TECHNICAL ARTICLE

Crystal structure of levalbuterol hydrochloride polymorph A (Xopenex), $C_{13}H_{22}NO_3Cl$

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(Received 29 December 2014; accepted 18 February 2015)

The crystal structure of levalbuterol hydrochloride polymorph A has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Levalbuterol hydrochloride polymorph A crystallizes in space group $P2_1$ (#4) with a = 8.499 352(15), b = 6.511 726(13), c = 13.182 256(25) Å, β = 102.1157(2)°, V = 713.327(2) Å^3, and Z = 2. The most prominent feature of the structure is the two different sorts of hydrogen bonds. Both of the ammonium hydrogens and O17–H40 act as donors to Cl18. The graph sets are C1,2(4) and C1,2(7). The result is a zig-zag chain parallel to the b-axis. The two hydroxy groups at the phenyl end of the molecule form another set of chains, both with graph set C1,1(6), also resulting in a chain parallel to the b-axis. The bulk of the molecule connects these chains in the (101) plane to form a three-dimensional network. The powder pattern is included in the Powder Diffraction File™ as entry 00-064-1494. © *2015 International Centre for Diffraction Data.*
[doi:10.1017/S0885715615000172]

Key words: levalbuterol, Xopenex, powder diffraction, Rietveld, density functional theory

I. INTRODUCTION

Levalbuterol, as a β_2-adrenergic receptor on airway smooth muscle, is used for the treatment of asthma and chronic obstructive pulmonary disease (Jat and Khairwa, 2013). The systematic name (CAS registry number 50293-90-8) is (*R*)-α^1-{[(1,1-dimethylethyl)amino]methyl}-4-hydroxy-1,3-benzenedimethanol hydrochloride. A two-dimensional (2D) molecular structure diagram is shown in Figure 1.

The presence of high-quality reference powder patterns in the Powder Diffraction File (PDF; ICDD, 2014) 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 databases. Sometimes experimental patterns are reported, but they are generally of low quality. Accordingly, a collaboration among ICDD, Illinois Institute of Technology (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 significantly from those measured at ambient conditions. These peak shifts can result in failure of default 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

Levalbuterol hydrochloride was commercial reagent, purchased from United States Pharmacopeia (USP) (Lot FOG162), 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

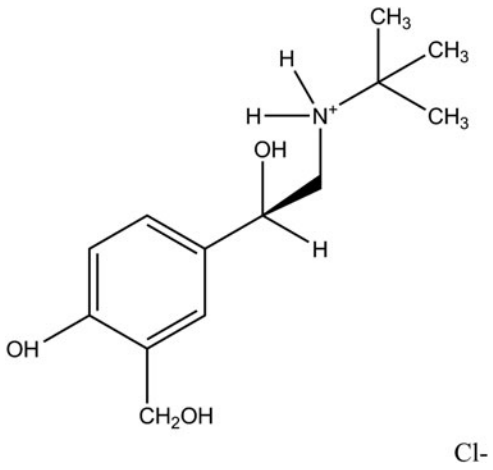


Figure 1. The molecular structure of levalbuterol hydrochloride.

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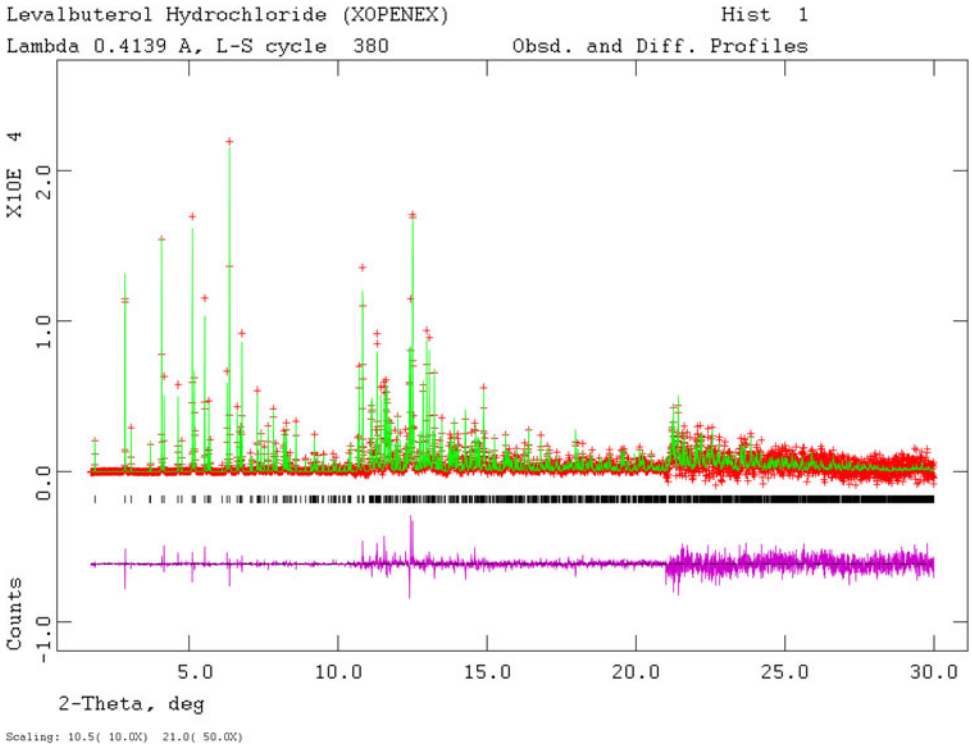


Figure 2. (Colour online) The Rietveld plot for the refinement of levalbuterol hydrochloride polymorph A. The red crosses represent the observed data points, and the green line is the calculated pattern. The magenta curve is the difference pattern, plotted at the same vertical scales as the other patterns. The vertical scale has been multiplied by a factor of 10 for $2\theta > 10.5°$, and by a factor of 50 for $2\theta > 21.0°$.

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 the Argonne National Laboratory using a wavelength of 0.413 914 Å from 0.5° to 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 $a = 8.4982$, $b = 6.5092$, $c = 13.1788$ Å, $\beta = 102.107°$, $V = 712.80$ Å^3, and $Z = 2$ using DICVOL06 (Louër and Boultif, 2007). A search of this cell in the Cambridge Structural Database (Allen, 2002) yielded 42 hits, but no crystal structure for levalbuterol hydrochloride. Analysis of the systematic absences using EXPO2009 (Altomare *et al.*, 2009) indicated the space group to be $P2_1$ (a common space group for chiral organic compounds), which was confirmed by successful solution and refinement of the structure.

A levalbuterol cation was built and its conformation optimized using Spartan′14 (Wavefunction, 2013), and saved as a mol2 file. This file was converted into a Fenske–Hall *Z*-matrix file using OpenBabel (O'Boyle *et al.*, 2011). This molecule and a chlorine atom were used to solve the structure with FOX (Favre-Nicolin and Černý, 2002). The maximum $\sin\theta/\lambda$ used in the solution was 0.26 Å^{-1}.

Rietveld refinement was carried out using GSAS (Larson and Von Dreele, 2004). Only the 1.7–30° 2θ portion of the pattern was included in the refinement. 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 C1–C6 aromatic ring was subjected to a planar restraint with a standard deviation of 0.01 Å. The restraints contributed 0.5% to the final χ^2. Isotropic displacement coefficients were refined, grouped by chemical similarity. The hydrogen atoms were included in calculated positions, which were recalculated during the refinement. 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 12-term shifted Chebyshev polynomial. The final refinement of 84 variables using 28 343 observations yielded the residuals $wRp = 0.0806$, $Rp = 0.0665$, and $\chi^2 = 1.969$. The largest peak (0.20 Å from N9) and hole (0.187 Å from O17) in the difference Fourier map were 0.52 and −0.57 e(Å^{-3}), respectively. The Rietveld plot is included as Figure 2. The largest errors are in the shapes and positions of the lowest-angle peaks, and may reflect subtle changes in the specimen during the measurement.

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), and the basis set for Cl was that of Apra *et al.* (1993). The calculation used 8 *k*-points and the B3LYP functional.

III. RESULTS AND DISCUSSION

The observed powder pattern corresponds to the pattern of levalbuterol hydrochloride Polymorph A reported in U.S. Patent 7,465,831 (Merli *et al.*, 2008). The pattern of Polymorph B is reported in U.S. Patent 7,488,758 (Merli *et al.*, 2009). The refined atom coordinates of levalbuterol hydrochloride polymorph A are reported in Table I, and the coordinates from the density functional theory (DFT) optimization in Table II. The root-mean-square deviation of the non-hydrogen atoms is 0.13 Å, and the maximum deviation is

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TABLE I. Rietveld refined fractional atomic coordinates and isotropic displacement parameters (Å^2) of levalbuterol hydrochloride polymorph A. Space group $P2_1$, a = 8.499 352(15), b = 6.511 726(13), c = 13.182 256 (25) Å, β = 102.1157(2)°, V = 713.327(2) Å^3, and Z = 2.

	x	y	z	U_{iso}
C1	0.6304 (5)	0.5920 (7)	0.2044 (3)	0.0365 (6)
C2	0.6479 (4)	0.6989 (8)	0.1158 (3)	0.0365 (6)
C3	0.7074 (5)	0.6055 (8)	0.0359 (3)	0.0365 (6)
C4	0.7539 (5)	0.4022 (8)	0.0517 (3)	0.0365 (6)
C5	0.7349 (5)	0.2899 (7)	0.1388 (3)	0.0365 (6)
C6	0.6688 (5)	0.3840 (7)	0.2145 (3)	0.0365 (6)
C7	0.5651 (5)	0.6883 (8)	0.2911 (3)	0.0474 (7)
C8	0.3857 (5)	0.6845 (9)	0.2692 (3)	0.0474 (7)
N9	0.3207 (4)	0.7400 (6)	0.3634 (2)	0.0474 (7)
C10	0.1458 (5)	0.7365 (9)	0.3572 (3)	0.0474 (7)
C11	0.0646 (5)	0.8936 (7)	0.2805 (3)	0.0382 (9)
C12	0.1137 (4)	0.7895 (7)	0.4657 (3)	0.0382 (9)
C13	0.0773 (5)	0.5215 (8)	0.3239 (3)	0.0382 (9)
C14	0.7227 (5)	0.7284 (9)	−0.0570 (3)	0.0579 (8)
O15	0.8374 (3)	0.8962 (5)	−0.0255 (3)	0.0579 (8)
O16	0.8162 (3)	0.3087 (5)	−0.0252 (2)	0.0579 (8)
O17	0.6272 (3)	0.9000 (5)	0.2975 (2)	0.0474 (7)
Cl18	0.563 55 (15)	0.700 11	0.584 22 (9)	0.0457 (5)
H19	0.6155	0.867 73	0.097 19	0.0474 (8)
H20	0.765 12	0.134 87	0.1411	0.0474 (8)
H21	0.648 51	0.310 68	0.273 28	0.0474 (8)
H22	0.624 75	0.652 67	0.355 64	0.0616 (9)
H23	0.314 31	0.748 39	0.198 75	0.0616 (9)
H24	0.360 69	0.507 54	0.262 82	0.0616 (9)
H25	0.384	0.671 51	0.425 94	0.0616 (9)
H26	0.351 07	0.9	0.375 13	0.0616 (9)
H27	0.103 85	1.049 59	0.307 29	0.0496 (12)
H28	−0.074 27	0.900 09	0.287 56	0.0496 (12)
H29	0.059 98	0.869 77	0.203 38	0.0496 (12)
H30	0.176 88	0.914 94	0.498 32	0.0496 (12)
H31	−0.008	0.778 51	0.469 91	0.0496 (12)
H32	0.173 93	0.647 05	0.521 01	0.0496 (12)
H33	0.152 47	0.397 47	0.365 29	0.0496 (12)
H34	0.076 55	0.493 03	0.238 22	0.0496 (12)
H35	−0.0454	0.500 58	0.330 77	0.0496 (12)
H36	0.958 09	0.856 58	−0.003 31	0.0753 (10)
H37	0.628 07	0.800 79	−0.101 98	0.0753 (10)
H38	0.789 02	0.638 18	−0.115 71	0.0753 (10)
H39	0.822 36	0.1559	−0.0241	0.0753 (10)
H40	0.564 74	1.001 54	0.330 27	0.0616 (9)

TABLE II. DFT (CRTYSTAL09) optimized fractional atomic coordinates and isotropic displacement parameters (Å^2) of levalbuterol hydrochloride polymorph A. Space group $P2_1$, a = 8.499 352(15), b = 6.511 726(13), c = 13.182 256(25) Å, β = 102.1157(2)°, V = 713.327(2) Å^3, and Z = 2.

	x	y	z	U_{iso}
C1	0.626 29	0.603 95	0.195 55	0.0365
C2	0.648 58	0.707 15	0.106 94	0.0365
C3	0.715 38	0.610 94	0.030 77	0.0365
C4	0.758 18	0.402 97	0.044 06	0.0365
C5	0.732 00	0.295 42	0.130 93	0.0365
C6	0.666 85	0.395 48	0.205 89	0.0365
C7	0.562 91	0.714 89	0.280 20	0.0474
C8	0.381 62	0.672 52	0.268 16	0.0474
N9	0.320 31	0.746 03	0.360 49	0.0474
C10	0.138 95	0.730 71	0.356 97	0.0474
C11	0.053 17	0.898 27	0.284 06	0.0382
C12	0.119 98	0.770 13	0.468 58	0.0382
C13	0.078 19	0.516 79	0.320 56	0.0382
C14	0.741 87	0.734 74	−0.061 20	0.0579
O15	0.848 31	0.906 62	−0.030 89	0.0579
O16	0.828 83	0.308 38	−0.028 70	0.0579
O17	0.597 10	0.927 27	0.273 56	0.0474
Cl18	0.565 38	0.706 00	0.581 71	0.0457
H19	0.615 50	0.867 73	0.097 19	0.0474
H20	0.765 12	0.134 87	0.141 10	0.0474
H21	0.648 51	0.310 68	0.273 28	0.0474
H22	0.624 75	0.652 67	0.355 64	0.0616
H23	0.314 31	0.748 39	0.198 75	0.0616
H24	0.360 69	0.507 54	0.262 82	0.0616
H25	0.384 00	0.671 51	0.425 94	0.0616
H26	0.351 07	0.900 00	0.375 13	0.0616
H27	0.103 85	1.049 59	0.307 29	0.0496
H28	−0.074 27	0.900 09	0.287 56	0.0496
H29	0.059 98	0.869 77	0.203 37	0.0496
H30	0.176 88	0.914 94	0.498 32	0.0496
H31	−0.008 00	0.778 51	0.469 91	0.0496
H32	0.173 93	0.647 05	0.521 01	0.0496
H33	0.152 47	0.397 47	0.365 29	0.0496
H34	0.076 55	0.493 03	0.238 22	0.0496
H35	−0.045 40	0.500 58	0.330 77	0.0496
H36	0.958 09	0.856 58	−0.003 31	0.0753
H37	0.628 07	0.800 79	−0.101 98	0.0753
H38	0.789 02	0.638 18	−0.115 71	0.0753
H39	0.822 36	0.155 90	−0.024 10	0.0753
H40	0.564 74	1.001 54	0.330 27	0.0616

0.30 Å, at O17 (Figure 3). The discussion of the geometry 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 bond distances and angles fall within the normal ranges indicated by a Mercury Geometry Check. The O15–C14–C3–C2 and O15–C14–C3–C4 torsion angles, which describe the relation of the hydroxymethyl and phenyl groups, are flagged as unusual. The position of the C15–C14–C3–C2 torsion in the distribution is illustrated in Figure 6. A conformational energy analysis in Spartan suggests that the cation conformation in the crystal structure is higher in energy than the minimum energy conformation. Presumably the cation has distorted to accommodate the hydrogen bonding.

An analysis of the contributions to the total crystal energy using the Forcite module of Materials Studio (Accelrys, 2013) suggests that the bond, angle, and torsion angle distortion contributions are small. The energy appears to be dominated by electrostatic contributions, which in this force-field-based analysis include hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation.

The most prominent feature of the structure is the two different types of hydrogen bonds (Table III). Both of the

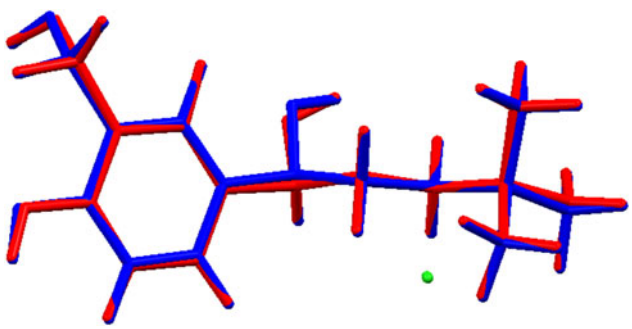


Figure 3. (Colour online) Comparison of the refined and optimized structures of levalbuterol hydrochloride polymorph A. The Refined structure is colored red, and the DFT-optimized structure is in blue.

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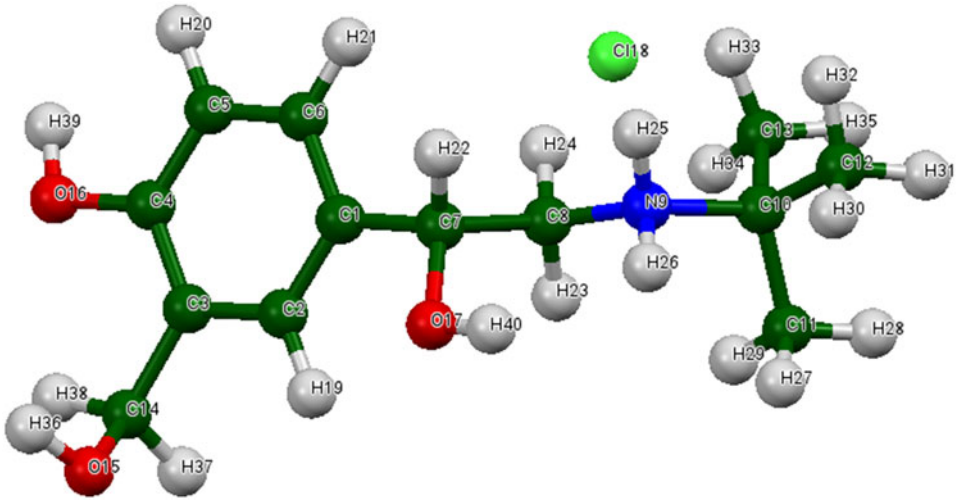


Figure 4. (Colour online) The molecular structure of levalbuterol hydrochloride polymorph A, with the atom numbering. The atoms are represented by 50% probability spheroids.

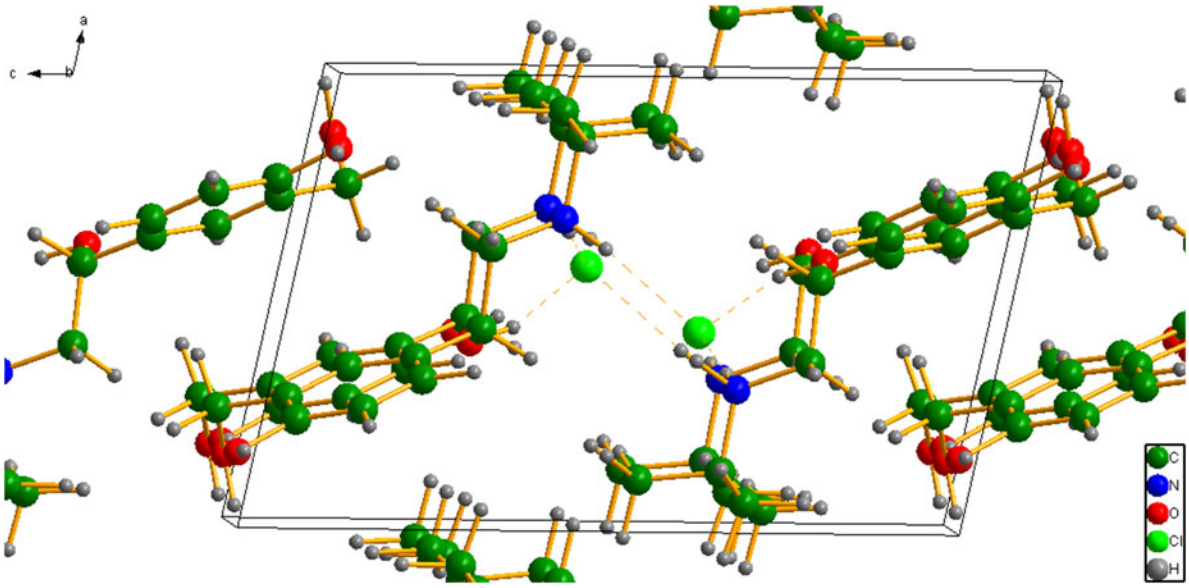


Figure 5. (Colour online) The crystal structure of levalbuterol hydrochloride polymorph A, viewed down the *b*-axis.

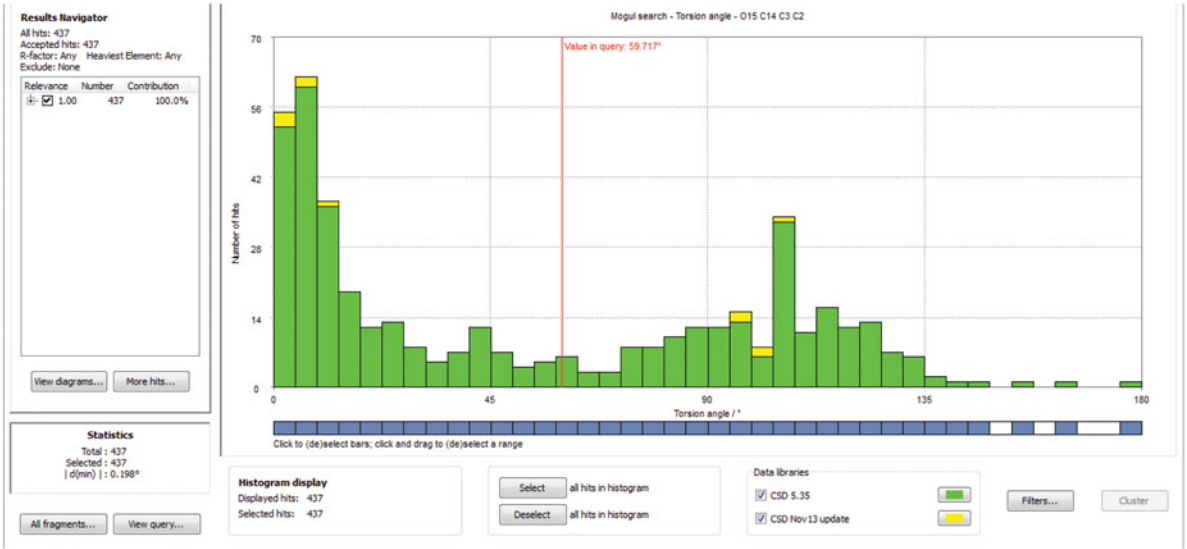


Figure 6. (Colour online) The O15–C14–C3–C2 torsion angle in relation to the distribution from the Mogul geometry search. This angle is unusual, but not unprecedented.

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TABLE III. Hydrogen bonds in levalbuterol hydrochloride polymorph A.

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Overlap (*e*)
O15–H36···O16	0.983	1.799	2.766	167.2	0.060
O16–H39···O15	0.997	1.643	2.622	166.1	0.071
N9–H26···Cl18	1.044	2.151	3.191	173.9	0.073
N9–H25···Cl18	1.038	2.305	3.219	146.1	0.033
O17–H40···Cl18	0.977	2.209	3.154	162.3	0.046

ammonium hydrogens and O17–H40 act as donors to Cl18. The graph sets (Etter, 1990; Bernstein *et al.*, 1995; Shields *et al.*, 2000) are *C*1,2(4) and *C*1,2(7). The result is a zig-zag chain parallel to the *b*-axis. The two hydroxy groups at the phenyl end of the molecule form another set of chains, both with graph set, *C*1,1(6), also resulting in a chain parallel to the *b*-axis. The bulk of the molecule connects these chains in the (101) plane to form a three-dimensional network.

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect platy morphology for levalbuterol hydrochloride polymorph A, with {001} as the principal faces; no preferred orientation correction was necessary. The powder pattern of levalbuterol hydrochloride polymorph A is included in the PDF as entry 00-064-1494.

SUPPLEMENTARY MATERIALS AND METHODS

The supplementary material for this article can be found at http://www.journals.cambridge.org/PDJ

ACKNOWLEDGMENTS

Use of the Advanced Photon Source at Argonne National Laboratory was supported by the U.S. 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. The authors thank Lynn Ribaud for his assistance in data collection.

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