Crystal structure of atomoxetine hydrochloride (Strattera), $C_{17}H_{22}NOCl$

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Commercial atomoxetine hydrochloride crystallizes in the orthorhombic space group $P2_12_12_1$ (#19), with $a = 7.362\,554(12)$, $b = 13.340\,168(27)$, $c = 16.701\,887(33)$ Å, $V = 1640.421(5)$ Å^3, and $Z = 4$. The structure was solved and refined using synchrotron powder diffraction data, and Rietveld and density functional techniques. The most prominent feature of the structure is zigzag chains of N–H···Cl hydrogen bonds along the *a*-axis. The powder pattern has been submitted to the ICDD for inclusion in future releases of the Powder Diffraction File™. © *2014 International Centre for Diffraction Data.*
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Key words: atomoxetine, hydrochloride, powder diffraction, Rietveld, density functional

I. INTRODUCTION

Atomoxetine is a drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD) in children age 6 and older, adolescents, and adults. It is marketed under the trade name Strattera by Eli Lilly and Company and is described as a norepinephrine re-uptake inhibitor. In 2011, it was among the top 200 s sold in the USA by total dollar value. The chemical formula for atomoxetine hydrochloride is $C_{17}H_{21}NO{\bullet}HCl$ and the IUPAC name for this molecule is (3*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenyl-1-propanamine hydrochloride (1:1). A two-dimensional structural diagram is shown in Figure 1.

CSD entries YIGNEI and YIGNEI01 (Stephenson and Liang, 2006) correspond to orthorhombic and monoclinic polymorphs of atomoxetine hydrochloride, but neither contains atom coordinates. The coordinates of the non-hydrogen atoms in the orthorhombic polymorph are reported in European Patent 1,798,215 (Malpezzi *et al.*, 2007).

The presence of high-quality reference powder patterns in the Powder Diffraction File (PDF) (ICDD, 2013) is important for phase identification, particularly by pharmaceutical, forensic, and law enforcement scientists. The crystal structures of a significant fraction of the largest dollar volume pharmaceuticals have not been published, and thus calculated powder patterns are not present in the PDF-4 Organics database. Sometimes experimental patterns are reported, but they are generally of low quality. Accordingly, a collaboration among the ICDD, IIT, Poly Crystallography Inc., and Argonne National Laboratory has been established to measure high-quality synchrotron powder patterns of commercial pharmaceutical ingredients, include these reference patterns in the PDF, and determine the crystal structures of these Active Pharmaceutical Ingredients (APIs).

Even when the crystal structure of an API is reported, the single-crystal structure was often determined at low temperature. Most powder measurements are performed at ambient conditions. Thermal expansion (often anisotropic) means that the peak positions calculated from a low-temperature single-crystal structure often differ from those measured at ambient conditions. These peak shifts can result in failure of normal search/match algorithms to identify a phase, even when it is present in the sample. High-quality reference patterns measured at ambient conditions are thus critical for easy identification of APIs using standard powder diffraction practices.

II. EXPERIMENTAL

The atomoxetine hydrochloride 99% was commercial material, purchased from AK Scientific, Inc. (Lot #LC24205), and was used as-received. The white powder was packed into a 1.5 mm diameter Kapton capillary, and rotated during the experiment at ~50 rotations per second. The powder pattern was measured at the beamline 11-BM (Lee *et al.*, 2007; Wang *et al.*, 2008; Ribaud *et al.*, 2008) of the Advanced Photon Source at the Argonne National Laboratory using a wavelength of 0.413 891 Å at 296 K from 0.5 to 50° 2θ with a step size of 0.001° and a counting time of 0.1 s per step. The pattern was indexed using Jade 9.5 (MDI, 2012). The

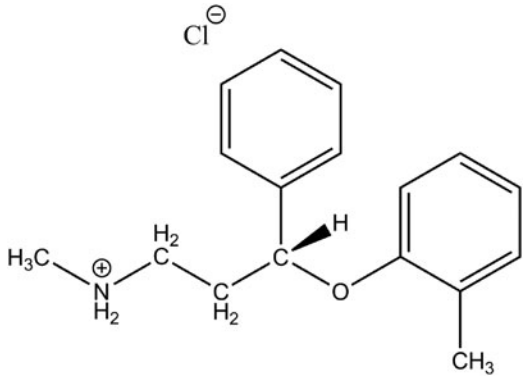

Figure 1. Molecular structure of atomoxetine hydrochloride.

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systematic absences determined the space group to be $P2_12_12_1$ (#19) (a common space group for chiral organic compounds), which was confirmed by successful solution and refinement of the structure. A protonated atomoxetine cation was built, and its conformation optimized, using Spartan '10 (Wavefunction, 2011). It was saved as a mol2 file, and converted into a Fenske-Hall *Z*-matrix using OpenBabel (O'Boyle *et al.*, 2011). The structure was solved with FOX (Favre-Nicolin and Černý, 2002) using an atomoxetine cation and a chlorine atom as fragments.

The Rietveld refinement was carried out using GSAS (Larson and Von Dreele, 2004). Only the 2–25° portion of the pattern was included in the refinement. The phenyl groups were refined as rigid bodies, and 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 0.19% to the final χ^2. Isotropic displacement coefficients were refined, grouped by chemical similarity. The U_{iso} of 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, which includes the Stephens (1999) anisotropic strain broadening model. The background was modeled using a two-term shifted Chebyshev polynomial, and a six-term diffuse scattering function to describe the scattering from the Kapton capillary and any amorphous content of the sample. The final refinement of 54 variables using 22 999 observations yielded the residuals $wRp = 0.1040$, $Rp = 0.0892$, and $\chi^2 = 2.745$. The largest peak and hole in the difference Fourier map were 0.57 and $-0.59\ e\text{Å}^{-3}$, respectively. The largest peak lies in one of the C–C bonds of a phenyl ring, and the largest holes lie between pairs of hydrogen but not close to either of them. The Rietveld plot is included as Figure 2. The largest errors are in the positions and shapes of low-angle peaks, and probably indicate non-uniformity in the crystallites.

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, N, and O atoms were those of Gatti *et al.* (1994). The basis set for Cl was that of (Apra *et al.*, 1993). The calculation used eight *k*-points and the B3LYP functional.

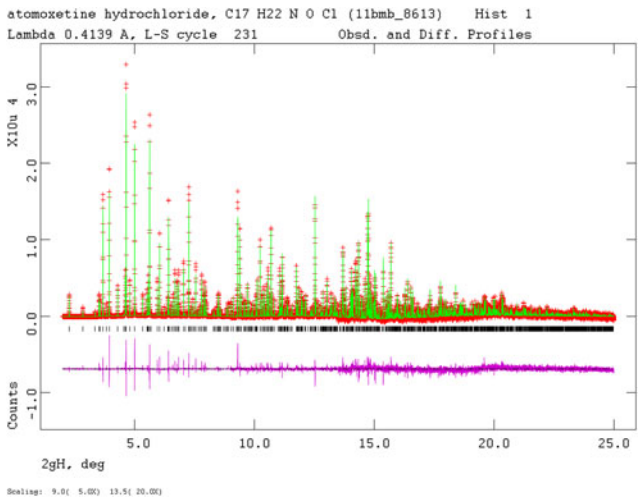

Figure 2. (Color online) Observed, calculated, and difference patterns of atomoxetine hydrochloride. The red crosses represent the observed data points, the green solid line the calculated pattern, and the magenta line the difference (observed – calculated) pattern. The vertical scale is multiplied by a factor of 5 above 9° 2θ and by a factor of 20 above 13.5°.

III. RESULTS AND DISCUSSION

The refined atom coordinates of orthorhombic atomoxetine hydrochloride are reported in Table I, and the coordinates from the density functional theory (DFT) optimization in Table II. The root-mean-square (rms) deviation of the non-hydrogen atoms is 0.07 Å, and the maximum deviation is 0.14 Å (Figure 3). The rms deviation of the non-hydrogen atoms in the DFT structure and that reported in Malpezzi *et al.* (2007) is 0.06 Å, and the maximum deviation is 0.12 Å. The discussion of the geometry uses the optimized structure. The asymmetric unit (with atom numbering) is illustrated in Figure 4, and the crystal structure is presented in Figure 5.

TABLE I. Rietveld refined structure of orthorhombic atomoxetine hydrochloride. Space group $P2_12_12_1$ (#19), with $a = 7.362\ 554(12)$, $b = 13.340\ 168(27)$, $c = 16.701\ 887(33)$ Å, $V = 1640.421(5)$ Å^3, and $Z = 4$.

Name	*X*	*Y*	*Z*	U_i/U_e*100
C1	0.669 57(80)	0.090 20(40)	0.079 81(35)	5.24(7)
H2	0.805 82	0.068 69	0.056 04	6.82(10)
H3	0.614 12	0.017 18	0.106 28	6.82(10)
C4	0.679 48(73)	0.175 42(45)	0.136 99(33)	5.24(7)
H5	0.539 11	0.189 59	0.159 31	6.82(10)
H6	0.735 52	0.237 37	0.111 31	6.82(10)
C7	0.793 10(64)	0.155 05(35)	0.212 37(32)	5.24(7)
H8	0.931 04	0.130 93	0.194 43	6.82(10)
N9	0.5486(6)	0.118 73(34)	0.012 72(29)	5.24(7)
C10	0.509 24(72)	0.034 78(42)	−0.043 97(37)	5.24(7)
H11	0.645 30	0.002 40	−0.070 14	6.82(10)
H12	0.450 73	−0.031 93	−0.012 99	6.82(10)
H13	0.429 17	0.054 90	−0.093 63	6.82(10)
O14	0.7927(4)	0.248 09(28)	0.256 07(22)	5.24(7)
C15	0.720 91(54)	0.067 58(29)	0.261 35(24)	6.35(7)
C16	0.579 67(54)	0.087 92(21)	0.314 31(28)	9.71(14)
C17	0.507 17(35)	0.011 37(36)	0.361 07(20)	6.35(7)
C18	0.575 92(50)	−0.085 52(28)	0.354 87(20)	6.35(7)
C19	0.717 17(51)	−0.105 86(22)	0.301 91(24)	6.35(7)
C20	0.789 66(36)	−0.029 31(38)	0.255 15(18)	6.35(7)
H21	0.5323(8)	0.154 74(25)	0.318 59(42)	8.26(9)
H22	0.4098(5)	0.025 40(56)	0.397 59(27)	8.26(9)
H23	0.5259(8)	−0.138 30(41)	0.387 11(29)	8.26(9)
H24	0.7646(8)	−0.172 67(27)	0.297 63(37)	8.26(9)
H25	0.8871(5)	−0.043 34(58)	0.218 62(25)	8.26(9)
C26	0.906 31(48)	0.261 63(34)	0.318 86(17)	6.35(7)
C27	0.868 72(40)	0.347 39(28)	0.363 35(25)	6.35(7)
C28	0.973 70(54)	0.370 57(21)	0.430 14(23)	6.35(7)
C29	1.116 26(47)	0.307 99(31)	0.452 46(17)	6.35(7)
C30	1.153 84(39)	0.222 22(26)	0.407 97(24)	6.35(7)
C31	1.048 87(54)	0.199 05(23)	0.341 17(22)	6.35(7)
H32	0.9478(8)	0.429 71(26)	0.460 82(33)	8.26(9)
H33	1.1886(7)	0.323 97(47)	0.498 51(23)	8.26(9)
H34	1.2522(5)	0.179 07(39)	0.423 36(37)	8.26(9)
H35	1.0748(8)	0.139 90(29)	0.310 49(32)	8.26(9)
C36	0.717 36(73)	0.417 62(43)	0.340 60(37)	8.09(27)
H37	0.582 54	0.370 95	0.367 85	8.00
H38	0.694 25	0.418 39	0.283 37	8.00
H39	0.722 50	0.479 23	0.377 27	8.00
H40	0.604 98	0.175 11	−0.018 42	6.83
H41	0.424 41	0.136 81	0.032 71	6.83
Cl42	0.342 24(21)	0.825 56(13)	0.561 15(10)	5.94(6)

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TABLE II. Density functional optimized structure of atomoxetine hydrochloride. Space group $P2_12_12_1$ (#19), with $a = 7.362\,554$, $b = 13.340\,168$, $c = 16.701\,887$ Å, $V = 1640.421$ Å^3, and $Z = 4$.

Atom	Type	X	y	z	U_{iso}
C1	C	0.670 90	0.085 42	0.079 82	0.052 40
H2	H	0.805 82	0.068 69	0.056 04	0.068 20
H3	H	0.614 12	0.017 18	0.106 28	0.068 20
C4	C	0.677 10	0.171 02	0.139 85	0.052 40
H5	H	0.539 11	0.189 59	0.159 31	0.068 20
H6	H	0.735 52	0.237 37	0.111 31	0.068 20
C7	C	0.792 24	0.147 62	0.214 03	0.052 40
H8	H	0.931 04	0.130 93	0.194 43	0.068 20
N9	N	0.550 68	0.112 77	0.010 88	0.052 40
C10	C	0.517 11	0.028 67	−0.045 52	0.052 40
H11	H	0.645 30	0.002 40	−0.070 14	0.068 20
H12	H	0.450 73	−0.031 93	−0.012 99	0.068 20
H13	H	0.429 17	0.054 90	−0.093 63	0.068 20
O14	O	0.789 63	0.240 03	0.258 27	0.052 40
C15	C	0.716 50	0.061 94	0.263 76	0.063 50
C16	C	0.572 57	0.079 13	0.316 90	0.063 50
C17	C	0.503 40	0.000 67	0.362 92	0.063 50
C18	C	0.576 19	−0.095 71	0.356 22	0.063 50
C19	C	0.716 72	−0.113 78	0.302 02	0.063 50
C20	C	0.786 82	−0.035 05	0.256 29	0.063 50
H21	H	0.517 18	0.154 20	0.322 47	0.082 60
H23	H	0.526 05	−0.154 97	0.394 59	0.082 60
H22	H	0.394 67	0.014 49	0.405 42	0.082 60
H24	H	0.775 84	−0.188 08	0.297 58	0.082 60
H25	H	0.897 10	−0.049 61	0.214 66	0.082 60
C26	C	0.906 77	0.255 02	0.320 67	0.063 50
C27	C	0.870 18	0.341 10	0.367 14	0.063 50
C28	C	0.985 89	0.363 00	0.431 11	0.063 50
C29	C	1.133 52	0.301 57	0.450 19	0.063 50
C30	C	1.167 35	0.217 18	0.403 48	0.063 50
C31	C	1.055 10	0.193 39	0.338 62	0.063 50
H32	H	0.959 20	0.429 94	0.466 18	0.082 60
H33	H	1.221 27	0.318 88	0.500 55	0.082 60
H34	H	1.281 57	0.169 06	0.417 59	0.082 60
H35	H	1.084 67	0.128 10	0.302 38	0.082 60
C36	C	0.709 18	0.406 43	0.347 76	0.080 90
H37	H	0.582 54	0.370 95	0.367 85	0.080 00
H38	H	0.694 25	0.418 39	0.283 37	0.080 00
H39	H	0.722 50	0.479 23	0.377 27	0.080 00
H40	H	0.604 98	0.175 11	−0.018 42	0.068 30
H41	H	0.424 41	0.136 81	0.032 71	0.068 30
Cl42	Cl	0.345 65	0.828 59	0.559 91	0.059 40

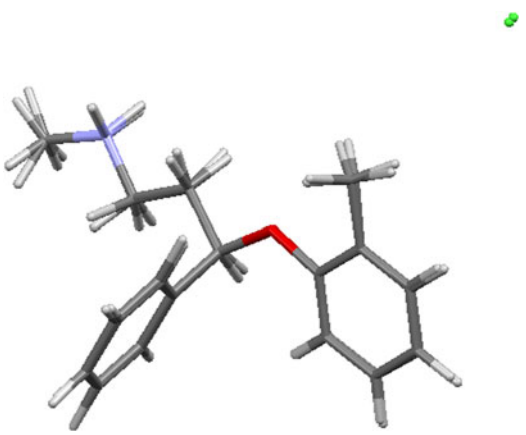

Figure 3. (Color online) Comparison of the Rietveld-refined and DFT-optimized structures of atomoxetine hydrochloride. The RMS difference between the non-hydrogen atom positions is 0.07 Å.

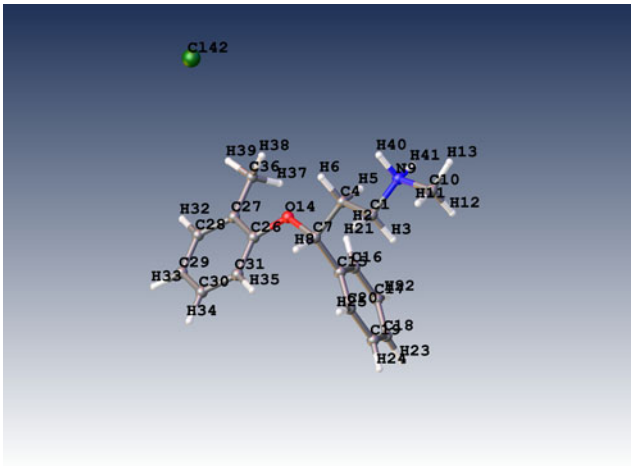

Figure 4. (Color online) The asymmetric unit of atomoxetine hydrochloride, with the atom numbering.

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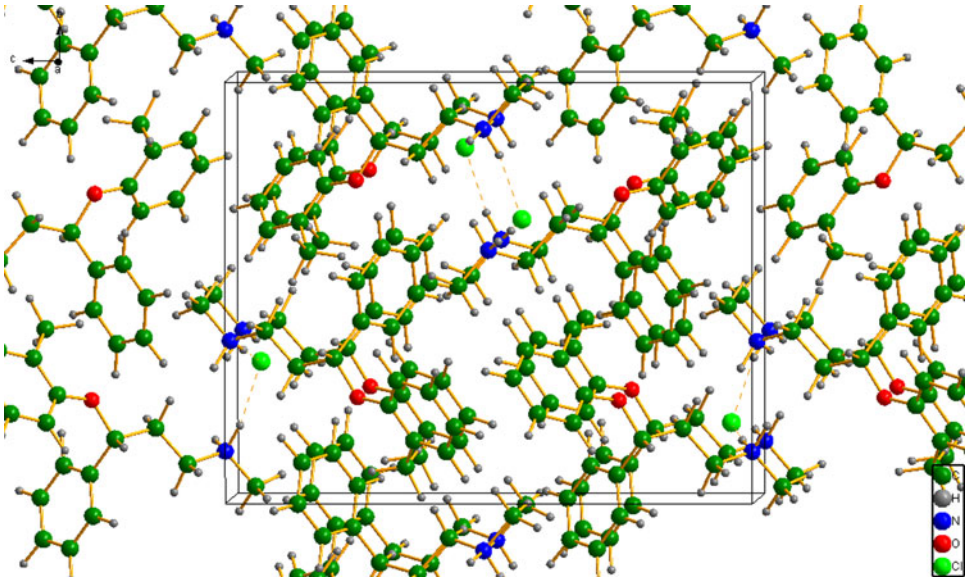

Figure 5. (Color online) Crystal structure of atomoxetine hydrochloride. The view is approximately down the *a*-axis.

TABLE III. Hydrogen bonds in orthorhombic atomoxetine hydrochloride.

D–H···*A*	*D*–H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*–H···*A* (?)	Overlap (*e*)
N9–H40···Cl42	1.044	2.192	3.205	162.8	0.065
N9–H41···Cl42	1.049	2.091	3.130	170.3	0.087

All bond distances, angles, and torsion angles fall within the normal ranges indicated by a Mercury Geometry Check. There are no voids in the crystal structure. The most prominent features of the crystal structure are the N–H···Cl hydrogen bonds (Table III). They form a zigzag chain parallel to the *a*-axis. The graph set (Etter, 1990; Bernstein *et al.*, 1995; Motherwell *et al.*, 2000) is $C1,2(4) > a < b$. The symbol means that the pattern is a four-atom chain containing one acceptor and two donors; traversing the chain, one hydrogen bond is encountered donor-to-acceptor and the other is acceptor-to-donor. The Mulliken overlap populations indicate that these hydrogen bonds are normal strength. The average N···Cl in such hydrogen bonds in the CSD is 3.15(33) Å, so these hydrogen bonds are geometrically typical. The Mulliken overlap populations indicate that none of the other potential short intermolecular contacts (such as C–H···Cl) represent real bonding interactions. Other than the hydrogen bonds, the crystal structure is dominated by van der Waals contacts.

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) crystal morphology is not especially anisotropic. There might be a slight tendency to form needles with ⟨100⟩ as the long axis, or plates with {01-1} as the principal faces. We would not expect preferred orientation to be significant for this compound.

The powder pattern of atomoxetine hydrochloride has been submitted to the ICDD for inclusion in future releases of the PDF.

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