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Ampicillin trihydrate from synchrotron powder diffraction data

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Key indicators

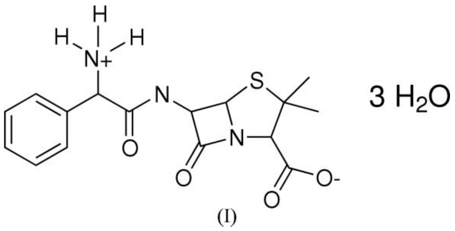
Powder synchrotron study
T = 290 K
Mean σ(C–C) = 0.006 Å
R factor = 0.025
wR factor = 0.030
Data-to-parameter ratio = 75.44

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The crystal structure of ampicillin trihydrate {systematic name: 6-[D(−)-α-aminophenylacetamido]penicillanic acid trihydrate}, $C_{16}H_{19}N_3O_4S\cdot3H_2O$, a broad-spectrum β-lactam antibiotic of the aminopenicillin type, has been determined from synchrotron X-ray powder diffraction data. The three water molecules form an infinite hydrogen-bonded chain through the crystal structure, with hydrogen bonds to the NH_3^+, COO^-, C=O and NH groups of the ampicillin molecules.

Comment

The title compound, (I), has been used as a broad-spectrum antibiotic since 1961. The crystal structure was reported in 1968 (James *et al.*, 1968), but no atomic coordinates were given in the paper or deposited. Boles *et al.* (1978) published the crystal structure of a related compound, amoxycillin trihydrate. They apparently had access to the atomic coordinates of the crystal structure of compound (I), because in their paper they show that the two crystal structures are isostructural. However, the atomic coordinates of the title compound have not been published to date. We report the crystal structure here, determined from synchrotron X-ray powder diffraction.



(I)

The structural model of compound (I) obtained in the present work (Fig. 1*a*) is both chemically reasonable and in accord with the figures given by James *et al.* (1968). Selected geometric parameters are given in Table 1. We note, however, that the hydrogen bond O26‴···O25‴ in their Fig. 1, which appears to link four water molecules together into a closed tetramer, is spurious, and instead should have formed a chain (Fig. 1*b*). Both the pattern of hydrogen bonding, and the positions of the H atoms of the water molecules in the structure, are chemically sensible and compare well with those from the crystal structure of the isostructural amoxycillin trihydrate (Boles *et al.*, 1978). Details of the O—H···O and N—H···O hydrogen bonds are given in Table 2 and Fig. 1.

Experimental

The sample of compound (I) was a gift from Setauket Pharmacy, Setauket, New York, USA, in the form of a gelatin capsule of the

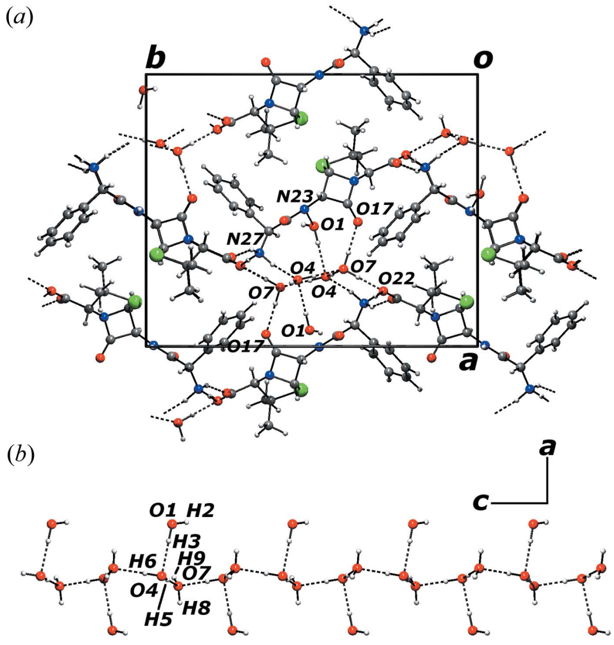


Figure 1
(*a*) A view, along the *c* axis, of the crystal structure of compound (I), showing the O—H···O and N—H···O hydrogen bonds as dashed lines (see Table 2 for details). (*b*) A view along the *b* axis of the hydrogen-bonded (dashed lines) water network in the crystal structure of compound (I). [A screw axis is present at ($\frac{1}{4}$, 0, *z*)].

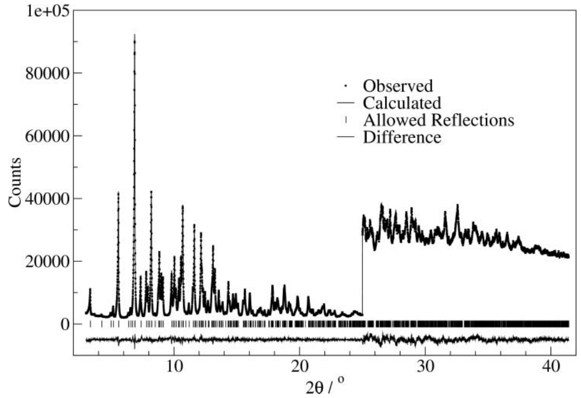


Figure 2
Observed, calculated and difference X-ray powder diffraction profiles for compound (I). The region 25–42° in 2θ has been magnified 10 times.

compound. Some of the contents were loaded into a thin-walled glass capillary of 1.5 mm nominal diameter. Any excipients that might have been present were not crystalline. A diffraction pattern was collected at the X3B1 beamline of the National Synchrotron Light Source, Brookhaven National Laboratory. The wavelength of 0.7003 (1) Å was selected by a double Si(111) monochromator and the diffracted beam analyzed by a Ge(111) crystal before the detector. The beam on the sample had dimensions 2 mm × 8 mm. Data were collected from 2θ = 3–41.6° in steps of 0.005°, with counting time increasing quadratically from 1–8 s per point. The incident beam was monitored by an ion chamber, which was used to normalize the data for decay and fluctuations of the intensity.

Crystal data

$C_{16}H_{19}N_3O_4S\cdot 3H_2O$
M_r = 403.06
Orthorhombic, $P2_12_12_1$
a = 15.52275 (16) Å
b = 18.9256 (3) Å
c = 6.67375 (8) Å
V = 1960.60 (3) Å^3
Z = 4
D_x = 1.367 Mg m^{-3}
Synchrotron radiation
λ = 0.7003 Å
T = 290 K
Specimen shape: cylinder
0.7 × 20 mm
Particle morphology: powder, white

Data collection

Huber 424 Q -2Q diffractometer on X3B1 beamline
Specimen mounting: Lindemann glass capillary
Specimen mounted in transmission mode
Scan method: step
T = 290 K
2θ_{min} = 3, 2θ_{max} = 41.6°
Increment in 2θ = 0.005°

Refinement

R_p = 0.025
R_{wp} = 0.030
R_{exp} = 0.013
S = 2.37
2θ_{min} = 3, 2θ_{max} = 41.6°
Increment in 2θ = 0.005°
Wavelength of incident radiation: 0.7003 Å
Excluded region(s): none
Profile function: CW profile function number 3 with 19 terms. Pseudo-Voigt profile coefficients as parameterized in Thompson *et al.* (1987). Asymmetry correction of Finger *et al.* (1994). Peak tails are ignored where the intensity is below 0.0010 times the peak
10788 reflections
143 parameters
H-atom parameters constrained
Weighting scheme based on measured s.u. values
$(\Delta/\sigma)_{max}$ = 0.03
Preferred orientation correction: none

Table 1
Selected geometric parameters (Å, °).

S10—C11	1.859 (4)	N13—C12	1.473 (5)
S10—C14	1.797 (3)	N13—C14	1.506 (5)
O17—C16	1.201 (5)	N13—C16	1.384 (5)
O21—C20	1.222 (6)	N23—C15	1.433 (5)
O22—C20	1.273 (6)	N23—C24	1.348 (7)
O25—C24	1.213 (5)	N27—C26	1.475 (6)
C11—S10—C14	90.10 (18)	N23—C15—C16	115.5 (3)
C12—N13—C14	117.0 (3)	N23—C15—C14	116.5 (3)
C12—N13—C16	128.1 (3)	O17—C16—C15	135.4 (3)
C14—N13—C16	93.1 (3)	O17—C16—N13	131.0 (4)
C15—N23—C24	123.3 (3)	N13—C16—C15	93.0 (3)
S10—C11—C19	107.5 (3)	O21—C20—C12	118.0 (4)
S10—C11—C12	104.6 (2)	O21—C20—O22	126.3 (4)
S10—C11—C18	110.0 (3)	O22—C20—C12	115.6 (4)
N13—C12—C11	105.6 (3)	O25—C24—N23	124.5 (5)
N13—C12—C20	112.8 (3)	O25—C24—C26	122.1 (5)
N13—C14—C15	87.1 (2)	N23—C24—C26	113.2 (3)
S10—C14—N13	103.6 (2)	N27—C26—C24	110.0 (3)
S10—C14—C15	119.5 (2)	N27—C26—C28	112.9 (3)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H3···O4	0.98	2.02	2.9968	180
O4—H5···O7^{i}	0.98	1.80	2.7850	180
O4—H6···O7	0.98	1.82	2.7967	180
O7—H8···O17	0.98	1.84	2.8225	180
O7—H9···O22^{ii}	0.98	1.74	2.7166	179
N27—H38···O4^{iii}	1.001 (15)	1.86	2.8272	161
N27—H39···O21^{iv}	1.00 (3)	1.83 (3)	2.742 (6)	151.1 (15)

o798 Burley *et al.* • $C_{16}H_{19}N_3O_4S\cdot 3H_2O$ *Acta Cryst.* (2006). E**62**, o797–o799

D—H···A	D—H	H···A	D···A	D—H···A
N27—H40···O22^{v}	1.00 (3)	1.80 (2)	2.688 (6)	147 (2)
N23—H51···O1	1.002 (10)	1.97	2.9161	156

Symmetry codes: (i) $-x+\frac{3}{2}, -y+1, z-\frac{1}{2}$; (ii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $-x+\frac{3}{2}, -y+1, z+\frac{1}{2}$; (iv) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (v) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$.

The starting model for Rietveld refinement was obtained by solving the crystal structure from the powder diffraction pattern. This also provided an independent check that the published crystal structure is correct. However, with the crystal structure being known, its determination from the powder pattern is mainly academic. The crystal structure was determined with the program *DASH* (David *et al.*, 2004). For the structure solution, the data were truncated at 22.855° in 2θ, corresponding to a real-space resolution of 1.767 Å. The background was subtracted with a Bayesian high-pass filter (David & Sivia, 2001). Peak positions for indexing were obtained by fitting with an asymmetry-corrected Voigt function, followed by indexing with the program *DICVOL* (Boultif & Louer, 1991). An orthorhombic and several monoclinic unit cells were obtained. However, all the monoclinic unit cells were pseudo-orthorhombic with nearly the same parameters as the orthorhombic cell, indicating that the orthorhombic unit cell is the correct one. The figures of merit given by *DICVOL* were $M(20) = 62.1$ and $F(20) = 337.1$ (0.0014, 42). The space group reported for the single-crystal structure, $P2_12_12_1$, gave an excellent Pawley fit.

Simulated annealing was used to solve the crystal structure of compound (I) from the powder pattern in direct space. The starting molecular geometry was taken from the anhydrate (Boles & Girven, 1976), entry AMCILL in the Cambridge Structural Database (Allen, 2002). The molecule is a zwitterion, in agreement with the single-crystal study. Because H atoms do not contribute significantly to the powder diffraction pattern, due to their low X-ray scattering power, they were ignored during the structure solution process. Hence, the water molecule can be reduced to an O atom, which reduces its number of degrees of freedom from six to three. The molecule has five flexible torsion angles, which, when combined with the three water molecules, give a total of 20 degrees of freedom. In ten simulated annealing runs, the correct crystal structure was found twice, with a profile $\chi^2 = 81.7$, 11 times the Pawley χ^2. The next-best crystal structure had a profile $\chi^2 = 240$. The low success rate and high profile χ^2 are caused by the high R factor of 10.6% of the crystal structure of AMCILL from which the starting model was taken; when the structure solution was repeated with a better starting model (obtained from Rietveld refinement against the powder data), the correct structure was found four times in ten runs, with a profile $\chi^2 = 20$, less than three times the Pawley χ^2.

The background subtraction, peak fitting, indexing, Pawley refinement and simulated-annealing algorithms used are as implemented in the program *DASH*.

For the Rietveld refinement (Fig. 2), H atoms were included in the initial model in calculated positions. Bond lengths, bond angles and planar groupings were subjected to suitable constraints, including bonds to H atoms. Data were included to 41.42° in 2θ, corresponding to a real-space resolution of 0.99 Å. The refinement was not particularly sensitive to the position of the water H atoms and these were included in calculated positions, with the water molecules being fixed in position for the final refinement cycles. The refinement proceeded smoothly to reach a minimum characterized by an excellent fit to the diffraction profile ($\chi^2 = 5.637$, $R_p = 0.0296$, $R_{wp} = 0.0296$ and $R_{Bragg} = 0.0295$).

Data collection: local software; cell refinement: *GSAS* (Larson & Von Dreele, 2000); data reduction: local software; program(s) used to solve structure: *DASH* (David *et al.*, 2004); program(s) used to refine structure: *GSAS*; molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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Acta Cryst. (2006). E**62**, o797–o799 Burley *et al.* • $C_{16}H_{19}N_3O_4S\cdot3H_2O$ **o799**