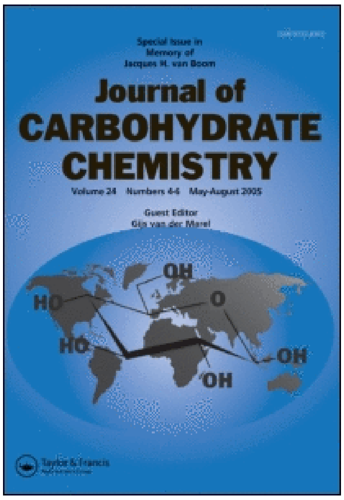

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Occurrence of the Unusual $^2C_5$ ($^1C_4$) Chair Conformation in Two Carbohydrates and the Reverse Anomeric Effect. X-Ray Structures of 3,4,5,7-Tetra-O-Acetyl-2,6-Anhydro-D-Glycero-D-Ido-Heptonamide (1) and 3,4,5,7-Tetra-O-Acetyl-2,6-Anhydro-D-Glycero-L-Gluco-Heptonamide (2)

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OCCURRENCE OF THE UNUSUAL $^2C_5$ ($^1C_4$) CHAIR CONFORMATION IN TWO CARBOHYDRATES AND THE REVERSE ANOMERIC EFFECT. X-RAY STRUCTURES OF 3,4,5,7-TETRA-*O*-ACETYL-2,6-ANHYDRO-*D*-*GLYCERO*-*D*-*IDO*-HEPTONAMIDE (**1**) AND 3,4,5,7-TETRA-*O*-ACETYL-2,6-ANHYDRO-*D*-*GLYCERO*-*L*-*GLUCO*-HEPTONAMIDE (**2**)

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Received February 15, 1982

ABSTRACT

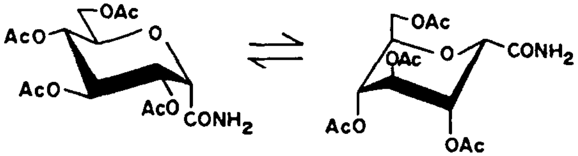
The title compounds **1** and **2** (both $C_{15}O_{15}NH_{21}$) crystallized in the monoclinic space group $P2_1$ (Z=2) with *a*=8.864(1), *b*=8.346(1), *c*=13.569(1)Å, β =114.12(1)°, V=918.1(2)$Å^3$, D(calc)=1.358 g/cc for compound **1**, and *a*=15.045(1), *b*=8.106(1), *c*=7.491(1)Å, β =97.23(1)°, V=906.4(3)$Å^3$ D(calc)=1.375 g/cc, for compound **2**. The structures were solved by direct methods and refined by the full-matrix least squares technique to R indices of 0.040 and 0.046, respectively. Both compounds are in the α-D configuration and adopt the unusual $^2C_5$ ($^1C_4$) chair conformation with the carbamoyl groups on the anomeric carbon atoms equatorially oriented. In this conformation the orientations of the substituents are 2e, 3a, 4a, 5a and 6a in **1** and 2e, 3a, 4a, 5e and 6a in **2** which leads to unfavorable 1,3-diaxial interactions. The "reverse

anomeric effect" which induces the $^2C_5$ chair conformation in these compounds, may have its origin in the unfavorable steric interactions found in the $^5C_2$ ($^4C_1$) conformation where the carbamoyl group is axially oriented. Furthermore, the $^2C_5$ conformation is stabilized by the N-H...O intramolecular hydrogen bond between the carbamoyl nitrogen atom and the pyranosyl ring oxygen atom. Semi-empirical energy calculations reveal that the rotational freedom of the carbamoyl group is greater for the equatorial orientation ($^2C_5$) than for the axial orientation ($^5C_2$).

INTRODUCTION

NMR studies of compounds 1 and 2 have revealed that these C-glycosides display a conformational equilibrium consisting of the $^2C_5$ ($^1C_4$) chair conformation and the $^5C_2$ ($^4C_1$) conformation. The $^2C_5$ conformation predominates in nonpolar solvents while the $^5C_2$ conformation predominates in polar solvents.[1] The X-ray structure analyses of these compounds crystallized from ethanol/acetone solutions show that they occur in the $^2C_5$ conformation. To our knowledge, this is the first x-ray crystal structure determination of the $^2C_5$ conformation in 'simple' carbohydrates.

1



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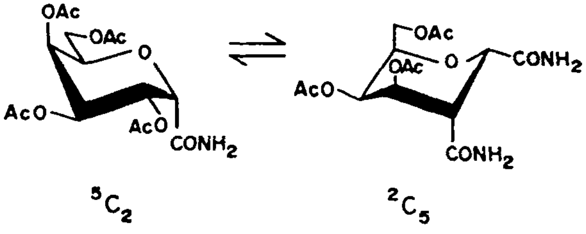

RESULTS AND DISCUSSION

The atomic positional and thermal parameters for both compounds are presented in Table 1. Anisotropic thermal parameters and lists of the observed and calculated structure factors for both compounds are given as supplementary material. B_{eq} [$= 4/3 \Sigma_i \Sigma_j B_{ij}(\underline{a}_i \cdot \underline{a}_j)$] are given for nonhyrogen atoms in Table 1 and isotropic thermal parameters (B_{iso}) are given for hydrogen atoms. ORTEP[2] drawings of the structures indicating atom numbering and overall molecular conformation are shown in Fig. 1a and 1b. The bond lengths and angles involving the nonhydrogen atoms are tabulated in Table 2. The average C-C and C-O bond lengths for the pyranoside ring are 1.528(8)Å and 1.434(5)Å in compound 1, respectively, and 1.522(7)Å and 1.436(5)Å in compound 2. Both sets agree well with the values previously reported in other pyranosides.[4-6] The two adjacent endocyclic C-O bond lengths C-2-O-6 [1.422(2)Å and 1.426(3)Å] and O-6-C-6 [1.428(2)Å and 1.424(3)Å] are equal (within experimental error). The geometries of the carbamoyl groups are identical in the two compounds. The bond lengths of the acetyl groups are very similar; the average C-O bond distance is 1.346(5)Å, the C=O distance is 1.192(6)Å, and the C-C distance is 1.493(7)Å.

The bond angles in structures 1 and 2 generally agree with each other (see below) and with most values reported in the literature for $^4C_1$ pyranosides.[3,4] The bond angle at O-6 is 114.7(2)° for both compounds and is similar to the mean value of 114.2° observed for β-D-pyranosides.[3] The exocyclic bond angle O-6-C-2-C-1 at the anomeric carbon atom is 109.4(2)° for 1 and 110.6(2)° for 2. These values are significantly larger than the mean value of 107.5° found in β-D-pyranosides.[3]

In compound 1 there are two pairs of 1,3-diaxial interactions; one above the ring involving the O-4 and

Table 1: Atomic parameters for compounds 1 and 2. Fractional positional parameters are multiplied by 10^4 for nonhydrogen atoms and 10^3 for hydrogen atoms.

Compound 1	x	y	z	B_{eq} or B(Å^2)
C-1	1725(2)	10036(3)	5553(2)	3.65(4)
O-1	450(2)	10573(3)	5559(2)	5.29(5)
N	2639(2)	10799(3)	5140(2)	4.94(5)
C-2	2318(2)	8380(3)	6025(1)	3.27(4)
C-3	2441(2)	8289(3)	7169(1)	3.71(4)
O-3	3575(2)	9530(2)	7758(1)	4.26(3)
C-8	3430(4)	10126(4)	8634(2)	5.40(7)
O-8	2417(3)	9657(5)	8936(2)	9.17(7)
C-12	4697(5)	11386(5)	9149(2)	7.32(11)
C-4	3127(2)	6664(3)	7669(1)	3.86(4)
O-4	1810(2)	5539(3)	7173(1)	4.73(4)
C-9	1466(3)	4529(4)	7819(2)	4.70(5)
O-9	2184(3)	4595(4)	8770(2)	9.70(8)
C-13	156(3)	3366(4)	7215(2)	5.87(8)
C-5	4605(2)	6080(3)	7460(2)	3.72(5)
O-5	6047(2)	6842(2)	8261(1)	4.24(4)
C-10	7457(3)	5978(4)	8573(2)	5.25(7)
O-10	7514(3)	4722(4)	8189(3)	8.49(9)
C-14	8878(4)	6840(6)	9409(3)	6.57(10)
C-6	4495(2)	6480(3)	6328(1)	3.31(4)
O-6	3879(1)	8062	6002(1)	3.29(3)
C-7	3545(2)	5211(3)	5512(1)	3.50(4)
O-7	3554(2)	5730(2)	4499(1)	3.94(3)
C-11	2762(2)	4786(3)	3639(1)	3.61(4)
O-11	2151(2)	3530(2)	3686(1)	4.82(4)
C-15	2807(3)	5485(4)	2639(2)	5.11(6)
H-1A	207(5)	1152(7)	466(4)	9.4(13)
H-1B	366(4)	1034(6)	525(3)	6.6(9)
H-2	149(3)	759(4)	564(2)	3.8(6)
H-3	139(3)	852(5)	723(2)	4.8(6)
H-12A	435(4)	1207(6)	966(3)	7.2(10)
H-12B	485(5)	1217(9)	850(4)	10.3(15)
H-12C	569(8)	1111(10)	938(6)	15.0(22)
H-4	350(3)	679(5)	845(2)	4.7(6)
H-13A	-36(5)	296(8)	771(4)	10.3(15)
H-13B	-72(3)	397(4)	685(2)	4.1(6)
H-13C	30(4)	272(6)	654(3)	8.2(12)
H-5	466(3)	485(4)	756(2)	4.3(6)
H-14A	860(5)	759(8)	995(4)	9.6(14)
H-14B	1002(5)	631(7)	968(3)	8.2(11)
H-14C	940(6)	728(10)	910(5)	11.5(17)
H-6	561(3)	655(4)	631(2)	4.0(5)
H-7A	243(2)	504(3)	539(2)	2.8(4)
H-7B	412(3)	408(4)	569(2)	3.5(5)
H-15A	356(5)	498(7)	242(4)	9.2(12)
H-15B	166(5)	533(9)	202(4)	9.8(14)
H-15C	302(5)	656(8)	281(4)	8.8(12)

(continued)

Compound 2	x	y	z	B_{eq} or B(Å^2)
C-1	9300(2)	5181(3)	4430(3)	3.59(5)
O-1	9229(1)	6381(3)	3428(3)	5.18(5)
N	10059(2)	4386(4)	4928(4)	4.70(6)
C-2	8471(1)	4605(3)	5215(3)	3.04(5)
C-3	8224(1)	5912(3)	6533(3)	3.04(5)
O-3	8989(1)	6056(2)	7891(2)	3.47(4)
C-8	9194(1)	7573(3)	8567(3)	3.04(5)
O-8	8724(1)	8743(3)	8225(3)	4.78(5)
C-12	10074(2)	7558(4)	9736(4)	4.63(6)
C-4	7412(1)	5358(3)	7415(3)	3.07(5)
O-4	6652(1)	5383(2)	6026(2)	3.78(4)
C-9	6100(1)	6699(3)	5982(3)	3.85(6)
O-9	6233(2)	7841(4)	6990(4)	7.56(7)
C-13	5351(2)	6510(5)	4470(5)	5.19(7)
C-5	7533(1)	3598(3)	8124(3)	3.07(5)
O-5	6693(1)	2991(3)	8584(2)	3.80(4)
C-10	6436(2)	3506(4)	10154(3)	4.15(6)
O-10	6903(2)	4302(5)	11229(3)	6.68(6)
C-14	5487(2)	3007(6)	10276(4)	5.31(7)
C-6	7873(1)	2374(3)	6795(3)	3.17(5)
O-6	8633(1)	3063(2)	6112(2)	3.27(3)
C-7	7152(1)	1768(3)	5347(3)	3.60(5)
O-7	7588(1)	685(3)	4207(2)	4.23(5)
C-11	7035(2)	-120(4)	2959(3)	4.24(6)
O-11	6236(2)	0	2846(3)	6.02(6)
C-15	7537(3)	-1117(6)	1734(5)	7.35(9)
H-1A	1061(2)	469(5)	462(4)	4.8(7)
H-1B	1002(2)	368(6)	583(4)	5.0(7)
H-2	798(1)	459(4)	430(3)	3.1(5)
H-3	815(2)	697(4)	598(3)	2.6(4)
H-12A	990(3)	726(9)	1081(6)	9.1(13)
H-12B	1051(3)	712(7)	892(6)	7.3(11)
H-12C	1036(2)	841(7)	1020(5)	6.6(10)
H-4	730(2)	602(4)	819(4)	3.5(5)
H-13A	567(4)	669(9)	374(8)	11.1(16)
H-13B	509(3)	566(9)	461(6)	8.6(12)
H-13C	492(3)	745(8)	417(6)	8.1(12)
H-5	791(1)	364(4)	913(3)	2.9(5)
H-14A	546(2)	200(7)	1027(5)	6.8(10)
H-14B	513(4)	378(12)	951(8)	12.8(19)
H-14C	538(3)	319(8)	1167(6)	7.7(11)
H-6	813(2)	137(5)	763(4)	4.7(7)
H-7A	673(2)	124(4)	581(3)	2.2(4)
H-7B	684(2)	265(6)	466(5)	6.3(9)
H-15A*	815	-78	187	4.0
H-15B	737(5)	-107(14)	62(9)	14.8(22)
H-15C*	750	-225	203	4.0

* The H-C distance for these atoms was fixed at 0.95Å.

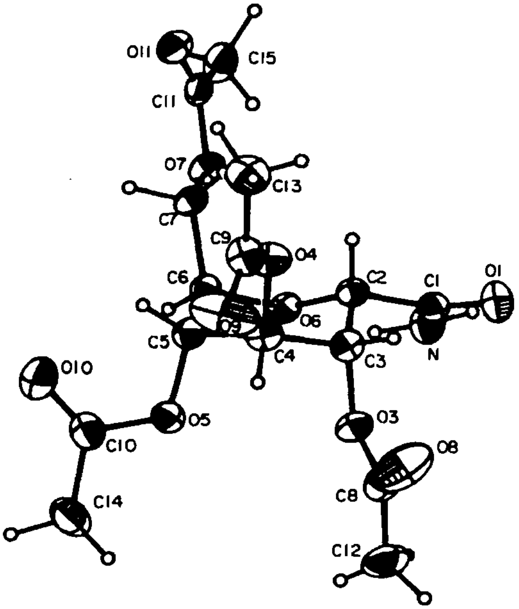

Figure 1a: An ORTEP drawing of compound 1 showing atom numbering. The nonhydrogen atoms are represented by 30% probability ellipsoids while the hydrogen atoms are drawn as spheres of arbitrary size.

C-7 atoms, the other below the ring involving the O-3 and O-5 atoms. Due to the 1,3-diaxial interactions, the axial C-3-O-3 and C-5-O-5 bonds are splayed by 19.4° while the C-4-O-4 and C-6-C-7 bonds are splayed by 16.3° The distance between the O-3 and O-5 atoms is 3.013(3)Å and between O-4 and C-7 is 3.128(3)Å. In compound 2 there is only one pair of 1,3-diaxial interactions involving the O-4 and C-7 atoms. The C-4-O-4 and C-6-C-7 bonds display a splaying angle of 19.9° and an O-4-C-7 distance of 3.084(3)Å. These nonbonded distances involving the axial substituents are within the expected range for van der Waals contacts.

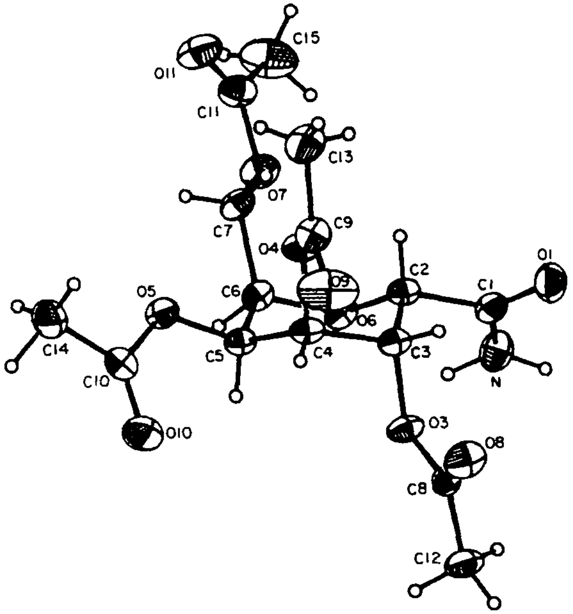

Figure 1b: An ORTEP drawing of compound 2 showing atom numbering. The nonhydrogen atoms are represented by 30% probability ellipsoids while the hydrogen atoms are drawn as spheres of arbitrary size.

The presence of the axial-axial interactions on both sides of the ring in compound 1 results in a significant flattening of the ring (around the C-5 atom) from the ideal chair conformation. The torsion angles most affected are C-3-C-4-C-5-C-6 and C-4-C-5-C-6-O-6 which are reduced by approximately 20° from the ideal value of 60° in compound 1, and reduced by 12° from the ideal value in compound 2.

Endocyclic Torsion Angle	1	2
C-2-C-3-C-4-C-5	44.1(3)°	48.7(3)°
C-3-C-4-C-5-C-6	-37.6(3)	-46.3(3)

Table 2: Bond lengths(Å) and angles(°) for compounds 1 and 2. Estimated standard deviations are in parentheses.

Bond	1	2	Angle	1	2
C-1-O-1	1.219(3)	1.225(3)	N-C-1-O-1	123.8(3)	124.4(3)
C-1-N	1.323(3)	1.323(4)	N-C-1-C-2	116.7(3)	117.6(3)
C-1-C-2	1.524(3)	1.518(4)	O-1-C-1-C-2	119.5(3)	118.0(3)
C-2-C-3	1.516(2)	1.526(3)	C-1-C-2-C-3	110.2(2)	108.4(2)
C-2-O-6	1.422(2)	1.426(3)	C-1-C-2-O-6	109.4(2)	110.6(2)
C-3-O-3	1.438(3)	1.442(2)	O-6-C-2-C-3	110.5(2)	110.2(2)
C-3-C-4	1.528(3)	1.528(3)	C-2-C-3-C-4	110.5(2)	110.4(2)
C-4-O-4	1.434(3)	1.440(3)	C-2-C-3-O-3	106.0(2)	106.0(2)
C-4-C-5	1.529(3)	1.525(3)	O-3-C-3-C-4	109.3(2)	109.2(2)
C-5-O-5	1.445(3)	1.438(2)	C-3-C-4-C-5	114.6(2)	111.0(2)
C-5-C-6	1.539(3)	1.518(3)	C-3-C-4-O-4	105.8(2)	106.7(2)
C-6-O-6	1.428(2)	1.424(3)	O-4-C-4-C-5	107.4(2)	108.2(2)
C-6-C-7	1.516(3)	1.516(3)	C-4-C-5-C-6	114.1(2)	114.4(2)
C-7-O-7	1.447(2)	1.439(3)	C-4-C-5-O-5	106.3(2)	109.5(2)
C-8-O-3	1.344(3)	1.351(3)	O-5-C-5-C-6	109.5(2)	108.6(2)
C-8-O-8	1.196(5)	1.192(3)	C-5-C-6-C-7	111.7(2)	114.0(2)
C-8-C-12	1.488(5)	1.493(4)	C-5-C-6-O-6	111.8(2)	109.1(2)
C-9-O-4	1.339(4)	1.350(3)	C-7-C-6-O-6	113.0(2)	113.9(2)
C-9-O-9	1.186(4)	1.196(4)	C-3-O-3-C-8	117.5(2)	117.6(2)
C-9-C-13	1.478(4)	1.502(4)	C-4-O-4-C-9	117.6(2)	117.2(2)
C-10-O-5	1.352(3)	1.350(3)	C-5-O-5-C-10	114.9(2)	117.4(2)
C-10-O-10	1.181(5)	1.190(4)	C-6-O-6-C-2	114.7(2)	114.6(2)
C-10-C-14	1.492(5)	1.498(4)	C-7-O-7-C-11	116.6(2)	114.9(2)
C-11-O-7	1.345(2)	1.340(3)	O-3-C-8-C-12	110.6(3)	110.9(2)
C-11-O-11	1.194(3)	1.198(4)	O-3-C-8-O-8	122.7(3)	122.8(3)
C-11-C-15	1.495(3)	1.497(5)	O-8-C-8-C-12	126.7(4)	126.2(3)
			O-4-C-9-C-13	112.7(3)	109.8(3)
			O-4-C-9-O-9	121.4(3)	122.9(3)
			O-9-C-9-C-13	125.9(3)	127.3(3)
			O-5-C-10-C-14	111.5(3)	110.5(3)
			O-5-C-10-O-10	122.4(3)	123.3(3)
			O-10-C-10-C-14	126.1(4)	126.2(4)
			O-7-C-11-C-15	111.3(2)	112.0(3)
			O-7-C-11-O-11	123.7(2)	122.6(3)
			O-11-C-11-C-15	124.9(2)	125.4(4)

C-4-C-5-C-6-O-6	41.4(3)	49.3(3)
C-5-C-6-O-6-C-2	-56.0(2)	-58.6(3)
C-6-O-6-C-2-C-3	64.3(3)	63.9(3)
O-6-C-2-C-3-C-4	-55.9(2)	-56.7(3)

A more quantitative measure of the ring flattening is given by the Cremer-Pople ring puckering parameters:[5]

Puckering parameters	Q	θ	ϕ
Compound 1:	0.615(4)A	164.8(3)$^{\circ}$	222(1)$^{\circ}$
Compound 2:	0.539(4)A	172.1(3)$^{\circ}$	218(2)$^{\circ}$

The presence of two diaxial interactions in compound 1 distorts the ring by 15° on θ from the ideal $^{2}C_{5}$ chair conformation (θ=180°) while by only 8° for compound 2 with one diaxial interaction. Concomitant with the ring flattening there is also a significant widening of the endocyclic bond angles at C-4 and C-6. In compound 1 these angles are 114.6(2)$^{\circ}$ and 111.8(2)$^{\circ}$, respectively, while they are decreased to 111.0(2)$^{\circ}$ and 109.1(2)$^{\circ}$ in compound 2. In contrast, the exocyclic C-5-C-6-C-7 bond angle of 111.7(2)$^{\circ}$ for compound 1 is less than the angle of 114.0(2)$^{\circ}$ found for compound 2. The exocyclic C-5-C-6-C-7-O-7 torsion angle is found in the *trans* conformation: -179.5(3)$^{\circ}$ for 1 and 178.4(3)$^{\circ}$ for 2. The *gauche*$^{+}$ conformation, often observed for the $^{4}C_{1}$ pyranoside structures,[6] is prohibited for the title compounds due to severe steric conflict between the acetoxy groups on C-7 and C-4.

MOLECULAR PACKING AND HYDROGEN BONDING

The crystal packing diagrams are shown in Fig. 2. In compound 1, both protons on the carbamoyl nitrogen atom engage in hydrogen bonding; H-1A is hydrogen bonded to O-11 of a neighboring molecule while the other proton is

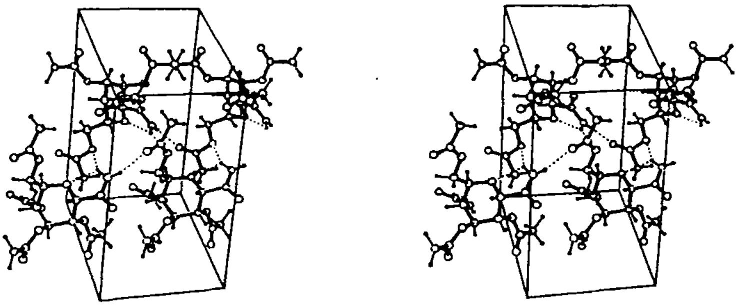

Figure 2a: A stereographic view of the packing for compound 1 with hydrogen bonds indicated by dotted lines.

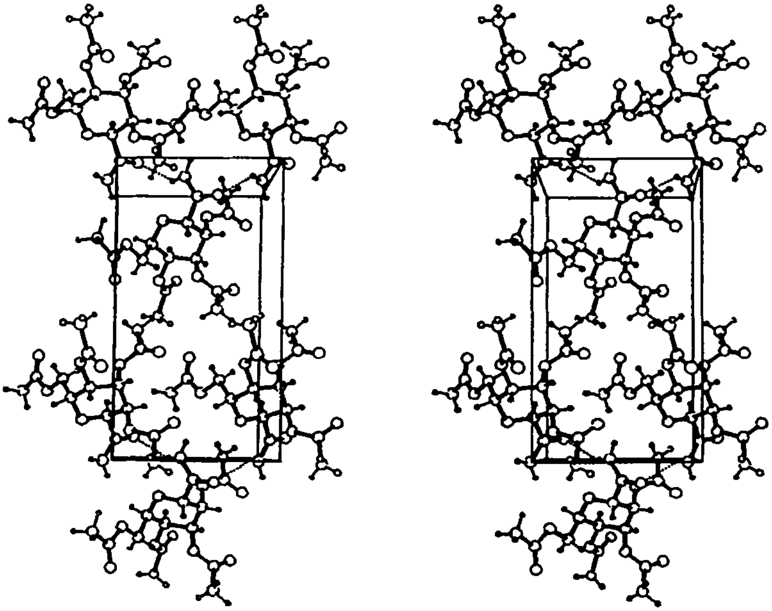

Figure 2b: A stereographic view of the packing for compound 2 with hydrogen bonds indicated by dotted lines.

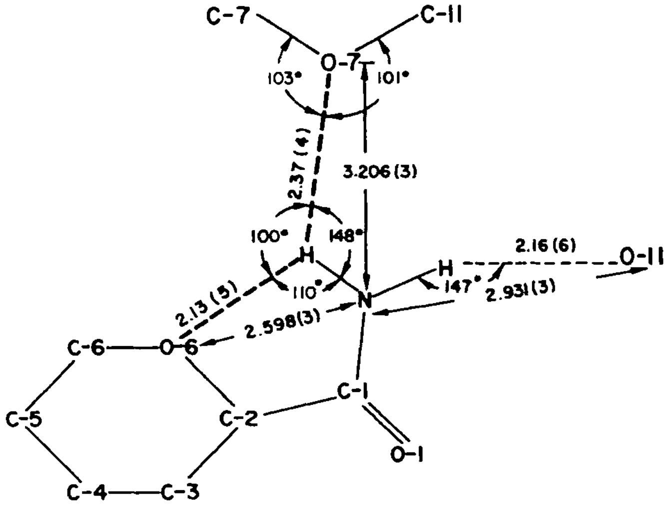

Figure 3a: Hydrogen bond distances and angles for the carbamoyl group in compound 1. Notice the bifurcated hydrogen bond.

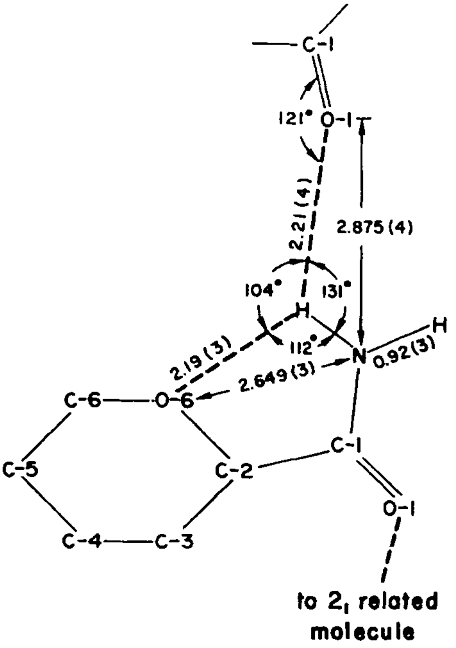

Figure 3b: Hydrogen bond distances and angles for the carbamoyl group in compound 2. Notice that one of the hydrogen atoms on the carbamoyl group is not involved in hydrogen bonding and that the other is involved in a stronger bifurcated hydrogen bond than in compound 1.

involved in a bifurcated hydrogen bond. The bifurcated hydrogen bond involves an intramolecular hydrogen bond to the ring oxygen atom O-6 and a weak intermolecular hydrogen bond to the ester O-7 atom of a symmetry related molecule (Fig. 3a). In compound 2, H-1A is not engaged in hydrogen bonding but H-1B is involved in a stronger bifurcated hydrogen bond involving an intramolecular interaction with the ring O-6 atom as in 1 and an intermolecular interaction with the O-1 atom of a symmetry related molecule. The geometry about the bifurcated hydrogen bonds agrees well with Jeffreys' conditions for a three-center hydrogen bond.[7,8] The intramolecular hydrogen bond holds the carbamoyl moiety nearly coplanar with O-6. The O-6-C-2-C-1-N torsion angle is 5.4(3)° for compound 1 and -11.4(2)° for compound 2.

Figures 1a and 1b show several atoms having large thermal vibrations in both molecules, in particular atoms O-8 and O-9 in 1 and O-9 and C-15 in 2. The weak van der Waals contacts around these atoms results in the increased freedom of movement of these atoms.

CONFORMATIONAL ENERGY CALCULATIONS

Energy calculations employing semi-empirical potential functions[9,10] were performed in order to determine the allowed conformations about the glycosyl C-2-C-1 bond for compound 1 in both the $^2C_5$ and $^5C_2$ conformations. The total potential energy has been estimated taking into account van der Waals interactions (V_{nb}), electrostatic interactions (V_{es}), and torsional potential for rotation about single bonds (V_t): $V_{tot} = V_{nb} + V_{es} + V_t$.

The nonbonded van der Waals interactions are estimated using the Lennard-Jones potential function: $V_{nb}(r) = -A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12}$ where the parameters A_{ij} are evaluated in the usual manner from the knowledge of the atomic polarizabilities and effective number of electrons using the Slater-Kirwood equation[11] and the B_{ij} are chosen such that the Lennard-Jones potential function displays a minimum when $r_{ij} = r_i^o + r_j^o + 0.2Å$ where r_i^o and r_j^o are the van der Waals radii of the interacting pair of atoms.[12] The electrostatic interactions are estimated in the monopole approximation using the expression $V_{es} = 332e_ie_j/\epsilon r_{ij}$ where e_i and e_j are the magnitudes of the partial electronic charges[13,14] and ϵ is the effective dielectric constant which was set to 4.[12] A 3-fold potential function has been assumed for the torsional energy about the C-1-C-2 bond. The function $V_t = V_0/2(1+3\cos\emptyset)$ was used assuming a rotational barrier height (V_0) of 0.4 kcal/mol.[9] Energy contributions due to hydrogen bonding or the anomeric effect were not included.

The potential energy of compound <u>1</u> was computed by varying the torsion angle Ø (O-6-C-2-C-1-N) over 360° at intervals of 10°. The variation of the energy with the glycosyl torsion angle is shown in Fig. 4. It can be seen that the regions of low energy for the $^2C_5$ ring conformation are between -60° and 220° with the local minimum near 310°, and between 20° and 180° for the $^5C_2$ ring conformation with a local minimum near 70°. Outside these limits the energy rises to very high values. It can be seen that the allowed conformational space (range of 280°) for the equatorial orientation of the carbamoyl group is significantly greater than that allowed (range of 160°) for the axial carbamoyl group. The conformations observed in the crystal structures are indicated by asterisks in Fig. 4. Inclusion of the hydrogen bonding energy would be expected to lower the potential minimum and reduce the calculated energy in the vicinity of the observed conformation due to the presence of the intramolecular hydrogen bond.

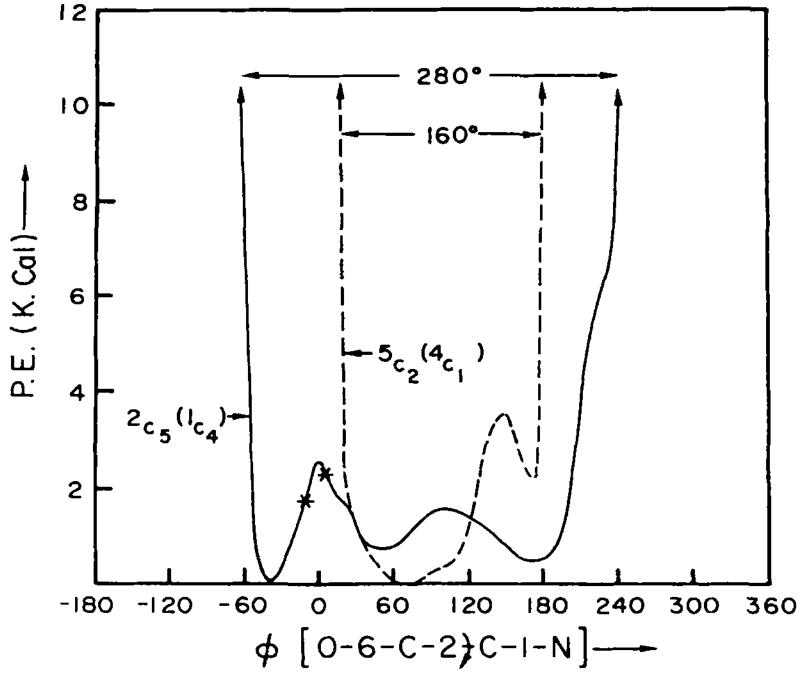

Fig. 4: The variation of potential energy with ∅ for $^2C_5$ (solid line) and $^5C_2$ (dashed line) ring conformations for compound 1. A similar energy profile would be expected for compound 2.

CONCLUSIONS

Chmielewski, et al. observed in NMR studies of these structures that the polarity of the solvent has a profound effect on the $^2C_5$ to $^5C_2$ conformational equilibrium:[1]

	Percent $^2C_5$	
	DMSO (polar)	$CHCl_3$ (nonpolar)
Compound 1	6%	56%
Compound 2	8%	72%

In a polar solvent, the predominant conformation is $^5C_2$ while in a nonpolar solvent, the $^2C_5$ conformation is preferred. To explain these dramatic shifts, Chmielewski, et al. invoked the "reverse anomeric effect" originally introduced by Lemieux and Morgan to explain the strong preference of the $^1C_4$ conformation in the pyridinium α-glycopyranosides.[15] Lemiuex and Morgan explained that the instability of the $^4C_1$ conformation is due to unfavorable electrostatic interactions between the positively charged 4-methyl pyridinium group (C-1-N$^+$ bond) in the axial position and the ring C-5-O-5 bond. In addition to the electrostatic interaction, nonbonded interactions were also envisaged to play a significant role in promoting the "reverse anomeric effect." Similarly, Chmielewski, et al. reasoned that in nonpolar solvents the partial positive charge at the carbamoyl group of the title compounds produces unfavorable interactions in the $^5C_2$ conformation thus shifting the equilibrium towards $^2C_5$.

The x-ray structures of the title compounds are found in the $^2C_5$ conformation despite the repulsion between the 1,3-diaxial acetoxy groups. The flattening of the pyranosyl ring and the splaying of the substituents are able to alleviate the 1,3-diaxial nonbonded interactions. Apparently the space demands of the axial acetoxy groups are less than that of the axial carbamoyl group. The intramolecular hydrogen bond observed in the crystal may play a role in stabilizing the $^2C_5$ conformation. In polar solvents, the predominance of the $^5C_2$ conformation may be due to the solvent destabilization of the intramolecular hydrogen bond. Our potential energy calculations reveal that nonbonded contacts greatly restrict the freedom of rotation of the carbamoyl moiety in the axial orientation ($^5C_2$) as compared to the equatorial orientation ($^2C_5$). This may also contribute to the preference of the $^2C_5$ conformation.

Structural studies of the heptonamide series have demonstrated that their saccharide rings display unusual conformational flexibility which is ordinarily not encountered in saccharides with an oxygen substituent at the anomeric center. It appears that an α-D-pyranosyl system suitably substituted (e.g. carbamoyl group) at the anomeric carbon atom can display both the $^4C_1$ and $^1C_4$ conformations where the equilibrium can be influenced by the solvent polarity. A similar equilibrium may be envisioned to play a profound role in biological systems where microenvironmental polarity changes could cause significant conformational shifts in certain saccharidic moieties of membranes or glycoproteins. It is conceivable that evolutionary discrimination against the $^1C_4$ conformation may have occurred by selecting substituents at the anomeric center which are incapable of inducing the "reverse anomeric effect."

EXPERIMENTAL

Crystals of compound 1 were obtained by slow evaporation of a solution containing the substance in an ethanol-acetone mixture. A crystal with dimensions 0.4 x 0.2 x 0.2 mm, was chosen for data collection on an Enraf-Nonius CAD4 diffractometer using Ni filtered Cu-Kα radiation ($\lambda = 1.5418$Å). Out of 2021 reflections collected up to a 2θ limit of 154°, 1911 intensities with I/σ(I) greater than 1.5 were used for the structure analysis. Three reflections were monitored during data collection; since no significant decay was observed, no correction was applied. An empirical Ø curve as well as Lorentz and polarization corrections were applied to the intensities.

Compound 2 was crystallized by evaporation from a 100% acetone solution. Intensity data were collected using a crystal with dimensions 0.6 x 0.2 x 0.1 mm. Of a total of 2167 reflections, 2122 reflections with I/σ(I) greater than 1.5 were used for the structure analysis.

Similiar corrections were applied to the intensity data as described above.

Structure Determination and Refinement: Both structures were solved by application of the multi-solution tangent formula technique using the computer program MULTAN.[16] Of the 32 phase sets generated for compound 1, an E map computed with the phase set having the highest absolute figure of merit and the lowest residual revealed the positions of all the nonhydrogen atoms. Three cycles of full-matrix least squares refinement resulted in an R-index $[\Sigma ||Fo|-|Fc||/\Sigma |Fo|]$ of 0.10. At this stage a difference Fourier synthesis revealed the positions of all the hydrogen atoms. Four additional cycles of least-squares refinement using anisotropic thermal parameters for the nonhydrogen atoms and isotropic thermal parameters for the hydrogen atoms yielded a final R-index of 0.040. A modified counting statistics weighting scheme with the weight of each reflection proportional to $1/[\sigma^{-2}(F) + (0.01|Fo|)^2]$ was used.[17] The shift over error ratio was less than 0.01 for all parameters in the final cycle of refinement.

For compound 2, 64 solutions were generated by MULTAN and submitted to tangent refinement. The correct solution which had the lowest NQEST figure of merit[18], revealed 22 of 26 non-hydrogen atoms in the structure. The remaining non-hydrogen atoms were found by subsequent structure factor calculations and difference Fourier syntheses. Least squares refinement of all nonhydrogen atoms using anisotropic thermal parameters yielded an R-index of 0.12. All 21 hydrogen atoms were located in a subsequent difference Fourier synthesis and were submitted to least squares refinement using isotropic thermal parameters. Two of the hydrogen atoms bonded to C-15 failed to converge and were fixed from geometric considerations (see Table 1). A final refinement of all the atoms using anisotropic thermal parameters for the nonhydrogen atoms and isotropic thermal parameters for the hydrogen atoms yielded a final R-index of 0.046 using weights proportional to $1/[\sigma^2(F) + (0.03|Fo|)^2]$. The maximum values of the shift over error ratios were 0.09 and 0.33 for the nonhydrogen and hydrogen atoms, respectively.

Scattering factors for the oxygen, nitrogen and carbon atoms were taken from Cromer and Waber[19] and those for the hydrogen atoms were from Stewart, Davidson and Simpson.[20] Supplementary material can be obtained as noted.[21]

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REFERENCES AND FOOTNOTES

1. M. Chmielewski, J. N. BeMiller, and D. P. Cerretti, J. Org. Chem., 46, 3903 (1981).
2. C. K. Johnson, ORTEP-II, Report ORNL-5138, Oak Ridge National Laboratories, Tennessee (1976).
3. G. A. Jeffrey in: "Anomeric Effect, Origin and Consequences," (Eds., W. A. Szarek and D. Horton), Am. Chem. Soc. Symp. Ser., Washington, D. C., 87, 50 (1979).
4. D. C. Fries, S. T. Rao, and M. Sundaralingam, Acta Cryst., B27, 994 (1971).
5. D. Cremer and J. A. Pople, J. Am. Chem. Soc., 97, 1354 (1975).
6. M. Sundaralingam, Biopolymers, 6, 189 (1968).
7. C. Ceccarelli, G. A. Jeffrey, and R. Taylor, J. Molecular Struc., 70, 255 (1981).
8. G. A. Jeffrey and H. Maluszynska, Int. J. Biol. Macromol., 4, 173 (1982).

9. G. N. Ramachandran and V. Sasisekharan, Adv. Prot. Chem., 23, 283 (1968).

10. N. Yathindra and M. Sundaralingam, Biochim. Biophys. Acta, 308, 17 (1973).

11. R. A. Scott and H. A. Scheraga, J. Chem. Phys., 45, 2091 (1966).

12. D. A. Brant, W. G. Miller, and P. J. Flory, J. Mol. Biol., 23, 47 (1967).

13. D. Poland and H. A. Scheraga, Biochemistry, 6, 3791 (1967).

14. V. Renugopalakrishnan, A. V. Lakshminaryanan, and V. Sasisekharan, Biopolymers, 10, 1159 (1971).

15. R. U. Lemieux and A. R. Morgan, Can. J. Chem., 43, 2205 (1965).

16. P. Main, M. M. Woolfson, L. Lessinger, G. Germain and J. P. DeClercq, MULTAN. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Univs. of York, England and Louvain, Belgium (1974).

17. G. H. Stout and L. H. Jensen, X-ray Structure Determination. A Practical Guide. New York: McMillan (1968).

18. G. DeTitta, J. W. Edwards, D. A. Langs, and H. Hauptman, Acta Cryst., A31, 472 (1975).

19. D. T. Cromer and J. T. Waber, Acta Cryst., 18, 104 (1965).

20. R. F. Stewart, E. R. Davidson, and W. T. Simpson, J. Chem. Phys., 42, 3175 (1965).

21. Anisotropic Thermal Parameters for 1 and 2, and Structure Factor Tables for 1 and 2 can be obtained from the Journal Editorial Department, Marcel Dekker, Inc., 270 Madison Avenue, New York, N. Y. 10016.