Supramolecular stacking motifs in the solid state of amide and triazole derivatives of cellobiose

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ABSTRACT

1-Acetamido-1-deoxy-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) (**5**) and 1-deoxy-1-(4-phenyl-1,2,3-triazolyl)-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) (**7**) were synthesised from 1-azido-1-deoxy-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) (**2**) and crystallised as dihydrates. Crystal structural analysis of **5**.2H_2O displayed an acetamide C(4) chain and stacked cellobiose residues. The structure of **7**.2H_2O featured π–π stacking and stacking of the cellobiose residues.

Keywords: Cellobiose, Crystal structure, Sugar amide, Sugar triazole

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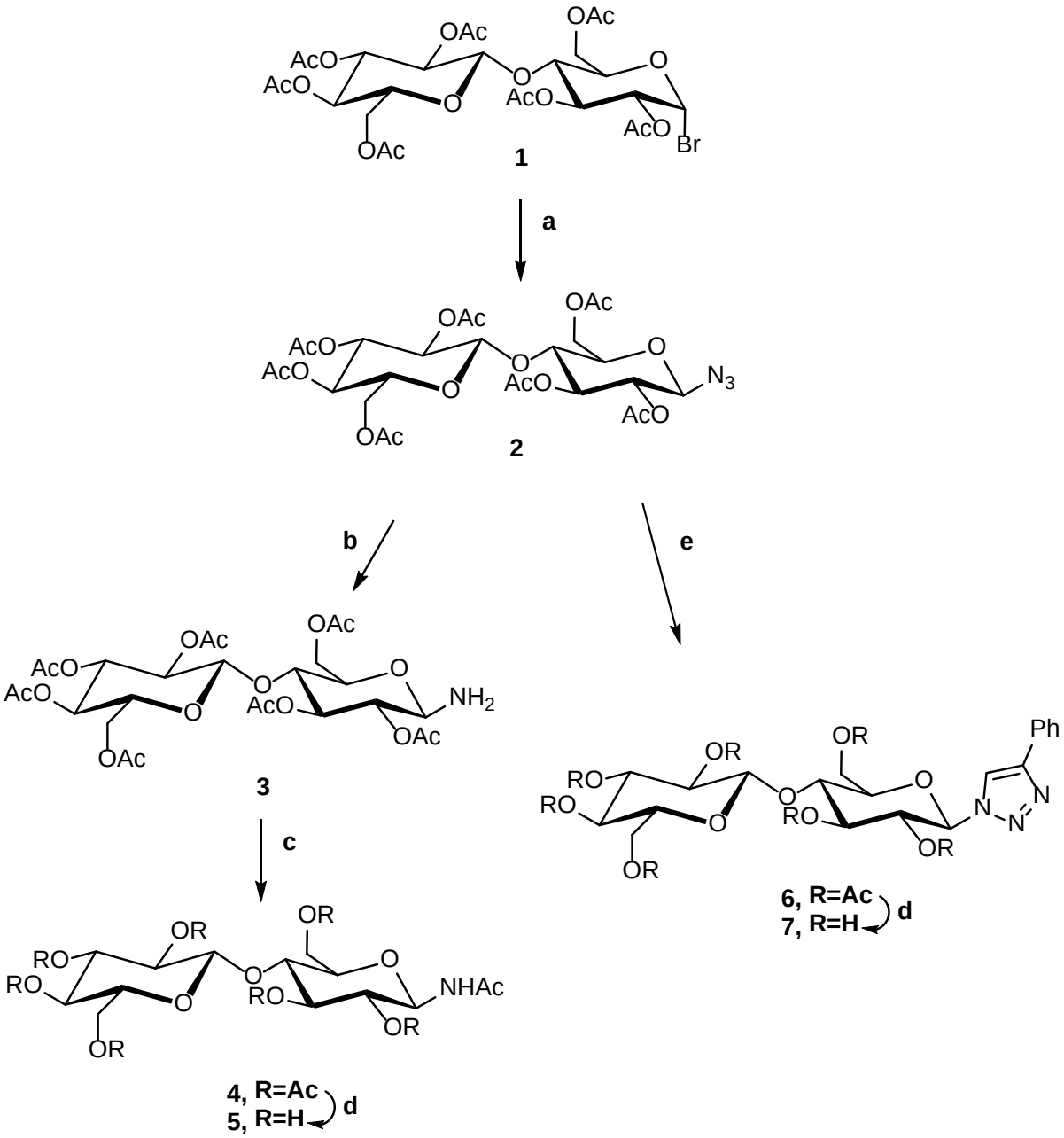
Cellobiose derivatives have been extensively studied as small-molecule models for cellulose because the crystal chemistry of these compounds can be more readily investigated then that of cellulose itself.[1] Key features that are examined include the pyranose ring puckering, torsional angles for the primary hydroxyl groups and acetal linkages[2] and supramolecular features such as hydrogen bonding motifs.[3] Examples of cellobiose derivatives designed to act as cellulose fragments include methyl 4-*O*-methyl-β-D-glucopyranosyl(1-4)-β-D-glucopyranoside[4] and cyclohexyl 4'-*O*-cyclohexyl β-D-cellobioside.[5]

One approach to designing such compounds would be to couple cellobiose to groups which provide well established supramolecular motifs for crystal engineering. Crystal engineering exploits structural units known as supramolecular synthons which assemble by known intermolecular interactions or motifs.[6] Amides, which form well known hydrogen bonded networks in the solid state, are good examples of such synthons.[7] For example, secondary amides often form hydrogen bonded chains in crystal structures between the amide N-H and carbonyl groups.[8] As these chains consist of a repeating unit containing four atoms linked by N-H···O=C hydrogen bonds, they can be labelled as C(4) chains using Etter's notation for describing hydrogen bonding motifs.[9] Such hydrogen bonding motifs occur in many amido-sugars including acetamido-lactoses,[10] and *N*-glycoprotein models.[11] Another group, 1,2,3-triazoles, have been exploited in the crystal engineering of metal-organic frameworks (MOFs),[12] in particular, and as supramolecular hydrogen bonding acceptors.[13] Both groups can be obtained readily from azides.

In addition to providing small-molecule cellulose analogues, cellobioses functionalised with groups with strong propensities for forming supramolecular motifs will also further investigation of the crystal engineering of sugars. For sugars, crystal state properties affect issues such as hygroscopicity, flow, blending and compression into tablets.[14] An ability to

control the molecular assembly of sugar molecules in crystalline solids in a rational manner would have applications in areas such as pharmaceutical formulation. In the work described here, acetamido and 4-phenyl-1,2,3-triazolyl derivatives of cellobiose have been synthesised and the crystal chemistry of these compounds examined. Both groups give rise to supramolecular stacking motifs with potential for exploitation in crystal engineering.

1-Acetamido-1-deoxy-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) (**5**) and 1-deoxy-1-(4-phenyl-1,2,3-triazolyl)-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) (**7**) were prepared from the corresponding azide (**2**)[15] which was in turn obtained from the bromide (**1**) as outlined in Scheme 1. Hydrogenation of azide (**2**) over Pd/C at 200 psi gave the amine (**3**) as a single epimer. *N*-Acetylation followed by *O*-deacetylation gave the target acetamido-cellobiose (**5**). Triazole (**6**) was obtained by Cu(I) catalysed azide 1,3-dipolar cycloaddition to phenylacetylene with microwave assistance.[16] Deacetylation of (**6**) gave the second target compound, triazolyl-cellobiose (**7**).



Scheme 1. (a) NaN_3, DMSO, 1 h; (b) H_2, 10% Pd/C, 9:1 MeOH:THF, 200 psi, 16 h; (c) Ac_2O, pyridine, THF, reflux, 24 h; (d) KOMe, MeOH, 4 h; (e) phenylacetylene, $CuSO_4.5H_2O$ (10 mol%), sodium ascorbate (15 mol%), DMF, MW (300 W), 80 ^oC, 30 min.

Crystals of compounds (**5**) and (**7**) suitable for single-crystal X-ray diffraction were grown by slow evaporation from aqueous methanol. Both compounds were found to be dihydrates and

their crystallographic data are given in Table 1. Endotherms corresponding to loss of water molecules were observed in the DSC of both materials with corresponding mass loss in TGA (Supplementary Material). Features common to both structures includes donation by the 3-OH of the reducing glucopyranose to the oxygen of the non-reducing glucopyranose, forming a 7 atom hydrogen bonded ring [an S(7) motif in Etter's notation[9]] (Figures 1 and 2), a common feature reported in a number of cellulose polymorphs[17] and models.[18, 19] The conformation of the both rings in both structures is the $^4C_1$ chair conformation typical of glucopyranoses.[19, 20] The angle and surrounding torsional angles at the acetal oxygens linking the two glucopyranose rings in both structures are typical for small molecules cellulose analogues.[19, 20] There are close packing contacts of 2.1 Å between H-1' and H-4 in both structures with both C-H bonds axial and approximately parallel, consistent with the geometry of the acetal linkage. These bonds would correspond to a twofold screw axis if present in an extended cellulose-like polymer, i.e. glucopyranose residues in alternating orientations.[19] In both structures, the conformation of the primary hydroxyl in the non-reducing glucopyranose is *gauche-trans* and that in the reducing glucopyranose is *gauche-gauche*, these being typical conformations for small molecules cellulose analogues.[19, 20]

Table 1. Crystallographic data for compounds **5** and **7**

Compound reference	**5**.2H_2O	**7**.2H_2O
Chemical formula	$C_{14}H_{25}NO_{11}.2H_2O$	$C_{20}H_{27}N_3O_{10}.2H_2O$
Formula Mass	419.38	505.48
Crystal system	Triclinic	Monoclinic
a/Å	5.0161(8)	10.813(2)
b/Å	7.6405(11)	4.9094(9)
c/Å	12.965(2)	21.507(4)
α/°	89.437(5)	90
β/°	86.681(5)	97.769(8)
γ/°	74.033(5)	90
Unit cell volume/Å^3	476.91(13)	1131.2(4)
Temperature/K	300(2)	100(2)
Space group	*P*1	$P2_1$
No. of formula units per unit cell, *Z*	1	2
Radiation type	MoKα	MoKα
Absorption coefficient, μ/mm^{-1}	0.130	0.123
No. of reflections measured	4647	11924
No. of independent reflections	1661	2884
R_{int}	0.0224	0.0640
Final R_1 values ($I > 2\sigma(I)$)	0.0273	0.0489
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.0769	0.0897
Final R_1 values (all data)	0.0313	0.0567
Final $wR(F^2)$ values (all data)	0.0928	0.0925
Goodness of fit on F^2	1.176	1.139

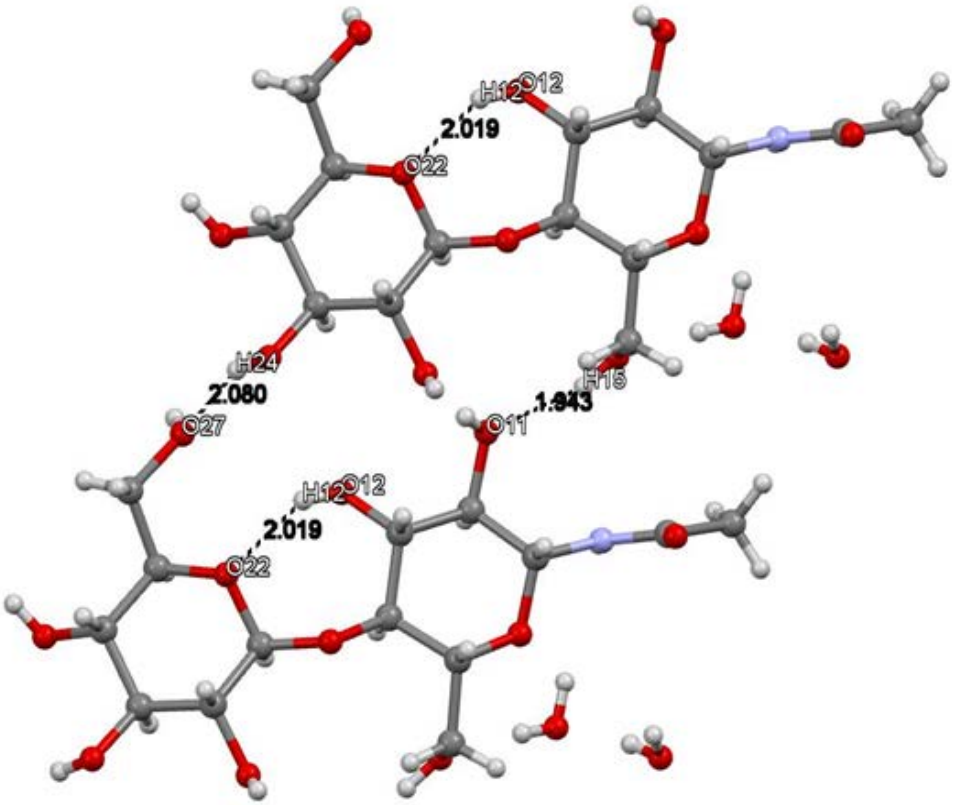


Figure 1 View of the crystal structure of compound (**5**) dihydrate showing S(7) intramolecular hydrogen bonding [O12H12···O22], and C(7) and C(8) intermolecular hydrogen bonding motifs [O24H24···O27 and O15H15···O11 respectively].

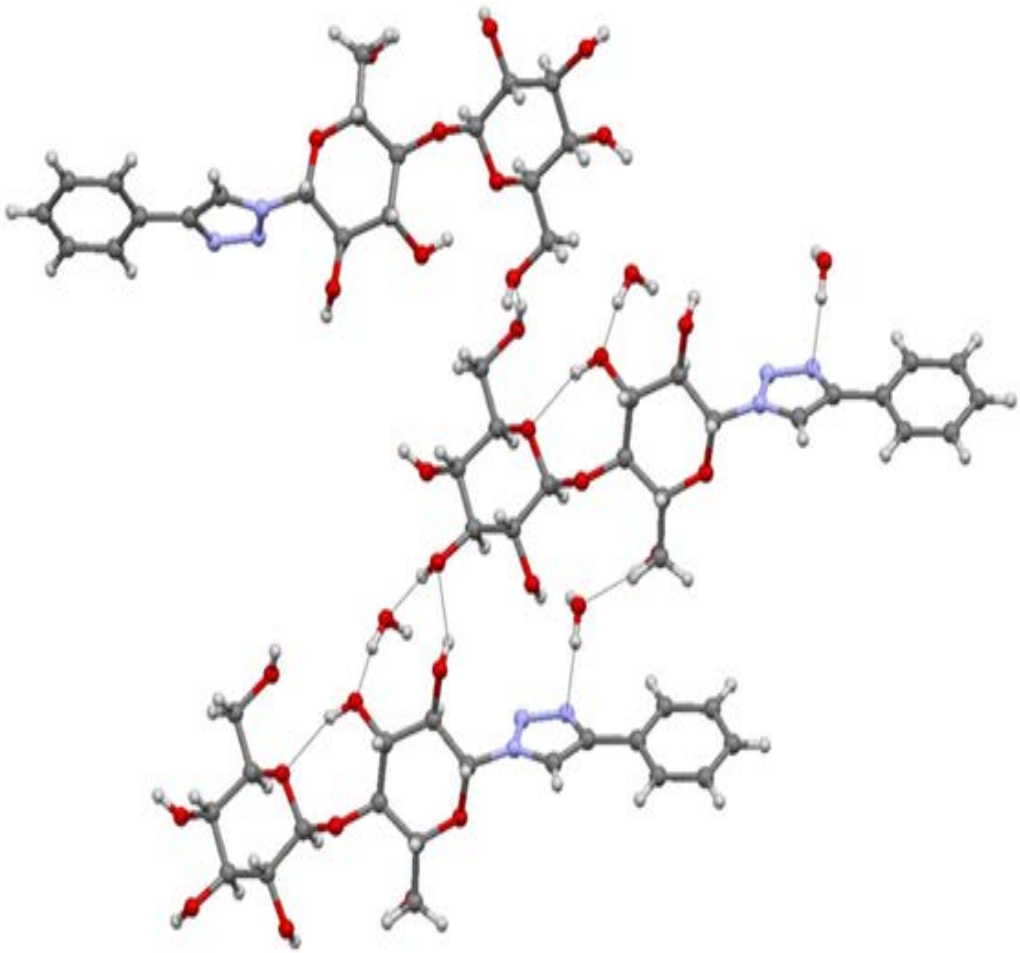


Figure 2 Intramolecular S(7) and intermolecular hydrogen bonds between 6-OH groups in the structure of compound (**7**).

Compound (**5**) crystallised with one acetamidocellobiose molecule and two unique water molecules per unit cell. The acetamidocellobiose molecules are stacked upon each other with an amide C(4) hydrogen bonding motif (Figure 3). Hence, the amide C(4) provides a supramolecular stacking motif which guides the packing of the modified cellobiose molecules. The amide bond torsional angles Φ_N and Ψ_N (defined by Loganathan and co-workers [11]) are −101.63º and 174.73º respectively. The Ψ_N value is in the range observed for amidodeoxyglucose models of glycoamide linkages, while the Φ_N value is marginally higher than those reported.[11]

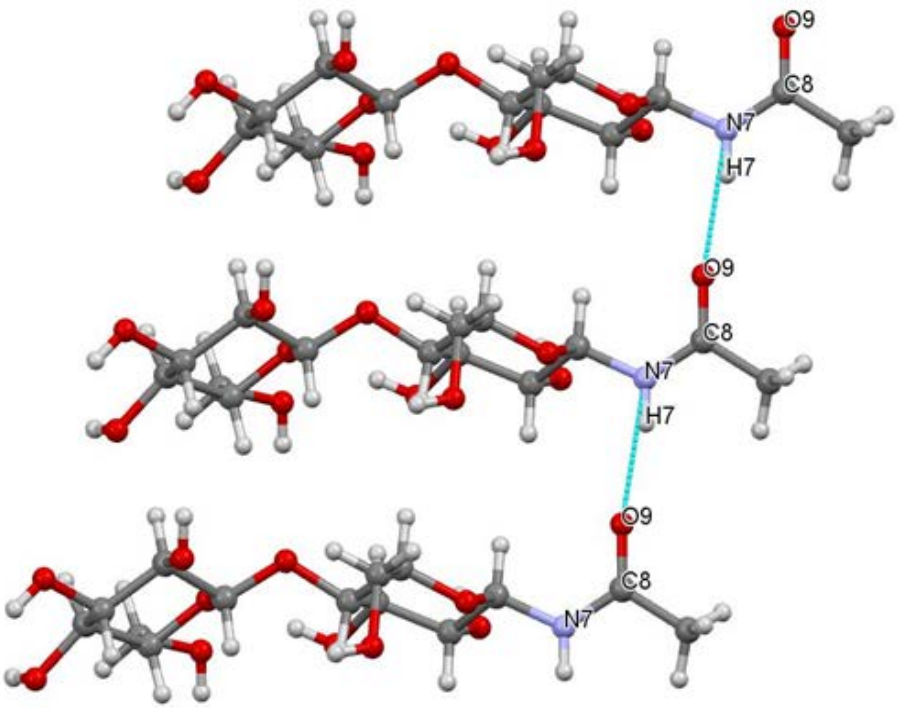


Figure 3. Hydogen bonded amide C(4) chain motif [N7H7···O9] in the crystal structure of compound (**5**) dihydrate.

The 6-OH of the reducing glucopyranose donates a hydrogen bond to the 2-OH of the reducing glucopyranose of an adjacent molecule, forming a C(8) hydrogen bonded chain motif (Figure 1). Similarly, the 3-OH of the non-reducing end donates a hydrogen bond to the 6-OH of the non-reducing glucopyranose of the same adjacent molecules, forming a C(7) chain (Figure 1). Hence, each acetamidocellobiose has one intramolecular hydrogen bond, intermolecular amide hydrogen bonds to the molecules 'above and below' (the supramolecular

stacking motif), and intermolecular hydrogen bonds to the molecules on either side. The intermolecular hydrogen bond from 3-OH to 6-OH is typical of cellulose forms,[18] while the 6-OH to 2-OH bonding is observed in some model compounds.[19] The amidocellobiose molecules pack in a parallel arrangement which is slightly tilted, consistent with the 6-OH to 2-OH bonding. The two water molecules are involved in a one-dimensional chain of hydrogen bonding running through the structure.

Compound (**7**) crystallised with two triazole and four water molecules per unit cell and the two triazole molecules are related by a 2_1 screw axis. The 4-phenyltriazolyl groups exhibit π–π stacking along the *b* axis with the distance between the centre of the phenyl rings being 4.9Å. This gives rise to anti-parallel π-stacked columns related by the 2_1 axis (Figure 4), constituting a supramolecular stacking motif which guides the intermolecular assembly of the modified cellobiose molecules. For the non-reducing end of the cellobiose residue the primary hydroxyl acts as both a hydrogen bond donor and acceptor to the primary hydroxyl on the non-reducing end of an adjacent cellobiose residue (Figure 2). The 2-OH of the reducing end of the cellobiose residue donates an intermolecular hydrogen bond to 3-OH of the non-reducing end of an adjacent molecule, while 4-OH of the non-reducing end donates a hydrogen bond to the 3-OH of the non-reducing end of an adjacent residue (Supplementary Material, Figure 7). The water molecules are filling voids in the lattice without hydrogen bonding between them.

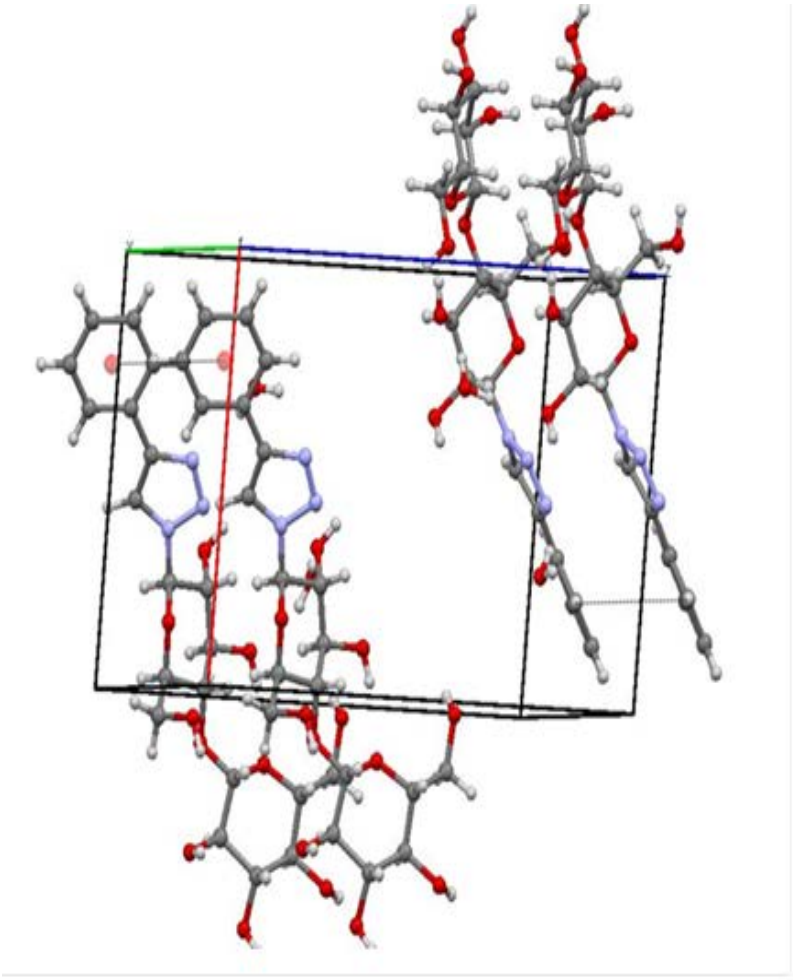


Figure 4 View of the unit cell of compound (**7**) showing the 2_1 screw axis between the two molecules in the unit cell and π-π stacking extending along the crystallographic *b* axis.

In summary, acetamidocellobiose derivative (**5**) and phenyltriazolylcellobiose derivative (**7**) were prepared from azide (**2**) and crystallised as dihydrates. In the crystal structure of compound (**5**), the cellobiose molecules are stacked upon each other with an amide C(4) hydrogen bonding chain. In the phenyltriazolyl derivative (**7**), the two molecules in the unit cell are related by a 2_1 screw axis and the 4-phenyltriazolyl groups exhibit π–π stacking. Hence in both structures, stacking of both the modifying group, i.e. the amide in (**5**) and the phenyltriazolyl group in (**7**), and the cellobiose residues are observed. The intermolecular bonding between these groups provides supramolecular stacking motifs which assist the

coordination and packing of the modified cellobiose molecules in their crystalline forms. Both structures display hydrogen bonding motifs typical of cellodextrins, such as intramolecular S(7) rings involving the reducing end 3-OH and the non-reducing glucopyranose. However, the intermolecular hydrogen bonding between cellobiose residue in the two structures are different. The success of the acetamido and phenyltriazolyl groups in promoting stacking of the glucopyranose unit could be further exploited by extension to cellotriose and larger cellodextrins, although there are likely to be increased difficulty in growing crystals suitable for crystal structure analysis as the molecular size increases.

1. Experimental

1.1. General methods

All commercial reagents were purchased from Sigma-Aldrich and were used without further purification. All solvents were either of a HPLC grade or distilled prior to use. Column chromatography was conducted using Merck silica gel 60, typically with a 30:1 ratio of silica to sample. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. The NMR spectra were recorded on a Bruker AVANCE 300 spectrometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shift values (δ_H and δ_C) are expressed as parts per million (ppm). Two dimensional heteronuclear HETCOR and COSY experiments were employed for spectral assignments. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier LC-MS instrument in electrospray ionisation (ESI) positive mode using 50 % MeCN-H_2O containing 0.1 % HCO_2H as eluant; samples were made up in MeCN. Microwave assisted synthesis was conducted on a CEM Discover S-Class synthesiser in conjunction with Synergy software.

1.2. Synthesis

1.2.1. 1-Azido-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose (2)

1-Bromo-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-α-D-glucopyranose[15] **1** (5.0 g, 7.16 mmol) was dissolved in DMSO (35 mL) and NaN_3 (1.39 g, 21.48 mmol) was added. The resulting solution was stirred at room temperature for 1 h after which the solution was poured into water (150 mL). The resulting cloudy solution was stirred at room temperature for 20 min and the precipitate collected by filtration. Recrystallisation from hot MeOH yielded the azide as a white solid (3.07 g, 65%). Mp 170-175 ^{o}C (Lit[15]= 182-182.5 ^{o}C); IR (KBr): ν 2970 (C-H), 2119 (N_3), 1755 (C=O), 1374 (C-H), 1241 (O-C=O) and 1059 (O-C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.91 (3H, s, OAc), 1.94 (3H, s, OAc), 1.95 (3H, OAc), 1.96 (3H, s, OAc), 2.00 (3H, s, OAc), 2.02 (3H, s, OAc), 2.08 (3H, s, OAc), 3.56-3.64 (2H, m, H-5, H-5'), 3.72 (1H, t, ^{3}J = 9.3 Hz, H-4), 3.96 (1H, dd, ^{3}J = 12.0, 3.0 Hz), 4.04 (1H, dd, ^{3}J = 12.0, 3.0 Hz), 4.31 (1H, dd, ^{3}J = 12.0, 3.0 Hz), 4.42-4.49 (2H, m), 4.56 (1H, d, ^{3}J = 8.7 Hz, H-1), 4.77-4.89 (2H, m), 5.00 (1H, t, ^{3}J = 9.3 Hz), 5.05 (1H, t, ^{3}J = 9.3 Hz, H-4'), 5.12 (1H, t, ^{3}J = 9.3 Hz, H-3).

1.2.2. 1-Amino-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose (3)

1-Azido-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose **2** (10.0 g, 15.12 mmol) was dissolved in a 9:1 mixture of MeOH: THF (200 mL) and Pd/C (0.32 g, 0.30 mmol of active palladium) was added. The resulting suspension was placed in a Parr pressure reactor APP 600, combined with a Texol HYG 600 H_2 generator and a Watlow series 945 overhead stirrer under a positive atmosphere of H_2 at 200 psi. The H_2 atmosphere was maintained at 200 psi and the mixture was agitated for 16 h. The catalyst was removed by filtration on a bed of Celite® and the solvent removed under reduced

pressure to yield an off white solid in quantitative yield. Mp 195-187 ^{o}C; IR (KBr): ν 3411, 3500 (NH_2), 2955 (CH), 1746 (CO), 1379 (CH), 1228 (O-C=O) and 1035 (C-O-C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.91 (3H, s, OAc), 1.94 (3H, s, OAc), 1.95 (3H, OAc), 1.96 (6H, 2 × OAc), 2.01 (3H, s, OAc), 2.07 (3H, s, OAc), 3.61-3.76 (2H, m), 3.92-4.04 (3H, m), 4.21-4.32 (3H, m), 4.53 (1H, t, ^{3}J = 9.3 Hz), 4.63 (1H, t, ^{3}J = 9.6 Hz), 4.81 (1H, d, ^{3}J = 8.1 Hz, H-1), 4.87 (1H, t, ^{3}J = 9.1 Hz), 5.10 (1H, t, ^{3}J = 9.3 Hz), 5.24 (1H, t, ^{3}J = 9.3 Hz).

1.2.3. 1-Acetamido-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose (4)

1-Amino-1-deoxy- 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose **3** (0.69 g, 1.086 mmol) and pyridine (0.04 mL, 0.543 mmol) were added to a round bottom flask containing acetic anhydride (0.113 mL, 1.195 mmol) and THF (15 mL). The reaction mixture was heated to reflux for 24 h and the solvent was removed under vacuum. The reaction mixture was then diluted with dichloromethane (30 mL), washed with sat. aq. $NaHCO_3$ (2 × 20 mL), aq. $CuSO_4.5H_2O$ (2 × 20 mL), water (30 mL), brine (30 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude solid was recrystallised from a minimum of hot MeOH to yield a white solid (0.61 g, 83%). IR (KBr): ν 3377 (N-H), 2959 (C-H), 1755 (CO), 1629 (NHC=O), 1371 (CH), 1234 (O-C=O) and 1042 (C-O-C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.98 (3H, s, NHAc), 1.99 (3H, s, OAc), 2.01 (3H, s, OAc), 2.03 (3H, s, OAc), 2.05 (3H, s, OAc), 2.10 (3H, s, OAc), 2.13 (3H, s, OAc), 2.23 (3H, OAc), 3.66 (1H, m), 3.75 (2H, m), 4.04 (1H, dd, ^{3}J = 12.5, 2.2 Hz), 4.13 (1H, m), 4.38 (1H, dd, ^{3}J = 12.7, 4.4Hz,), 4.49 (2H, m), 4.83 (1H, t, ^{3}J = 9.6 Hz), 4.93 (1H, t, ^{3}J = 8.7 Hz), 5.12 (2H, m), 5.26 (1H, m), 6.20 (1H, d, ^{3}J = 9.4 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 19.55-19.71 (1 x

NH*Ac*, 7 x O*Ac*), 60.58 (CH_2), 60.87 (CH_2), 66.76 (CH), 69.81 (CH), 70.48 (CH), 70.93 (CH), 71.10 (CH), 71.87 (CH), 73.42 (CH), 75.21 (CH), 77.07 (CH), 99.60 (C-1), 168.01 (NHAc), 168.31 (OAc), 168.39 (OAc), 169.24 (OAc), 169.22 (2 × OAc), 169.51 (OAc), 170.32 (OAc).

1.2.4. 1-Acetamido-1-deoxy-(4-*O*-β-D-glucopyranosyl)-β-D-glucopyranose (5)

To a solution of 1-acetamido-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose **4** (2.0 g, 2.95 mmol) in dry MeOH (50 mL) was added MeOK (41 mg, 0.59 mmol) and the solution stirred for 4 h. The solution was neutralized with Amberlyst® ion exchange resin (to pH 7) and was stirred for 30 min. The resin was removed by gravity filtration and the solvent removed under vacuum. The crude solid was recrystallised from a minimum of hot MeOH to yield a white crystalline solid (0.84 g, 74%). Mp 155 ^{o}C; IR (KBr): ν 3414 (O-H), 2952 (C-H) and 1667 (C=O) cm^{-1}; ^{1}H NMR (D_2O): δ 2.06 (3H, s, NHAc), 3.28-3.31 (1H, m), 3.37-3.53 (4H, m), 3.66-3.97 (7H, m), 4.50 (1H, d, ^{3}J = 8.1 Hz), 4.96 (1H, d, ^{3}J = 9.0 Hz, H-1); ^{13}C NMR (D_2O): δ 21.99 (NHAc), 59.68 (CH_2), 60.49 (CH_2), 69.36 (CH), 71.45 (CH), 73.05 (CH), 74.88 (CH), 75.37 (CH), 75.90 (CH), 76.26 (CH), 77.87 (CH), 78.98 (CH), 102.42 (C-1), 175.42 (NHAc). MS-ESI: Found m/z, 406.1316; calcd for $C_{14}H_{25}NO_{11}Na$ [$M+Na^{+}$], 406.1325.

1.2.5. 1-Deoxy-1-(4-phenyl-1,2,3-triazolyl)-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (6)

1-Azido-1-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranose (**2**) (1.5 g, 2.27 mmol), $CuSO_4.5H_2O$ (56.7 mg, 0.27 mmol), and sodium ascorbate (67.3 mg, 0.34 mmol) was dissolved in DMF (20 mL) along with phenylacetylene (0.27 mL, 2.49 mmol) and 4 of drops of water. The mixture was then subjected to

microwave radiation (300 W, 30 min) at 80 ^{o}C. The resulting cloudy yellow suspension was diluted with $CHCl_3$ (50 mL) and filtered through a bed of Celite®. The organic layer was thoroughly washed with water (2 × 20 mL), brine (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to yield a pale yellow solid. Recrystallisation from hot MeOH yielded a white solid (1.59 g, 92%). Mp 266.78 ^{o}C; IR (KBr): ν 2874-3126 (C-H), 1757 (C=O), 1371 (C-H), 1231 (O-C=O) and 1070 (C-O-C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.88 (3H, s, OAc), 1.92 (3H, s, OAc), 1.95 (3H, s, OAc), 1.98 (6H, s, 2 × OAc), 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 3.63 (1H, ddd, ^{3}J = 9.0, 4.8, 2.4 Hz), 3.82-3.91 (2H, m), 4.01 (1H, dd, ^{3}J = 12.3, 2.4 Hz), 4.10 (1H, dd, ^{3}J = 12.3, 4.8 Hz), 4.32 (1H, dd, ^{3}J = 12.3, 4.2 Hz), 4.45 (1H, d, ^{3}J = 11.7 Hz), 4.51 (1H, d, ^{3}J = 7.8 Hz), 4.89 (1H, t ^{3}J = 9.3 Hz), 5.02 (1H, t, ^{3}J = 9.3 Hz), 5.10 (1H, t, ^{3}J = 9.3 Hz), 5.34 (1H, t, ^{3}J = 9.3 Hz), 5.49 (1H, t, ^{3}J = 9.3 Hz), 5.86 (1H, d, ^{3}J = 9.0 Hz), 7.35-7.45 (3H, m), 7.82 (2H, d, ^{3}J = 7.5 Hz), 7.92 (1H, s). ^{13}C NMR ($CDCl_3$): δ 20.22 (OAc), 20.45 (2 × OAc), 20.52 (OAc), 20.67 (2 × OAc), 20.77 (OAc), 61.58 (CH_2), 61.70 (CH_2), 67.76 (CH), 70.36 (CH), 71.59 (CH), 72.14 (CH), 72.43 (CH), 72.84 (CH), 75.91 (CH), 75.99 (CH), 85.61 (CH), 100.81 (C-1), 117.80 (*C*H=Cq), 125.88 (2 × ArCH), 128.57 (ArCq), 128.87 (ArCH), 129.9 (2 × ArCH), 148.34 (CH=*Cq*), 169.05 (OAc), 169.21 (OAc), 169.29 (OAc), 169.52 (OAc), 170.16 (OAc), 170.18 (OAc), 170.45 (OAc).

1.2.6. 1-Deoxy-1-(4-phenyl-1,2,3-triazolyl)-(4-*O*-β-D-glucopyranosyl)-β-D-glucopyranose (7)

To a solution of 1-deoxy-1-(4-phenyl-1,2,3-triazolyl)-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (**6**) (1.0 g, 1.31 mmol) in dry MeOH (25 mL) was added MeOK (18 mg, 0.26 mmol) and the solution stirred for 4 h. The solution was neutralized with Amberlyst® ion exchange resin (to pH 7) and was allowed to stir for 30 min. The resin was removed by gravity filtration and the solvent removed under vacuum.

The crude solid was recrystallised from a minimum of hot MeOH to yield an off white crystalline solid (0.58 g; 95%) Mp 266 ^{o}C; IR (KBr): ν 3385 (OH), 2961 (CH), 1672 (C=C), 1231 (O-C=O) and 1045 (C-O-C) cm^{-1}; ^{1}H NMR (D_2O): δ 3.35-3.58 (5H, m), 3.78 (1H, dd, ^{3}J = 12.0, 6.0 Hz), 3.91-4.13 (6H, m), 4.59 (1H, d, ^{3}J = 7.8 Hz), 5.80 (1H, d, ^{3}J = 9.3 Hz), 7.44-7.53 (3H, m, Ar-H), 7.78 (2H, d, ^{3}J = 7.1 Hz, Ar-H), 8.48 (1H, s, C=CH); ^{13}C NMR (D_2O): δ 59.80 (CH_2), 60.64 (CH_2), 69.50 (CH), 72.15 (CH), 73.19 (CH), 74.51 (CH), 75.53 (CH), 76.07 (CH), 77.73 (2 × CH), 87.38 (CH), 102.54 (*C*-1), 121.24 (*C*H=C*q*), 125.75 (2 × *Ar*CH), 129.02 (ArCH), 129.06 (ArCq), 129.21 (2 × ArCH), 142.48 (CH=*Cq*). MS-ESI: Found m/z, 470.1752; calcd for $C_{20}H_{28}N3O_{10}$ [M+H^{+}], 470.1775.

1.3. Solid state characterisation

Crystals of compounds (**5**) and **(7**) suitable for single-crystal X-ray diffraction were grown by slow evaporation of aqueous methanol solutions. Single-crystal X-ray diffraction measurements for compound (**5**) were collected on a Bruker SMART X2S diffractometer as previously described.[21] A Rigaku FR-E+ diffractometer fitted with VariMax HF optics to give monochromatized Mo Kα radiation was used for compound (**7**) following previously described procedures.[22] Calculations for (**5**) were made using the APEX2 v2009.3-0 software[23] incorporating the SHELX suite of programs for structure solution and refinement.[24] Calculations for (**7**) were made using CrystalClear-SM Expert 2.0 r13 software.[25] The structure was solved by Superflip[26] and refined using SHELXL-97.[24] All diagrams were prepared using Mercury.[27]

Supplementary data

The crystallographic data on compounds (**5**) and (**7**) (dihydrates) have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 976571 and 976572**.** These

data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif . Full data on all hydrogen bonds are given in the Supplementary data. Thermal analysis data and PXRD patterns for compounds (**5**) and (**7**) are provided as Supplementary data.

Acknowledgments

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References

1. Yoneda, Y.; Kawada, T.; Rosenau, T.; Kosma, P. *Carbohydr. Res.* **2005**, *340*, 2428-2435; Peralta-Inga, Z.; Johnson, G. P.; Dowd, M. K.; Rendleman, J. A.; Stevens, E. D.; French, A. D. *Carbohydr. Res.*, **2002**, *337*, 851-861; Meiland, M.; Heinze, T.; Guenther, W.; Liebert, T. *Carbohydr. Res.*, **2010**, *245*, 257-263; Ham, J. T.; Williams, D. G. *Acta Crystallogr.*, **1970**, *B26*, 1373-1383.

2. Pangborn, W.; Langs, D.; Pérez, S. *Int. J. Bio. Macromol.* **1985**, *7*, 363-369.

3. Kamitori, S.; Ueda, A.; Tahara, Y.; Yosida, H.; Ishii, T.; Uenishi, *J. Carbohydr. Res.* **2011**, *346*, 1182-1185.

4. Rencurosi, A.; Röhrling, J.; Pauli, J.; Potthast, A.; Jäger, C.; Pérez, S.; Kosma, P.; Imberty, A. *Angew. Chem. Int. Ed.*, **2002**, *41*, 4277-4281.

5. Yoneda, Y.; Mereiter, K.; Jaegar, C.; Brecker, L.; Kosma, P.; Rosenau, T.; French, A. *J. Am. Chem. Soc.*, **2008**, *130*, 16678-16690.

6. Desiraju, G. R. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311-2327.

7. Aakeröy, C. B.; Panikkattu, S. V.; DeHaven, B.; Desper, J. *Cryst. Growth Des.* **2012**, *12*, 2579-2587; Seo, M.; Park, J.; Kim, S. Y. *Org. Biomol. Chem.* **2012**, *10*, 5332-5342; Kuduva, S. S.; Bläser, D.; Boese, R.; Desiraju, G. R. *J. Org. Chem.* **2001**, *66*, 1621-1626.

8. Williams, L. J.; Jagadish, B.; Lansdown, M. G.; Carducci, M. D.; Mash, E. A. *Tetrahedron* **1999**, *55*, 14301-14322.

9. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120-126.

10. Lakshmanan, T.; Sriram, D.; Loganathan, D. *Acta Crystallogr. C*, **2001**, *57*, 825-826.

11. Naseer Ali, M. M.; Aich, U.; Pérez, S.; Imberty, A.; Loganathan, D. *Carbohydr. Res.*, **2009**, *344*, 355-361; Mathiselvam, M.; Varghese, B.; Loganathan, D. *Glycoconjucate. J.*, **2011**, *28*, 573-580; Sriram, D.; Lakshmanan, T.; Loganathan, D.; Srinivasan, S.; *Carbohydr. Res*. **1998**, *309*, 227-236.

12. Urankar, D.; Pevec, A.; Turel, I.; Košmrlj, J. *Cryst. Growth and Des.*, **2010**, *10*, 4920-4927; Zou, J.-Y.; Gao, H.-L.; Shi W.; Cui, J.-Z.; Cheng, P. *CrystEngComm*, **2013**, *15*, 2682-2687.

13. Zhu, Y.-Y.; Wang, G.-T.; Wang, R.-X.; Li, Z.-T. *Cryst. Growth and Des.*, **2009**, *9*, 4778-4783; Cunha, A. C.; Ferreira, V. F.; Jordão, A. K.; de Souza, M. C. B. V.; Wardell, S. M. S. V; Wardell J. L.; Tan, P. A.; Bettens, R. P. A.; Seth, S. K.; Tiekink, E. R. T. *CrystEngComm*, **2013**, *15*, 4917-4929.

14. Ardizzone, S.; Dioguard, F. S.; Mussini, T.; Mussini, P. R.; Rondini, S.; Vercelli, B.; Vertova, A. *Cellulose* **1999**, *6*, 57-69; Garnier, S.; Petit, S.; Coquerel, G. *J. Therm. Anal. Calorim.*, **2002**, *68*, 489-502.

15. Zheng, X.; Morgan, J.; Pandey, S. K.; Chen, Y.; Tracy, E.; Baumann, H.; Missert, J. R.; Batt, C.; Jackson, J.; Bellnier, D. A.; Henderson, B. W.; Pandey, R. K. *J. Med. Chem.* **2009**, *52*, 4306-4318.

16. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599.

17. Koyama, M.; Helbert, W.; Imai, T.; Sugiyama, J.; Henrissat, B. *Proc. Natl. Acad. Sci. USA*, **1997**, *94*, 9091-9095; Bernet, B.; Xu, J.; Vasella, A. *Helv. Chim. Acta*, **2000**, *83*, 2072-2114; Qian, X.; Ding, S-.Y.; Nimlos, M. R.; Johnson, D. K.; Himmel, M. E. *Macromolecules*, **2005**, *38*, 10580-10589; Matthews, J. F.; Skopec, C. E.; Mason, P. E.; Zuccato, P.; Torget, R. W.; Sugiyama, J.; Himmel, M. E.; Brady, J. W. *Carbohydr. Res.*, **2006**, *341*, 138-152.

18. Esrafili, M. D.; Ahmadin, H. *Carbohydr. Res.*, **2012**, *347*, 99-106; Raymond, S.; Henrissat, B.; Tran Qui, D.; Kvick, Å; Chanzy, H. *Carbohydr. Res.*, **1995**, *277*, 209-229;

19. French, A. D.; Johnson, G. P. *Cellulose* **2004**, *11*, 5-22.

20. French, A. *Adv. Carbohyd. Chem. Biochem.* **2012**, *67*, 19-93; Marchessault, H. R.; Perez, S. *Biopolymers* **1979**, *18*, 2369-2374.

21. Eccles, K. S.; Stokes, S. P.; Daly, C. A.; Barry, N. M.; McSweeney, S. P.; O'Neill, D. J.; Kelly, D. M.; Jennings, W. B.; Ni Dhubhghaill, O. M.; Moynihan, H. A.; Maguire, A. R.; Lawrence, S. E. *J. Appl. Crystallogr.*, **2011**, *44*, 213–215

22. Coles, S. J.; Gale, P. A.; *Chem. Sci.*, **2012**, *3*, 683-689.

23. *APEX2 v2009.3-0; Bruker AXS: Madison, WI,* **2009**.

24. Sheldrick, G. M. *Acta Crystallogr. A,* **2008**, *64*, 112-122.

25. CrystalClear-SM Expert 2.0 r13 program suite, *Rigaku Corporation, Japan*, 2011.

26. Palatinus, L; Chapuis, G. *J. Appl. Crystallogr.*, **2007**, *40*, 786-790.

27. Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edginton, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor R.; van de Streek, J.; Wood, P. A. *J. Appl. Crystallogr.* **2008**, *41***,** 466-470.

Supramolecular stacking motifs in the solid state of amide and triazole derivatives of cellobiose

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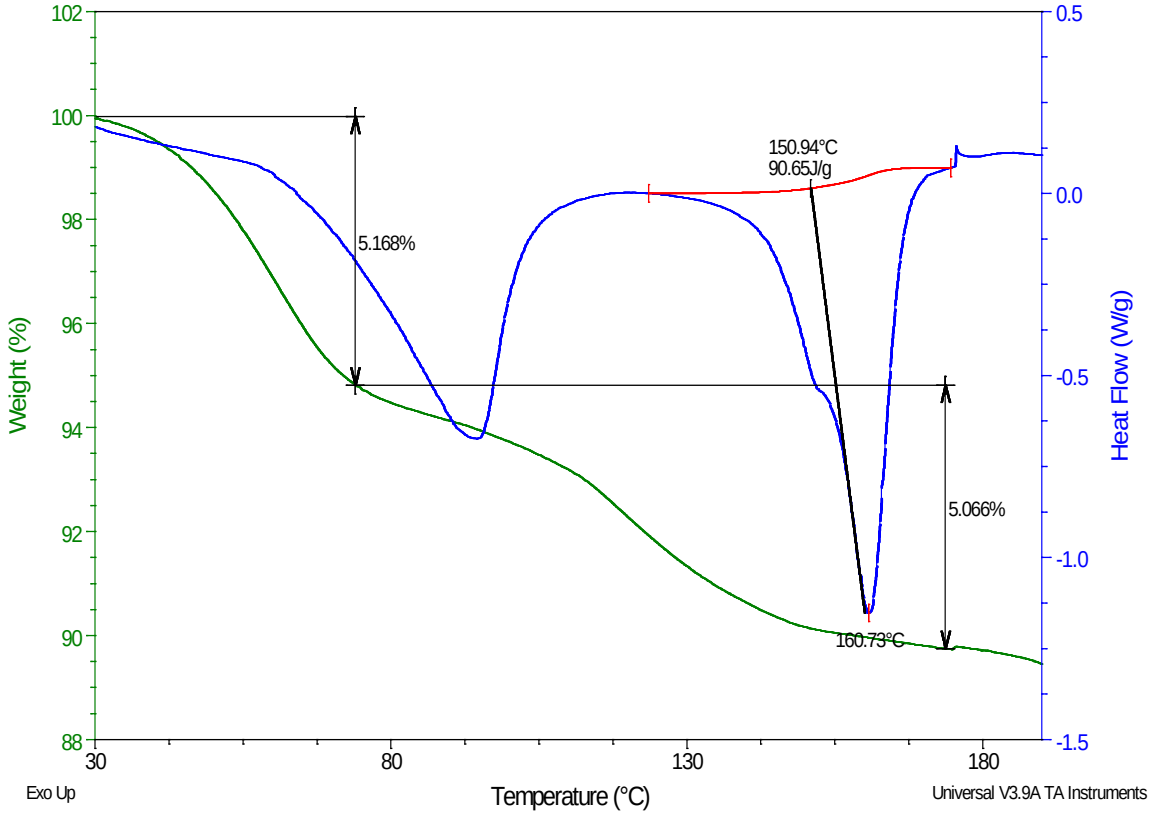
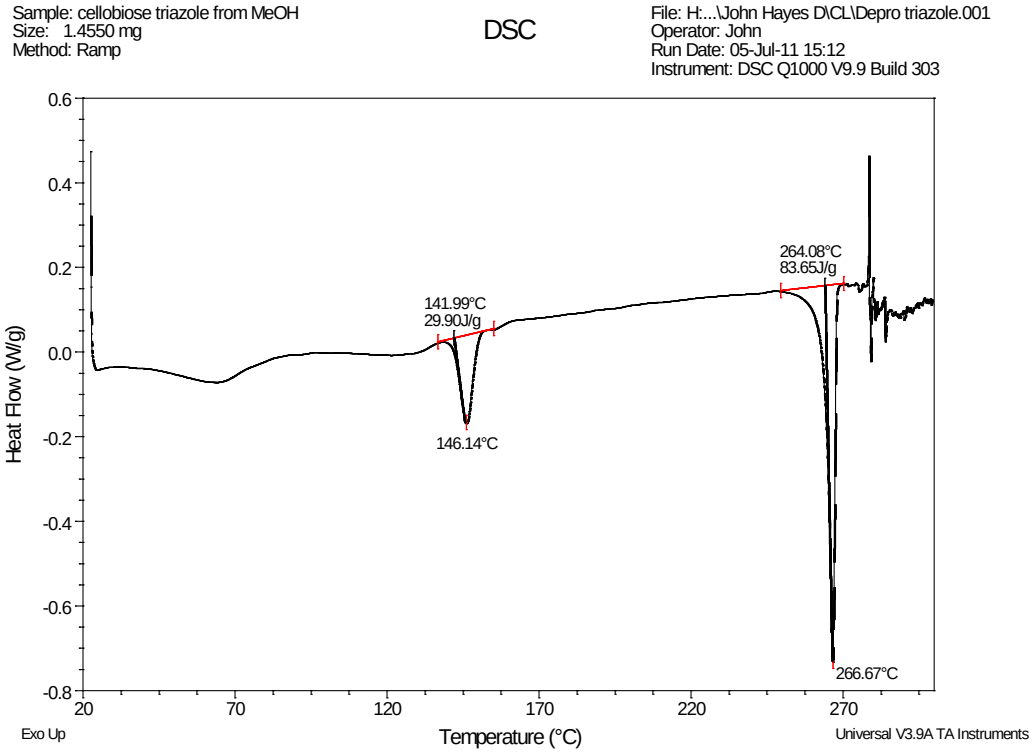
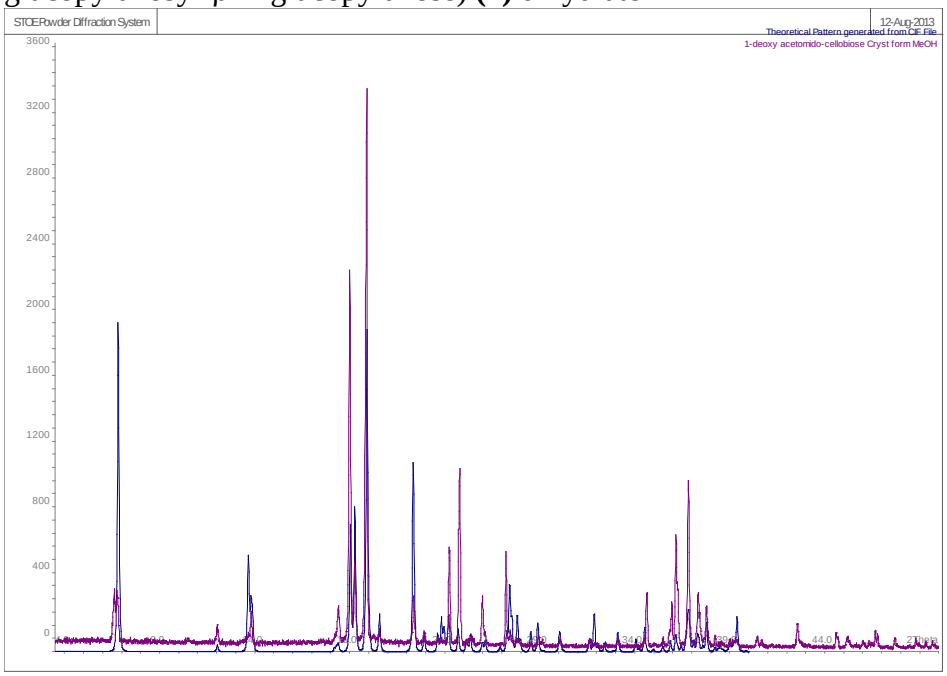
SUPPLEMENTARY DATA



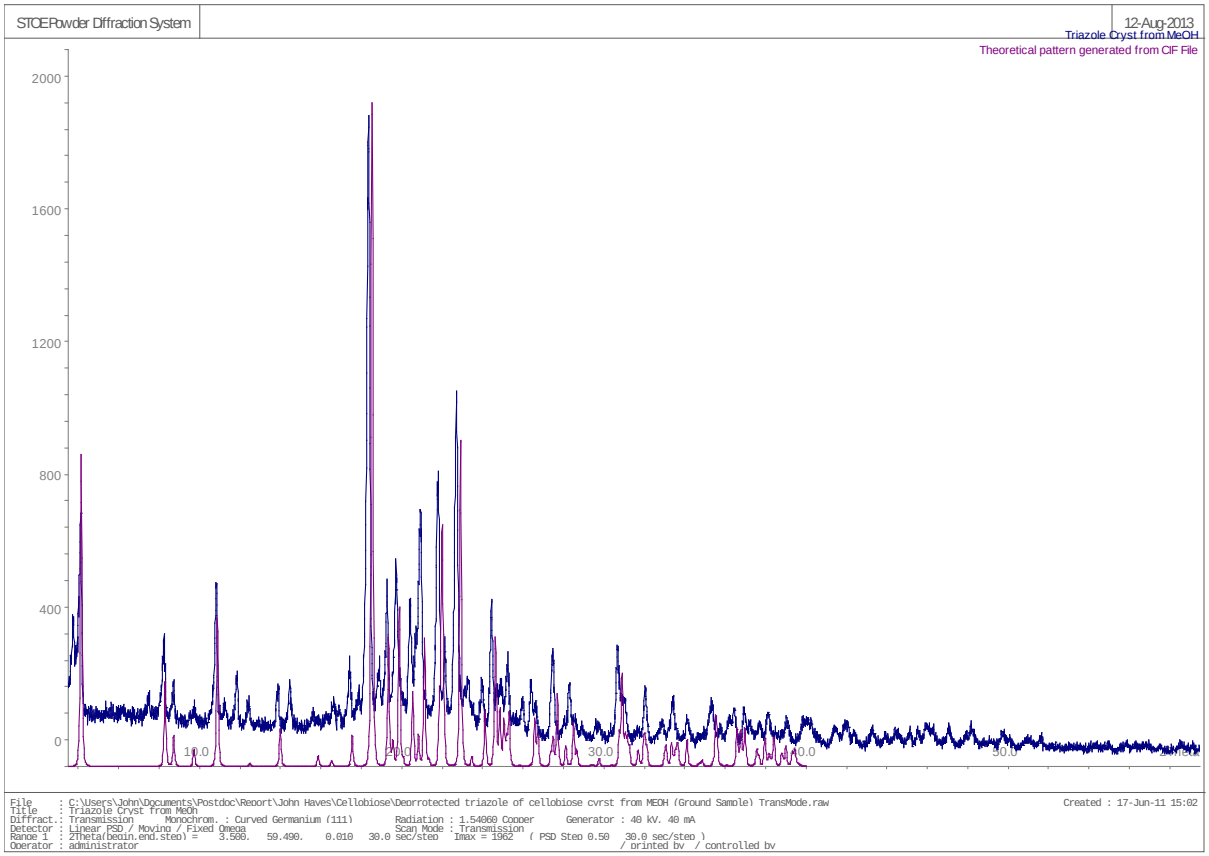
Supplementary Figure 1: DSC (blue) and TGA (green) overlay of 1-acetamido-1-deoxy-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose (**5**) dihydrate



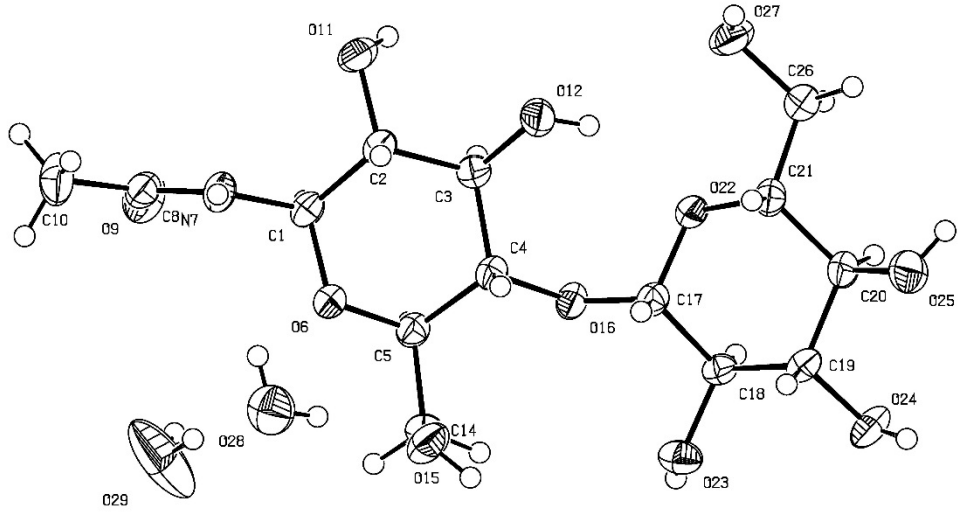
Supplementary Figure 2: DSC of 1-deoxy-1-(4-phenyl-1,2,3-triazolyl)-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) **(7)** dihydrate



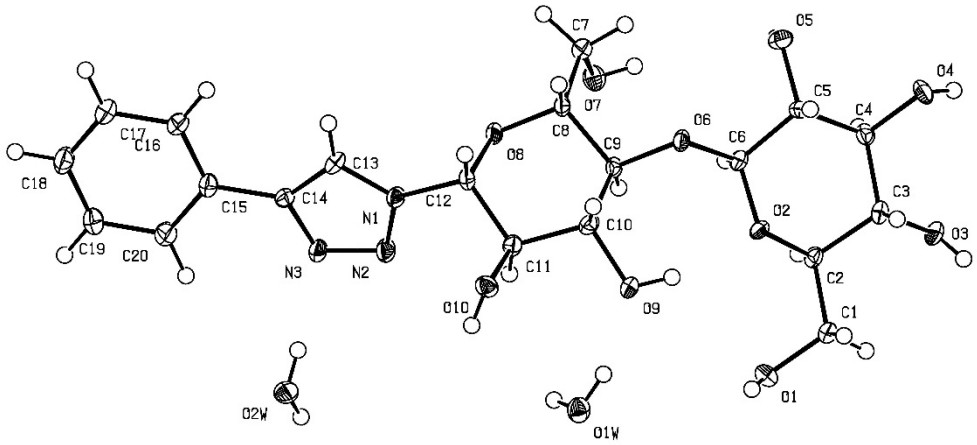
Supplementary Figure 3: Experimental PXRD pattern (purple) of 1-acetamido-1-deoxy-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose (**5**) dihydrate with overlay of calculated pattern (blue) from solved crystal structure.



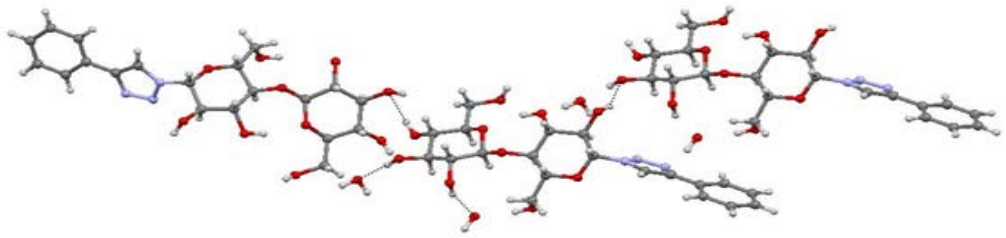
Supplementary Figure 4: Experimental (blue) and theoretical (purple) PXRD pattern for the 1-deoxy-1-(4-phenyl-1,2,3-triazolyl)-(4-*O*-β-D-glucopyranosyl-β-D-glucopyranose) **(7)** dehydrate. The diffraction peaks seen in the experimental pattern not corresponding to the calculated pattern are taken to arise from a phase impurity in the bulk sample.



Supplementary Figure 5: Numbered Ortep diagram for compound **(5)** dihydrate. Ellipsoids are drawn at the 50% probability level. [PLATON: Spek, A. *Acta Crystallographica Section D* **2009**, *65*, 148.]



Supplementary Figure 6: Numbered Ortep diagram for compound (**7**) dihydrate. [PLATON: Spek, A. *Acta Crystallographica Section D* **2009**, *65*, 148.]



Supplementary Figure 7: Intermolecular hydrogen bonding observed for compound (**7**), between the 2-OH of the reducing glucopyranose and the 3-OH of the non-reducing end of an adjacent molecule, and between the 4-OH of the non-reducing end of the first molecule and the 3-OH of the non-reducing end of a third molecule.

Supplementary Table 1 Cremer-Pople parameters for both glucopyranose molecules of compounds **5** and **7**.

	Q	θ	ϕ
(**5**) Reducing End	0.557(2) Å	5.74 (12)^o	23.24 (3)^o
(**5**) Non-Reducing End	0.575(2) Å	11.35 (11)^o	73.40 (11)^o
(**7**) Reducing End	0.574(2) Å	8.9 (3)^o	197.0 (2)^o
(**7**) Non-Reducing End	0.579(3) Å	10.3 (3)^o	184.2 (17)^o

Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354-1358.

Table of Hydrogen Bonding Data

Compound 5

Nr	Type	Res	Donor --- H....Acceptor	[ARU]	D - H	H...A	D...A	D-H...A
1		1	N(7) --H(7) ..O(9)	[1655.01]	0.86(4)	2.05(4)	2.890(3)	165(3)
2		1	O(11) --H(11) ..O(23)	[1465.01]	0.82	1.86	2.675(3)	174
3	Intra	1	O(12) --H(12) ..O(22)	[ ]	0.82	2.02	2.754(2)	149
4	Intra	1	O(12) --H(12) ..O(27)	[ ]	0.82	2.49	3.091(3)	131
5		1	O(15) --H(15) ..O(11)	[1645.01]	0.82	1.94	2.736(2)	162
6		1	O(23) --H(23) ..O(12)	[1545.01]	0.82	1.96	2.752(3)	161
7		1	O(24) --H(24) ..O(27)	[1645.01]	0.82	2.08	2.859(3)	159
8		1	O(25) --H(25) ..O(29)	[1654.03]	0.82	1.87	2.685(4)	172
9		1	O(27) --H(27) ..O(24)	[1565.01]	0.82	1.93	2.748(3)	173
10		2	O(28) --H(28A) ..O(9)	[1655.01]	0.823(18)	2.122(19)	2.888(3)	155(4)
11		2	O(28) --H(28B) ..O(15)	[ ]	0.82(3)	1.94(3)	2.754(3)	175(3)
12		3	O(29) --H(29A) ..O(28)	[1455.02]	0.82(4)	1.98(4)	2.776(4)	164(4)
13		3	O(29) --H(29B) ..O(28)	[ ]	0.81(3)	2.04(3)	2.849(4)	171(3)
14	Intra	1	C(1) --H(1) ..O(9)	[ ]	0.98	2.4	2.783(3)	102
15	Intra	1	C(4) --H(4) ..O(15)	[ ]	0.98	2.55	2.931(3)	103

Compound 7

Nr	Type	Res	Donor --- H....Acceptor	[ARU]	D - H	H...A	D...A	D-H...A
1		1	O1 --H1 ..O1 O1W --H1WA	[2556.01]	0.84	1.96	2.748(3)	156
2		2	..O9 O1W --H1WB	[ ]	0.84(2)	2.02(3)	2.802(3)	154(2)
3		2	..O10 O2W --H2WA	[1545.01]	0.84(3)	1.98(3)	2.811(3)	173(3)
4		3	..N3	[ ]	0.85(2)	2.00(3)	2.779(3)	152(3)

5		1	O3 --H3A ..O4	[2446.01]	0.84	2.27	3.035(3)	152
6		3	O2W --H2WB ..O5	[1645.01]	0.834(18)	1.95(2)	2.770(3)	168(3)
7		1	O4 --H4A ..O1W	[1455.02]	0.84	1.83	2.659(3)	168
8		1	O5 --H5A ..O2W	[1455.03]	0.84	2.03	2.836(3)	160
9		1	O7 --H7 ..O2W	[1455.03]	0.84	1.97	2.801(3)	173
10	Intra	1	O9 --H9A ..O2	[ ]	0.84	2	2.812(3)	162
11		1	O10 --H10A ..O4	[1655.01]	0.84	2.06	2.831(3)	151
12		1	C1 --H1A ..O1W	[2546.02]	0.99	2.58	3.532(4)	161
13		1	C1 --H1B ..O1W	[2556.02]	0.99	2.47	3.403(4)	157
14		1	C3 --H3 ..O3	[2456.01]	1	2.53	3.164(4)	121
15		1	C8 --H8 ..O7	[1565.01]	1	2.35	3.236(4)	148
16	Intra	1	C9 --H9 ..O7	[ ]	1	2.55	2.902(4)	100
17		1	C17 --H17 ..O8	[2657.01]	0.95	2.5	3.340(4)	148
18		1	C18 --H18 ..O7	[2657.01]	0.95	2.52	3.439(4)	162
19	Intra	1	C20 --H20 ..N3	[ ]	0.95	2.6	2.909(4)	100