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Crystal structure and Hirshfeld surface analysis of ketorolac tromethamine

Anna M. Shaposhnyk,[a]* Vitalii V. Rudiuk[b] and Vyacheslav N. Baumer[a]

[a]Institute of Functional Materials Chemistry, SSI 'Institute for Single Crystals' NAS of Ukraine, 60 Nauky Ave., Kharkiv 61001, Ukraine, and [b]Farmak JSC, 63 Kyrylivska str., Kyiv 04080, Ukraine. *Correspondence e-mail: annapuzan199114@gmail.com

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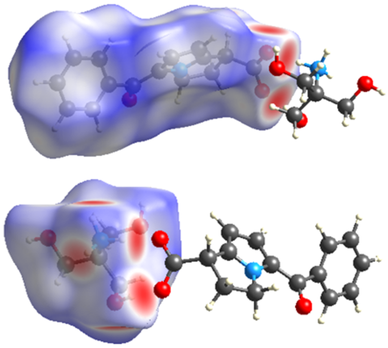
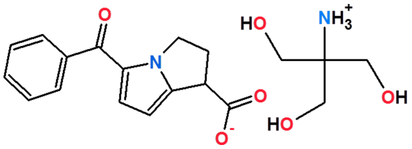
Ketorolac tromethamine or 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate, $C_{15}H_{12}NO_3^+ \cdot C_4H_{12}NO_3^-$, was studied by single-crystal and powder X-ray diffraction methods. One cation and one anion are present in the asymmetric unit. In the crystal, N—H···O and O—H···O hydrogen bonds link the cation and anion. All the hydrogen-bond interactions result in the formation of a di-periodic layer in the (100) crystallographic plane.



1. Chemical context

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that belongs to the class of heteroaryl acetic acid derivatives and the nonselective COX inhibitor group (Gilman, 2001).



Ketorolac tromethamine produces analgesia and decreases inflammation by inhibiting the enzyme cyclooxygenase, resulting in a decrease in the formation of prostaglandins and sensitization to pain at sites of inflammation (Boyer *et al.*, 2010). It has also been used effectively for analgesia in advanced cancer (Joishy & Walsh, 1998). It has a chiral centre and is composed of (+)*R* and (−)*S* enantiomers in equal proportions. The pharmacological (analgesic and COX inhibitory) activity is retained almost exclusively in the *S*-enantiomer (Mroszczak *et al.*, 1990). It is commercially available as a tromethamine salt, which augments its water solubility (Litvak *et al.*, 1990) and can be given *via* routes such as intravenous, subcutaneous, oral and intramuscular, and is the only NSAID currently available as a nasal spray (He & Hersh, 2012). The analgesic efficacy of ketorolac depends on the racemic mixture concentrations of *S* and *R* enantiomers (Jamali *et al.*, 1989; Mroszczak *et al.*, 1996). In the present work, we have analyzed the molecular and crystal structures of ketorolac tromethamine (denoted **KT**) or 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate.

2. Structural commentary

KT crystallizes in the monoclinic space group *I*2/*a*, with the asymmetric unit containing one anion and one cation (Fig. 1).

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The positive charge of the cation is located at the protonated amino group of the tromethamine molecule. A result of protonation of the amino group is a lengthening of the N1—C17 distance [1.489 (3) Å] in the cation compared to the average C*sp*^{3}—N value of 1.467 Å (Orpen *et al.*, 1994). The H atoms on atom N1 were determined from a difference Fourier map. A negative charge is located on the deprotonated carboxylate group of ketorolac, as follows from the lengthening of the C4—C1 distance [1.530 (3) Å] compared to the average C*sp*^{3}—C*sp*^{2}(carboxylic acid) value of 1.502 Å (Orpen *et al.*, 1994), and the C4—O1 [1.245 (3) Å] and C4—O2 [1.258 (3) Å] distances (C—O^{2-} = 1.254 Å; Orpen *et al.*, 1994). In the 2,3-dihydro-1*H*-pyrrolizine fragment, the saturated ring adopts an envelope conformation, where the deviation of the C2 atom from the C1/C7*A*/N4/C3 plane is 0.116 Å. The arene group of the benzaldehyde fragment is located in a +synperiplanar (+sp) position with respect to the 2,3-dihydro-1*H*-pyrrolizine bicycle [the C6—C5—C8—C9 torsion angle is 13.0 (4)°] and is turned with respect to the C8═O3 bond [the O3—C8—C9—C14 torsion angle is 39.5 (3)°]. The carboxylate group is in an equatorial position with respect to the 2,3-dihydro-1*H*-pyrrolizine fragment and is almost coplanar with the endocyclic C1—C2 bond [the C3—C2—C1—C4 and C2—C1—C4—O2 torsion angles are 127.8 (3) and −8.1 (3)°, respectively]. The cation and anion are connected by intermolecular N1—H1*A*···O1 and O6—H6*A*···O2 hydrogen bonds (Table 1), which form a characteristic $R_2^2(9)$ graph-set motif (Etter *et al.*, 1990).

3. Supramolecular features

The main packing fragment in **KT** is a mono-periodic layer in the (100) plane with a characteristic $R_4^4(18)$ graph-set motif (Etter *et al.*, 1990). In one layer, tromethamine cations form one-dimensional chains along [010], which are repeated over *a*/2 and *c*/2 *via* the O5—H5···O6^{ii} hydrogen bonds (Table 1). One cation interacts with four ketorolac anions *via* a series of hydrogen bonds (O4—H4···O3^{i}, O6—H6*A*···O2, N1—H1*A*···O1, N1—H1*B*···O2 and N1—H1*C*···O1; Table 1), forming a layer in the (100) plane. Van der Waals interactions are observed between neighbouring layers (Fig. 2).

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O3^{i}	0.82	1.92	2.731 (3)	172
O5—H5···O6^{ii}	0.82	1.95	2.762 (3)	174
O6—H6*A*···O2	0.82	1.85	2.667 (2)	177
N1—H1*A*···O1	0.89	1.89	2.771 (2)	172
N1—H1*B*···O2^{iii}	0.89	2.05	2.926 (3)	169
N1—H1*C*···O1^{iv}	0.89	1.92	2.756 (3)	155

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

4. Database survey

A search of the Cambridge Structural Database (CSD, Version 5.44, last update June 2024; Groom *et al.*, 2016) for the 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate unit resulted in one hit (CSD refcode HOJSAB; Jasinski *et al.*, 2008). In this structure, 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate exists as a neutral molecule. A search for the 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium unit or tromethamine as a cation resulted in 88 hits. 40 of these hits contain the compound as an anion with the carboxylic acid group deprotonated, for example, CIKQIY (Zhang *et al.*, 2013), COZBAX (Rossi *et al.*, 2020) and EDALEC (Bhattacharya *et al.*, 2012).

5. Synthesis and crystallization

Crystals of the title compound suitable for X-ray diffraction analysis were grown by recrystallization of the API ketorolac tromethamine from a water solution by the diffusion method with isopropyl alcohol at room temperature over a period of one week.

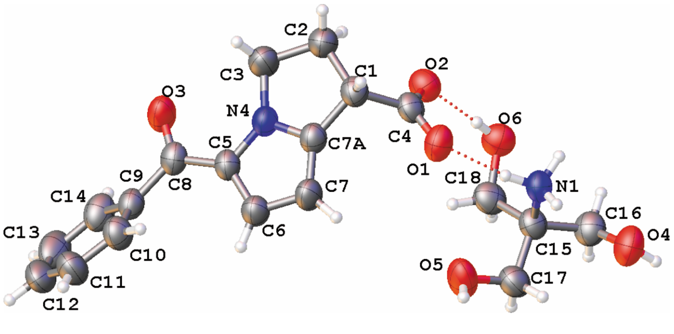

Figure 1
The molecular structure of **KT**. Displacement ellipsoids are drawn at the 50% probability level. O—H···O and N—H···O hydrogen bonds are indicated by dotted lines.

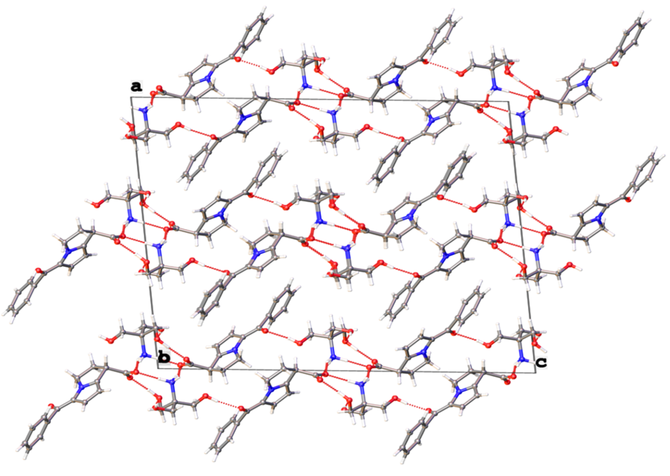

Figure 2
The crystal packing of **KT**, viewed along [010]. Hydrogen bonds are shown as dashed lines.

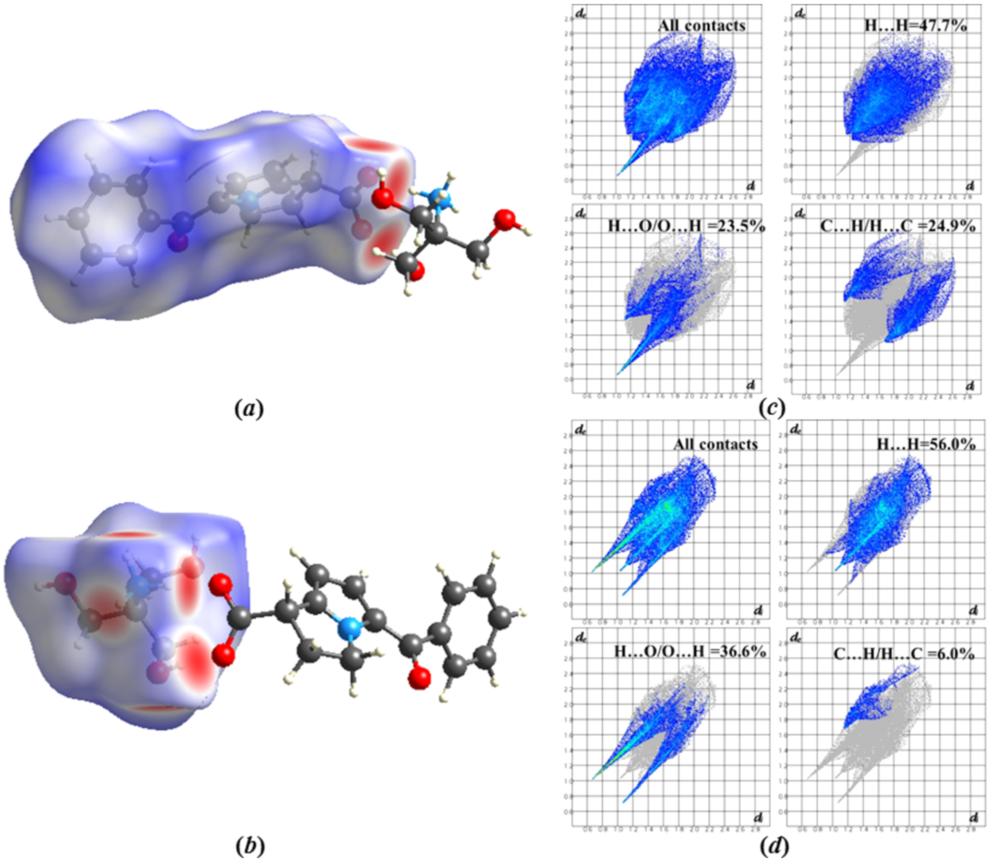

Figure 3
Hirshfeld surfaces mapped over $d_{\rm norm}$ for (*a*) the anion and (*b*) the cation of **KT**. Contributions of interactions of different types to the total Hirshfeld surface of (*c*) the anion and (*d*) the cation of **KT**.

6. Hirshfeld surface analysis

Intermolecular interactions can be analyzed using Hirshfeld surface analysis and 2D fingerprint plots (Turner *et al.*, 2017). Analysis and calculation of the Hirshfeld surface were carried out with *CrystalExplorer17.5* (Spackman *et al.*, 2021).

The Hirshfeld surfaces were calculated for the structure under study using a standard high surface resolution, mapped over $d_{\rm norm}$ [Figs. 3(*a*) and 3(*b*)]. The red spots, corresponding to contacts that are shorter than the van der Waals radii sum of the closest atoms, are observed at the carboxylate and carbonyl groups. To compare intermolecular interactions of different types in a more quantitative way, their contributions to the total Hirshfeld surfaces were analysed and the main contributions are presented in Figs. 3(*c*) and 3(*d*). The main contribution for the cation and anion is provided by H$\cdots$H short contacts. Stronger contributions of N—H$\cdots$O and O—H$\cdots$O hydrogen bonds are observed in the structure. The contribution of C$\cdots$H/H$\cdots$C short contacts is significant for the anion [Fig. 3(*c*)].

7. Powder diffraction characterization

An X-ray powder diffraction pattern of **KT** was recorded using a Siemens D500 powder diffractometer (Cu *Kα* radiation, Bragg–Brentano geometry, curved graphite monochromator on the counter arm, 4° < 2θ < 60°, 2θ = 0.02°). A Rietveld refinement (Fig. 4) on the basis of the obtained pattern was

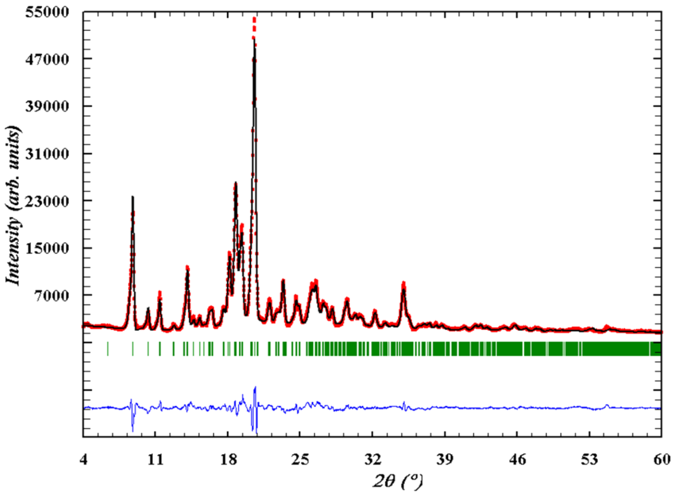

Figure 4
Final Rietveld plots for **KT**. Observed data points are indicated by red circles, the best-fit profile (black upper trace) and the difference pattern (blue lower trace) are shown as solid lines. The vertical green bars correspond to the Bragg reflections.

Table 2
Experimental data of the X-ray powder diffraction study performed at 293 K.

Crystal system, space group	Monoclinic, $I2/a$
a (Å)	20.3347 (15)
b (Å)	6.6301 (5)
c (Å)	27.981 (2)
β (°)	96.306 (4)
V (Å^3)	3749.5 (5)
D_x (Mg m^{-3})	1.334
Refinement	
R_p	0.0720
R_{wp}	0.0915
R_{exp}	0.0178
R_B	0.0580
R_F	0.0727

carried out with the *FullProf* and *WinPLOTR* programs (Rodriguez-Carvajal & Roisnel, 1998) using data of an external standard (NIST SRM1976) for the calculation of the instrumental profile function and the single-crystal data as the structure model for refinement. The main results of the Rietveld refinement are shown in Table 2. On the basis of the Rietveld refinement, the experimental powder X-ray diffraction pattern coincides with the theoretical pattern calculated from the single-crystal X-ray study.

8. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. The H atoms were placed in calculated positions and treated as riding, with C—H = 0.96 Å, O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(C,O) for methyl and hydroxyl groups, and C_{ar}—H = 0.93 Å (ar is aromatic), Csp^2—H = 0.97 Å, N—H = 0.89 Å and U_{iso}(H) = 1.2U_{eq}(C,N) for all other H atoms.

Table 3
Experimental details.

Crystal data	
Chemical formula	$C_{15}H_{12}NO_3^+ \cdot C_4H_{12}NO_3^-$
M_r	376.40
Crystal system, space group	Monoclinic, $I2/a$
Temperature (K)	293
a, b, c (Å)	20.3154 (13), 6.6466 (4), 28.0770 (15)
β (°)	96.389 (6)
V (Å^3)	3767.6 (4)
Z	8
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.10
Crystal size (mm)	0.56 × 0.22 × 0.07
Data collection	
Diffractometer	Rigaku Xcalibur Sapphire3
Absorption correction	Multi-scan (*CrysAlis PRO*; Rigaku OD, 2018)
T_{min}, T_{max}	0.584, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	14262, 3734, 2314
R_{int}	0.085
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.619
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.057, 0.179, 1.04
No. of reflections	3734
No. of parameters	249
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.16, −0.19

Computer programs: *CrysAlis PRO* (Rigaku OD, 2018), *SHELXS97* (Sheldrick, 2008), *SHELXL2018* (Sheldrick, 2015) and *OLEX2* (Dolomanov *et al.*, 2009).

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References

Bhattacharya, A., Chattopadhyay, B., Chakraborty, S., Roy, B. N., Singh, G. P., Godbole, H. M., Rananaware, U. B. & Mukherjee, A. K. (2012). *J. Pharm. Biomed. Anal.* **70**, 280–287.

Boyer, K. C., McDonald, P. & Zoetis, T. (2010). *Int. J. Toxicol.* **29**, 467–478.

Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.

Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262.

Gilman, G. (2001). *The Pharmacological Basis of Therapeutics*, 10th ed., p. 1825. New York: McGraw–Hill Professional.

Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* B**72**, 171–179.

He, A. & Hersh, E. V. (2012). *Curr. Med. Res. Opin.* **28**, 1873–1880.

Jamali, F., Mehvar, R. & Pasutto, F. M. (1989). *J. Pharm. Sci.* **78**, 695–715.

Jasinski, J., Butcher, R., Narayana, B., Swamy, M. & Yathirajan, H. (2008). *Anal. Sci. X*, **24**, X205–X206.

Joishy, S. K. & Walsh, D. (1998). *J. Pain Symptom Manage.* **16**, 334–339.

Litvak, K. M. & McEvoy, G. K. (1990). *Clin. Pharm.* **9**, 921–935.

Mroszczak, E., Combs, D., Chaplin, M., Tsina, I., Tarnowski, T., Rocha, C., Tam, Y., Boyd, A., Young, J., Depass, L. & Clin, J. (1996). *Pharmacology*, **36**, 521–539.

Mroszczak, E. J., Jung, D., Yee, J., Bynum, L., Sevelius, H. & Massey, I. (1990). *Pharmacotherapy*, **10**, 33S–39S.

Orpen, A. G., Brammer, L., Allen, F. H., Kennard, O., Watson, D. G. & Taylor, R. (1994). *Structure Correlation*, edited by H. Bürgi & J. Dunitz, pp. 752–858. Weinheim: VCH Publishers.

Rigaku OD (2018). *CrysAlis PRO*. Rigaku Oxford Diffraction Ltd, Yarnton, Oxfordshire, England.

Rodriguez-Carvajal, J. & Roisnel, T. (1998). *Int. Union Crystallogr. Newslett.* **20**, 35–36.

Rossi, P., Paoli, P., Chelazzi, L., Milazzo, S., Biagi, D., Valleri, M., Ienco, A., Valtancoli, B. & Conti, L. (2020). *Cryst. Growth Des.* **20**, 226–236.

Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.

Spackman, P. R., Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Jayatilaka, D. & Spackman, M. A. (2021). *J. Appl. Cryst.* **54**, 1006–1011.

Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Spackman, P. R., Jayatilaka, D. & Spackman, M. A. (2017). *CrystalExplorer17*. University of Western Australia. https://crystalexplorer.net/.

Zhang, Ch.-G., Li, Yu., Luo, Ya.-H. & Sun, B.-W. (2013). *J. Chem. Crystallogr.* **43**, 576–584.

supporting information

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Computing details

1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate

Crystal data

$C_{15}H_{12}NO_3^+\cdot C_4H_{12}NO_3^-$
$M_r = 376.40$
Monoclinic, $I2/a$
$a = 20.3154$ (13) Å
$b = 6.6466$ (4) Å
$c = 28.0770$ (15) Å
$\beta = 96.389$ (6)°
$V = 3767.6$ (4) Å^3
$Z = 8$
$F(000) = 1600$
$D_x = 1.327$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 2134 reflections
$\theta = 3.4$–22.7°
$\mu = 0.10$ mm^{-1}
$T = 293$ K
Prism, colourless
0.56 × 0.22 × 0.07 mm

Data collection

Rigaku Xcalibur Sapphire3 diffractometer
Detector resolution: 16.1827 pixels mm^{-1}
ω scans
Absorption correction: multi-scan (CrysAlis PRO; Rigaku OD, 2018)
$T_{min} = 0.584$, $T_{max} = 1.000$
14262 measured reflections
3734 independent reflections
2314 reflections with $I > 2\sigma(I)$
$R_{int} = 0.085$
$\theta_{max} = 26.1°$, $\theta_{min} = 3.2°$
$h = -23 \rightarrow 25$
$k = -8 \rightarrow 8$
$l = -34 \rightarrow 33$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.057$
$wR(F^2) = 0.179$
$S = 1.04$
3734 reflections
249 parameters
0 restraints
Hydrogen site location: inferred from neighbouring sites
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0717P)^2 + 0.7854P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.48593 (10)	0.3303 (3)	0.44078 (6)	0.0655 (5)
O2	0.46522 (9)	0.0085 (3)	0.42405 (6)	0.0637 (5)
O3	0.35641 (11)	0.1436 (3)	0.20682 (6)	0.0760 (6)
O4	0.40104 (11)	0.3531 (3)	0.61861 (7)	0.0787 (6)
H4	0.384403	0.347567	0.643885	0.118*
O5	0.35501 (13)	0.5730 (3)	0.48159 (7)	0.0869 (7)
H5	0.364973	0.692435	0.483945	0.130*
O6	0.39150 (10)	−0.0296 (3)	0.49643 (7)	0.0668 (5)
H6A	0.415208	−0.019853	0.474738	0.100*
N1	0.45003 (10)	0.3145 (3)	0.53307 (6)	0.0518 (5)
H1A	0.457862	0.325858	0.502620	0.062*
H1B	0.470895	0.206582	0.546029	0.062*
H1C	0.464673	0.423879	0.549180	0.062*
N4	0.42765 (10)	0.2619 (3)	0.29261 (6)	0.0528 (5)
C1	0.50058 (13)	0.2230 (4)	0.36263 (8)	0.0555 (6)
H1	0.542985	0.294588	0.364741	0.085 (3)*
C2	0.50442 (16)	0.0358 (4)	0.33042 (9)	0.0688 (8)
H2A	0.549840	0.012643	0.324234	0.085 (3)*
H2B	0.488949	−0.082141	0.346188	0.085 (3)*
C3	0.46117 (17)	0.0740 (4)	0.28378 (10)	0.0738 (8)
H3A	0.487734	0.087891	0.257319	0.085 (3)*
H3B	0.429569	−0.034252	0.276724	0.085 (3)*
C4	0.48286 (13)	0.1827 (4)	0.41333 (9)	0.0535 (6)
C5	0.38028 (13)	0.3803 (4)	0.26721 (8)	0.0523 (6)
C6	0.37220 (14)	0.5445 (4)	0.29638 (9)	0.0602 (7)
H6	0.343025	0.650623	0.288933	0.072*
C7	0.41437 (15)	0.5256 (4)	0.33830 (9)	0.0639 (7)
H7	0.418692	0.615070	0.363935	0.077*
C7A	0.44886 (13)	0.3480 (4)	0.33472 (8)	0.0533 (6)
C8	0.34637 (14)	0.3153 (4)	0.22233 (8)	0.0562 (6)
C9	0.30014 (13)	0.4507 (4)	0.19276 (8)	0.0545 (6)
C10	0.31445 (15)	0.6490 (4)	0.18368 (9)	0.0645 (7)
H10	0.351325	0.709561	0.200381	0.077*
C11	0.27477 (18)	0.7578 (5)	0.15022 (10)	0.0821 (9)
H11	0.285832	0.889880	0.143567	0.099*
C12	0.21897 (18)	0.6728 (6)	0.12661 (11)	0.0872 (10)
H12	0.192488	0.746515	0.103745	0.105*
C13	0.20222 (16)	0.4788 (7)	0.13672 (11)	0.0866 (10)
H13	0.163240	0.423167	0.121828	0.104*
C14	0.24326 (15)	0.3657 (5)	0.16906 (10)	0.0714 (8)
H14	0.232702	0.232434	0.174914	0.086*
C15	0.37749 (13)	0.2929 (4)	0.53536 (8)	0.0551 (6)
C16	0.36743 (15)	0.2196 (4)	0.58508 (9)	0.0663 (7)
H16A	0.320578	0.217037	0.588954	0.085 (3)*
H16B	0.384926	0.084518	0.589999	0.085 (3)*

C17	0.34462 (15)	0.4973 (4)	0.52700 (9)	0.0673 (7)
H17A	0.297458	0.484927	0.529118	0.085 (3)*
H17B	0.362784	0.590435	0.551643	0.085 (3)*
C18	0.35096 (14)	0.1436 (4)	0.49694 (10)	0.0646 (7)
H18A	0.306589	0.103162	0.502539	0.085 (3)*
H18B	0.348183	0.208564	0.465850	0.085 (3)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0780 (14)	0.0680 (12)	0.0499 (10)	−0.0143 (10)	0.0042 (9)	−0.0046 (9)
O2	0.0646 (13)	0.0603 (11)	0.0655 (11)	−0.0026 (9)	0.0045 (9)	0.0066 (8)
O3	0.1105 (18)	0.0615 (12)	0.0521 (10)	0.0029 (11)	−0.0087 (10)	−0.0072 (9)
O4	0.0914 (16)	0.0912 (14)	0.0542 (11)	−0.0137 (12)	0.0111 (11)	−0.0006 (10)
O5	0.128 (2)	0.0646 (12)	0.0634 (12)	0.0050 (13)	−0.0105 (12)	0.0097 (9)
O6	0.0719 (14)	0.0568 (11)	0.0715 (12)	−0.0045 (9)	0.0081 (10)	−0.0008 (9)
N1	0.0542 (14)	0.0564 (12)	0.0435 (10)	−0.0057 (9)	−0.0004 (9)	0.0008 (8)
N4	0.0605 (14)	0.0546 (12)	0.0425 (11)	−0.0005 (10)	0.0014 (9)	−0.0023 (9)
C1	0.0518 (16)	0.0641 (15)	0.0495 (13)	−0.0002 (12)	0.0014 (11)	0.0004 (11)
C2	0.077 (2)	0.0726 (18)	0.0556 (15)	0.0166 (15)	0.0014 (14)	−0.0042 (13)
C3	0.093 (2)	0.0651 (17)	0.0601 (16)	0.0177 (16)	−0.0038 (15)	−0.0089 (13)
C4	0.0460 (15)	0.0620 (16)	0.0500 (13)	0.0002 (11)	−0.0059 (10)	0.0021 (12)
C5	0.0540 (16)	0.0590 (14)	0.0425 (12)	−0.0018 (12)	−0.0003 (11)	0.0009 (11)
C6	0.0700 (18)	0.0572 (15)	0.0514 (14)	0.0053 (13)	−0.0021 (12)	−0.0032 (11)
C7	0.078 (2)	0.0625 (16)	0.0483 (13)	0.0064 (14)	−0.0069 (13)	−0.0095 (12)
C7A	0.0583 (16)	0.0537 (14)	0.0465 (13)	−0.0026 (11)	0.0002 (11)	−0.0022 (10)
C8	0.0624 (17)	0.0608 (15)	0.0450 (13)	−0.0079 (12)	0.0043 (11)	0.0004 (11)
C9	0.0526 (16)	0.0680 (16)	0.0421 (12)	−0.0010 (12)	0.0020 (11)	−0.0045 (11)
C10	0.0650 (19)	0.0667 (17)	0.0588 (15)	−0.0027 (13)	−0.0068 (13)	−0.0028 (12)
C11	0.096 (3)	0.077 (2)	0.0690 (18)	0.0207 (18)	−0.0128 (18)	0.0017 (15)
C12	0.077 (2)	0.116 (3)	0.0642 (19)	0.033 (2)	−0.0136 (16)	−0.0076 (18)
C13	0.0513 (19)	0.139 (3)	0.0670 (19)	0.003 (2)	−0.0064 (14)	−0.022 (2)
C14	0.0592 (18)	0.095 (2)	0.0592 (16)	−0.0165 (16)	0.0048 (14)	−0.0107 (14)
C15	0.0510 (16)	0.0599 (15)	0.0525 (14)	−0.0032 (12)	−0.0029 (11)	0.0013 (11)
C16	0.0646 (19)	0.0730 (18)	0.0619 (16)	−0.0060 (14)	0.0102 (14)	0.0032 (13)
C17	0.0662 (19)	0.0673 (17)	0.0658 (17)	0.0085 (14)	−0.0042 (14)	0.0018 (13)
C18	0.0521 (17)	0.0678 (17)	0.0708 (17)	−0.0031 (13)	−0.0068 (13)	−0.0043 (13)

Geometric parameters (Å, º)

O1—C4	1.245 (3)	C5—C8	1.434 (3)
O2—C4	1.258 (3)	C6—H6	0.9300
O3—C8	1.247 (3)	C6—C7	1.382 (4)
O4—H4	0.8200	C7—H7	0.9300
O4—C16	1.413 (3)	C7—C7A	1.382 (4)
O5—H5	0.8200	C8—C9	1.486 (4)
O5—C17	1.408 (3)	C9—C10	1.379 (4)
O6—H6A	0.8200	C9—C14	1.388 (4)

O6—C18	1.416 (3)	C10—H10	0.9300
N1—H1A	0.8900	C10—C11	1.374 (4)
N1—H1B	0.8900	C11—H11	0.9300
N1—H1C	0.8900	C11—C12	1.370 (5)
N1—C15	1.489 (3)	C12—H12	0.9300
N4—C3	1.457 (3)	C12—C13	1.371 (5)
N4—C5	1.379 (3)	C13—H13	0.9300
N4—C7A	1.341 (3)	C13—C14	1.385 (4)
C1—H1	0.9800	C14—H14	0.9300
C1—C2	1.545 (4)	C15—C16	1.514 (3)
C1—C4	1.530 (3)	C15—C17	1.521 (4)
C1—C7A	1.491 (3)	C15—C18	1.520 (3)
C2—H2A	0.9700	C16—H16A	0.9700
C2—H2B	0.9700	C16—H16B	0.9700
C2—C3	1.515 (4)	C17—H17A	0.9700
C3—H3A	0.9700	C17—H17B	0.9700
C3—H3B	0.9700	C18—H18A	0.9700
C5—C6	1.385 (3)	C18—H18B	0.9700

C16—O4—H4	109.5	O3—C8—C5	120.1 (2)
C17—O5—H5	109.5	O3—C8—C9	118.5 (2)
C18—O6—H6A	109.5	C5—C8—C9	121.4 (2)
H1A—N1—H1B	109.5	C10—C9—C8	123.3 (2)
H1A—N1—H1C	109.5	C10—C9—C14	118.8 (3)
H1B—N1—H1C	109.5	C14—C9—C8	117.5 (3)
C15—N1—H1A	109.5	C9—C10—H10	119.7
C15—N1—H1B	109.5	C11—C10—C9	120.6 (3)
C15—N1—H1C	109.5	C11—C10—H10	119.7
C5—N4—C3	135.6 (2)	C10—C11—H11	119.9
C7A—N4—C3	113.9 (2)	C12—C11—C10	120.3 (3)
C7A—N4—C5	110.5 (2)	C12—C11—H11	119.9
C2—C1—H1	109.0	C11—C12—H12	120.0
C4—C1—H1	109.0	C11—C12—C13	119.9 (3)
C4—C1—C2	115.8 (2)	C13—C12—H12	120.0
C7A—C1—H1	109.0	C12—C13—H13	120.0
C7A—C1—C2	102.7 (2)	C12—C13—C14	120.1 (3)
C7A—C1—C4	111.2 (2)	C14—C13—H13	120.0
C1—C2—H2A	110.1	C9—C14—H14	119.9
C1—C2—H2B	110.1	C13—C14—C9	120.1 (3)
H2A—C2—H2B	108.4	C13—C14—H14	119.9
C3—C2—C1	108.0 (2)	N1—C15—C16	107.9 (2)
C3—C2—H2A	110.1	N1—C15—C17	109.1 (2)
C3—C2—H2B	110.1	N1—C15—C18	107.9 (2)
N4—C3—C2	103.5 (2)	C16—C15—C17	109.1 (2)
N4—C3—H3A	111.1	C16—C15—C18	111.8 (2)
N4—C3—H3B	111.1	C18—C15—C17	111.0 (2)
C2—C3—H3A	111.1	O4—C16—C15	107.9 (2)
C2—C3—H3B	111.1	O4—C16—H16A	110.1

H3A—C3—H3B	109.0	O4—C16—H16B	110.1
O1—C4—O2	125.0 (2)	C15—C16—H16A	110.1
O1—C4—C1	115.9 (2)	C15—C16—H16B	110.1
O2—C4—C1	119.1 (2)	H16A—C16—H16B	108.4
N4—C5—C6	105.4 (2)	O5—C17—C15	110.6 (2)
N4—C5—C8	121.5 (2)	O5—C17—H17A	109.5
C6—C5—C8	132.8 (2)	O5—C17—H17B	109.5
C5—C6—H6	125.4	C15—C17—H17A	109.5
C7—C6—C5	109.2 (2)	C15—C17—H17B	109.5
C7—C6—H6	125.4	H17A—C17—H17B	108.1
C6—C7—H7	126.7	O6—C18—C15	112.2 (2)
C7A—C7—C6	106.7 (2)	O6—C18—H18A	109.2
C7A—C7—H7	126.7	O6—C18—H18B	109.2
N4—C7A—C1	111.3 (2)	C15—C18—H18A	109.2
N4—C7A—C7	108.2 (2)	C15—C18—H18B	109.2
C7—C7A—C1	140.4 (2)	H18A—C18—H18B	107.9

O3—C8—C9—C10	−133.1 (3)	C6—C5—C8—O3	−168.6 (3)
O3—C8—C9—C14	39.5 (3)	C6—C5—C8—C9	13.0 (4)
N1—C15—C16—O4	53.9 (3)	C6—C7—C7A—N4	−0.8 (3)
N1—C15—C17—O5	60.4 (3)	C6—C7—C7A—C1	−179.8 (3)
N1—C15—C18—O6	45.6 (3)	C7A—N4—C3—C2	5.9 (3)
N4—C5—C6—C7	0.5 (3)	C7A—N4—C5—C6	−1.0 (3)
N4—C5—C8—O3	4.4 (4)	C7A—N4—C5—C8	−175.7 (2)
N4—C5—C8—C9	−174.0 (2)	C7A—C1—C2—C3	6.5 (3)
C1—C2—C3—N4	−7.5 (3)	C7A—C1—C4—O1	−69.9 (3)
C2—C1—C4—O1	173.4 (2)	C7A—C1—C4—O2	108.6 (3)
C2—C1—C4—O2	−8.1 (3)	C8—C5—C6—C7	174.3 (3)
C2—C1—C7A—N4	−3.0 (3)	C8—C9—C10—C11	169.7 (3)
C2—C1—C7A—C7	176.0 (3)	C8—C9—C14—C13	−172.6 (2)
C3—N4—C5—C6	−178.0 (3)	C9—C10—C11—C12	2.4 (5)
C3—N4—C5—C8	7.4 (4)	C10—C9—C14—C13	0.4 (4)
C3—N4—C7A—C1	−1.9 (3)	C10—C11—C12—C13	0.7 (5)
C3—N4—C7A—C7	178.8 (2)	C11—C12—C13—C14	−3.1 (5)
C4—C1—C2—C3	127.8 (3)	C12—C13—C14—C9	2.5 (4)
C4—C1—C7A—N4	−127.5 (2)	C14—C9—C10—C11	−2.9 (4)
C4—C1—C7A—C7	51.5 (4)	C16—C15—C17—O5	178.0 (2)
C5—N4—C3—C2	−177.2 (3)	C16—C15—C18—O6	−72.9 (3)
C5—N4—C7A—C1	−179.5 (2)	C17—C15—C16—O4	−64.5 (3)
C5—N4—C7A—C7	1.2 (3)	C17—C15—C18—O6	165.0 (2)
C5—C6—C7—C7A	0.2 (3)	C18—C15—C16—O4	172.3 (2)
C5—C8—C9—C10	45.3 (4)	C18—C15—C17—O5	−58.4 (3)
C5—C8—C9—C14	−142.0 (2)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O3^{i}	0.82	1.92	2.731 (3)	172

O5—H5···O6^{ii}	0.82	1.95	2.762 (3)	174
O6—H6*A*···O2	0.82	1.85	2.667 (2)	177
N1—H1*A*···O1	0.89	1.89	2.771 (2)	172
N1—H1*B*···O2^{iii}	0.89	2.05	2.926 (3)	169
N1—H1*C*···O1^{iv}	0.89	1.92	2.756 (3)	155

Symmetry codes: (i) *x*, −*y*+1/2, *z*+1/2; (ii) *x*, *y*+1, *z*; (iii) −*x*+1, −*y*, −*z*+1; (iv) −*x*+1, −*y*+1, −*z*+1.