Crystal structure of hydrocortisone acetate, $C_{23}H_{32}O_6$

James A. Kaduk,[1,2,a)] Amy M. Gindhart,[3] and Thomas N. Blanton[3]
[1]*Illinois Institute of Technology, 3101 S. Dearborn St., Chicago, Illinois 60616*
[2]*North Central College, 30 N. Brainard St., Naperville, Illinois 60540*
[3]*International Centre for Diffraction Data, 12 Campus Blvd., Newtown Square, Pennsylvania 19073-3273*

(Received 30 May 2016; accepted 4 December 2016)

The crystal structure of hydrocortisone acetate has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Hydrocortisone acetate crystallizes in space group $P2_1$ (#4) with $a = 8.85173(3)$ Å, $b = 13.53859(3)$ Å, $c = 8.86980(4)$ Å, $\beta = 101.5438(3)°$, $V = 1041.455(6)$ Å^3, and $Z = 2$. Both hydroxyl groups form hydrogen bonds to the ketone oxygen atom on the steroid ring system, resulting in a three-dimensional hydrogen bond network. The powder pattern has been submitted to ICDD for inclusion in the Powder Diffraction File™. © *2017 International Centre for Diffraction Data.* [doi:10.1017/S0885715616000713]

Key words: hydrocortisone acetate, powder diffraction, Rietveld refinement, density functional theory

I. INTRODUCTION

Hydrocortisone acetate is a corticosteroid anti-inflammatory that can be mixed in a cream [typically 1% hydrocortisone as the active pharmaceutical ingredient (API)] and applied as a topical treatment for eczema, dermatitis, or other skin rashes (i.e. Sigmacort®, Cortic-DS®, and Exederm®). Hydrocortisone acetate can also be administered as a cream, ointment, or suppository (typically 1–2.5% hydrocortisone as the API) for the treatment of hemorrhoids, fissures, or other rectal irritations (i.e. Anucort-HC® and Encort®). Hydrocortisone acetate is often combined with Pramoxine HCl with the Praxomine HCl functioning as a local anesthetic (i.e. Analpram-HC®). The systematic IUPAC name (CAS Registry number 50-03-3) is [2-[(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate. A two-dimensional molecular diagram is shown in Figure 1.

A low-precision pattern of hydrocortisone acetate is included in the Powder Diffraction File (ICDD, 2015) as entry 00-015-1017 (Parsons *et al.*, 1962), which replaced a deleted entry 00-007-0616. Crystallographic data for hydrocortisone acetate were reported by Shell (1955). Biles (1963) stated that there is evidence for two polymorphs of hydrocortisone acetate. Callow and Kennard (1961) reported five crystalline forms, four of which are unstable in the presence of water and convert to the stable Form I.

This work was carried out as part of a project (Kaduk *et al.*, 2014) to determine the crystal structures of large-volume commercial pharmaceuticals at ambient conditions, and include high-quality powder diffraction data for these pharmaceuticals in the Powder Diffraction File.

II. EXPERIMENTAL

Hydrocortisone acetate was a commercial reference standard, purchased from the US Pharmacopoeia (Lot #L0L246), and was used as-received. The white powder was packed into a 1.5 mm diameter Kapton capillary, and rotated during the measurement at ~50 cycles s^{-1}. The powder pattern was measured at 295 K at beam line 11-BM (Lee *et al.*, 2008; Wang *et al.*, 2008) of the Advanced Photon Source at Argonne National Laboratory using a wavelength of 0.413342 Å from 0.5°–50° 2θ with a step size of 0.001° and a counting time of 0.1 s step^{-1}. The pattern was indexed on a primitive monoclinic unit cell having $a = 8.852$ Å, $b = 13.542$ Å, $c = 8.871$ Å, $\beta = 101.5°$, $V = 1041.9$ Å^3, and $Z = 2$ using Jade (MDI, 2014). Analysis of the systematic absences suggested the space group $P2_1$, which was confirmed by successful solution and refinement of the structure. A reduced cell search in the Cambridge Structural Database (Groom *et al.*, 2016) combined with the chemistry "C H O only" yielded eight hits, among which was ZZZGCU (Shell, 1955), which contained no atom coordinates.

A hydrocortisone molecule was extracted from CSD entry CORTMS01 (Shikii *et al.*, 2004). The acetate group was added using Spartan '14 (Wavefunction, 2013), and the minimum energy conformation was determined. This file was converted into a Fenske–Hall *Z*-matrix file using OpenBabel

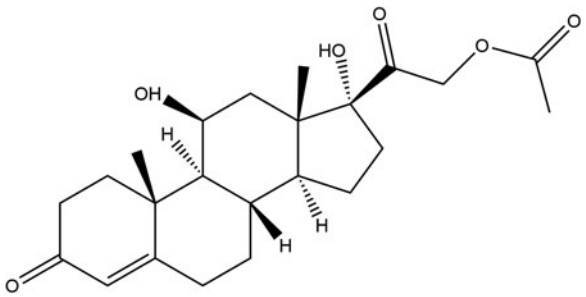

Figure 1. The molecular structure of hydrocortisone acetate.

a)Author to whom correspondence should be addressed. Electronic mail: kaduk@polycrystallography.com

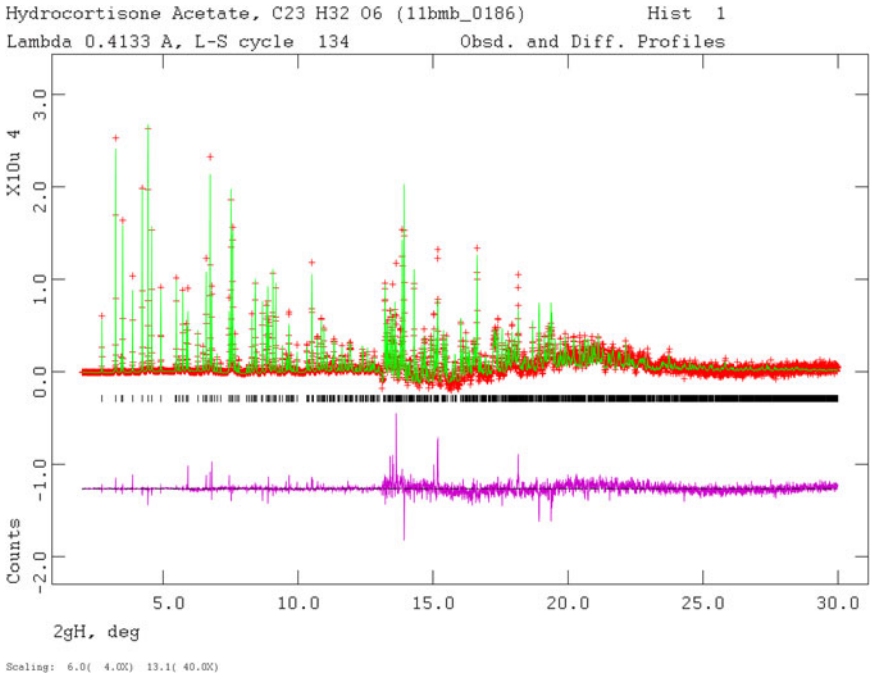

Figure 2. (Color online) The Rietveld plot for the refinement of hydrocortisone acetate. The red crosses represent the observed data points, and the green line is the calculated pattern. The magenta curve is the difference pattern, plotted at the same vertical scale as the other patterns. The vertical scale has been multiplied by a factor of 4 for $2\theta > 6.0°$, and by a factor of 40 for $2\theta > 13.1°$.

(O'Boyle *et al.*, 2011). The structure was solved with FOX (Favre-Nicolin and Černý, 2002). The maximum $\sin\theta/\lambda$ used in the structure solution was 0.40 Å^{-1}.

Rietveld refinement was carried out using GSAS (Toby, 2001; Larson and Von Dreele, 2004). Only the 2.0°–30.0° portion of the pattern was included in the refinement (d_{min} = 0.798 Å). All non-H bond distances and angles were subjected to restraints, based on a Mercury/Mogul Geometry Check (Bruno *et al.*, 2004; Sykes *et al.*, 2011) of the molecule. The Mogul average and standard deviation for each quantity were used as the restraint parameters. The restraints contributed 5.1% to the final χ^2. A single U_{iso} was refined for all of the ring system carbon atoms, another U_{iso} for the ring substituent heavy atoms, and a third for the acetate substituent heavy atoms. The hydrogen atoms were included in calculated positions, which were recalculated during the refinement. The U_{iso} of each hydrogen atom was fixed at 0.06 Å^2. The peak profiles were described using profile function #4 (Thompson *et al.*, 1987; Finger *et al.*, 1994), which includes the Stephens (1999) anisotropic strain broadening model. The background was modeled using a three-term shifted Chebyshev polynomial, with a six-term diffuse scattering function to model the Kapton capillary and any amorphous component. The final refinement of 121 variables using 28 086 observations (28 002 data points and 84 restraints) yielded the residuals R_{wp} = 0.0813, R_p = 0.0642, and χ^2 = 2.177. The largest peak (1.33 Å from H35) and hole (1.93 Å from O28) in the difference Fourier map were 0.54 and −0.47 e(Å^{-3}), respectively. The Rietveld plot is included as Figure 2. The largest errors in the fit are in the shapes and positions of some of the low-angle peaks.

A density functional geometry optimization (fixed experimental unit cell) was carried out using CRYSTAL09 (Dovesi *et al.*, 2005). The basis sets for the H, C, and O atoms were those of Gatti *et al.* (1994). The calculation was run on a 2.8 GHz PC, used eight *k*-points and the B3LYP functional, and took ∼16 days.

III. RESULTS AND DISCUSSION

The refined atom coordinates of hydrocortisone acetate and the coordinates from the density functional theory (DFT) optimization are reported in the CIFs (Crystallographic Information Frameworks) submitted as Supplementary Material. The root-mean-square deviation of the non-hydrogen atoms in the hydrocortisone acetate molecules is only 0.066 Å (Figure 3). The largest difference is 0.119 Å, at C22. The excellent agreement between the refined and optimized structures is evidence

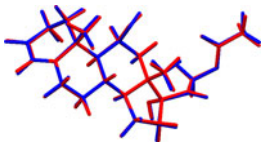

Figure 3. (Color online) Comparison of the refined and optimized structures of hydrocortisone acetate. The Rietveld refined structure is in red, and the DFT-optimized structure is in blue.

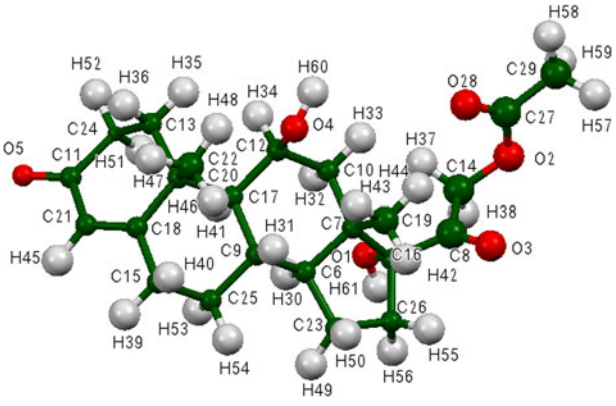

Figure 4. (Color online) The asymmetric unit of hydrocortisone acetate, with the atom numbering. The atoms are represented by 50% probability spheroids.

https://doi.org/10.1017/S0885715616000713 Published online by Cambridge University Press

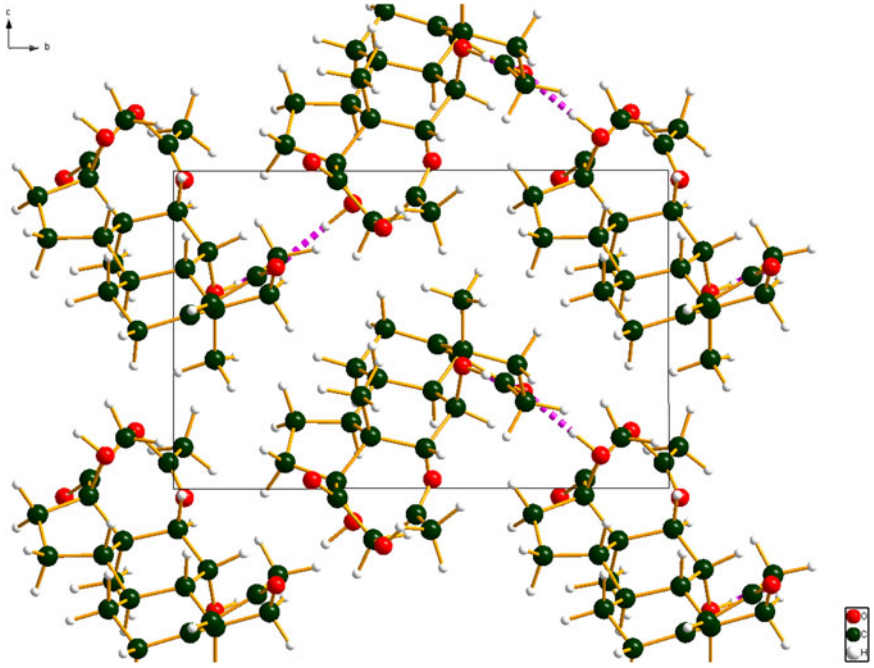

Figure 5. (Color online) The crystal structure of hydrocortisone acetate, viewed down the *a*-axis. The hydrogen bonds are indicated by dashed lines.

TABLE I. Hydrogen bonds in hydrocortisone acetate.

H-bond	D–H (Å)	H• • • A (Å)	D• • • A (Å)	D–H• • • A (E)	Overlap, (*e*)	Energy, (kcal mole^{-1})
O1–H61• • • O5	0.983	1.774	2.755	175.8	0.058	13.2
O4–H60• • • O5	0.979	1.845	2.819	172.9	0.057	13.0
C22–H48• • • O4	1.088	2.265	2.895	114.8	0.013	

that the experimental structure is correct (van de Streek and Neumann, 2014). This discussion uses the DFT-optimized structure. The asymmetric unit (with atom numbering) is illustrated in Figure 4, and the crystal structure is presented in Figure 5.

All of the bond distances, bond angles, and torsion angles (the bonds and angles were restrained) fall within the normal ranges indicated by a Mercury Mogul Geometry check (Macrae *et al.*, 2008). Quantum chemical geometry optimization (Hartree–Fock/6-31G*/water) using Spartan '14 (Wavefunction, 2013) indicated that the observed conformation of hydrocortisone acetate in the solid state is 9.4 kcal mole^{-1} higher in energy than a local minimum energy conformation of an isolated molecule. A molecular mechanics conformational analysis indicated that the global minimum energy conformation is more compact, and thus intermolecular interactions are important in determining the solid-state conformation.

Analysis of the contributions to the total crystal energy using the Forcite module of Materials Studio (Dassault, 2014) suggests that angle, bond, and torsion distortion terms are significant in the intramolecular deformation energy. The intermolecular energy contains significant contributions from electrostatic attractions, which in this force-field-based analysis include hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation.

Both hydroxyl groups form fairly strong hydrogen bonds to the ketone oxygen atom O5 (Table I). These hydrogen bonds result in chains having graph sets (Etter, 1990; Bernstein *et al.*, 1995; Shields *et al.*, 2000) C1,1(9) (H60) and C1,1(12) (H61). These chains form a three-dimensional hydrogen bond network. An intramolecular C–H• • • O hydrogen bond also seems to contribute to the crystal energy.

The volume enclosed by the Hirshfeld surface (Figure 6; Hirshfeld, 1977; McKinnon *et al.*, 2004; Spackman and Jayatilaka, 2009; Wolff *et al.*, 2012) is 513.44 Å^3, 98.6% of 1/2 the unit-cell volume. The molecules are thus not tightly packed. The only significant close contacts (red in Figure 6) involve the hydrogen bonds.

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect a blocky morphology for

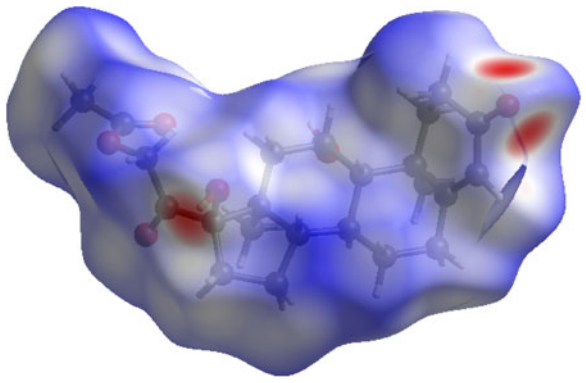

Figure 6. (Color online) Hirshfeld surface of hydrocortisone acetate. Intermolecular contacts longer than the sums of the van der Waal's radii are colored blue, and contacts shorter than the sums of the radii are colored red. Contacts equal to the sums of radii are white.

https://doi.org/10.1017/S0885715616000713 Published online by Cambridge University Press

hydrocortisone acetate. A fourth-order spherical harmonic preferred orientation model was included in the refinement; the texture index was 1.065, indicating that there was some preferred orientation in this rotated capillary specimen. The powder pattern of hydrocortisone acetate has been submitted to ICDD for inclusion in future releases of the Powder Diffraction File as entry 00-066-1610.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0885715616000713.

ACKNOWLEDGEMENTS

Use of the Advanced Photon Source at Argonne National Laboratory was supported by the US Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357. This work was partially supported by the International Centre for Diffraction Data. We thank Lynn Ribaud for his assistance in data collection.

Bernstein, J., Davis, R. E., Shimoni, L., and Chang, N. L. (**1995**). "Patterns in hydrogen bonding: functionality and graph set analysis in crystals," Angew. Chem. Int. Ed. Enl. **34**(15), 1555–1573.

Biles, J. A. (**1963**). "Some crystalline modifications of the tert-Butylacetates of prednisolone and hydrocortisone," J. Pharm. Sci. **52**, 1066–1070.

Bravais, A. (**1866**). *Etudes Cristallographiques* (Gauthier Villars, Paris).

Bruno, I. J., Cole, J. C., Kessler, M., Luo, J., Motherwell, W. D. S., Purkis, L. H., Smith, B. R., Taylor, R., Cooper, R. I., Harris, S. E., and Orpen, A. G. (**2004**). "Retrieval of crystallographically-derived molecular geometry information," J. Chem. Inf. Comput. Sci. **44**, 2133–2144.

Callow, R. K. and Kennard, O. (**1961**). "Polymorphism of cortisone acetate," J. Pharm. Pharmacol. **13**, 723–733.

Dassault Systèmes (**2014**). *Materials Studio 8.0* (BIOVIA, San Diego, CA).

Donnay, J. D. H. and Harker, D. (**1937**). "A new law of crystal morphology extending the law of Bravais," Am. Mineral. **22**, 446–467.

Dovesi, R., Orlando, R., Civalleri, B., Roetti, C., Saunders, V. R., and Zicovich-Wilson, C. M. (**2005**). "CRYSTAL: a computational tool for the *ab initio* study of the electronic properties of crystals," Z. Kristallogr. **220**, 571–573.

Etter, M. C. (**1990**). "Encoding and decoding hydrogen-bond patterns of organic compounds," Acc. Chem. Res. **23**(4), 120–126.

Favre-Nicolin, V. & Černý, R. (**2002**). "FOX, Free objects for crystallography: a modular approach to ab initio structure determination from powder diffraction," J. Appl. Crystallogr. **35**, 734–743.

Finger, L. W., Cox, D. E., and Jephcoat, A. P. (**1994**). "A correction for powder diffraction peak asymmetry due to axial divergence," J. Appl. Crystallogr. **27**(6), 892–900.

Friedel, G. (**1907**). "Etudes sur la loi de Bravais," Bull. Soc. Fr. Mineral. **30**, 326–455.

Gatti, C., Saunders, V. R., and Roetti, C. (**1994**). "Crystal-field effects on the topological properties of the electron-density in molecular crystals – the case of urea," J. Chem. Phys. **101**, 10686–10696.

Groom, C. R., Bruno, I. J., Lightfoot, M. P., and Ward, S. C. (**2016**). "The Cambridge Structural Database," Acta Crystallogr. B: Struct. Sci. Cryst. Eng. Mater. **72**, 171–179.

Hirshfeld, F. L. (**1977**). "Bonded-atom fragments for describing molecular charge densities," Theor. Chem. Acta **44**, 129–138.

ICDD (**2015**). PDF-4+ 2015 (Database). International Centre for Diffraction Data, edited by Dr. Soorya Kabekkodu (Newtown Square, PA, USA).

Kaduk, J. A., Crowder, C. E., Zhong, K., Fawcett, T. G., and Suchomel, M. R. (**2014**). "Crystal structure of atomoxetine hydrochloride (Strattera), $C_{17}H_{22}NOCl$," Powder Diffr. **29**(3), 269–273.

Larson, A. C. and Von Dreele, R. B. (**2004**). *General Structure Analysis System, (GSAS)* (Report LAUR 86-784). Los Alamos National Laboratory.

Lee, P. L., Shu, D., Ramanathan, M., Preissner, C., Wang, J., Beno, M. A., Von Dreele, R. B., Ribaud, L., Kurtz, C., Antao, S. M., Jiao, X., and Toby, B. H. (**2008**). "A twelve-analyzer detector system for high-resolution powder diffraction," J. Synchrotron Radiat. **15**(5), 427–432.

Macrae, C. F., Bruno, I. J., Chisholm, J. A., Eddington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J., and Wood, P. A. (**2008**). "Mercury CSD 2.0 B new features for the visualization and investigation of crystal structures," J. Appl. Crystallogr. **41**, 466–470.

McKinnon, J. J., Spackman, M. A., and Mitchell, A. S. (**2004**). "Novel tools for visualizing and exploring intermolecular interactions in molecular crystals," Acta Crystallogr. B: Struct. Sci. Cryst. Eng. Mater. **60**, 627–668.

MDI (**2014**). *Jade 9.5* (Materials Data. Inc., Livermore, CA).

O'Boyle, N., Banck, M., James, C. A., Morley, C., Vandermeersch, T., and Hutchison, G. R. (**2011**). "Open Babel: an open chemical toolbox," J. Chem. Informatics **3**, 33. doi: 10.1186/1758-2946-3-33.

Parsons, J., Wong, S. T., Beher, W. T., and Baker, G. D. (**1962**). "X-ray diffraction powder data for steroids: supplement II," Henry Ford Hosp. Med. Bull. **10**, 471–486.

Shell, J. W. (**1955**). "Hydrocortisone acetate," Anal. Chem. **27**, 1665–1666; CSD Refcode ZZZGCU.

Shields, G. P., Raithby, P. R., Allen, F. H., and Motherwell, W. S. (**2000**). "The assignment and validation of metal oxidation states in the Cambridge Structural Database," Acta Crystallogr. B: Struct. Sci. Cryst. Eng. Mater. **56**(3), 455–465.

Shikii, K., Sakamoto, S., Seki, H., Utsumi, H., and Yamaguchi, K. (**2004**). "Narcissistic aggregation of steroid compounds in diluted solution elucidated by CSI-MS, PFG NMR and X-ray analysis," Tetrahedron **60**, 3487–3492; CSD Refcode CORTMS01.

Spackman, M. A. and Jayatilaka, D. (**2009**). " A Hirshfeld surface analysis," CrystEngComm **11**, 19–32.

Stephens, P. W. (**1999**). "Phenomenological model of anisotropic peak broadening in powder diffraction," J. Appl. Crystallogr. **32**, 281–289.

Sykes, R. A., McCabe, P., Allen, F. H., Battle, G. M., Bruno, I. J., and Wood, P. A. (**2011**). "New software for statistical analysis of Cambridge Structural Database data," J. Appl. Crystallogr. **44**, 882–886.

Thompson, P., Cox, D. E., and Hastings, J. B. (**1987**). "Rietveld refinement of Debye–Scherrer synchrotron X-ray data from Al_2O_3," J. Appl. Crystallogr. **20**(2), 79–83.

Toby, B. H. (**2001**). "EXPGUI, a graphical user interface for GSAS," J. Appl. Crystallogr. **34**, 210–213.

van de Streek, J. and Neumann, M. A. (**2014**). "Validation of molecular crystal structures from powder diffraction data with dispersion-corrected density functional theory (DFT-D)," Acta Crystallogr. B: Struct. Sci., Cryst. Eng. Mater. **70**(6), 1020–1032.

Wang, J., Toby, B. H., Lee, P. L., Ribaud, L., Antao, S. M., Kurtz, C., Ramanathan, M., Von Dreele, R. B., and Beno, M. A. (**2008**). "A dedicated powder diffraction beamline at the advanced photon source: commissioning and early operational results," Rev. Sci. Instrum. **79**, 085105.

Wavefunction, Inc. (**2013**). Spartan '14 Version 1.1.0, Wavefunction Inc., 18401 Von Karman Ave., Suite 370, Irvine CA 92612.

Wolff, S. K., Grimwood, D. J., McKinnon, M. J., Turner, M. J., Jayatilaka, D., and Spackman, M. A. (**2012**). *CrystalExplorer Version 3.1* (University of Western Australia).