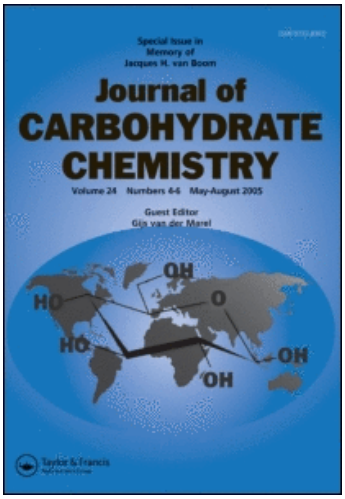

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Crystal Structures of β-1-*N*-Chloroacetamido Derivatives of D-Glucose and D-Galactose

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ABSTRACT

Crystal structures of 1-*N*-(*β*-D-glucopyranosyl)chloroacetamide (**1**), an inhibitor of glycogen phosphorylase, and the corresponding galactopyranosyl amide (**2**) have been determined. Both crystals belong to $P2_12_12_1$ space group with **1** having the unit cell dimensions of $a = 7.939(3)$, $b = 9.547(3)$ and $c = 14.157(2)$ Å, while those of **2** are, $a = 7.636(10)$, $b = 9.004(8)$ and $c = 14.807(5)$ Å. The sugar ring takes a $^4C_1$ conformation and the amide linkage exists in *Z-anti* conformation in both crystals. The torsion angle O5–C1–N1–C1′ is $-93.9(5)$ for **1** and $-111.5(3)^\circ$ for **2**. The conformational preference of Cl and N1 in **1** and **2** is found to be between *anti* and *gauche*. The molecular assembly in both **1** and **2** is stabilized by a finite chain of hydrogen bonds starting from N1H and ending at O1′, whereas a ten membered hydrogen-bonded ring involving O4H and O5 is observed in **1**.

Key Words: X-ray crystal structure; β-1-*N*-Chloroacetamido sugar derivatives; D-Glucopyranose; D-Galactopyranose; Conformation.

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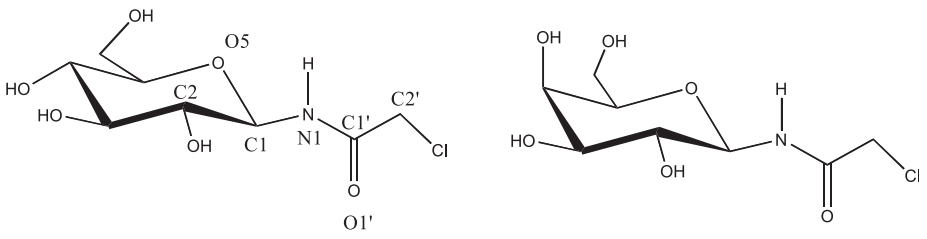
INTRODUCTION

β-1-*N*-Chloroacetamide derivatives of sugars have been demonstrated to be versatile and useful intermediates for the synthesis of neoglycoconjugates[1–4] with potential use as novel probes for examining lectin–carbohydrate interactions and glycotargeting of therapeutic agents. These derivatives can be readily prepared in good yields using a two step procedure starting from the parent sugars.[1,5] Besides the synthetic utility, derivatives such as *N*-(*β*-D-glucopyranosyl)chloroacetamide (**1**) and *N*-(α-D-galactopyranosyl)chloroacetamide (**2**) are known to inhibit glycogen phosphorylase[6] and α-galactosidase from *Trichoderma reesei*,[7] respectively. Elucidation of their conformation and molecular recognition features would contribute toward the design and development of more potent analogs, for example, of **1** as non-insulin dependent anti-diabetic agents.

A major program of our laboratory is focused on the three dimensional structure of the *N*-glycoprotein linkage region based on X-ray crystallography. Knowledge of the glycoprotein linkage region conformation is fundamental to obtaining a better understanding of carbohydrate–protein interactions. Our efforts, directed towards this objective, have led to the first report on the crystal structure of a hydrated linkage region model, N^1-(2-acetamido-2-deoxy-*β*-D-glucopyranosyl)acetamide[8] and that of a variant linkage, *N*-(*β*-D-glucopyranosyl)acetamide.[9] As part of our comprehensive study aimed at examining the systematic changes in the attached sugar and the aglycon structure on the linkage region conformation, we report herein the crystal structures of *N*-(*β*-D-glucopyranosyl)chloroacetamide (**1**) and *N*-(*β*-D-galactopyranosyl)chloroacetamide (**2**) (Figure 1). This is the first study on the crystal structures of free *N*-(glycopyranosyl)chloroacetamides.

RESULTS AND DISCUSSION

N-Chloroacylation of *β*-D-glycosylamines has been performed earlier either in 1M sodium bicarbonate medium using 10 fold molar excess of chloroacetic anhydride[1] or in DMF.[5] In both the cases, the isolation of product involved tedious work-up and in some cases, chromatographic purification. The present procedure involving methanol



1 **2**

Figure 1. Structures of *N*-(*β*-D-glucopyranosyl)chloroacetamide (**1**) and *N*-(*β*-D-galactopyranosyl)chloroacetamide (**2**).

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as a solvent is very convenient since the crystalline product is obtained by simple filtration and recrystallization. The details of crystal data, intensity data collection and structure refinement are provided in Table 1. Both the compounds are in the anhydrous form. The ORTEP depictions for **1** and **2** with atom numbering are shown in Figures 2 and 3, respectively.

The ring C1–O5 bond lengths, 1.432(5) and 1.423(4) Å, of compounds **1** and **2** are shorter than C5–O5 as observed for Glcβ Asn.[10] This shortening can be attributed to the delocalization of the nitrogen lone pair of electrons into the anti-bonding orbital of the C1–O5 bond. The C1–N1 distances, 1.428(5) and 1.440(3), are close to

Table 1. Crystal structure determination and refinement data.

Parameter	Compound **1**	Compound **2**
Empirical formula	$C_8H_{14}ClNO_6$	$C_8H_{14}ClNO_6$
Formula weight	255.65	255.65
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system space group	$P2_12_12_1$, Orthorhombic	$P2_12_12_1$, Orthorhombic
Unit cell dimensions	$a = 7.939(3)$ Å, $b = 9.547(3)$ Å, $c = 14.157(2)$ Å	$a = 7.636(10)$ Å, $b = 9.004(8)$ Å, $c = 14.807(5)$ Å
Volume	1072.9(5) A^3	1018.0(16) A^3
Z	4	4
Calculated density	1.583 mg/m^3	1.668 mg/m^3
Absorption coefficient	0.370 mm^{-1}	0.390 mm^{-1}
F (000)	536	536
Crystal size	0.3 × 0.3 × 0.3 mm	0.3 × 0.3 × 0.3 mm
Theta range for data collection	2 to 25°	2 to 25°
Index ranges	0<=h<=9, 0<=k<=11, 0<=l<=16	0<=h<=9, 0<=k<=10, 0<=l<=17
Reflections collected/unique	1186/1186 [R (int) = 0.0000]	1060/1060 [R (int)= 0.0000]
Completeness to 2 theta	100.0%	99.8%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data restraint parameters	1186/0/202	1060/0/202
Goodness-of-fit on F^2	1.090	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1246	R1 = 0.0253, wR2 = 0.0686
R indices (all data)	R1 = 0.0524, wR2 = 0.1296	R1 = 0.0310, wR2 = 0.0721
Absolute structure parameter	− 0.05(16)	− 0.12(10)
Extinction coefficient	0.000(4)	0.005(3)
Largest difference peak and hole	0.685 and − 0.457 e A^{-3}	0.217 and − 0.235 e A^{-3}

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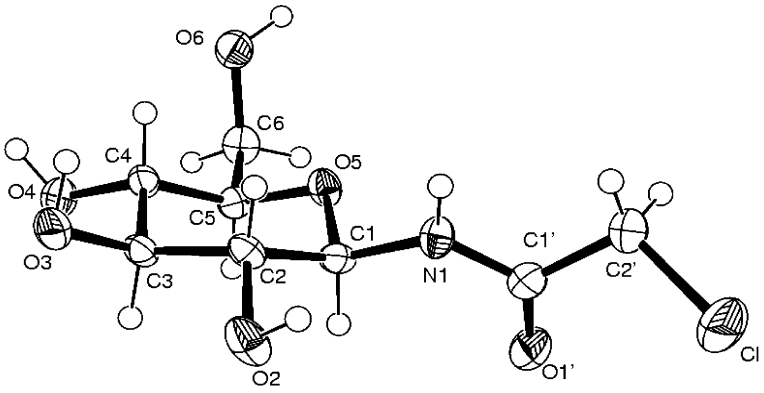

Figure 2. ORTEP diagram of *N*-(*β*-D-glucopyranosyl)chloroacetamide (**1**) with atom notations and thermal ellipsoid drawn at 50% probability level.

1.431(4) and 1.432(4) Å reported for Glc**β**NHAc,[9] and Gal**β**NHAc,[11] respectively. However, they are shorter than the alkyl C–N distances of 1.50 and 1.55 Å in the two independent molecules present in the asymmetric unit of *N*-methylchloroacetamide.[12] The C2′–Cl bond lengths of **1** and **2** are found to be 1.752(5) and 1.762(3) Å, respectively.

The exocyclic bond angles C4–C5–C6 as well as O5–C5–C6 for **1** and **2** differ by 6–7° as noted for several *N*-linked pyranoses[13] and such differences have been attributed to the effect of lone pair of electrons causing a bend at the oxygen atom O5. The *N*-glycosidic valence angle C1–N1–C1′ of 124.7(3) and 123.2(2)° observed for **1** and **2**, respectively, differ from 116.5(1.7) and 114.3(1.6)° reported[12] for the two independent molecules of *N*-methylchloroacetamide, while there is good agreement in the bond angles of C1′–C2′–Cl, N1–C1′–C2′, O1′–C1′–C2′ and N1–C1′–O1′ between these sets of compounds.

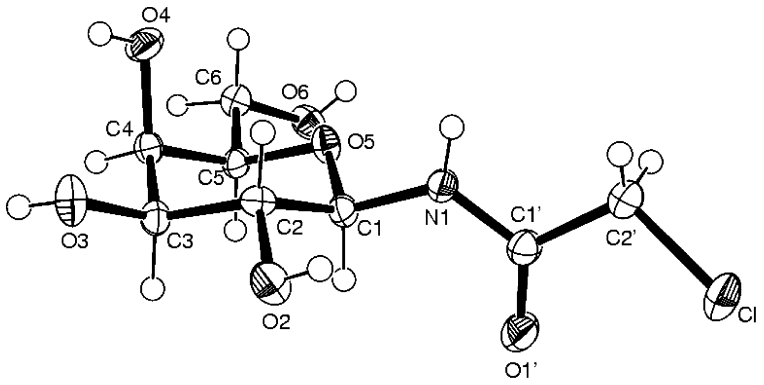

Figure 3. ORTEP diagram of *N*-(*β*-D-galactopyranosyl)chloroacetamide (**2**) with atom notations and thermal ellipsoid drawn at 50% probability level.

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Table 2. Major torsion angles.

Torsion angles	Compound **1**	Compound **2**	Torsion angles	Compound **1**	Compound **2**
O5–C1–C2–C3	50.2(4)	55.8(3)	C2–C1–O5–C5	−61.6(4)	−60.1(3)
C1–C2–C3–C4	−46.1(4)	−53.6(3)	O5–C5–C6–O6	−69.0(4)	61.7(3)
C2–C3–C4–C5	50.8(4)	55.1(3)	O5–C1–N1–C1′	−93.9(5)	−111.5(3)
C3–C4–C5–O5	−59.6(4)	−57.7(3)	C1–N1–C1′–C2′	169.9(4)	176.6(3)
C4–C5–O5–C1	66.8(4)	61.0(3)	N1–C1′–C2′–Cl	131.3(4)	153.3(2)

Molecular Conformation

The ORTEP diagrams (Figures 2 and 3) and the puckering parameters (**1**: Q = 0.568 Å, $\theta = 10.6°$, $\Phi = 320.56°$; **2**: Q = 0.575 Å, $\theta = 1.4°$, $\Phi = 297.22°$) establish the $^4C_1$ conformation of the pyranose ring in these compounds. A similar conformation is adopted in solution as evident from the coupling constant ($J_{1,2}$) of 8.8 Hz observed for both **1** and **2**. The torsion angle, O5–C5–C6–O6, listed in Table 2 indicates the orientation of the primary hydroxyl group as *gg* in **1** and *gt* in **2** consistent with the

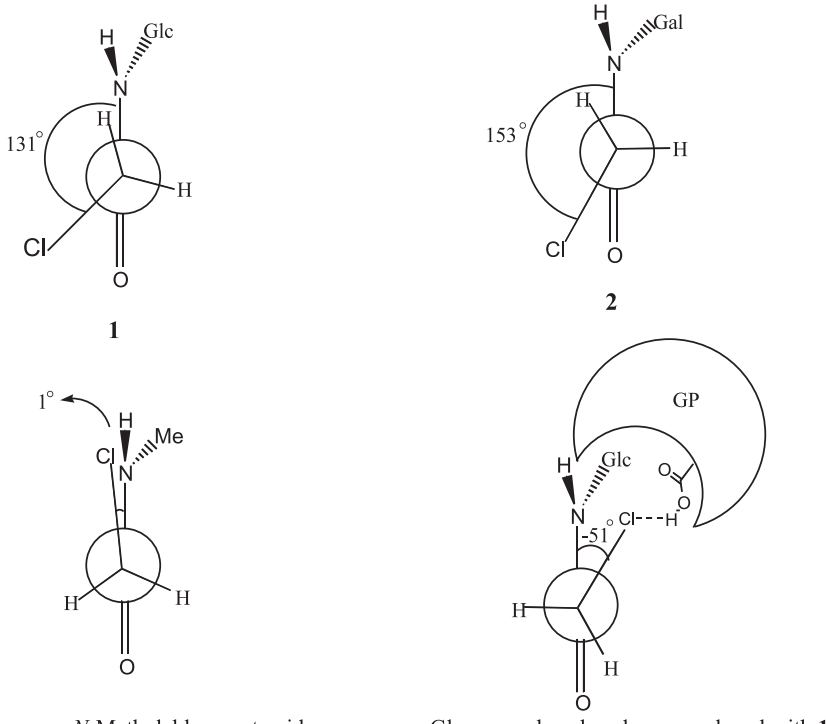

Figure 4. Comparison of the conformations of the chloroacetamide moiety in **1**, **2**, *N*-methylchloroacetamide and compound **1** complexed with glycogen phosphorylase. (From Ref. [6].)

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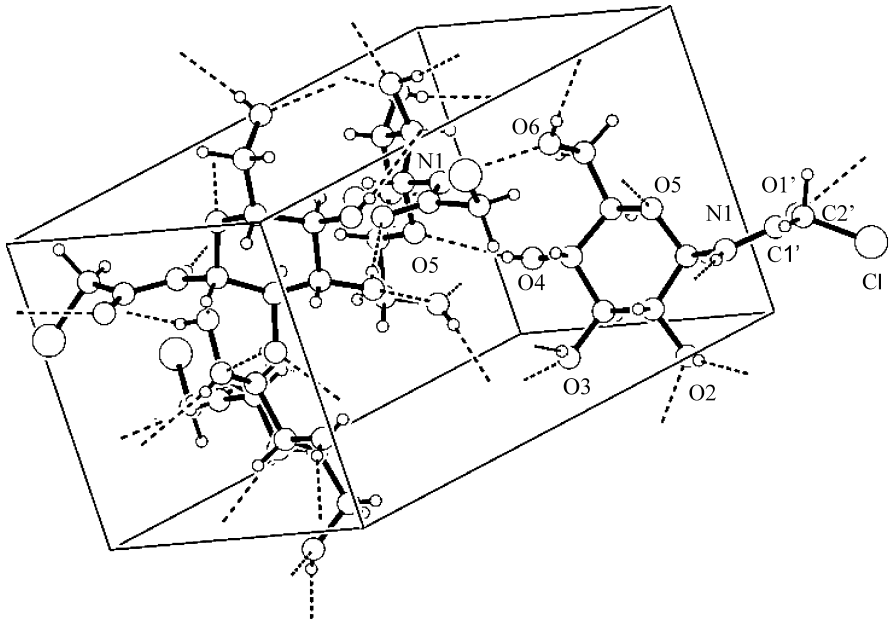

Figure 5. Molecular packing of compound **1** depicting a hydrogen bond network along different axes.

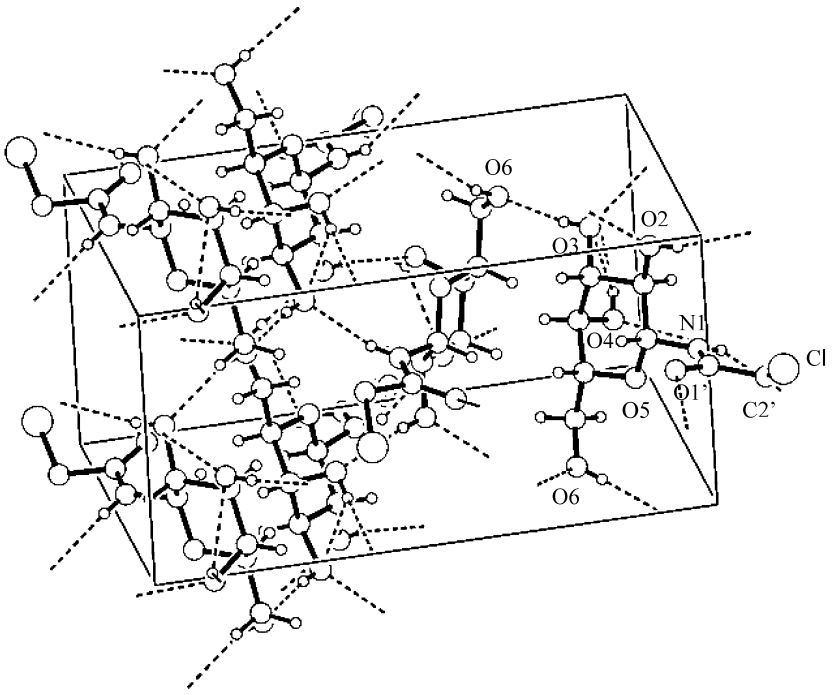

Figure 6. Molecular packing of compound **2** depicting a hydrogen bond network along different axes.

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earlier observations made in the solid state for such glycopyranoses.[14] The amide groups adopt the *Z-anti* conformation as revealed by the torsions about N1–C1′ and C1–N1 (Table 2). This characteristic stereochemical feature of the *N*-glycosidic linkage has been observed in the model compound Glc**β**NHAc by us[9] and also in Glc**β**Asn.[10] The torsion angle, C1–N1–C1′–C2′ of 169.9° observed for **1** is close to the values of −179.2° and 174.0° reported for Glc**β**NHAc[9] and Glc**β**Asn,[10] respectively. The values of the *N*-glycosidic torsion angle, O5–C1–N1–C1′ of **1** and of Glc**β**NHAc (−93.7°) are the same, while that of Glc**β**Asn[10] was found to be lower (−83.6°).

Considering the importance of C_α–C′ torsion in determining the peptide conformation, *N*-methylchloroacetamide has earlier been investigated as a peptide model by X-ray crystallography.[12] As mentioned earlier, the asymmetric unit cell contains two crystallographically independent molecules in both of which the Cl–C bond is *cis* to the C–N bond. In contrast to this, the orientation of Cl with respect to N1 in both **1** and **2** is in between *anti* and *gauche* (Figure 3) as evident from the N1–C1′–C2′–Cl torsions (Table 2).

Interestingly, N1–C1′–C2′–X (where X = Cl/Br) torsions reported for the complexes of the glycogen phosphorylase with **1** and its bromo analog are −51 and −46° respectively, pointing out a *gauche* conformation in these cases. In spite of the potential repulsive interactions between N and Cl in these complexes, the *gauche* conformation is possibly preferred due to stabilization through hydrogen bonds between Cl as well as Br and Asp339 of the enzyme (Figure 4).[6] Out of more than 100 compounds evaluated as inhibitors of glycogen phosphorylase,[15] *N*-(**β**-D-glucopyranosyl)acetamide is the best inhibitor (K_i = 32 **μ**M) and the next best being **1** and its bromo analog with a K_i of 45 and 44 **μ**M, respectively. The hydrogen bond involving the halogen atom and replacement of two water molecules appear to account for the observed high affinity of **1** and its bromo analog. Incidentally, the angle N1–C1′–C2′–X [where X = $CH(NH_3^+)COO^-$] reported for GlcAsn[10] is 166.5°, revealing a near *anti*

Table 3. Hydrogen bonds in compound **1** and compound **2**.

Donor D–H	Acceptor A	d (D–H)	d (H–A)	d (D–A)	<DHA
Compound **1**					
N1–H	$O6^{i}$	0.94(1)	1.89(1)	2.825(5)	177(5)
O6–H	$O2^{ii}$	0.90(1)	1.87(1)	2.759(4)	171(6)
O2–H	$O3^{iii}$	0.90(1)	1.89(2)	2.763(5)	163(6)
O3–H	$O1'^{iv}$	0.90(1)	1.97(2)	2.846(4)	165(6)
O4–H	$O5^{v}$	0.90(1)	2.08(2)	2.957(4)	163(5)
Compound **2**					
N1–H	$O3^{vi}$	0.94(1)	2.15(2)	2.988(3)	148(3)
O3–H	$O6^{vii}$	0.90(1)	1.89(1)	2.778(3)	172(4)
O6–H	$O2^{viii}$	0.90(1)	2.00(2)	2.834(3)	153(3)
O2–H	$O4^{ix}$	0.90(1)	2.13(1)	3.011(3)	165(4)
O4–H	$O1'^{x}$	0.90(1)	2.27(2)	3.112(4)	156(3)

Symmetry codes: (i) 1 − x, −1/2 + y, 1/2 − z; (ii) −1 + x, y, z; (iii) 2 − x, −1/2 + y, 1/2 − z; (iv) 3/2 − x, 1 − y, −1/2 + z; (v) 1 − x, 1/2 + y, 1/2 − z; (vi) −1/2 + x, 1/2 − y, −z; (vii) 1 − x, 1/2 + y, 1/2 − z; (viii) −1 + x, y, z; (ix) 1/2 + x, 1/2 − y, −z; (x) x, 1 + y, z.

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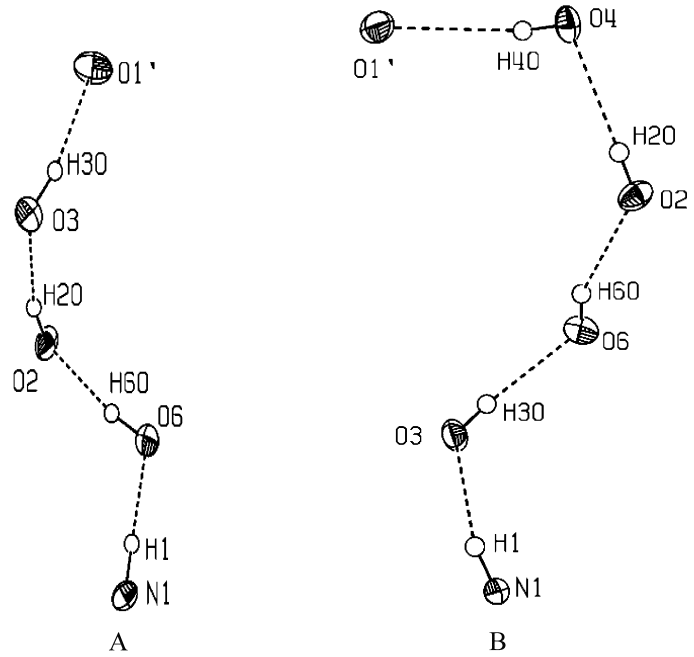

Figure 7. The finite chain of hydrogen bonds connecting symmetry related neighboring molecules along the b axis in **1** (**A**) and along the c axis in **2** (**B**). Donor and acceptor atoms alone are shown for clarity.

orientation of the glycosidic N with respect to the α-carbon atom, as compared to 131.3° for N1–C1′–C2′–Cl in **1**.

Molecular Packing

The packing of molecules in the unit cells of **1** and **2** are shown in Figures 5 and 6, respectively. The hydrogen-bond parameters are listed in Table 3. A finite chain of hydrogen bonds starting from N1H as the donor and ending at O1′ is a common feature of packing observed in both the compounds. In compound **1**, the chain passes through O6 (1 − x, − 1/2 + y, 1/2 − z), O2 (− 1 + x, y, z) and O3 (2 − x, − 1/2 + y, 1/2 − z) of symmetry related neighboring molecules (Figure 7A). In addition, O4H is connected

Table 4. Van der Waals contacts.

Atoms in contact	Compound **1**	Compound **2**
Cl–C1′	3.397 Å (1/2 + x, 1/2 − y, 1 + z)	3.366 Å (1/2 + x, − 1/2 − y, − z)
Cl–O5	2.989 Å (1/2 + x, 1/2 − y, 1 + z)	3.181 Å (1/2 + x, − 1/2 − y, − z)
Cl–H6O	–	2.794 Å (1/2 + x, − 1/2 − y, − z)

to the ring oxygen O5 (1 − x, 1/2 + y, 1/2 − z) forming a ten membered hydrogen-bonded ring.

On the other hand, in the case of **2** bearing an axial hydroxyl group at C4, O5 is not involved in any hydrogen bonding due probably to steric crowding. The finite chain of hydrogen bonds in compound **2** starting from N1H is connected to O1′ (x, 1 + y, z) through O3 (− 1/2 + x, 1/2 − y, − z), O6 (1 − x, 1/2 + y, 1/2 − z), O2 (− 1 + x, y, z) and O4 (1/2 + x, 1/2 − y, − z) (Figure 7B). The molecular packing is also stabilized by several Van der Waals contacts (Table 4). The Cl–C1′ distances are shorter than 3.61 Å reported for *N*-methylchloroacetamide.[12] The additional interaction of Cl with H6O observed in **2**, besides those with C1′and O5, may be responsible for the difference in the conformations of the chloroacetyl moiety of these compounds.

EXPERIMENTAL

Melting points were determined on a Toshniwal melting point apparatus. Infrared spectra were recorded on a Shimadzu R-470 spectrophotometer. NMR spectra were recorded on a Bruker AV400 instrument using tetramethylsilane as an internal standard.

Synthesis of *N*-(β-D-glycopyranosyl)chloroacetamide (general procedure). To a solution of β-D-glycopyranosylamine (5.37 g, 0.03 mol)[16] in dry methanol (25 mL) cooled to 0°C, chloroacetic anhydride (12.75 g, 0.075 mol) was added, in portions, and the reaction mixture stirred for 2 h at 0°C, followed by stirring at room temperature overnight. The solid separated out from the solution was filtered, washed with cold methanol and recrystallised from aqueous methanol (3:2) to give the pure amide. The yield of **1** is 65% and that of **2** is 60%.

Physical and spectroscopic data for compound 1: mp 208°C (Lit.,[5] 205–206°C); IR (ν, cm^{-1}): 3503, 3280, 3007, 2954, 1680, 1593, 1456, 1340, 1251, 1080, 1036, 947, 892, 585; ^{1}H NMR (400 MHz, D_2O): δ 4.98 (d, 1H, $J_{1,2}$ 8.8 Hz, H-1), 4.19 (s, 2H, $-CH_2Cl$), 3.86 (dd, 1H, H6a), 3.70 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, $J_{6b,5}$ 5.3 Hz, H6b), 3.53 (t, 1H, H-5), 3.46–3.37 ppm (m, 3H, H-2, H-3, H-4); ^{13}C NMR: δ 170.8 (C-1′), 79.6 (C-1), 77.6, 76.3, 71.7, 69.1, 60.5 (C-6), 42.2 (C-2′) ppm.

Physical and spectroscopic data for compound 2: mp 220°C (Lit,[5] 217–219°C)}; IR (ν, cm^{-1}): 3456, 3296, 2912, 1689, 1539, 1452, 1411, 1363, 1280, 1251, 1212, 1139, 1110, 1084, 1043, 1020, 886, 857, 774, 697, 649, 551; ^{1}H NMR (400 MHz, D_2O): δ 4.91 (d, 1H, $J_{1,2}$ 8.8 Hz, H-1), 4.17(s, 2H, $-CH_2Cl$), 3.93 (d, 1H, $J_{3,4}$ 2.8 Hz, H-4), 3.77–3.60 ppm (m, 5H, H-5, H-2, H-3, H-6a, H-6b); ^{13}C NMR: δ 170.9 (C-1′), 80.02 (C-1), 76.9, 73.3, 69.2, 68.6, 60.9 (C-6), 42.2 (C-2′) ppm.

Preparation of single crystals and X-ray analysis: Crystals suitable for analysis were obtained from an aqueous methanol solution by the slow evaporation method. X-ray diffraction data were collected at room temperature in the ω−2θ scan mode on an Enraf–Nonius CAD4 diffractometer equipped with a Mo source. The structure was solved by the direct methods procedure and refined by the full matrix least squares

method, using SHELX.[17] The diagrams showing molecular packing were drawn using PLATON 2000.[18]

SUPPLEMENTARY DATA

Complete structural data (CCDC #201905 and 201906) have been deposited at the Cambridge Crystallographic Data Centre, which may be obtained from the Cambridge Crystallographic Data Centre, 12 Union, Cambridge, CB2 IEZ, UK.

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