PCCP

Cite this: *Phys. Chem. Chem. Phys.*, 2012, **14**, 1113–1116

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COMMUNICATION

Revealing the true crystal structure of L-phenylalanine using solid-state density functional theory†

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Received 6th September 2011, Accepted 17th November 2011
DOI: 10.1039/c1cp22831e

Solid-state density functional theory can be used for crystal structure determination from powder X-ray diffraction data of molecular crystals that are too large and complex for conventional refinement methods.

The determination of molecular crystal structures is essential for the pharmaceutical industry and for gaining a better understanding of growth kinetics and energetics important for crystal design and engineering. It is often found that obtaining crystals of some organic materials suitable for single-crystal X-ray measurements is prohibitively difficult, thereby requiring alternative methods for structural determination. Powder X-ray diffraction (PXRD) is commonly used in such cases, although elucidating structural information at the atomic level, particularly for large organic molecules, is most often not possible.[1–5] For most systems measured by PXRD, retrievable structural information is, at best, limited to lattice dimensions and possible space group symmetries. When any atomic information can be resolved, complicated multi-step procedures such as a Rietveld refinement or simulated annealing are needed to refine the estimated atomic positions in order to best reproduce the experimental diffraction pattern.[6–8] Given the excessive number of parameters required for these routines, they are prone to fail for large systems or for those with diffraction patterns containing a limited amount of crystallographic observables.[8,9]

A promising alternative to conventional refinement procedures is solid-state density functional theory (DFT). Advancements in technology now make high-level computational techniques readily accessible in that calculations once thought as requiring time on shared-use supercomputers are now easily achieved using desktop hardware and user-friendly software packages. This availability has led to the rapid progression of solid-state DFT applications.[10–13] Recently, the reliability of DFT for accurately reproducing crystal structures of organic molecules has been further improved by the incorporation of corrections for London-type dispersion forces (DFT-D).[14–16] In the current study, solid-state DFT-D has, for the first time, been utilized for the refinement of the crystal structure of a large organic crystal system from PXRD data, enabling the determination of accurate structural details unobtainable through traditional methods.

Previous attempts have been made to experimentally determine the crystal structure of the important amino acid, phenylalanine. Early PXRD studies initially proposed that L-phenylalanine crystallized in the $P222_1$ space group, followed by later studies by the same group suggesting that there are two stable polymorphs of L-phenylalanine, both in this same orthorhombic space group.[17–19] Later improvements in X-ray instrumentation and analysis have since discounted these results and have shown that the stable L-phenylalanine crystal form is indeed monoclinic.[20,21] A few claims of additional polymorphs have arisen from vapor deposition[22] and interfacial crystallization techniques,[23,24] although no structural details could be resolved from the data. The most complete structural determination for phenylalanine was made by Wiessbuch *et al*. for the D enantiomer.[20] The unit cell structure was reported in the space group *C*2, despite some difficulties in the complete refinement of the atomic positions. The poor quality refinement was interpreted as orientational disorder of the phenyl side groups. Therefore, the phenyl ring positions were assumed in order to accommodate the chosen space group, placing two irreducible phenylalanine molecules in the asymmetric unit of the $Z = 8$ unit cell (Fig. 1A). The *C*2 symmetry forced the phenyl rings of adjacent molecules to be coplanar along the crystallographic *b*-axis, creating unrealistically short H···H contacts (1.66 and 1.75 Å) between phenyl rings of neighbouring molecules. With no advanced method for structural refinement for such a large system, and the disregard for the energies associated with molecular packing, the molecular orientations constrained to *C*2 symmetry provided the best reasonable answer allowing a four-fold reduction of the unit cell to the two-molecule asymmetric unit. Here we demonstrate that this molecular arrangement is not an energetically favoured configuration, and propose the correct crystal space group symmetry and atomic positions obtained through solid-state DFT-D calculations.

The DFT-D optimizations of the L-phenylalanine unit cell were performed using the CRYSTAL09 software package.[25,26]

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† Electronic supplementary information (ESI) available: Materials and Methods section and calculated L-phenylalanine *P*2 crystal structure in CIF format. CCDC reference numbers 842118. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cp22831e

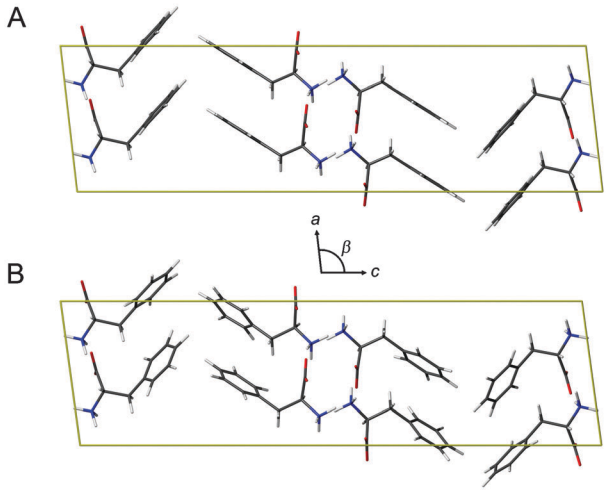

Fig. 1 (**A**) Unit cell of L-phenylalanine in previously reported *C*2 symmetry. (**B**) *P*2 unit cell of L-phenylalanine optimized using solid-state DFT-D.

Calculations utilized the PBE density functional[27] with the atom-centered 6-31G(d,p) basis set,[28] and incorporated a $1/R^6$ dispersion correction term.[29,30] The computational parameters were chosen based on previous performances in periodic DFT calculations of molecular crystals.[15,16,31–33] Detailed computational methods are provided as ESI.† A full L-phenylalanine unit cell containing all eight molecules was initially constructed using *C*2 symmetry. The complete unit cell was subsequently optimized in *P*1 symmetry, such that no constraints were placed on lattice dimensions or atomic positions. The energy minimization resulted in the phenyl rings of the L-phenylalanine molecules being rotated from their coplanar *C*2 geometry into a more energetically favourable staggered orientation (Fig. 1B). The hydrogen bonding configuration and general molecular positions were preserved over the course of the optimizations, although the unconstrained conformational freedom of the *P*1 geometry allowed for the establishment of more suitable hydrogen bonding geometries. The resulting unit cell could be reduced to a *P*2 space group with four molecules in the asymmetric unit. The calculated energy of the *P*2 structure was 5.31 kJ mol^{-1} $molecule^{-1}$ (42.45 kJ mol^{-1} per unit cell) lower in energy than the unit cell optimized in the constrained *C*2 symmetry. This large difference in energy implies that the optimized *P*2 crystal structure is considerably more stable. As a verification, analogous calculations using the hybrid B3LYP[34,35] functional were performed. Likewise results were obtained, with the *P2* structure being 6.22 kJ mol^{-1} $molecule^{-1}$ lower in energy.

The PXRD pattern for L-phenylalanine was measured and could be reliably indexed. The measurement yielded unit cell dimensions consistent with those reported by Wiessbuch *et al.*, with lattice dimensions of a = 8.778 Å, b = 6.065 Å, c = 31.597 Å, and β = 96.78° (Table 1).[20] Comparing the experimental lattice dimensions with those calculated for the *P*2 and *C*2 unit cells supports the likelihood of L-phenylalanine crystallizing in the *P*2 space group. An average error in lattice vector lengths between the experimental and calculated structures of only 0.49% was observed for the optimized *P*2 unit cell. The calculated unit cell was slightly contracted along all axes, resulting in a decrease in volume of 25.39 $Å^3$ (−1.52%). This suggests a minor overestimation in the corrections for dispersion forces applied in the DFT-D calculations. Regardless, the reproduction of the experimental unit cell dimensions was of very high quality. In contrast, the unit cell optimized in *C*2 symmetry produced much larger errors on all axes, including a 2.46% expansion along the *b*-axis and a 1.30% contraction along the *c*-axis. The expansion along the *b*-axis is most likely due to the repulsive forces of the inadequately spaced H···H contacts of the coplanar phenyl groups. The non-uniform changes of the *C*2 unit cell led to an increase in unit cell volume of 32.79 $Å^3$, or 1.97%. The energetic and geometric results of the DFT-D structural refinements strongly support the calculated *P*2 structure as the true L-phenylalanine crystal structure.

Closer examination of the experimental PXRD pattern and those calculated from the optimized crystal structures provided additional confirmation that L-phenylalanine crystallizes in *P*2 symmetry (Fig. 2). The raw PXRD pattern shown in Fig. 2A can be indexed to yield lattice dimensions and the correct crystal system, but the space group cannot be unequivocally determined. By taking the square root of the PXRD scattering intensities, the locations of low-intensity reflections could be more easily observed (Fig. 2B). Two reflections at 14.9 and 15.7 degrees 2θ (indicated by arrows in Fig. 2B) were critical in verifying the *P*2 crystal structure. These reflections cannot be indexed using the *C*2 space group. They can, however, be accounted for by indexing the diffraction pattern in a primitive monoclinic setting, such as *P*2. The calculated PXRD pattern generated from the predicted *P*2 unit cell shows low-intensity scattering at precisely these locations (Fig. 2C), whereas they are not present in the calculated *C*2 diffraction pattern (Fig. 2D). To be certain these key reflections in the experimental pattern were not a product of a sample impurity, additional PXRD data was obtained from another separately prepared L-phenylalanine sample, which produced these same peaks with analogous relative intensities. Analysis of the calculated and experimental PXRD patterns verified that the L-phenylalanine crystal structure was in the primitive *P*2 space group.

Without the application of robust DFT-D calculations, the crystal structure of L-phenylalanine could not be determined. Even with proper and thorough analysis of the experimental PXRD data, the unit cell structure could not have been ultimately established. Comparison of the calculated diffraction patterns of the *P*2 and *C*2 crystal structures clearly demonstrates that substantial reorientations of molecules within a large unit cell may have little influence on the PXRD pattern. No conventional approach to structural refinement could reposition such a large number of atoms in such a way as to accurately reproduce the experimental PXRD pattern while simultaneously yielding a physically meaningful molecular structure. The number of parameters required for any refinement technique far exceeds the available data obtainable from the PXRD pattern. In the case of the *P*2 crystal structure of L-phenylalanine, a total of 92 atoms reside in the asymmetric unit—finding a logical approach to correctly refine this number of atomic positions by conventional methods would be nearly impossible.

Table 1 Lattice parameters for experimental and calculated L-phenylalanine crystal structures

			DFT-D		Errors[a]	
	PXRD[b]	Ref. 20[c]	P2	C2	P2	C2
a/Å	8.778	8.804	8.7407	8.8406	−0.037 (−0.43)	0.063 (0.71)
b/Å	6.065	6.041	6.0412	6.2140	−0.024 (−0.39)	0.149 (2.46)
c/Å	31.597	31.564	31.3941	31.1856	−0.203 (−0.64)	−0.411 (−1.30)
β (°)	96.78	96.6	97.745	96.895	0.97 (1.00)	0.12 (0.12)
V/Å^3	1668.01	1667.6	1642.62	1700.80	−25.39 (−1.52)	32.79 (1.97)
d/g cm^{-3}	1.32	1.32	1.335	1.289	0.02 (1.14)	−0.031 (−2.35)

[a] Absolute changes (percent changes in parentheses) in parameter value between calculated and experimental PXRD structures; [b] This work; [c] D-phenylalanine indexed in *C*2 symmetry.

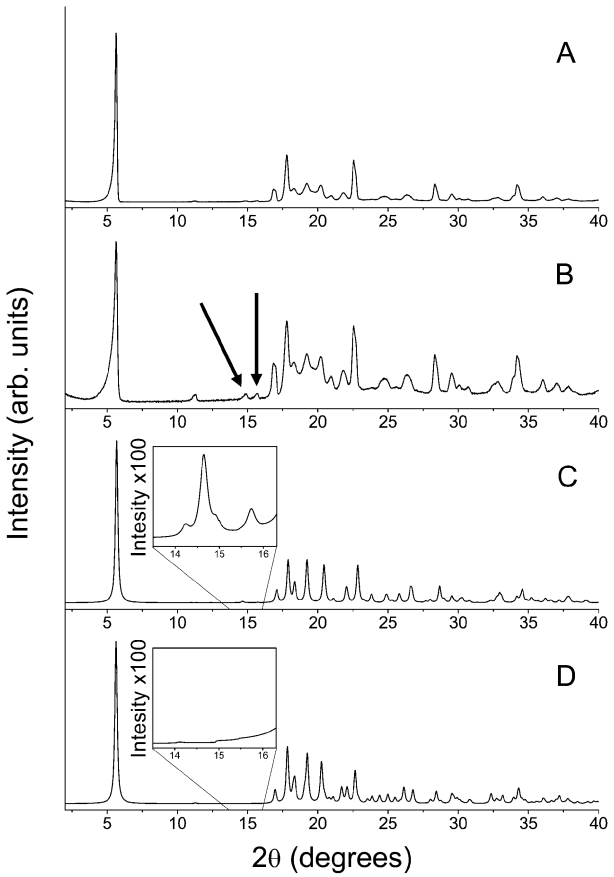

Fig. 2 (**A**) Experimental PXRD pattern of L-phenylalanine. (**B**) Square-root of experimental PXRD intensities to better reveal low-intensity reflections. Arrows indicate peaks at 14.9 and 15.7 degrees 2θ that cannot be indexed using *C*2 crystal symmetry. (**C**) Calculated PXRD pattern from optimized *P*2 unit cell. Inset shows the presence of the two indicated peaks observed in the experimental pattern. (**D**) Calculated PXRD pattern using unit cell improperly constrained to *C*2 symmetry.

The accuracy of the predicted *P*2 lattice dimensions of L-phenylalanine in comparison to those obtained from the indexed PXRD pattern demonstrates the feasibility for using DFT-D as an alternative refinement method for large molecular crystal systems. The incorporation of dispersion forces allows for molecules to arrange in such a way that represents the actual intermolecular interactions exhibited in the solid state. This provides the necessary information to determine the proper molecular configurations and space group symmetry that would otherwise be inaccessible through other refinement techniques. In addition to the refinement of large crystal structures, DFT-D may also act as a bridge between X-ray measurements and conventional crystal refinement procedures for smaller molecular systems by supplying sensible starting points for Rietveld refinements. In discovering the true crystal structure for L-phenylalanine, the results of this study set a benchmark for the application of DFT-D in complete structural determinations from limited crystallographic diffraction data.

Conclusions

Recent technological advancements have made computational resources readily accessible that enable the utilization of high-level solid-state theory for large molecular crystal systems. The reliability for accurate reproduction of crystal structures by DFT-D methods will undoubtedly lead to the expansion of potential applications. This was demonstrated here in the calculation of the correct L-phenylalanine crystal structure based on a DFT-D refinement of PXRD data. Elucidating the proper molecular geometry configurations in *P*2 symmetry within the large $Z = 8$ unit cell was possible only through the rigorous DFT-D optimization. This level of detail would not be possible using traditional refinement methods, such as Rietveld or simulating annealing. This work represents a new approach towards full crystal structure determination of complex organic molecules by PXRD and DFT-D methods.

Acknowledgements

This research was funded by a grant from the National Science Foundation CAREER Program (CHE-0847405). The authors thank Syracuse University for continued support.

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