Crystal structure of imepitoin, C\textsubscript{13}H\textsubscript{14}ClN\textsubscript{3}O\textsubscript{2}

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The crystal structure of imepitoin has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Imepitoin crystallizes in space group P\textit{bca} (\#61) with \(a = 12.35541(2), b = 28.43308(8), c = 7.340917(7)\) \(\text{Å}\), \(V = 2578.882(7)\) \(\text{Å}^3\), and \(Z = 8\). The roughly planar molecules stack along the \(c\)-axis. There are no traditional hydrogen bonds in the structure, but several intramolecular and intermolecular C–H⋯O, C–H⋯N, and C–H⋯Cl hydrogen bonds contribute to the crystal energy. The powder pattern has been submitted to ICDD for inclusion in the Powder Diffraction File™ (PDF®).

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I. INTRODUCTION

Imepitoin (sold under the brand name Pexion®) is an anticonvulsant which is used in veterinary medicine to treat epilepsy and noise aversion in dogs. It is a centrally acting antiepileptic drug, which acts as a low affinity partial agonist of the benzodiazepine receptor. Imepition was originally developed for treatment of epilepsy in humans but was abandoned for human use when efficacy was found to be reduced in smokers. The systematic name (CAS Registry Number 188116-07-6) is 3-(4-chlorophenyl)-5-morpholin-4-yl-4H-imidazol-2-one. A two-dimensional molecular diagram is shown in Figure 1.

Imepitoin is the subject of US Patent 9,469,611 (Rundfeldt \textit{et al.}, 2016; Boehringer Ingelheim), but no X-ray powder diffraction data are provided. We are unaware of any published powder data for imepitoin.

This work was carried out as part of a project (Kaduk \textit{et al.}, 2014) to determine the crystal structures of large-volume commercial pharmaceuticals, and include high-quality powder diffraction data for them in the Powder Diffraction File (Gates-Rector and Blanton, 2019).

II. EXPERIMENTAL

Imepitoin was a commercial reagent, purchased from TargetMol (Batch #119530), and was used as-received. The white powder was packed into a 1.5 mm diameter Kapton capillary and rotated during the measurement at \(\sim 50\) Hz. The powder pattern was measured at 295 K at beamline 11-BM (Antao \textit{et al.}, 2008; Lee \textit{et al.}, 2008; Wang \textit{et al.}, 2008) of the Advanced Photon Source at Argonne National Laboratory using a wavelength of 0.458208(2) \(\text{Å}\) from 0.5 to 50° \(2\theta\) with a step size of 0.001° and a counting time of 0.1 s per step. The high-resolution powder diffraction data were collected using twelve silicon crystal analyzers that allow for high angular resolution, high precision, and accurate peak positions. A silicon (NIST SRM 640c) and alumina (SRM 676a) standard (ratio Al\textsubscript{2}O\textsubscript{3}:Si = 2:1 by weight) was used to calibrate the instrument and refine the monochromatic wavelength used in the experiment.

The pattern was indexed using JADE Pro 8.1 (MDI, 2021) and N-TREOR (Altomare \textit{et al.}, 2013) on a high-quality primitive orthorhombic unit cell with \(a = 12.35862, b = 28.44084, c = 7.34228\) \(\text{Å}\), \(V = 2580.74\) \(\text{Å}^3\), and \(Z = 8\). The suggested space group was P\textit{bca}, which was confirmed by successful solution and refinement of the structure. A reduced cell search in the Cambridge Structural Database (Groom \textit{et al.}, 2016)
combined with C, H, Cl, N, and O only, yielded five hits, but no structures of imepitoin derivatives.

The structure was solved by direct methods as implemented in EXP02014 (Altomare et al., 2013), using the COVMAP option on all trials. Some atom types had to be reassigned manually. The hydrogen atoms were added in positions calculated using Materials Studio (Dassault, 2021); the positions were re-calculated during the refinement.

Rietveld refinement was carried out using GSAS-II (Toby and Von Dreele, 2013). Only the 1.8–25.0° portion of the pattern was included in the refinement ($d_{\text{min}} = 1.058$ 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). The Mogul average and standard deviation for each quantity were used as the restraint parameters. The restraints contributed 3.3% to the final $\chi^2$. The hydrogen atoms were included in calculated positions, which were recalculated using Materials Studio (Dassault, 2021). The $U_{\text{iso}}$ were grouped by chemical similarity. The $U_{\text{iso}}$ for the H atoms were fixed at 1.3× the $U_{\text{iso}}$ of the heavy atoms to which they are attached. The peak profiles were described using the generalized microstrain model. The background was modeled using a 6-term shifted Chebyshev polynomial, plus a peak at 5.76° 2θ to model the scattering from the Kapton capillary and any amorphous component.

The final refinement of 82 variables using 23 237 observations and 50 restraints yielded the residuals $R_{\text{wp}} = 0.0704$ and GOF = 1.34. The largest peak (0.11 Å from Cl1) and hole (1.92 Å from C14) in the difference Fourier map were 0.33 (6) and −0.27(6) eÅ$^{-3}$, respectively. The largest errors in the difference plot (Figure 2) are in the shapes of some of the strong low-angle peaks.

The structure of imepitoin was optimized using VASP (Kresse and Furthmüller, 1996) (fixed experimental unit cell) through the MedeA graphical interface (Materials Design, 2016). The calculation was carried out on 16 2.4 GHz processors (each with 4 GB RAM) of a 64-processor HP Proliant DL580 Generation 7 Linux cluster at North Central College. The calculation used the GGA-PBE functional, a plane wave cutoff energy of 400.0 eV, and a k-point spacing of 0.5 Å$^{-1}$ leading to a 2 × 1 × 2 mesh, and took ~28 h. A single-point density functional calculation (fixed experimental cell) and population analysis were carried out using CRYSTAL17 (Dovesi et al., 2018). The basis sets for the H, C, N, and O atoms in the calculation were those of Gatti et al. (1994), and that for Cl was that of Peintinger et al. (2013). The calculations were run on a 3.5 GHz PC using 8 k-points and the B3LYP functional, and took ~2.2 h.

III. RESULTS AND DISCUSSION

The root-mean-square (rms) Cartesian displacement between the Rietveld-refined and DFT-optimized structures of imepitoin is 0.025 Å (Figure 3). The excellent agreement provides strong evidence that the structure is correct (van de Streek and Neumann, 2014). This discussion concentrates on the DFT-optimized structure. The asymmetric unit (with atom numbering) is illustrated in Figure 4. The best view of the crystal structure is down the c-axis (Figure 5). The roughly planar molecules stack along the c-axis.

All of the bond distances and angles fall within the normal ranges indicated by a Mercury/Mogul Geometry check.
Quantum chemical geometry optimization of the imepitoin molecule (DFT/B3LYP/6-31G*/water) using Spartan ’18 (Wavefunction, 2020) indicated that the observed conformation is within 1.2 kcal mol$^{-1}$ of the global minimum-energy conformation.

Analysis of the contributions to the total crystal energy of the structure using the Forcite module of Materials Studio (Dassault, 2021) suggests that the intramolecular deformation energy is dominated by angle deformation terms. The intermolecular energy is dominated by electrostatic attractions, which in this force field analysis also include hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation. There are no traditional hydrogen bonds in the structure (Table I), but several intramolecular and intermolecular C–H⋯O, C–H⋯N, and C–H⋯Cl hydrogen bonds contribute to the crystal energy.

The volume enclosed by the Hirshfeld surface of the imepitoin molecule (Figure 6; Hirshfeld, 1977; Turner et al., 2020).
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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

Altomare, A., Cuoci, C., Giacovazzo, C., Moliterni, A., Rizzi, R., Corriero, N., and Falcicchio, A. (2013). “EXPO2013: a kit of tools for phasing crystal structures from powder data,” J. Appl. Crystallogr. 46, 1231–1235.

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The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect platy morphology for imepitoin, with [010] as the major faces. A second-order spherical harmonic model was included in the refinement. The texture index was 1.002(0), indicating that preferred orientation was slight in this rotated capillary specimen. The powder pattern of imepitoin from this synchrotron dataset has been submitted to ICDD for inclusion in the Powder Diffraction File.

IV. DEPOSITED DATA

The Crystallographic Information Framework (CIF) files containing the results of the Rietveld refinement (including the raw data) and the DFT geometry optimization were deposited with the ICDD. The data can be requested at pdj@icdd.com.

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