Acta Cryst E
CRYSTALLOGRAPHIC COMMUNICATIONS

ISSN 2056-9890

Partial charge transfer in the salt co-crystal of L-ascorbic acid and 4,4′-bipyridine

Eric Sylvester,[a] Mitchell McGovern,[a] An Young Lee,[a] Phanxico Nguyen,[a] Jungeun Park[a] and Jason B. Benedict[b]*

[a]730 Natural Sciences Complex, Buffalo, 14260-3000, USA, and [b]771 Natural Sciences Complex, Buffalo, 14260-3000, ., USA. *Correspondence e-mail: jbb6@buffalo.edu

Received 14 February 2019
Accepted 18 April 2019

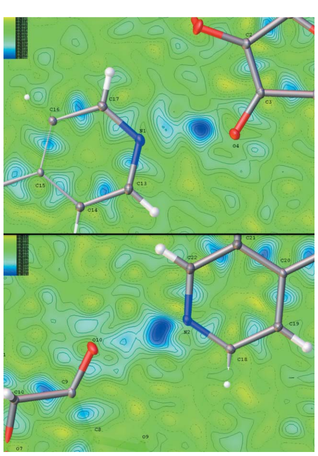
Edited by E. V. Boldyreva, Russian Academy of Sciences, Russia

Keywords: crystal structure; co-crystal; charge transfer; L-ascorbic acid; 4,4′-bipyridine.

CCDC reference: 1910963

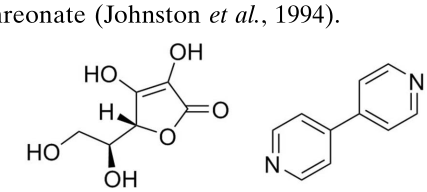
Supporting information: this article has supporting information at journals.iucr.org/e

In the title 1:2 co-crystal, $C_{10}H_9N_2^+\cdot(C_6H_{7.75}O_6\cdot C_6H_{7.25}O_6)^-$, L-ascorbic acid (LAA) and 4,4′-bipyridine (BPy) co-crystallize in the chiral space group $P2_1$ with two molecules of LAA, and one molecule of bpy in the asymmetric unit. The structure was modeled in two parts due to possible proton transfer from LAA to the corresponding side of the bpy molecule having an occupancy of approximately 0.25 and part 2 with an occupancy of approximately 0.75. In this structure, LAA forms hydrogen bonds with neighboring LAA molecules, forming extended sheets of LAA molecules which are bridged by bpy molecules. A comparison to a related and previously published co-crystal of LAA and 3-bromo-4-pyridone is presented.



1. Chemical context

L-Ascorbic acid (LAA) is an antioxidant and integral vitamin, vitamin C, for many biological systems (Frei *et al.*, 1989; Yogeswaran *et al.*, 2007). Since humans cannot synthesize LAA naturally, vitamin C is often obtained from digesting fruits and vegetables, including citrus fruits, tomatoes and potatoes (Medicine, 2000; Yu *et al.*, 2016). Vitamin C is also produced through the ingestion of dietary supplements composed of LAA or many other ascorbate-containing derivatives including calcium ascorbate, dehydroascorbate, and calcium threonate (Johnston *et al.*, 1994).



Co-crystallization, a process in which two or more molecules form a crystalline single phase material generally in a stoichiometric ratio (Trask, 2007), can tailor pharmaceutically important physical properties including solubility, hygroscopicity, and, active lifetime without altering the active pharmaceutical ingredient (Rodriquez-Honedo *et al.*, 2007; Ross *et al.*, 2016; Shan & Zaworotko, 2008; Thipparaboina *et al.*, 2016). Co-crystal structures are key to identifying important structure-directing interactions in the solid-state (Childs *et al.*, 2007). In this paper, we report the synthesis and single crystal structure determination of a salt co-crystal containing LAA and a commonly used co-former, 4,4′-bipyridine (BPy) (Aakeröy *et al.*, 2015, Cherukuvada *et al.*, 2016), which is known to be a secondary building component often used as a pillaring ligand to give three-dimensionality in what would

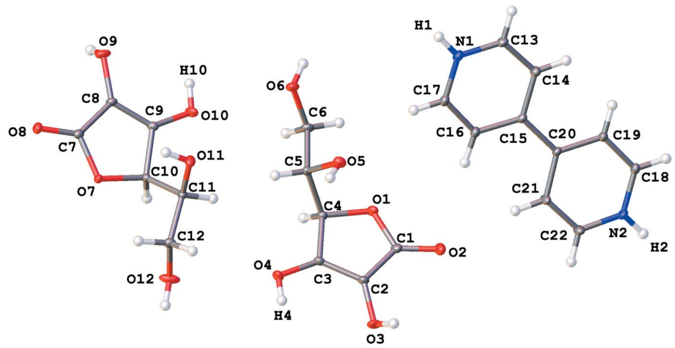


Figure 1
Asymmetric unit of the title compound, showing the numbering scheme.

normally be stacking of two-dimensional sheets in crystalline systems (Dinesh *et al.*, 2015; López-Cabrelles *et al.*, 2015).

2. Structural commentary

LAA and BPy co-crystallize in the chiral space group $P2_1$ with two molecules of LAA, and one molecule of BPy in the asymmetric unit (Fig. 1). While the lattice is composed of molecules in a variety of charge states (*vide infra*), the neutral molecule abbreviations (LAA and BPy) provide a convenient method for describing the structure in terms of these fragments.

The overall three-dimensional structure is formed by interlocking sheets of LAA bridged by BPy molecules. Initial attempts to refine the structure as neutral molecules were not satisfactory and suggested the presence of disorder in the positions of the protons involved in intermolecular hydrogen bonding between LAA and Bpy (H4 and H10). Fourier difference maps produced following a refinement using all atoms except the suspected disorders protons (H4, H10) revealed the presence of two peaks of electron density between the two pairs of heavy atoms involved in the hydrogen bonding (N1 and O4; N2 and O10, Fig. 2). The positions of the two protons were initially modeled independently (model 1) in two parts to account for the disorder arising from proton transfer from LAA to Bpy. In this model, the occupancy of H10 and its disorder partner atom H2 refined to 0.22736 and 0.70972, respectively. The occupancy of H4 and its disorder partner atom H1 refined to 0.70972 and 0.23932, respectively. The similarity of the occupancies for the two pairs indicated that the disorder was likely correlated.

An additional refinement was performed in which the occupancies were constrained to be identical for the pairs of atoms (single part command for both pairs, model 2). The occupancies for model 2 were determined to be 0.73718 and 0.26282 for the pairs, similar to what was observed in model 1. The R_1 values for both model 1 and model 2 were found to be 3.94%. Given the same values for R_1 for both models, the model with the fewer parameters, model 2, will be reported. There has been an active debate in the community whether an organic salt due to proton transfer is considered a co-crystal (Aakeröy *et al.*, 2007; Cruz-Cabeza, 2012; Wang *et al.*, 2018).

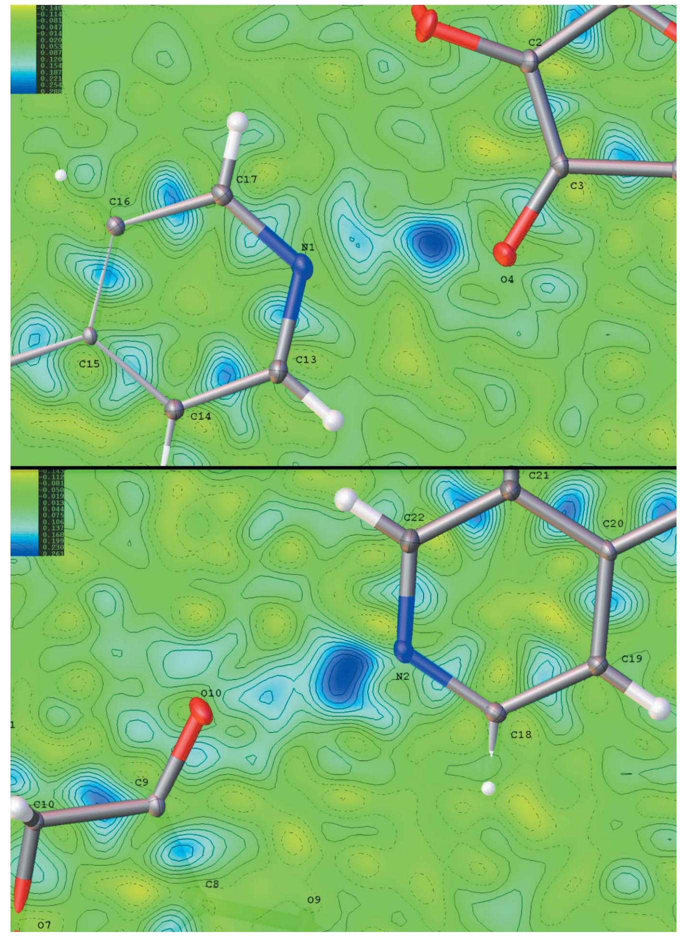


Figure 2
Fourier difference map of the LAA–BPy salt co-crystal showing two peaks of electron density between N1···O4 (upper) and N2···O10 (lower).

However, as we cannot rule out the presence of a non-ionized species within the lattice, we will refer to the obtained product as a salt co-crystal (Cherukuvada *et al.*, 2016).

3. Supramolecular features

In the structure, LAA forms hydrogen bonds with neighboring LAA molecules, giving rise to extended sheets of LAA mol-

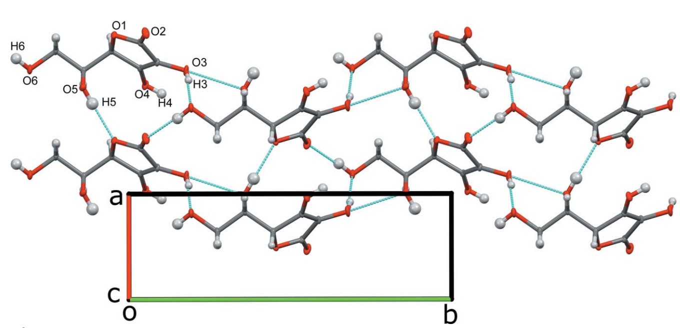


Figure 3
Diagram illustrating the hydrogen-bonding interactions (dashed lines, see Table 1) present in the two-dimensional sheets of LAA molecules, looking down [001]; BPy interactions were omitted for clarity.

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O10^{i}	0.86 (3)	1.74 (3)	2.5862 (14)	169 (2)
O3—H3···O5^{ii}	0.817 (19)	2.531 (19)	2.8832 (13)	107.5 (15)
O3—H3···O6^{ii}	0.817 (19)	1.903 (19)	2.7117 (14)	170.0 (19)
O4—H4···N1^{ii}	0.93 (3)	1.64 (3)	2.5428 (14)	163 (3)
O5—H5···O1^{iii}	0.85 (2)	2.00 (2)	2.8510 (13)	173 (2)
O6—H6···O2^{iv}	0.83 (2)	1.84 (2)	2.6616 (14)	173 (2)
O9—H9···O12^{v}	0.79 (2)	1.91 (2)	2.6902 (14)	175 (2)
O11—H11···O10^{iii}	0.79 (2)	1.91 (2)	2.6663 (13)	162 (2)
O12—H12···O8^{vi}	0.87 (2)	1.81 (2)	2.6683 (14)	169 (2)
C5—H5A···O11	1.00 (1)	2.44 (1)	3.2950 (14)	143 (1)
C12—H12B···O4	0.99 (1)	2.50 (1)	3.3249 (16)	141 (1)
C14—H14···O8^{vii}	0.95 (1)	2.40 (1)	3.3311 (15)	166 (1)
C16—H16···O2	0.95 (1)	2.51 (1)	3.4513 (16)	170 (1)
C17—H17···O5	0.95 (1)	2.55 (1)	3.4651 (14)	163 (1)
C19—H19···O7^{vii}	0.95 (1)	2.56 (1)	3.2181 (14)	127 (1)
C19—H19···O8^{vii}	0.95 (1)	2.48 (1)	3.4267 (15)	174 (1)
C21—H21···O2	0.95 (1)	2.40 (1)	3.3418 (17)	173 (1)
C22—H22···O6^{viii}	0.95 (1)	2.44 (1)	3.1860 (16)	136 (1)

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

ecules which are bridged by BPy molecules (Table 1, Fig. 3). The LAA–LAA interactions consist of O—H···O—H hydrogen bonds where each LAA forms a total of three hydrogen bonds with three different LAA molecules, O—H···O═hydrogen bond where each LAA forms a hydrogen bond with one different LAA, and O—H···O$_{ether}$ where each LAA forms a hydrogen bond with one different LAA. The LAA–BPy interaction consists of O—H···N$_{pyridyl}$ hydrogen bonds such that each BPy forms a hydrogen bond with two neighboring LAA molecules (Fig. 4). C—H···O interactions also occur.

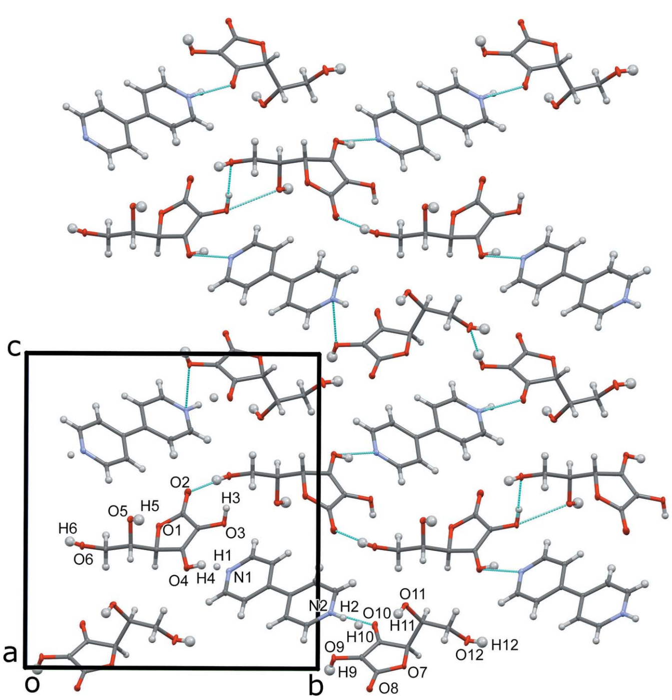


Figure 4
View down [100] showing the packing of the title compound.

4. Database survey

Recently the co-crystal structure of LAA and 3-bromo-4-pyridone (BrPyd) was reported (Wang *et al.*, 2016). While the LAA molecules in each structure contain similar interactions, LAA–BPy and LAA–BrPyd demonstrate important differences with regard to the three-dimensional structure because of the different binding synthons of BrPyd compared to BPy (Fig. 5). In the structure of LAA–BrPyd, the carbonyl on the BrPyd hydrogen bonds with both hydroxyl groups located on the five-membered ring of LAA, whereas the carbonyl located on the five-membered ring of LAA hydrogen bonds with the pyridinium group of BrPyd. The corresponding hydrogen-bond network results in two-dimensional sheets. The three-dimensional aspect of LAA–BrPyd arises from stacking of the sheets, which are held together by hydrogen bonding of the terminal hydroxyl group of the aliphatic carbon chain with the hydroxyl group on the five-membered ring on the LAA in the adjacent sheet.

5. Synthesis and crystallization

All chemicals were obtained commercially and used as received. Solid L-ascorbic acid (0.0450 g, 0.256 mmol) and 4,4′-bipyridine (0.0200 g, 0.128 mmol) were added to a 25 ml scintillation vial. To this were added approximately 12 ml of 200 proof ethanol followed by gentle heating. The loosely capped vial was then placed into a dark cabinet. Plate crystals of the title compound suitable for single crystal X-ray diffraction measurements were obtained.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All H atoms were located in a difference-Fourier map and freely refined. As the Flack parameter is 0.4, the absolute configuration of LAA cannot be

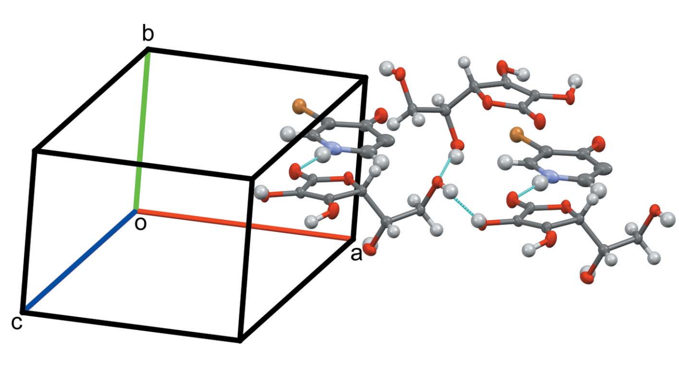


Figure 5
Diagram illustrating the hydrogen-bonding network of the previously reported structure of LAA–BPyBr (Wang *et al.*, 2016).

determined by the crystal structure; however, the co-crystal was synthesized using an enantiomerically pure starting material.

Funding information

Funding for this research was provided by: National Science Foundation, Directorate for Mathematical and Physical Sciences (award No. DMR-1455039).

References

Aakeröy, C. B., Fasulo, M. E. & Desper, J. (2007). *Mol. Pharm.* **4**, 317–322.

Aakeröy, C. B., Spartz, C. L., Dembowski, S., Dwyre, S. & Desper, J. (2015). *IUCrJ*, **2**, 498–510.

Bourhis, L. J., Dolomanov, O. V., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2015). *Acta Cryst.* A**71**, 59–75.

Bruker (2013). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

Cherukuvada, S., Kaur, R. & Guru Row, T. N. (2016). *CrystEngComm*, **18**, 8528–8555.

Childs, S. L., Stahly, G. P. & Park, A. (2007). *Mol. Pharm.* **4**, 323–338.

Cruz-Cabeza, A. J. (2012). *CrystEngComm*, **14**, 6362–6365.

Dinesh, D., Subhadip, N. & Carolina, S. E. K. B. P. (2015). *Chem. Eur. J.* **21**, 17422–17429.

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

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Frei, B., England, L. & Ames, B. N. (1989). *Proc. Natl Acad. Sci. USA*, **86**, 6377–6381.

Johnston, C. S. & Luo, B. (1994). *J. Am. Diet. Assoc.* **94**, 779–781.

López-Cabrelles, J., Giménez-Marqués, M., Mínguez Espallargas, G. & Coronado, E. (2015). *Inorg. Chem.* **54**, 10490–10496.

Medicine, I. O. (2000). *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, p 529. Washington, DC: The National Academies Press.

Rodriquez-Honedo, N., Nehm, S. J. & Jayasanker, A. (2007). *Pharmaceutical Technology*, 3rd ed., pp 615–635. London: Taylor & Francis.

Ross, S. A., Lamprou, D. A. & Douroumis, D. (2016). *Chem. Commun.* **52**, 8772–8786.

Shan, N. & Zaworotko, M. J. (2008). *Drug Discovery Today*, **13**, 440–446.

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

Thipparaboina, R., Kumar, D., Chavan, R. B. & Shastri, N. R. (2016). *Drug Discovery Today*, **21**, 481–490.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{10}H_9N_2^+ \cdot (C_6H_{7.75}O_6 \cdot C_6H_{7.25}O_6)^-$
M_r	508.44
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	90
a, b, c (Å)	4.7724 (6), 14.4069 (17), 15.6857 (19)
β (°)	98.393 (2)
V (Å^3)	1066.9 (2)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.13
Crystal size (mm)	0.2 × 0.1 × 0.02
Data collection	
Diffractometer	Bruker *SMART* APEXII area detector
Absorption correction	Multi-scan (*SADABS*; Bruker, 2013)
T_{min}, T_{max}	0.683, 0.747
No. of measured, independent and observed [$I \geq 2u(I)$] reflections	31611, 9452, 8448
R_{int}	0.039
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.809
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.040, 0.099, 1.06
No. of reflections	9452
No. of parameters	357
No. of restraints	1
H-atom treatment	All H-atom parameters refined
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.47, −0.29
Absolute structure	Flack (1983)
Absolute structure parameter	0.4 (6)

Computer programs: *APEX2* and *SAINT* (Bruker, 2013), *SHELXS* (Sheldrick, 2008), *olex2.refine* (Bourhis *et al.*, 2015) and *OLEX2* (Dolomanov *et al.*, 2009).

Trask, A. V. (2007). *MolPharma* 301–309.

Wang, J.-R., Fan, X., Ding, Q. & Mei, X. (2016). *J. Mol. Struct.* **1119**, 269–275.

Wang, T., Stevens, J. S., Vetter, T., Whitehead, G. F. S., Vitorica-Yrezabal, I. J., Hao, H. & Cruz-Cabeza, A. J. (2018). *Cryst. Growth Des.* **18**, 6973–6983.

Yogeswaran, U., Thiagarajan, S. & Chen, S. M. (2007). *Anal. Biochem.* **365**, 122–131.

Yu, A., Tang, L. & Czech, J. (2016). *Food Sci.* **34**, 503–510.

supporting information

Acta Cryst. (2019). E**75**, 728-731   [https://doi.org/10.1107/S2056989019005334]

Partial charge transfer in the salt co-crystal of L-ascorbic acid and 4,4′-bi-pyridine

Eric Sylvester, Mitchell McGovern, An Young Lee, Phanxico Nguyen, Jungeun Park and Jason B. Benedict

Computing details

Data collection: *APEX2* (Bruker, 2013); cell refinement: *SAINT* (Bruker, 2013); data reduction: *SAINT* (Bruker, 2013); program(s) used to solve structure: *SHELXS* (Sheldrick, 2008); program(s) used to refine structure: *olex2.refine* (Bourhis *et al.*, 2015); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *OLEX2* (Dolomanov *et al.*, 2009).

L-Ascorbic acid–4,4′-bipyridine (1/1)

Crystal data

$C_{10}H_9N_2^{+}\cdot C_6H_{7.75}O_6 0.25^{-}\cdot C_6H_{7.25}O_6 0.75^{-}$—
M_r = 508.44
Monoclinic, $P2_1$
a = 4.7724 (6) Å
b = 14.4069 (17) Å
c = 15.6857 (19) Å
β = 98.393 (2)°
V = 1066.9 (2) Å^3
Z = 2
F(000) = 532.3832
D_x = 1.583 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 8756 reflections
θ = 2.6–36.2°
μ = 0.13 mm^{-1}
T = 90 K
Plate, yellow
0.2 × 0.1 × 0.02 mm

Data collection

Bruker SMART APEXII area detector diffractometer
Radiation source: microfocus rotating anode, Incoatec Iμs
Mirror optics monochromator
Detector resolution: 7.9 pixels mm^{-1}
ω and φ scans
Absorption correction: multi-scan (SADABS; Bruker, 2013)
T_{min} = 0.683, T_{max} = 0.747
31611 measured reflections
9452 independent reflections
8448 reflections with $I \geq 2u(I)$
R_{int} = 0.039
θ_{max} = 35.1°, θ_{min} = 1.9°
h = −7→7
k = −23→23
l = −25→25

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.099
S = 1.06
9452 reflections
357 parameters
1 restraint
37 constraints
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0536P)^2 + 0.0945P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.47 e Å^{-3}

$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Absolute structure: Flack (1983)
Absolute structure parameter: 0.4 (6)

Special details

Refinement. X-ray diffraction data was collected on a Bruker SMART APEX2 CCD diffractometer installed at a rotating anode source (MoKα radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems (Cryostream700) nitrogen gas-flow apparatus. The data were collected by the rotation method with a 0.5° frame-width (ω scan) and a 15 second exposure per frame. Three sets of data (360 frames in each set) were collected, nominally covering complete reciprocal space. The structure was solved in the Olex2 (Dolomanov, O. V. B. *et al.*, 2009) crystallography program using the XS structure solution program (Sheldrick,G. M, 2008) using the Charge Flipping method and refined using the olex2.refine refinement package(Bourhis, L. J., *et al.*, 2015) using least-squares minimization.

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

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O1	0.49355 (18)	0.45455 (6)	0.44984 (6)	0.01210 (15)	
O2	0.4742 (2)	0.55289 (7)	0.55860 (6)	0.01868 (18)	
O3	0.8313 (2)	0.67789 (6)	0.46065 (6)	0.01575 (17)	
H3	0.921 (4)	0.6856 (13)	0.5086 (12)	0.014 (4)*	
O4	0.9691 (2)	0.55149 (6)	0.31883 (6)	0.01423 (16)	
H4	1.069 (6)	0.607 (2)	0.3253 (17)	0.0213 (2)*	0.75 (2)
O5	0.98812 (19)	0.35794 (6)	0.47231 (5)	0.01216 (15)	
H5	1.142 (5)	0.3877 (16)	0.4705 (14)	0.031 (6)*	
O6	0.8176 (2)	0.19330 (6)	0.38768 (6)	0.01444 (16)	
H6	0.716 (5)	0.1509 (15)	0.4013 (13)	0.026 (5)*	
C1	0.5661 (2)	0.53643 (8)	0.49141 (8)	0.01170 (19)	
C2	0.7521 (2)	0.58827 (7)	0.44491 (7)	0.01084 (18)	
C3	0.8080 (2)	0.53592 (7)	0.37784 (7)	0.00969 (18)	
C4	0.6454 (2)	0.44679 (7)	0.37658 (7)	0.00959 (17)	
H4a	0.5081 (2)	0.44220 (7)	0.32212 (7)	0.0115 (2)*	
C5	0.8294 (2)	0.35942 (8)	0.38832 (7)	0.00976 (17)	
H5a	0.9613 (2)	0.35849 (8)	0.34430 (7)	0.0117 (2)*	
C6	0.6423 (2)	0.27408 (8)	0.37799 (8)	0.01268 (19)	
H6a	0.5258 (2)	0.27417 (8)	0.32035 (8)	0.0152 (2)*	
H6b	0.5135 (2)	0.27418 (8)	0.42206 (8)	0.0152 (2)*	
O7	0.86622 (18)	0.29619 (5)	0.00750 (5)	0.00983 (14)	
O8	1.02947 (19)	0.17939 (6)	−0.06529 (6)	0.01324 (16)	
O9	0.6792 (2)	0.05632 (6)	0.03244 (6)	0.01390 (16)	
H9	0.558 (5)	0.0416 (17)	−0.0046 (16)	0.032 (6)*	
O10	0.39236 (18)	0.19546 (6)	0.13751 (6)	0.01330 (15)	
H10	0.353 (13)	0.1386 (9)	0.137 (4)	0.0199 (2)*	0.25 (2)
O11	1.0111 (2)	0.30023 (6)	0.20099 (5)	0.01293 (15)	
H11	1.115 (4)	0.2763 (15)	0.1732 (13)	0.026 (5)*	
O12	0.7556 (2)	0.51222 (7)	0.09005 (7)	0.01958 (19)	
H12	0.845 (5)	0.5638 (16)	0.0855 (14)	0.033 (6)*	
C7	0.8780 (2)	0.20343 (7)	−0.01219 (7)	0.00978 (18)	
C8	0.6981 (2)	0.15146 (7)	0.03486 (7)	0.00985 (18)	
C9	0.5682 (2)	0.21089 (7)	0.08490 (7)	0.00962 (18)	
C10	0.6682 (2)	0.30805 (7)	0.06851 (7)	0.00877 (17)	

H10a	0.5036 (2)	0.34608 (7)	0.04143 (7)	0.0105 (2)*	
C11	0.8137 (2)	0.35734 (8)	0.14937 (7)	0.00942 (17)	
H11a	0.6630 (2)	0.37406 (8)	0.18475 (7)	0.0113 (2)*	
C12	0.9591 (2)	0.44733 (8)	0.12926 (8)	0.01143 (18)	
H12a	1.0989 (2)	0.43428 (8)	0.08998 (8)	0.0137 (2)*	
H12b	1.0615 (2)	0.47396 (8)	0.18315 (8)	0.0137 (2)*	
N1	0.7273 (2)	0.19521 (7)	0.69016 (6)	0.01118 (16)	
H1	0.8437 (2)	0.15248 (7)	0.67582 (6)	0.0134 (2)*	0.25 (2)
N2	−0.1522 (2)	0.54416 (7)	0.82171 (6)	0.01059 (16)	
H2	−0.249 (5)	0.5896 (18)	0.8370 (15)	0.01271 (19)*	0.75 (2)
C13	0.5899 (2)	0.18296 (8)	0.75790 (8)	0.01196 (19)	
H13	0.6182 (2)	0.12658 (8)	0.78939 (8)	0.0144 (2)*	
C14	0.4091 (2)	0.24834 (8)	0.78414 (8)	0.01189 (19)	
H14	0.3166 (2)	0.23705 (8)	0.83281 (8)	0.0143 (2)*	
C15	0.3638 (2)	0.33182 (7)	0.73790 (7)	0.00892 (17)	
C16	0.5031 (2)	0.34329 (8)	0.66607 (7)	0.01098 (19)	
H16	0.4744 (2)	0.39804 (8)	0.63217 (7)	0.0132 (2)*	
C17	0.6837 (2)	0.27425 (8)	0.64452 (7)	0.01128 (18)	
H17	0.7792 (2)	0.28315 (8)	0.59609 (7)	0.0135 (2)*	
C18	−0.1299 (2)	0.46219 (8)	0.86276 (7)	0.01123 (19)	
H18	−0.2282 (2)	0.45253 (8)	0.91050 (7)	0.0135 (2)*	
C19	0.0339 (3)	0.39174 (8)	0.83650 (7)	0.01045 (18)	
H19	0.0474 (3)	0.33395 (8)	0.86598 (7)	0.0125 (2)*	
C20	0.1802 (2)	0.40554 (7)	0.76632 (7)	0.00874 (17)	
C21	0.1521 (3)	0.49220 (8)	0.72563 (8)	0.0149 (2)	
H21	0.2475 (3)	0.50417 (8)	0.67768 (8)	0.0179 (3)*	
C22	−0.0134 (3)	0.56029 (8)	0.75481 (8)	0.0146 (2)	
H22	−0.0293 (3)	0.61916 (8)	0.72725 (8)	0.0176 (3)*	

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0126 (4)	0.0088 (3)	0.0165 (4)	−0.0019 (3)	0.0075 (3)	0.0001 (3)
O2	0.0275 (5)	0.0128 (4)	0.0190 (4)	0.0043 (3)	0.0144 (4)	0.0019 (3)
O3	0.0253 (4)	0.0062 (3)	0.0153 (4)	−0.0035 (3)	0.0013 (3)	−0.0006 (3)
O4	0.0203 (4)	0.0101 (4)	0.0142 (4)	−0.0039 (3)	0.0089 (3)	0.0005 (3)
O5	0.0126 (3)	0.0114 (3)	0.0122 (3)	−0.0020 (3)	0.0007 (3)	0.0016 (3)
O6	0.0203 (4)	0.0068 (3)	0.0170 (4)	−0.0012 (3)	0.0053 (3)	0.0003 (3)
C1	0.0138 (5)	0.0078 (4)	0.0143 (5)	0.0021 (4)	0.0050 (4)	0.0008 (4)
C2	0.0145 (5)	0.0064 (4)	0.0121 (5)	−0.0009 (3)	0.0036 (4)	0.0011 (3)
C3	0.0114 (4)	0.0073 (4)	0.0106 (4)	−0.0012 (3)	0.0022 (3)	0.0015 (3)
C4	0.0103 (4)	0.0079 (4)	0.0109 (4)	−0.0006 (3)	0.0028 (3)	0.0006 (3)
C5	0.0125 (4)	0.0073 (4)	0.0098 (4)	−0.0011 (3)	0.0027 (3)	−0.0002 (3)
C6	0.0152 (5)	0.0073 (4)	0.0155 (5)	−0.0021 (4)	0.0021 (4)	0.0004 (4)
O7	0.0139 (3)	0.0068 (3)	0.0100 (3)	0.0000 (3)	0.0060 (3)	−0.0005 (3)
O8	0.0184 (4)	0.0109 (4)	0.0118 (4)	0.0030 (3)	0.0067 (3)	−0.0004 (3)
O9	0.0167 (4)	0.0056 (3)	0.0182 (4)	−0.0009 (3)	−0.0016 (3)	−0.0008 (3)
O10	0.0126 (3)	0.0093 (3)	0.0198 (4)	−0.0007 (3)	0.0086 (3)	0.0026 (3)

O11	0.0173 (4)	0.0122 (3)	0.0095 (3)	0.0056 (3)	0.0029 (3)	0.0017 (3)
O12	0.0169 (4)	0.0100 (4)	0.0295 (5)	−0.0025 (3)	−0.0044 (4)	0.0079 (4)
C7	0.0125 (4)	0.0077 (4)	0.0089 (4)	0.0009 (3)	0.0006 (3)	0.0000 (3)
C8	0.0115 (4)	0.0061 (4)	0.0120 (5)	−0.0003 (3)	0.0019 (4)	−0.0001 (3)
C9	0.0088 (4)	0.0078 (4)	0.0122 (4)	−0.0004 (3)	0.0015 (3)	0.0015 (3)
C10	0.0106 (4)	0.0063 (4)	0.0103 (4)	0.0008 (3)	0.0047 (3)	0.0010 (3)
C11	0.0123 (4)	0.0073 (4)	0.0093 (4)	0.0015 (3)	0.0037 (3)	0.0007 (3)
C12	0.0134 (5)	0.0081 (4)	0.0127 (4)	−0.0013 (4)	0.0016 (4)	0.0000 (4)
N1	0.0116 (4)	0.0101 (4)	0.0121 (4)	0.0017 (3)	0.0027 (3)	−0.0020 (3)
N2	0.0117 (4)	0.0083 (4)	0.0125 (4)	0.0025 (3)	0.0039 (3)	−0.0013 (3)
C13	0.0147 (5)	0.0086 (4)	0.0132 (5)	0.0026 (4)	0.0039 (4)	0.0005 (4)
C14	0.0144 (5)	0.0094 (4)	0.0130 (5)	0.0022 (4)	0.0059 (4)	0.0013 (4)
C15	0.0095 (4)	0.0073 (4)	0.0104 (4)	0.0006 (3)	0.0027 (3)	−0.0012 (3)
C16	0.0135 (5)	0.0097 (4)	0.0104 (4)	0.0014 (3)	0.0038 (4)	−0.0006 (3)
C17	0.0135 (4)	0.0106 (4)	0.0104 (4)	0.0015 (4)	0.0040 (3)	−0.0014 (4)
C18	0.0135 (5)	0.0102 (4)	0.0110 (5)	0.0003 (3)	0.0052 (4)	−0.0009 (3)
C19	0.0144 (5)	0.0083 (4)	0.0096 (4)	0.0008 (3)	0.0046 (4)	0.0000 (3)
C20	0.0100 (4)	0.0069 (4)	0.0098 (4)	0.0006 (3)	0.0034 (3)	−0.0014 (3)
C21	0.0204 (5)	0.0099 (5)	0.0171 (5)	0.0055 (4)	0.0118 (4)	0.0041 (4)
C22	0.0204 (5)	0.0093 (5)	0.0162 (5)	0.0051 (4)	0.0092 (4)	0.0038 (4)

Geometric parameters (Å, º)

O1—C1	1.3677 (14)	C8—C9	1.3694 (16)
O1—C4	1.4494 (13)	C9—C10	1.5130 (15)
O2—C1	1.2223 (15)	C10—H10a	1.0000
O3—H3	0.816 (19)	C10—C11	1.5290 (16)
O3—C2	1.3579 (14)	C11—H11a	1.0000
O4—H4	0.93 (3)	C11—C12	1.5251 (16)
O4—C3	1.3062 (14)	C12—H12a	0.9900
O5—H5	0.86 (2)	C12—H12b	0.9900
O5—C5	1.4207 (14)	N1—H1	0.8800
O6—H6	0.83 (2)	N1—C13	1.3394 (15)
O6—C6	1.4283 (15)	N1—C17	1.3449 (15)
C1—C2	1.4376 (16)	N2—H2	0.85 (3)
C2—C3	1.3523 (16)	N2—C18	1.3419 (15)
C3—C4	1.4991 (15)	N2—C22	1.3403 (15)
C4—H4a	1.0000	C13—H13	0.9500
C4—C5	1.5306 (16)	C13—C14	1.3802 (16)
C5—H5a	1.0000	C14—H14	0.9500
C5—C6	1.5142 (16)	C14—C15	1.4049 (16)
C6—H6a	0.9900	C15—C16	1.3992 (15)
C6—H6b	0.9900	C15—C20	1.4858 (14)
O7—C7	1.3746 (13)	C16—H16	0.9500
O7—C10	1.4499 (13)	C16—C17	1.3897 (15)
O8—C7	1.2296 (14)	C17—H17	0.9500
O9—H9	0.79 (3)	C18—H18	0.9500
O9—C8	1.3739 (13)	C18—C19	1.3803 (16)

O10—H10	0.8400	C19—H19	0.9500
O10—C9	1.2794 (14)	C19—C20	1.4012 (15)
O11—H11	0.79 (2)	C20—C21	1.3998 (15)
O11—C11	1.4134 (14)	C21—H21	0.9500
O12—H12	0.86 (2)	C21—C22	1.3789 (16)
O12—C12	1.4217 (15)	C22—H22	0.9500
C7—C8	1.4240 (16)		

C4—O1—C1	108.88 (8)	C11—C10—O7	109.96 (9)
C2—O3—H3	113.0 (13)	C11—C10—C9	113.89 (9)
C5—O5—H5	107.8 (15)	C11—C10—H10a	109.35 (6)
C6—O6—H6	105.8 (15)	C10—C11—O11	112.89 (9)
O2—C1—O1	118.74 (10)	H11a—C11—O11	107.21 (5)
C2—C1—O1	109.77 (10)	H11a—C11—C10	107.21 (6)
C2—C1—O2	131.48 (11)	C12—C11—O11	109.14 (9)
C1—C2—O3	125.30 (11)	C12—C11—C10	112.86 (9)
C3—C2—O3	126.19 (10)	C12—C11—H11a	107.21 (6)
C3—C2—C1	108.15 (10)	C11—C12—O12	110.23 (9)
C2—C3—O4	131.22 (10)	H12a—C12—O12	109.61 (7)
C4—C3—O4	119.67 (10)	H12a—C12—C11	109.61 (6)
C4—C3—C2	109.11 (10)	H12b—C12—O12	109.61 (6)
C3—C4—O1	103.96 (9)	H12b—C12—C11	109.61 (6)
H4a—C4—O1	109.96 (6)	H12b—C12—H12a	108.1
H4a—C4—C3	109.96 (6)	C17—N1—C13	118.57 (10)
C5—C4—O1	108.21 (9)	C22—N2—C18	120.98 (10)
C5—C4—C3	114.57 (9)	H13—C13—N1	118.44 (6)
C5—C4—H4a	109.96 (6)	C14—C13—N1	123.12 (11)
C4—C5—O5	110.05 (9)	C14—C13—H13	118.44 (7)
H5a—C5—O5	109.63 (6)	H14—C14—C13	120.45 (7)
H5a—C5—C4	109.63 (6)	C15—C14—C13	119.10 (10)
C6—C5—O5	108.26 (9)	C15—C14—H14	120.45 (6)
C6—C5—C4	109.62 (9)	C16—C15—C14	117.47 (10)
C6—C5—H5a	109.63 (6)	C20—C15—C14	120.67 (9)
C5—C6—O6	108.86 (9)	C20—C15—C16	121.84 (9)
H6a—C6—O6	109.91 (6)	H16—C16—C15	120.14 (6)
H6a—C6—C5	109.91 (6)	C17—C16—C15	119.73 (10)
H6b—C6—O6	109.91 (6)	C17—C16—H16	120.14 (7)
H6b—C6—C5	109.91 (6)	C16—C17—N1	122.00 (10)
H6b—C6—H6a	108.3	H17—C17—N1	119.00 (6)
C10—O7—C7	108.36 (8)	H17—C17—C16	119.00 (7)
C8—O9—H9	109.1 (18)	H18—C18—N2	119.58 (6)
C11—O11—H11	111.1 (15)	C19—C18—N2	120.83 (10)
C12—O12—H12	106.7 (15)	C19—C18—H18	119.58 (7)
O8—C7—O7	118.26 (10)	H19—C19—C18	120.03 (7)
C8—C7—O7	110.31 (9)	C20—C19—C18	119.94 (10)
C8—C7—O8	131.42 (10)	C20—C19—H19	120.03 (6)
C7—C8—O9	123.53 (10)	C19—C20—C15	121.17 (9)
C9—C8—O9	127.32 (10)	C21—C20—C15	121.48 (9)

C9—C8—C7	109.03 (10)	C21—C20—C19	117.33 (10)
C8—C9—O10	130.96 (10)	H21—C21—C20	119.85 (6)
C10—C9—O10	121.55 (10)	C22—C21—C20	120.30 (11)
C10—C9—C8	107.50 (9)	C22—C21—H21	119.85 (7)
C9—C10—O7	104.79 (8)	C21—C22—N2	120.61 (11)
H10a—C10—O7	109.35 (5)	H22—C22—N2	119.70 (6)
H10a—C10—C9	109.35 (6)	H22—C22—C21	119.70 (7)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O10^{i}	0.86 (3)	1.74 (3)	2.5862 (14)	169 (2)
O3—H3···O5^{ii}	0.817 (19)	2.531 (19)	2.8832 (13)	107.5 (15)
O3—H3···O6^{ii}	0.817 (19)	1.903 (19)	2.7117 (14)	170.0 (19)
O4—H4···N1^{ii}	0.93 (3)	1.64 (3)	2.5428 (14)	163 (3)
O5—H5···O1^{iii}	0.85 (2)	2.00 (2)	2.8510 (13)	173 (2)
O6—H6···O2^{iv}	0.83 (2)	1.84 (2)	2.6616 (14)	173 (2)
O9—H9···O12^{v}	0.79 (2)	1.91 (2)	2.6902 (14)	175 (2)
O11—H11···O10^{iii}	0.79 (2)	1.91 (2)	2.6663 (13)	162 (2)
O12—H12···O8^{vi}	0.87 (2)	1.81 (2)	2.6683 (14)	169 (2)
C5—H5A···O11	1.00 (1)	2.44 (1)	3.2950 (14)	143 (1)
C12—H12B···O4	0.99 (1)	2.50 (1)	3.3249 (16)	141 (1)
C14—H14···O8^{vii}	0.95 (1)	2.40 (1)	3.3311 (15)	166 (1)
C16—H16···O2	0.95 (1)	2.51 (1)	3.4513 (16)	170 (1)
C17—H17···O5	0.95 (1)	2.55 (1)	3.4651 (14)	163 (1)
C19—H19···O7^{vii}	0.95 (1)	2.56 (1)	3.2181 (14)	127 (1)
C19—H19···O8^{vii}	0.95 (1)	2.48 (1)	3.4267 (15)	174 (1)
C21—H21···O2	0.95 (1)	2.40 (1)	3.3418 (17)	173 (1)
C22—H22···O6^{viii}	0.95 (1)	2.44 (1)	3.1860 (16)	136 (1)

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