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

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The title compound, C12H24NO10 + Cl−·H2O, (I), crystallizes in the monoclinic space group P21 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).

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-recognition 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-GlcNH₂Cl−·H₂O (I)⁷ | α-pyranose, 4C₁ | 116.0 | −95.2 | +90.7 | O10···H−O2 (1.98; 2.743; 159) |
| Gal-β1→4-GlcNHCOCH₂H₂O (N-acetyllactosamine, LacNAc·H₂O)⁸ | α-pyranose, 4C₁b | 116.3 | −88.1 | +97.8 | O5···H−O2 (2.64; 2.964; 106) |
| LacNAc/ toad galectin⁹ | α-pyranose, 4C₁ | 118.2; 113.6 | −66.9; −67.8 | +132.4; +132.6 | O5···H−O6 (2.40; 2.868; 122) |
| Gal-β1→4-Glc·H₂O (α-lactose)⁹ | α-pyranose, 4C₁a | 117.1 | −75 | +135 | O10···H−O2 (2.02; 2.819; 159) |
| Gal-β1→4-Glc (β-lactose)⁹ | β-pyranose, 4C₁ | 116.5 | −76.3 | +106.4 | O10···H−O2 (n.d.; 2.707; 101) |
| Gal-β1→4-Glc·HCOCH₂H₂O (N-acetyllactosamine)⁹ | β-pyranose, 4C₁a | 117.4 | −89.3 | +81.5 | O5···H−O2 (2.06; 2.767; 144) |

Notes: (a) This work; (b) Longchambon et al. (1981); (c) Blanchet 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 α-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 α-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 protonated, as would be expected for a hydrochloride salt. The conformation of the α-glucosamine α-pyranose ring is a relaxed 4C₁ chair, with puckering parameters 〈Q₁, 〈θ₁, 〈φ₁〉. The β-galactoside β-pyranose ring similarly adopts the 4C₁ conformation, with puckering parameters 〈Q₂, 〈θ₂, 〈φ₂〉. 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 (Ψ) 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—O 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-acetyllactosamine (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 O1W; the chloride ions are in contact with O1, O3, O8, and O1W; the water molecules are involved in the network by serving as both donors (to Cl1 and O3) and acceptors (to two different H1A—N1—H1C 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.
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 ß-lactose 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, and the syrup was kept at 277 K to produce crystalline material suitable for the X-ray diffraction studies.

Synthesis and crystallization

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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 (3S,4R,5R,7S,8R,9S,10S,11R) configuration, which was assigned for this system on the basis of the known configuration for the starting material ß-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

| 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 W | 0.82 (5) | 2.31 (6) | 3.130 (7) | 172 (9) |
| O6—H6—O9 W | 0.82 (5) | 1.84 (6) | 2.654 (8) | 171 (9) |
| O7—H7—O2 W | 0.81 (5) | 1.92 (6) | 2.697 (8) | 158 (9) |
| O8—H8—Cl1 W | 0.78 (5) | 2.32 (6) | 3.080 (5) | 166 (8) |
| O9—H9—O6 W | 0.83 (5) | 1.88 (5) | 2.707 (8) | 178 (9) |
| N1—H1A—O1W | 0.90 (4) | 1.96 (5) | 2.819 (9) | 159 (7) |
| N1—H1B—O7 W | 0.90 (4) | 2.26 (7) | 2.862 (8) | 124 (6) |
| N1—H1C—O8 W | 0.90 (4) | 2.16 (6) | 2.922 (8) | 142 (7) |
| N1—H1C—O1 | 0.91 (4) | 2.34 (8) | 2.787 (9) | 110 (6) |
| N1—H1C—O1W W | 0.91 (4) | 2.35 (6) | 3.162 (11) | 149 (7) |
| O1W—H1WA—O3 W | 0.90 (6) | 1.85 (7) | 2.746 (8) | 170 (10) |
| O1W—H1WB—CH2 | 0.89 (6) | 2.50 (7) | 3.335 (7) | 156 (9) |

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

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) | 3.964 (8) | 106 (6) |
| N1—H1B—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—H2A—O1 W | 0.98 | 2.34 | 3.199 (10) | 146 |
| C9—H9A—O8 W | 0.98 | 2.58 | 3.309 (9) | 132 |
| C10—H10—Cl1 W | 0.98 | 2.82 | 3.741 (9) | 157 |

Symmetry codes: (i) x + 1, y, z; (ii) x + 1, y, z − 1.
Table 4
Experimental details.

| Crystal data | Chemical formula | C_{12}H_{24}NO_{10}·Cl^-·H_2O |
|--------------|-----------------|-------------------------------|
| M_0          |                  | 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) |
| \(\beta\) (°) | 93.940 (9) |
| \(V\) (Å³) | 855.5 (12) |
| Z | 2 |
| Radiation type | Mo Kα |
| \(\mu\) (mm⁻¹) | 0.28 |
| Crystal size (mm) | 0.08 × 0.05 × 0.01 |

Data collection

| Diffractometer | Bruker APEXII area detector |
|-----------------|----------------------------|
| Absorption correction | Multi-scan (AXScales; Bruker, 2016) |
| \(T_{min} \rightarrow T_{max}\) | 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 |
| \(\Delta F_{max}, \Delta F_{min}\) (e Å⁻³) | 0.44, −0.57 |
| Absolute structure | Flack x determined using 729 quotients \([|F^X|−|F^Y|]/(|F^X|+|F^Y|)]\) (Parsons et al., 2013) |
| Absolute structure parameter | 0.02 (11) |

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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**

**Crystal data**

\[
\text{C}_{12}\text{H}_{24}\text{NO}_{10}^+\cdot\text{Cl}^-\cdot\text{H}_{2}\text{O}
\]

\[
M_r = 395.79
\]

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\(^3\)

\(Z = 2\)

**Data collection**

Bruker APEXII area detector
diffractometer

Radiation source: Sealed Source Mo with
TRIUMPH optics

\(\omega\) and phi scans

Absorption correction: multi-scan

(AXScale; Bruker, 2016)

\(T_{\text{min}} = 0.483, T_{\text{max}} = 0.746\)

**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

\(F(000) = 420\)

\(D_x = 1.536\ \text{Mg m}^{-3}\)

\(\text{Mo}\ Kα\ radiation, \lambda = 0.71073\ \text{Å}\)

Cell parameters from 1276 reflections

\(θ = 3.0–20.6°\)

\(μ = 0.28\ \text{mm}^{-1}\)

\(T = 273\ \text{K}\)

Plate, colourless

0.08 × 0.05 × 0.01 mm

11475 measured reflections

3787 independent reflections

2216 reflections with \(I > 2\sigma(I)\)

\(R_m = 0.133\)

\(θ_{\text{max}} = 27.2°, θ_{\text{min}} = 1.5°\)

\(h = −6→6\)

\(k = −17→17\)

\(l = −17→16\)

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

\(w = 1/[σ(F^2) + (0.0475P)^2]\)

where \(P = (F^2 + 2F_c^2)/3\)

\((Δ/σ)_{\text{max}} < 0.001\)

\(Δρ_{\text{max}} = 0.44\ \text{e Å}^{-3}\)

\(Δρ_{\text{min}} = −0.37\ \text{e Å}^{-3}\)

Absolute structure: Flack \(x\) determined using

729 quotients \([I(I)−(I)]/[I(I)+(I)]\) (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)

| Atom  | x       | y       | z       | Uiso/Unw | Ueq/Unw |
|-------|---------|---------|---------|----------|---------|
| 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) |
| O10   | 0.321 (13) | 0.933 (6) | −0.082 (6) | 0.038*    |
| 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) 0.7402 (6) −0.1230 (5)  0.0204 (17)
H9A  0.559991  0.570369 −1.05595   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) 0.642 (6) −0.042 (6)  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)

|       | U¹¹  | U²²  | U³³ (10) | U¹² (9) | U¹³ (8) | U²³ (10) |
|-------|------|------|----------|---------|---------|----------|
| 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)   |
| Cl1   | 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, °)**

| Bond/Angle   | Length/Distance (Å) | Bond/Angle   | Length/Distance (Å) |
|--------------|---------------------|--------------|---------------------|
| 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—C6A       | 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)           | C5—C6—H6B    | 110.0               |
| C8—O6—H6     | 102 (6)             | C6—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               |
| Bond            | Length (Å) | Angle (°) | Length (Å) | Angle (°) |
|-----------------|------------|-----------|------------|-----------|
| C1—C2—H1D      | 1.090      | 1.090     | 1.090      | 1.090     |
| O7—C9—C10      | 1.086 (6)  | 1.068 (6) | 1.118 (6)  | 1.095 (6) |
| N1—C2—C3       | 1.124 (6)  | 1.099 (6) | 1.110 (6)  | 1.109 (6) |
| C3—C2—C1       | 1.112 (6)  | 1.109 (6) | 1.112 (6)  | 1.112 (6) |
| C1—C2—H2A      | 1.081      | 1.081     | 1.081      | 1.081     |
| C1—C2—H1D      | 1.090      | 1.090     | 1.090      | 1.090     |
| O7—C9—C8       | 1.081      | 1.081     | 1.081      | 1.081     |
| C10—C9—C8      | 1.095 (6)  | 1.095 (6) | 1.095 (6)  | 1.095 (6) |
| C10—C9—H9A     | 1.090      | 1.090     | 1.090      | 1.090     |
| C8—C9—H9A      | 1.090      | 1.090     | 1.090      | 1.090     |
| C10—C9—H9A     | 1.090      | 1.090     | 1.090      | 1.090     |

**Hydrogen-bond geometry (Å, °)**

| Bond            | D—H (Å) | H···A (Å) | D···A (Å) | D—H···A (Å) |
|-----------------|---------|-----------|-----------|-------------|
| 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···Cl1i    | 0.82 (5) | 2.31 (6)  | 3.130 (7) | 172 (9)     |
| O6—H6···O9ii    | 0.82 (5) | 1.84 (6)  | 2.654 (8) | 171 (9)     |
| O7—H7···O2iii   | 0.81 (5) | 1.92 (6)  | 2.697 (8) | 159 (8)     |
| O8—H8···Cl1iv   | 0.78 (5) | 2.32 (6)  | 3.080 (5) | 166 (8)     |
| O9—H9···O6iv    | 0.83 (5) | 1.88 (5)  | 2.707 (8) | 178 (9)     |
| N1—H1···O1W     | 0.90 (4) | 1.96 (5)  | 2.819 (9) | 159 (7)     |
| N1—H1···O7iv    | 0.90 (4) | 2.26 (7)  | 2.862 (8) | 124 (6)     |
| N1—H1···O8iv    | 0.90 (4) | 2.16 (6)  | 2.922 (8) | 142 (7)     |
| N1—H1···O1Wvii  | 0.91 (4) | 2.34 (8)  | 2.787 (9) | 110 (6)     |
| O1W—H1···O3viii | 0.90 (6) | 1.85 (7)  | 2.746 (8) | 170 (10)    |
| O1W—H1···O1Wvii | 0.89 (6) | 2.50 (7)  | 3.355 (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.