Crystal structure of methylprednisolone acetate form II, $C_{24}H_{32}O_6$

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The crystal structure of methylprednisolone acetate form II, $C_{24}H_{32}O_6$, has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Methylprednisolone acetate crystallizes in space group $P2_12_12_1$ (#19) with $a = 8.17608(2)$, $b = 9.67944(3)$, $c = 26.35176(6)$ Å, $V = 2085.474(6)$ Å^3, and $Z = 4$. Both hydroxyl groups act as hydrogen bond donors, resulting in a two-dimensional hydrogen bond network in the *ab* plane. C–H···O hydrogen bonds also contribute to the crystal energy. The powder pattern is included in the Powder Diffraction File™ as entry 00-065-1412. © *2018 International Centre for Diffraction Data*. [doi:10.1017/S0885715617001233]

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

I. INTRODUCTION

Methylprednisolone acetate (marketed under the trade-name Depo-Medrol®) is a synthetically manufactured corticosteroid medication (drug class corticosteroid hormone) administered primarily as an intramuscular, intra-articular, soft tissue, or intralesional injection in a dosage-dependent manner, or in pill form. It functions as an anti-inflammatory glucocorticoid, which is termed adrenocortical steroid. The use of analogous glucocorticoid pharmacology is a synthetic alternative often practiced in adrenocortical deficiency conditions. It is commonly used in the treatment of pain and swelling in arthritis patients (along with other joint disorders), certain cancers (leukemia, lymphoma, and multiple myeloma) alongside chemotherapy, as well as severe allergic reactions, and immune system and organ system disorders. Methylprednisolone acetate helps in reducing sickness during chemotherapy, aids in the reduction of immune system response, and is clinically proven to help the treatment of cancer itself. The IUPAC name (CAS Registry number 53-36-1) is [2-[(6*S*,8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-1117-dihydroxy-6,1013-trimethyl-3-oxo-7,8,9,11,12,14,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate. A two-dimensional molecular diagram is shown in Figure 1.

This work was carried out as part of a project (Kaduk *et al.*, 2014) to determine the crystal structures of large-volume commercial pharmaceuticals, and include high-quality powder diffraction data for these pharmaceuticals in the Powder Diffraction File (ICDD, 2017).

II. EXPERIMENTAL

Methylprednisolone acetate was a commercial reagent, purchased from USP (Lot # H0D148), and was analyzed 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 0.413685 Å from 0.5–50° 2θ with a step size of 0.001° and a counting time of 0.1 s/step. The pattern was indexed on a primitive orthorhombic unit cell having $a = 8.17523$, $b = 9.68097$, $c = 26.37087$ Å, $V = 2087.1$ Å^3, and $Z = 4$ using N-TREOR as incorporated in EXPO2014 (Altomare *et al.*, 2013). Analysis of the systematic absences suggested the space group $P2_12_12_1$, 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 26 hits, but no entry for methylprednisolone acetate.

The structure of the methylprednisolone acetate molecule was built and its conformation optimized using Spartan '16 (Wavefunction, 2017). The resulting mol2 file was converted into a Fenske-Hall Z-matrix file using OpenBabel (O'Boyle

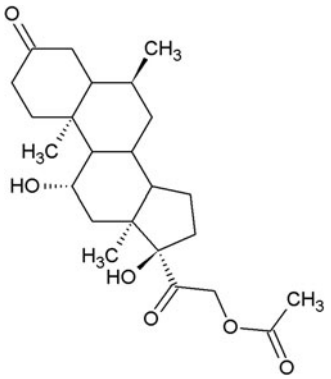

Figure 1. The molecular structure of methylprednisolone acetate.

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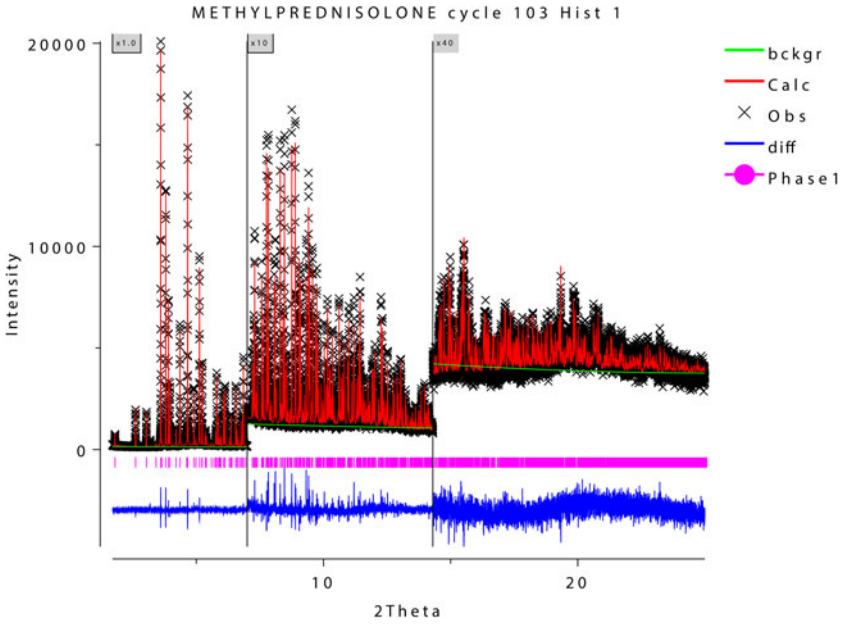

Figure 2. (Colour online) The Rietveld plot for methylprednisolone acetate. The black crosses represent the observed data points, and the red line is the calculated pattern. The blue curve is the difference pattern, plotted at the same vertical scale as the other patterns. The vertical scale has been multiplied by a factor of 10 for $2\theta > 7.0°$, and by a factor of 40 for $2\theta > 14.3°$.

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 0.4 $Å^{-1}$. A total of 59 cycles at two million trials/run were carried out. The lowest cost factor was the very low value 32 113. Many runs had similarly low cost factors.

Rietveld refinement was carried out using GSAS (Toby, 2001; Larson and Von Dreele, 2004). Only the 1.7–25.0° portion of the pattern was included in the refinement ($d_{min} = 0.955$ Å). All non-H bond distances and angles were subjected to restraints, based on a Mercury/Mogul Geometry Check (Sykes *et al.*, 2011; Bruno *et al.*, 2004) of the molecule. The Mogul average and standard deviation for each quantity were used as the restraint parameters. The restraints contributed 1.9% to the final χ^2. The hydrogen atoms were included in calculated positions, which were recalculated during the refinement using Materials Studio (Dassault, 2016). A common U_{iso} was refined for the non-H atoms of the ring system,

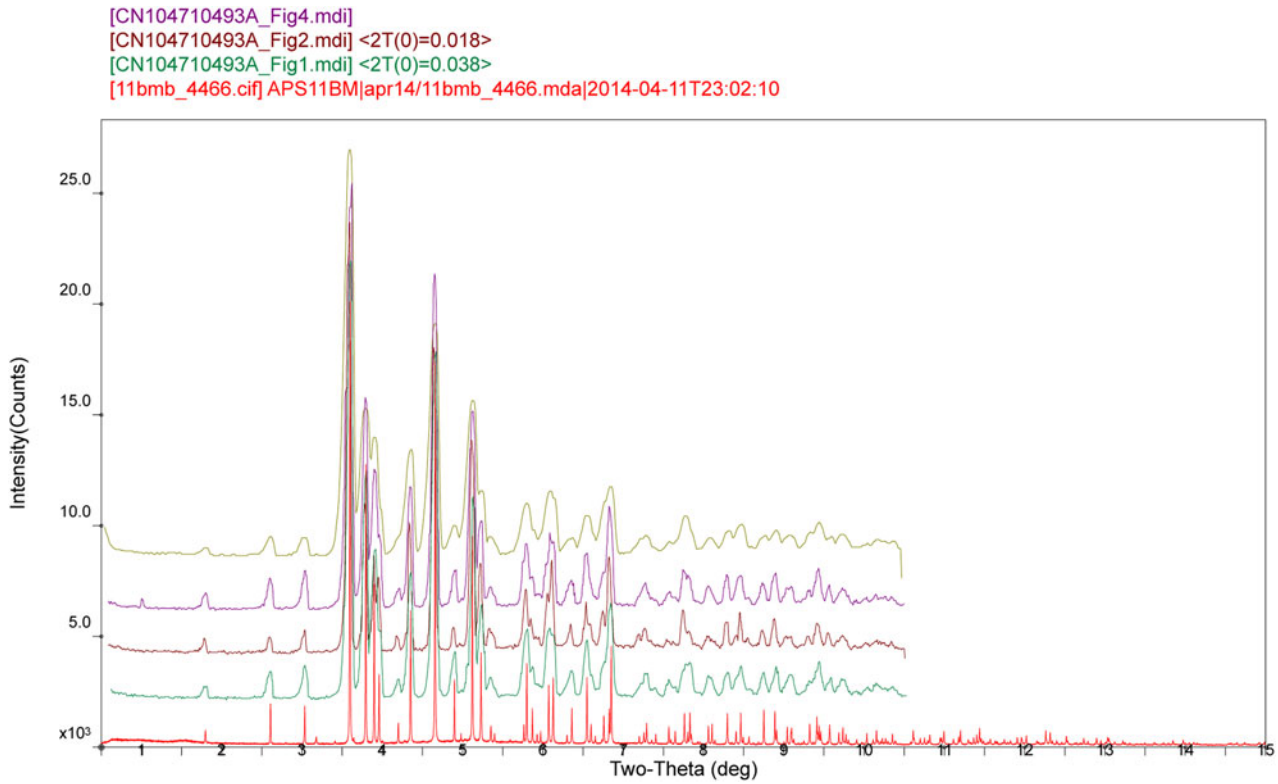

Figure 3. (Colour online) Comparison of (a) the synchrotron pattern of methylprednisolone acetate from this study to those of (b) USP reference methylprednisolone and (c) commercial Depo-Medrol® suspension injection and to two patterns of form II (d), (e). Plots 3b–e from Chinese Patent Application CN104710493A.

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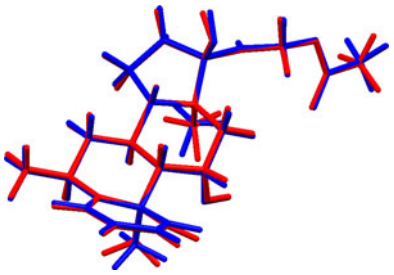

Figure 4. (Colour online) Comparison of the refined and optimized structures of methylprednisolone acetate. The Rietveld refined structure is in red, and the DFT-optimized structure is in blue.

another U_{iso} for the non-H substituent atoms, and a third U_{iso} for the acetate side chain. The U_{iso} for each hydrogen atom was constrained to be 1.3 × that of the heavy atom to which it is attached. 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 114 variables using 23 388 observations (23 303 data points and 85 restraints) yielded the residuals $Rwp = 0.0840$, $Rp = 0.0668$, and $\chi^2 = 1.497$. The largest peak (1.61 Å from C59) and hole (also 1.61 Å from C59) in the difference Fourier map were 0.61 and −0.61 eÅ^{-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, perhaps reflecting specimen decomposition.

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 using 8 *k*-points and the B3LYP functional, and took ∼12 days on a 2.8 GHz PC.

III. RESULTS AND DISCUSSION

The synchrotron powder pattern [Figure 3(a)] is similar enough to those of USP reference methylprednisolone acetate and commercial Depo-Medrol® suspension injection from Chinese Patent Application CN104710493A (He and Han, 2015) to conclude that they are the same material [Figure 3 (b–c), digitized using UN-SCAN-IT 7.0 (Silk Scientific, 2013)]. All three patterns are similar enough to the pattern of form II in the same patent application to conclude that they all represent form II. The same form has also been obtained by recrystallization from tetrahydrofuran, acetone, and methanol by Sacha *et al.* (2006) [Figure 3(d–e)].

The refined atom coordinates of methylprednisolone acetate and the coordinates from the DFT optimization are reported in the Crystallographic Information Frameworks (CIFs) attached as Supplementary Material. The root-mean-square deviation of the non-hydrogen atoms in the methylprednisolone acetate molecules is 0.091 Å (Figure 4). The largest deviation is 0.234 Å at the hydroxyl group O20. The excellent agreement between the refined and optimized structures is evidence that the experimental structure is correct (van de Streek and Neumann, 2014). The following discussion uses the DFT-optimized structure. The asymmetric unit (with atom numbering) is illustrated in Figure 5, and the crystal structure is presented in Figure 6.

All of the bond distances, bond angles, and torsion angles fall within the normal ranges indicated by a Mercury Mogul Geometry check (Macrae *et al.*, 2008). Quantum chemical geometry optimizations (DFT/6-31G*/water) using Spartan '16 (Wavefunction, 2017) indicated that the observed conformation of methylprednisolone acetate is within 1 kcal/mole of the local minimum energy conformation. Molecular

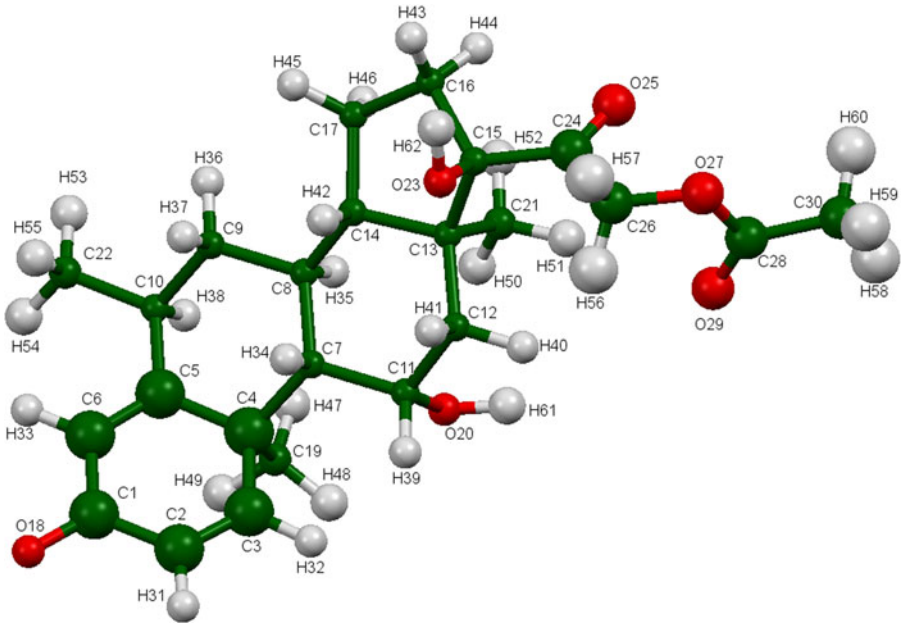

Figure 5. (Colour online) The asymmetric unit of methylprednisolone acetate, with the atom numbering. The atoms are represented by 50% probability spheroids.

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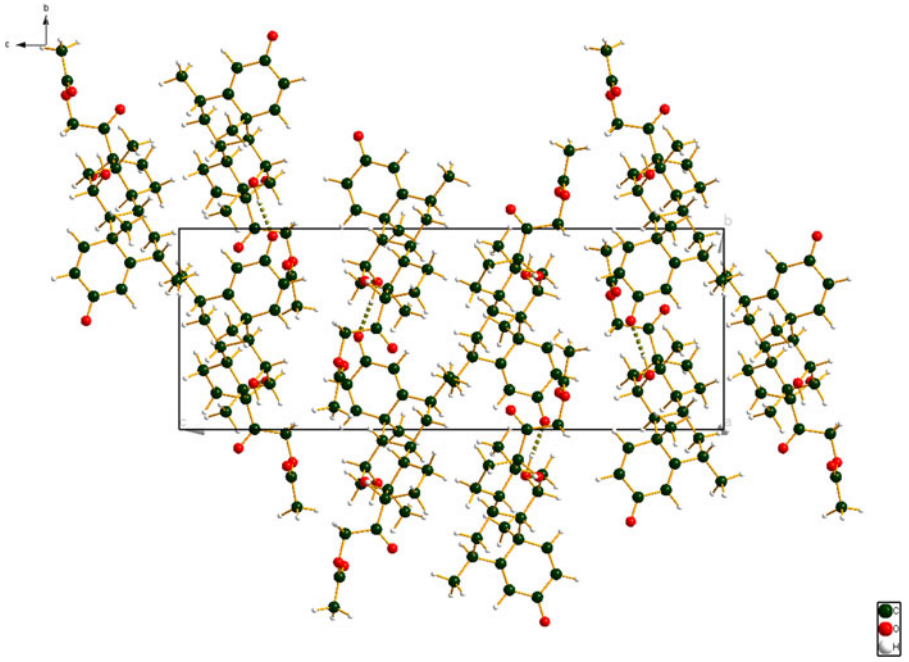

Figure 6. (Colour online) The crystal structure of methylprednisolone acetate, viewed down the *a*-axis.

mechanics conformational analysis indicated that the global minimum energy conformation has a different orientation of the acetate group. The conformational analysis showed that several different orientations of the acetate had energies within 1 kcal/mole of the minimum energy conformation. Since the acetate does not participate in hydrogen bonds, we cannot rule out other orientations in the crystal structure but see no evidence for them.

Analysis of the contributions to the total crystal energy using the Forcite module of Materials Studio (Dassault, 2016) suggests that angle, bond, and torsion distortion terms are significant in the intramolecular deformation energy, as might be expected from a fused ring system. The intermolecular energy contains significant contributions from electrostatic attractions, which in this force-field-based analysis including hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation.

The hydroxyl group O23-H62 donates a proton to the hydroxyl group O20, to form a chain with graph set (Etter, 1990; Bernstein *et al.*, 1995; Shields *et al.*, 2000) *C*1,1(7) along the *a*-axis (Table I). The hydroxyl group O20-H61 donates a proton to the carbonyl oxygen atom O18 to form a chain with graph set *C*1,1(9) along the *b*-axis. The result is a two-dimensional hydrogen bond network in the *ab* plane. Three C–H···O hydrogen bonds (one intramolecular) also contribute to the crystal energy.

The volume enclosed by the Hirshfeld surface (Figure 7; Hirshfeld, 1977; McKinnon *et al.*, 2004; Spackman and Jayatilaka, 2009; Wolff *et al.*, 2012) is 513.98 Å^3, 98.6% of 1/4 the unit-cell volume. The molecules are thus not tightly packed. Some of the significant close contacts (red in Figure 7) involve the hydrogen bonds, while others indicate other close contacts.

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect platy morphology for methylprednisolone acetate, with {002} as the principal faces. A second-order spherical harmonic preferred orientation model was included in the refinement; the texture index was 1.0004, indicating that preferred orientation was not significant in this rotated capillary specimen. The powder pattern of methylprednisolone acetate is included in the Powder Diffraction File as entry 00-065-1412.

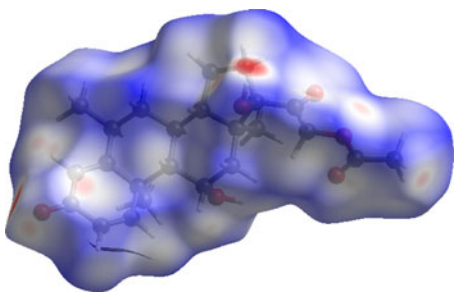

Figure 7. (Colour online) The Hirshfeld surface of methylprednisolone acetate. Intermolecular contacts longer than the sums of the van der Waals radii are colored blue, and contacts shorter than the sums of the radii are colored red. Contacts equal to the sums of radii are white.

TABLE I. Hydrogen bonds in methylprednisolone acetate.

H-Bond	D–H, Å	H···A, Å	D···A, Å	D–H···Å, degrees	Overlap, *e*
O23-H62···O20	0.978	1.999	2.975	175.5	0.055
O20-H61···O18	0.982	1.806	2.773	167.2	0.061
C30-H59···O18	1.092	2.431	3.408	148.1	0.016
C26-H57···O18	1.089	2.429	3.125	120.4	0.012
C19-H48···O23[a]	1.086	2.350	3.414	165.8	0.028

[a]Intramolecular.

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SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0885715617001233

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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