

Accurate molecular structures and hydrogen bonding in two polymorphs of *ortho*-acetamidobenzamide by single-crystal neutron diffraction

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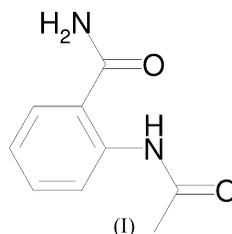
The structures of both known forms of the polymorphic material *ortho*-acetamidobenzamide, C₉H₁₀N₂O₂, have been determined by low-temperature neutron single-crystal diffraction. Neutron diffraction allows the full description of the H-atom positions in this molecular material, which is vital in benchmarking related crystal-structure predictions. Significant conformational differences are indicated by a number of the torsion angles involving H atoms when compared with previous X-ray studies. A comprehensive description of the hydrogen-bonding scheme in both polymorphs is given.

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1. Introduction

Computational methods of crystal-structure prediction for flexible molecules can only be successful if they can accurately model the energy changes involved in conformational polymorphism (Nowell & Price, 2005; Bernstein, 2002). A molecule can change its conformation, giving rise to an intramolecular energy penalty, if it thereby improves its interactions with other molecules such that the lower intermolecular lattice energy more than compensates for the increase due to the conformational change. The balance of these interactions is very sensitive to the positions of the protons involved in hydrogen-bonding interactions, and computationally optimizing the geometries of amide groups can have a marked effect on the calculated relative stability of crystal structures (Karamertzanis & Price, 2006). The two polymorphs of *ortho*-acetamidobenzamide (I) provide a particularly stringent test (Buttar *et al.*, 1998) of whether computational methods can model the balance between intermolecular and intramolecular forces sufficiently adequately to allow realistic crystal-structure prediction studies.



The α -form of the title compound (I) exhibits an intramolecular hydrogen bond between the O atom of the amide group and the N–H of the acetamido group, whereas the β form has a more twisted geometry and no intramolecular hydrogen bond (Errede *et al.*, 1981; Etter, 1983). The total energy difference between the two forms has been calculated as *ca* 20 kJ mol⁻¹ (Buttar *et al.*, 1998; Day, 2002) and is

Table 1
Crystal data and refinement details for (I).

	α form	β form
Crystal data		
Chemical formula	C ₉ H ₁₀ N ₂ O ₂	C ₉ H ₁₀ N ₂ O ₂
M_r	178.19	178.19
Cell setting, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$
Temperature (K)	30 (2)	30 (2)
a, b, c (Å)	4.8591 (12), 14.395 (3), 12.250 (3)	7.788 (1), 8.972 (2), 12.547 (2)
β (°)	92.151 (16)	101.12 (1)
V (Å ³)	856.3 (3)	860.2 (3)
Z	4	4
D_x (Mg m ⁻³)	1.382	1.376
Radiation type	Neutron	Neutron
Crystal form, colour	Block, colourless	Block, colourless
Crystal size (mm)	5.0 × 2.0 × 1.0	3.5 × 1.5 × 1.5
Data collection		
Diffractometer	SXD	SXD
Data collection method	Time-of-flight LAUE diffraction	Time-of-flight LAUE diffraction
Absorption correction	None	Gaussian
No. of measured, independent and observed reflections	5267, 5267, 5267	11 484, 11 484, 11 484
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.000	0.000
θ_{max} (°)	81.7	82.5
Refinement		
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.057, 0.128, 1.04	0.058, 0.148, 1.03
No. of reflections	5267	11 484
No. of parameters	274	274
H-atom treatment	Refined independently	Refined independently
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0826P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0926P)^2 + 11.2116P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\text{max}}$	<0.0001	<0.0001
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (fm Å ⁻³)	2.003, -1.487	2.346, -2.384
Extinction method	SHELXL	SHELXL
Extinction coefficient	0.00129 (6)	0.0450 (7)

Computer programs used: *SXD*2001 (Gutmann, 2005), *SHELXS*97 (Sheldrick, 1990), *SHELXL*97 (Sheldrick, 1997a), *SHELXTL* (Sheldrick, 1997b).

considerably larger than expected for polymorphs of the same compound (*ca* 4 kJ mol⁻¹; Bernstein, 2002). Thus, the structure of the less stable β form would be rejected if generated during a crystal-structure prediction study (Buttar *et al.*, 1998). The exact energy difference, defined as the difference between the conformational energies plus the difference between the intermolecular lattice energies, is highly dependent on:

- the particular *ab initio* or semi-empirical method used to calculate the conformational energies, with high-level correlated methods differing in the estimated intramolecular energy penalty by over 20 kJ mol⁻¹ (Mourik *et al.*, 2006) and
- the molecular models used in calculating the conformational energies (Buttar *et al.*, 1998; Day, 2002).

In previous studies, these conformational energies have been derived from the published single-crystal X-ray coordinates obtained by Errede *et al.* (1981) for the α and β forms, but both Buttar *et al.* and Day emphasize the influence that small deviations from expected bond lengths and angles (especially those involving H atoms) can have on the calculated energies. ‘Standardization’ of C–H and N–H bond lengths to 1.08 and 1.01 Å, respectively, while effective in correcting errors in X-

ray determined H-atom positions, does not alter errors in bond angles and bond torsions, nor does it address the possibility of the geometry of the NH₂ group being affected by crystal packing (Day, 2002). Thus, accurate determinations of the full molecular structures of (I) in its two polymorphs are essential for the development of methods for calculating the relative stability of conformational polymorphs that differ so markedly in their hydrogen-bonding motifs. This work sets out to provide such accurate starting models for the α and β forms of (I) by employing single-crystal neutron diffraction (where the atomic positions of H atoms, as defined by the position of the nucleus of the atom, are typically obtained with greater accuracy and precision than from corresponding X-ray experiments) at a time-of-flight neutron source.

2. Experimental

ortho-Acetamidobenzamide (C₉H₁₀N₂O₂) was prepared according to the literature method of Baker & Almaula (1962). All starting chemicals were purchased from the Aldrich Chemical Company and were used without further purification. The yield was 82% and microanalysis showed excellent agreement between found

(C 61.0, H 5.7, N 15.7) and calculated (C 60.7, H 5.7, N 15.7) percentages. X-ray powder diffraction confirmed the product to be the α form.

Crystals of the α form, suitable for single-crystal neutron diffraction, were obtained relatively easily by slow evaporation from a dilute solution of (I) in methanol. The single crystals of the β form of (I) were produced in the same way, but only after some partially deuterated polycrystalline acetamidobenzamide (shown to be the β form by X-ray powder diffraction) had been prepared in the laboratory.

Neutron diffraction data were collected from crystals of the β form (dimensions 3.5 × 1.5 × 1.0 mm³) and the α form (dimensions 5.0 × 2.0 × 1.0 mm³); each crystal was mounted on a closed-cycle refrigerator on a vertically mounted ω -orienter. Data were collected on the SXD instrument (Wilson, 1990; Keen & Wilson, 1996; Keen *et al.*, 2006) at the ISIS spallation neutron source, using the time-of-flight Laue diffraction method. This method uses a wavelength-sorted white neutron beam, along with 11 large area position-sensitive detectors, to allow a large volume of reciprocal space to be measured in a single-crystal setting (a ‘frame’). The full data

Table 2
Comparison of bond lengths (Å) involving H atoms in (I).

X–H	α form		β form	
	X-ray (room temperature)	Neutron (30 K)	X-ray (room temperature)	Neutron (30 K)
N1–H1B	0.764	1.015 (3)	0.855	1.025 (2)
N1–H1A	0.946	1.026 (4)	0.997	1.025 (2)
N2–H2	0.819	1.025 (3)	0.836	1.020 (2)
C3–H3	0.928	1.088 (3)	0.898	1.090 (2)
C4–H4	0.959	1.092 (5)	0.958	1.086 (2)
C5–H5	0.883	1.099 (4)	0.832	1.090 (2)
C6–H6	1.189	1.082 (3)	0.944	1.086 (2)
C9–H9A	0.790	1.076 (5)	0.936	1.088 (2)
C9–H9B	0.899	1.078 (4)	0.980	1.090 (3)
C9–H9C	0.968	1.087 (4)	0.912	1.087 (3)

collection comprises a series of such frames, each collected with a stationary crystal-detector arrangement.

For both crystals the temperature was held at 30 ± 5 K throughout the experiment. A total of six frames, each

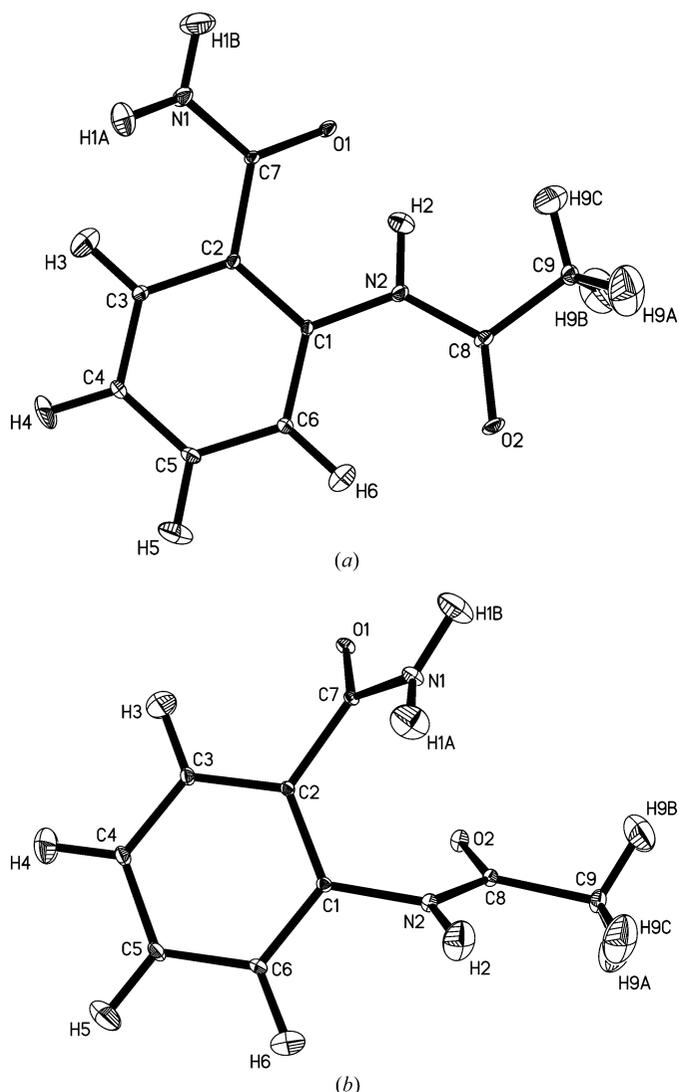


Figure 1
The molecular structure of (a) the α form of (I) at 30 K and (b) the β form of (I) at 30 K. All displacement ellipsoids are drawn at the 50% level.

Table 3
Comparison of bond angles ($^\circ$) involving H-atoms in (I).

X–Y–H	α form		β form	
	X-ray (room temperature)	Neutron (30 K)	X-ray (room temperature)	Neutron (30 K)
C7–N1–H1A	118	120.6 (2)	124	119.1 (1)
C7–N1–H1B	116	117.6 (2)	121	119.8 (1)
H1A–N1–H1B	122	118.8 (3)	114	120.3 (2)
C1–N2–H2	110	112.3 (2)	115	119.1 (1)
C8–N2–H2	120	118.1 (2)	122	118.7 (1)
C2–C3–H3	114	119.2 (3)	118	119.7 (1)
C3–C4–H4	122	119.5 (3)	122	120.7 (1)
C5–C4–H4	119	121.4 (3)	119	119.3 (1)
C4–C3–H3	125	119.5 (3)	120	119.9 (1)
C4–C5–H5	125	120.5 (3)	120	120.0 (1)
C6–C5–H5	112	118.3 (2)	119	120.2 (1)
C1–C6–H6	130	119.4 (3)	118	119.0 (1)
C5–C6–H6	108	120.7 (3)	123	120.6 (1)
C8–C9–H9A	109	108.5 (3)	111	109.0 (1)
C8–C9–H9B	114	109.6 (4)	105	108.9 (1)
C8–C9–H9C	110	111.7 (3)	116	112.9 (2)
H9A–C9–H9B	96	107.2 (4)	95	107.9 (3)
H9A–C9–H9C	106	111.2 (5)	121	109.3 (2)
H9B–C9–H9C	120	108.6 (3)	103	108.7 (2)

containing information from 11 detectors, was collected, with a typical exposure time of 8 h ($1300 \mu\text{A h}$) for each frame for the β form crystal and 4 h ($700 \mu\text{A h}$) for each frame for the α -form crystal. The difference in exposure time required was a result of the difference in crystal size and diffraction quality.

Reflection intensities were extracted and reduced to structure factors using standard SXD procedures, as implemented in the computer program *SXD2001* (Gutmann, 2005). A total of 11 488 reflections were collected for the β form and 5267 reflections for the α form. Crystal data and refinement details are given in Table 1.¹ Refinements were carried out using *SHELXL97* (Sheldrick, 1997a) using anisotropic displacement parameters for all atoms, including the H atoms. The resulting molecular structures are shown in Fig. 1, with the bond lengths involving H atoms detailed in Table 2.

3. Results and discussion

Unsurprisingly, with respect to the non-H atoms, the molecular and crystal structures obtained show good agreement with previously published X-ray structures. The r.m.s. difference between the non-H atoms of the neutron derived structure (30 K) and the corresponding non-H atoms of the published X-ray structures (room temperature) was 0.027 \AA for α -AABA and 0.030 \AA for β -AABA. Equally unsurprisingly, the differences with respect to the H atoms are substantial and these are summarized in Tables 2 and 3. In Table 2 those bond lengths and angles involving H atoms are compared for the models derived from the neutron data and the published X-ray structures. Differences in bond lengths

¹ Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM5034). Services for accessing these data are described at the back of the journal.

Table 4
Hydrogen bonds in (I).

Hydrogen bond	Label	Form	O...H	O...N	O—H—N	Symmetry relation	Graph set
O1...H2—N2	1	α	1.771 (3)	2.649 (2)	141.2 (3)	O1 ⁱ ...H2 ⁱ —N2 ⁱ	S(6)
		β	2.024 (2)	3.032 (1)	169.3 (1)	O1 ⁱ ...H2 ⁱⁱ —N2 ⁱⁱ	C(6)
O1...H1B—N1	2	α	1.852 (5)	2.871 (3)	171.5 (4)	O1 ⁱ ...H1B ⁱⁱⁱ —N1 ⁱⁱⁱ	R ₂ ² (8)
		β	1.943 (2)	2.955 (1)	168.7 (2)	O1 ⁱ ...H1B ^{iv} —N1 ^{iv}	R ₂ ² (8)
O2...H1A—N1	3	α	1.917 (3)	2.893 (2)	160.6 (5)	O2 ⁱ ...H1A ^v —N1 ^v	C(8)
		β	1.818 (3)	2.843 (1)	177.3 (2)	O2 ⁱ ...H1A ⁱⁱ —N1 ⁱⁱ	C(8)
O2...H2—N2	4	β	2.703 (2)	3.116 (1)	104.4 (1)	O2 ⁱ ...H2 ^{vi} —N2 ^{vi}	C(4)
N2...H1A—N1	5	β	2.690	3.000	97.37	N2 ⁱ ...H1A ⁱ —N1 ⁱ	S(6)

Symmetry codes: (i) x, y, z ; (ii) $1-x, y-\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x-1, -y, -z$; (iv) $1-x, 1-y, -z$; (v) $-x-\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$; (vi) $1-x, -\frac{1}{2}+y, \frac{1}{2}-z$.

are as expected, with the X-ray distances being systematically shorter than their neutron counterparts. For the NH₂ groups, the X-ray structures give H atoms in the correct general locations, but there are significant differences in the angles.

interactions occurring between the same chemical groups in each polymorph. These short hydrogen bonds are numbered 1–3 in the diagrams and tables. The main difference in the hydrogen-bonding patterns of the two polymorphs is that the

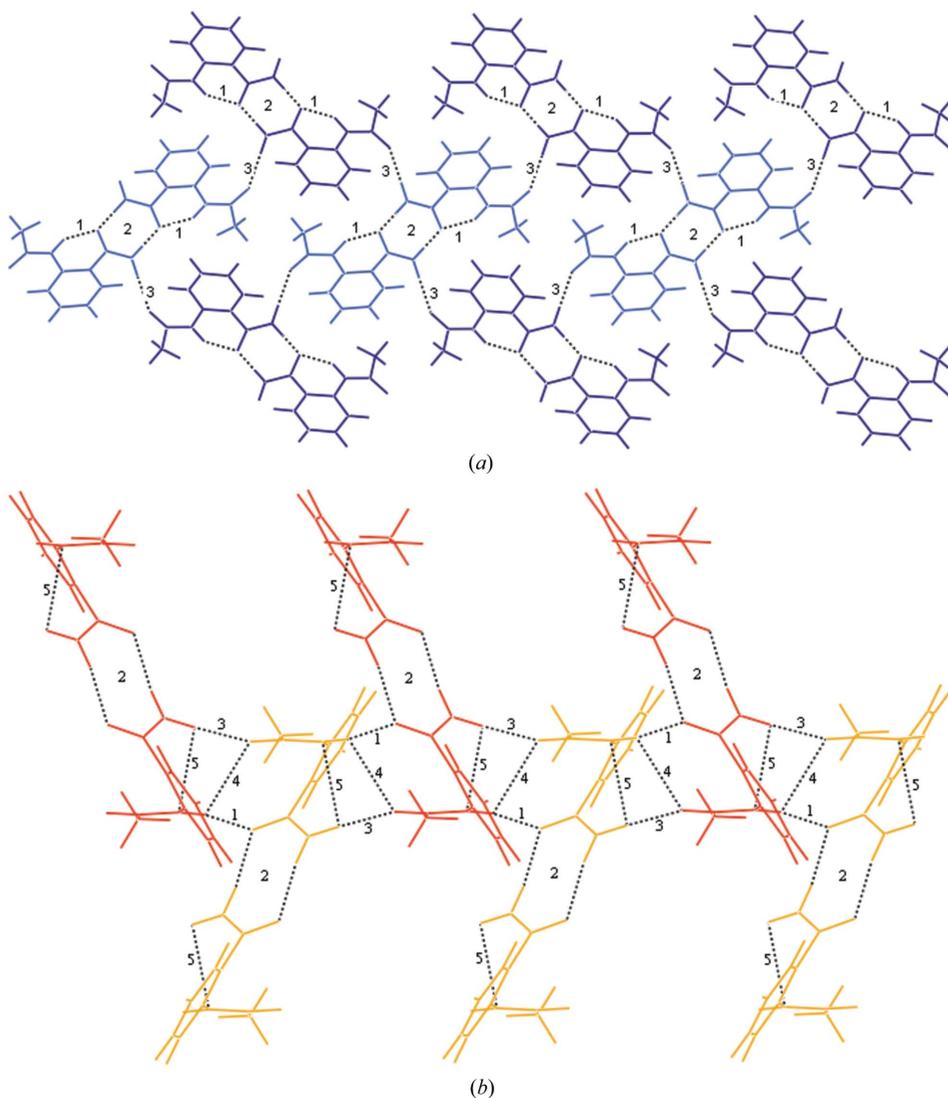


Figure 2
Herring-bone arrangement of (a) dimers in the α -form of (I) and (b) dimers in the β form of (I). Hydrogen bonds are labelled according to the scheme used in Table 4. Dimers are coloured for clarity only; chemically and crystallographically there is no difference between the differently coloured dimers.

The pyramidalization of the NH₂ groups in the neutron structures (as defined by the distance d of the nitrogen N1 from the C7—H1A—H1B plane) is almost identical to that found in the X-ray structures: $d_{\text{neutron}} = +0.113$ (3) Å, $d_{\text{X-ray}} = +0.112$ Å for the α form; $d_{\text{neutron}} = +0.060$ (1) Å, $d_{\text{X-ray}} = +0.041$ Å for the β form.

The intermolecular interactions present in the two polymorphic forms are summarized in Figs. 2(a) and (b) and in Table 4. Both forms exhibit the same number of short hydrogen bonds, those present in the two polymorphic forms are summarized in Figs. 2(a) and (b) and in Table 4. Both forms exhibit the same number of short hydrogen bonds, those interactions occurring between the same chemical groups in each polymorph. These short hydrogen bonds are numbered 1–3 in the diagrams and tables. The main difference in the hydrogen-bonding patterns of the two polymorphs is that the O1...H2—N2 hydrogen bond (1) is *intra*-molecular in the α form and *inter*-molecular in the β form. In terms of graph-set notation (Etter, 1990), the hydrogen bond 1 has the motif S(6) in the α form and C(6) in the β form, with the same six atoms being involved in each polymorph. Both forms exhibit the same dimer (hydrogen bond 2 O1...H1B—N1) and C(8) chain (hydrogen bond 3 O2...H1A—N1) motifs that link the molecules into sheets. However, as can be seen from Figs. 2(a) and (b), the appearance of these sheets is very different. In the α form the molecules lie approximately planar within the sheet and the dimers are arranged in a herringbone arrangement with adjacent dimers linked by hydrogen bond 3. In the β form, the plane of the molecules lies approximately normal to the plane of the sheet, and hydrogen bonds 1 and 3 are involved in linking adjacent dimers. In addition to the hydrogen bonds discussed above,

Table 5

Effects of computer modelling on the crystal structures.

Positive values indicate an increase with respect to the lattice-energy-minimized (LEM) neutron unit cell

	LEM neutron structures [†]	Difference between LEM X-ray [‡] and LEM neutron structures	Difference between LEM neutron structure and experimental neutron structure
<i>α</i> -AABA			
<i>a</i> (Å)	4.874	−0.002	−0.015
<i>b</i> (Å)	14.562	−0.040	−0.167
<i>c</i> (Å)	12.359	−0.076	−0.109
<i>β</i> (°)	91.672	+0.183	+0.479
<i>V</i> (Å ³)	876.8	−8.2	−20.5
Lattice energy (kJ mol ^{−1})	−122.41	−0.42	−
<i>β</i> -AABA			
<i>a</i> (Å)	7.856	+0.008	−0.068
<i>b</i> (Å)	9.270	−0.120	−0.298
<i>c</i> (Å)	12.650	+0.005	−0.103
<i>β</i> (°)	101.35	−0.50	−0.23
<i>V</i> (Å ³)	903.3	−9.0	−43.10
Lattice energy (kJ mol ^{−1})	−141.63	+0.69	−
ΔE [§]	19.22	−1.11	−

[†] Lattice-energy-minimization calculations were performed as described in Coombes *et al.* (1996), keeping the neutron molecular structure rigid, and modelling the intermolecular forces by the FIT model potential and a distributed multipole model of the MP2 6-31G(d,p) charge density. [‡] For the room-temperature X-ray structures, the corresponding wavefunctions were calculated using C–H and N–H bond lengths elongated to the standard neutron values of 1.08 and 1.01 Å, respectively (Allen *et al.*, 1987). [§] ΔE is the difference between the lattice energies of the *α* and *β* polymorphs.

there are a further two long hydrogen bonds (**4** and **5**) that occur only in the *β* form of (I).

Lattice-energy minimizations were performed in order to ascertain whether the differences between the neutron and X-ray molecular structures have a significant effect on computational modelling of this system. Comparison of the lattice parameters and lattice energies (approximately −0.4 and +0.7 kJ mol^{−1} for the *α* and *β* forms, respectively) obtained by the static rigid-molecule lattice-energy minimization (Table 5) reveals that the differences are small but significant. In particular, they are significant:

(*a*) compared with the differences between the lattice-energy-minimized structures and the actual single-crystal neutron structures, which also reflect the errors in neglecting thermal effects at 30 K, the zero-point molecular motion, and errors in the intermolecular forces; and

(*b*) compared with the usual lattice-energy differences (*ca* 4–8 kJ mol^{−1}) between polymorphs that exist under the same conditions of temperature and pressure (Bernstein, 2002).

The more accurate neutron-derived model does reduce the difference in the lattice energy of the two forms by *ca* 1 kJ mol^{−1}.

4. Conclusions

The crystal structures presented here represent a significant improvement upon existing X-ray derived structures and as such have removed a great deal of structural uncertainty, particularly with respect to the H-atom positions and atomic

displacement parameters. The improved starting models yield small but significant improvements in the lattice-energy calculations, resulting in a slight reduction in the large (*ca* 20 kJ mol^{−1}) lattice stabilization that results from the additional intermolecular hydrogen bond present in the *β* form. The structures thus provide a reliable starting point for future computational studies that seek to provide more reliable estimates of the relative stability of the two forms of (I).

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