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β-D-Galactopyranosyl-(1→4)–2-amino-2-deoxy-α-D-glucopyranose hydrochloride monohydrate (lactosamine)

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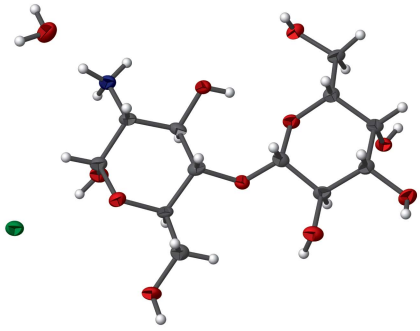
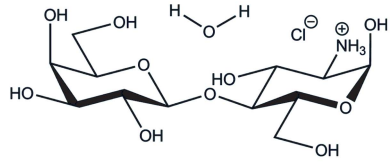
The title compound, $C_{12}H_{24}NO_{10}^{+}\cdot Cl^{-}\cdot H_2O$, (**I**), crystallizes in the monoclinic space group $P2_1$ and exists as a monohydrate of a monosubstituted ammonium chloride salt, with the reducing carbohydrate portion existing exclusively as the α-pyranose tautomer. The glycosidic bond geometry in (**I**) is stabilized by an intramolecular hydrogen bond and is close to that found in crystalline α-lactose. All heteroatoms except glucopyranose ring O4 participate in an extensive hydrogen-bonding network, which propagates in all directions in the crystal structure of (**I**).

3D view



Chemical scheme



Structure description

Lactosamine is an important endogenous and food-related glycoepitope that provides for recognition of glycoproteins by both plant and animal β-galactoside-specific lectins, such as tomato lectin (Acarin *et al.*, 1994) or a family of mammalian galectins (Boscher *et al.*, 2011; Mossine *et al.*, 2008). In free and oligomeric form, *N*-acetyllactosamine is present in human milk and is believed to participate in the immune protection of infants (Kulinich & Liu, 2016). Therefore, structural aspects of lactosamine interaction with carbohydrate-recognizing proteins are of significant interest to the biomedical glycobiology field (Seetharaman *et al.*, 1998; Guardia *et al.*, 2011). As a part of our research program on the structure and anti-tumorigenic potential of aminoglycoconjugates (Glinskii *et al.*, 2012; Mossine *et al.*, 2018), we have prepared a number of 2-amino-2-deoxysaccharides, including lactosamine. Although the crystal parameters and hydrogen-bonding geometry of (**I**) were previously reported in a patent (Dekany *et al.*, 2014), no other structural data have been provided. Here we report details of the molecular geometry of (**I**) and compare it to related disaccharide structures.

Table 1
Conformational features (Å, °) of the glycosidic bond in (**I**) and related disaccharide structures with the Gal-β1→4-Glc link.

Sugar	Tautomer, conformation	τ	Φ	Ψ	Intramolecular contacts around glycosidic bond (O···H; O···O; O···H—O)
Gal-β1→4-GlcNH$_3^+$Cl$^-$·H$_2$O (**I**)[a]	α-pyranose, $^4C_1$	116.0	−95.2	+90.7	O10···H—O2 (1.98; 2.743; 159) O5···H—O2 (2.64; 2.964; 106)
Gal-β1→4-GlcNHCOCH$_3$·H$_2$O (*N*-acetyllactosamine, LacNAc·H$_2$O)[b]	α-pyranose, $^4C_1$[b]	116.3	−88.1	+97.8	O10···H—O2 (1.98; 2.787; 139) O5···H—O6 (2.40; 2.868; 122)
LacNAc/ toad galectin[c]	α-pyranose, $^4C_1$	118.2; 113.6	−66.9; −67.8	+132.4; +132.6	Not reported
LacNAc calculations[d]	α-pyranose, $^4C_1$[d]	117.1	−75	+135	O10···H—O2
Gal-β1→4-Glc·H$_2$O (α-lactose)[e]	α-pyranose, $^4C_1$	116.9	−93.4	+95.9	O10···H—O2 (2.02; 2.819; 159) O5···H—O2 (2.65; 2.992; 106)
Gal-β1→4-Glc (β-lactose)[f]	β-pyranose, $^4C_1$	116.5	−76.3	+106.4	O10···H—O2 (n.d.; 2.707; 101)
Gal-β1→4-GlcNHCOCH$_3$·2H$_2$O (*N*-acetyllactosylamine)[g]	β-pyranose, $^4C_1$	117.4	−89.3	+81.5	O10···H—O2 (2.06; 2.767; 144) O9···H—O2 (2.45; 3.126; 141)

Notes: (*a*) This work; (*b*) Longchambon *et al.* (1981); (*c*) Bianchet *et al.* (2000); (*d*) Imberty *et al.* (1991); (*e*) Smith *et al.* (2005); (*f*) Hirotsu & Shimada (1974); (*g*) Lakshmanan *et al.* (2001).

The molecular structure and atomic numbering for the title compound (**I**) are shown in Fig. 1. Lactosamine is a disaccharide made of the non-reducing β-D-galactoside unit and the D-glucosamine portion, which is a reducing end sugar moiety and thus can exist in several tautomeric forms, such as α- and β-pyranose, or α- and β-furanose. In the crystalline state of (**I**), the D-glucosamine residue exists exclusively as the α-pyranose anomer, which is also a predominant tautomer in aqueous solutions of lactosamine (Dekany *et al.*, 2014). The amino group in (**I**) is fully protonated, as would be expected for a hydrochloride salt. The conformation of the D-glucosamine α-pyranose ring is a relaxed $^4C_1$ chair, with puckering parameters Q_1 = 0.579 (8) Å, θ_1 = 1.0 (8)°, and φ_1 = 100 (27)°. The D-galactoside β-pyranose ring similarly adopts the $^4C_1$ conformation, with puckering parameters Q_2 = 0.607 (8) Å, θ_2 = 2.0 (8)°, and φ_2 = 123 (38)°.

The conformation around the β1→4 glycosidic link in disaccharide (**I**) is an important structural characteristic and, for the purpose of the structure comparison, can be conventionally described by the valence angle C4—O5—C7 (also referred to as 'τ''), torsion angles C4—O5—C7—O10 ('Φ'') and C3—C4—O5—C7 ('Ψ'). As can be seen in Table 1, values of these angles are typical for other Gal-β1→4-Glc disaccharides, with α-lactose monohydrate (Smith *et al.*, 2005) being conformationally the closest structure to (**I**). It is believed that the O10···H—O2 intramolecular hydrogen bond linking the two carbohydrate units is primarily responsible for stabilization of the spatial arrangement around the glycosidic bond, both in the crystal state and in solutions of Gal-β1→4-Glc di- and oligosaccharides (Imberty *et al.* 1991). Moreover, this contact may be further stabilized by its involvement in multicenter hydrogen-bonding patterns. For instance, the H2 proton is involved in bifurcated hydrogen bonding with the O5 and O10 acceptors in (**I**) and α-lactose (Tables 2 and 3), while in *N*-acetyllactosamine (Longchambon *et al.*, 1981) and *N*-acetyllactosylamine (Lakshmanan *et al.*, 2001), additional intramolecular links between the galactopyranoside and glucopyranose moieties are represented by the O5···H6—O6 and the O9···H2—O2 contacts, respectively (Table 2).

The molecular packing of (**I**) features an extensive intermolecular hydrogen-bonding network (Table 2), which propagates in all directions (Fig. 2). The ammonium groups, chloride ions, and water molecules serve as the hydrogen-bonding network 'hubs', each being in short, H-mediated, contact with four or five heteroatoms. For the ammonium group, these are O1, O7, O8, and two different O1*W*; the chloride ions are in contact with O1, O3, O8, and O1*W*; the water molecules are involved in the network by serving as both donors (to Cl1 and O3) and acceptors (to two different H1*A*—N1—H1*C* groups) of strong hydrogen bonding

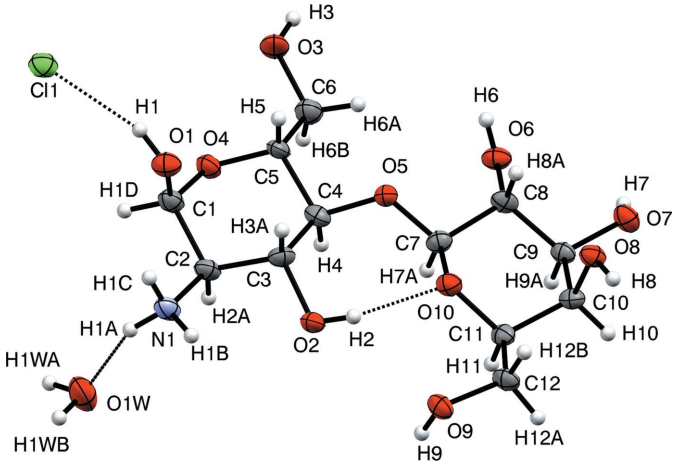


Figure 1
Atomic numbering and displacement ellipsoids at the 50% probability level for (**I**). Hydrogen bonds are shown as dotted lines.

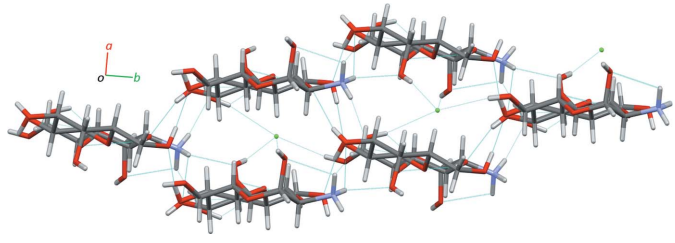


Figure 2
The molecular packing in (**I**) as viewed along the *c* axis. Hydrogen bonds are shown as cyan dotted lines.

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···Cl1	0.83 (5)	2.28 (6)	3.075 (6)	163 (9)
O2—H2···O10	0.80 (5)	1.98 (6)	2.743 (7)	159 (8)
O3—H3···Cl1^{i}	0.82 (5)	2.31 (6)	3.130 (7)	172 (9)
O6—H6···O9^{ii}	0.82 (5)	1.84 (6)	2.654 (8)	171 (9)
O7—H7···O2^{iii}	0.81 (5)	1.92 (6)	2.697 (8)	158 (9)
O8—H8···Cl1^{iv}	0.78 (5)	2.32 (6)	3.080 (5)	166 (8)
O9—H9···O6^{v}	0.83 (5)	1.88 (5)	2.707 (8)	178 (9)
N1—H1*A*···O1*W*	0.90 (4)	1.96 (5)	2.819 (9)	159 (7)
N1—H1*B*···O7^{vi}	0.90 (4)	2.26 (7)	2.862 (8)	124 (6)
N1—H1*B*···O8^{vi}	0.90 (4)	2.16 (6)	2.922 (8)	142 (7)
N1—H1*C*···O1	0.91 (4)	2.34 (8)	2.787 (9)	110 (6)
N1—H1*C*···O1*W*^{vii}	0.91 (4)	2.35 (6)	3.162 (11)	149 (7)
O1*W*—H1*WA*···O3^{viii}	0.90 (6)	1.85 (7)	2.746 (8)	170 (10)
O1*W*—H1*WB*···Cl1^{ix}	0.89 (6)	2.50 (7)	3.335 (7)	156 (9)

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

(Table 2). In this way, each molecule of lactosamine is surrounded by four hydrogen-bonded molecules of lactosamine, three water molecules, and three chloride ions (Fig. 3); each water molecule coordinates three lactosamines and one chloride (Fig. 4); every chloride is hydrogen-bonded to three lactosamines and one water as well (Fig. 2).

Synthesis and crystallization

The synthesis of (**I**) was performed following a Heyns rearrangement protocol described previously by Wrodnigg & Stütz (1999). A mixture of 34.2 g (100 mmoles) of D-lactulose and 75 ml (700 mmoles) of benzylamine was stirred for 18 h in a screw-capped glass flask at 318 K. The reaction progress was followed by TLC. The excess of benzylamine was removed by four successive extractions with benzene (2 L total), the residue was dissolved in 500 ml MeOH containing 20 ml of glacial acetic acid and left for 18 h at room temperature. The reaction mixture was then hydrogenated in the presence of 2.0 g of 10% Pd/C and 5 ml of 80% formic acid, until the reaction was judged complete by TLC. After filtration, the solvents were removed under reduced pressure, a syrupy residue was dissolved in 1.5 L of water and passed through a column charged with 250 ml of ion-exchange resin Amberlite IRN-77 (H^+-form). The column was washed with water and eluted with 0.2 *M* ammonium acetate. The eluate fractions containing lactosamine were pooled, evaporated to a syrup, re-dissolved in 0.5 L of water and passed through a column filled with 1L of Amberlite IRN-78 (Cl^-). The eluate fractions containing (**I**) were pooled, evaporated to a syrup, and the syrup was kept at 277 K to produce crystalline material suitable for the X-ray diffraction studies.

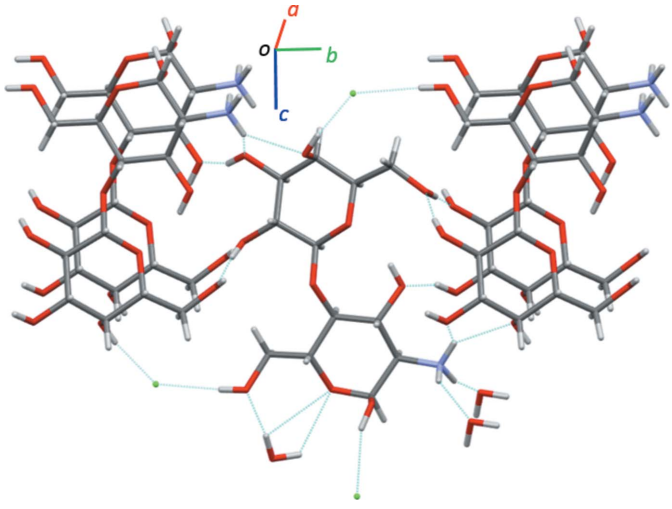


Figure 3
Hydrogen-bonded lactosamine molecular ions, chloride ions, and water molecules surrounding the central lactosamine molecular ion in the crystal structure of (**I**).

Table 3
Additional D—H···A contacts (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O5	0.80 (7)	2.64 (8)	2.964 (8)	106 (6)
N1—H1*B*···O2	0.90 (6)	2.55 (7)	2.855 (9)	101 (5)
O7—H7···O6	0.81 (8)	2.63 (8)	2.847 (8)	97 (8)
C2—H2*A*···O1^{i}	0.98	2.34	3.199 (10)	146
C9—H9*A*···O8^{i}	0.98	2.58	3.309 (9)	132
C10—H10···Cl1^{ii}	0.98	2.82	3.741 (9)	157

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

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 4. The Flack absolute structure parameter determined [0.02 (11) for 729 quotients (Parsons *et al.*, 2013)] is consistent with the (3*S*,4*R*,5*R*,7*S*,8*R*,9*S*,10*S*,11*R*) configuration, which was assigned for this system on the basis of the known configuration for the starting material D-lactulose (McNaught, 1996). Data were collected out to 0.80 Å; however, because of the small size of the crystal, most of the high-angle diffraction peaks are effectively indistinguishable from the noise. The inclusion of this high-angle data results in

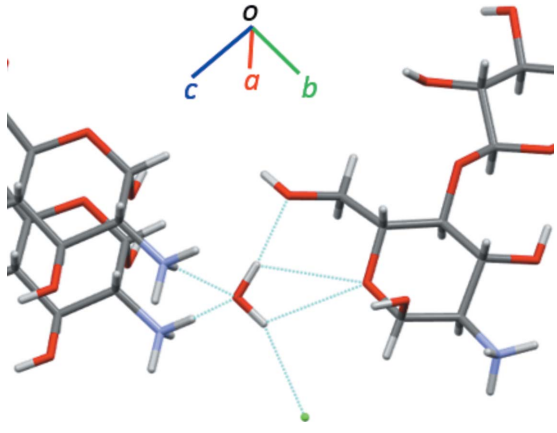


Figure 4
Hydrogen-bonded coordination sphere around the water molecule in the crystal structure of (**I**)

Table 4
Experimental details.

Crystal data	
Chemical formula	$C_{12}H_{24}NO_{10}^{+}\cdot Cl^{-}\cdot H_2O$
M_r	395.79
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	273
a, b, c (Å)	4.785 (4), 13.523 (11), 13.254 (11)
β (°)	93.940 (9)
V (Å^3)	855.5 (12)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.28
Crystal size (mm)	0.08 × 0.05 × 0.01
Data collection	
Diffractometer	Bruker APEXII area detector
Absorption correction	Multi-scan (*AXScale*; Bruker, 2016)
T_{min}, T_{max}	0.483, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11475, 3787, 2216
R_{int}	0.133
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.643
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.066, 0.131, 1.01
No. of reflections	3787
No. of parameters	262
No. of restraints	26
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.44, −0.37
Absolute structure	Flack x determined using 729 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter	0.02 (11)

Computer programs: *APEX3* and *SAINT* (Bruker, 2016), *SHELXS* (Sheldrick, 2008), *SHELXL2017/1* (Sheldrick, 2015), and *OLEX2* (Dolomanov *et al.*, 2009).

a high value for R_{int}, and the precision of the bond distances is low (*ca* 0.01 Å) because most of the high-angle data are not usable for refinement.

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full crystallographic data

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β-D-Galactopyranosyl-(1→4)–2-amino-2-deoxy-*α*-D-glucopyranose hydrochloride monohydrate (lactosamine)

Valeri V. Mossine, Steven P. Kelley and Thomas P. Mawhinney

β-*D*-Galactopyranosyl-(1→4)–2-amino-2-deoxy-*α*-*D*-glucopyranose hydrochloride monohydrate

Crystal data

$C_{12}H_{24}NO_{10}^{+}\cdot Cl^{-}\cdot H_2O$
M_r = 395.79
Monoclinic, $P2_1$
a = 4.785 (4) Å
b = 13.523 (11) Å
c = 13.254 (11) Å
β = 93.940 (9)°
V = 855.5 (12) Å^3
Z = 2
$F(000)$ = 420
D_x = 1.536 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 1276 reflections
θ = 3.0–20.6°
μ = 0.28 mm^{-1}
T = 273 K
Plate, colourless
0.08 × 0.05 × 0.01 mm

Data collection

Bruker APEXII area detector diffractometer
Radiation source: Sealed Source Mo with TRIUMPH optics
ω and phi scans
Absorption correction: multi-scan (*AXScale*; Bruker, 2016)
T_{min} = 0.483, T_{max} = 0.746
11475 measured reflections
3787 independent reflections
2216 reflections with $I > 2\sigma(I)$
R_{int} = 0.133
θ_{max} = 27.2°, θ_{min} = 1.5°
h = −6→6
k = −17→17
l = −17→16

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.131
S = 1.01
3787 reflections
262 parameters
26 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0475P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}
Absolute structure: Flack x determined using 729 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter: 0.02 (11)

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.

Refinement. Hydroxy and nitrogen-bound H atoms were located in difference-Fourier analyses and were allowed to refine fully. Other H atoms were placed at calculated positions and treated as riding. All chemically equivalent N—H and O—H bond distances were restrained to be equal within 0.05 Å.

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

	x	*y*	*z*	U_{iso}*/U_{eq}
Cl1	−0.3280 (4)	0.75359 (14)	0.61589 (14)	0.0286 (5)
O1	−0.1394 (11)	0.7867 (4)	0.4014 (4)	0.0272 (13)
H1	−0.195 (16)	0.765 (7)	0.455 (5)	0.041*
O1W	0.6240 (15)	1.0329 (4)	0.4269 (5)	0.0462 (19)
H1WA	0.71 (2)	1.021 (8)	0.488 (6)	0.069*
H1WB	0.58 (2)	1.096 (5)	0.433 (8)	0.069*
O2	0.2355 (12)	0.8551 (4)	0.1351 (4)	0.0260 (14)
H2	0.186 (17)	0.830 (6)	0.082 (5)	0.039*
O3	0.1487 (12)	0.4761 (4)	0.3861 (4)	0.0341 (14)
H3	0.18 (2)	0.416 (4)	0.387 (7)	0.051*
O4	0.2482 (10)	0.6815 (4)	0.3919 (4)	0.0253 (13)
O5	0.1019 (10)	0.6413 (4)	0.1208 (4)	0.0223 (12)
O6	0.3161 (10)	0.4684 (4)	0.0307 (4)	0.0263 (12)
H6	0.175 (14)	0.446 (6)	0.055 (6)	0.039*
O7	0.3237 (11)	0.4742 (4)	−0.1838 (4)	0.0266 (13)
H7	0.431 (16)	0.434 (5)	−0.157 (6)	0.040*
O8	−0.0409 (10)	0.6292 (4)	−0.2120 (4)	0.0229 (12)
H8	−0.091 (17)	0.658 (6)	−0.261 (5)	0.034*
O9	0.1635 (11)	0.9157 (4)	−0.1046 (4)	0.0255 (13)
H9	0.321 (13)	0.933 (6)	−0.082 (6)	0.038*
O10	0.1420 (10)	0.7280 (3)	−0.0250 (4)	0.0226 (13)
N1	0.1495 (15)	0.9460 (5)	0.3249 (5)	0.0267 (17)
H1A	0.270 (14)	0.978 (6)	0.369 (5)	0.040*
H1B	0.104 (16)	0.980 (6)	0.268 (4)	0.040*
H1C	−0.023 (11)	0.946 (6)	0.350 (6)	0.040*
C1	0.1489 (16)	0.7791 (5)	0.4024 (6)	0.0250 (18)
H1D	0.231817	0.807016	0.465797	0.030*
C2	0.2409 (16)	0.8418 (5)	0.3134 (6)	0.0227 (18)
H2A	0.445983	0.840893	0.315433	0.027*
C3	0.1292 (16)	0.7968 (5)	0.2135 (6)	0.0228 (18)
H3A	−0.076034	0.799022	0.208350	0.027*
C4	0.2270 (15)	0.6906 (6)	0.2095 (6)	0.0224 (18)
H4	0.431371	0.689282	0.207687	0.027*
C5	0.1419 (16)	0.6315 (6)	0.3013 (5)	0.0226 (17)
H5	−0.062765	0.627481	0.300031	0.027*
C6	0.2641 (17)	0.5292 (6)	0.3051 (6)	0.030 (2)

H6A	0.219239	0.495436	0.241483	0.036*
H6B	0.466372	0.532736	0.316291	0.036*
C7	0.2534 (15)	0.6458 (6)	0.0341 (5)	0.0222 (17)
H7A	0.453220	0.655704	0.052771	0.027*
C8	0.2081 (16)	0.5518 (5)	−0.0258 (6)	0.0217 (17)
H8A	0.007235	0.542472	−0.042707	0.026*
C9	0.3596 (16)	0.5604 (5)	−0.1230 (5)	0.0204 (17)
H9A	0.559991	0.570369	−0.105595	0.024*
C10	0.2464 (15)	0.6483 (6)	−0.1834 (6)	0.0213 (17)
H10	0.350340	0.656234	−0.244111	0.026*
C11	0.2853 (15)	0.7402 (6)	−0.1168 (5)	0.0220 (17)
H11	0.485554	0.750477	−0.099407	0.026*
C12	0.1643 (16)	0.8313 (5)	−0.1692 (6)	0.0241 (18)
H12A	0.272384	0.846504	−0.226525	0.029*
H12B	−0.026310	0.817433	−0.194879	0.029*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0323 (11)	0.0230 (11)	0.0302 (10)	−0.0014 (9)	−0.0006 (8)	0.0045 (10)
O1	0.027 (3)	0.023 (3)	0.032 (4)	0.002 (2)	0.004 (3)	0.004 (3)
O1W	0.075 (5)	0.027 (4)	0.034 (4)	−0.003 (3)	−0.012 (3)	−0.002 (3)
O2	0.035 (3)	0.021 (3)	0.022 (3)	−0.010 (2)	−0.001 (3)	0.001 (2)
O3	0.056 (4)	0.016 (3)	0.030 (3)	−0.003 (3)	0.004 (3)	0.007 (3)
O4	0.033 (3)	0.017 (3)	0.026 (3)	−0.002 (2)	−0.001 (3)	0.000 (2)
O5	0.027 (3)	0.021 (3)	0.020 (3)	−0.005 (2)	0.002 (2)	0.001 (2)
O6	0.025 (3)	0.021 (3)	0.033 (3)	0.001 (3)	0.005 (2)	0.006 (3)
O7	0.032 (3)	0.016 (3)	0.031 (3)	0.005 (2)	−0.001 (2)	−0.001 (3)
O8	0.025 (3)	0.019 (3)	0.024 (3)	−0.001 (2)	−0.001 (2)	0.004 (2)
O9	0.026 (3)	0.019 (3)	0.032 (3)	0.000 (2)	0.001 (3)	−0.003 (3)
O10	0.024 (3)	0.017 (3)	0.026 (3)	0.003 (2)	0.003 (2)	0.003 (2)
N1	0.035 (4)	0.021 (4)	0.023 (4)	−0.005 (3)	−0.006 (3)	0.004 (3)
C1	0.030 (5)	0.018 (4)	0.026 (4)	−0.002 (3)	−0.001 (3)	0.003 (3)
C2	0.025 (4)	0.016 (4)	0.026 (5)	−0.003 (3)	−0.001 (4)	0.004 (3)
C3	0.023 (4)	0.021 (4)	0.024 (4)	−0.002 (3)	0.002 (3)	0.008 (3)
C4	0.020 (4)	0.019 (4)	0.029 (5)	−0.004 (3)	0.000 (3)	0.000 (4)
C5	0.029 (4)	0.016 (4)	0.023 (4)	−0.009 (3)	−0.001 (3)	0.002 (3)
C6	0.037 (5)	0.023 (5)	0.028 (5)	−0.003 (4)	0.000 (4)	0.003 (4)
C7	0.023 (4)	0.021 (4)	0.023 (4)	0.001 (3)	0.002 (3)	0.004 (4)
C8	0.024 (4)	0.015 (4)	0.026 (5)	0.003 (3)	−0.002 (3)	0.005 (3)
C9	0.021 (4)	0.016 (4)	0.024 (4)	0.002 (3)	0.002 (3)	−0.001 (4)
C10	0.020 (4)	0.019 (4)	0.025 (4)	−0.002 (3)	0.004 (3)	0.003 (3)
C11	0.021 (4)	0.020 (4)	0.027 (4)	−0.001 (3)	0.007 (3)	−0.002 (4)
C12	0.026 (4)	0.014 (4)	0.032 (5)	0.001 (3)	0.004 (4)	0.000 (4)

Geometric parameters (Å, º)

O1—C1	1.382 (9)	N1—H1C	0.91 (4)
O1—H1	0.83 (5)	C1—C2	1.541 (10)
O1W—H1WA	0.90 (6)	C1—H1D	0.9800
O1W—H1WB	0.89 (6)	C2—C3	1.521 (10)
O2—C3	1.426 (9)	C2—H2A	0.9800
O2—H2	0.80 (5)	C3—C4	1.512 (10)
O3—C6	1.434 (10)	C3—H3A	0.9800
O3—H3	0.82 (5)	C4—C5	1.533 (10)
O4—C1	1.414 (9)	C4—H4	0.9800
O4—C5	1.440 (8)	C5—C6	1.502 (11)
O5—C7	1.402 (9)	C5—H5	0.9800
O5—C4	1.445 (9)	C6—H6A	0.9700
O6—C8	1.431 (9)	C6—H6B	0.9700
O6—H6	0.82 (5)	C7—C8	1.507 (10)
O7—C9	1.420 (9)	C7—H7A	0.9800
O7—H7	0.81 (5)	C8—C9	1.526 (10)
O8—C10	1.424 (9)	C8—H8A	0.9800
O8—H8	0.78 (5)	C9—C10	1.513 (10)
O9—C12	1.426 (9)	C9—H9A	0.9800
O9—H9	0.83 (5)	C10—C11	1.528 (10)
O10—C7	1.441 (8)	C10—H10	0.9800
O10—C11	1.447 (8)	C11—C12	1.510 (10)
N1—C2	1.486 (10)	C11—H11	0.9800
N1—H1A	0.90 (4)	C12—H12A	0.9700
N1—H1B	0.90 (4)	C12—H12B	0.9700
C1—O1—H1	110 (6)	C6—C5—H5	109.6
H1WA—O1W—H1WB	101 (9)	C4—C5—H5	109.6
C3—O2—H2	108 (6)	O3—C6—C5	108.5 (7)
C6—O3—H3	115 (7)	O3—C6—H6A	110.0
C1—O4—C5	114.7 (5)	C5—C6—H6A	110.0
C7—O5—C4	116.0 (5)	O3—C6—H6B	110.0
C8—O6—H6	102 (6)	C5—C6—H6B	110.0
C9—O7—H7	105 (6)	H6A—C6—H6B	108.4
C10—O8—H8	112 (6)	O5—C7—O10	106.7 (5)
C12—O9—H9	114 (6)	O5—C7—C8	109.3 (6)
C7—O10—C11	111.5 (5)	O10—C7—C8	109.3 (5)
C2—N1—H1A	110 (5)	O5—C7—H7A	110.5
C2—N1—H1B	117 (5)	O10—C7—H7A	110.5
H1A—N1—H1B	114 (7)	C8—C7—H7A	110.5
C2—N1—H1C	109 (6)	O6—C8—C7	110.8 (6)
H1A—N1—H1C	109 (8)	O6—C8—C9	109.1 (6)
H1B—N1—H1C	97 (7)	C7—C8—C9	108.7 (6)
O1—C1—O4	114.2 (6)	O6—C8—H8A	109.4
O1—C1—C2	106.8 (6)	C7—C8—H8A	109.4
O4—C1—C2	108.8 (6)	C9—C8—H8A	109.4

O1—C1—H1D	109.0	O7—C9—C10	108.6 (6)
O4—C1—H1D	109.0	O7—C9—C8	111.8 (6)
C2—C1—H1D	109.0	C10—C9—C8	109.5 (6)
N1—C2—C3	112.4 (6)	O7—C9—H9A	109.0
N1—C2—C1	109.9 (6)	C10—C9—H9A	109.0
C3—C2—C1	110.2 (6)	C8—C9—H9A	109.0
N1—C2—H2A	108.1	O8—C10—C9	107.6 (6)
C3—C2—H2A	108.1	O8—C10—C11	112.3 (6)
C1—C2—H2A	108.1	C9—C10—C11	107.9 (6)
O2—C3—C4	111.9 (7)	O8—C10—H10	109.7
O2—C3—C2	106.9 (6)	C9—C10—H10	109.7
C4—C3—C2	108.6 (6)	C11—C10—H10	109.7
O2—C3—H3A	109.8	O10—C11—C12	106.9 (6)
C4—C3—H3A	109.8	O10—C11—C10	110.3 (6)
C2—C3—H3A	109.8	C12—C11—C10	111.7 (6)
O5—C4—C3	110.8 (6)	O10—C11—H11	109.3
O5—C4—C5	106.7 (6)	C12—C11—H11	109.3
C3—C4—C5	111.6 (6)	C10—C11—H11	109.3
O5—C4—H4	109.3	O9—C12—C11	113.2 (6)
C3—C4—H4	109.3	O9—C12—H12A	108.9
C5—C4—H4	109.3	C11—C12—H12A	108.9
O4—C5—C6	106.8 (6)	O9—C12—H12B	108.9
O4—C5—C4	108.6 (6)	C11—C12—H12B	108.9
C6—C5—C4	112.5 (7)	H12A—C12—H12B	107.7
O4—C5—H5	109.6		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···Cl1	0.83 (5)	2.28 (6)	3.075 (6)	163 (9)
O2—H2···O10	0.80 (5)	1.98 (6)	2.743 (7)	159 (8)
O3—H3···Cl1^{i}	0.82 (5)	2.31 (6)	3.130 (7)	172 (9)
O6—H6···O9^{ii}	0.82 (5)	1.84 (6)	2.654 (8)	171 (9)
O7—H7···O2^{iii}	0.81 (5)	1.92 (6)	2.697 (8)	158 (9)
O8—H8···Cl1^{iv}	0.78 (5)	2.32 (6)	3.080 (5)	166 (8)
O9—H9···O6^{v}	0.83 (5)	1.88 (5)	2.707 (8)	178 (9)
N1—H1*A*···O1*W*	0.90 (4)	1.96 (5)	2.819 (9)	159 (7)
N1—H1*B*···O7^{vi}	0.90 (4)	2.26 (7)	2.862 (8)	124 (6)
N1—H1*B*···O8^{vi}	0.90 (4)	2.16 (6)	2.922 (8)	142 (7)
N1—H1*C*···O1	0.91 (4)	2.34 (8)	2.787 (9)	110 (6)
N1—H1*C*···O1*W*^{vii}	0.91 (4)	2.35 (6)	3.162 (11)	149 (7)
O1*W*—H1*WA*···O3^{viii}	0.90 (6)	1.85 (7)	2.746 (8)	170 (10)
O1*W*—H1*WB*···Cl1^{ix}	0.89 (6)	2.50 (7)	3.335 (7)	156 (9)

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