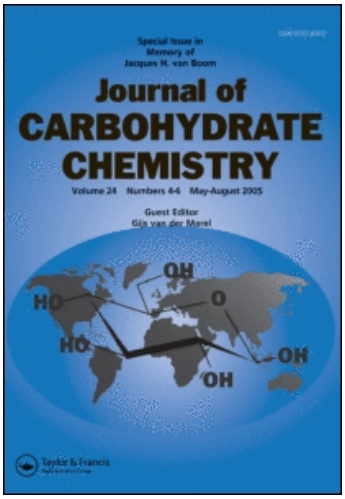

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Crystal Structure and Solid State NMR Analysis of *N*-(Methyl 3,4,6-Tri-*O*-Acetyl-2-Amino-2-Deoxy-β-D-Glucopyranoside)-*N'*Carbamoyl-D-Valine Ethyl Ester

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To cite this Article Anulewicz, Roma , Wawer, Iwona , Piekarska-Bartoszewicz, Boguslawa and Temeriusz, Andrzej(1997) 'Crystal Structure and Solid State NMR Analysis of *N*-(Methyl 3,4,6-Tri-*O*-Acetyl-2-Amino-2-Deoxy-β-D-Glucopyranoside)-*N'*Carbamoyl-D-Valine Ethyl Ester', Journal of Carbohydrate Chemistry, 16: 6, 739 — 749
To link to this Article: DOI: 10.1080/07328309708006538
URL: http://dx.doi.org/10.1080/07328309708006538

J. CARBOHYDRATE CHEMISTRY, 16(6), 739–749 (1997)

CRYSTAL STRUCTURE AND SOLID STATE NMR ANALYSIS OF *N*-(METHYL 3,4,6-TRI-*O*-ACETYL-2-AMINO-2-DEOXY-β-D-GLUCOPYRANOSIDE)-*N'*-CARBAMOYL-D-VALINE ETHYL ESTER

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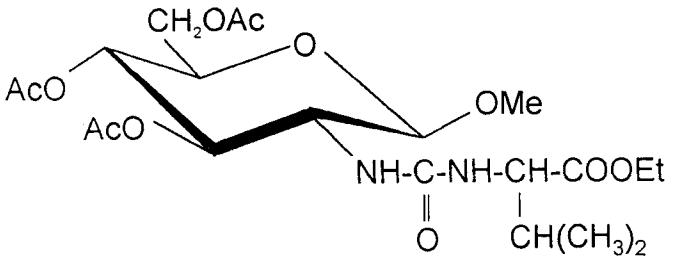
Received July 18, 1996 - Final Form March 3, 1997

ABSTRACT

The X-ray diffraction analysis of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine ethyl ester has been performed establishing that molecules are associated by two types of NH···O hydrogen bonds. The N-1–H forms an intermolecular hydrogen bond with carbonyl oxygen, and the N-3–H forms a hydrogen bond with the anomeric oxygen, with distances 2.927(6) Å and 3.063(7) Å, respectively. The urea moiety of the molecule is in the *anti-Z,Z* conformation. The signals in the ^{13}C CP MAS NMR spectrum are neither multiplied nor split, confirming that there is one molecule in the crystal asymmetric unit. The difference in chemical shifts between solid and solution spectra are significant for C-2, C-3 and OMe group of D-glucose moiety (1.7, 2.6 and 2.9 ppm respectively) and for NCON, Cα and Cβ D-valine carbon atoms.

INTRODUCTION

Ureidosugars are suitable starting materials for the synthesis of nitrosoureido sugars that possess significant antitumor activities.[1] As a part of our continuing work on the synthesis and structure analysis of ureido sugars we have investigated the structure and hydrogen-bonding pattern of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-D-valine ethyl ester (**1**). Recently we have reported synthesis and NMR studies on the structure of derivatives of 2-amino-2-deoxy-D-glucose and L-amino acid esters, but no crystal structure was available at that time.[2,3] An attempt to grow single crystals was successful in the case of **1**. According to the Cambridge Structural Database and to our best knowledge there is no X-ray data of ureido sugars except that published by us.[4] We now describe results of an X-ray diffraction study of a single crystal



1

of **1**. The aim of the present study is twofold; to establish the structure of **1** and contribute to the studies of the relationship between molecular conformations in the solid and solution.

RESULT AND DISCUSSION

X-ray diffraction. The resulting SHELXL93[5] view of **1** and numbering of atoms are shown in Fig. 1. The bond lengths and bond angles with their estimated standard deviations are given in Tables 3 and 4 respectively. The β-D-pyranose ring of the ureido compound in the solid state exists in a $^1C_4$ chair conformation, with Cremer-Pople[6] puckering parameters of Q = 0.557(6) Å, Θ = 175.4(3)°, Φ = 131.2(9)°. The deviation of C-1 and C-4 from the plane defined by C-2, C-3, C-5 and O-5 are -0.665(8) Å and 0.630(8) Å, respectively. The orientation of the acetyl groups of **1** is similar to that observed in many peracetylated

Table 1. Crystal data and structure refinement for *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine

Molecular formula	$C_{21}H_{34}N_2O_{12}$
Molecular weight	506.50
Melting point (K)	440
$[\alpha]_D^{20}$(°, *c* 1, chloroform)	-1.6
Temperature (K)	293(2) K
Wavelength (Å)	1.54178
Crystal system	orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions (Å)	
a	9.068(2)
b	15.641(3)
c	17.999(4)
Volume (Å^3)	2552.8(9)
Z (molecules/cell)	4
Density (calculated, g cm^{-1})	1.318
Absorption coefficient (mm^{-1})	0.925
F(000)	1080
Crystal size (mm)	0.5 x 0.3 x 0.3
Θ range for data collection (°)	3.74 to 60
Index ranges data for collection (°)	$0 < h < 11$, $0 < k < 16$, $0 < 19$
Reflections collected	2113
Independent reflections	2113
Refinement method	Full-matrix least-squares on F^2
Data (restraints) parameters	2096/0/318
Goodness-of-fit on F^2	1.120
Final *R* indices [$I > 2\sigma(I)$]	
*R*1	0.0837
*wR*2	0.2380
R indices (all data)	
*R*1	0.0894
*wR*2	0.2617
Extinction coefficient	0.033(4)
Largest diff. peak and hole (e Å^{-3})	0.361 and -0.358

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine [U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor].

Atoms	*x*	*y*	*z*	U_{eq}
O-5	2156(4)	265(3)	4340(2)	66(1)
C-1	2647(6)	1130(4)	4401(3)	57(1)
O-11	1542(5)	1624(3)	4090(2)	69(1)
C-11	1542(10)	1644(6)	3297(4)	93(2)
C-2	2819(6)	1383(3)	5208(3)	54(1)
N-1	3420(5)	2220(3)	5280(3)	60(1)
C-21	2552(6)	2916(4)	5444(3)	58(1)
O-21	1217(4)	2866(3)	5528(2)	65(1)
N-3	3305(6)	3659(3)	5490(3)	65(1)
C-22	2578(6)	4425(4)	5706(3)	58(1)
C-23	3504(7)	5209(4)	5484(4)	67(2)
C-24	2777(9)	6037(4)	5697(5)	81(2)
C-25	3816(9)	5185(5)	4659(4)	81(2)
O-25	3170(7)	4174(5)	6978(3)	110(2)
C-26	2320(7)	4427(4)	6533(4)	68(2)
O-27	1002(6)	4754(4)	6705(3)	86(2)
C-27	701(13)	4872(7)	7492(5)	110(3)
C-28	-742(13)	5086(9)	7629(6)	124(4)
C-3	3847(6)	749(4)	5583(3)	57(1)
O-31	3811(5)	905(3)	6371(2)	67(1)
C-31	5053(9)	1041(5)	6726(4)	83(2)
O-32	6219(7)	1103(5)	6412(4)	118(2)
C-32	4848(15)	1104(7)	7526(5)	118(3)
C-4	3399(6)	-153(4)	5450(3)	58(1)
O-41	4618(5)	-682(3)	5693(2)	68(1)
C-41	4371(10)	-1301(5)	6204(4)	77(2)
O-42	3188(8)	-1434(5)	6455(4)	112(2)
C-42	5738(12)	-1753(6)	6367(5)	99(3)
C-5	3177(7)	-330(4)	4631(3)	63(2)
C-6	2571(9)	-1234(4)	4492(4)	78(2)
O-61	3188(7)	-1591(3)	3847(3)	87(2)
C-61	4253(9)	-2202(5)	3964(6)	90(2)
O-62	4628(9)	-2390(5)	4565(5)	131(3)
C-62	4858(15)	-2524(8)	3289(10)	160(6)
O-11	5637(18)	8168(9)	1495(7)	194(4)

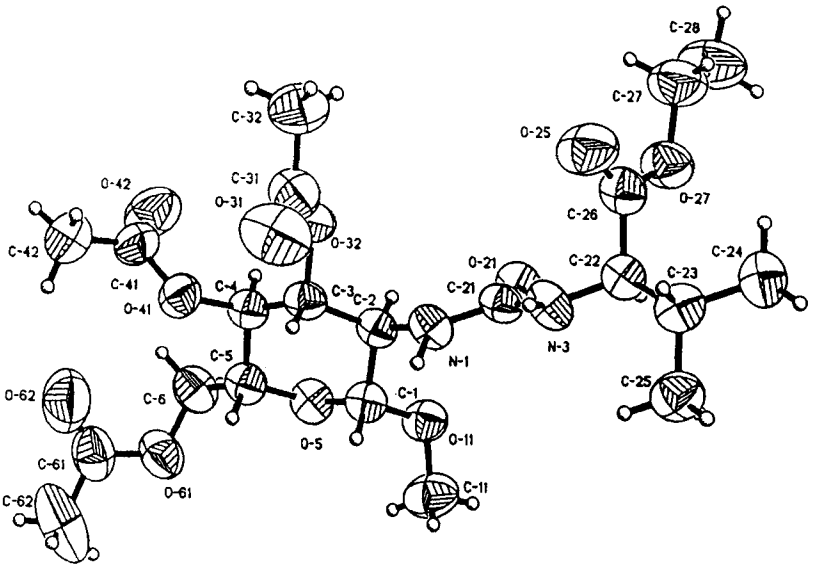


Fig. 1. Molecular structure and atomic numbering of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine ethyl ester (**1**). Thermal ellipsoids are drawn at 50% probability.

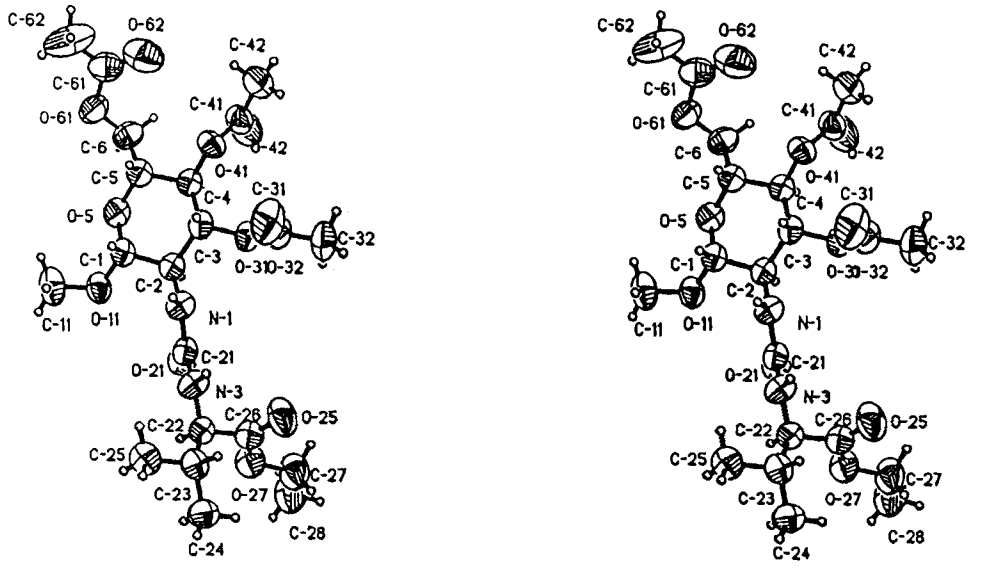


Fig. 2. Stereoview of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine ethyl ester (**1**).

Table 3. Selected bond lengths [Å] for *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine

Atoms		Atoms		Atoms	
O-5–C-5	1.414(7)	C-22–C-23	1.539(8)	C-4–O-41	1.448(7)
O-5–C-1	1.428(7)	C-23–C-24	1.505(10)	C-4–C-5	1.513(8)
C-1–O-11	1.384(7)	C-23–C-25	1.512(10)	O-41–C-41	1.355(8)
C-1–C-2	1.514(8)	O-25–C-26	1.180(9)	C-41–O-42	1.183(10)
O-11–C-11	1.427(8)	C-26–O-27	1.336(8)	C-41–C-42	1.458(13)
C-2–N-1	1.423(7)	O-27–C-27	1.455(9)	C-5–C-6	1.538(9)
C-2–C-3	1.519(8)	C-27–C-28	1.372(14)	C-6–O-61	1.404(9)
N-1–C-21	1.376(7)	C-3–O-21	1.439(7)	O-61–C-61	1.375(10)
C-21–O-21	1.221(7)	C-3–C-4	1.487(8)	C-61–O-62	1.168(11)
C-21–N-3	1.351(8)	O-31–C-31	1.312(9)	C-61–C-62	1.43(2)
N-3–C-22	1.420(8)	C-31–O-32	1.203(10)		
C-22–C-26	1.507(9)	C-31–C-32	1.455(13)		

pyranose molecules[7] and in methyl 2,3,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)ureido]-β-D-glucopyranoside.[4] The conformation about the anomeric bond is nearly *gauche*, the O-5–C-1–O-11–C-11 torsion angle is -78.8(7)°. 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 = 162.3 (6)°. The urea moiety -NH-CO-NH- is planar and adopts an *anti-Z,Z* conformation with the torsion angle C-2–N-1–C-21–O-21 = -1.2 (9)°. The above results of crystallographic analysis unambiguously support our earlier consideration based on solution ^{1}H, ^{13}C, and ^{15}N NMR data as to the *anti-Z,Z* conformation of the ureido fragment of analysed compound.[3] The main plane of the urea moiety makes angles of 76.3(7)° with the carboxyl group of the valine residue and the plane composed of N-3, C-22, C-23 makes angles of 56.0(7)° and 179.7(6)° with the methyl groups of the valine moiety.

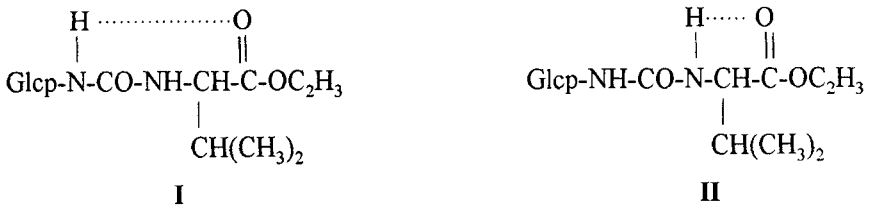
The crystal structure is in large part determined by the possibilities for hydrogen bonding. In the studied ureido sugar the molecules are associated by an intermolecular hydrogen-bonding network in which each molecule participates in two NH···O hydrogen bonds. The N-1–H forms a hydrogen bond with the carbonyl oxygen, and similarly the N-3–H interacts with the anomeric oxygen, distances being 2.927(6) Å and 3.063(7) Å, respectively. The H atoms of the Cα of the valine moiety are so close to the pyranoid ring

Table 4. Bond angles (°) for *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-gluco-pyranoside)-*N'*-carbamoyl-D-valine

Atoms		Atoms	
C-5–O-5–C-1	113.0(4)	C-28–C-27–O-27	112.6(8)
O-11–C-1–O-5	105.8(4)	C-31–C-3–C-4	108.2(5)
O-11–C-1–C-2	108.5(5)	O-31–C-3–C-2	108.3(4)
O-5–C-1–C-2	110.7(5)	C-4–C-3–C-2	112.4(5)
C-1–O-11–C-11	114.6(5)	C-31–O-31–C-3	119.2(5)
N-1–C-2–C-1	111.5(5)	O-32–C-31–O-31	122.6(7)
N-1–C-2–C-3	109.0(4)	O-32–C-31–C-32	124.9(8)
C-1–C-2–C-3	108.6(4)	O-31–C-31–C-32	112.5(9)
C-21–N-1–C-2	121.9(4)	O-41–C-4–C-3	106.6(5)
O-21–C-21–N-3	123.3(5)	O-41–C-4–C-5	106.8(5)
O-21–C-21–N-1	122.8(6)	C-3–C-4–C-5	111.6(5)
N-3–C-21–N-1	113.8(5)	C-41–O-41–C-4	119.1(5)
C-21–N-3–C-22	120.5(5)	O-42–C-41–O-41	122.4(7)
N-3–C-22–C-26	110.1(5)	O-42–C-41–C-42	127.5(7)
N-3–C-22–C-23	110.3(5)	O-41–C-41–C-42	110.1(7)
C-26–C-22–C-23	109.8(5)	O-5–C-5–C-4	109.1(5)
C-24–23-C–25	110.7(6)	O-5–C-5–C-6	108.1(5)
C-24–C-23–C-22	112.4(6)	C-4–C-5–C-6	112.1(5)
C-25–C-23–C-22	109.7(6)	O-61–C-6–C-5	111.0(6)
O-25–C-26–O-27	123.7(7)	C-61–O-61–C-6	115.4(7)
O-25–C-26–C-22	124.6(6)	O-62–C-61–O-61	121.4(8)
O-27–C-26–C-22	111.7(6)	O-62–C-61–C-62	125.9(10)
C-26–O-27–C-27	116.2(7)	O-61–C-61–C-62	112.6(10)

oxygen that weak CH···O interactions may conformationally stabilize this part of the molecule.

It seemed interesting to check the H-bonding pattern in the solid state of **1** when intramolecular H-bonds are present in addition to intramolecular type association. The possible types of intramolecular H-bonded forms are illustrated by Scheme 1. Formulas **I** and **II** show the seven- and the five- membered ring forms, respectively with the ureido NH group acting as the H-bonding donor.



Scheme 1

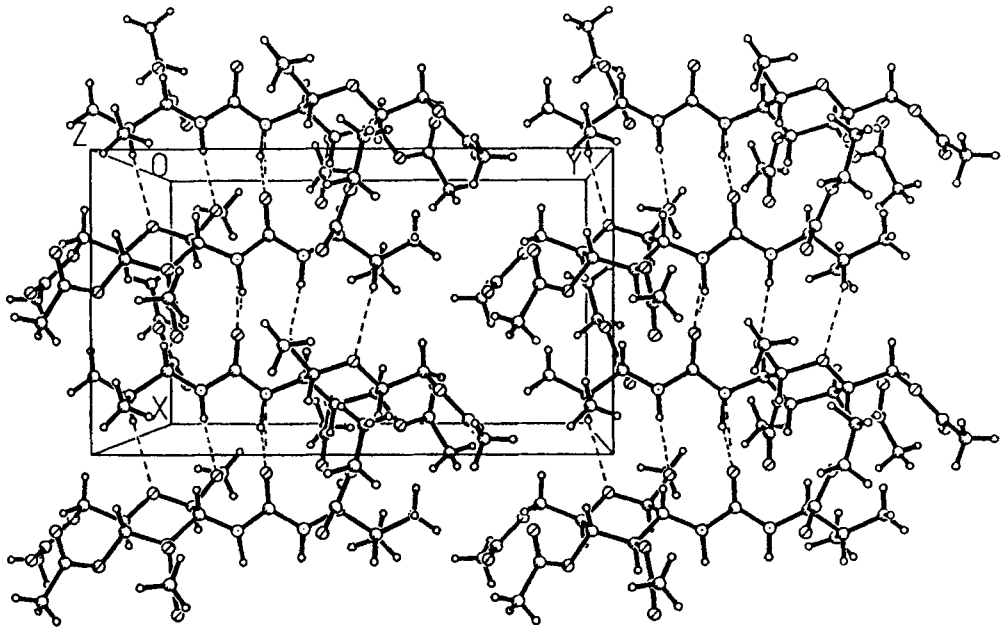


Fig. 3. The crystal structure of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N'*-carbamoyl-D-valine ethyl ester. The intermolecular NH···O hydrogen bonds are indicated by broken lines

The crystal structure presented in Fig. 3 indicated that there is no seven-membered ring with N-1–H···O=C hydrogen bond. The distance between N-3–H hydrogen and the oxygen atom of the carbonyl group is 2.800(7) Å thus enabling the interaction of N-3–H with the C=O of the valine residue. However, for geometrical reasons it is not the typical C_5 hydrogen bond cycle. In dilute $CHCl_3$ solution, without intermolecular H-bonds between molecules of ureido sugars, the intramolecular interactions become more significant and probably the rotation around $C\alpha_{Val}$–N-H yields a geometry suitable for N-3–H···O=C hydrogen bonds as revealed by IR studies.[8]

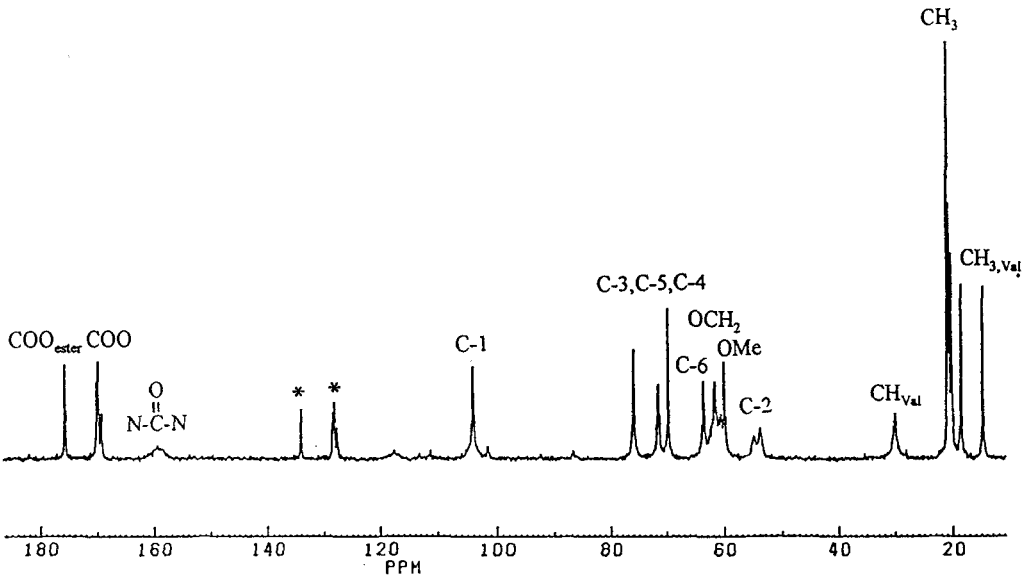


Fig. 4. ^{13}C CP MAS spectrum of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-D-valine ethyl ester (*, spinning side band)

Table 5. ^{13}C NMR chemical shifts of *N*-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-gluco-pyranoside)-*N*'-carbamoyl-D-valine ethyl ester in $CHCl_3$[2] and in solid state[3]

	C-1	C-2	C-3	C-4	C-5	C-6	OMe	N-CO-N	Cα	Cβ
in $CHCl_3$	102.9	55.9	73.1	69.0	71.8	62.3	56.9	157.6	58.0	31.5
in solid state	103.8	54.2	75.7	69.5	71.3	63.3	59.8	159.1	60.0	30.0.
$\delta_{solution}-\delta_{solid}$	-0.9	1.7	-2.6	-0.5	-0.5	1.0	-2.9	-1.5	-2.0	1.5

Solid state NMR. The solid state ^{13}C NMR spectrum of **1** is presented in Fig. 4. The number of carbon resonances (after eliminating spinning side bands) is the same as in the solution spectrum, and in accordance with the X-ray data, indicates that there is one molecule in asymmetric unit of the crystal structure. The signals of ureido C=O and $C\alpha_{Val}$ are broad and that of C-2 is split into an unsymmetrical doublet due to the residual ^{13}C-^{14}N coupling. The most prominent differences from the solution spectrum are the chemical shifts of C-2, C-3, OMe, N-CO-N and Cα, Cβ carbons of the valine residue.

The deshielding of OMe and the ureido carbonyl carbon results from their participation in intermolecular H-bond interactions. Considering the effect of the OMe group as an indication of hydrogen bonding of N-3–H with anomeric oxygen, this type of association found for D-valine derivatives **1** seems to be different compared to ureido sugars with L-amino acid residues.[3] It is worth to noting that significant chemical shifts changes for Cα and Cβ carbons of the D-valine residue appear (Table 5) and reflect conformational differences in solution due to rotation about the Cα-Cβ and Cα-CO bonds.

EXPERIMENTAL

N-(methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside)-*N*'-carbamoyl-D-valine ethyl ester (**1**) was synthesized according to the described procedure[2] from methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-D-glucopyranoside and D-valine ethyl ester. A transparent single crystal was obtained by recrystallization from chloroform.

^{1}H and ^{13}C NMR spectra were measured on a Bruker AM 500 spectrometer for solution in $CDCl_3$. The cross polarisation magic angle spinning (CP MAS) ^{13}C NMR spectrum of the 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 were accumulated with a contact time of 5 ms a repetition time of 6 s, and the spectral width was 20 kHz. Chemical shifts were calibrated indirectly through the glycine CO signal observed at 176.3 ppm relative to Me_4Si.

The X-ray measurements of the crystal were made on a KM-4 diffractometer with graphite monochromated CuKα 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 polarization effects but no absorption correction was applied. The structure was solved by direct methods[9] and refined using SHELXL.[5] 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.[10,11]

ACKNOWLEDGEMENT

This work was supported by Grant BST 532/14/96.

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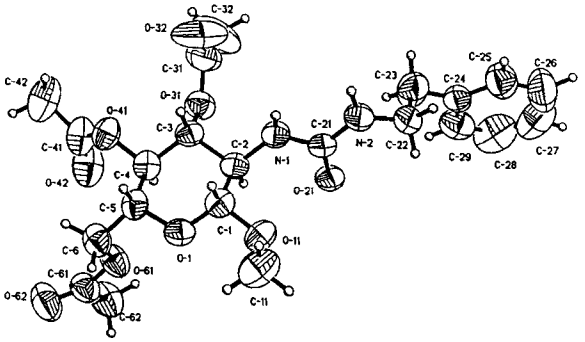
11. Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ UK.

* By computer mistake incorrect structure is given in the ref. 4; figures 1, 2, and 3 of the cited paper showed the mirror images of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)-ureido]-β-D-glucopyranoside.



Correct molecular structure of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenyl-ethyl)-ureido]-β-D-glucopyranoside.