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Molecular and crystal structures of two 1,6-anhydro-β-maltotriose derivatives

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Abstract

Crystal structures of two 1,6-anhydro-β-maltotriose derivatives, 1,6-anhydro-β-maltotriose nonaacetate and 6″-bromo-6″-deoxy-1,6-anhydro-β-maltotriose octaacetate, have been determined. Both structures are isomorphous and belong to the orthorhombic system, space group of $P2_12_12_1$, with cell dimensions of $a = 15.659(3)$ Å, $b = 20.587(6)$ Å, $c = 13.023(2)$ Å and $a = 15.402(7)$ Å, $b = 19.737(8)$ Å, $c = 13.481(5)$ Å, respectively. Each molecule has three α-(1 → 4)-linked glucose units, and two of them have a typical $^4C_1$ chair conformation, while the glucose unit with the 1,6-anhydro bridge has a $^1C_4$ chair–envelope intermediate conformation. In spite of introducing the 1,6-anhydro bridge and acetyl groups, the conformations of the glycosidic linkages in these molecules are almost the same as those of other α-(1 → 4)-linked oligosaccharides. Crystal structures are stabilized by hydrophobic interactions and by a weak intermolecular hydrogen bond of C–H · · · O.

Keywords: 1,6-Anhydro-β-maltoriose derivatives; X-Ray structure; Single crystal

1. Introduction

The 1,6-anhydro bridge is one of the most effective modifications of oligosaccharides [1,2], because a glucose ring with a 1,6-anhydro bridge has the reversed ring conforma-

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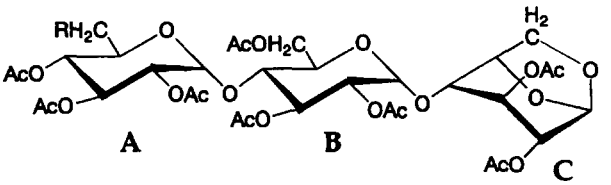

MNA: R = OAc

BMOA: R = Br

Fig. 1. Chemical structures of MNA and BMOA.

tion of $^1C_4$ to the usual glucose ring conformation of $^4C_1$, and because the 1,6-anhydro bridge efficiently protects both 1- and 6-hydroxyl groups.

1,6-Anhydromaltotriose [3] is a precursor to dihydroacarbose [4,5], which is an efficient inhibitor of α-D-glucosidases, and the 1,6-anhydro bridge was introduced to block the nonreducible terminal in the total synthesis of dihydroacarbose. Three-dimensional structures of 1,6-anhydromaltotriose or its derivatives are very informative in understanding how a 1,6-anhydro bridge distorts the glucose ring and how it affects the adjacent residue and the structure of the entire molecule.

Herein, we report the crystal structures of two 1,6-anhydromaltotriose derivatives, 1,6-anhydro-β-maltotriose nonaacetate (MNA) and 6″-bromo-6″-deoxy-1,6-anhydro-β-maltotriose octaacetate (BMOA). Their structures are shown in Fig. 1.

2. Experimental

Data collection.—A crystal of MNA with the dimensions of 0.60 × 0.20 × 0.10 mm and a crystal of BMOA with 0.60 × 0.20 × 0.10 mm were mounted on glass fibers. Diffraction data were collected by a Rigaku AFC7R diffractometer on a Rigaku rotation anode X-ray generator with a graphite monochromated Cu K_α radiation. Cell constants and an orientation matrix for data collection were determined by a least-squares refinement using 25 carefully centered reflections in the range of $41.25° < 2\theta < 49.82°$. Both crystals (MNA and BMOA) belong to an orthorhombic system with a space group of $P2_12_12_1$. The cell dimensions are $a = 15.659(3)$, $b = 20.587(6)$, $c = 13.023(2)$ Å for MNA and $a = 15.402(7)$, $b = 19.737(8)$, $c = 13.481(5)$ Å for BMOA. A total of 3539 reflections (MNA) and 3160 reflections (BMOA) were collected at room temperature, using the ω–2θ scan technique to a maximum 2θ value of 120°. Scans of $(2.10 + 0.30 \tan \theta)°$ were made at 16.0°/min (in omega). The data were corrected for Lorentz and polarization effects. Absorption and decay corrections were not applied.

Structure determination and refinement.—Both structures were solved by direct methods using the program SHELX-86 [6] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced by geometrical calculations but were not refined. The final cycles of full-matrix least-squares

refinement were based on 2349 reflections [$I_o > 2.0\sigma(I_o)$] and 541 variable parameters for MNA, and 1905 reflections [$I_o > 2.0\sigma(I_o)$] and 514 variable parameters for BMOA. Final R-factors and R_w-factors [$w = 1/\sigma^2(F_o)$] are 0.084 and 0.055 for MNA, and 0.070 and 0.079 for BMOA, respectively. The maximum peaks on the final Fourier map are 0.38 e/Å^3 for MNA and 0.29 e/Å^3 for BMOA. Atom scattering factors were taken from International Tables for X-ray Crystallography, Vol. IV. All calculations of data collection, structure determination and refinement were performed using the teXsan crystallographic software package of Molecular Structure Corporation [7].

Final atomic coordinates and temperature factors of non-hydrogen atoms of MNA are listed in Table 1. Tables of final atomic coordinates and temperature factors of non-hydrogen atoms of BMOA, the anisotropic temperature factors of non-hydrogen atoms, complete bond distances and angles, and observed and calculated structure factor amplitudes, are deposited with the Cambridge Crystallographic Data Center [1].

3. Results and discussion

Overall structure and glycosidic linkage.—Both crystal structures of MNA and BMOA are isomorphous, so the overall molecular structures are almost identical, as shown in Fig. 2 [8]. Molecules of MNA and BMOA with three glucose rings form the bent structure like an arch shape. For clarity, the glucose rings are designated as the A-, B-, C-ring, as indicated in Figs. 1 and 2.

The torsion angles of glycosidic linkages of O-5–C-1–O-1–C-4* (* means the adjacent glucose ring) and C-1–O-1–C-4*–C-3* are listed in Table 2. These values are almost same as those of *p*-nitrophenyl α-maltohexaoside [9]. In the crystal structure of *p*-nitrophenyl α-maltohexaoside, which is to date the largest linear oligosaccharide structure ever solved [9], two molecules (Molecules 1 and 2) exist in an asymmetrical unit with 10 α-(1 → 4)-linkages in two independent molecules that have almost identical conformations to form a helical structure. The mean values of torsion angles around the α-(1 → 4)-linkages are 100° for O-5–C-1–O-1–C-4* and 109° for C-1–O-1–C-4*–C-3* in Molecule 1, and 86° and 100° in Molecule 2, respectively. Similar torsion angles of 84° for O-5–C-1–O-1–C-4* and 87° for C-1–O-1–C-4*–C-3* are found in the crystal structure of β-maltose octaacetate [10]. These torsion angle values of glycosidic linkages make the primary groups of all glucose rings direct to one site, and the secondary groups direct to another site. Thus, the torsion angles of about 100° and the location of the primary groups on the same side and the secondary groups on the other side are thought to be characteristic of the α-(1 → 4)-glycosidic linkage [9,10]. It is expected that the introduction of a 1,6-anhydro bridge and/or the substitution of hydroxyl groups by acetyl groups do not affect the conformation of the α-(1 → 4)-glycosidic linkage very much, because this characteristic feature of the α-(1 → 4)-glycosidic linkage is preserved in the present structures of MNA and BMOA, as well as in the crystal structure of β-maltose octaacetate.

[1] Data may be obtained from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 1
Final atomic coordinates and temperature factors with estimated standard deviations (esds) of non-hydrogen atoms of MNA

Atom	x	y	z	B(eq) [a]
C-1A	0.5577(9)	0.6880(6)	0.042(1)	3.8(3)
C-2A	0.5047(9)	0.7505(6)	0.024(1)	3.9(3)
C-3A	0.4490(8)	0.7465(7)	−0.073(1)	3.5(3)
C-4A	0.511(1)	0.7398(6)	−0.158(1)	3.9(4)
C-5A	0.564(1)	0.6775(7)	−0.147(1)	4.3(4)
C-6A	0.632(1)	0.6783(7)	−0.229(1)	5.0(4)
O-1A	0.4986(5)	0.6369(4)	0.0559(6)	3.2(2)
O-2A	0.4463(5)	0.7606(4)	0.1117(7)	4.6(2)
O-3A	0.4066(6)	0.8085(4)	−0.0791(7)	3.6(2)
O-4A	0.4625(6)	0.7371(4)	−0.2543(7)	5.3(3)
O-5A	0.6075(5)	0.6782(4)	−0.0511(6)	3.9(2)
O-6A	0.6714(6)	0.6152(5)	−0.2281(7)	5.6(3)
C-21A	0.475(1)	0.8029(8)	0.185(1)	5.3(4)
C-22A	0.403(1)	0.8253(7)	0.250(1)	6.6(5)
O-22A	0.5480(7)	0.8186(5)	0.1892(8)	5.9(3)
C-31A	0.321(1)	0.8063(7)	−0.098(1)	4.1(4)
C-32A	0.2826(6)	0.7580(5)	−0.1099(8)	6.2(3)
C-41A	0.486(1)	0.782(1)	−0.328(1)	8.1(7)
C-42A	0.423(1)	0.775(1)	−0.413(1)	10.5(7)
O-42A	0.548(1)	0.8118(8)	−0.326(1)	9.8(5)
C-61A	0.716(1)	0.6035(7)	−0.318(1)	5.1(4)
C-62A	0.758(1)	0.5395(7)	−0.313(1)	5.4(4)
O-62A	0.7179(8)	0.6411(5)	−0.3870(8)	7.3(3)
C-1B	0.4698(8)	0.4838(6)	0.260(1)	3.6(3)
C-2B	0.5260(8)	0.5360(7)	0.2912(9)	3.5(3)
C-3B	0.5155(8)	0.5989(6)	0.2375(9)	3.1(3)
C-4B	0.5296(7)	0.5850(6)	0.1140(9)	2.9(3)
C-5B	0.4791(7)	0.5250(6)	0.0857(9)	3.1(3)
C-6B	0.5050(7)	0.5016(6)	−0.0243(8)	3.2(3)
O-1B	0.3839(5)	0.5022(4)	0.2615(6)	3.8(2)
O-2B	0.5023(6)	0.5517(5)	0.4013(6)	4.8(3)
O-3B	0.5821(6)	0.6421(4)	0.2664(6)	4.5(2)
O-5B	0.4929(5)	0.4693(4)	0.1503(6)	3.7(2)
O-6B	0.5944(6)	0.4847(4)	−0.0231(6)	4.3(2)
C-21B	0.543(1)	0.517(1)	0.471(1)	7.6(6)
C-22B	0.511(1)	0.534(1)	0.580(1)	9.1(6)
O-22B	0.5976(9)	0.4777(8)	0.453(1)	9.9(5)
C-31B	0.560(1)	0.6912(9)	0.334(1)	5.9(5)
C-32B	0.638(1)	0.7254(8)	0.365(1)	7.0(5)
O-32B	0.4896(8)	0.6987(6)	0.3629(8)	6.9(4)
C-61B	0.625(1)	0.4590(7)	−0.109(1)	4.7(4)
C-62B	0.716(1)	0.4375(8)	−0.097(1)	6.6(5)
O-62B	0.5838(7)	0.4538(6)	−0.1858(7)	7.3(3)
C-1C	0.1570(9)	0.5023(7)	0.274(1)	4.7(4)
C-2C	0.2054(9)	0.5268(7)	0.367(1)	3.8(4)
C-3C	0.2829(8)	0.4827(6)	0.3922(9)	3.5(3)
C-4C	0.3245(8)	0.4521(6)	0.295(1)	3.6(3)
C-5C	0.260(1)	0.4375(8)	0.214(1)	4.8(4)
C-6C	0.188(1)	0.3933(7)	0.245(1)	5.3(5)

Table 1 (continued)

Atom	x	y	z	B(eq) [a]
O-1C	0.1261(6)	0.4383(5)	0.2875(7)	4.9(3)
O-2C	0.2333(6)	0.5908(4)	0.3425(6)	4.4(2)
O-3C	0.2472(6)	0.4305(4)	0.4589(6)	4.6(2)
O-5C	0.2158(6)	0.4995(5)	0.1898(6)	5.0(3)
C-21C	0.231(1)	0.6347(7)	0.414(1)	6.4(5)
C-22C	0.268(1)	0.6969(6)	0.378(1)	6.2(4)
O-22C	0.203(1)	0.6235(5)	0.4990(7)	15.1(5)
C-31C	0.306(1)	0.3983(8)	0.518(1)	5.2(4)
C-32C	0.262(1)	0.3491(7)	0.583(1)	6.7(5)
O-32C	0.3797(6)	0.4097(5)	0.5140(7)	5.3(3)

[a] $B(\mathrm{eq}) = (8/3)\pi^2(U_{11}\ (aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$.

In both structures, the methyl groups of the secondary acetyl groups form favorable van der Waals contacts between the A- and C-rings, as shown by the dotted lines in Fig. 2. The distances between them are 3.77 Å in MNA and 3.75 Å in BMOA. These methyl–methyl van der Waals contacts cause hydrophobic–hydrophobic interactions between them and stabilize the bent structures of molecules. There is another van der Waals contact (3.57 Å) between primary acetyl groups in MNA, which is indicated by a dotted line in Fig. 2. This contact also plays a role to stabilize the molecular structure, and it is closely related with the conformations of the primary acetyl groups of the A-ring, as will be mentioned later.

Conformations of glucose rings.—Puckering parameters of Q and THETA for six glucose rings in MNA and BMOA are listed in Table 3 [11]. The A- and B-rings in both structures have a normal $^4C_1$ chair conformation, while the 1,6-anhydro bridges in the C-rings extremely affect the ring conformations. The conformations of the C-rings appear to be almost a $^1C_4$ chair conformation from the views of Fig. 2, but those are not the precisely inverse conformation of $^4C_1$, because the puckering parameters of THETA are not precisely 180° but about 150°. This means the C-rings have the highly distorted $^1C_4$ conformation that is intermediate between chair and envelope conformations.

Conformations of acetyl groups.—Torsion angles of acetyl groups are listed in Table 2. All of the conformations of the secondary acetyl groups are the same. The torsion angles of C(g)–C(g)–O(g)–C(a), where (g) and (a) mean atoms of the glucose ring and atoms of the acetyl group, respectively, are in the range from 83° to 151° and −160° to −102°, and those of C(g)–O(g)–C(a)=O(a) are almost 0°. Although the conformations of C(g)–C(g)–O(g)–C(a) are eclipsed, these conformations, which are called the *cis,cis* conformation based on the torsion angles of H(g)–C(g)–O(g)–C(a) and C(g)–O(g)–C(a)=O(a), are usually found in acetylated oligosaccharides [12], and this *cis,cis* conformation is thought to be the most stable conformation of acetyl groups attached to the secondary sites of a glucose ring [12]. Usually, the conformation of primary groups is defined as *gauche–gauche*, *gauche–trans*, and *trans–gauche* by using the torsion angles of O-5(g)–C-5(g)–C-6(g)–O-6(g) (or Br-6 in BMOA) and C-4(g)–C-5(g)–C-

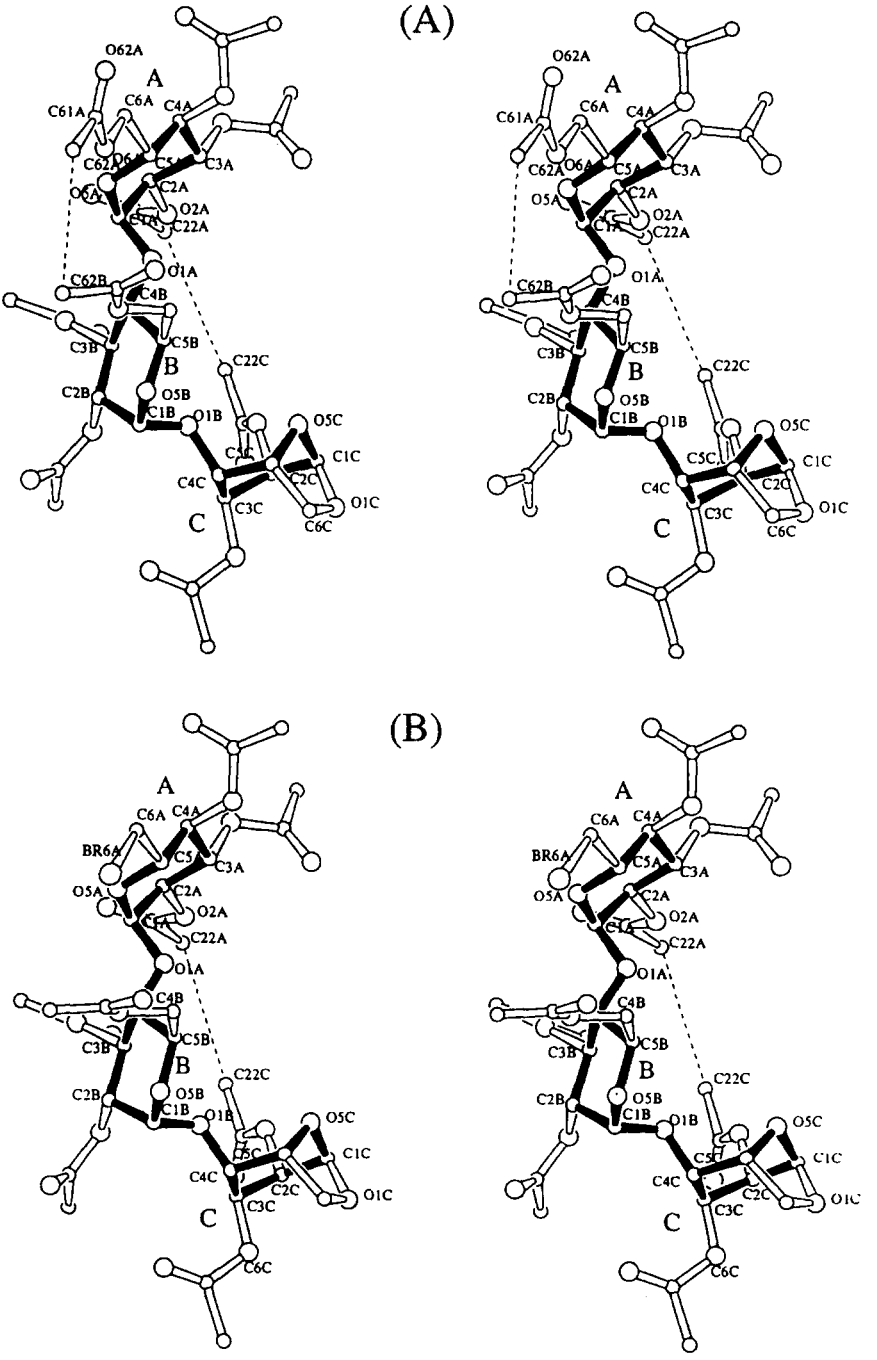

Fig. 2. Stereoviews of molecular structures of MNA (A) and BMOA (B) with selected numbering of atoms. Carbon atoms are drawn by relatively small circles compared to those of other atoms. Hydrogen atoms are not included. Glucose rings and glycosidic linkages are shown in solid bonds. Intramolecular short van der Waals contacts are indicated by dotted lines.

Table 2
Selected torsion angles with estimated standard deviations (esds) of MNA and BMOA [a]

	MNA			BMOA		
Glycosidic linkage						
O-5A–C-1A–O-1A–C-4B	91(1)			87(1)		
C-1A–O-1A–C-4B–C-3B	86(1)			90(1)		
O-5B–C-1B–O-1B–C-4C	102(1)			98(1)		
C-1B–O-1B–C-4C–C-3C	119(1)			123(1)		
Acetyl groups						
	A	B	C	A	B	C
C-1–C-2–O-2–C-21	97(1)	88(1)	141(1)	90(2)	83(2)	151(1)
*H-2–C-2–O-2–C-21	24	−32	22	−22	−39	35
C-2–O-2–C-21–O-22	−16(2)	3(3)	−3(2)	−11(2)	0(3)	0(3)
C-2–C-3–O-3–C-31	−133(1)	−105(1)	−160(1)	−124(1)	−102(1)	−159(1)
*H-3–C-3–O-3–C-31	−11	19	−44	10	28	−29
C-3–O-3–C-31–O-32	0(2)	−3(2)	−2(2)	−2(2)	−6(2)	177(1)
C-3–C-4–O-4–C-41	125(1)	–	–	125(2)	–	–
*H-4–C-4–O-4–C-41	7	–	–	8	–	–
C-4–O-4–C-41–O-42	15(3)	–	–	10(3)	–	–
O-5–C-5–C-6–O-6	72(1)	−63(1)	–	70(1)	−66(1)	–
C-4–C-5–C-6–O-6	−171(1)	62(1)	–	−175(2)	55(2)	–
C-5–C-6–O-6–C-61	161(1)	175(1)	–	–	160(2)	–
C-6–O-6–C-61–O-62	−2(2)	5(2)	–	–	2(3)	–

[a] The esds of torsion angles indicated by * are not given, because hydrogen atoms were not refined.

6(g)–O-6(g). In both structures of MNA and BMOA, the primary groups of the A- and B-rings have *gauche–trans* and *gauche–gauche* conformations, respectively. Although the *gauche–gauche* conformation is mostly found in the peracetylated oligosaccharide, the primary groups of the A-rings in both structures adopt the *gauche–trans* conformation. It is because the *gauche–trans* conformations can avoid the steric hindrance with the 4-*O*-acetyl groups of the A-rings, and because in MNA the *gauche–trans* conformation of primary acetyl group in A-ring and the *gauche–gauche* conformation in B-ring cause the favorable short van der Waals contact of 3.57 Å between methyl groups of them to form hydrophobic–hydrophobic interactions. The torsion angles of C-5(g)–C-6(g)–O-6(g)–C(a) are 161° (A-ring of MNA), 175° (B-ring of MNA), and 160° (B-ring of BMOA), as well as in another acetylated oligosaccarides [12]. All of the conformations of C-6(g)–O-6(g)–C(a)=O(a) are *cis*, as well as in the secondary groups.

Molecular packing in the crystal.—A molecular packing diagram of MNA is shown

Table 3
Puckering parameters of glucose rings of MNA and BMOA [11]

	MNA			BMOA		
	A	B	C	A	B	C
Q (Å)	0.592	0.556	0.631	0.573	0.567	0.601
THETA (°)	9.77	7.64	150.99	7.30	10.15	150.63

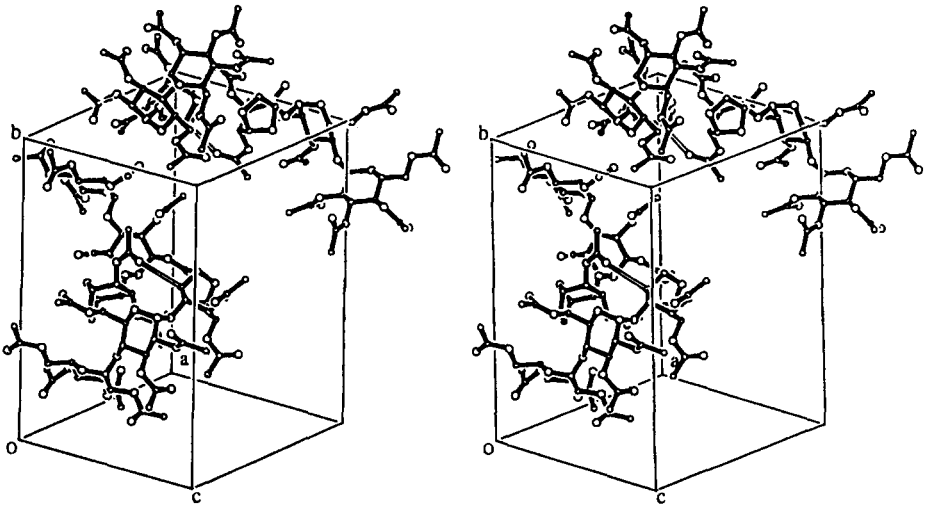

Fig. 3. A stereoview of the molecular packing of MNA in the crystal. Intermolecular hydrogen bonds between O-22C and C-5C are indicated by open bonds.

in Fig. 3. Molecules are located along three 2_1 axes parallel to the *a*-, *b*- and *c*-axes. In the crystal structures of both MNA and BMOA, there are methyl(acetyl group)–methylene(glucose ring), methyl–methyl and methylene–methylene van der Waals contacts. These contacts are expected to form hydrophobic–hydrophobic interactions, stabilizing the crystal structures.

The distances between O-22C (the carbonyl oxygen of the 2-*O*-acetyl group of the C-ring) and C-5C (C-5 atom of the C-ring) of the symmetry operated molecule are 3.13(2) Å in MNA and 3.25(2) Å in BMOA. These distances are significantly shorter compared to the usual van der Waals contact between them, and also the distances between O-22C and H-5C and the angles of O-22C–H-5C–C-5C are 2.14 Å and 154° in MNA, and 2.37 Å and 149° in BMOA, respectively. This geometry strongly suggests the existence of attractive interactions, maybe weak hydrogen-bond interactions, between them, as indicated by the open bonds in Fig. 3. These C–H · · · O intermolecular hydrogen bonds, which are found in other crystal structures of oligosaccharides [13], also contribute to the stable molecular packing in crystals.

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