organic papers

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ() = 0.000 Å
Disorder in main residue
R factor = 0.059
wR factor = 0.141
Data-to-parameter ratio = 166.7

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

4-Imino-1,3-diazabicyclo[3.1.0]hexan-2-one

The title compound, also known as imexon, $C_4H_5N_3O$, is an iminopyrrolidone that, due to its selective growth inhibitory effect against multiple myeloma, has been under investigation as an anticancer agent since the 1970s. Crystals of the title compound were grown from absolute ethanol saturated with imexon at 296 K, by slow evaporation. Under these conditions, imexon crystallizes as plates with well developed (100) faces. The crystals readily twin by a twofold rotation about the *a* axis. When crystallized *via* rapid evaporation of solvent, the resulting powder has a slightly larger unit cell. Simulation of the powder pattern using the atomic parameters and the larger powder cell agree well with measured powder patterns but indicate some preferred orientation towards the (100) plane. The anticancer molecule crystallizes as a zwitterion, with the imino N atom doubly protonated. Each molecule makes four hydrogen bonds which form continuous tapes of molecules along [010].

Comment

The crystallinity of a drug substance has an effect on its aqueous solubility, dissolution rate and melting point. Kuehl *et al.* (2006) have shown that the solubility of imexon, (I), is directly related to temperature and that the dissolution of (I) is very rapid. Preliminary solid-state characterization, *via* differential scanning calorimetery and thermogravimetric analysis, failed to indicate that (I) was crystalline as it decomposes prior to melting, beginning near 438 K. Examination of crystallites of (I), under magnification with cross-polarized light, showed birefringence. Powder X-ray diffraction analysis confirmed that (I) is indeed a crystalline solid (Den Brok, Nuijen, Hillebrand *et al.*, 2005; Den Brok, Nuijen, Lutz *et al.*, 2005; Kuehl *et al.*, 2006). For a better understanding of the solid-state characteristics of (I), a single-crystal X-ray diffraction study and its relationship to powder diffraction data are presented here.

(I)
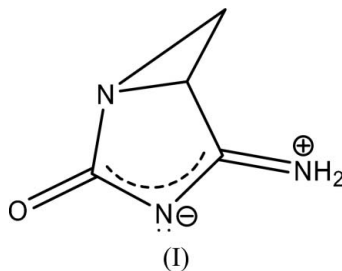
Compound (I) crystallizes in a zwitterionic form (Fig. 1), with the doubly protonated atom N8 having a positive charge
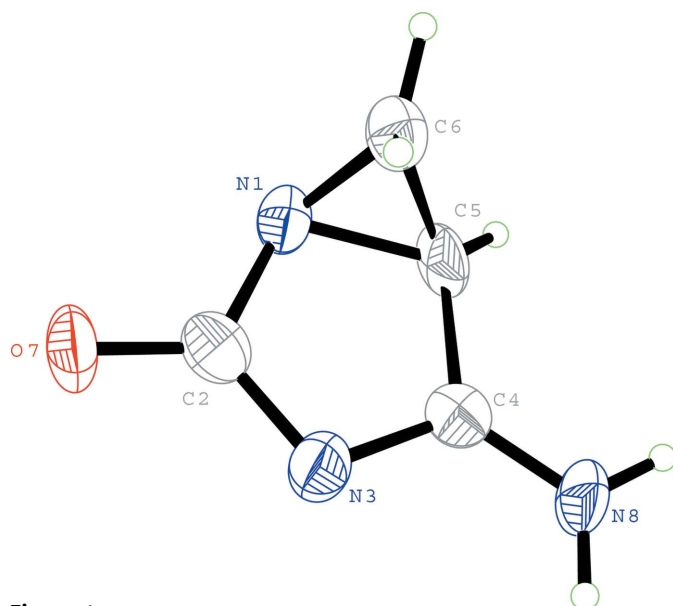
Figure 1
The molecular structure of (I), with 50% probability displacement ellipsoids. H atoms are shown as spheres of arbitrary radii.
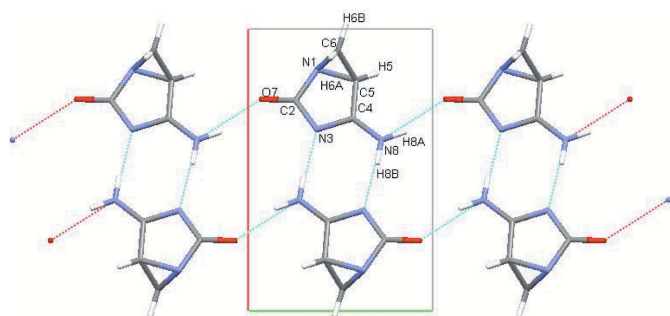

Figure 2
A partial packing diagram of (I), showing intermolecular hydrogen bonds (dashed lines), which form infinite tapes.

and with a negative charge distributed over atoms C2, N3 and C4. The zwitterion is stabilized by conjugation from the carbonyl group to N8. This is further confirmed by the almost equal C2—N3 and C4—N3 bond lengths of 1.36 (1) Å, typical for a delocalized double bond. All other bond lengths and angles are normal (Lide, 1991). The five-membered ring is planar (r.m.s. deviation of all non-H atoms except C6 is 0.03 Å), with the aziridine ring above the ring [displacement of C6 from the plane is 1.239 (2) Å]

Hydrogen bonds (Table 1) connect the molecules into continuous tapes of pairs of molecules along the [010] axis, shown in Fig. 2, with no strong interactions noted between adjacent tapes. A small amount of whole-molecule disorder, 3.17 (11)%, was detected in which each molecule may rotate 180° about the carbonyl axis without disrupting the overall hydrogen-bonding network or introducing significant steric strain. Rotation about the carbonyl group displaces the predominant hydrogen bonds N8—H8B···N3[i] and N8—H8A···O7[ii], replacing them with the structurally equivalent hydrogen bonds N8B—H8D···O7[ii] and N8B—H8C···N1[iii] (Table 1).
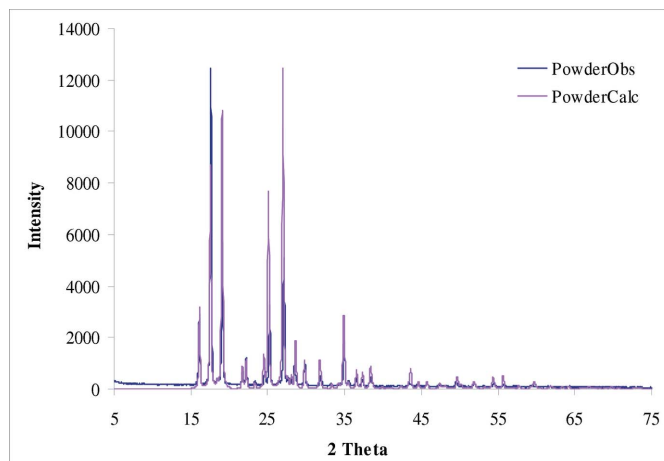

Figure 3
Calculated (purple) and observed (blue) powder patterns.

Crystals of (I) twin readily by a twofold rotation about the *a* axis. Since no strong interactions are present between adjacent tapes, no interactions are disrupted as a result of the twinning. In this sample, the twin component fractions were determined to be 35.73 (7)% and 64.27 (7)%.

Compound (I) was also examined *via* powder X-ray diffractometry. The observed powder patterns differed little from the patterns calculated using single-crystal atomic parameters and a unit cell refined from the observed powder pattern, as shown in Fig. 3. A typical cell refined from the powder data was $a = 10.4200 (9)$ Å, $b = 6.553 (2)$ Å, $c = 7.310 (2)$ Å, $\alpha = 90°$, $\beta = 104.000 (9)°$ and $\gamma = 90°$. Other refinements varied by less than 0.1 Å and 1.0°. The microcrystalline material used for powder X-ray analysis was crystallized by rapid evaporation of ethanol, while the single crystal utilized for X-ray diffraction data was grown under controlled slow evaporation of ethanol. This difference in crystallization rate leads to the observed small differences between the single-crystal data and the powder data.

Experimental

Raw pharmaceutical grade imexon was obtained as a free-flowing powder from Amplimed Corporation, Tucson, Arizona. Crystals of (I) were grown from solution in absolute ethanol. The ethanol was heated to 313 K, an excess of imexon was added and the heated solution was vortexed. Following vortexing, the solution was filtered through a 0.2 μm PTFE filter. The filtrate was allowed to cool slowly to room temperature (296 K) and was loosely capped to allow for slow evaporation of solvent. Plate-like crystals were observed within 1 d. Crystals were mounted on a glass fibre using paratone-N oil. Recrystallization from normal saline solution gave a powder indistinguishable from the raw starting material. Powder patterns were measured on a Philips XPert MPD powder diffractometer using unfiltered Cu Kα radiation and an XCelerator RTMS detector. Samples were sprinkled on an off-axis cut single-crystal silicon 'zero-background' holder which was rotated in the sample plane. Powder pattern indexing, cell refinement and simulations were performed using *XPert Plus* software (PANalytical, 2003).

Crystal data

$C_4H_5N_3O$
$M_r = 111.11$
Monoclinic, $P2_1/c$
$a = 10.3612 (12)$ Å
$b = 6.5999 (6)$ Å
$c = 7.2077 (11)$ Å
$\beta = 103.685 (9)°$
$V = 478.89 (10)$ Å^3

$Z = 4$
$D_x = 1.540$ Mg m^{-3}
Mo $K\alpha$ radiation
$\mu = 0.12$ mm^{-1}
$T = 173 (2)$ K
Plate, colourless
$0.28 \times 0.16 \times 0.03$ mm

Data collection

Bruker APEXII CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*TWINABS*; Sheldrick, 2005) $T_{min} = 0.938$, $T_{max} = 0.997$

13504 measured reflections
13504 independent reflections
4436 reflections with $I > 2\sigma(I)$
$\theta_{max} = 26.0°$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.059$
$wR(F^2) = 0.141$
$S = 0.70$
13504 reflections
81 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0342P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N8—H8B$\cdots$N3^i	0.88	2.01	2.8805 (19)	172
N8—H8A$\cdots$O7^{ii}	0.88	1.95	2.7966 (14)	160
N8B—H8D$\cdots$O7^{ii}	0.88	2.30	3.02 (3)	139
N8B—H8C$\cdots$N1^{iii}	0.88	1.85	2.68 (2)	155

Symmetry codes: (i) $-x + 1, -y + 1, -z$; (ii) $x, y + 1, z$; (iii) $-x + 2, -y + 1, -z + 1$.

Non-merohedral twinning of the single crystals examined was obvious from initial diffraction patterns and concurrent difficulty in indexing. The correct unit cell and the twin law relating the two components were determined using the program *CELL_NOW* (Sheldrick, 2005). Twinning occurred *via* a 180° rotation about the real *a* axis. Reflections from both components, including overlaps, were integrated simultaneously using *SAINT* (Bruker, 2005) and two orientation matrices. Merging of equivalent reflections was not performed due to the overlap of the twin components. A whole-molecule disorder, involving rotation about the carbonyl group, was modelled with the minor component [3.17 (11)%] restrained to have approximately the same geometry as the dominant component. Atom components which could not be separated were constrained to have identical positions and displacement parameters. Displacement parameter similarity and rigid-bond restraints were applied. All H atoms were positioned geometrically and allowed to ride on their parent atom, with C—H = 0.99 or 1.00 Å and N—H = 0.88 Å, and with $U_{iso}(H) = 1.2$ or 1.5 times $U_{eq}(C,N)$.

Data collection: *APEX2* (Bruker, 2005); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXTL*.

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