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# Theoretical investigations of conformational aspects of polymorphism.

## Part 1: *o*-acetamidobenzamide

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*o*-Acetamidobenzamide crystallises in two polymorphs designated  $\alpha$  and  $\beta$ . In the  $\alpha$ -polymorph an intramolecular hydrogen bond is present, which is not found in the conformation adopted in the  $\beta$ -polymorph. The geometries of the molecules found in the crystal structures have been studied in detail using molecular mechanics, semi empirical and *ab initio* quantum chemistry techniques. Conformational energy differences have been evaluated, and gas phase potential energy surfaces generated to explore the conformational freedom of *o*-acetamidobenzamide.

It has been found that both observed solid state conformations occur close to, but not actually at, minima on the calculated gas phase potential energy surfaces. Conformational energy differences of 8–10 kcal mol<sup>-1</sup> have been found between the conformers found in the crystals, depending on the method used for the calculation. Based on lattice energy calculations for both polymorphs it would appear that the less stable conformation is not compensated for by an equivalent stabilisation of the crystal lattice. The total (intra- and inter-molecular) energy difference between polymorphs is greater than that conventionally accepted.

The difficulties of using theoretical tools in conformational studies and the implications of our findings for *ab initio* crystal structure prediction are discussed.

### Introduction

When a molecule crystallises in more than one distinct packing arrangement, it is said to be polymorphic. Virtually all classes of molecular materials have been found to exhibit some degree of polymorphism, but the precise frequency of its occurrence is a matter of some debate. It is often quoted that 'the number of forms known for a given compound is proportional to the time and energy spent in research on that compound'.<sup>1</sup> However, a recent review of the Cambridge Structural Database (CSD)<sup>2</sup> showed that only 5% of compounds are classed as polymorphic.<sup>3</sup> Polymorphism is of importance across a wide range of industries, including pharmaceuticals, agrochemicals, dyes and foodstuffs. The recent well publicised court cases concerning the drug Zantac illustrates the potential commercial importance of the phenomenon.<sup>4</sup> Polymorphism can be both beneficial and problematic to industry. For example, copper phthalocyanine exists in a number of solid state forms. These are different colours and consequently sold as different pigment products. Oxotitanium phthalocyanine exists in four well known packing arrangements, type IV being the most photosensitive charge generation material, whilst type III is inactive.<sup>5</sup>

Crystallisation and the properties of solid state arrangements are dependent upon a molecular recognition process which occurs on a grand scale. Crystals can be regarded as 'supramolecular assemblies *par excellence*'.<sup>6</sup> Polymorphism occurs when a slightly different balance of subtle intermolecular interactions is recognised. This can be a consequence of packing rigid molecules into different arrangements or of packing different conformations of the same molecule into the same and/or different packing motifs.

The study of polymorphism in molecular materials has experienced something of a renaissance in recent times. Progress has been made in *ab initio* crystal structure prediction,<sup>7–10</sup> structure determination from powder diffraction data<sup>11,12</sup> and the stabilisation of metastable polymorphs.<sup>13,14</sup> Current prediction methodologies employ an *in vacuo* optimised molecular

structure as input to a solid state search and packing algorithm. Changes in conformation are not assessed during the packing procedures. The best packing arrangements obtained from the rigid body search are then subject to lattice energy minimisations. Only in one approach is the molecular structure allowed to relax,<sup>7</sup> but this is within the confines of the selected packing arrangement. Gross conformational changes are not possible due to close contact with the surrounding molecules within the crystal. In reality, the most common approach for conformationally flexible molecules is to run separate searches for each conformation. Even in the field of crystal structure determination from powders, conformational flexibility has received only limited attention.

Conformationally flexible molecules have more degrees of freedom than rigid molecules, so a greater scope for polymorphism might be expected. Previous studies of conformational polymorphism have shown that bond lengths and angles do not differ significantly between polymorphs, and it would appear that the relatively high energies required to perturb these parameters significantly are not present in the crystal field.<sup>15–18</sup> The energies involved in rotating about single bonds are comparable to the energy differences observed between polymorphs and so it is perhaps not surprising that molecules which possess torsional degrees of freedom can exhibit different conformational polymorphs.

Gas phase rotational barriers and conformational minima have been the subject of many computational studies. It seems that molecular mechanics, semi empirical and small basis set *ab initio* calculations often disagree over the energy ordering of minima when compared to the most accurate studies.<sup>19</sup> It has also been reported that minima located with less rigorous approaches are not always present at higher levels. It would seem that reproducing experimental or high quality theoretical rotational profiles with more accessible methods is not always successful.<sup>20–22</sup>

The solid state structural arrangement(s) adopted by a molecule will depend upon the equilibrium between the intra- and inter-molecular interactions achievable within particular packing arrangements. Our current understanding of the relationship between the packing pattern and molecular conformation

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is not sufficient, either experimentally or computationally, to permit a definitive study of the polymorphism phenomena. If crystal engineering techniques are to prove fruitful in the design and construction of solid state assemblies, a greater understanding of conformational polymorphism is essential. In addition, routine polymorph prediction is hampered by problems including force field accuracy, global minimum location and conformational flexibility.

In this paper (the first of a series on conformational polymorphs) we have selected *o*-acetamidobenzamide as an example in which the difference in solid state conformations involves the breaking of an intramolecular hydrogen bond. In future work more subtle differences between conformers will be explored. Our general objectives in this study were to: (1) Investigate and compare the gas phase potential energy surfaces (PESs) for *o*-acetamidobenzamide at various levels of theory. (2) Map the observed solid state conformations onto these surfaces and examine the geometric and energetic differences between solid state conformations and those found in the gas phase. These differences are important as gas phase structures are used as the input to both *ab initio* crystal structure prediction techniques and crystal structure solution from powder diffraction data. (3) Use gas phase conformational energy differences and calculated intermolecular lattice energies to evaluate a total energy difference between polymorphs. (4) Compare the results with the generally accepted maximum energy difference between polymorphs (within 10% of the lattice energy or 1–2 kcal mol<sup>-1</sup> for total energies).<sup>7,9,10</sup> These values are commonly used in polymorph prediction methods as a limit for the selection of potential polymorphs. (5) Examine the suitability of theoretical methods currently used to generate input for *ab initio* crystal structure prediction strategies.

## Methodology

### Conformational energies

To evaluate the energy differences between conformers, the MOPAC 93<sup>23</sup> semi empirical molecular orbital program was used to calculate AM1<sup>24</sup> and PM3<sup>25</sup> heats of formation for the structures. Various constraints were imposed during optimisation to determine the best approach for calculating the relative energies. The EF minimiser<sup>26</sup> was used for all MOPAC calculations performed in this paper. *Ab initio* studies using the GAMESS-UK<sup>27</sup> program were also performed to calculate the energy difference between conformations. Tripos<sup>28</sup> force field (FF) energies were calculated using SYBYL v6.3<sup>29</sup> and Dreiding values<sup>30</sup> were computed using CERIU2 v2.0.<sup>31</sup> Force fields usually have an electrostatic term to allow them to treat non-bonded interactions more accurately. However, Dreiding was parametrised with only a rudimentary charge system, whilst parametrisation of the Tripos FF involved no charges at all, which 'must be considered a serious flaw in the program'.<sup>32</sup> With this in mind, we decided to incorporate electrostatics into all the force field calculations through the use of atom-centred point charges calculated using AM1.

Single point calculations on each polymorph might seem to be the best measure of relative energy. However there are slight differences in the experimental bond lengths and angles between each polymorphic form as well as between the crystal structures and theoretically calculated gas phase structures. Small differences between the structures of the polymorphs under study will lead to large differences in energy and consequently bias the results in an unpredictable manner. In addition, for unknown polymorphs, the solid state conformation will not be known. Therefore, to study the conformational energy differences, we have evaluated the semi empirical heats of formation in six ways, the conditions of which are now listed. These allow an increasingly large number of degrees of freedom to relax. (1) A single point energy for the structures found in the crystal ( $\Delta_r H^{\text{cryst}}$ ). This allows us to compare the energy differ-

ences of the structures as they are found in the crystal, and thus will be subject to the problems described previously. (2) An energy for the structures in which the positions of only the hydrogen atoms have been allowed to relax ( $\Delta_r H^1$ ). This will go some way towards relieving the unpredictable effects discussed above because hydrogen atoms are most likely to be ill-defined in X-ray studies. (3) An energy for the structures where hydrogen positions and bond lengths are allowed to optimise but bond and torsion angles are held at the values observed in the crystal structure ( $\Delta_r H^2$ ). (4) An energy for the structures where hydrogen positions, bond lengths and angles are allowed to optimise. All torsion angles are fixed at the values observed in the crystal structure ( $\Delta_r H^3$ ). (5) An energy for the structures in which all parameters are allowed to optimise except the torsion angles chosen to define the crystal conformation ( $\Delta_r H^4$ ). (6) A fully optimised structure ( $\Delta_r H^5$ ). Such structures are on the gas phase PES at the minimum closest to the crystal structure geometry. Hence they will have no strain introduced by the spurious effects discussed above. However, the energy is calculated for a structure that may be considerably different to that found in the crystal.

Full and partial *ab initio* optimisations have also been performed. The latter involved optimisation of all parameters except the two torsion angles defining the crystal conformation. Differences between energies of partially optimised structures are equivalent to the differences between  $\Delta_r H^4$ . Differences between two fully optimised energies relate to the  $\Delta_r H^5$  results. In addition, optimisations using the 6-31G\*\* basis set were performed in which only the hydrogen positions were optimised. The differences in these energies are equivalent to  $\Delta_r H^1$ .

We have also evaluated the Tripos and Dreiding force field energy differences equivalent to  $\Delta_r H^1$ ,  $\Delta_r H^4$  and  $\Delta_r H^5$ . In these calculations, electrostatics were evaluated using AM1 charges calculated at the individual crystal geometries of each polymorph. This leads to differences in charges between the various forms. The choice of charges and the geometry at which they are calculated is very important in force field calculations, and can significantly alter the results. AM1 charges have been chosen because they are easily calculated and are consistent with the lattice energy calculations reported in this work.

### Torsional scans

We have defined two torsion angles that describe the major differences between the conformations observed in the two polymorphs. Ideally, we would like to perform large basis set optimisations at each point on a PES, with full optimisation of the other degrees of freedom. However, this is not feasible, and we need to resort to faster, more approximate methods to handle the large number of energy calculations required. The conformational space was searched using the Tripos FF (as implemented in SYBYL v6.3) in 10° steps from -180 to 180° for both torsion angles. AM1 charges calculated at the  $\alpha$ -conformation were used for the electrostatic part of the force field. At each point of the scan, all other geometrical parameters were allowed to relax. This process was repeated with AM1 and PM3 using 15° steps and the in-built torsional search methodology in MOPAC. As for the conformational energy calculations, the EF minimiser was employed.

The two-dimensional scans have been displayed with the GMT program,<sup>33</sup> and both topographical and contour maps have been generated. These surfaces are dependent upon the search methodology employed, the choice of starting structure and z-matrix ordering as well as the grid density and interpolation used to generate smooth surfaces. The plots give an overview of the conformational PES, but regions of special interest have been studied in detail.

We have also employed *ab initio* HF/SCF calculations to confirm the occurrence and position of minima on the PES and to evaluate energy differences between possible conformers. The time-consuming nature of these calculations has made it neces-

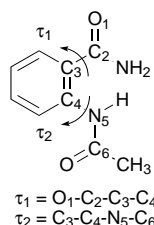
sary to restrict the studies to full optimisations starting from the individual polymorphic conformations (equivalent to  $\Delta_r H^5$ ) and to constrained optimisations in which the relevant torsion angles were frozen at the experimental values (equivalent to  $\Delta_r H^4$ ). The largest feasible basis set has been used, although some comparison with smaller basis sets has also been carried out.

### Lattice energy calculations

Lattice energy calculations<sup>9,10</sup> using several FFs have been performed to evaluate the solid state energy differences between polymorphs. The Momany FF was specifically designed to reproduce intermolecular interactions in carboxylic acids and amides.<sup>34</sup> Dreiding and Tripos are more general molecular mechanics FFs, not specifically derived for crystal packing studies, although the former is the FF used in one particular polymorph prediction strategy.<sup>7</sup> AM1 charges calculated at the crystal structure geometry were used to evaluate the electrostatic part of the intermolecular energy. Dreiding calculations were also performed in which minimisation of the packing was allowed. Two rigid body minimisation strategies were employed. In the first case, the unit cell dimensions were held fixed, but molecular rotations and translations were allowed. In the second case, the unit cell dimensions were allowed to relax. The lattice energy calculations were performed using HABIT95<sup>35</sup> and CERIU2 v2.0.

## Results and discussion

### General structural features



*o*-Acetamidobenzamide has been found to crystallise in two distinct forms, designated  $\alpha$  (CSD refcode ACBNZA) and  $\beta$  (ACBNZA01).<sup>36</sup> Details of the structures of the two forms are given in Table 1. Experimental details show that the  $\beta$ -form is produced by growing crystals slowly from polar solvents, whilst the  $\alpha$ -form is made either by supercooling from concentrated solutions or rapid cooling of the melt.<sup>36</sup> Fig. 1(a) shows the crystal packing of the  $\alpha$ -form in the *bc* plane (viewed down the *a*-axis, with the hydrogen bonds shown in green). Within each molecule there is an intramolecular hydrogen bond at 1.92 Å. The packing is dominated by hydrogen bonded dimers at 1.95 Å. Each molecule forms two further intermolecular N-H...O=C contacts (2.19 Å) giving a total for each molecule of one intra- and four inter-molecular hydrogen bonds. Fig. 1(b) shows the packing of the  $\beta$ -form viewed down the *a*-axis. The structure consists of hydrogen bonded N-H...O=C stacks at 2.02 and 2.27 Å. The stacks are held together by alternating centrosymmetric dimers at 1.99 Å. In this packing arrangement, each molecule forms a total of six intermolecular hydrogen bonds.

Two torsion angles are required to define the conformation of the flexible amide groups, designated  $\tau_1$  and  $\tau_2$  and these differ markedly in the two crystal structures. The centrosymmetric nature of the hydrogen bonded dimers in the two crystal structures leads to two symmetry related values for the torsion angles (Table 1).

### Conformational maps

The conformational maps for torsion angles  $\tau_1$  and  $\tau_2$  are shown in Fig. 2(a) (FF), (b) (AM1) and (c) (PM3). The FF and AM1 maps show that the solid state conformations of the  $\alpha$ - and  $\beta$ -

**Table 1** Crystal structure details of the  $\alpha$ - and  $\beta$ -polymorphs of *o*-acetamidobenzamide

	CSD Refcode	
	ACBNZA	ACBNZA01
Form	$\alpha$	$\beta$
<i>R</i> -factor	0.060	0.040
Molecules/unit	4	4
Space group	$P2_1/n$	$P2_1/c$
<i>a</i> /Å	4.952	7.807
<i>b</i> /Å	14.492	9.039
<i>c</i> /Å	12.471	12.706
$\alpha^\circ$	90	90
$\beta^\circ$	93.99	101.12
$\gamma^\circ$	90	90
<i>V</i> /Å <sup>3</sup>	893	880
$D_x/\text{mg m}^{-3a}$	1.325	1.345
$D_M/\text{mg m}^{-3b}$	1.312	—
$\tau_1^\circ$	$\pm 28.1$	$\pm 131.4$
$\tau_2^\circ$	$\pm 169.6$	$\pm 60.2$
Inter H-bond/Å	1.950	1.991
Intra H-bond/Å	1.915	—

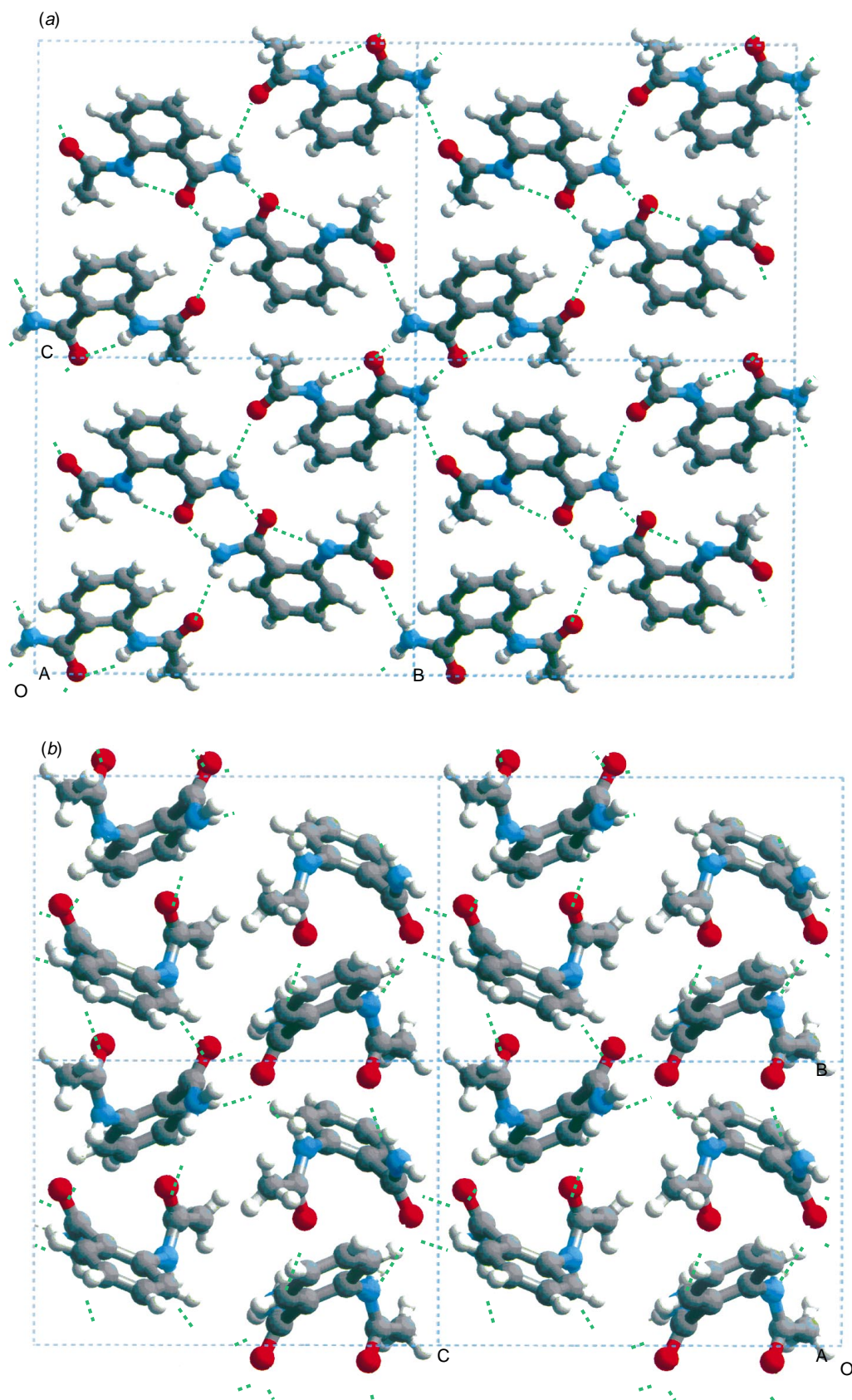
<sup>a</sup> Experimental density (computed from unit cell). <sup>b</sup> Measured density.

structures are close to (but not actually at) gas phase energy minima. The  $\alpha$ -conformation is close to the global minimum in all the maps and the  $\beta$ -conformation is close to a local minimum found in the FF and AM1 maps. The FF map shows that the  $\alpha$ -conformation is 6 kcal mol<sup>-1</sup> more stable than the  $\beta$ -conformation and there is a relatively low energy pathway between the two conformations, with a barrier of *ca.* 8 kcal mol<sup>-1</sup> for  $\alpha$  to  $\beta$ , but only *ca.* 2 kcal mol<sup>-1</sup> for  $\beta$  to  $\alpha$ . The AM1 map is similar in nature to the FF surface. The PM3 map is noticeably different from the other two, especially around the  $\beta$ -conformation, which appears not to be near a minimum. A full PM3 optimisation starting at the  $\beta$ -conformation (131.4, -60.2) confirms this with resulting torsions of (53.6, -141.1°). The PM3 minimum nearest to the  $\alpha$ -conformation is planar and there are two additional shallow potential wells close by.

The AM1 surface indicates an additional minimum at a geometry not observed in the published crystal structures at about (-110, -80°). Full optimisation of this geometry and subsequent characterisation by a force calculation confirms a minimum at (-116.0, -85.0°) with a heat of formation of -51.79 kcal mol<sup>-1</sup>. This is noticeably more stable (*ca.* 3 kcal mol<sup>-1</sup>) than the optimised  $\beta$ -conformation, but the barrier to transformation to the  $\alpha$ -form is only about 1 kcal mol<sup>-1</sup>. There is no minimum visible at this location on the PM3 surface. In this case, a minimisation starting at (-110, -80°) moves to an optimised geometry of (-60.8, -138.6°) with a heat of formation of -57.66 kcal mol<sup>-1</sup>. This PM3 minimum is geometrically close to the  $\alpha$ -conformation, and is approximately 2 kcal less stable. It is slightly more stable than the optimised  $\beta$ -form. A second minimum is also present on the AM1 surface at about (-110, -160°). A full optimisation located a minimum at (-111.7, -163.1°) with a heat of formation of -53.20 kcal mol<sup>-1</sup>.

The PM3 full optimisation of the  $\alpha$ -form indicates that a planar conformation exists as a minimum on the PES. However AM1 identified this conformation as a transition state. A 6-31G\*\* optimisation of this structure remains planar, but is also a transition state ( $\nu_i = -192$  cm<sup>-1</sup>). This structure is 1.3 kcal mol<sup>-1</sup> higher in energy than the optimised  $\alpha$ -form but 8.5 kcal mol<sup>-1</sup> more stable than the  $\beta$ -form. It is interesting to note that there are no published structures containing a planar conformation, and there would seem to be no reason that one should not exist on the grounds of conformational energetics.

The FF map also shows several minima which are more stable than the  $\beta$ -conformation. These are not identical to those found on the AM1 and PM3 maps although the minima at (-120, -90°) and (-145, -135°) could be related to the



**Fig. 1** (a) Crystal structure of *o*-acetamidobenzamide (ACBNZA,  $\alpha$ -form) viewed down the *a*-axis; (b) crystal structure of *o*-acetamidobenzamide (ACBNZA01,  $\beta$ -form) viewed down the *a*-axis (hydrogen bonds highlighted in green)

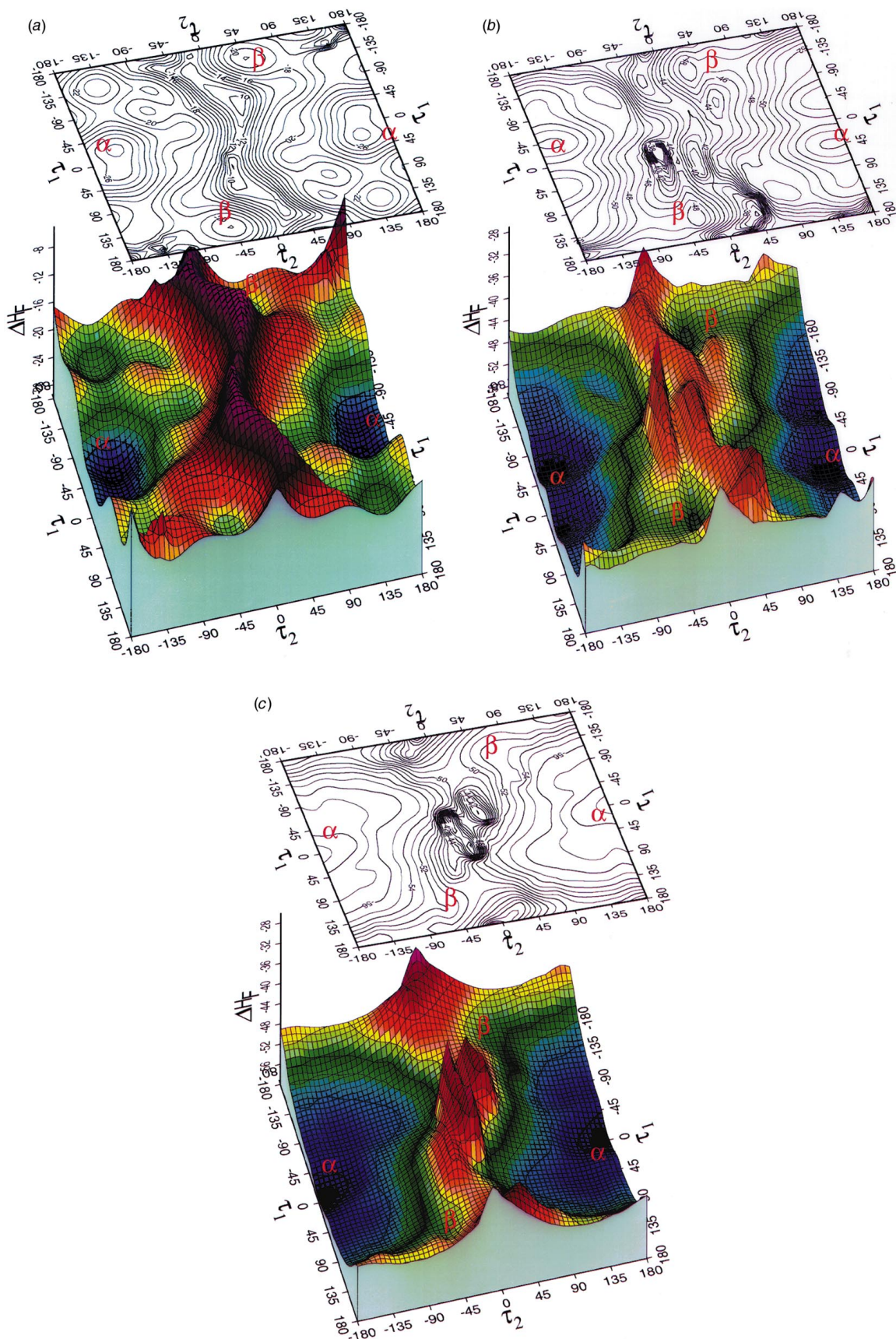
two minima on the AM1 surface discussed previously. The minimum on the FF map found at  $(-70, -75^\circ)$  does not seem to have an equivalent on either the AM1 or PM3 surfaces.

#### Conformational energies

According to the AM1 energies and the calculated differences in the heats of formation ( $\Delta\Delta H$  in Table 2) the  $\alpha$ -conformation

is more stable than the  $\beta$ -conformation. The one exception to this is the  $\Delta_r H^\ddagger$  values. However both the actual magnitude of the energies and the differences are, as previously suggested, biased by deviations between the individual crystal structure determinations. The hydrogen positions seem to be the major source of these errors. In the crystal structure of the  $\alpha$ -form, the hydrogen *ortho* to the acetamido group deviates considerably





**Fig. 2** Potential energy surfaces and projected contour maps of *o*-acetamidobenzamide, with conformation of observed polymorphs labelled. (a) Tripos force field, (b) AM1, (c) PM3.

from the plane of the phenyl group. Optimising the hydrogen positions greatly reduces the individual heats of formation and the calculated difference. The rest of the AM1 results in Table 2 indicate that the  $\alpha$ -conformation is more stable than the  $\beta$ -conformation by between 7.3 ( $\Delta_r H^3$ ) and 8.7 kcal mol<sup>-1</sup> ( $\Delta_r H^5$ ).

Perhaps the most interesting result is  $\Delta_r H^4$  which indicates that the difference due to the two major torsion angles studied is 8.5 kcal mol<sup>-1</sup> in favour of the  $\alpha$ -conformation.

PM3 results (Table 2) confirm both the problems with the hydrogen positions and the resultant switch of relative stabili-

**Table 2** Semi empirical heats of formation and force field energies with the respective enthalpy ( $\Delta\Delta H$ ) and energy ( $\Delta\Delta E$ ) differences between the two polymorphs of *o*-acetamidobenzamide (all results in kcal mol<sup>-1</sup>)

Method	AM1			PM3			Dreiding			Tripos		
	$\alpha$	$\beta$	$\Delta\Delta H$	$\alpha$	$\beta$	$\Delta\Delta H$	$\alpha$	$\beta$	$\Delta\Delta E$	$\alpha$	$\beta$	$\Delta\Delta E$
$\Delta_r H^{\text{cryst}}$	198.57	137.09	-61.48	172.42	115.35	-57.07	130.00	94.12	-35.88	121.18	89.12	-32.06
$\Delta_r H^1$	-44.26	-39.00	5.26	-49.06	-41.91	7.15	15.69	27.83	12.14	-14.69	-7.91	6.78
$\Delta_r H^2$	-52.57	-45.97	6.60	-55.45	-49.13	6.32	—	—	—	—	—	—
$\Delta_r H^3$	-55.45	-46.68	8.77	-58.19	-51.56	6.63	—	—	—	—	—	—
$\Delta_r H^4$	-55.63	-47.13	8.50	-58.34	-52.08	6.26	0.86	11.38	10.52	-21.68	-12.93	8.75
$\Delta_r H^5$	-56.23	-47.55	8.68	-59.39	-57.31	2.08	0.24	10.24	10.00	-23.16	-14.20	8.96

**Table 3** Results of *ab initio* calculations, with energies (au<sup>a</sup>) and relative conformational energies (kcal mol<sup>-1</sup>)

Conformation	Basis set	$E_{\text{Hopt}}$	$E_{\text{partopt}}$	$E_{\text{fullopt}}$	$\Delta E_{\text{Hopt}}$	$\Delta E_{\text{partopt}}$	$\Delta E_{\text{fullopt}}$
$\alpha$	STO-3G	—	-597.605 53	-597.606 99	—	0.00	0.00
$\beta$	STO-3G	—	-597.594 37	-597.595 29	—	7.00	7.34
$\alpha$	3-21G	—	-601.941 30	-601.941 84	—	0.00	0.00
$\beta$	3-21G	—	-601.917 17	-601.920 11	—	15.14	13.63
$\alpha$	6-31G**	-605.329 96	-605.334 57	-605.334 59	0.00	0.00	0.00
$\beta$	6-31G**	-605.309 65	-605.318 94	-605.320 63	12.75	9.81	8.76
Planar <sup>b</sup>	6-31G**	—	—	-605.332 44	—	—	1.35

<sup>a</sup> 1 au = 627.472 37 kcal mol<sup>-1</sup>. <sup>b</sup> Optimisation starting from PM3 planar structure near  $\alpha$ -conformation. Final structure characterised by a force calculation as a transition state.

ties upon hydrogen geometry optimisation. In general the PM3 results agree with the AM1 results on both the relative stability trends and the rough magnitude of the differences. The notable exception is the full PM3 optimisation of both forms ( $\Delta_r H^5$ ) which gives structures separated by only 2.1 kcal mol<sup>-1</sup>. This is in contrast with AM1 and the PM3 results preceding this in Table 2. The optimised structure of the  $\alpha$ -form using PM3 is planar in disagreement with the AM1 and FF results.

Full optimisations of the two forms using the Dreiding and Tripos FFs (with AM1 charges calculated at the crystal structure geometries) were also performed (Table 2). These are equivalent to  $\Delta_r H^5$  results carried out using the semi empirical methods. The FF calculations show that the  $\alpha$ -form is more stable by 9.0 (Tripos) and 10.0 kcal mol<sup>-1</sup> (Dreiding). The calculated torsion angles are reasonably close to the crystal structures, as discussed in the following section. Calculations equivalent to  $\Delta_r H^4$  were carried out using the FFs. The resultant differences of 8.7 (Tripos) and 10.5 kcal mol<sup>-1</sup> (Dreiding) are consistent with the fully optimised results. The ordering of the differences is in agreement with those obtained with AM1, although the magnitude is slightly higher.

The results equivalent to  $\Delta_r H^{\text{cryst}}$  and  $\Delta_r H^1$  from the force field studies are in agreement with the semi empirical calculations. The same switch in relative stabilities found on going from  $\Delta_r H^{\text{cryst}}$  to  $\Delta_r H^1$  for the semi empirical calculations is also observed. The Tripos  $\Delta\Delta E$  of 6.8 kcal mol<sup>-1</sup> is similar to the AM1 and PM3 results, whereas the Dreiding result (12.1 kcal mol<sup>-1</sup>) is considerably greater.

Both partial and full *ab initio* optimisations equivalent to  $\Delta_r H^4$  and  $\Delta_r H^5$  respectively, were carried out using STO-3G, 3-21G and 6-31G\*\* basis sets. The results are given in Table 3. The calculated energy differences for the two forms differs depending upon the basis set used. It is interesting to note that the energy difference calculated by STO-3G is very similar to the 6-31G\*\* value, whereas the 3-21G value is significantly larger for both  $\Delta_r H^4$  and  $\Delta_r H^5$  results. All the *ab initio* results confirm that the  $\alpha$ -conformation is more stable than the  $\beta$ -molecular arrangement. The 6-31G\*\* results indicate that the difference between the optimised  $\alpha$ - and  $\beta$ -conformers is 8.7 kcal mol<sup>-1</sup> in favour of the  $\alpha$ -conformation. Single point MP2/6-31G\*\*//HF/6-31G\*\* calculations confirm this result, with an energy difference of 8.6 kcal mol<sup>-1</sup>. Thus it is clear that the energy differences for this molecule have converged at the

Hartree Fock level for this basis set. The HF/6-31G\*\* difference between the partially optimised forms (*i.e.* torsion angles set at the crystal structure values) is 9.8 kcal mol<sup>-1</sup>, again in favour of the  $\alpha$ -conformer. These results reflect that there is little difference between the energy of the partially optimised  $\alpha$ -form and the nearest minimum. The difference between the  $\beta$ -form and its 6-31G\*\* optimised equivalent is *ca.* 1 kcal mol<sup>-1</sup> but there is a torsional difference of nearly 20° for  $\tau_1$ .

Optimisation of the hydrogen positions using the 6-31G\*\* basis set produces an energy difference of 12.75 kcal mol<sup>-1</sup> in favour of the  $\alpha$ -conformation. This is in line with the other conformational energy differences calculated with this basis set. It is significantly larger than the  $\Delta_r H^1$  value calculated with AM1, but close to the Dreiding value quoted above (Table 2).

The calculations  $\Delta_r H^1$  to  $\Delta_r H^5$  involve a gradual shift between evaluating the energy of the molecule as it is found in the crystal to evaluating the gas phase optimised energy. At the same time, errors introduced by poorly defined atoms in the crystal structure (especially hydrogens) gradually reduce. Another method to estimate the relative stabilities of the two conformations within the two crystal modifications is to optimise the structure of a central molecule within the crystal framework. This preserves the essential features of the individual crystal conformations but allows the chosen theoretical method to smooth out anomalies generated by differences between the experimental and optimal gas phase structures. The calculations involve extracting a suitably sized segment of each crystal structure and optimising only the central molecule. The large size of these clusters [14 molecules ( $\alpha$ ) and 16 molecules ( $\beta$ )] means that such calculations have to be performed using force fields. AM1 charges determined on a single molecule from the crystal structure were propagated onto each molecule in the cluster. Once the central molecule has been optimised, it can be extracted from the cluster and a single point energy calculation performed. The Tripos energy values are -22.5 ( $\alpha$ ) and -11.6 ( $\beta$ ) kcal mol<sup>-1</sup>, corresponding to an energy difference of 10.9. Equivalent values calculated using the Dreiding FF are 1.0 ( $\alpha$ ) and 11.9 ( $\beta$ ) giving the same energy difference of 10.9 kcal mol<sup>-1</sup>. These values are only slightly larger than those determined from the  $\Delta_r H^4$  calculations and vindicate the use of energy differences calculated at gas phase geometries.

**Table 4** Experimental and calculated torsion angles. Methods closest to the crystal structures are highlighted in bold italics.

CSD Refcode	ACBNZA			ACBNZA01			Overall average <sup>a</sup>
	$\alpha$		Average diff. <sup>a</sup>	$\beta$		Average diff. <sup>a</sup>	
	$\tau_1/^\circ$	$\tau_2/^\circ$		$\tau_1/^\circ$	$\tau_2/^\circ$		
X-Ray	$\pm 28.1$	$\pm 169.6$	—	$\pm 131.4$	$\mp 60.2$	—	—
AM1	43.5	162.6	11.2	<b>137.1</b>	<b>-53.7</b>	<b>6.1</b>	8.7
PM3	0.0	180.0	19.2	53.6	-141.1	79.8	49.5
STO-3G	10.7	177.0	12.4	150.2	-60.3	9.5	11.0
3-21G	18.6	175.1	7.5	162.9	-70.4	20.9	14.2
6-31G**	<b>26.8</b>	<b>167.2</b>	<b>1.8</b>	151.1	-68.7	14.1	<b>7.9</b>
Tripos	25.1	145.0	13.8	149.4	-47.4	16.0	14.9
Dreiding	34.4	158.6	8.6	153.2	-55.9	13.0	10.8

<sup>a</sup> Compared to X-ray structures.

### Geometries

It is of interest to examine how close the optimised torsion angles are to the 'real' gas phase minima and additionally how close the calculated structures are to those found in the solid state. It may be quite possible for a lower level theoretical method to produce optimised torsion angles closer to those found in the solid state than those from the best method available. However, such a result would be entirely fortuitous because it is impossible to predict the influence of packing effects without examining the appropriate crystal structure.

Experience of theoretical methods tells us that HF/6-31G\*\* energies and geometries are very reliable for organic molecules, and thus we assume in this analysis that this method gives us a true picture of the gas phase PES, although it is obviously possible to go to even larger basis sets and to include electron correlation effects. Taking the 6-31G\*\* calculations as a reference, the mean differences in the torsion angles across the two forms can be calculated from Table 4. In ascending order, these values are: 3-21G (7.2°), Dreiding (7.8°), STO-3G (9.0°), Tripos (11.7°), AM1 (12.6°) and PM3 (52.4°). The results of all these methods apart from those for PM3 are encouraging, although only limited conclusions can be drawn from studies of a single molecule.

As input to the packing and search algorithms, crystal structure and polymorph prediction strategies employ gas phase structures optimised at various levels of theory. In order to examine the validity of such an approach, the fully optimised Tripos, Dreiding, AM1, PM3 and *ab initio* torsion angles are compared with experimental values in Table 4. The results show that the 6-31G\*\* values are very close to experiment for the  $\alpha$ -form with an average difference for the two torsion angles of only 1.8°. These are then followed by 3-21G, Dreiding, AM1, STO-3G, Tripos and PM3 in descending order of agreement. In terms of *ab initio* polymorph prediction, this agreement is encouraging because it means that the crystal relaxation phase of the technique described previously will only have to make minor changes to the gas phase structure to obtain the solid state packing arrangement. The results for the  $\beta$ -form are somewhat different. Based on the average difference for the two torsion angles, the best results are seen for AM1 followed in order by STO-3G, Dreiding, 6-31G\*\*, Tripos and the 3-21G results. The results for PM3 are very poor, showing no correlation with either the crystal structure or the other theoretical methods. The consequences of this disparity between gas phase and solid state torsion angles for polymorph prediction are more worrying, with changes in  $\tau_1$  of about 20° (6-31G\*\*) being required to pack the gas phase  $\beta$ -conformation into the solid state.

In an attempt to rationalise the 6-31G\*\* result, the fully optimised 6-31G\*\* gas phase structures have been superimposed onto their respective crystal structures, through fitting of the phenyl carbon atoms. Examination of the hydrogen

bonding distances to the gas phase optimised conformation fitted into the  $\alpha$ -form shows only small deviations from the values observed in the crystal structure. In contrast, superposition of the optimised  $\beta$ -conformation onto the  $\beta$ -crystal results in a considerable increase (0.4 Å) in two of the important intermolecular hydrogen bonds. These hydrogen bonds are involved in determining the conformation of the primary amide group and this may explain the greater difference between the calculated and experimental torsion ( $\tau_1$ ) for the  $\beta$ -form.

An average of the differences between the calculated and observed torsion angles (Table 4) indicates a measure of the deviation from the crystal structure. The results show that the 6-31G\*\* results are marginally closer than AM1 which is slightly better than Dreiding. These are then followed by the Tripos force field results. In the generation of molecular structures for polymorph prediction, the benefits of using high level *ab initio* calculations over simple force fields are not dramatic for *o*-acetamidobenzamide.

The differences between torsion angles observed in the crystal and those obtained from the Tripos minimisations within a small crystalline cluster gave values of 1.0 ( $\tau_1$ ,  $\alpha$ ), 16.3 ( $\tau_2$ ,  $\alpha$ ), 0.1 ( $\tau_1$ ,  $\beta$ ) and 2.1° ( $\tau_2$ ,  $\beta$ ). The equivalent Dreiding FF values are 2.3, 2.5, 6.9 and 6.4° respectively. Apart from the Tripos ( $\tau_2$ ,  $\alpha$ ) value, these are all very small, and they are all less than the differences between the crystal structures and the nearest gas phase minimum.

### Lattice energy calculations

The experimental sublimation enthalpy of *o*-acetamidobenzamide is not known. To validate our choice of methodology, we calculated the lattice energy for benzamide, a related structure for which the experimental lattice enthalpy is available (-23.2 to -24.3 kcal mol<sup>-1</sup>).<sup>38</sup> This is in excellent agreement with the value calculated using our methodology of -22.9 kcal mol<sup>-1</sup> (experimental crystal structure, CSD refcode BZAMID01<sup>39</sup>) and -23.5 kcal mol<sup>-1</sup> (full rigid body and lattice minimisation).

The lattice energy calculations carried out using HABIT95 and CERIUS are reported in Table 5. The results predict that the  $\beta$ -polymorph packing is 2.9 (Dreiding), 2.2 (Momany) or 2.4 kcal mol<sup>-1</sup> (Tripos) more stable than the  $\alpha$ -form. It is well known that single point lattice energy calculations (using the experimental structure) successfully reproduce experimental values.<sup>10,37,40</sup> However, to ensure that lattice minimisation is not important in this case, we have investigated its effect on the lattice energy differences. During an initial lattice minimisation, the molecular structures were allowed to rotate and translate but the unit cell dimensions and space group symmetry were fixed at the experimental values. The difference in lattice energies remained at 2.9 kcal mol<sup>-1</sup>. During this minimisation, both lattice energies decreased by only 0.2 kcal mol<sup>-1</sup>. Under full minimisation, the difference in lattice energies drops slightly to 2.6 kcal mol<sup>-1</sup>. There is a further

**Table 5** Lattice energy calculations for the two polymorphs of *o*-acetamidobenzamide (results in kcal mol<sup>-1</sup>)

Refcode	Experimental structure			Minimised structure	
	Momany <sup>a</sup>	Tripos <sup>a</sup>	Dreiding <sup>b</sup>	Dreiding <sup>b,c</sup>	Dreiding <sup>b,d</sup>
ACBNZA ( $\alpha$ )	-25.7	-24.9	-30.6	-30.8	-31.3
ACBNZA01 ( $\beta$ )	-27.9	-27.3	-33.5	-33.7	-33.9
$\Delta E_{\text{latt}}$	-2.2	-2.4	-2.9	-2.9	-2.6

<sup>a</sup> As implemented in HABIT95. <sup>b</sup> As implemented in CERIU5-2. <sup>c</sup> Lattice energy minimisation, with rigid body rotation and translation (unit cell fixed). <sup>d</sup> Lattice energy minimisation, with rigid body rotation and translation (unit cell relaxed).

decrease in lattice energies of about 0.3 kcal mol<sup>-1</sup>. In this case, optimisation of the crystal structures has had little effect on either the calculated lattice energies or the difference between them.

It is interesting to note that the optimised unit cell dimensions of *o*-acetamidobenzamide are in excellent agreement with those determined by experiment. The unsigned average difference of the six cell lengths for the two polymorphs is 0.07 Å, with a maximum deviation of 0.18 Å (in the *a*-axis of the  $\alpha$ -polymorph). The monoclinic angle deviates by 2.3 and 0.4° in the minimised  $\alpha$ - and  $\beta$ -forms, respectively.

We already have confidence in the use of Momany in this area of chemistry since it was derived for acids and amides.<sup>34</sup> It is also clear that Dreiding is able to reproduce both the energetics and crystal packing of amide-type structures. The agreement of the Dreiding single point lattice differences with those obtained from the Momany and Tripos FFs gives us added confidence in the use of any of these methods.

These values appear to be consistent with the current theories on the difference in the lattice energies between polymorphs being around 10% of the lattice energy.<sup>37</sup> In this case that would be around 3 kcal mol<sup>-1</sup>.

## Discussion

The conformational results indicate that in this case all methods predict the  $\alpha$ -conformation to be more stable than the  $\beta$ -conformation. The range lies between 2.08 (PM3,  $\Delta_r H^{\ddagger}$ ) and 15.1 kcal mol<sup>-1</sup> (full optimisation at 3-21G). Excluding these two extremes, the bulk of the results from force fields, semi empirical and *ab initio* results indicate a preference for the  $\alpha$ -conformation of around 8.5 or 8.7 kcal mol<sup>-1</sup> based on the average results for  $\Delta_r H^{\ddagger}$  and  $\Delta_r H^{\ddagger}$  respectively.

If the crystal lattice must supply energy for the stabilisation of an energetically unfavourable conformation, it might be expected that the  $\beta$ -structure will have a lattice energy around 8.5 kcal mol<sup>-1</sup> more stable than the  $\alpha$ -structure. The calculations carried out in this paper indicate that the difference in lattice energy is between 2.2 to 2.9 kcal mol<sup>-1</sup> with the average being 2.6 kcal mol<sup>-1</sup> in favour of the  $\beta$ -structure. This difference in lattice energies is in agreement with previous literature values.

The total energy of a system can be defined as the sum of the intramolecular (*i.e.* conformational energy) and the intermolecular energy (*i.e.* lattice energy) of the crystal, and we would expect the total energies of the two forms to be similar. However, relative total energies computed for the two forms indicate a large discrepancy between them. Using the best of the methods we have employed in this study (*i.e.* 6-31G\*\* conformations and Momany lattice energies) the difference is 7.6 kcal mol<sup>-1</sup>. Using the same force field to evaluate the conformational aspects and lattice energies gives differences of 7.6 (Dreiding) and 6.3 kcal mol<sup>-1</sup> (Tripos). The differences in the total energies calculated with these methods are consistently larger than might be expected from experience.<sup>7,9,15</sup> The implication for polymorph prediction methods is considerable. The large number of structures generated by polymorph prediction strategies means that many of the less stable packing arrangements are discarded. An energy window of at most 1–2 kcal

mol<sup>-1</sup> is normally employed. In this case, there is a danger that one of the observed polymorphs ( $\beta$ ) would be overlooked.

It could be suggested from Table 2 that the best comparison for conformationally polymorphic materials might be  $\Delta_r H^{\ddagger}$ . It provides an energy difference in which the errors resulting from poorly defined hydrogen positions are removed but the other structural consequences of packing in different arrangements are retained. From our calculations this would give differences in conformational energies in favour of the  $\alpha$ -conformer of 5.3 and 7.1 kcal mol<sup>-1</sup> for AM1 and PM3 respectively. Using an average lattice energy of 2.6 kcal mol<sup>-1</sup> in favour of the  $\beta$ -polymorph this would give differences in total energies between the polymorphs of 2.7 and 4.5 kcal mol<sup>-1</sup> for AM1 and PM3. These results are still larger than expected but approaching the typical values reported in the literature.<sup>7,9</sup> The danger of using this measure of the differences are two-fold. First, the calculated energy differences can still be biased to one form purely as a result of the bond lengths and angles in that structure being closer to the 'ideal' values expected by the calculation method. Secondly, in terms of predictions, these numbers would not be available as the crystal structures would not be known.

It is difficult to compare the theoretical results directly with experimental observations. The  $\beta$ -polymorph has the most stable lattice energy and the highest density (see Table 1). This is in general agreement with previous studies on the thermodynamics of polymorphism.<sup>37</sup> It has been observed experimentally that a solid state transformation from the  $\alpha$ - to the  $\beta$ -polymorph occurs at 150 °C, with a heat of transformation of 0.7 kcal mol<sup>-1</sup>.<sup>36</sup> Care must be taken however in comparing calculated lattice energies and/or total energies with specific heats of transformations at given temperatures as the enthalpy differences are temperature dependent.

To investigate the mechanism for the formation of such a high energy conformer, calculations were also performed to assess the effect of polar and non-polar environments upon the conformational equilibrium. The AMSOL program<sup>41</sup> was used to calculate AM1/SM2.1<sup>42</sup> and AM1/SM4<sup>43</sup> energies which are self consistent reaction field methodologies representing the effects of water and hexane respectively. The non-polar environment has little effect upon the relative energies [ $\Delta G_{\text{soliv}} = -10.63$  ( $\alpha$ ),  $-11.93$  ( $\beta$ ) kcal mol<sup>-1</sup>]. By contrast, the free energies of solvation in water are  $-13.95$  ( $\alpha$ ) and  $-16.72$  kcal mol<sup>-1</sup> ( $\beta$ ). It is presumably the capacity of the  $\beta$ -conformation to interact more favourably with polar solvents that lowers the energy pathway to the formation of the  $\beta$ -conformation and hence the  $\beta$ -polymorph. However, in water, the energy of the  $\alpha$ -conformation is still 5.4 kcal mol<sup>-1</sup> more stable. The reduction in the energy difference between the two conformations compared to the gas phase is not sufficiently large to significantly alter the estimated Boltzmann populations but it is enough to bring the total energy differences between polymorphs down to values approaching the expected differences (*ca.* 3 kcal mol<sup>-1</sup>). It should also be noted that the underestimation of hydrogen bonding to solvent by SCRF methods may push the results further in favour of the  $\beta$ -form.

There are a number of reasons why the calculated total energies and experiment observation may not agree quantitatively:



(1) The possibility of experimental error should not be discounted, and doubt has been expressed as to the reliability of experimental estimates of polymorph stabilities.<sup>37</sup> (2) The difficulty inherent in estimating the energy of a conformation in a crystal is apparent from the number of methods used in this work, and the problem of which method gives the best measure of stability remains. However we are confident in the 6-31G\*\* results and in the agreement between this and most of the other methods used. (3) This method of calculating total energy may be oversimplified, and other terms, which could contribute significantly may need to be included. For example, the energies involved in the subtle differences in entropy and/or polarisation between polymorphs may need to be evaluated.

### Conclusions

- (1) The observed torsion angles in the solid state of the  $\alpha$ - and  $\beta$ -polymorphs exist close to, though not actually at, minima on the calculated gas phase potential energy surfaces.
- (2) There are more minima on the potential energy surfaces than there are observed conformations in the solid state. The majority of the minima are more stable than the observed conformation found in the  $\beta$ -polymorph.
- (3) All calculations confirm that the  $\alpha$ -conformation is more stable than  $\beta$ -conformation. The magnitude of the energy difference between the  $\alpha$ - and  $\beta$ -conformations is method dependent. However, excluding two extremes, we obtain an average difference of 8.5 kcal mol<sup>-1</sup> in favour of the  $\alpha$ -conformation.
- (4) Optimisation of the respective molecular conformations within the confines of a rigid crystal cluster gives energy differences consistent with the gas phase results.
- (5) Optimisations of the hydrogen positions is crucial before any assessment of energy differences is undertaken. Failure to do so biases the results in an unpredictable manner.
- (6) The lattice energy differences show that the  $\beta$ -polymorph is more stable than the  $\alpha$ -polymorph by an average of 2.6 kcal mol<sup>-1</sup>.
- (7) The total energy differences (intra- and inter-molecular interactions) between the two polymorphs is around 6 kcal mol<sup>-1</sup>. This is much larger than expected.
- (8) The implication for polymorph prediction methods is considerable. The large number of structures generated by polymorph prediction strategies means that many of the less stable packing arrangements have to be discarded. A total energy window between 1–2 kcal mol<sup>-1</sup> is normally employed. Using this criterion the  $\beta$ -polymorph of *o*-acetamidobenzamide would be overlooked.
- (9) In terms of reproduction of the two important torsion angles defining the solid state conformations, the benefit of high level quantum chemistry over simple force field calculations is not dramatic for *o*-acetamidobenzamide.
- (10) In a recent study,<sup>44</sup> it was shown that torsion angles associated with high strain energy (>1 kcal mol<sup>-1</sup>)<sup>44</sup> appear to be very unusual in crystal structures, and it was concluded that crystal packing effects rarely have a strong systematic effect on molecular conformations. It was also suggested that large energetic differences might be found when strong intermolecular forces compete with intramolecular interactions. We have observed this in the case of *o*-acetamidobenzamide, for which there is a conformational energy difference of 9.8 kcal mol<sup>-1</sup> (6-31G\*\* result).
- (11) It has already been shown that in terms of polymorph prediction, the quality of the results is dramatically affected by how well the force field of choice describes the key interactions present.<sup>45</sup> In the case of *o*-acetamidobenzamide, the Dreiding force field appears to reproduce the torsional and intermolecular characteristics quite well and prediction studies are currently in progress.

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