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Crystal structure and solid-state NMR analysis of methyl 2,3,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside

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Abstract

The X-ray diffraction analysis of methyl 2,3,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside has been performed, establishing that molecules are associated by two types of NH · · · O hydrogen bonds, N-1–H with carbonyl-oxygen and N-3–H with anomeric oxygen, with N · · · O distances 2.902 and 2.904 Å, respectively. The urea moiety of the molecule is in *anti Z,Z* conformation. The signals in the ^{13}C CP MAS NMR spectrum are neither multiplied nor split, indicating that there is one molecule in the crystal asymmetric unit. The difference in chemical shifts between solid- and liquid-state spectra are significant for C-2 and C-3 of D-glucose moiety (2.3–2.5 ppm) and for NCH_2, CH_2Ph carbon atoms.

Keywords: Ureido sugars; Crystal structure; Hydrogen bonding; ^{13}C CP MAS solid-state NMR

1. Introduction

Ureidosugars are suitable starting materials for the synthesis of nitrosoureidosugars that possess significant antitumor activities [1]. Recently we have reported the synthesis and structure analysis of some glucosylureas, using high-field ^{15}N, ^{1}H, and ^{13}C NMR as well as ^{13}C CP MAS [2]. As part of our continuing work on these compounds we have investigated the structure and hydrogen-bonding pattern of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside in the solid state and in solu-

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Table 1
Crystal data and structure refinement for methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside

Molecular formula	$C_{22}H_{30}N_2O_9 \times H_2O$
Molecular weight	484.64
Melting point (K)	401
$[\alpha]_D^{20}$ (°, *c* 1, chloroform)	+8.2
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	monoclinic
Space group	$P_{2(1)}$
Unit cell dimensions (Å)	
a	10.875(2)
b	8.637(2)
c	14.128(3)
β (°)	98.10(3)
Volume (Å^3)	1313.8(5)
Z (molecules/cell)	2
Density (calculated, g cm^{-3})	1.220
Absorption coefficient (mm^{-1})	0.820
F(000)	516
Crystal size mm	0.2 × 0.22 × 0.4
θ range for data collection (°)	3.16 to 80.26
Index ranges for data collection	$-13 \le h \le 13$, $0 \le k \le 9$, $0 \le l \le 17$
Reflections collected	2910
Independent reflections	2804 [*R*(int) = 0.0784]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2794/0/427
Goodness of fit on F^2	1.028
Final *R* indices [$I > 2\sigma(I)$]	
*R*1	0.0519
*wR*2	0.1491
R indices (all data)	
*R*1	0.0766
*wR*2	0.1860
Absolute structure parameter	−0.1(4)
Extinction coefficient	0.010(2)
Largest diff. peak and hole (e Å^{-3})	0.191 and −0.209

tion (see Tables 1 and 2). There have been relatively few examples where the crystal structure analysis and solid-state NMR have focused on the same molecule; one of the first such study of carbohydrates is that of lactulose [3]. According to Cambridge Structural Database and to our knowledge there is no X-ray data of ureido sugars.

2. Result and discussion

X-ray diffraction.—The resulting ORTEP [4] view of the molecule and the numbering of atoms are shown in Figs. 1 and 2. The bond lengths, bond angles and selected

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside

Atoms	*x*	*y*	*z*	U_{eq} [a]
O-1	1565(2)	6382(5)	2535(2)	63(1)
C-1	832(3)	7095(6)	1741(3)	57(1)
O-11	−180(2)	6125(5)	1483(2)	66(1)
C-11	−1116(5)	6212(11)	2105(6)	96(2)
C-2	1559(3)	7208(6)	907(3)	54(1)
N-1	850(3)	7908(6)	77(2)	59(1)
C-21	250(3)	7055(6)	−644(3)	55(1)
O-21	391(3)	5622	−698(2)	64(1)
N-2	−494(4)	7851(6)	−1312(3)	69(1)
C-22	−1058(4)	7145(7)	−2183(3)	67(1)
C-23	−226(6)	7070(11)	−2948(4)	99(2)
C-24	−753(4)	6152(7)	−3795(3)	70(1)
C-25	−1724(6)	6666(12)	−4440(5)	103(2)
C-26	−2200(8)	5739(22)	−5218(6)	144(5)
C-27	−1742(13)	4329(22)	−5345(7)	149(5)
C-28	−800(13)	3840(16)	−4725(10)	145(4)
C-29	−295(6)	4691(9)	−3950(5)	95(2)
C-3	2732(3)	8156(6)	1229(3)	56(1)
O-31	3518(3)	8114(5)	498(2)	69(1)
C-31	3688(5)	9429(9)	40(4)	93(2)
O-32	3226(7)	10608(8)	210(5)	147(2)
C-32	4491(10)	9208(21)	−703(8)	159(5)
C-4	3459(3)	7485(6)	2117(3)	58(1)
O-41	4429(2)	8555(5)	2447(2)	67(1)
C-41	5604(4)	8030(8)	2649(4)	80(1)
O-42	5870(3)	6690(7)	2648(3)	108(2)
C-42	6491(5)	9319(12)	2885(7)	114(3)
C-5	2636(3)	7265(6)	2903(3)	60(1)
C-6	3251(5)	6417(7)	3771(3)	72(1)
O-61	3674(3)	4949(5)	3446(2)	76(1)
C-61	4366(4)	4078(7)	4084(3)	70(1)
O-62	4550(4)	4373(7)	4909(3)	104(1)
C-62	4798(7)	2674(9)	3634(5)	100(2)
O-10	2683(6)	13850(10)	−595(6)	169(3)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor. $U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

torsion angles, with their estimated standard deviations, are given in Tables 3–5, respectively. The β-D-pyranose ring of the ureido compound in the solid state exists in a $^1C_4$ chair conformation, with Cremer–Pople [5] puckering parameters of $Q = 0.573$ Å, $\Theta = 175.9°$, $\Psi = 238.9°$. The deviation of C-1 and C-4 from the plane defined by C-2, C-3, C-5 and O are 0.687 and −0.642 Å, respectively. All acetyl groups of the investigated compound are almost planar. Their orientation is similar to that observed in many peracetylated pyranose molecules [6]. The conformation about the C-5–C-6 bond of the primary acetate group is *gauche*, i.e. the torsion angle C-4–C-5–C-6–O-61 = −56.4(0.5)° with the C-6–O-61 and C=O bonds eclipsed [torsion angle C-6–O-61–C-

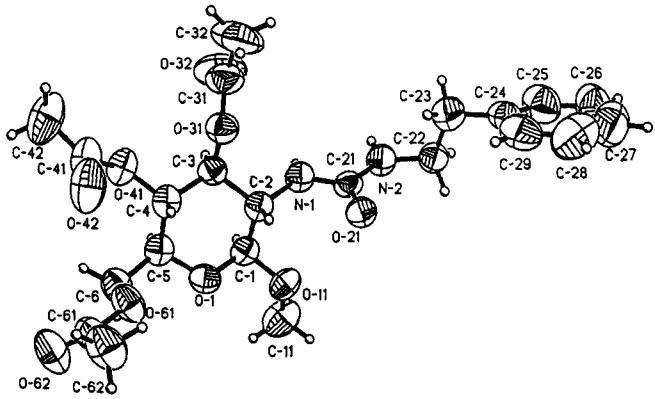


Fig. 1. Molecular structure and atomic numbering of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside. Thermal ellipsoids are drawn at 50% probability.

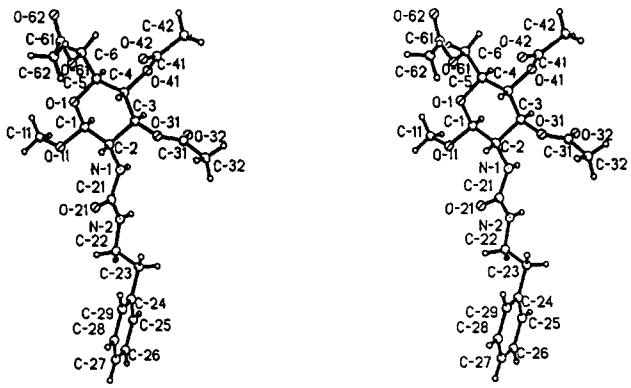


Fig. 2. Stereoview of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside.

Table 3
Bond lengths (Å) for methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside

Atoms		Atoms		Atoms	
O-1–C-1	1.422(5)	C-23–C-24	1.482(8)	C-4–O-41	1.430(5)
O-1–C-5	1.427(5)	C-24–C-25	1.368(7)	C-4–C-5	1.533(5)
C-1–O-11	1.391(5)	C-24–C-29	1.385(9)	O-41–C-41	1.349(5)
C-1–C-2	1.511(5)	C-25–C-26	1.40(2)	C-41–O-42	1.192(7)
O-11–C-11	1.437(6)	C-26–C-27	1.34(2)	C-41–C-42	1.480(9)
C-2–N-1	1.443(5)	C-27–C-28	1.32(2)	C-5–C-6	1.503(6)
C-2–C-3	1.530(5)	C-28–C-29	1.368(14)	C-6–O-61	1.445(6)
N-1–C-21	1.348(5)	C-3–O-31	1.432(5)	O-61–C-61	1.324(5)
C-21–O-21	1.250(5)	C-3–C-4	1.502(5)	C-61–O-62	1.182(6)
C-21–N-2	1.342(5)	O-31–C-31	1.333(7)	C-61–C-62	1.476(8)
N-2–C-22	1.432(6)	C-31–O-32	1.175(10)		
C-22–C-23	1.505(7)	C-31–C-32	1.470(12)		

Table 4
Bond angles (°) for methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside

Atoms		Atoms	
C-1–O-1–C-5	113.2(3)	O-31–C-3–C-4	107.2(3)
O-11–C-1–O-1	106.3(3)	O-31–C-3–C-2	109.2(3)
O-11–C-1–C-2	108.4(3)	C-4–C-3–C-2	111.1(3)
O-1–C-1–C-2	110.3(3)	C-31–O-31–C-3	117.8(4)
C-1–O-11–C-11	144.3(4)	O-32–C-31–O-31	123.2(6)
N-1–C-2–C-1	112.5(3)	O-32–C-31–C-32	125.0(8)
N-1–C-2–C-3	110.2(3)	O-31–C-31–C-32	111.8(8)
C-1–C-2–C-3	108.0(3)	O-41–C-4–C-3	107.5(3)
C-21–N-1–C-2	122.1(3)	O-41–C-4–C-5	108.9(3)
O-21–C-21–N-2	122.1(4)	C-3–C-4–C-5	111.1(3)
O-21–C-21–N-1	122.5(4)	C-41–O-41–C-4	119.0(4)
N-2–C-21–N-1	115.5(3)	O-42–C-41–O-41	123.3(5)
C-21–N-2–C-22	121.9(4)	O-42–C-41–C-42	125.5(5)
N-2–C-22–C-23	114.1(4)	O-41–C-41–C-42	111.2(5)
C-24–C-23–C-22	113.6(4)	O-1–C-5–C-6	106.5(4)
C-25–C-24–C-29	116.8(6)	O-1–C-5–C-4	109.4(3)
C-25–C-24–C-23	122.6(7)	C-6–C-5–C-4	114.4(3)
C-29–C-24–C-23	120.6(6)	C-61–C-6–C-5	107.0(3)
C-24–C-25–C-26	120.2(10)	C-61–O-61–C-6	117.3(3)
C-27–C-26–C-25	121.5(9)	O-62–C-61–O-61	123.3(5)
C-28–C-27–C-26	118.1(9)	O-62–C-61–C-62	125.6(5)
C-27–C-28–C-29	123.1(11)	O-61–C-61–C-62	111.0(4)
C-28–C-29–C-24	120.3(9)		

61–O-62 = 7.3(0.7)°]. The secondary acetyl groups also are almost planar, have *cis* conformation with the C–O and C=O bond eclipsed and the C=O group syndiaxial to the C–H bonds at the ring carbon atoms to which the acetyl groups are attached. The H atoms of the C ring atoms and carbonyl O atoms are so close to each other that weak CH · · · O hydrogen bonds stabilise this conformation [7]. The conformation about the anomeric bond is nearly *gauche*; the O-1–C-1–O-11–C-11 torsion angle is 76.0(0.5)°. The methoxyl group is so oriented that O-11–C-11 is almost *trans* to C-1–C-2 with C-2–C-1–O-11–C-11 = −165.3(0.5)°. The urea moiety –NH–CO–NH– is planar within 0.02 Å and adopts *anti Z,Z* conformation with the torsion angle C-2–N-1–C-21–O-21 = −9.1(0.6)°. The above results of the crystallographic analysis unambiguously support our earlier consideration based on liquid-state ^{1}H, ^{13}C, and ^{15}N NMR data as does the *anti Z,Z* conformation of the ureido fragment of the analysed compound [2]. The main plane of the urea moiety makes an angle of −82.8(0.6)° with the ethylene group of the ethylphenyl residue, and the plane composed of N-2, C-22 and C-23 makes an angle of 72.2(0.8)° with the benzene ring.

The hydrogen-bonding pattern is not as frequently found in the crystals of substituted ureas where both NH protons interact with the same carbonyl oxygen of the parent molecule. In the studied ureido sugar, the N-1–H forms a hydrogen bond with carbonyl oxygen. In the crystal, the molecules are associated by an intermolecular hydrogen-bonding network in which each molecule participated in two NH · · · O hydrogen bonds.

Table 5
Selected torsion angles (°) in methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido)-D-glucopyranoside

Angles		Angles	
C-5–O-1–C-1–O-11	−178.5(3)	C-2–C-3–O-31–C-31	112.9(4)
C-5–O-1–C-1–C-2	64.1(4)	C-3–O-31–C-31–O-32	−0.0(8)
O-1–C-1–O-11–C-11	76.1(5)	C-3–O-31–C-31–C-32	−178.7(7)
C-2–C-1–O-11–C-11	−165.3(5)	O-31–C-3–C-4–O-41	69.1(4)
O-11–C-1–C-2–N-1	63.3(4)	C-2–C-3–C-4–O-41	−171.6(3)
O-1–C-1–C-2–N-1	179.3(3)	O-31–C-3–C-4–C-5	−171.9(3)
O-11–C-1–C-2–C-3	−174.9(3)	C-2–C-3–C-4–C-5	−52.6(4)
O-1–C-1–C-2–C-3	−58.9(4)	C-3–C-4–O-41–C-41	−129.7(4)
C-1–C-2–N-1–C-21	−97.3(4)	C-5–C-4–O-41–C-41	109.9(4)
C-3–C-2–N-1–C-21	142.2(3)	C-4–O-41–C-41–O-42	−6.8(7)
C-2–N-1–C-21–O-21	−9.1(6)	C-4–O-41–C-41–C-42	174.3(5)
C-2–N-1–C-21–N-2	172.1(4)	C-1–O-1–C-5–C-6	176.1(3)
O-21–C-21–N-2–C-22	−7.6(6)	C-1–O-1–C-5–C-4	−59.8(4)
N-1–C-21–N-2–C-22	171.3(4)	O-41–C-4–C-5–O-1	171.6(3)
C-21–N-2–C-22–C-23	−82.8(6)	C-3–C-4–C-5–O-1	53.4(4)
N-2–C-22–C-23–C-24	172.1(5)	O-41–C-4–C-5–C-6	−69.1(5)
C-22–C-23–C-24–C-25	72.2(8)	C-3–C-4–C-5–C-6	172.8(3)
C-22–C-23–C-24–C-29	−105.8(7)	O-1–C-5–C-6–O-61	65.0(4)
N-1–C-2–C-3–O-31	−64.2(4)	C-4–C-5–C-6–O-61	−56.0(5)
C-1–C-2–C-3–O-31	172.5(3)	C-5–C-6–O-61–C-61	172.9(4)
N-1–C-2–C-3–C-4	177.7(3)	C-6–O-61–C-61–O-62	7.3(7)
C-1–C-2–C-3–C-4	54.5(4)	C-6–O-61–C-61–C-62	−176.1(5)
C-4–C-3–O-31–C-31	−126.5(4)		

The hydrogen-bond interactions are illustrated in Fig. 3. The X-ray diffraction study of *N-tert*-butyl-*N'*-methylurea indicated that the C–NH–CO–N'H–C part of the molecule adopts a *Z,Z* orientation which enabled the formation of two intermolecular hydrogen bonds with the neighbouring molecule. It is worth noting that the distances of N · · · O (2.965 Å) and N' · · · O (2.951 Å) are not equal [8].

This type of hydrogen bonding is known from other X-ray diffraction data of asymmetrically substituted ureas [9]. The sugar substituent at one nitrogen atom enables more possibilities for hydrogen bonds NH · · · O. There are several acceptor sites in the molecule. However, for steric reasons the choice is limited to the anomeric oxygen and oxygen atoms of the substituent at C-3.

Since there are more hydrogen-bond acceptors than donors, a number of CH · · · O interactions can be exptected. The interatomic distance is in the range 2.86–3.05 Å. Such interaction known as "short contact" can also be characterised as weak hydrogen bonds. The crystal structure is stabilised by numerous CH · · · O interactions, for example: C-1–H-1 · · · O-21, O-21–H-1 · · · O-10, C-26–H-26 · · · O-42, etc.

Solid state NMR.—The ^{13}C NMR spectrum (Fig. 4) recorded with cross-polarisation and magic angle spinning (CP MAS) techniques at 75.5 MHz enabled the interpretation of all carbon resonances. The signals are neither multiplied nor split, indicating that there is one molecule in the crystal asymmetric unit, in accordance with X-ray data. The

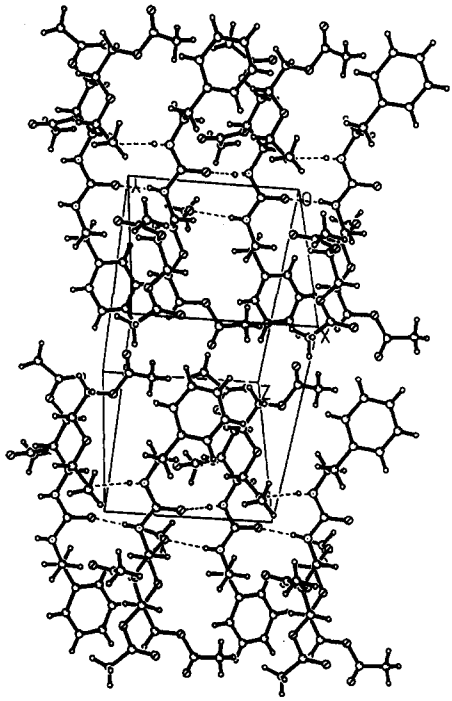
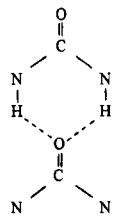


Fig. 3. The crystal structure of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-gluco-pyranoside. The intermolecular NH · · · O hydrogen bonds are indicated by broken lines.

assignment of carbon resonances can be made on the basis of chemical shifts in $CDCl_3$ solution. The signals of carbon atoms linked to nitrogen atoms: N–CO–N, N-1–C-2 and N-3–C-H, are broader due to the residual $^{13}C-^{14}N$ interaction and can be easily distinguished from other resonances (Fig. 4). The chemical shift of N–CO–N carbonyl carbon is 160 ppm in the solid and 158 ppm in solution (Table 6), and a downfield shift of 2 ppm is due to the hydrogen-bonding effect. The formation of a hydrogen bond in the solid state and in solution causes a downfield shift of the C=O resonance; a linear relationship between the N · · · O distance in the range 2.7–3.1 Å (determined by X-ray) and a carbon chemical shift of C=O of glycine was found in peptides [10]. There is not



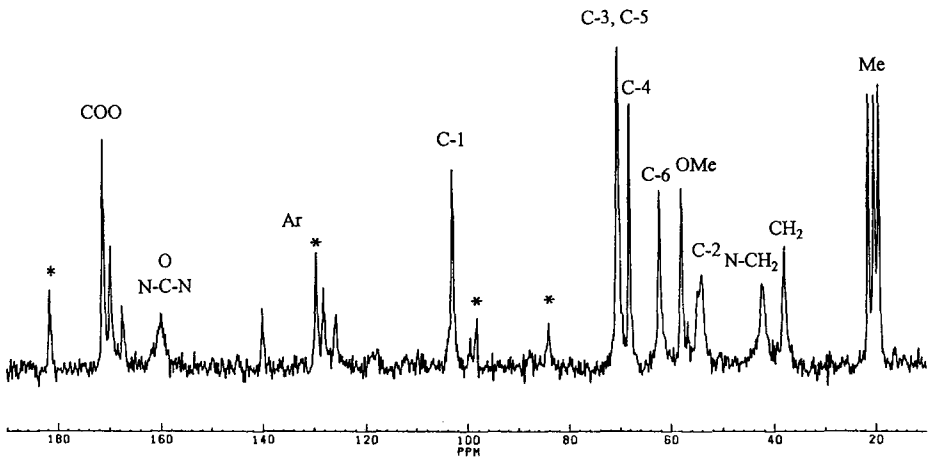


Fig. 4. ^{13}C CP MAS spectrum of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside (*: spinning side band).

enough X-ray data on 2-deoxypyranoses bearing amino, amido or ureido functions and, therefore, we cannot relate the NH · · · O hydrogen-bond lengths with chemical shifts.

Comparison of the solid-state and solution chemical shifts provides the ability to recognise rigid and flexible fragments of the structure, the latter being assumed to undergo larger changes of screening. For rigid systems like the chair-shaped ring of 2-deoxy-D-glucopyranoside, the solution conformation should be close to that in the solid state with the exception of the OCH_3 group at the anomeric carbon C-1 and of the acetyl substituent at C-5 which can exhibit reorientation [2].

Inspection of the solid-state spectrum shows similarity to the solution spectrum with the chemical shifts of aromatic carbons and carbonyl carbons of acetyl groups within 1 ppm. For glucose carbons C-1 and C-6 the differences, $\Delta = \delta_{liquid} - \delta_{solid}$, are less than 0.2 ppm, indicating that the structure does not change significantly. The separation of C-3 and C-5 resonances is 1 ppm in the liquid-state spectrum and disappears in the solid state; because of the upfield shift of C-3, Δ 2.5 ppm, and of C-5, Δ 1.4 ppm, the two resonances overlap. An increase in the shielding of C-2 of 2.3 ppm should also be noticed and is explained by various interactions of ureido substituent. The liquid-state spectrum recorded at 500 MHz exhibits one signal for the methyl resonances of the three acetyl groups because the separation of the signals is less than 0.1 ppm. The solid-state spectrum shows three distinct signals separated by ca. 1 ppm. The differences $\Delta = \delta_{liquid}$

Table 6
^{13}C NMR chemical shifts of methyl 2,3,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-glucopyranoside. The signals of aromatic and ester carbon atoms are neglected

	C-1	C-2	C-3	C-4	C-5	C-6	OMe	NH-CO	NCH_2	CH_2
In $CDCl_3$	103.2	56.3	72.9	66.8	71.8	62.2	57.0	158.0	41.6	36.1
Solid state	102.9	54.0	70.4	68.1	70.4	62.2	57.9	160.0	42.3	38.0

$-\delta_{solid}$ are negligible (−0.6 and 0.4 ppm) for two methyl resonances, but the third one is shifted upfield by 1.2 ppm. The analysis of the crystal structure (Fig. 3) suggests that it can be ascribed to CH_3 of the acetyl group at C-6 because it is located in the shielding zone of the aromatic ring. Deshielding effects, Δ −0.8 and −1.9 ppm, observed for $N-CH_2$ and $Ph-CH_2$ groups, respectively, can be related to the "freezing out" of the conformation, as found in the crystal, whereas in solution various conformational populations exist arising from rotation around C–N and C–C bonds.

3. Experimental

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside was synthesised according to the described procedure [11] from methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-D-glucopyranoside and 2-phenylethylamine. A transparent single crystal was obtained by recrystallisation from ethanol. ^1H and ^{13}C NMR spectra were on a Bruker AM 500 spectrometer recorded for solutions in $CDCl_3$. A cross-polarisation magic angle spinning (CP MAS) ^{13}C NMR spectrum of solid ureido sugar was recorded on a Bruker MSL-300 spectrometer at 75.5 MHz. The sample was spun 3.1 kHz in a 7 mm ZrO_2 rotor, 350 scans was accumulated with a contact time of 5 ms, a repetition time of 6 s and a spectral width of 20 kHz. Chemical shifts were calibrated indirectly through the glycine CO signal observed at 176.3 ppm relatively to Me_4Si.

The X-ray measurements of the crystal were made on a KM-4 diffractometer with graphite monochromated Cu $K\alpha$ radiation. The data were collected at room temperature using the ω–2θ scan technique. The intensity of control reflections for the compound varied by less than 5% and a linear correction factor was applied to account for this effect. The data were also corrected for Lorentz and polarisation effects but no absorption correction was applied. The structure was solved by direct methods [12] and refined using SHELXL [4]. Non-hydrogen atoms were refined anisotropically, whereas H atoms were placed in calculated positions and their thermal parameters were refined isotropically; in the last cycles they were refined with isotropic displacement parameters. Atomic scattering factors were taken from the International Tables [13].

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