

Received 8 February 2023

Accepted 8 March 2023

Edited by J. T. Mague, Tulane University, USA

Keywords: crystal structure; slow evaporation; hydrogen bonding; Hirshfeld surface analysis; antibacterial drug.

CCDC reference: 2194837

Supporting information: this article has supporting information at journals.iucr.org/e

Co-crystal of nadifloxacin with oxalic acid

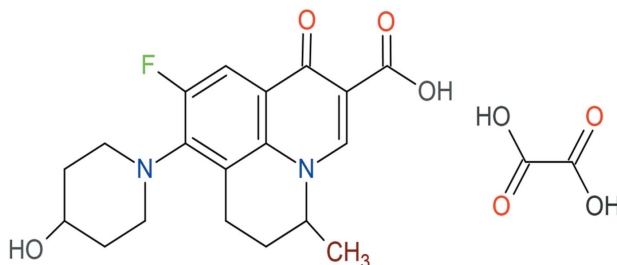
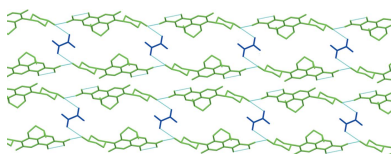
Geethanjali N. Karthammaiah, Sreenivasa Rao Amaraneni and Anand K. Solomon*

Dayananda Sagar University, Karnataka, India. *Correspondence e-mail: anand.dcb@gmail.com

The 2:1 co-crystal of nadifloxacin [systematic name: 9-fluoro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2-*l*-*ij*]quinoline-2-carboxylic acid] with oxalic acid, C₁₉H₂₁FN₂O₄·0.5C₂H₂O₄, was prepared by slow evaporation from a chloroform:acetone solvent system. Nadifloxacin belongs to the group of antibacterial drugs. The co-crystal is stabilized through an intramolecular O—H···O bond and intermolecular hydrogen bonds. It was studied by FT-IR spectroscopy, differential scanning calorimetry and X-ray diffraction. Hirshfeld surface analysis indicated that the major contribution to the packing is from O···H/H···O interactions.

1. Chemical context

A co-crystal is a multi-component molecular complex with a definite stoichiometric ratio of two compounds that can interact through hydrogen bonds, van der Waals forces, and π -stacking interactions to name just a few (Stahly 2009; Vishweshwar *et al.*, 2006). The formation of multi-component crystals, *i.e.* salts and co-crystals through a crystal-engineering approach has been demonstrated to be a versatile tool to improve the physicochemical properties of APIs (active pharmaceutical ingredients) including solubility, dissolution rate, stability, tableability, *etc.* (Mannava *et al.*, 2021, 2022). Co-crystals can be synthesized by various methods such as solvent-assisted grinding, sonication and slow evaporation among others. Co-crystals of fluoroquinolone antibiotics with organic acids have been reported to exhibit higher solubility than the parent molecule (Reddy *et al.*, 2011). Nadifloxacin fluoroquinolone (Kido & Hashimoto, 1994) is an antibiotic used for the treatment of commonly formed acne, acting against *Staphylococcus aureus*, *Streptococcus* spp., coagulase-negative staphylococci (CNS), *Propionibacterium acnes*, and *Propionibacterium granulosum* strains (Nenoff *et al.*, 2004). It also shows antibacterial activity against skin infections (Kumar & Khatak, 2021). Here we report the structure of a co-crystal formed between nadifloxacin (NAD) and oxalic acid (OA), which is stabilized through intermolecular hydrogen bonds.



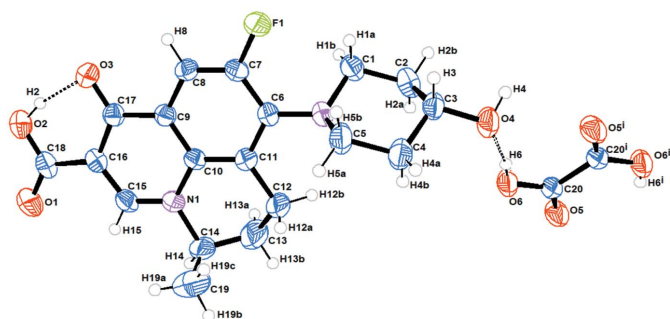


Figure 1
A perspective view of the title compound with labeling scheme and 50% probability ellipsoids. Symmetry code: (i) $-x + 2, -y + 2, -z + 2$.

2. Structural commentary

The title co-crystal is shown in Fig. 1. The asymmetric unit is comprised of one NAD molecule in a general position and half of an OA molecule, located about a center of inversion, so the co-crystal is formulated as a 2:1 NAD:OA adduct. NAD is a non-planar molecule [$C7-C6-N2-C5 = 104.0(3)^\circ$]. The adduct forms through $O6-H6 \cdots O4$ hydrogen bonds (Table 1) and crystallizes in the triclinic crystal system in space group $P\bar{1}$. An intramolecular $O2-H2 \cdots O3$ hydrogen bond is formed in the NAD molecule with an $R_1^1(6)$ ring motif of (Fig. 1).

3. Supramolecular features

In the crystal, $O4-H4 \cdots O1^{iii}$ hydrogen bonds (Fig. 2, Table 1) forms chains of NAD molecules [graph-set motif $S(6)$] (Etter

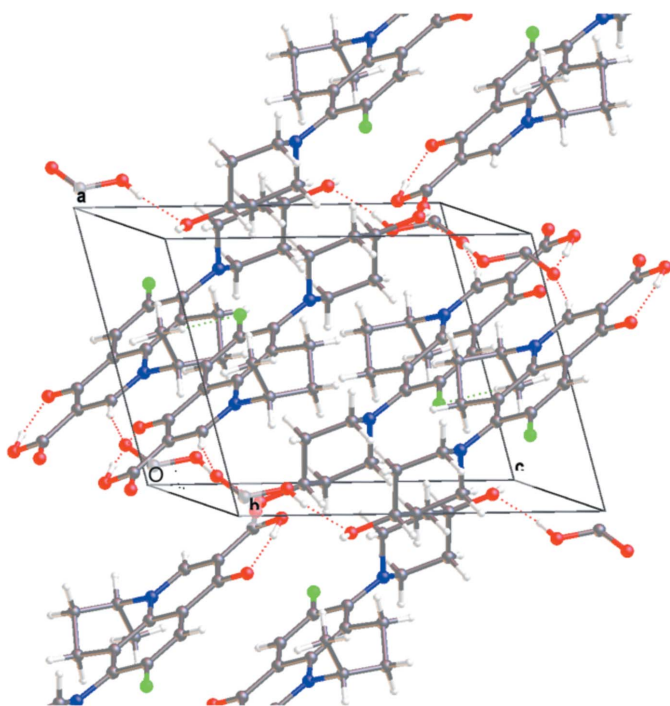


Figure 2
Packing of the title compound with hydrogen bonds depicted by dashed lines.

Table 1
Hydrogen-bond geometry ($\text{\AA}, ^\circ$).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$C15-H15 \cdots O5^i$	0.93	2.35	3.266 (3)	167
$C19-H19B \cdots F1^{ii}$	0.96	2.50	3.456 (4)	174
$O4-H4 \cdots O1^{iii}$	0.87 (4)	1.99 (4)	2.833 (3)	161 (4)
$O2-H2 \cdots O3$	0.87 (5)	1.68 (5)	2.536 (3)	165 (5)
$O6-H6 \cdots O4$	0.81 (4)	1.85 (4)	2.644 (3)	169 (4)

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

et al., 1990)] extending parallel to $(10\bar{1})$. The chains are linked by inversion-related $O6-H6 \cdots O4$ hydrogen bonds between NAD and OA, forming ribbons of the 2:1 adducts parallel to $(11\bar{1})$ (Fig. 3). The hydroxyl oxygen $O4$ of NAD is involved in a bifurcated interaction acting as both acceptor ($O6-H6 \cdots O4$) and donor ($O4-H4 \cdots O1^{iii}$). A larger ring motif is formed with two molecules of nadifloxacin and two molecules of oxalic acid having an $R_4^4(32)$ graph-set motif (Fig. 4).

4. Database survey

A number of related structures have been reported in the literature, including a norfloxacin-oxalate dihydrate adduct with an $R_3^3(12)$ ring motif and ciprofloxacin malonate dihydrate in which an $R_4^4(16)$ ring motif is observed. Both adducts are connected through tetrameric clusters of water molecules (Reddy *et al.*, 2011). In the ofloxacin adduct with diphenic acid, the components are connected by charge-assisted strong bifurcated $N-H^+ \cdots O$ hydrogen bonds, forming $R_1^1(4)$ ring motifs (Suresh *et al.*, 2020). An enrofloxacin-pimelic acid adduct shows an $R_8^8(20)$ ring motif of (Yang *et al.*, 2022), a norfloxacin-pimelic acid adduct an $R_2^2(8)$ ring motif while in

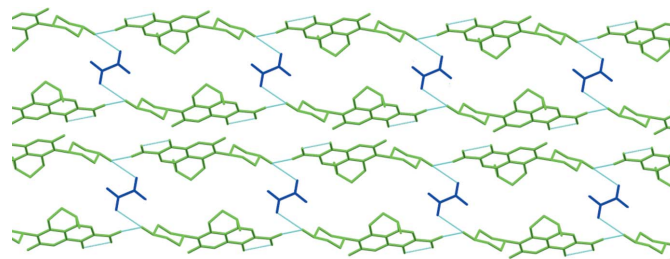


Figure 3
Two ribbons of NAD and OA formed by hydrogen bonds.

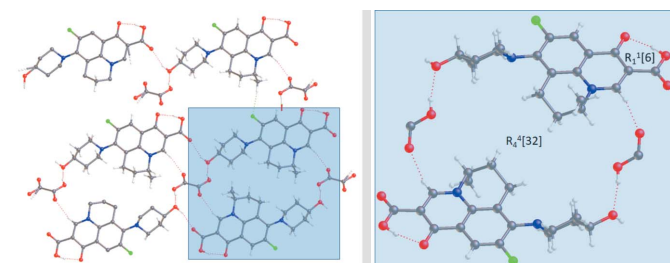


Figure 4
The ring motif between oxalic acid and nadifloxacin in the co-crystal.

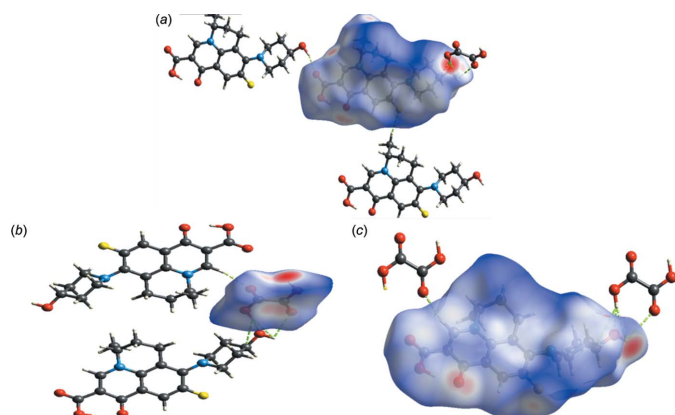


Figure 5
 Calculated Hirshfeld surfaces mapped over d_{norm} for (a) NAD, (b) OA and (c) the NAD–OA co-crystal to visualize the intermolecular interactions.

the structure of a ciprofloxacin–suberic acid co-crystal, $R_6^4(12)$ and $R_3^3(15)$ ring motifs are observed (O'Malley *et al.*, 2022) and a pefloxacin–oxalic acid salt forms an $R_1^2(5)$ ring motif (Nangia *et al.*, 2018). Several polymorphs of nalidixic acid and co-crystals of it with various hydroxyl compounds show bifurcated hydrogen bonds (Gangavaram *et al.*, 2012), while a nicorandil–fumaric acid co-crystal features hydrogen bonds with a dimeric $R_2^2(1)$ ring motif (Mannava *et al.*, 2021, 2022). Pharmaceuticals co-crystals (Vishweshwar *et al.*, 2006) pave way for new chemical entities with tuned physicochemical properties.

5. Synthesis and crystallization

NAD was purchased from Swapnroop Drugs and Pharmaceuticals, India, and the remaining chemicals were purchased from Sigma-Aldrich, India. All chemicals and solvents were of analytical grade.

NAD (50 mg, 0.360 mmol) and OA (17 mg, 0.126 mmol) were dissolved in a mixed chloroform–acetone solvent (5 ml:5 ml), heated on a water bath for 15–20 min and then kept undisturbed for slow evaporation. Crystals were obtained

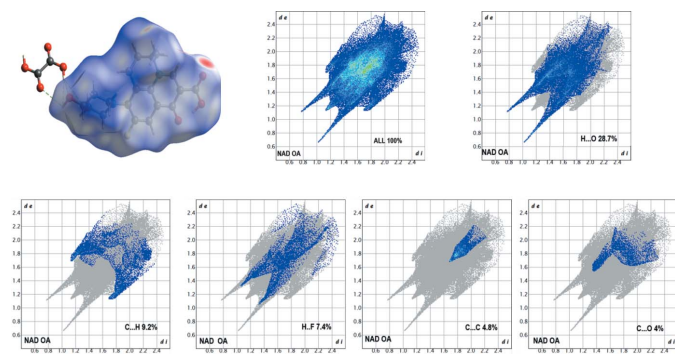


Figure 6
 Two-dimensional fingerprint plots and relative contribution of various interactions to the Hirshfeld surface of the NAD molecule.

at room temperature after 24–48 h. They were characterized by FTIR, DSC, and single crystal XRD.

Infrared spectra of NAD·OA crystals were recorded using FT–IR spectroscopy (Thermo-Nicolet 6700 FTIR–NIR spectrometer) with the samples made in KBr pellets. *Omic* software (Thermo Scientific, Waltham, MA) was used to analyze the data. Each sample was scanned in the range 400–4000 cm^{-1}

In the IR spectrum, the $\text{C}=\text{O}$ stretching frequencies for NAD (carboxylic acid group) and OA were observed at 1716 cm^{-1} and 1682 cm^{-1} , respectively, while in the co-crystal, the former now appears at 1734 cm^{-1} . Differential Scanning Calorimetric (DSC) analysis indicated the melting points of NAD and OA to be 478.9 K and 387.8 K, respectively, while the melting point of the co-crystal is 438.8 K.

6. Hirshfeld Surface analysis

Hirshfeld analyses performed using *Crystal Explorer17* (Spackman *et al.*, 2009, 2021) are shown in Fig. 5. The surface mapping of this function highlights the donor and acceptor equally and it is therefore a powerful tool for analyzing intermolecular interactions such as hydrogen bonds. Intermolecular interactions within the crystal were mapped by d_{norm} and were determined for NAD and OA separately, as well as for the adduct of the two [Fig. 5(a)–(c), respectively (Bairagi *et al.*, 2019)]. The interactions generating the crystal packing were investigated from the Hirshfeld analysis using the two-dimensional fingerprint plots (Fig. 6). These show that for NAD, $\text{H}\cdots\text{H}$ contacts make the highest contribution to the interactions (43.4%), while $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ contribute 28.7%, $\text{C}\cdots\text{H}/\text{H}\cdots\text{C}$ 9.2% and $\text{F}\cdots\text{H}/\text{H}\cdots\text{F}$ 7.4%. The smallest contributions are from $\text{C}\cdots\text{O}$ and $\text{O}\cdots\text{O}$ contacts (4.8% and 0.7%, respectively). The two-dimensional fingerprint plots for oxalic acid (Fig. 7) show that $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ contacts make the highest contribution (71.7%), with $\text{H}\cdots\text{H}$ at 14.7%, and the smallest interactions being $\text{C}\cdots\text{O}$ (6.7%) and $\text{O}\cdots\text{O}$ (4.7%).

7. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. C-bound H atoms were positioned

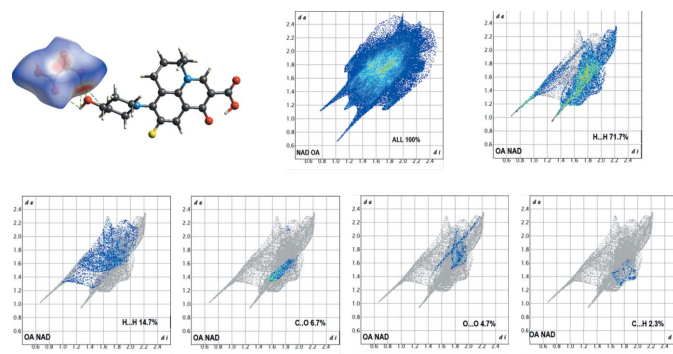


Figure 7
 Two-dimensional fingerprint plots and relative contribution of various interactions to the Hirshfeld surface of the OA molecule.

Table 2

Experimental details.

Crystal data	
Chemical formula	C ₁₉ H ₂₁ FN ₂ O ₄ ·0.5C ₂ H ₂ O ₄
<i>M</i> _r	405.39
Crystal system, space group	Triclinic, <i>P</i> $\bar{1}$
Temperature (K)	297
<i>a</i> , <i>b</i> , <i>c</i> (Å)	8.8187 (4), 9.6963 (4), 12.3804 (6)
α , β , γ (°)	100.099 (2), 97.556 (2), 109.858 (2)
<i>V</i> (Å ³)	959.16 (8)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.11
Crystal size (mm)	0.23 × 0.18 × 0.05
Data collection	
Diffractometer	Bruker D8 VENTURE with PHOTON II detector
Absorption correction	Multi-scan (<i>SADABS</i> ; Bruker, 2016)
<i>T</i> _{min} , <i>T</i> _{max}	0.680, 0.960
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	40338, 3753, 2936
<i>R</i> _{int}	0.066
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.617
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.062, 0.204, 1.07
No. of reflections	3753
No. of parameters	274
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.82, -0.37

Computer programs: *APEX3*, *SAINT* and *XPREP* (Bruker, 2016), *SHELXT2018/2* (Sheldrick, 2015a), *SHELXL2018/3* (Sheldrick, 2015b), *ORTEP-3 for Windows* (Farrugia, 2012) and *Mercury* (Macrae *et al.*, *et al.*, 2020).

geometrically (C–H = 0.93–0.98 Å) and refined as riding with *U*_{iso}(H) = 1.2–1.5*U*_{eq}(C). C-bound O atoms were freely refined.

Acknowledgements

Support of the SCXRD data collection and structure solution by IIT Madras is duly acknowledged. Authors contribution are as follows. Conceptualization, methodology and supervision, AKS; visualization, validation and project administration, SRA; investigation and writing – original draft, GNK.

References

- Bairagi, K. M., Pal, P., Bhandary, S., Venugopala, K. N., Chopra, D. & Nayak, S. K. (2019). *Acta Cryst.* **E75**, 1712–1718.
- Bruker. (2016). *APEX3*, *SAINT*, *XPREP* and *SADABS*. Bruker AXS Inc. Madison, Wisconsin, USA.
- Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* **B46**, 256–262.
- Farrugia, L. J. (2012). *J. Appl. Cryst.* **45**, 849–854.
- Gangavaram, S., Raghavender, S., Sanphui, P., Pal, S., Manjunatha, S. G., Nambiar, S. & Nangia, A. K. (2012). *Cryst. Growth Des.* **12**, 4963–4971.
- Kido, M. & Hashimoto, K. (1994). *Chem. Pharm. Bull.* **42**, 4, 872–876. Vol. 42 No. 4. DOI: 10.1248/cpb.42.872
- Kumar, P. & Khatak, S. (2021). *Int. Res. J. Pharm.* **12**, 4, 23–33. DOI: 10.7897/2230-8407.1204130.
- Macrae, C. F., Sovago, I., Cottrell, S. J., Galek, P. T. A., McCabe, P., Pidcock, E., Platings, M., Shields, G. P., Stevens, J. S., Towler, M. & Wood, P. A. (2020). *J. Appl. Cryst.* **53**, 226–235.
- Mannava, C. M. K., Bommaka, M. K., Dandela, R., Solomon, A. K. & Nangia, A. K. (2022). *Chem. Commun.* **58**, 5582–5585.
- Mannava, C. M. K., Gunnam, A., Lodagekar, A., Shastri, N. R., Nangia, A. K. & Solomon, A. K. (2021). *CrystEngComm*, **23**, 227–237.
- Nangia, A., Gunnam, A. & Kuthuru, S. (2018). *Cryst. Growth Des.* **18**, 5, 2824–2835.
- Nenoff, P., Hausteine, U. F. & Hittel, N. (2004). *Chemotherapy*, **50**, 196–201.
- O'Malley, C., McArdle, P. & Erxleben, A. (2022). *Cryst. Growth Des.* **22**, 3060–3071.
- Reddy, S. J., Ganesh, S. V., Nagalapalli, R., Dandela, R., Solomon, A. K., Kumar, K. A., Goud, R. N. & Nangia, A. K. (2011). *J. Pharm. Sci.* **100**, 3160–3176.
- Sheldrick, G. M. (2015a). *Acta Cryst.* **A71**, 3–8.
- Sheldrick, G. M. (2015b). *Acta Cryst.* **C71**, 3–8.
- Spackman, M. A. & Jayatilaka, D. (2009). *CrystEngComm*, **11**, 19–32.
- 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.
- Stahly, G. P. (2009). *Cryst. Growth Des.* **9**, 10, 4212–4229. DOI: 10.1021/cg900873t.
- Suresh, A., Gonde, S., Mondal, P. K., Sahoo, J. & Chopra, D. (2020). *J. Mol. Struct.* **20**, 128806.
- Vishweshwar, P., McMahon, J. A., Bis, J. A. & Zaworotko, M. J. (2006). *J. Pharm. Sci.* **95**, 499–516.
- Yang, S., Zhao, F., Pang, H., Chen, L., Shi, R. & Fang, B. (2022). *J. Mol. Struct.* **1265**, 133335.

supporting information

Acta Cryst. (2023). E79, 319-322 [https://doi.org/10.1107/S2056989023002244]

Co-crystal of nadifloxacin with oxalic acid

Geethanjali N. Karthammaiah, Sreenivasa Rao Amaraneni and Anand K. Solomon

Computing details

Data collection: *APEX3* (Bruker, 2016); cell refinement: *APEX3/SAINT* (Bruker, 2016); data reduction: *SAINT/XPREP* (Bruker, 2016); program(s) used to solve structure: *SHELXT2018/2* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2018/3* (Sheldrick, 2015b); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012) and *Mercury* (Macrae *et al.*, *et al.*, 2020); software used to prepare material for publication: *SHELXL2018/3* (Sheldrick, 2015b).

9-Fluoro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid–oxalic acid (2/1)

Crystal data

$C_{19}H_{21}FN_2O_4 \cdot 0.5C_2H_2O_4$

$M_r = 405.39$

Triclinic, $P\bar{1}$

$a = 8.8187$ (4) Å

$b = 9.6963$ (4) Å

$c = 12.3804$ (6) Å

$\alpha = 100.099$ (2)°

$\beta = 97.556$ (2)°

$\gamma = 109.858$ (2)°

$V = 959.16$ (8) Å³

$Z = 2$

$F(000) = 426$

$D_x = 1.404$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 9915 reflections

$\theta = 3.2$ – 30.5 °

$\mu = 0.11$ mm⁻¹

$T = 297$ K

Block, colourless

$0.23 \times 0.18 \times 0.05$ mm

Data collection

Bruker D8 VENTURE

diffractometer with PHOTON II detector

Radiation source: fine-focus sealed tube

Graphite monochromator

ω and ϕ scan

Absorption correction: multi-scan

(SADABS; Bruker, 2016)

$T_{\min} = 0.680$, $T_{\max} = 0.960$

40338 measured reflections

3753 independent reflections

2936 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.066$

$\theta_{\max} = 26.0$ °, $\theta_{\min} = 2.5$ °

$h = -10 \rightarrow 10$

$k = -11 \rightarrow 11$

$l = -15 \rightarrow 15$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.062$

$wR(F^2) = 0.204$

$S = 1.07$

3753 reflections

274 parameters

0 restraints

Primary atom site location: dual

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1129P)^2 + 0.4888P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.82$ e Å⁻³

$\Delta\rho_{\min} = -0.36$ 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 (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.7236 (3)	0.5092 (3)	0.5094 (2)	0.0446 (6)
H1A	0.786613	0.448224	0.487203	0.054*
H1B	0.610683	0.442369	0.503059	0.054*
C2	0.7960 (3)	0.6000 (3)	0.6298 (2)	0.0483 (6)
H2A	0.729953	0.657665	0.652556	0.058*
H2B	0.793775	0.531942	0.678930	0.058*
C3	0.9705 (3)	0.7053 (3)	0.64044 (19)	0.0409 (5)
H3	1.036372	0.644849	0.620463	0.049*
C4	0.9767 (4)	0.8070 (3)	0.5603 (2)	0.0622 (8)
H4A	1.090432	0.869057	0.563484	0.075*
H4B	0.919365	0.873448	0.582464	0.075*
C5	0.8971 (4)	0.7143 (3)	0.4413 (2)	0.0553 (7)
H5A	0.895998	0.781043	0.391546	0.066*
H5B	0.960975	0.655339	0.416318	0.066*
C6	0.6212 (3)	0.5592 (3)	0.32960 (19)	0.0373 (5)
C7	0.5750 (3)	0.4119 (3)	0.2639 (2)	0.0389 (5)
C8	0.4657 (3)	0.3567 (3)	0.16488 (19)	0.0383 (5)
H8	0.437499	0.257443	0.125721	0.046*
C9	0.3953 (3)	0.4508 (2)	0.12182 (18)	0.0341 (5)
C10	0.4407 (3)	0.5999 (3)	0.18365 (19)	0.0363 (5)
C11	0.5518 (3)	0.6541 (3)	0.2878 (2)	0.0438 (6)
C12	0.5871 (5)	0.8099 (3)	0.3573 (3)	0.0769 (11)
H12A	0.686634	0.881068	0.343893	0.092*
H12B	0.603838	0.809967	0.436303	0.092*
C13	0.4368 (6)	0.8586 (4)	0.3244 (3)	0.0826 (11)
H13A	0.338644	0.791540	0.342407	0.099*
H13B	0.460161	0.960507	0.366295	0.099*
C14	0.4095 (4)	0.8514 (3)	0.2020 (2)	0.0561 (7)
H14	0.311979	0.876237	0.183147	0.067*
C15	0.2626 (3)	0.6402 (3)	0.0415 (2)	0.0434 (6)
H15	0.218651	0.705629	0.015085	0.052*
C16	0.2152 (3)	0.4969 (3)	-0.02349 (19)	0.0394 (5)
C17	0.2785 (3)	0.3925 (3)	0.01480 (19)	0.0368 (5)
C18	0.0973 (3)	0.4525 (3)	-0.1316 (2)	0.0477 (6)
C19	0.5417 (6)	0.9504 (4)	0.1580 (4)	0.0956 (13)
H19A	0.507225	0.933707	0.078356	0.143*
H19B	0.564730	1.053863	0.192970	0.143*
H19C	0.639225	0.928141	0.173803	0.143*
N1	0.3677 (3)	0.6916 (2)	0.14029 (17)	0.0433 (5)

N2	0.7286 (3)	0.6134 (2)	0.43631 (16)	0.0421 (5)
O1	0.0470 (3)	0.5392 (3)	-0.17064 (18)	0.0693 (6)
O2	0.0451 (3)	0.3099 (2)	-0.18472 (17)	0.0653 (6)
O3	0.2365 (3)	0.2583 (2)	-0.03941 (15)	0.0532 (5)
O4	1.0425 (3)	0.7963 (2)	0.75214 (15)	0.0552 (5)
F1	0.6444 (2)	0.31952 (17)	0.30200 (13)	0.0590 (5)
H4	1.051 (5)	0.732 (5)	0.791 (3)	0.093 (13)*
H2	0.103 (6)	0.276 (5)	-0.142 (4)	0.112 (16)*
C20	0.9337 (3)	1.0187 (3)	0.9660 (2)	0.0412 (6)
O5	0.8664 (3)	1.0949 (2)	1.01002 (15)	0.0561 (5)
O6	0.8992 (3)	0.9631 (2)	0.85737 (15)	0.0536 (5)
H6	0.950 (5)	0.913 (5)	0.834 (4)	0.092 (14)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0415 (13)	0.0485 (13)	0.0435 (14)	0.0148 (11)	0.0034 (10)	0.0178 (11)
C2	0.0440 (14)	0.0684 (17)	0.0382 (13)	0.0241 (12)	0.0092 (10)	0.0195 (12)
C3	0.0438 (13)	0.0481 (13)	0.0298 (11)	0.0211 (11)	0.0023 (9)	0.0026 (9)
C4	0.0716 (19)	0.0521 (16)	0.0402 (15)	0.0018 (14)	-0.0051 (13)	0.0095 (12)
C5	0.0579 (17)	0.0545 (15)	0.0343 (13)	0.0001 (13)	-0.0008 (11)	0.0119 (11)
C6	0.0375 (12)	0.0398 (12)	0.0336 (12)	0.0151 (10)	0.0024 (9)	0.0087 (9)
C7	0.0409 (13)	0.0393 (12)	0.0414 (13)	0.0216 (10)	0.0055 (10)	0.0108 (10)
C8	0.0426 (13)	0.0344 (11)	0.0389 (12)	0.0181 (10)	0.0067 (10)	0.0048 (9)
C9	0.0355 (11)	0.0354 (11)	0.0334 (11)	0.0143 (9)	0.0094 (9)	0.0089 (9)
C10	0.0409 (12)	0.0362 (11)	0.0350 (12)	0.0180 (9)	0.0061 (9)	0.0099 (9)
C11	0.0535 (15)	0.0369 (12)	0.0385 (13)	0.0183 (11)	0.0005 (11)	0.0063 (10)
C12	0.121 (3)	0.0481 (16)	0.0536 (18)	0.0454 (18)	-0.0242 (18)	-0.0043 (13)
C13	0.114 (3)	0.065 (2)	0.067 (2)	0.051 (2)	-0.004 (2)	-0.0057 (16)
C14	0.0712 (19)	0.0397 (13)	0.0593 (17)	0.0322 (13)	-0.0038 (14)	0.0053 (12)
C15	0.0500 (14)	0.0463 (13)	0.0405 (13)	0.0241 (11)	0.0058 (11)	0.0166 (10)
C16	0.0411 (13)	0.0466 (13)	0.0350 (12)	0.0179 (10)	0.0100 (10)	0.0161 (10)
C17	0.0378 (12)	0.0392 (12)	0.0337 (11)	0.0140 (9)	0.0091 (9)	0.0090 (9)
C18	0.0507 (15)	0.0589 (15)	0.0347 (13)	0.0191 (12)	0.0081 (11)	0.0170 (11)
C19	0.114 (3)	0.0472 (18)	0.110 (3)	0.0189 (19)	0.006 (3)	0.0145 (19)
N1	0.0534 (12)	0.0386 (11)	0.0415 (11)	0.0242 (9)	0.0019 (9)	0.0099 (8)
N2	0.0453 (11)	0.0430 (11)	0.0349 (10)	0.0148 (9)	0.0002 (8)	0.0107 (8)
O1	0.0829 (16)	0.0725 (14)	0.0525 (12)	0.0332 (12)	-0.0100 (11)	0.0234 (10)
O2	0.0846 (16)	0.0617 (13)	0.0379 (11)	0.0229 (11)	-0.0088 (10)	0.0073 (9)
O3	0.0690 (13)	0.0427 (10)	0.0407 (10)	0.0210 (9)	-0.0027 (8)	0.0015 (7)
O4	0.0696 (13)	0.0608 (12)	0.0309 (9)	0.0292 (10)	-0.0026 (8)	-0.0004 (8)
F1	0.0711 (11)	0.0514 (9)	0.0583 (10)	0.0405 (8)	-0.0105 (8)	0.0040 (7)
C20	0.0503 (14)	0.0362 (11)	0.0362 (12)	0.0201 (10)	-0.0004 (10)	0.0053 (9)
O5	0.0732 (13)	0.0612 (12)	0.0443 (10)	0.0454 (10)	0.0012 (9)	0.0052 (8)
O6	0.0681 (13)	0.0586 (11)	0.0337 (9)	0.0343 (10)	-0.0064 (8)	0.0006 (8)

Geometric parameters (Å, °)

C1—N2	1.464 (3)	C11—C12	1.508 (4)
C1—C2	1.520 (4)	C12—C13	1.580 (5)
C1—H1A	0.9700	C12—H12A	0.9700
C1—H1B	0.9700	C12—H12B	0.9700
C2—C3	1.504 (4)	C13—C14	1.488 (5)
C2—H2A	0.9700	C13—H13A	0.9700
C2—H2B	0.9700	C13—H13B	0.9700
C3—O4	1.433 (3)	C14—C19	1.473 (6)
C3—C4	1.510 (4)	C14—N1	1.497 (3)
C3—H3	0.9800	C14—H14	0.9800
C4—C5	1.519 (4)	C15—N1	1.333 (3)
C4—H4A	0.9700	C15—C16	1.371 (3)
C4—H4B	0.9700	C15—H15	0.9300
C5—N2	1.461 (3)	C16—C17	1.429 (3)
C5—H5A	0.9700	C16—C18	1.478 (3)
C5—H5B	0.9700	C17—O3	1.258 (3)
C6—C11	1.399 (3)	C18—O1	1.216 (3)
C6—C7	1.406 (3)	C18—O2	1.313 (3)
C6—N2	1.417 (3)	C19—H19A	0.9600
C7—C8	1.351 (3)	C19—H19B	0.9600
C7—F1	1.358 (3)	C19—H19C	0.9600
C8—C9	1.404 (3)	O2—H2	0.87 (5)
C8—H8	0.9300	O4—H4	0.87 (4)
C9—C10	1.405 (3)	C20—O5	1.199 (3)
C9—C17	1.456 (3)	C20—O6	1.311 (3)
C10—N1	1.400 (3)	C20—C20 ⁱ	1.531 (5)
C10—C11	1.407 (3)	O6—H6	0.81 (4)
N2—C1—C2	108.9 (2)	C11—C12—C13	109.2 (3)
N2—C1—H1A	109.9	C11—C12—H12A	109.8
C2—C1—H1A	109.9	C13—C12—H12A	109.8
N2—C1—H1B	109.9	C11—C12—H12B	109.8
C2—C1—H1B	109.9	C13—C12—H12B	109.8
H1A—C1—H1B	108.3	H12A—C12—H12B	108.3
C3—C2—C1	110.4 (2)	C14—C13—C12	108.7 (3)
C3—C2—H2A	109.6	C14—C13—H13A	110.0
C1—C2—H2A	109.6	C12—C13—H13A	110.0
C3—C2—H2B	109.6	C14—C13—H13B	110.0
C1—C2—H2B	109.6	C12—C13—H13B	110.0
H2A—C2—H2B	108.1	H13A—C13—H13B	108.3
O4—C3—C2	112.4 (2)	C19—C14—C13	118.6 (3)
O4—C3—C4	109.1 (2)	C19—C14—N1	108.4 (3)
C2—C3—C4	110.1 (2)	C13—C14—N1	108.4 (2)
O4—C3—H3	108.4	C19—C14—H14	107.0
C2—C3—H3	108.4	C13—C14—H14	107.0
C4—C3—H3	108.4	N1—C14—H14	107.0

C3—C4—C5	110.6 (2)	N1—C15—C16	124.0 (2)
C3—C4—H4A	109.5	N1—C15—H15	118.0
C5—C4—H4A	109.5	C16—C15—H15	118.0
C3—C4—H4B	109.5	C15—C16—C17	119.7 (2)
C5—C4—H4B	109.5	C15—C16—C18	119.1 (2)
H4A—C4—H4B	108.1	C17—C16—C18	121.2 (2)
N2—C5—C4	110.3 (2)	O3—C17—C16	122.8 (2)
N2—C5—H5A	109.6	O3—C17—C9	121.5 (2)
C4—C5—H5A	109.6	C16—C17—C9	115.8 (2)
N2—C5—H5B	109.6	O1—C18—O2	120.3 (2)
C4—C5—H5B	109.6	O1—C18—C16	123.6 (3)
H5A—C5—H5B	108.1	O2—C18—C16	116.1 (2)
C11—C6—C7	117.4 (2)	C14—C19—H19A	109.5
C11—C6—N2	119.0 (2)	C14—C19—H19B	109.5
C7—C6—N2	123.6 (2)	H19A—C19—H19B	109.5
C8—C7—F1	118.0 (2)	C14—C19—H19C	109.5
C8—C7—C6	123.9 (2)	H19A—C19—H19C	109.5
F1—C7—C6	118.1 (2)	H19B—C19—H19C	109.5
C7—C8—C9	119.3 (2)	C15—N1—C10	120.8 (2)
C7—C8—H8	120.4	C15—N1—C14	118.32 (19)
C9—C8—H8	120.4	C10—N1—C14	120.8 (2)
C8—C9—C10	118.7 (2)	C6—N2—C5	116.53 (19)
C8—C9—C17	119.6 (2)	C6—N2—C1	118.84 (19)
C10—C9—C17	121.7 (2)	C5—N2—C1	111.8 (2)
N1—C10—C9	118.0 (2)	C18—O2—H2	101 (3)
N1—C10—C11	120.8 (2)	C3—O4—H4	104 (3)
C9—C10—C11	121.1 (2)	O5—C20—O6	122.4 (2)
C6—C11—C10	119.5 (2)	O5—C20—C20 ⁱ	121.6 (3)
C6—C11—C12	120.2 (2)	O6—C20—C20 ⁱ	116.1 (3)
C10—C11—C12	120.1 (2)	C20—O6—H6	117 (3)
N2—C1—C2—C3	-58.9 (3)	N1—C15—C16—C18	179.9 (2)
C1—C2—C3—O4	178.4 (2)	C15—C16—C17—O3	178.0 (2)
C1—C2—C3—C4	56.6 (3)	C18—C16—C17—O3	-1.1 (4)
O4—C3—C4—C5	-178.5 (2)	C15—C16—C17—C9	-1.7 (3)
C2—C3—C4—C5	-54.7 (3)	C18—C16—C17—C9	179.2 (2)
C3—C4—C5—N2	55.8 (4)	C8—C9—C17—O3	1.3 (3)
C11—C6—C7—C8	-1.5 (4)	C10—C9—C17—O3	-178.9 (2)
N2—C6—C7—C8	176.2 (2)	C8—C9—C17—C16	-178.9 (2)
C11—C6—C7—F1	178.4 (2)	C10—C9—C17—C16	0.8 (3)
N2—C6—C7—F1	-3.8 (4)	C15—C16—C18—O1	5.1 (4)
F1—C7—C8—C9	-178.3 (2)	C17—C16—C18—O1	-175.8 (2)
C6—C7—C8—C9	1.6 (4)	C15—C16—C18—O2	-173.8 (2)
C7—C8—C9—C10	-0.2 (3)	C17—C16—C18—O2	5.3 (4)
C7—C8—C9—C17	179.5 (2)	C16—C15—N1—C10	1.3 (4)
C8—C9—C10—N1	-179.2 (2)	C16—C15—N1—C14	179.5 (3)
C17—C9—C10—N1	1.1 (3)	C9—C10—N1—C15	-2.2 (4)
C8—C9—C10—C11	-1.3 (3)	C11—C10—N1—C15	179.9 (2)

C17—C9—C10—C11	179.0 (2)	C9—C10—N1—C14	179.6 (2)
C7—C6—C11—C10	0.0 (4)	C11—C10—N1—C14	1.7 (4)
N2—C6—C11—C10	-177.9 (2)	C19—C14—N1—C15	-83.7 (3)
C7—C6—C11—C12	175.9 (3)	C13—C14—N1—C15	146.4 (3)
N2—C6—C11—C12	-1.9 (4)	C19—C14—N1—C10	94.5 (3)
N1—C10—C11—C6	179.2 (2)	C13—C14—N1—C10	-35.4 (4)
C9—C10—C11—C6	1.4 (4)	C11—C6—N2—C5	-78.3 (3)
N1—C10—C11—C12	3.3 (4)	C7—C6—N2—C5	104.0 (3)
C9—C10—C11—C12	-174.6 (3)	C11—C6—N2—C1	143.2 (2)
C6—C11—C12—C13	-151.7 (3)	C7—C6—N2—C1	-34.5 (3)
C10—C11—C12—C13	24.2 (4)	C4—C5—N2—C6	159.0 (2)
C11—C12—C13—C14	-57.1 (4)	C4—C5—N2—C1	-59.7 (3)
C12—C13—C14—C19	-62.3 (4)	C2—C1—N2—C6	-158.9 (2)
C12—C13—C14—N1	61.7 (4)	C2—C1—N2—C5	60.9 (3)
N1—C15—C16—C17	0.7 (4)		

Symmetry code: (i) $-x+2, -y+2, -z+2$.

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C15—H15 \cdots O5 ⁱⁱ	0.93	2.35	3.266 (3)	167
C19—H19B \cdots F1 ⁱⁱⁱ	0.96	2.50	3.456 (4)	174
O4—H4 \cdots O1 ^{iv}	0.87 (4)	1.99 (4)	2.833 (3)	161 (4)
O2—H2 \cdots O3	0.87 (5)	1.68 (5)	2.536 (3)	165 (5)
O6—H6 \cdots O4	0.81 (4)	1.85 (4)	2.644 (3)	169 (4)

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