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A co-crystal of nonahydrated disodium(II) with mixed anions from *m*-chlorobenzoic acid and furosemide

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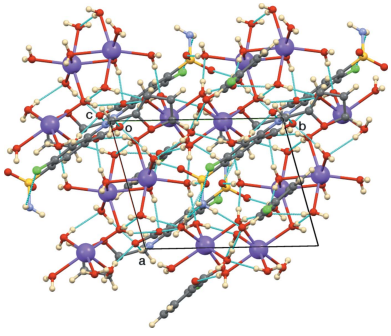
In the title compound, $[Na_2(H_2O)_9](C_7H_4ClO_2)(C_{12}H_{10}ClN_2O_5S)$ {systematic name: *catena*-poly[[[triaquasodium(I)]-di-μ-aqua-[triaquasodium(I)]-μ-aqua] 3-chlorobenzoate 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoate]}, both the original *m*-chlorobenzoic acid and furosemide exist with deprotonated carboxylates, and the sodium cations and water molecules exist in chains with stoichiometry $[Na_2(OH_2)_9]^{2+}$ that propagate in the $[\bar{1}10]$ direction. Each of the two independent Na^+ ions is coordinated by three monodentate water molecules, two double-water bridges, and one single-water bridge. There is considerable cross-linking between the $[Na_2(OH_2)_9]^{2+}$ chains and to furosemide sulfonamide and carboxylate by intermolecular O—H···O hydrogen bonds. All hydrogen-bond donors participate in a complex two-dimensional array parallel to the *ab* plane. The furosemide NH group donates an intramolecular hydrogen bond to the carboxylate group, and the furosemide NH_2 group donates an intramolecular hydrogen bond to the Cl atom and an intermolecular one to the *m*-chlorobenzoate O atom. The plethora of hydrogen-bond donors on the cation/water chain leads to many large rings, up to graph set $R_4^4(24)$, involving two chains and two furosemide anions. The chlorobenzoate is involved in only one $R_2^2(8)$ ring, with two water molecules *cis*-coordinated to Na. The furan O atom is not hydrogen bonded.

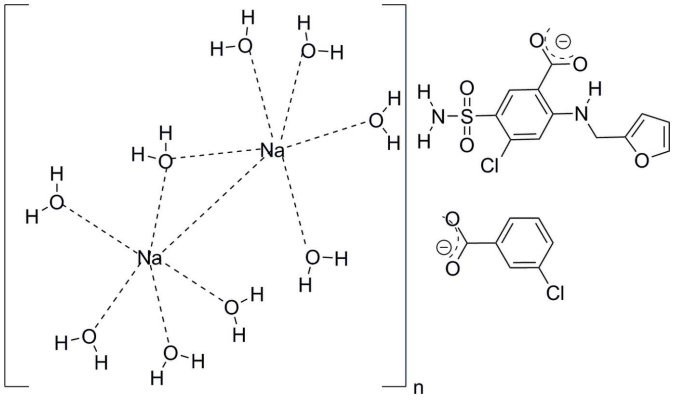
1. Chemical context

Furosemide is a widely used diuretic for the treatment of hypertension and edema (Krumlovsky & del Greco, 1976; Musini *et al.*, 2015), and to a lesser extent, hypercalcemia (Belen *et al.*, 2014; Carvalhana *et al.*, 2006). While this furan-containing compound is of interest, the toxicity elicited by these core compounds is not well understood. The free furan itself is a known hepato-carcinogen and toxicant, as studied in rats (Gill *et al.*, 2010) and mice (Terrell *et al.*, 2014). The epoxide metabolite of furans, formed in CYP450-mediated oxidations, can isomerize to highly reactive electrophilic intermediates such as *cis*-2-butene-1,4-dial (Chen *et al.*, 1995; Peterson 2015; Vargas *et al.*, 1998).

We have performed the oxidation of furosemide with *m*-chloroperbenzoic acid (*m*-CPBA), and isolated various epoxide and isomerized products in support of our efforts to understand this type of toxicity mechanism, and to also identify potential biomarkers for furosemide in humans. During the separation and drying of the products of the furosemide–*m*-CPBA reaction, we observed the formation of crystals in the mother liquor (the organic layer). Analysis of these crystals by X-ray crystallography revealed a disodium



nonahydrate co-crystal with furosemide (starting material) and *m*-chlorobenzoic acid (an inadvertent contaminant or the reduced product of *m*-CPBA). Analogous to the known properties of co-crystals of furosemide with nicotinamide and their pharmaceutical importance (Aitipamula *et al.*, 2012; Chadha *et al.*, 2012; Goud *et al.*, 2012; Stepanovs & Mishnev, 2012; Ueto *et al.*, 2012), we believe that the co-crystals of furosemide with *m*-chlorobenzoic acid could have useful applications in drug development and may lead to formulations with improved potency, solubility, and stability. Therefore, this serendipitous finding may have important applications for improving furosemide bioavailability.



2. Structural commentary

The asymmetric unit is illustrated in Fig. 1. The furosemide moiety is present as the monoanion, with the COOH group deprotonated, N2 as NH and the primary amine nitrogen N1 as NH_2. The *m*-chlorobenzoic acid moiety is also deprotonated. Balancing the charge of the two types of anions are two independent sodium cations, both of which are hexacoordinate, with Na···O(water) distances in the range 2.3558 (13)–2.4500 (13) Å. Each Na^+ cation is coordinated by three monodentate water molecules, two double-water bridge molecules, and one single-water bridge molecule, as shown in Fig. 2. Thus, centrosymmetric $Na_2(OH_2)_8$ units are linked by single water bridges, forming chains in the [$\bar{1}$10] direction.

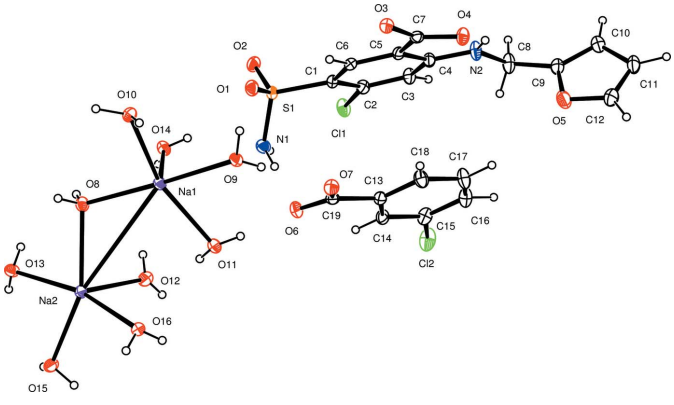


Figure 1
The asymmetric unit with 50% ellipsoids.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H11*N*···Cl1	0.839 (18)	2.767 (17)	3.2848 (16)	121.6 (14)
N1—H12*N*···O6	0.872 (18)	1.920 (18)	2.7905 (17)	175.3 (17)
N2—H2*N*···O4	0.860 (18)	1.906 (18)	2.6199 (16)	139.4 (16)
O8—H81···O3^{i}	0.83 (2)	2.07 (2)	2.8737 (16)	162 (2)
O8—H82···O15^{ii}	0.82 (2)	2.00 (2)	2.8025 (16)	168 (2)
O9—H91···O16^{iii}	0.86 (2)	1.99 (2)	2.8499 (15)	172 (2)
O9—H92···O7	0.81 (2)	2.10 (2)	2.8867 (16)	167 (2)
O10—H101···O11^{iii}	0.78 (2)	1.96 (2)	2.7444 (16)	174 (2)
O10—H102···O3^{iv}	0.93 (2)	1.90 (2)	2.8271 (15)	171 (2)
O11—H111···O6	0.84 (2)	1.89 (2)	2.7296 (16)	176 (2)
O11—H112···O12	0.81 (2)	2.08 (2)	2.8641 (16)	162 (2)
O12—H121···O4^{i}	0.85 (2)	1.96 (2)	2.7962 (16)	171 (2)
O12—H122···O2^{v}	0.76 (2)	2.12 (2)	2.8593 (15)	165 (2)
O13—H131···O7^{i}	0.81 (2)	2.01 (2)	2.8082 (15)	169 (2)
O13—H132···O3^{i}	0.85 (2)	1.97 (2)	2.7939 (15)	165 (2)
O14—H141···O4^{i}	0.76 (2)	1.99 (2)	2.7265 (16)	164 (2)
O14—H142···O1	0.74 (2)	2.31 (2)	3.0019 (17)	156 (2)
O15—H151···O14^{v}	0.85 (2)	1.92 (2)	2.7766 (16)	178 (2)
O15—H152···O7^{i}	0.80 (2)	2.14 (2)	2.8545 (16)	149 (2)
O16—H161···O10^{v}	0.798 (19)	1.990 (19)	2.7857 (16)	175.7 (18)
O16—H162···O1^{v}	0.80 (2)	2.20 (2)	2.9852 (15)	165.8 (17)

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

3. Supramolecular features

Hydrogen bonding is extensive (Table 1), with all 21 hydrogen-bond donors involved. Notable features of the two-dimensional hydrogen-bonding pattern (Etter *et al.*. 1990) are sulfonamide N—H···O bonds to *m*-chlorobenzoate, secondary amine N—H···O hydrogen bonds to furosemide

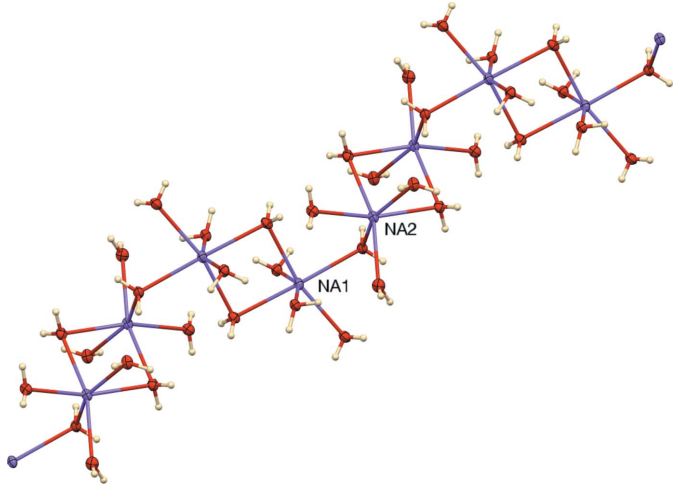


Figure 2
A portion of the Na–water chain, showing the centrosymmetric $Na_2(OH_2)_2$ bridges and the single water bridges.

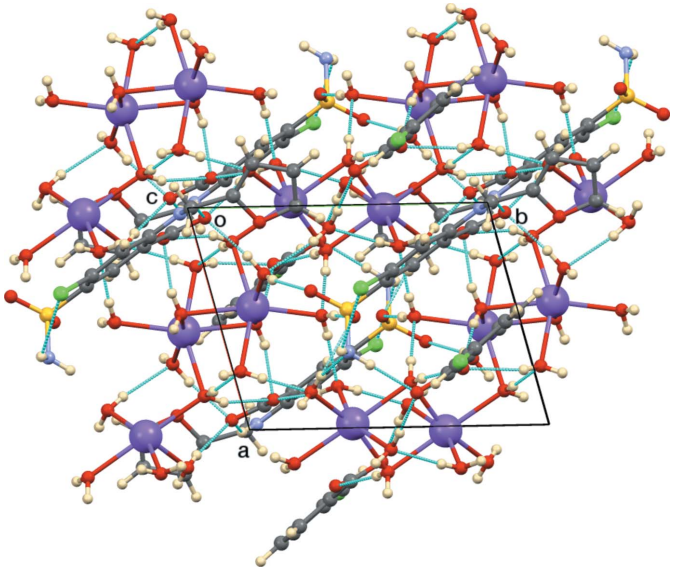


Figure 3
A supramolecular layer of the title compound in the *ab* plane.

anion (carboxylate), and water O—H···O hydrogen bonds to the sulfonamide O atom, to both types of carboxylates, and to other water molecules. The direction of the normal to the hydrogen-bonding network is [001]. The furan oxygen atom O5 is not involved in the hydrogen bonding. A supramolecular layer in the ab plane is shown in Fig. 3.

4. Synthesis and crystallization

Furosemide (8.2 mmol; 2.71 g), dissolved in 3 ml of dichloromethane (DCM), was added dropwise over 5 min to a solution of 8.2 mmol of *m*-CPBA (1.84 g) and 10.5 mmol $NaHCO_3$ (0.88 g) in 20 ml of DCM on ice with rapid stirring (Fig. 4). After 2 h, an additional 4 mmol of *m*-CPBA in 10 ml of DCM was added to the reaction mixture. Upon removal from the ice bath, 4 ml of aqueous sodium sulfite solution (10%) was added with stirring for an additional 15 min. After partitioning the layers with deionized water (resistance 18.2 $M\ \Omega\ cm^{-1}$), the organic layer was collected and the aqueous layer was extracted with another 10 ml of DCM. The combined mixture of the organic layer was washed with 10 ml of aqueous solution of $NaHCO_3$ (5%, *w*/*v*), dried over anhydrous Na_2SO_4, and then subjected to partial evaporation under low pressure (*ca* 4 psi) at 308 K. The partially evaporated sample was left at ambient pressure and temperature overnight. Crystals were formed with slow evaporation.

Table 2
Experimental details.

Crystal data	
Chemical formula	$[Na_2(OH_2)_9](C_7H_4ClO_2)$-$(C_{12}H_{10}ClN_2O_5S)$
M_r	693.41
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	100
a, *b*, *c* (Å)	7.908 (2), 10.224 (3), 19.631 (4)
α, β, γ (°)	85.46 (2), 81.80 (2), 74.96 (2)
V (Å^3)	1515.7 (7)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.39
Crystal size (mm)	0.30 × 0.25 × 0.07
Data collection	
Diffractometer	Nonius KappaCCD
Absorption correction	Multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.893, 0.974
No. of measured, independent and observed [$I > 2s(I)$] reflections	17752, 10267, 7760
R_{int}	0.035
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.751
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.043, 0.107, 1.05
No. of reflections	10267
No. of parameters	442
No. of restraints	120
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.47, −0.55

Computer programs: *COLLECT* (Nonius, 1999), *HKL SCALEPACK* and *DENZO* and *SCALEPACK* (Otwinowski & Minor 1997), *SIR97* (Altomare *et al.*, 1999), *SHELXL97* (Sheldrick, 2008) and *ORTEP-3 for Windows* (Farrugia, 2012).

5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. H atoms on C were idealized with C—H distances of 0.95 Å for sp^2 C and 0.99 Å for CH_2. Those on N and O were assigned from difference maps, and their positions refined, with O—H distances restrained to be equal. U_{iso}(H) were assigned as 1.2 times U_{eq} of the attached atoms (1.5 for water). Six reflections with *Fo*<<*Fc* were omitted from the calculations.

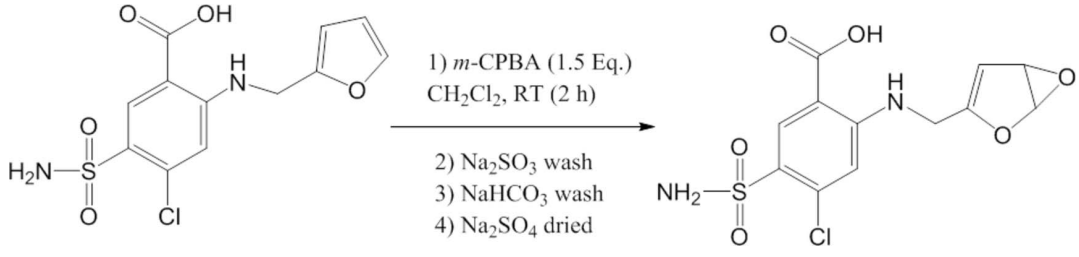


Figure 4
Proposed scheme of reactions of furosemide with *m*-chloroperoxybenzoic acid.

Acknowledgements

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References

Aitipamula, S., *et al.* (2012). *Cryst. Growth Des.* **12**, 2147–2152.
Altomare, A., Burla, M. C., Camalli, M., Carrozzini, B., Cascarano, G. L., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Rizzi, R. (1999). *J. Appl. Cryst.* **32**, 339–340.
Belen, B., Oguz, A., Okur, A. & Dalgic, B. (2014). *BMJ Case Rep*. pii: bcr2014203746. doi: 10.1136/bcr-2014-203746.
Carvalhana, V., Burry, L. & Lapinsky, S. E. (2006). *J. Crit. Care*, **21**, 316–321.
Chadha, R., Saini, A., Arora, P. & Bhandari, S. (2012). *Crit. Rev. Ther. Drug Carrier Syst.* **29**, 183–218.
Chen, L. J., Hecht, S. S. & Peterson, L. A. (1995). *Chem. Res. Toxicol.* **8**, 903–906.
Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262.
Farrugia, L. J. (2012). *J. Appl. Cryst.* **45**, 849–854.
Gill, S., Bondy, G., Lefebvre, D. E., Becalski, A., Kavanagh, M., Hou, Y., Turcotte, A. M., Barker, M., Weld, M., Vavasour, E. & Cooke, G. M. (2010). *Toxicol. Pathol.* **38**, 619–630.
Goud, N. R., Gangavaram, S., Suresh, K., Pal, S., Manjunatha, S. G., Nambiar, S. & Nangia, A. (2012). *J. Pharm. Sci.* **101**, 664–680.
Krumlovsky, F. A. & del Greco, F. (1976). *Postgrad. Med.* **59**, 105–110.
Musini, V. M., Rezapour, P., Wright, J. M., Bassett, K. & Jauca, C. D. (2015). *Cochrane Database Syst. Rev. 8*, CD003825. doi: 10.1002/14651858.CD003825.pub3.
Nonius (1999). *KappaCCD Software*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Peterson, L. A. (2015). *Drug Metab. Rev*. **38**, 615–626.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Stepanovs, D. & Mishnev, A. (2012). *Acta Cryst.* C**68**, o488–o491.
Terrell, A. N., Huynh, M., Grill, A. E., Kovi, R. C., O'Sullivan, M. G., Guttenplan, J. B., Ho, Y. Y. & Peterson, L. A. (2014). *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **770**, 46–54.
Ueto, T., Takata, N., Muroyama, N., Nedu, A., Sasaki, A., Tanida, S. & Terada, K. (2012). *Cryst. Growth Des.* **12**, 485–494.
Vargas, F., Martinez Volkmar, I., Sequera, J., Mendez, H., Rojas, J., Fraile, G., Velasquez, M. & Medina, R. (1998). *J. Photochem. Photobiol. B*, **42**, 219–225.

supporting information

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Computing details

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor 1997); data reduction: *HKL DENZO* and *SCALEPACK* (Otwinowski & Minor 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012); software used to prepare material for publication: *SHELXL97* (Sheldrick, 2008).

catena-Poly[[[triaquasodium(I)]-di-μ-aqua-[triaquasodium(I)]-μ-aqua] 3-chlorobenzoate 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoate]

Crystal data

$[Na_2(OH_2)_9](C_7H_4ClO_2)(C_{12}H_{10}ClN_2O_5S)$
M_r = 693.41
Triclinic, $P\overline{1}$
Hall symbol: -P 1
a = 7.908 (2) Å
b = 10.224 (3) Å
c = 19.631 (4) Å
α = 85.46 (2)°
β = 81.80 (2)°
γ = 74.96 (2)°
V = 1515.7 (7) Å^3
Z = 2
$F(000)$ = 720
D_x = 1.519 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 17752 reflections
θ = 2.5–32.6°
μ = 0.39 mm^{-1}
T = 100 K
Lath fragment, colorless
0.30 × 0.25 × 0.07 mm

Data collection

Nonius KappaCCD diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
ω and φ scans
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.893, T_{max} = 0.974
17752 measured reflections
10267 independent reflections
7760 reflections with $I > 2s(I)$
R_{int} = 0.035
θ_{max} = 32.3°, θ_{min} = 2.7°
h = −11→11
k = −13→15
l = −29→29

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.107
S = 1.05
10267 reflections
442 parameters
120 restraints
Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map	$w = 1/[\sigma^2(F_o^2) + (0.058P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
Hydrogen site location: inferred from neighbouring sites	$(\Delta/\sigma)_{max} = 0.001$
H atoms treated by a mixture of independent and constrained refinement	$\Delta\rho_{max} = 0.47$ e Å^{-3}
	$\Delta\rho_{min} = -0.55$ e Å^{-3}

Special details

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

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
Cl1	0.62548 (4)	0.49926 (3)	0.089838 (16)	0.01988 (8)
S1	0.53103 (4)	0.56412 (3)	0.252718 (16)	0.01360 (7)
O1	0.49898 (12)	0.54858 (10)	0.32676 (5)	0.01772 (19)
O2	0.61708 (13)	0.66762 (9)	0.22345 (5)	0.0186 (2)
O3	0.86565 (12)	0.10830 (9)	0.36913 (5)	0.01511 (18)
O4	0.95416 (13)	−0.04844 (9)	0.29000 (5)	0.01778 (19)
O5	0.92982 (13)	−0.22550 (10)	0.12326 (6)	0.0250 (2)
N1	0.34022 (15)	0.59988 (12)	0.22586 (6)	0.0171 (2)
H11N	0.345 (2)	0.6226 (18)	0.1837 (10)	0.021*
H12N	0.282 (2)	0.5394 (18)	0.2404 (9)	0.021*
N2	0.97465 (16)	0.03032 (12)	0.15946 (6)	0.0191 (2)
H2N	1.009 (2)	−0.0258 (18)	0.1927 (9)	0.023*
C1	0.65991 (16)	0.40639 (13)	0.22332 (6)	0.0133 (2)
C2	0.70427 (17)	0.37919 (13)	0.15334 (7)	0.0149 (2)
C3	0.81105 (18)	0.25674 (13)	0.13183 (7)	0.0165 (2)
H3	0.8422	0.2422	0.0840	0.020*
C4	0.87486 (17)	0.15226 (13)	0.18053 (7)	0.0147 (2)
C5	0.83234 (16)	0.17957 (12)	0.25209 (6)	0.0128 (2)
C6	0.72692 (16)	0.30566 (13)	0.27139 (7)	0.0131 (2)
H6	0.6996	0.3237	0.3190	0.016*
C7	0.88889 (16)	0.07359 (13)	0.30778 (7)	0.0133 (2)
C8	1.0003 (2)	−0.01178 (14)	0.08920 (7)	0.0215 (3)
H8A	1.0944	0.0249	0.0619	0.026*
H8B	0.8900	0.0247	0.0682	0.026*
C9	1.05072 (18)	−0.16262 (14)	0.08795 (7)	0.0179 (3)
C10	1.19245 (19)	−0.25494 (14)	0.05907 (7)	0.0193 (3)
H10	1.2949	−0.2372	0.0325	0.023*
C11	1.1573 (2)	−0.38525 (14)	0.07659 (7)	0.0211 (3)
H11	1.2312	−0.4709	0.0634	0.025*

C12	0.9991 (2)	−0.36173 (15)	0.11544 (9)	0.0252 (3)
H12	0.9430	−0.4302	0.1348	0.030*
Cl2	0.28737 (6)	0.23829 (4)	0.026181 (19)	0.02904 (9)
O6	0.15314 (12)	0.41020 (9)	0.27976 (5)	0.01757 (19)
O7	0.25838 (13)	0.23500 (10)	0.35073 (5)	0.01731 (19)
C13	0.31680 (17)	0.20440 (13)	0.22941 (7)	0.0147 (2)
C14	0.27177 (18)	0.25472 (13)	0.16425 (7)	0.0162 (2)
H14	0.1917	0.3408	0.1589	0.019*
C15	0.34577 (19)	0.17705 (14)	0.10766 (7)	0.0191 (3)
C16	0.4648 (2)	0.05117 (14)	0.11350 (8)	0.0230 (3)
H16	0.5148	−0.0002	0.0740	0.028*
C17	0.5091 (2)	0.00209 (15)	0.17849 (8)	0.0243 (3)
H17	0.5903	−0.0836	0.1836	0.029*
C18	0.43507 (18)	0.07803 (14)	0.23614 (7)	0.0198 (3)
H18	0.4654	0.0434	0.2804	0.024*
C19	0.23698 (16)	0.28915 (13)	0.29148 (7)	0.0140 (2)
Na1	0.01996 (6)	0.65083 (5)	0.45870 (3)	0.01372 (11)
Na2	−0.44798 (7)	0.87445 (5)	0.44265 (3)	0.01394 (11)
O8	−0.15551 (12)	0.88218 (10)	0.46379 (5)	0.01546 (18)
H81	−0.126 (2)	0.9400 (19)	0.4362 (10)	0.023*
H82	−0.175 (2)	0.9155 (18)	0.5017 (10)	0.023*
O9	0.19980 (12)	0.42119 (10)	0.45986 (5)	0.01525 (18)
H91	0.295 (2)	0.4001 (18)	0.4793 (9)	0.023*
H92	0.217 (2)	0.3797 (19)	0.4253 (10)	0.023*
O10	0.18912 (12)	0.66647 (10)	0.54828 (5)	0.01560 (18)
H101	0.169 (2)	0.6053 (19)	0.5718 (10)	0.023*
H102	0.158 (2)	0.7401 (18)	0.5767 (9)	0.023*
O11	−0.10007 (13)	0.54861 (10)	0.37594 (5)	0.01550 (18)
H111	−0.026 (2)	0.5051 (18)	0.3452 (10)	0.023*
H112	−0.161 (2)	0.6123 (19)	0.3560 (9)	0.023*
O12	−0.30234 (14)	0.80747 (10)	0.33026 (5)	0.0182 (2)
H121	−0.221 (2)	0.8455 (19)	0.3142 (10)	0.027*
H122	−0.329 (2)	0.7843 (19)	0.2985 (10)	0.027*
O13	−0.47562 (13)	1.11930 (10)	0.43409 (5)	0.01560 (18)
H131	−0.543 (2)	1.1568 (19)	0.4070 (10)	0.023*
H132	−0.380 (2)	1.1303 (18)	0.4114 (10)	0.023*
O14	0.16422 (13)	0.76011 (10)	0.36697 (5)	0.01745 (19)
H141	0.108 (3)	0.802 (2)	0.3408 (10)	0.026*
H142	0.236 (3)	0.713 (2)	0.3462 (10)	0.026*
O15	−0.73738 (13)	0.97411 (10)	0.41518 (5)	0.01661 (19)
H151	−0.770 (2)	0.9090 (19)	0.4010 (9)	0.025*
H152	−0.753 (2)	1.0342 (19)	0.3861 (10)	0.025*
O16	−0.49332 (13)	0.65364 (10)	0.46360 (5)	0.01549 (18)
H161	−0.582 (2)	0.6532 (18)	0.4885 (10)	0.023*
H162	−0.494 (2)	0.6123 (18)	0.4305 (10)	0.023*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.02539 (17)	0.01556 (15)	0.01459 (14)	0.00207 (12)	−0.00343 (12)	0.00125 (11)
S1	0.01423 (14)	0.01061 (14)	0.01548 (15)	−0.00184 (11)	−0.00167 (11)	−0.00254 (11)
O1	0.0191 (5)	0.0175 (5)	0.0155 (4)	−0.0020 (4)	−0.0016 (4)	−0.0041 (4)
O2	0.0209 (5)	0.0136 (4)	0.0221 (5)	−0.0062 (4)	−0.0016 (4)	−0.0022 (4)
O3	0.0167 (4)	0.0147 (4)	0.0138 (4)	−0.0036 (4)	−0.0024 (3)	−0.0002 (3)
O4	0.0240 (5)	0.0108 (4)	0.0176 (5)	−0.0022 (4)	−0.0036 (4)	−0.0001 (3)
O5	0.0199 (5)	0.0182 (5)	0.0335 (6)	−0.0016 (4)	0.0032 (4)	−0.0038 (4)
N1	0.0153 (5)	0.0159 (5)	0.0194 (6)	−0.0022 (4)	−0.0036 (4)	0.0003 (4)
N2	0.0276 (6)	0.0118 (5)	0.0141 (5)	0.0027 (5)	−0.0032 (5)	−0.0016 (4)
C1	0.0137 (5)	0.0117 (6)	0.0144 (6)	−0.0022 (4)	−0.0020 (4)	−0.0027 (4)
C2	0.0170 (6)	0.0129 (6)	0.0146 (6)	−0.0027 (5)	−0.0039 (5)	0.0015 (4)
C3	0.0207 (6)	0.0137 (6)	0.0134 (6)	−0.0014 (5)	−0.0019 (5)	−0.0013 (4)
C4	0.0158 (6)	0.0120 (6)	0.0155 (6)	−0.0018 (5)	−0.0019 (5)	−0.0021 (4)
C5	0.0138 (5)	0.0108 (5)	0.0141 (6)	−0.0035 (5)	−0.0022 (4)	−0.0006 (4)
C6	0.0129 (5)	0.0128 (6)	0.0147 (6)	−0.0044 (5)	−0.0023 (4)	−0.0019 (4)
C7	0.0118 (5)	0.0137 (6)	0.0155 (6)	−0.0050 (5)	−0.0019 (4)	0.0002 (4)
C8	0.0317 (8)	0.0147 (6)	0.0144 (6)	0.0003 (6)	−0.0010 (5)	−0.0025 (5)
C9	0.0205 (6)	0.0153 (6)	0.0169 (6)	−0.0024 (5)	−0.0022 (5)	−0.0028 (5)
C10	0.0205 (6)	0.0173 (6)	0.0179 (6)	−0.0011 (5)	−0.0019 (5)	−0.0015 (5)
C11	0.0266 (7)	0.0137 (6)	0.0210 (7)	0.0011 (5)	−0.0064 (5)	−0.0033 (5)
C12	0.0252 (7)	0.0158 (7)	0.0351 (8)	−0.0059 (6)	−0.0027 (6)	−0.0037 (6)
Cl2	0.0479 (2)	0.02199 (18)	0.01606 (16)	−0.00506 (16)	−0.00745 (15)	−0.00001 (13)
O6	0.0176 (4)	0.0127 (4)	0.0196 (5)	0.0003 (4)	−0.0008 (4)	−0.0010 (4)
O7	0.0203 (5)	0.0165 (5)	0.0149 (4)	−0.0031 (4)	−0.0048 (4)	−0.0003 (3)
C13	0.0144 (6)	0.0130 (6)	0.0168 (6)	−0.0029 (5)	−0.0032 (5)	−0.0016 (4)
C14	0.0187 (6)	0.0114 (6)	0.0182 (6)	−0.0026 (5)	−0.0038 (5)	0.0002 (5)
C15	0.0268 (7)	0.0167 (6)	0.0146 (6)	−0.0067 (5)	−0.0036 (5)	0.0006 (5)
C16	0.0299 (7)	0.0166 (7)	0.0204 (7)	−0.0033 (6)	0.0017 (6)	−0.0047 (5)
C17	0.0282 (7)	0.0137 (6)	0.0257 (7)	0.0036 (6)	−0.0017 (6)	−0.0020 (5)
C18	0.0217 (7)	0.0156 (6)	0.0192 (6)	0.0000 (5)	−0.0031 (5)	0.0012 (5)
C19	0.0119 (5)	0.0137 (6)	0.0170 (6)	−0.0037 (5)	−0.0039 (4)	−0.0002 (4)
Na1	0.0119 (2)	0.0117 (2)	0.0173 (3)	−0.00179 (19)	−0.00343 (19)	−0.00038 (19)
Na2	0.0129 (2)	0.0116 (2)	0.0173 (3)	−0.00220 (19)	−0.00328 (19)	−0.00089 (19)
O8	0.0164 (4)	0.0126 (4)	0.0164 (5)	−0.0017 (4)	−0.0026 (4)	−0.0003 (4)
O9	0.0129 (4)	0.0153 (4)	0.0168 (5)	−0.0006 (4)	−0.0040 (4)	−0.0025 (3)
O10	0.0168 (4)	0.0128 (4)	0.0182 (5)	−0.0054 (4)	−0.0022 (4)	−0.0011 (4)
O11	0.0138 (4)	0.0139 (4)	0.0173 (5)	−0.0006 (4)	−0.0022 (4)	−0.0006 (4)
O12	0.0196 (5)	0.0178 (5)	0.0187 (5)	−0.0063 (4)	−0.0044 (4)	−0.0014 (4)
O13	0.0127 (4)	0.0158 (5)	0.0181 (5)	−0.0030 (4)	−0.0036 (4)	0.0012 (4)
O14	0.0142 (5)	0.0155 (5)	0.0207 (5)	−0.0006 (4)	−0.0008 (4)	−0.0025 (4)
O15	0.0168 (5)	0.0142 (5)	0.0205 (5)	−0.0047 (4)	−0.0065 (4)	−0.0005 (4)
O16	0.0138 (4)	0.0150 (5)	0.0184 (5)	−0.0041 (4)	−0.0020 (4)	−0.0031 (4)

Geometric parameters (Å, º)

Cl1—C2	1.7411 (14)	C14—H14	0.9500
S1—O2	1.4418 (10)	C15—C16	1.391 (2)
S1—O1	1.4427 (10)	C16—C17	1.392 (2)
S1—N1	1.6120 (13)	C16—H16	0.9500
S1—C1	1.7604 (14)	C17—C18	1.393 (2)
O3—C7	1.2572 (16)	C17—H17	0.9500
O4—C7	1.2761 (16)	C18—H18	0.9500
O5—C9	1.3664 (17)	Na1—O14	2.3558 (13)
O5—C12	1.3703 (18)	Na1—O10	2.3946 (12)
N1—H11N	0.839 (18)	Na1—O9^{i}	2.4090 (12)
N1—H12N	0.872 (18)	Na1—O9	2.4091 (13)
N2—C4	1.3512 (17)	Na1—O8	2.4134 (13)
N2—C8	1.4483 (18)	Na1—O11	2.4200 (12)
N2—H2N	0.860 (18)	Na2—O15	2.3709 (13)
C1—C6	1.3919 (18)	Na2—O16	2.3718 (13)
C1—C2	1.4001 (18)	Na2—O12	2.4016 (13)
C2—C3	1.3755 (19)	Na2—O13^{ii}	2.4108 (12)
C3—C4	1.4163 (18)	Na2—O8	2.4294 (12)
C3—H3	0.9500	Na2—O13	2.4500 (13)
C4—C5	1.4295 (18)	O8—H81	0.83 (2)
C5—C6	1.3892 (18)	O8—H82	0.821 (19)
C5—C7	1.5066 (18)	O9—Na1^{i}	2.4090 (12)
C6—H6	0.9500	O9—H91	0.862 (19)
C8—C9	1.4907 (19)	O9—H92	0.806 (19)
C8—H8A	0.9900	O10—H101	0.784 (19)
C8—H8B	0.9900	O10—H102	0.932 (18)
C9—C10	1.3501 (19)	O11—H111	0.842 (19)
C10—C11	1.436 (2)	O11—H112	0.811 (19)
C10—H10	0.9500	O12—H121	0.848 (19)
C11—C12	1.344 (2)	O12—H122	0.76 (2)
C11—H11	0.9500	O13—Na2^{ii}	2.4108 (12)
C12—H12	0.9500	O13—H131	0.807 (19)
Cl2—C15	1.7510 (15)	O13—H132	0.848 (19)
O6—C19	1.2637 (16)	O14—H141	0.76 (2)
O7—C19	1.2623 (16)	O14—H142	0.74 (2)
C13—C18	1.3938 (19)	O15—H151	0.853 (19)
C13—C14	1.3995 (18)	O15—H152	0.803 (19)
C13—C19	1.5158 (19)	O16—H161	0.798 (19)
C14—C15	1.3857 (19)	O16—H162	0.80 (2)
O2—S1—O1	118.19 (6)	O7—C19—O6	124.65 (13)
O2—S1—N1	106.89 (7)	O7—C19—C13	118.41 (12)
O1—S1—N1	106.20 (7)	O6—C19—C13	116.94 (12)
O2—S1—C1	108.39 (6)	O14—Na1—O10	99.71 (4)
O1—S1—C1	106.54 (6)	O14—Na1—O9^{i}	163.93 (4)
N1—S1—C1	110.57 (6)	O10—Na1—O9^{i}	91.71 (4)

C9—O5—C12	106.30 (11)	O14—Na1—O9	103.75 (5)
S1—N1—H11N	112.4 (11)	O10—Na1—O9	81.57 (4)
S1—N1—H12N	112.1 (11)	O9^{i}—Na1—O9	89.00 (4)
H11N—N1—H12N	116.8 (16)	O14—Na1—O8	77.59 (4)
C4—N2—C8	124.07 (12)	O10—Na1—O8	95.33 (4)
C4—N2—H2N	113.6 (12)	O9^{i}—Na1—O8	90.19 (4)
C8—N2—H2N	121.6 (12)	O9—Na1—O8	176.78 (4)
C6—C1—C2	118.22 (12)	O14—Na1—O11	89.24 (4)
C6—C1—S1	118.85 (10)	O10—Na1—O11	159.01 (4)
C2—C1—S1	122.88 (10)	O9^{i}—Na1—O11	83.87 (4)
C3—C2—C1	121.58 (12)	O9—Na1—O11	77.85 (4)
C3—C2—Cl1	117.22 (10)	O8—Na1—O11	105.17 (4)
C1—C2—Cl1	121.21 (10)	O15—Na2—O16	94.41 (4)
C2—C3—C4	120.46 (12)	O15—Na2—O12	99.60 (4)
C2—C3—H3	119.8	O16—Na2—O12	88.32 (4)
C4—C3—H3	119.8	O15—Na2—O13^{ii}	96.08 (4)
N2—C4—C3	120.49 (12)	O16—Na2—O13^{ii}	81.69 (4)
N2—C4—C5	121.12 (12)	O12—Na2—O13^{ii}	162.00 (4)
C3—C4—C5	118.38 (12)	O15—Na2—O8	153.51 (4)
C6—C5—C4	119.11 (12)	O16—Na2—O8	111.98 (4)
C6—C5—C7	118.49 (11)	O12—Na2—O8	83.99 (4)
C4—C5—C7	122.30 (11)	O13^{ii}—Na2—O8	85.91 (4)
C5—C6—C1	122.19 (12)	O15—Na2—O13	74.54 (4)
C5—C6—H6	118.9	O16—Na2—O13	166.06 (4)
C1—C6—H6	118.9	O12—Na2—O13	101.72 (4)
O3—C7—O4	123.35 (12)	O13^{ii}—Na2—O13	90.90 (4)
O3—C7—C5	119.00 (11)	O8—Na2—O13	79.02 (4)
O4—C7—C5	117.62 (11)	Na1—O8—Na2	105.44 (4)
N2—C8—C9	110.13 (12)	Na1—O8—H81	118.9 (13)
N2—C8—H8A	109.6	Na2—O8—H81	106.7 (12)
C9—C8—H8A	109.6	Na1—O8—H82	116.0 (13)
N2—C8—H8B	109.6	Na2—O8—H82	102.7 (12)
C9—C8—H8B	109.6	H81—O8—H82	105.7 (17)
H8A—C8—H8B	108.1	Na1^{i}—O9—Na1	91.00 (4)
C10—C9—O5	110.48 (12)	Na1^{i}—O9—H91	105.6 (12)
C10—C9—C8	134.27 (13)	Na1—O9—H91	120.6 (12)
O5—C9—C8	115.26 (12)	Na1^{i}—O9—H92	109.7 (13)
C9—C10—C11	106.27 (13)	Na1—O9—H92	118.4 (13)
C9—C10—H10	126.9	H91—O9—H92	108.7 (17)
C11—C10—H10	126.9	Na1—O10—H101	97.5 (13)
C12—C11—C10	106.22 (13)	Na1—O10—H102	122.0 (11)
C12—C11—H11	126.9	H101—O10—H102	105.4 (17)
C10—C11—H11	126.9	Na1—O11—H111	116.0 (11)
C11—C12—O5	110.72 (13)	Na1—O11—H112	104.5 (13)
C11—C12—H12	124.6	H111—O11—H112	105.9 (17)
O5—C12—H12	124.6	Na2—O12—H121	115.2 (13)
C18—C13—C14	119.61 (13)	Na2—O12—H122	135.5 (14)
C18—C13—C19	121.12 (12)	H121—O12—H122	103.8 (19)

C14—C13—C19	119.27 (12)	Na2^{ii}—O13—Na2	89.10 (4)
C15—C14—C13	119.01 (12)	Na2^{ii}—O13—H131	123.6 (13)
C15—C14—H14	120.5	Na2—O13—H131	111.3 (13)
C13—C14—H14	120.5	Na2^{ii}—O13—H132	126.5 (12)
C14—C15—C16	122.04 (13)	Na2—O13—H132	106.2 (12)
C14—C15—Cl2	119.23 (11)	H131—O13—H132	98.4 (17)
C16—C15—Cl2	118.73 (11)	Na1—O14—H141	117.4 (14)
C15—C16—C17	118.54 (14)	Na1—O14—H142	113.1 (15)
C15—C16—H16	120.7	H141—O14—H142	104 (2)
C17—C16—H16	120.7	Na2—O15—H151	104.6 (12)
C16—C17—C18	120.34 (13)	Na2—O15—H152	119.8 (13)
C16—C17—H17	119.8	H151—O15—H152	106.5 (18)
C18—C17—H17	119.8	Na2—O16—H161	112.4 (13)
C17—C18—C13	120.46 (13)	Na2—O16—H162	117.0 (13)
C17—C18—H18	119.8	H161—O16—H162	106.8 (18)
C13—C18—H18	119.8		

O2—S1—C1—C6	119.77 (10)	C10—C11—C12—O5	0.73 (17)
O1—S1—C1—C6	−8.40 (12)	C9—O5—C12—C11	−0.22 (17)
N1—S1—C1—C6	−123.38 (11)	C18—C13—C14—C15	0.23 (19)
O2—S1—C1—C2	−57.59 (12)	C19—C13—C14—C15	179.71 (12)
O1—S1—C1—C2	174.23 (10)	C13—C14—C15—C16	−0.7 (2)
N1—S1—C1—C2	59.26 (13)	C13—C14—C15—Cl2	179.03 (10)
C6—C1—C2—C3	−0.01 (19)	C14—C15—C16—C17	0.5 (2)
S1—C1—C2—C3	177.37 (10)	Cl2—C15—C16—C17	−179.18 (12)
C6—C1—C2—Cl1	179.75 (10)	C15—C16—C17—C18	0.1 (2)
S1—C1—C2—Cl1	−2.87 (16)	C16—C17—C18—C13	−0.5 (2)
C1—C2—C3—C4	2.1 (2)	C14—C13—C18—C17	0.3 (2)
Cl1—C2—C3—C4	−177.66 (10)	C19—C13—C18—C17	−179.15 (13)
C8—N2—C4—C3	−10.5 (2)	C18—C13—C19—O7	−10.56 (19)
C8—N2—C4—C5	170.04 (13)	C14—C13—C19—O7	169.97 (11)
C2—C3—C4—N2	177.67 (12)	C18—C13—C19—O6	169.39 (12)
C2—C3—C4—C5	−2.87 (19)	C14—C13—C19—O6	−10.09 (18)
N2—C4—C5—C6	−178.95 (12)	O14—Na1—O8—Na2	117.64 (5)
C3—C4—C5—C6	1.59 (18)	O10—Na1—O8—Na2	−143.56 (4)
N2—C4—C5—C7	−2.64 (19)	O9^{i}—Na1—O8—Na2	−51.83 (5)
C3—C4—C5—C7	177.90 (11)	O11—Na1—O8—Na2	31.87 (5)
C4—C5—C6—C1	0.48 (19)	Na1^{i}—Na1—O8—Na2	−54.90 (7)
C7—C5—C6—C1	−175.97 (11)	O15—Na2—O8—Na1	−165.17 (8)
C2—C1—C6—C5	−1.29 (18)	O16—Na2—O8—Na1	20.07 (6)
S1—C1—C6—C5	−178.78 (10)	O12—Na2—O8—Na1	−65.67 (5)
C6—C5—C7—O3	−12.06 (17)	O13^{ii}—Na2—O8—Na1	99.40 (5)
C4—C5—C7—O3	171.61 (11)	O13—Na2—O8—Na1	−168.88 (5)
C6—C5—C7—O4	166.10 (11)	Na2^{ii}—Na2—O8—Na1	145.27 (4)
C4—C5—C7—O4	−10.23 (18)	O14—Na1—O9—Na1^{i}	−170.12 (4)
C4—N2—C8—C9	−156.88 (13)	O10—Na1—O9—Na1^{i}	91.87 (4)
C12—O5—C9—C10	−0.43 (16)	O9^{i}—Na1—O9—Na1^{i}	0.0
C12—O5—C9—C8	179.48 (12)	O11—Na1—O9—Na1^{i}	−83.94 (4)

N2—C8—C9—C10	−119.97 (17)	O15—Na2—O13—Na2^{ii}	96.06 (4)
N2—C8—C9—O5	60.15 (16)	O16—Na2—O13—Na2^{ii}	57.56 (17)
O5—C9—C10—C11	0.86 (16)	O12—Na2—O13—Na2^{ii}	−167.08 (4)
C8—C9—C10—C11	−179.02 (15)	O13^{ii}—Na2—O13—Na2^{ii}	0.0
C9—C10—C11—C12	−0.96 (16)	O8—Na2—O13—Na2^{ii}	−85.65 (4)

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

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H11*N*···Cl1	0.839 (18)	2.767 (17)	3.2848 (16)	121.6 (14)
N1—H12*N*···O6	0.872 (18)	1.920 (18)	2.7905 (17)	175.3 (17)
N2—H2*N*···O4	0.860 (18)	1.906 (18)	2.6199 (16)	139.4 (16)
O8—H81···O3^{iii}	0.83 (2)	2.07 (2)	2.8737 (16)	162 (2)
O8—H82···O15^{ii}	0.82 (2)	2.00 (2)	2.8025 (16)	168 (2)
O9—H91···O16^{i}	0.86 (2)	1.99 (2)	2.8499 (15)	172 (2)
O9—H92···O7	0.81 (2)	2.10 (2)	2.8867 (16)	167 (2)
O10—H101···O11^{i}	0.78 (2)	1.96 (2)	2.7444 (16)	174 (2)
O10—H102···O3^{iv}	0.93 (2)	1.90 (2)	2.8271 (15)	171 (2)
O11—H111···O6	0.84 (2)	1.89 (2)	2.7296 (16)	176 (2)
O11—H112···O12	0.81 (2)	2.08 (2)	2.8641 (16)	162 (2)
O12—H121···O4^{iii}	0.85 (2)	1.96 (2)	2.7962 (16)	171 (2)
O12—H122···O2^{v}	0.76 (2)	2.12 (2)	2.8593 (15)	165 (2)
O13—H131···O7^{iii}	0.81 (2)	2.01 (2)	2.8082 (15)	169 (2)
O13—H132···O3^{iii}	0.85 (2)	1.97 (2)	2.7939 (15)	165 (2)
O14—H141···O4^{iii}	0.76 (2)	1.99 (2)	2.7265 (16)	164 (2)
O14—H142···O1	0.74 (2)	2.31 (2)	3.0019 (17)	156 (2)
O15—H151···O14^{v}	0.85 (2)	1.92 (2)	2.7766 (16)	178 (2)
O15—H152···O7^{iii}	0.80 (2)	2.14 (2)	2.8545 (16)	149 (2)
O16—H161···O10^{v}	0.798 (19)	1.990 (19)	2.7857 (16)	175.7 (18)
O16—H162···O1^{v}	0.80 (2)	2.20 (2)	2.9852 (15)	165.8 (17)

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