paracetamol (acetaminophen) has two reported metastable polymorphs, one with better tabletting properties than the stable form, and another which remains uncharacterized. We have therefore performed a systematic crystal structure prediction search for minima in the lattice energy of crystalline paracetamol. The stable monoclinic form is found as the global lattice-energy minimum, but there are at least a dozen energetically feasible structures found, including the well-characterized metastable orthorhombic phase. Hence, we require additional criteria to reduce the number of hypothetical crystal structures that can be considered as potential polymorphs. For this purpose the elastic properties and vapor growth morphology of the known and predicted structures have been estimated using second-derivative analysis and the attachment-energy model. These inexpensive calculations give reasonable agreement with the available experimental data for the known polymorphs. Some of the hypothetical structures are predicted to have a low growth rate and platelike morphology, and so are unlikely to be observed. Another is only marginally mechanically stable. Thus, this first consideration of such properties in a crystal-structure prediction study appears to reduce the number of predicted polymorphs while leaving a few candidates for the uncharacterized form.

Introduction

There is considerable commercial interest in polymorph prediction from the pharmaceutical industry to avoid dosage, processing, and patent problems. This, in addition to fundamental scientific interest, has led to many methods of predicting molecular crystal structures being proposed. A recent international blind test[1] organized by the Cambridge Crystallographic Data Centre (CCDC) showed some success in the prediction of crystal structures of simple organic molecules by using lattice-energy minimization techniques. These methods are built on the assumption that the experimental crystal structure corresponds to the global lattice-energy minimum. This implies that any local minima that are sufficiently close in energy to the global minimum represent energetically feasible polymorphs. Unfortunately, for most molecules studied, more energetically feasible crystal structures are found than experimentally observed polymorphs.

In some crystal-structure prediction studies of polymorphic systems, the known polymorphs correspond to the lowest-energy structures, as in the case of indigo[2] and in the most recent pressure-dependent study of benzene.[3] However, unknown structures are often found with a more favorable lattice energy than a known metastable form, as reported for tetrolic acid.[4,5] For larger, conformationally flexible molecules such as estrone,[6] primidone,[7] and 4-amidinoindanone guanylhydrazone,[8] X-ray powder patterns are needed to identify the known polymorphs from the plurality of possible, low lattice-energy crystal structures. Indeed, in the recent blind test[1] when 11 research groups put forward three predictions for the crystal structure of 3-oxabicyclo(3.2.0)hepta-1,4-diene, four groups proposed the metastable form, but none the stable form. Thus, the ab initio prediction of polymorphism clearly requires the consideration of other factors, such as growth rates and mechanical stability, which we consider for the first time in this study.

Polymorphism can also provide an opportunity to improve the physical properties of a crystalline product, without changing the molecule involved. This has led to considerable experimental research into the polymorphism of paracetamol (*p*-hydroxyacetanilide, Scheme 1). Paracetamol, also known as acetaminophen, has now grown to be the most widely used antipyretic (fever suppressant) and analgesic (pain killer) in the world.

Two forms of paracetamol have been extensively characterized by X-ray diffraction (Figure 1).[9−15] A neutron study of form I over a wide range of temperatures[16] has revealed the

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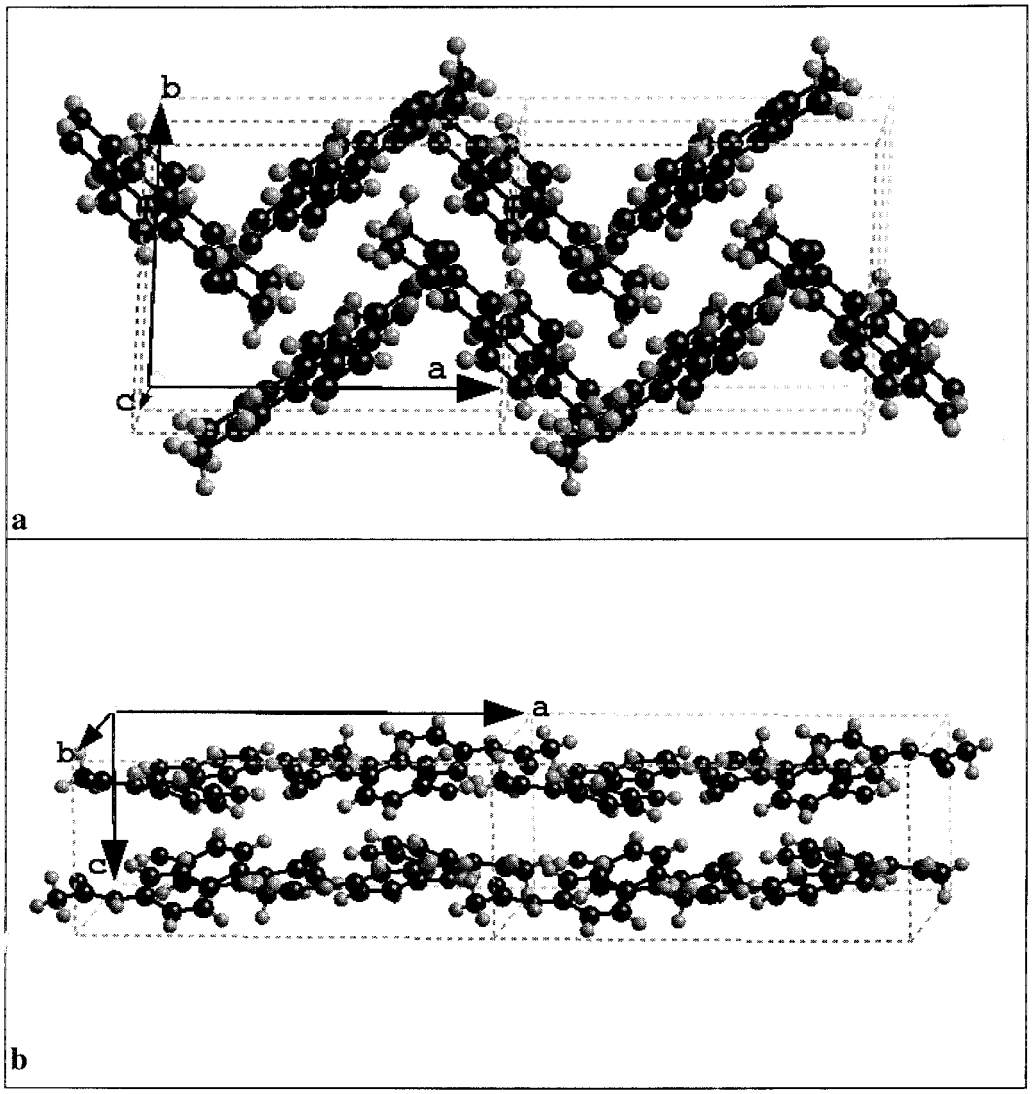
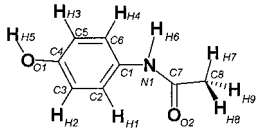


Figure 1. The crystal structures of paracetamol in (a) form I (determined at 20 K)[16] and (b) form II (123 K).[15]

Scheme 1: Molecular Structure of Paracetamol



large amplitude librational motion of the methyl group at high temperatures. A third polymorphic form III,[14] has been recently recrystallized under a microscope slide[17] but was too unstable for an experimental investigation of its crystal structure. A search for the third polymorph by slow evaporation of an aqueous solution of commercial paracetamol actually produced a coupled dimer oxidation product.[18]

The metastable polymorphs of paracetamol are of particular industrial interest because the commercial form I requires binders for tablet formation. The crystal structure of form I has pleated sheets stacked along the *b* axis (Figure 1a), making it relatively stiff, resulting in poor compression properties.[19] Although improved compression properties can be obtained by varying the habit of the crystallites,[20−22] such a production process has problems in completely eliminating the residues of the required solvent.[23] The crystal structure of the orthorhombic form II (Figure 1b) has parallel hydrogen-bonded sheets along the *c* axis, giving slip planes which allow plastic deformation.[15,19] Thus, the direct compression of the orthorhombic form II into tablets has been investigated for potential industrial use.[15] It has been found that a possible transition of form II to I in tablets during storage should be without consequences on the bioavailability.[23]

The morphology of paracetamol crystals also affects the industrial processing. Form I crystals grown from aqueous solution[24] have an elongated prismatic morphology when grown at low supersaturation, but for relatively high supersaturation

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the faces are equally developed, and so solvent molecules play a role in determining the habit.[25] The morphology of both forms when grown from supersaturated industrially methylated spirits (IMS) solution has been determined[15] and compared with predictions from the attachment-energy model, which is most appropriate for crystals grown from vapor. For the monoclinic form, the experimental prismatic-to-platelike morphology is well predicted[15] by the attachment-energy model using the Dreiding-2.21 force field.[26] However, the same model underestimates the *c* axis elongation of the prismatic habit for form II. This was attributed to the effect of the solvent and to the rapidity with which the orthorhombic crystal had been precipitated.

A crystal structure prediction study on paracetamol has already been undertaken with the MSI Polymorph Predictor,[6] using the Dreiding-2.21 force field[26] in combination with semiempirical MNDO-ESP atomic charges.[27] This found both experimentally known crystal structures in the correct stability order and a third potential polymorph in the $P2_12_12_1$ space group. After recalculation with a different force field, it was concluded[6] that this unknown structure was too unstable to exist.

Thus, the aim of this study is to investigate the ability of rigid molecule lattice modeling to provide a genuine prediction of the known polymorphs of paracetamol and their industrially important properties. We consider also the morphology and mechanical properties of the hypothetical structures, for the first time in a crystal-structure prediction study. This is to establish whether the properties provide any discrimination between the energetically plausible structures, either by suggesting that they are unlikely to be found or by showing that they would have desirable properties if they could be obtained experimentally. The crystallographic details of possible candidates for form III may prove useful in characterizing this elusive structure if, for example, powder diffraction diagrams could be obtained experimentally, and hence the structures are provided as Supporting Information.

Methods

The molecular model of paracetamol was obtained by ab initio optimization, using an SCF/6-31G** wave function and the program CADPAC.[28] This was used in the search, as an experimental solid-state molecular structure would not be available for a genuine structure prediction and also would bias the search toward its polymorph. The molecule was kept rigid, and so the modeling does not include the effects of crystal packing on the molecular structure.

The intermolecular potential consists of an ab initio-based distributed multipole model for the electrostatic contribution and an empirical isotropic atom−atom repulsion−dispersion potential of the type which successfully reproduces the crystal structures and heats of sublimation of a wide range of hydrogen-bonded organic crystals.[29] The electrostatic model includes all terms in the atom−atom multipole series up to R^{-5}, using atomic multipoles up to hexadecapole, which have been obtained by a distributed multipole analysis (DMA)[26] of the MP2/6-31G** wave function of the isolated molecular structure.

The empirical repulsion−dispersion potential has the form

$$U = \sum_{i\in1,k\in2} U_{ik} = \sum_{i\in1,k\in2} (A_\iota A_\kappa)^{1/2}\exp(-(B_\iota + B_\kappa)R_{ik}/2) - \frac{(C_\iota C_\kappa)^{1/2}}{R_{ik}^{\ 6}} \quad (1)$$

where atom i in molecule 1 is of type ι, and atom k in molecule 2 is of type κ. The parameters for the C, O, N and H_C atoms (where H_C denotes hydrogen bonded to carbon) were derived by empirical fitting to the crystal structures and heats of sublimation of non-hydrogen-bonded structures.[30,31] The parameters for the polar hydrogen atoms were empirically fitted to crystal structures involving $N-H_N\cdots N$ and $N-H_N\cdots O{=}C$.[29]

The search for possible crystal structures used the systematic search program MOLPAK[32] to generate densely packed, hypothetical crystal structures, with a common coordination environment with one molecule in the asymmetric unit. Such a search was performed for each of 22 MOLPAK coordination types, representing the space groups $P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12_1$, $Pna2_1$, $Pca2_1$, $Pbca$, and $C2/c$, by considering all orientations of the central molecule relative to the crystal axes, using a stepsize of 10°. At least the 25 densest structures (refined to 2°) in each coordination type were then used as starting points for lattice-energy minimization with the model intermolecular potential.

The lattice energies of all crystal structures were calculated and minimized using the program DMAREL,[33] using Ewald summation for the charge−charge, charge−dipole, and dipole−dipole contributions to the lattice energy, and direct summation to 15 Å for all shorter-range terms. Low-energy structures, which could have a surface-energy correction term,[34−37] were identified after the minimization. The space group symmetry was constrained during all minimizations, which used the analytic forces and torques on the rigid molecules and strain derivatives of the unit cell to locate stationary points in the potential energy surface with a modified Newton−Raphson procedure. The symmetry was subsequently relaxed to the appropriate subgroup if the second derivative (Hessian) matrix had any negative eigenvalues. The elastic constant matrix[38] was then calculated from the second derivatives,[33] using the analytic expressions relating the Taylor expansion of the energy density to the stiffness constants.[39−41] Thus, the calculated elastic constants correspond to the stress-free crystal structure in the classical 0 K state.

The morphologies of the experimental and various hypothetical crystal structures of paracetamol were calculated using two simple models that are most appropriate to vapor-grown crystals. The Bravais−Friedel−Donnay−Harker (BFDH)[42] model assumes that the growth rate of a crystal face is inversely proportional to the inter-planar spacing d_{hkl}. Hence the largest crystal faces are those with the greatest inter-planar spacings, usually reflecting the weakest interactions between the face and the next growth layer. This is better quantified in the attachment-energy model, which assumes that the growth rate is proportional to the energy per molecule released on the attachment of a stoichiometric growth slice to a growing (*hkl*) crystal surface.[43] The

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morphologies were calculated using the program[44] Cerius[2]3.5 and the Dreiding-2.21 force field[26] with equilibrium charges,[27] following the reasonable success of this method[15] in predicting the experimental morphologies grown from supersaturated IMS solution.

Results

The ab initio optimization of the molecular structure of paracetamol gave a planar structure where the relative positions of the non-hydrogenic atoms were within the range of the fourteen experimental determinations.[45] The experimental positions of the methyl hydrogens varied significantly with temperature and method of determination, because of the onset of significant librational motion[46] as well as the usual experimental errors in X-ray determinations of hydrogen positions. The only significant difference between the ab initio molecular model and the experimental structure, which probably arises from the influence of the crystalline environment, was a small out-of-plane torsion of the hydroxyl proton. This varied[45] from 16 to 19° in form I and was 23°, 22°, and 1° in the three X-ray determinations of form II.

The variations in the molecular structure have a small effect on the differences between the experimental structures and the lattice-energy minima.[45] Table 1 shows the highest- and the lowest-temperature determination of both forms, and the corresponding minima, using both the corresponding experimental and ab initio molecular structures. The minima obtained using the ab initio structure are the closest to the experimental structures that could be obtained in the crystal structure prediction search. Our model molecule and model potential are able to reproduce the experimental structures within a few percent in the cell lengths. The use of an ab initio molecular model reduces the lattice energy by up to 10 kJ/mol, probably because the low-energy torsion of the hydroxyl proton in the experimental structures reduces the O(−H)···O hydrogen bond length by about 0.2 Å. However, the calculations with the ab initio model predict that the orthorhombic form is metastable relative to the monoclinic form, in agreement with experimental observations,[47,48] with a plausible energy difference.

The lattice-energy minima found in the MOLPAK search using the ab initio molecular model and the same intermolecular potential are shown in Figure 2. The low-energy structures were compared in detail, using visual inspections and their reduced cells,[49] with the resulting clustering of very similar minima being confirmed by a similarity index analysis based on the coordination environment.[50] The 14 distinct crystal structures with a lattice energy within 10 kJ/mol of the global minimum, are listed in Table 1, designated by the MOLPAK coordination group and number.

The search readily found the monoclinic stable form as the global minimum (Table 1). The match of the structure designated AM30 with the minimum obtained from any of the experimental determinations of form I, using the rigid ab initio molecular model and same model potential, was exact. An extremely close match for the corresponding minimum for the metastable orthorhombic form was also found as CB47 after an extended search in the *Pbca* space group, using two sets of initial orientations of the probe molecule.

The hypothetical structures in Table 1 often involve different types of hydrogen-bonding motifs. The majority of these structures consist of stacks of hydrogen-bonded chains (AI22, AQ6, AQ14, CC8, AI16, AM4). Four structures form chains interlinked by OH···OH bonds (CC19, AK6, AK22, AK4). There is one sheet structure (CB9), and another structure (AY8) has a three-dimensional hydrogen-bonding network. Despite this variety, all of these structures are within the small energy range of plausible polymorphism and show only a 6% variation in density.

Elastic Constants and Morphology Calculations. The calculated elastic properties of the lowest-temperature crystal structures of both known forms of paracetamol are given in Table 2. The structural differences in the two polymorphic forms lead to distinct differences in the mechanical properties. In form I, the pleated sheets have N−H···O(H)−C hydrogen bonds approximately along the *a* axis, interlinked by O−H···O═C hydrogen bonds in the *c* direction (Figure 1). This results in larger elastic constants in this plane ($C_{11} \approx C_{33} \approx 21$ GPa) than in the *b* direction along which the pleated sheets are stacked ($C_{22} = 14$ GPa). All three shear elements of the stiffness matrix have relatively large values for molecular crystals ($C_{ii} > 5$ GPa, $i = 4,5,6$) describing resistance to shearing along the axial planes.

In contrast, the orthorhombic form II shows considerable anisotropy in both the axial (C_{11}:C_{22}:$C_{33} = 4.4$:2.2:1) and shear (C_{44}:C_{55}:$C_{66} = 4.7$:1:15.3) diagonal elements of the elastic tensor. The large axial matrix element along the *a* axis correlates with the O−H···O═C hydrogen bonds being predominantly along this axis. There is also significant intermolecular stiffness in the *b* direction due to the N−H···O(H)−C hydrogen bonding which completes the *ab* sheets. These hydrogen-bonded sheets are separated by approximately 3.7 Å along the *c* direction, and the weakness of the intermolecular forces between the sheets is reflected by a small value of C_{33}. The smallest shearing element for form II is C_{55}, representing the facile slippage of the *ab* plane along the *a* axis, which produces the desirable tabletability.

Quantitative experimental information on the elastic properties of paracetamol is limited. Values for the Young's modulus of a compaction of monoclinic paracetamol[51,52] vary by about 40%. The more recently determined[52] higher value of 11.7 GPa is bounded by the calculated Reuss[53] ($E_R = 11.5$ GPa) and Voigt[54] ($E_V = 14.9$ GPa) averages, which average over the compliance and stiffness tensors assuming a uniform stress or uniform strain throughout the aggregate, respectively. These two averages also assume a macroscopically homogeneous aggregate, which may not be valid as the habit of single crystals of monoclinic paracetamol is found to be prismatic to platelike.[9] In the limit of idealized stacked plates, the Voigt average is more appropriate.[55] However, all of the calculated elastic constants are expected to be too high (of order of 40% by comparison with other hydrogen-bonded molecular crystals[38]) because of the neglect of thermal softening. Thus, the results are in reasonable agreement with the known elastic properties of paracetamol and qualitatively explain the different tabletability of the two forms.

The elastic properties of the two lowest-energy crystal structures found in the search are also shown in Table 2, and

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Table 1. Low-Energy Crystal Structures of Paracetamol[a]

	space group	reduced cell parameters						hydrogen bonds[b]				U_{latt}/ kJ mol^{-1}	ΔU_{latt}[c]/ kJ mol^{-1}	density /g cm^{-3}
		a/Å	*b*/Å	*c*/Å	α/deg	*β*/deg	*γ*/deg	O−(H) ···O=C /Å (/deg)	N−(H) ···O−H /Å (/deg)	O−(H) ···O−H /Å (/deg)	N−(H) ···O=C /Å (/deg)			
Form I														
$Expt_{low}$	$P2_1/a$	7.073	9.166	11.546	90.0	98.1	90.0	2.65 (165)	2.90 (164)	–	–	−111.1	–	1.35
$Expt_{high}$	$P2_1/a$	7.085	9.370	11.706	90.0	97.5	90.0	2.66 (167)	2.93 (163)	–	–	−115.2	–	1.30
$Min_{exptlow}$	$P2_1/a$	7.297	9.326	11.554	90.0	100.0	90.0	2.86 (163)	2.92 (160)	–	–	−118.3	–	1.30
$Min_{expthigh}$	$P2_1/a$	7.201	9.120	11.829	90.0	100.9	90.0	2.82 (161)	2.90 (160)	–	–	−120.4	–	1.32
Min_{opt}	$P2_1/a$	7.278	8.944	12.120	90.0	100.0	90.0	2.88 (155)	2.91 (164)	–	–	−110.1	0	1.29
AM30	$P2_1/c$	7.277	8.944	12.119	90.0	100.0	90.0	2.88 (155)	2.91 (164)	–	–	−110.1	0	1.29
Form II														
$Expt_{low}$	$Pbca$	7.212	11.777	17.166	90.0	90.0	90.0	2.71 (171)	2.94 (164)	–	–	−111.9	–	1.38
$Expt_{high}$	$Pbca$	7.405	11.831	17.156	90.0	90.0	90.0	2.73 (144)	2.98 (160)	–	–	−108.2	–	1.34
$Min_{exptlow}$	$Pbca$	7.454	11.877	17.471	90.0	90.0	90.0	2.90 (172)	2.95 (161)	–	–	−117.4	–	1.30
$Min_{expthigh}$	$Pbca$	7.398	11.897	17.578	90.0	90.0	90.0	2.92 (156)	3.03 (157)	3.71 (95)	–	−112.2	–	1.30
Min_{opt}	$Pbca$	7.384	12.076	17.263	90.0	90.0	90.0	2.95 (146)	2.92 (153)	3.69 (99)	–	−106.5	3.6	1.30
CB47	$Pbca$	7.382	12.086	17.248	90.0	90.0	90.0	2.95 (145)	2.93 (153)	3.69 (99)	–	−106.5	3.6	1.30
Hypothetical structures which have not been experimentally characterized														
AI22	$P2_1/c$	6.749	8.248	13.540	96.8	90.0	90.0	2.80 (166)	–	–	–	−105.6	4.5	1.34
AY8[d]	$Pca2_1$	4.522	10.692	15.863	90.0	90.0	90.0	2.91 (163)	3.07 (168)	–	–	−105.4	4.7	1.31
CC19[e]	$P2_1/c$	5.073	9.886	31.121	97.8	90.0	90.0	–	–	2.92 (143) 2.87 (146)	3.38 (136) 3.54 (134)	−103.3	6.8	1.30
AQ6	$P2_12_12_1$	6.571	7.344	16.281	90.0	90.0	90.0	2.80 (163)	–	–	–	−102.8	7.3	1.28
AK6	$P2_1/c$	5.072	9.648	16.050	100.9	90.0	90.0	–	–	2.90 (143)	3.49 (135)	−101.9	8.2	1.30
AQ14	$P2_12_12_1$	6.776	7.071	15.834	90.0	90.0	90.0	2.80 (174)	3.98 (139)	–	–	−101.9	8.2	1.32
CB9	$Pbca$	7.266	12.207	17.432	90.0	90.0	90.0	3.06 (158)	2.96 (146)	–	3.96 (93)	−101.8	8.3	1.30
CC8	$Pbca$	6.848	13.491	16.664	90.0	90.0	90.0	2.79 (170)	–	–	–	−101.0	9.1	1.30
AK22	$P2_1/c$	5.071	9.861	15.834	93.3	90.0	90.0	–	–	2.89 (144)	3.43 (136)	−100.2	9.9	1.27
AI16	$P2_1/c$	7.553	8.112	12.716	90.0	103.5	90.0	3.19 (114)	3.04 (179)	–	–	−100.2	9.9	1.33
AM4	$P2_1/c$	5.937	7.590	17.071	90.0	99.3	90.0	2.96 (153)	–	3.84 (112)	4.00 (145)	−100.1	10.0	1.32
AK4	$P2_1/c$	5.293	8.080	19.034	101.6	90.0	90.0	–	–	2.91 (153)	3.34 (144)	−100.0	10.1	1.26

[a] The lowest ($Expt_{low}$)- and highest ($Expt_{high}$)-temperature experimental structures of paracetamol (20 and 330 K neutron structures for form I,[16] and 123 and 298 K X-ray structures for form II[15]) are contrasted with lattice-energy minima calculated using the same intermolecular potential. All minimizations used the ab initio optimized molecular structure, except $Min_{exptlow}$ and $Min_{expthigh}$, where the experimental molecular structures were used (X-ray bond lengths to hydrogen atoms were standardized[66]). The minima obtained with the ab initio structure Min_{opt} were the same for all experimental determinations of each form.[45] The lowest-energy crystal structures found in the MOLPAK/DMAREL search are designated by the MOLPAK coordination group and number, and the space group is that of the conventional setting of each structure, as provided in the Supporting Information. The Niggli reduced cell parameters[49] are tabulated here to aid comparison. [b] The hydrogen bonds were characterized using PLUTO,[67] tabulating the N/O···O distance (<4 Å) and N/O−H···O angle (>90°), and each hydrogen bond has one occurrence per molecule. [c] ΔU_{latt} is the energy above the global minimum found in the search. [d] This structure has a total dipole moment of 3.1 e Å per unit cell along *b*, which may produce a small destabilizing dipole correction term. [e] This $P2_1/c$ $Z' = 2$ structure was found as a true minimum from a *Pbca* starting structure.

for the other hypothetical structures in Table 3. The elastic properties calculated from the experimental structures are well reproduced by the corresponding structures found in the search (Table 2), apart from the underestimate of C_{11} for form II which can be attributed to the differences in the hydroxyl proton position in the two rigid molecular models. The predicted bulk properties of the known and hypothetical structures of paracetamol do not vary greatly, consistent with the small variation

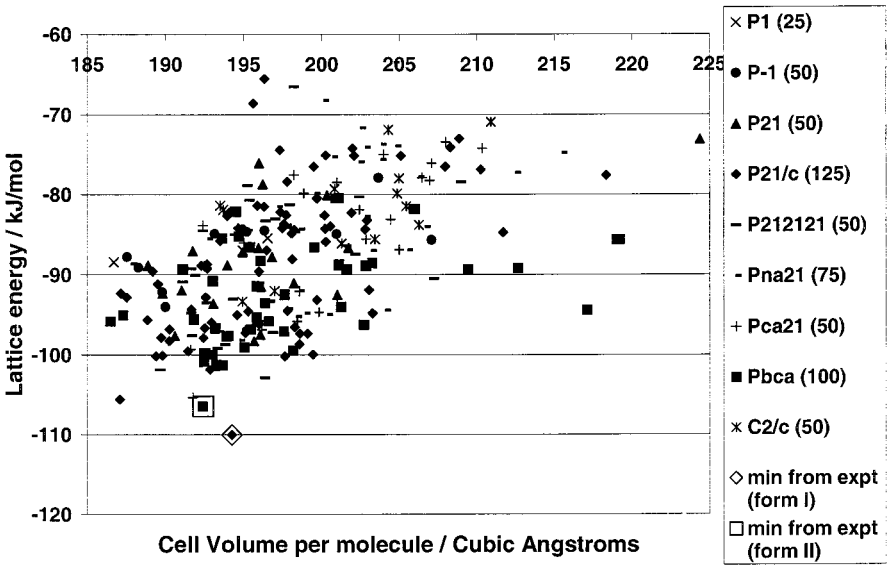

Figure 2. The minima in the lattice energy of paracetamol found by the MOLPAK/DMAREL search. The symbol denotes the space group of the MOLPAK starting structure and, in the legend, is followed by the number of minimizations performed for that space group. Two sets of minimizations were performed in *Pbca*. The initial search using the molecular axis system with the *xy* plane defined by C1, C4, C2, resulted in CB9 as the lowest *Pbca* structure, whereas a further search, using C1, C7, O2 to define the plane, found CB47 which is even more similar to form II. This unusual sensitivity to the initial probe orientation may arise from the nature of the potential energy surface for this type of sheet structure.

Table 2. Mechanical Properties for the Lowest-Temperature Forms of Paracetamol and the Closest Structures Found in the Search with the ab Initio Molecular Structure[a]

	form I $P2_1/c$			form II *Pbca*		
optical axes	*x*//*a**, *z*//*c*, *y* ⊥ *x*,*z*			*x*//*a*, *y*//*b*, *z*//*c*		
	$Min_{exptlow}$	Min_{opt}	AM30	$Min_{exptlow}$	Min_{opt}	CB47
C_{11}/GPa	21.2	22.1	22.1	53.2	30.3	30.0
C_{22}/GPa	14.4	12.0	12.0	26.3	22.7	22.7
C_{33}/GPa	21.6	20.1	20.4	12.0	12.7	12.5
C_{44}/GPa	5.5	5.1	5.3	3.5	3.0	3.0
C_{55}/GPa	5.9	6.1	6.0	0.7	0.8	0.8
C_{66}/GPa	8.9	5.9	5.8	11.3	7.6	7.6
C_{12}/GPa	12.3	11.5	11.4	21.2	14.5	14.5
C_{13}/GPa	10.5	12.1	12.0	3.6	4.3	4.4
C_{23}/GPa	11.0	10.3	10.4	8.3	8.8	8.7
C_{15}/GPa	−0.4	0.1	0.1			
C_{25}/GPa	1.4	2.0	2.0			
C_{35}/GPa	2.8	2.8	2.9			
C_{46}/GPa	2.3	2.4	2.4			
bulk modulus	12.9	11.0	11.0	10.8	10.6	10.6
/GPa	13.9	13.6	13.6	17.5	13.4	13.4
shear modulus	4.3	3.6	3.6	2.4	2.3	2.3
/GPa	5.6	4.8	4.8	7.0	4.8	4.8
Young's modulus	11.5	9.7	9.7	6.7	6.6	6.6
/GPa	14.9	12.9	12.9	18.5	12.9	12.9
experimental Young's modulus for form I[51,52] /GPa	8.4	11.7				

[a] The bulk mechanical properties of a macroscopically homogeneous aggregate have been estimated by both the Reuss and Voigt averages and given in the format Reuss above Voigt.

in the density. However, the anisotropy of the stiffness matrix varies considerably, as expected from the differences in the hydrogen-bonding networks.

All the elastic stiffness matrices C_{ij} are positive definite, satisfying the Born criteria for mechanical stability. However, one of the hypothetical structures, CC8, has C_{55} of only 0.2 GPa, only just satisfying the Born criterion and indicating that the structure is even more easily deformed than the orthorhombic form II.

The predicted morphologies for the experimental and low-energy structures found in the search are shown in Figure 3. The minor differences between the experimental structures and the corresponding search minima have a small effect on the predicted morphologies. As previously found,[15] the attachment-energy predictions are in reasonable agreement with the experimental morphology of mature crystals of form I grown from IMS solution, but are insufficiently elongated along *c* for form II, although the observed faces and chunky prismatic shape are correctly predicted. Many of the hypothetical low-energy structures are also predicted to have fairly equant prismatic habits. There are qualitative differences between the attachment energy and the BFDH model predictions for AM30 and AY8, as found for the experimental structures,[15] resulting from variations in relative areas of the main faces, and sometimes additional small faces. However, the two methods always predicted similar morphologies.

Figure 3 shows that the morphologies of four of the hypothetical structures (AK6, CC19, AK22, and AK4) have distinct platelike shapes. The distinction between these extreme platelike morphologies and the other approximately isodimensional morphologies is so marked that it is unlikely to be changed by the use of a more realistic force field or method of predicting morphologies.

The differences in morphology are quantified in Table 4, which gives the ratio of distances between the center and the furthest and nearest faces (the aspect ratio) for both the attachment energy and BDFH morphologies. Using the assumption that the growth rate of a face is proportional to the magnitude of its attachment energy, the slowest-growing face is tabulated for each crystal structure, along with its relative area and attachment energy. This is usually the morphologically dominant face, although if another slow-growing face occurs more frequently, this may have a larger relative surface area in the crystal. The attachment energies for any such faces, and for any faces which have a larger interplanar spacing than the slowest-growing face and so would be larger in the BDFH model morphology, are also given in Table 4. This shows that such faces only have moderately more attractive attachment energies and hence faster growth rates than the slowest-growing face.

Since all of the attachment energies in Table 4 are calculated for crystal structures of the same molecule, using the same

Table 3. Calculated Elastic Properties (in GPa) for the Energetically Feasible, Hypothetical Structures of Paracetamol[a]

	AI22	AY8	CC19	AQ6	AK6	AQ14	CB9	CC8	AK22	AI16	AM4	AK4
C_{11}	13.8	17.9	10.7	10.0	14.2	12.3	36.9	11.1	14.8	11.7	15.8	18.2
C_{22}	16.2	11.3	14.8	22.8	14.6	26.8	16.7	29.3	12.7	16.9	12.4	18.7
C_{33}	41.1	19.7	14.4	11.9	11.0	13.1	10.8	13.1	14.4	23.2	41.3	9.5
C_{44}	4.8	4.2	6.9	7.2	4.3	10.0	1.8	1.3	3.3	12.5	2.4	4.2
C_{55}	2.1	5.5	3.5	3.2	7.0	1.8	0.6	0.2	6.9	1.8	5.9	3.8
C_{66}	0.9	3.1	3.4	2.5	3.3	0.9	6.1	3.2	3.3	1.0	5.0	3.5
C_{12}	8.2	10.5	8.1	8.3	7.6	4.6	10.8	11.2	7.6	10.0	10.0	6.5
C_{13}	6.9	9.9	8.8	8.4	10.8	7.2	2.3	7.0	12.5	9.5	9.1	10.2
C_{23}	16.8	10.5	9.8	9.2	8.4	10.2	8.9	7.6	6.4	8.4	4.7	8.8
C_{15}	−0.01		1.0		2.8				−3.4	−0.04	−0.4	6.0
C_{25}	0.4		−3.1		−1.3				1.8	1.5	−1.2	−1.6
C_{35}	3.9		1.1		1.8				−5.5	−1.3	3.1	1.9
C_{46}	2.0		0.1		0.4				−0.1	0.9	−0.2	−0.5
K_R	11.5	11.1	9.0	9.4	10.0	9.5	9.1	9.4	9.3	11.1	10.8	7.7
K_V	15.0	12.3	10.4	10.7	10.4	10.7	12.0	11.7	10.5	12.0	13.0	10.8

[a] In all calculations the ab initio optimized molecular model is used. The optical axes are defined with *x* parallel to **a**, *y* to **b**, and *z* to **c**, for the orthorhombic crystals (AY8, AQ6, AQ14, CB9, CC8) and *z* parallel to **c**, *x* parallel to **a***, and *y* perpendicular to *xz* for the monoclinic crystals (AI22, CC19, AK6, AK22, AI6, AM4, AK4), using the hypothetical crystal structures as specified in the Supporting Information. The bounds on the bulk modulus of a homogeneous aggregate of paracetamol are estimated by the Reuss (K_R) and Voigt (K_V) averages.

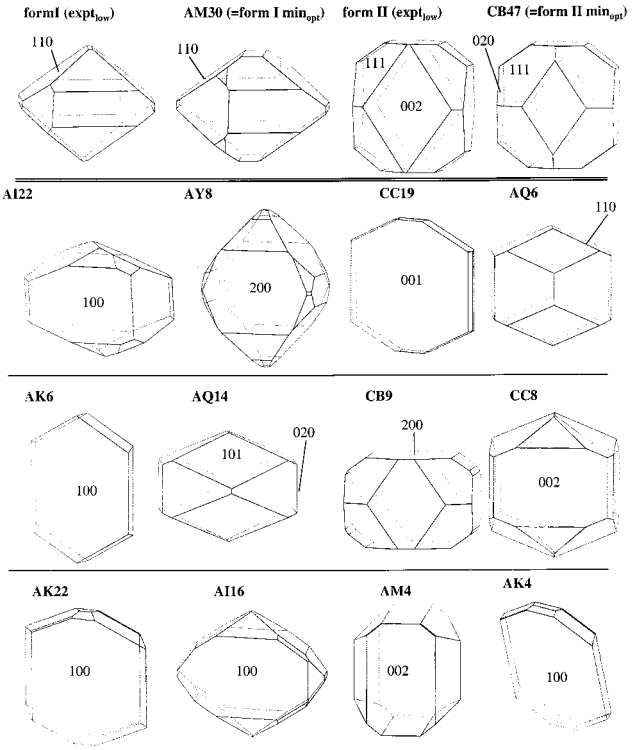

Figure 3. Attachment-energy predicted morphologies for the known and hypothetical crystal structures of paracetamol. The slowest-growing faces are labeled.

intermolecular potential, we can use them to estimate the relative growth rates of the different crystal structures. The attachment energies for the slowest-growing faces are largest for the experimental polymorphs, their corresponding structures found in the search, AY8 and AQ14. The hypothetical crystal structures which are predicted to form thin plates have attachment energies for the slowest-growing, morphologically dominant faces, which are less than a fifth of those for the experimentally observed forms. Hence, the thin plate crystals will grow considerably more slowly than the experimental and other more isodimensional morphologies.

Discussion

The systematic search for lattice-energy minima has found the known stable polymorph as the global minimum. Therefore, it would have been "predicted" with moderate confidence as the most likely crystal structure for paracetamol. However, there are at least a dozen crystal structures which are within 3.6 to 10 kJ/mol of the most stable form, and therefore within the energy range of possible polymorphism. The energies separating these energetically feasible crystal structures are so small that improvements in the model intermolecular potential, changes in the molecular model, including intramolecular distortion, or entropy effects would probably change the relative energies. Hence, it is probably fortuitous that the well-characterized

Table 4. Growth Rate and Morphology Predictions for the Known and Hypothetical Forms of Paracetamol[a]

	aspect ratio		slowest-growing faces for AE model (frequency of occurrence)	attachment energy /kJ mol^{-1}	% area of face[b]
	BFDH	AE			
form I, Expt$_{low}$	1.4	1.9	110 (4)	−12.8	48.5
form I, Min$_{opt}$ and AM30	1.4	1.7	110 (4)	−14.7	43.2
form II, Expt$_{low}$	1.8	1.7	002 (2)	−13.6	21.4
			111 (8)	−17.5	32.1
			*200 (2)	−19.1	
form II, Min$_{opt}$ and CB47	1.8	1.4	020 (2)	−15.2	16.5
			111 (8)	−15.6	42.3
			*200 (2)	−15.7	
AI22	1.5	2.8	100 (2)	−7.2	38.7
			*102 (2)	−19.0	
AY8	2.1	2.2	200 (2)	−14.1	33.2
CC19	7.7	13.9	001 (2)	−1.5	85.1
AQ6	1.7	1.5	110 (4)	−12.3	35.5
AK6	4.0	6.4	100 (2)	−3.1	71.0
AQ14	1.7	1.7	101 (4)	−13.7	34.7
			*020 (2)	−19.8	
CB9	1.8	1.8	200 (2)	−9.9	30.0
CC8	1.7	2.2	002 (2)	−8.1	33.9
			*020 (2)	−14.1	
AK22	4.0	7.7	100 (2)	−2.7	74.6
AI16	1.5	3.3	100 (2)	−6.0	47.3
AM4	1.9	1.8	002 (2)	−11.1	32.2
AK4	5.1	11.2	100 (2)	−1.7	81.7

[a] The morphologically dominant, slowest-growing face, in the attachment-energy (AE) prediction of the morphology is given in normal type, along with corresponding AE. For crystals where another face provides a higher percentage of the total surface area, because of a higher frequency of occurrence, this face is given in italics. The aspect ratio for the AE predicted morphology is contrasted with that using the BDFH model, and where the BFDH model predicts a different slowest-growing face, this is given after*. [b] 100×(total surface area of slowest-growing face)/total surface area.

metastable polymorph has the second-lowest lattice energy. Thus, there are various other hypothetical structures that appear as likely to be observed as the known metastable polymorph on the lattice-energy criterion used in crystal structure prediction. Hence, lattice-energy minimization is not sufficient to predict the polymorphism of paracetamol and has produced a larger number of hypothetical structures than the three suggested by the extensive experimental studies of this important compound. What other factors can be used to decide which of the energetically feasible crystal structures will be observed?

The effects of temperature need to be considered. The two structures CB9 and CB47 (form II) are very similar and only differ by a translation of the hydrogen-bonded sheets, producing a different stacking of the methyl groups. The two minima were located from similar starting structures, suggesting that the potential energy surface between the two minima is such that thermal motion would easily produce the transformation of CB9 to the more stable CB47. This is borne out by the small resistance to shear of the hydrogen-bonded sheets shown in Tables 2 and 3. Thus, the less stable CB9 is unlikely to be observed, whereas CB47 is form II within the limitations of the modeling.

This and other transformations from the hypothetical structures to more stable minima might be observed by performing molecular dynamics simulations, as this "shake up" has been reported to significantly reduce the number of minima in the case of acetic acid.[56] For example, inspection of the crystal structures and hydrogen-bonding motifs suggests transformations between AQ6 and AQ14 might be quite facile. However, given that this type of inspection would suggest a similar relationship between the known polymorphs of indigo[2] and terephthalic acid,[57] it is clear that more elaborate dynamical studies are required to determine whether the barrier is sufficient for both the similar crystal structures to be observed. Dynamical studies might also reveal sufficient differences in the thermal expansion and melting behavior[58] to differentiate between structures that appear equally plausible from their static lattice energy and density. Entropic differences may well alter the relative stability of the crystal structures. Simple harmonic approximation estimates of the intermolecular entropy differences between known sets of polymorphs in the Cambridge Structural Database suggested that this will not exceed 15 J/(K·mol).[59] Nevertheless, consideration of real and hypothetical hydrocarbon crystal structures[60] suggests that at 300 K, lattice-vibrational $T\Delta S$ differences may compete with ΔH differences. Hence, there is considerable scope for improving the thermodynamic basis of crystal structure prediction. This will require significant development of the computational modeling of organic crystals. However, metastable polymorphs are often observed; therefore, we have considered other, readily calculated, properties of the energetically feasible hypothetical structures to determine whether they are kinetically and mechanically plausible polymorphs.

The mechanical stability of the growing crystallite may also be a factor in determining which polymorphs are observed. Very soft crystallites are likely to be distorted by the stresses experienced during crystallization. Although all lattice-energy minima must satisfy the Born criteria for mechanical stability, those which have a very small diagonal shear elastic constant only just meet this criterion. Such hypothetical structures are less likely to be sufficiently mechanically stable to grow suitable crystals for structure determination. The fact that a small shear constant ($C_{55} \approx 0.7$ GPa) is calculated for the observed form II of paracetamol, but that it is an unusually deformable hydrogen-bonded molecular crystal, shows that a lower boundary for mechanical stability is less than 0.7 GPa. It seems unlikely that CC8, with a shear elastic constant of 0.2 GPa is likely to be sufficiently mechanically stable to grow in competition with forms of similar thermodynamic stability.

Kinetic factors certainly have a major influence on which polymorphs are formed. Using attachment-energy calculations, the observed forms are two of the four fastest growing crystal structures of paracetamol. Although it is physically reasonable that the fastest-growing of the approximately isoenergetic crystal structures should be the observed forms, and our results are consistent with this hypothesis, this remarkable success has to be viewed with caution. The attachment energy is only proportional to the growth rate of a strongly bound (flat, F-type) face[61] growing by a layer growth mechanism.[62] Although there are many reports of the success of the attachment-energy model in predicting the morphologies of organic crystals,[63] there are cases where it fails to predict all of the smaller faces,[64] and it cannot predict the major effects that solvent can have on growth rate and morphology. However, if we take the attachment energy of the slowest-growing, morphologically important face as a measure of the speed of growth of a crystal, and then if several low-energy crystal structures of paracetamol had nucleated and were growing, the observed forms are predicted to produce the largest crystals.

This argument can only compare the low-energy forms that nucleate and grow under the same crystallization conditions, and so we cannot make quantitative comparisons of the likelihood of observing crystal structures with reasonable growth rates. However, four of the hypothetical structures have particularly small attachment energies for their slowest-growing face, which in all cases dominates their thin platelike morphology. It has been observed that difficulties in growing crystals of a size suitable for X-ray diffraction are generally associated with thin platelike or fine needle morphologies.[65] Therefore, it seems unlikely that polymorphs of such habits will be found when structures with more equant habits are equally thermodynamically favorable.

Thus, consideration of simple models of mechanical properties and crystal growth rates can reduce the number of hypothetical structures that appear to be possible polymorphs, as summarized in Table 5. Undoubtedly, the relative thermodynamic stability of these structures will depend on temperature and pressure. The question arises as to whether the elusive third polymorph can be expected to be among the remaining four to six structures. As this is likely, the crystallographic coordinates are provided as Supporting Information for comparison with any experimental observations. However, since the third poly-

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Table 5. Summary of Properties of the Lowest-Energy Crystal Structures of Paracetamol Found in the Lattice-Energy Search[a]

crystal structure, space group	lattice energy/ kJ mol^{-1}	smallest C_{ii} elastic constant/ GPa	attachment energy of slowest-growing face/ kJ mol^{-1}	description of hydrogen-bonded motif
AM30, $P2_1/c$	−110.1	$C_{44} = 5.3$	AE(110) = −15.5	**KNOWN,** zigzag sheets hydrogen-bonded along *a*, stacked along *b*
CB47, *Pbca*	−106.5	$C_{55} = 0.8$	AE(020) = −15.9	**KNOWN,** flat sheets (slip planes) in *ab* plane, stacked along *c*
AI22, $P2_1/c$	−105.6	$C_{66} = 0.9$	AE(110) = −8.2	soft zigzag chains along *c*, approximately parallel, stacking along *a*
AY8, $Pca2_1$	−105.4	$C_{66} = 3.1$	AE(200) = −14.4	3D hydrogen-bonding network
CC19, $P2_1/c$	−103.3	$C_{66} = 3.4$	*AE (001) = −1.3*	**UNLIKELY,** chains interlinked by OH···OH bonds along *a*
AQ6, $P2_12_12_1$	−102.8	$C_{66} = 2.5$	AE(110) = −13.0	soft zigzag chains along *b*, packed approximately parallel (slightly tilted) along *a*
AK6, $P2_1/c$	−101.9	$C_{66} = 3.3$	*AE(100) = −2.9*	**UNLIKELY,** chains, interlinked by OH···OH bonds along *b*
AQ14, $P2_12_12_1$	−101.8	$C_{66} = 0.9$	AE(110) = −15.8	soft zig-zig chains along *b*, approximately parallel (slightly tilted) stacking along *a*
CB9, *Pbca*	−101.4	$C_{55} = 0.6$	AE(200) = −10.0	**UNLIKELY,** flat sheets (slip planes) in *ab* plane, stacked along *c*, *facile transformation to form II*
CC8, *Pbca*	−101.0	*$C_{55} = 0.2$*	AE(002) = −9.0	**UNLIKELY,** soft zigzag chains (buckled) along *b*, strong methyl−methyl group interaction
AK22, $P2_1/c$	−100.2	$C_{44} = C_{66} = 3.3$	*AE(100) = −2.3*	**UNLIKELY,** chains of dimers, interlinked by OH···OH bonds
AI16, $P2_1/c$	−100.2	$C_{66} = 1.0$	AE(100) = −6.9	soft zigzag chains along *c*, approximately parallel (slightly tilted) stacking along *a*
AM4, $P2_1/c$	−100.1	$C_{44} = 2.4$	AE(002) = −11.5	buckled chains along *c*, stacked along *b*
AK4, $P2_1/c$	−100.0	$C_{66} = 3.5$	*AE(100) = −1.4*	**UNLIKELY,** chains interlinked by OH···OH bonds along *b*

[a] Properties which make the structure unlikely to be an observed polymorph are in italic.

morph has only been observed[17] under the cover slip of a microscope slide, it may be a pressure-stabilized form and hence would not be found even by a more exhaustive search for minima in the lattice energy under conditions of zero pressure.

Conclusions

A systematic search for the rigid body lattice-energy minima of paracetamol correctly identifies the stable crystal structure as the global minimum. A variety of energetically feasible alternative structures are predicted, including the well-characterized orthorhombic form. Consideration of the predicted morphologies and growth rates, using the attachment-energy model, can be used to eliminate some of the hypothetical structures, as they are growing as thin plates so slowly that they are unlikely to be found in competition with equally thermodynamically stable structures.

Calculation of the elastic tensors of the experimental polymorphs quantifies the microscopic reason for the very different tabletabilities of the two forms. A few of the hypothetical structures (AI22 and AI6 in $P2_1/c$ and AQ14 in $P2_12_12_1$) also have the low resistance to shear that produces the desirable direct tableting of the known metastable orthorhombic form. However, this resistance to shear is so low for one hypothetical structure (CC8) that it is unlikely to be found.

Methods of predicting crystal structures and polymorphism by searching for minima in the lattice energy, often, as in this case, predict more energetically feasible structures than known, or probable, polymorphs. The lattice-energy criterion is therefore a necessary, but not sufficient condition, for a structure to be an observed polymorph. The proposed additional criteria of considering the growth rate, as practically and approximately computed through the attachment energy, and the mechanical stability, through eliminating structures that are only just stable according to the calculated elastic constants, are promising. Taken in conjunction with the lattice energy, this approach favors the experimentally known structures of paracetamol and reduces the number of hypothetical structures somewhat, although still leaving more than have been detected experimentally in this much-studied pharmaceutical. Further work on considering the attachment energies and elastic constants of real and hypothetical crystal structures of other organic molecules is required to test this hypothesis and delineate the boundaries more clearly. The approach is most likely to be useful when there are major structural differences between the low-energy crystal packings. However, this is a significant step in developing the computational prediction of polymorphism, as it considers kinetic as well as thermodynamic factors, albeit with the many approximations that are currently necessary in the computational modeling of organic crystals.

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Supporting Information Available: Atomic coordinates of the ab initio optimized molecular structure; cell parameters, space group and atomic coordinates for the lattice-energy minima of the known and low-energy hypothetical crystal structures (form I Min_{opt}, form II Min_{opt}, and all structures listed in Table 5) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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