X-ray powder diffraction analysis of imipenem monohydrate

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An experimental X-ray powder diffraction pattern was produced and analyzed for imipenem monohydrate, an antimicrobial pharmaceutical agent. Although there are no experimental powder patterns in the ICDD PDF-4/Organics Database, there is one powder pattern calculated with single-crystal X-ray diffraction data from the Cambridge Structural Database. Here, we report the refined experimental powder diffraction data for imipenem monohydrate. These data for imipenem monohydrate are consistent with an orthorhombic crystal system having reduced unit-cell parameters of $a = 8.2534(3)$ Å, $b = 11.1293(4)$ Å, and $c = 15.4609(6)$ Å. The resulting unit-cell volume, 1420.15(15) Å^3, indicates four formula units per unit cell. Observed peaks are consistent with the $P2_12_12_1$ space group. © *2012 International Centre for Diffraction Data.* [doi:10.1017/S0885715612000048]

Key words: imipenem, $C_{12}H_{17}N_3O_4S$, X-ray powder diffraction, β-lactam, hydrogen bonding

I. INTRODUCTION

Imipenem monohydrate, $C_{12}H_{17}N_3O_4S{\cdot}H_2O$ [6-(1-hydroxyethyl)-3-(2-(iminiomethylamino)ethylthio)-7-oxo-1-azabicyclo(3.2.0)hept-2-ene-2-carboxylate monohydrate] (Figure 1), has been used with cilastatin sodium as an antimicrobial injection. Imipenem monohydrate, such as penicillin, belongs to the β-lactam antibiotic class and is often used as a last resort in place of other antibiotics with similar pharmaceutical functions. The chemical structure of imipenem monohydrate, unlike penicillin and many other β-lactam antibiotics, has no sulfur in the five-membered ring fused to the β-lactam ring, and contains a double bond in this same five-membered ring. Despite the restricted use of β-lactam antibiotics as a result of the discovery of β-lactam-resistant bacteria, imipenem monohydrate has a broad application against a variety of bacteria.

Rietveld refinement of the imipenem monohydrate powder data confirmed an orthorhombic crystal system and a $P2_12_12_1$ space group. The molecular structure (Figure 1) includes a number of electronegative atoms, such as oxygen, nitrogen, and sulfur, in the forms of carboxyl, hydroxyl, imino, amino, and sulfide groups. The crystal structure also includes water, which contributes to intramolecular and intermolecular hydrogen bonding. This hydrogen-bonding network contributes greatly to the crystal packing arrangement. There have been few studies of this compound and only one concerning a single-crystal form (Ratcliffe *et al.*, 1989). However, its experimental powder data have not been explored. The PDF-4/Organics 2012 Database (ICDD, 2011) contains one powder pattern calculated from the single-crystal data (Needham et al., 2003). Here, we report our findings on the imipenem monohydrate experimental X-ray powder diffraction pattern.

II. EXPERIMENTAL

Imipenem monohydrate, purchased from United States Pharmacopeia (98–101% purity), was gently ground with an agate mortar and pestle. The powder was dusted on to a PANalytical PW1817/32 zero-background plate (obliquely cut silicon crystal) in a PANalytical PW1813/32 plate holder. The X-ray powder diffraction data were collected on a PANalytical X'Pert PRO system equipped with a copper X-ray source tube and an X'Celerator Detector. The scan range was 7–60° 2θ with a step size of 0.0167° 2θ. Two 0.02-rad Soller slits (for both incident and diffracted beams) were used to minimize the axial divergence aberration in the diffraction pattern. A 0.020-mm nickel filter was used to absorb Cu$K\beta$ radiation and a 0.125° antiscatter slit was used to reduce background. The experimental conditions are listed in Table I. The powder pattern is presented in Figure 2. This procedure with a zero-background holder gave a very good texture index of 1.03 after refinement, indicating very little preferred orientation.

III. RESULTS AND DISCUSSION

Analysis of the powder diffraction data was accomplished using PANalytical HighScore Plus (Needham *et al.*, 2006).

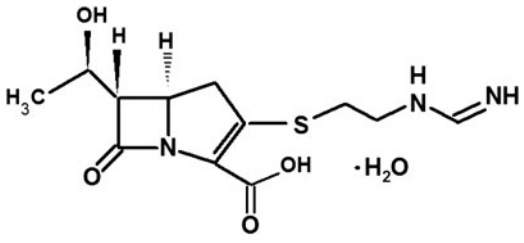

Figure 1. Structural formula of imipenem monohydrate.

Table I. XRD data collection conditions for imipenem monohydrate.

Diffractometer	PANalytical X'Pert-PRO
Divergence slits (°)	0.0625
Radiation	X-ray, Cu$K\alpha1$/$K\alpha2$
Power	45 kV, 40 mA
Detector	X'Celerator
Scan step size (°2θ)	0.0167
Sample rotation time (s)	4

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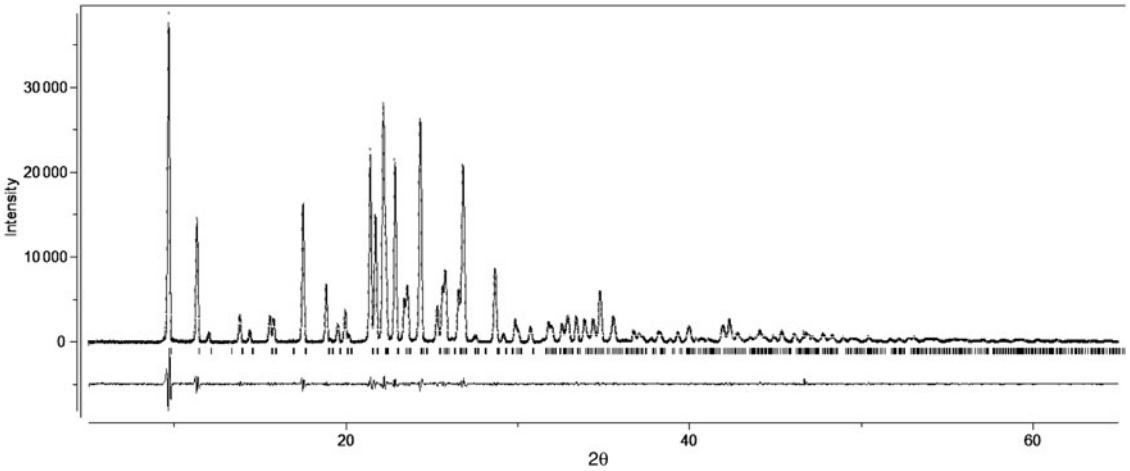

Figure 2. X-ray powder diffraction pattern for imipenem monohydrate. $a = 8.2534(3)$ Å, $b = 11.1293(4)$ Å, $c = 15.4609(6)$ Å, $R_p = 2.68\%$, W$R_p = 4.03\%$, and $\chi^2 = 3.883$.

Background subtraction and $K\alpha 2$ removal were performed before determining the location of the diffraction peaks. The extensive overlapping strong peaks below 35° 2θ makes peak search a challenging task. HighScore Plus (PANalytical, 2011) was used to find peaks. SQLAids (Sagnella, 2011) was used to evaluate the accuracy of these peak positions relative to the proposed orthorhombic cell. Results are shown in Table II. Rietveld refinement of the

Table II. XRD data for imipenem monohydrate.

h	k	l	$2\theta_{cal}$ (°)	$2\theta_{obs}$ (°)	$\Delta 2\theta$ (°)	d_{obs} (Å)	I/I_{max}
0	1	1	9.7840	9.7820	0.002	9.0347	100
0	0	2	11.437	11.432	0.005	7.7341	39
1	0	1	12.146	12.131	0.015	7.2900	3
0	1	2	13.937	13.926	0.011	6.3541	8
1	1	1	14.526	14.517	0.009	6.0967	4
1	0	2	15.694	15.701	−0.007	5.6396	9
0	2	0	15.914	15.906	0.008	5.5673	7
1	1	2	17.610	17.605	0.005	5.0337	46
0	1	3	18.961	18.973	−0.012	4.6737	19
0	2	2	19.641	19.623	0.018	4.5203	6
1	2	1	20.067	20.050	0.017	4.4250	10
1	0	3	20.299	20.278	0.021	4.3758	2
2	0	0	21.516	21.523	−0.007	4.1254	64
1	1	3	21.826	21.819	0.007	4.0701	43
2	0	1	22.279	22.276	0.003	3.9876	79
1	2	2	22.423	22.410	0.013	3.9641	31
2	1	0	22.967	22.958	0.009	3.8707	60
0	0	4	22.991	23.001	−0.010	3.8635	2
0	2	3	23.509	23.498	0.011	3.7829	15
2	1	1	23.685	23.668	0.017	3.7562	19
0	1	4	24.358	24.355	0.003	3.6517	9
2	0	2	24.432	24.441	−0.009	3.6391	75
1	0	4	25.425	25.418	0.007	3.5014	13
2	1	2	25.727	25.719	0.008	3.4611	20
1	2	3	25.898	25.879	0.019	3.4400	25
0	3	2	26.631	26.616	0.015	3.3464	6
1	1	4	26.675	26.665	0.010	3.3404	14
2	2	0	26.876	26.865	0.011	3.3160	31
1	3	1	26.952	26.973	−0.021	3.3029	46
2	0	3	27.670	27.661	0.009	3.2223	3
1	3	2	28.778	28.791	−0.013	3.0984	22
2	1	3	28.830	28.808	0.022	3.0966	7
2	2	2	29.293	29.281	0.012	3.0476	3
0	1	5	29.968	29.980	−0.012	2.9781	8
1	2	4	30.138	30.120	0.018	2.9646	4
1	0	5	30.855	30.843	0.012	2.8968	6
1	1	5	31.910	31.894	0.016	2.8037	8
2	2	3	32.080	32.100	−0.020	2.7861	4
0	4	0	32.145	32.125	0.020	2.7840	3

Continued

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Table II. Continued

h	k	l	$2\theta_{cal}$ (°)	$2\theta_{obs}$ (°)	$\Delta 2\theta$ (°)	d_{obs} (Å)	I/I_{max}
0	4	1	32.676	32.655	0.021	2.7400	4
2	1	4	32.722	32.706	0.016	2.7359	4
2	3	1	32.953	32.936	0.017	2.7173	5
3	0	1	33.045	33.054	−0.009	2.7079	7
3	1	0	33.527	33.517	0.010	2.6715	10
1	4	0	33.975	33.987	−0.012	2.6356	5
3	1	1	34.038	34.019	0.019	2.6332	5
0	4	2	34.224	34.219	0.005	2.6183	2
1	4	1	34.481	34.475	0.006	2.5994	3
2	3	2	34.490	34.481	0.009	2.5990	5
3	0	2	34.579	34.580	−0.001	2.5918	3
1	2	5	34.901	34.887	0.014	2.5697	21
2	2	4	35.654	35.632	0.022	2.5176	7
0	1	6	35.738	35.721	0.017	2.5116	5
3	2	1	36.878	36.876	0.002	2.4355	4
2	1	5	37.192	37.199	−0.007	2.4151	4
1	1	6	37.413	37.421	−0.008	2.4013	2
1	4	3	38.316	38.295	0.021	2.3485	4
0	2	6	38.468	38.456	0.012	2.3390	3
1	3	5	39.445	39.427	0.018	2.2836	4
1	2	6	40.046	40.058	−0.012	2.2491	5
2	3	4	40.124	40.113	0.011	2.2461	3
1	5	0	42.008	41.991	0.017	2.1499	4
2	1	6	42.097	42.072	0.025	2.1460	5
1	5	1	42.431	42.415	0.016	2.1294	10
2	4	3	42.917	42.908	0.009	2.1061	5
1	5	2	43.681	43.676	0.005	2.0708	2
4	0	1	44.251	44.244	0.007	2.0455	4
2	2	6	44.499	44.483	0.016	2.0351	2
4	1	1	45.032	45.019	0.013	2.0121	3
1	2	7	45.493	45.503	−0.010	1.9918	5
4	1	2	46.226	46.214	0.012	1.9628	3
4	2	0	46.927	46.915	0.012	1.9351	2
0	3	7	47.894	47.882	0.012	1.8982	2
4	2	2	48.465	48.453	0.012	1.8772	3
2	2	7	49.554	49.537	0.017	1.8386	2
0	6	2	50.563	50.571	−0.008	1.8034	2

$\lambda = 1.5406$ Å and I/I_{max} are based on peak height

powder data was performed using GSAS (Von Dreele and Larson, 2001). The refinement parameters used were Chebyshev polynomial background, scaling, sample displacement, peak asymmetry, peak shape profiles (Gaussian and Lorentzian), U_{iso} temperature factors, unit-cell parameters, and atomic coordinates. The results are shown in Figure 2, with final refinement statistics of $R_p = 2.68\%$, $wR_p = 4.03\%$, and $\chi^2 = 3.883$ (Figure 2). The refined unit-cell parameters are $a = 8.2534(3)$, $b = 11.1293(4)$, and $c = 15.4609(6)$ Å. These vary from the reported values [$a = 8.268(3)$, $b = 11.140(6)$, and $c = 15.452(9)$ Å] of single-crystal data in the PDF-4/Organics 2012 (Ratcliffe *et al.*, 1989) by −0.18, −0.14, and 0.06%, respectively. One value of U_{iso} was used for refinement. The resulting refined U_{iso} value is 0.0893. The refined atomic coordinates are listed in Table III.

Table IV lists three possible hydrogen bonds in addition to the water hydrogen bonds (Figure 3). Hydrogen bonds are shown as dotted lines in Figure 3. Two are intermolecular (N3/O2 and N3/O3) and one is intramolecular (O3/S1). Although the O3/S1 bonding distance is large and the sulfur atom has relatively weak electronegativity, the intramolecular proximity of the sulfur atom and hydroxyl hydrogen atom, and the resulting six-membered ring configuration makes its

Table III. Atomic coordinates of imipenem monohydrate.[a]

Atom	x	y	z
N1	0.1279(27)	0.8145(31)	−0.0628(16)
C1	0.1186(27)	0.6954(31)	−0.0736(17)
C2	0.0712(32)	0.6533(18)	0.0118(18)
C3	0.0688(32)	0.7594(24)	0.0889(16)
C4	0.1510(4)	0.8681(20)	0.0319(20)
C5	−0.0048(33)	0.9502(19)	0.0078(17)
C6	0.0080(4)	0.8977(24)	−0.0855(22)
C7	0.0581(4)	1.0862(25)	0.0055(19)
C8	−0.0687(27)	1.1790(19)	−0.0431(14)
C9	0.1104(32)	0.6341(5)	−0.1749(22)
C10	0.0462(21)	0.5220(30)	0.1559(19)
C11	−0.0130(35)	0.3965(20)	0.2012(13)
C12	−0.3060(4)	0.2680(31)	0.2048(16)
O1	−0.0849(23)	0.9105(15)	−0.1561(14)
O2	0.0710(17)	1.1261(12)	0.0973(11)
S1	0.0292(8)	0.5044(7)	0.0465(4)
O3	0.0771(22)	0.5197(17)	−0.1405(9)
O4	0.1622(4)	0.7041(34)	−0.2103(24)
N2	−0.1870(30)	0.3754(19)	0.2063(11)
N3	−0.2148(27)	0.1786(22)	0.1778(15)
O5	0.3144(16)	0.0946(13)	0.2084(10)

[a]U_{iso} value is 0.0893.

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Table IV. Hydrogen-bonding lengths in imipenem monohydrate.

Atom 1	Atom 2	Length reported in this study (Å)	Length reported by Ratcliffe *et al.* (1989) (Å)
O5	N2	2.90(2)	2.84
O5	O2	2.67(2)	2.68
O5	O3	2.72(2)	2.72
O5	O4	2.72(2)	2.79
N3	O2	2.80(2)	2.86
N3	O3	2.81(3)	2.79
O3	S1	2.92(1)	2.89

hydrogen bonding a very strong possibility. The water is hydrogen bonded to four molecules and the hydrogen-bonding length of water (Table IV) is similar to those of the reported values (Ratcliffe *et al.*, 1989). The O5/O2 and O5/O3 water hydrogen bonds are responsible for the head to tail packing of the fused rings of two adjacent molecules. Also, the O5/N2 and O5/O4 hydrogen bonds are orthogonal to the O5/O2 and O5/O3 bonds. The O5/O2 and O5/O3 hydrogen bonds are responsible for the arrangement of fused rings in a paralleled stacking fashion. The tetrahedral-like hydrogen bonding of the water molecule causes the stacking of fused rings in alternating fashion and hence forms a three-dimensional hydrogen-bonding network. The moderately long side chain with single bonds has a moderate amount of rotational freedom, which contributes to the conformational difference. The experimental unit cell is smaller than that derived from single-crystal data. The dusted powder samples on the zero-background plate minimized the preferred orientation effect. The thin layer of the experimental sample reduced the transparency aberration of the compound consisting of light elements. Finally, the zero-background sample holder minimized the background interference of the data analysis. The combination of all the advantages of the zero-background method for the imipenem monohydrate powder diffraction experiment enabled the successful resolution of overlapping peaks at low diffraction angles. This conclusion is supported by the more successful Rietveld refinement analysis as compared to other explored methods.

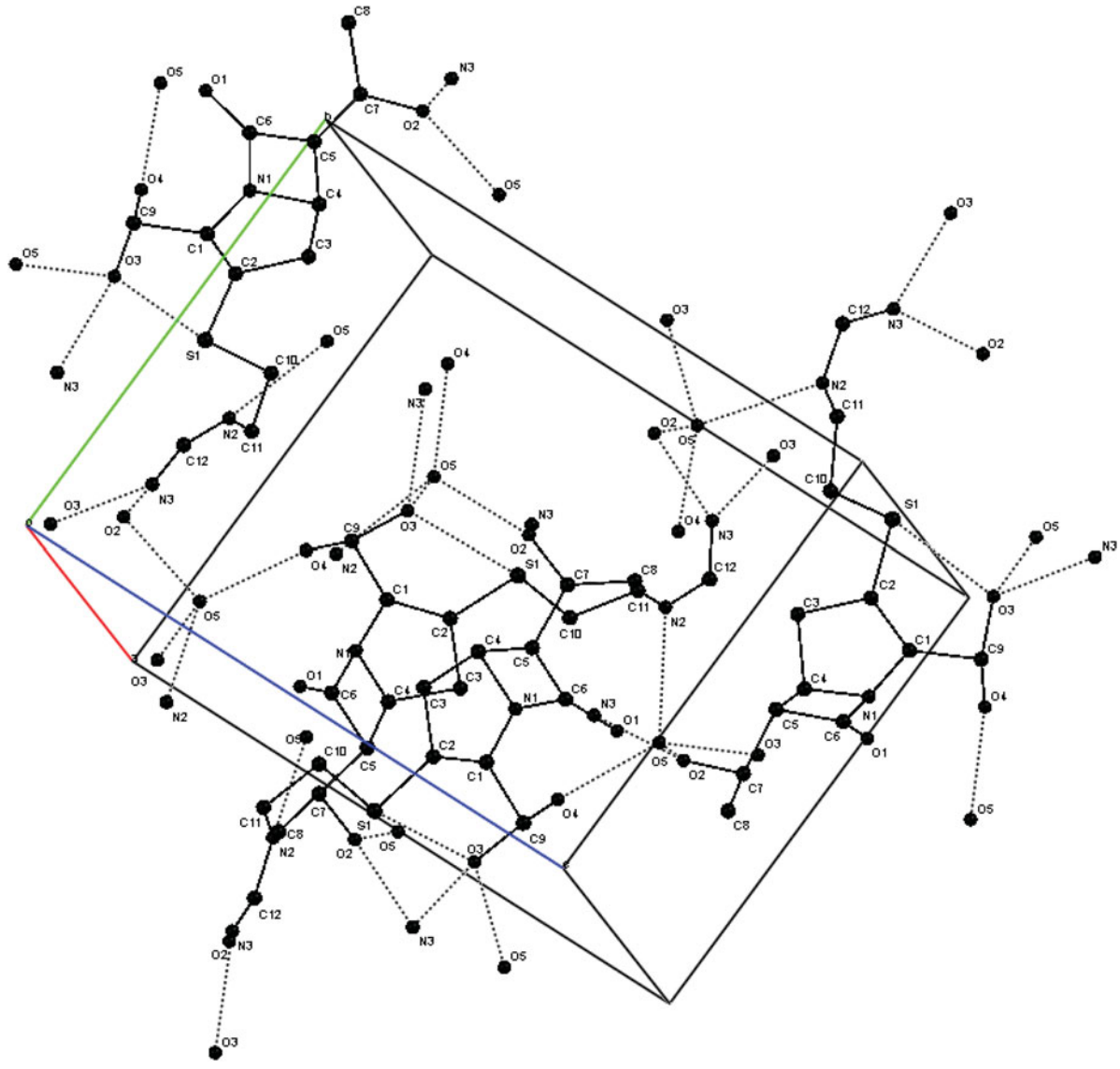

Figure 3. (Color online) Crystal structure of imipenem monohydrate.

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ICDD (**2011**). PDF-4/Organics 2012 Database, edited by S. Kabekkodu, International Centre for Diffraction Data, Newtown Square, Pennsylvania, USA.

Needham, F., Faber, J., and Fawcett, T. (**2006**). "X-ray powder diffraction analysis of tegafur," Powder Diffr. J. **21**(3), 245–247.

Needham, F. and Faber, J. (**2003**). "Total pattern analysis using the new organic powder diffraction file: PDF-4/Organics," Am. Pharm. Rev. **6**(4), 10–12.

PANalytical (**2011**). HighScore Plus, Version 3.0.3 (Computer Software), PANalytical, Netherlands.

Ratcliffe, R., Wildonger, K., Michele, L., Douglas, A., Hajdu, R., Goegelman, R., Springer, J., and Hirshfield, J. (**1989**). "Studies on the structures of imipenem, dehydropeptidase I hydrolyzed imipenem, and related analogues," J. Org. Chem. **54**, 653–660.

Sagnella, D. (**2011**). SQLAids (Computer Software), International Centre for Diffraction Data, Newtown Square, Pennsylvania, USA.

Von Dreele, R. and Larson, A. (**2001**). General Structure Analysis System (GSAS, Computer Software), University of California, USA.