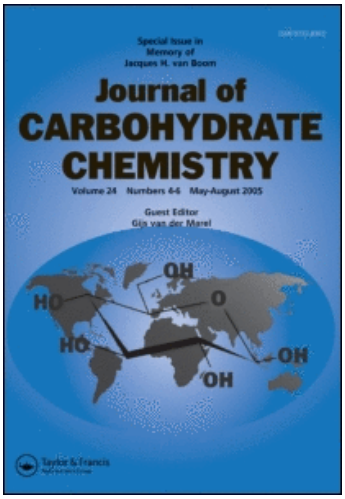

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The X-Ray Structure Of 3,4,5,7-Tetra-O-Acetyl 2,6-Anhydro-D-Glycero-D-Talo-Heptonamide

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THE X-RAY STRUCTURE OF 3,4,5,7-TETRA-O-ACETYL 2,6-ANHYDRO-D-GLYCERO-D-TALO-HEPTONAMIDE

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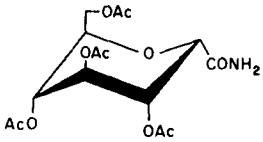
ABSTRACT

The title compound ($C_{15}H_{21}NO_{10}$), M_r=375.34, crystallized in the orthorhombic space group $P2_12_12_1$ with a=8.989(1), b=9.350(2), c=22.839(2)Å, V=1919.4(7)Å^3, Z=4 and Dc=1.299 Mgm^{-3}. The structure was solved by direct methods and refined to an R-index of 0.043. The compound is in the α-D-configuration and displays the $^5C_2$ conformation. The carbamoyl group is axially oriented and the remaining substituents are 3a, 4e, 5e and 6e. The absence of the anomeric effect in this C-glycoside results in equal and normal endocyclic C-O bond distances (1.425(3)Å). The carbamoyl nitrogen is involved in a bifurcated hydrogen bond, intramolecularly with the pyranosyl ring oxygen atom O-6, and intermolecularly with the carbonyl oxygen atom O-9.

 0732-8303/83/0202-0115$3.50/0

INTRODUCTION

NMR studies on a series of heptonamides have shown that several of these C-glycosides display a conformational equilibrium between the $^5C_2$ and $^2C_5$ conformations which is dependent upon the solvent polarity.[1] In two cases where the $^2C_5$ conformation predominates in solution, 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, the x-ray structures were found in the $^2C_5$ conformation.[2] We here describe the x-ray structure of a third heptonamide 3,4,5,7-tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo-heptonamide, 3, displaying a conformational equilibrium $^5C_2$:$^2C_5$ (9:1) in nonpolar solvent, which is found in the predominant $^5C_2$ chair conformation. Semi-empirical energy calculations were carried out to determine the contribution of nonbonded interactions on the conformational choice of the pyranosyl ring.



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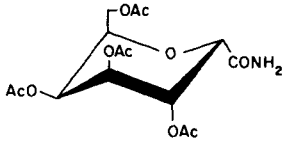

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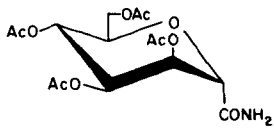

3

STRUCTURE DETERMINATION AND REFINEMENT

Crystals of the title compound ($C_{15}H_{21}NO_{10}$) were obtained by slow evaporation from an ethanol-acetone solution. A crystal, dimensions 0.2 mm x 0.2 mm x 0.1 mm, was used for data collection on an Enraf-Nonius CAD4 diffractometer. Of a total of 2272 independent reflections collected up to a 2θ limit of 154°, using

Ni-filtered Cu-K_α radiation (λ=1.5418Å), 1796 reflections with $I/\sigma(I)$ greater than 1.5 were used for structural analysis. An empirical ϕ curve correction for absorption and Lorentz and polarization corrections were applied to the intensities. No decay correction was necessary.

The structure was solved using the computer program MULTAN.[3] Of the 64 phase sets generated, the E-map computed with the phase set having the best combined figure of merit revealed the structure. Block diagonal least-squares refinement with isotropic temperature factors and subsequently anisotropic temperature factors resulted in an R-index of 0.077 ($R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$). Full-matrix least-squares refinement including the hydrogen atoms obtained from Fourier difference syntheses yielded a final R-index of 0.043. The weighting scheme used was $1/[\sigma^2(F) + (0.03)|F_o|^2]$.[4] The maximum shift over error for the nonhydrogen atoms was 0.06, with the exception of the methyl carbons which was 0.22, and 0.33 for the hydrogen atoms.

Scattering factors for the oxygen, nitrogen and carbon atoms were taken from Cromer and Waber[5] and those for the hydrogen atoms were from Stewart, Davidson and Simpson.[6]

RESULTS AND DISCUSSION

The atomic positional and thermal parameters for the D-talo-heptonamide are presented in Table 1. Anisotropic thermal parameters and a list of observed and calculated structure factors are given as supplementary material.[7] B_{eq} $[=\frac{4}{3}\Sigma_i\Sigma_j B_{ij}(\underline{a}_i \cdot \underline{a}_j)]$ for nonhydrogen and isotropic thermal parameters (B_{iso}) for the hydrogen atoms are given in Table 1. An ORTEP[8] drawing displays the atom numbering

TABLE 1

Atomic Parameters for 3,4,5,7-Tetra-O-Acetyl-2,6-Anhydro-D-Glycero-D-Talo Heptonamide.

Fractional positional parameters are multiplied by 10^4 for nonhydrogen atoms and 10^3 for hydrogen atoms.

	x	y	z	B_{eq} or B(Å^2)
C-1	8840(4)	8123(3)	7354(1)	5.15(9)
O-1	9001(4)	7047(3)	7652(1)	7.46(9)
N	9815(4)	9197(4)	7339(1)	6.29(9)
C-2	7427(4)	8334(3)	6987(1)	4.48(9)
C-3	6682(4)	6930(4)	6859(1)	4.23(9)
O-3	5170(2)	7259(3)	6682(1)	4.89(9)
C-8	4090(4)	6393(5)	6884(2)	6.54(12)
O-8	4361(4)	5409(4)	7196(1)	9.75(10)
C-12	2590(4)	6890(8)	6699(2)	8.91(17)
C-4	7450(3)	6138(3)	6366(1)	3.89(8)
O-4	6575(2)	4933(2)	6177(1)	4.53(3)
C-9	6704(4)	3725(4)	6486(2)	4.23(10)
O-9	7555(3)	3581(3)	6882(1)	7.45(9)
C-13	5661(6)	2587(5)	6281(2)	7.22(11)
C-5	7691(3)	7096(3)	5840(1)	3.68(5)
O-5	8539(2)	6306(2)	5424(1)	4.46(3)
C-10	8063(4)	6310(4)	4863(1)	4.89(9)
O-10	7056(4)	7069(4)	4702(1)	7.83(11)
C-14	8976(6)	5349(4)	4489(2)	6.84(12)
C-6	8546(3)	8429(3)	6038(1)	4.12(8)
O-6	7694(3)	9156(2)	6472(1)	4.65(4)
C-7	8788(4)	9486(4)	5550(1)	4.94(9)
O-7	9774(3)	10566(3)	5777(1)	6.06(8)
C-11	9661(5)	11865(4)	5567(2)	4.75(11)

(continued)

TABLE 1, continued

	x	y	z	B_{eq} or B($Å^2$)
O-11	8764(5)	12159(3)	5201(2)	11.54(12)
C-15	10710(6)	12870(4)	5840(2)	7.17(12)
H-1A	939(4)	1005(4)	715(1)	6.3(9)
H-1B	1049(5)	914(5)	754(2)	8.3(12)
H-2	672(3)	889(3)	723(1)	3.5(6)
H-3	668(3)	628(3)	723(1)	3.4(6)
H-12A	257(4)	670(5)	630(2)	7.3(11)
H-12B*	251(0)	789(0)	676(0)	4.0(0)
H-12C	216(7)	636(7)	695(2)	14.7(22)
H-4	833(3)	579(3)	652(1)	3.1(6)
H-13A*	580(0)	175(0)	651(0)	4.0(0)
H-13B	483(6)	296(5)	637(2)	8.1(12)
H-13C	570(8)	212(7)	583(2)	14.3(20)
H-5	664(3)	728(3)	569(1)	3.6(6)
H-14A	933(7)	470(6)	466(2)	11.4(16)
H-14B*	834(0)	481(0)	424(0)	4.0(0)
H-14C	953(6)	584(5)	419(2)	9.6(13)
H-6	940(3)	814(3)	617(1)	4.0(7)
H-7A	784(4)	988(4)	544(1)	4.6(7)
H-7B	917(4)	909(4)	519(1)	4.3(7)
H-15A	1174(7)	1301(5)	566(2)	10.7(14)
H-15B	1095(6)	1258(5)	615(2)	9.5(13)
H-15C	1038(8)	1049(7)	572(2)	14.6(20)

*These hydrogen atom coordinates were kept fixed during the final cycles of the refinement because they failed to converge.

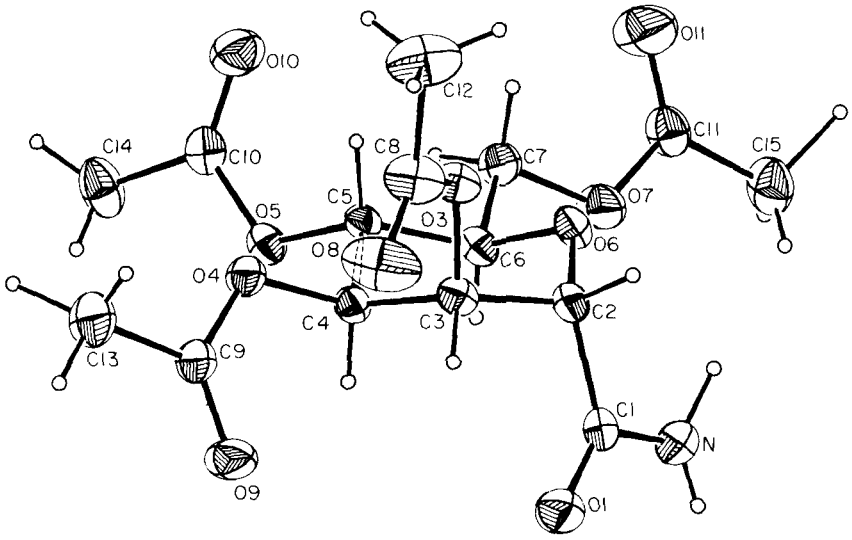

FIG. 1 An ORTEP drawing showing atom numbering. The nonhydrogen atoms are represented by 20% probability ellipsoids while the hydrogen atoms are drawn as spheres of arbitrary size.

and overall molecular conformation in Figure 1. The acetyl atoms, O-8, C-12 and O-11 in particular, exhibit large thermal vibrations. The increased freedom of movement of these atoms is a result of the weak van der Waals contacts and is prominent in two of the acetyl groups not involved in hydrogen bonding.

The bond lengths and angles involving the nonhydrogen atoms (Table 2) are very similar to those of the previously reported heptonamides.[2] The average C-C and C-O bond lengths for the pyranosyl ring are 1.516(13)Å and 1.439(11)Å, respectively, as compared to 1.525(7)Å and 1.435(5)Å for compounds 1 and 2.[2] The bond angle at O-6 is 114.0(3)° and identical to the values for compounds 1 and 2.[2] Significant differences between the present heptonamide and the previous

TABLE 2

Bond Lengths (Å) and Angles (°) for 3,4,5,7-Tetra-O-Acetyl-2,6-Anhydro-D-Glycero-D-Talo-Heptonamide.

Estimated Standard Deviations are in Parentheses.

Bond

C-1-O-1	1.223(4)	C-5-O-5	1.425(3)	C-9-O-9	1.192(5)
C-1-N	1.333(5)	C-5-C-6	1.532(4)	C-9-C-13	1.493(6)
C-1-C-2	1.534(5)	C-6-O-6	1.425(3)	C-10-O-5	1.351(3)
C-2-C-3	1.502(5)	C-6-C-7	1.505(4)	C-10-O-10	1.208(5)
C-2-O-6	1.425(3)	C-7-O-7	1.440(4)	C-10-C-14	1.487(6)
C-3-O-3	1.451(4)	C-8-O-3	1.346(5)	C-11-O-7	1.310(5)
C-3-C-4	1.514(4)	C-8-O-8	1.189(6)	C-11-O-11	1.193(6)
C-4-O-4	1.440(3)	C-8-C-12	1.487(6)	C-11-C-15	1.470(6)
C-4-C-5	1.514(4)	C-9-O-4	1.337(5)		

Angle

N-C-1-O-1	123.8(4)	C-3-O-3-C-8	116.9(4)
N-C-1-C-2	115.7(3)	C-4-O-4-C-9	117.1(3)
O-1-C-1-C-2	120.5(3)	C-5-O-5-C-10	117.5(3)
C-1-C-2-C-3	111.3(3)	C-6-O-6-C-2	114.0(3)
C-1-C-2-O-6	112.4(3)	C-6-C-7-O-7	106.5(3)
O-6-C-2-C-3	112.7(3)	C-7-O-7-C-11	118.1(4)
C-2-C-3-C-4	111.6(3)	O-3-C-8-C-12	111.6(5)
C-2-C-3-O-3	106.7(4)	O-3-C-8-O-8	121.6(4)
O-3-C-3-C-4	108.9(3)	O-8-C-8-C-12	126.7(5)
C-3-C-4-C-5	111.5(3)	O-4-C-9-C-13	112.5(4)
C-3-C-4-O-4	110.9(3)	O-4-C-9-O-9	123.5(4)
O-4-C-4-C-5	107.5(3)	O-9-C-9-C-13	124.1(4)
C-4-C-5-C-6	108.6(3)	O-5-C-10-C-14	111.6(4)
C-4-C-5-O-5	107.4(3)	O-5-C-10-O-10	121.9(4)
O-5-C-5-C-6	110.5(3)	O-10-C-10-C-14	126.4(4)
C-5-C-6-C-7	112.8(3)	O-7-C-11-C-15	112.8(4)
C-5-C-6-O-6	108.9(3)	O-7-C-11-O-11	121.5(5)
C-7-C-6-O-6	106.3(3)	O-11-C-11-C-15	125.7(5)

heptonamides are found in the bond angle C-4-C-5-C-6, which is 108.6(3)° and is more than 5° smaller than those found in structures 1 (114.1(2)°) and 2 (114.4(2)°). These differences arise from the differences in the orientation of the acyl groups at positions 4 and 6, equatorial in 3 versus axial in 1 and 2 (see below).

It is of interest to examine the geometry around the "anomeric" center of the heptonamides which are C-glycosides and are not expected to exhibit the anomeric effect.[9] All three heptonamides, 1, 2, and 3, exhibit similar endocyclic C-O bond distances (av. 1.425(3)Å). The axial C-1-C-2 glycosidic bond length in 3 (1.534(5)Å) appears to be only slightly longer (2σ) than the equatorially oriented glycosidic bonds in 1 (1.524(3)Å) and 2 (1.518(4)Å).[2] On the other hand, the exocyclic bond angle, C-1-C-2-O-6, is 112.4(3)° in 3, and is 2° to 3° larger than the values found for the equatorial C-glycosides ($^2C_5$); 1 (109.4(2)°) and 2 (110.6(2)°).[2] This increase may be a result of greater steric interactions of the axial carbamoyl group. It is interesting that similar trends for this angle are observed for the anomeric O-glycosides; axial (av. 111.4°) versus equatorial (av. 107.1°).[10]

The exocyclic torsion angle O-6-C-2-C-1-N-1 is gauche$^+$ (32.5(4)°) while the O-6-C-2-C-1-O-1 torsion angle is nearly trans (-149.9(4)°). This conformation for the carbamoyl group is probably favored in the heptonamides because of the ability of the N-1 nitrogen atom to form an intramolecular hydrogen bond to the ring oxygen atom. Furthermore, a gauche conformation for the O-6-C-2-C-1-O-1 torsion angle would result in unfavorable dipole-dipole interactions (see also Fig. 4) between the O-1 and O-6 oxygen

atoms.

The pyranosyl exhibits some flattening around the C-3 atom due to the axial interactions on C-2 and C-3. The torsion angles C-2-C-3-C-4-C-5 and O-6-C-2-C-3-C-4 are -49.6(4)° and 48.4(4)°, respectively. The endocyclic torsion angles are given below.

C-2-C-3-C-4-C-5	-49.6(4)	C-5-C-6-O-6-C-2	61.6(3)
C-3-C-4-C-5-C-6	55.1(4)	C-6-O-6-C-2-C-3	-56.1(4)
C-4-C-5-C-6-O-6	-59.9(3)	O-6-C-2-C-3-C-4	48.4(4)

The ring puckering parameters[11] are: Q=0.544(4)Å, θ=171.4(4)° and φ=38(3)°. The ring is distorted by 8° on θ from the ideal $^{5}C_{2}$ chair conformation (θ=180°). The exocyclic torsion angle O-6-C-6-C-7-O-7 is found in the gauche^{+} conformation, 68.8(4)°, while the C-5-C-6-C-7-O-7 torsion angle is trans (172.0(4)°) as observed in the previous heptonamides, 1 (-179.5(3)°) and 2 (178.4(3)°).

MOLECULAR PACKING AND HYDROGEN BONDING

The crystal packing diagram is shown in Figure 2. The hydrogen bonding closely resembles that found for the D-ido-heptonamide

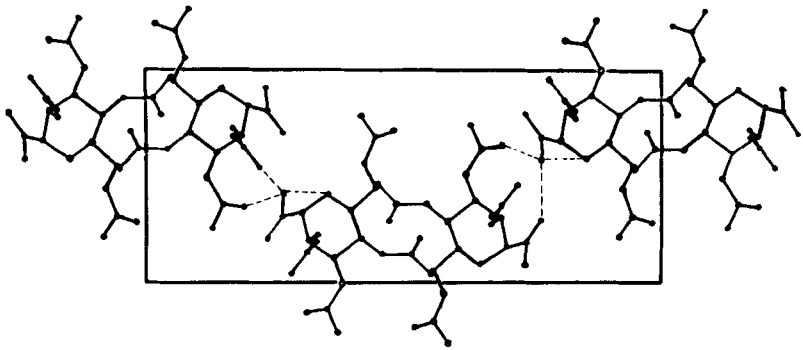

FIG. 2. A packing diagram of 3,4,5,7-tetra-O-acetyl-2, 6-anhydro-D-glycero-D-talo-heptonamide viewed down the a axis. The hydrogen atoms have been removed for clarity.

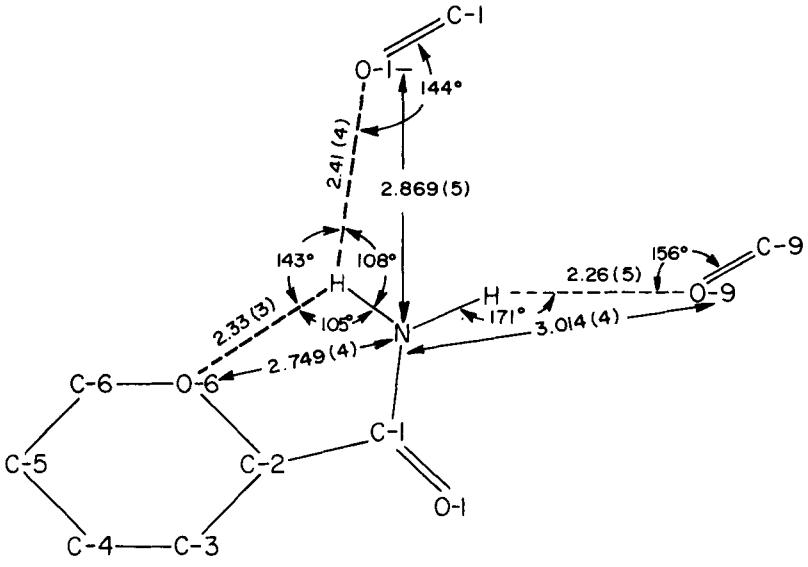

FIG. 3. Hydrogen bond distances and angles for the carbamoyl group. Notice the bifurcated hydrogen bond.

where both protons of the carbamoyl nitrogen atom are involved in hydrogen bonding.[2] Proton H-1A is hydrogen bonded to the carbonyl oxygen atom O-9 of a neighboring molecule, while proton H-1B is involved in a bifurcated hydrogen bond to the carbonyl oxygen atom O-1 of a neighboring molecule, and intramolecularly to the ring oxygen atom O-6 (Figure 3). The geometry around this bifurcated hydrogen bond is similar to that of the previously reported heptonamides,[2] however, the intramolecular hydrogen bond is less planar with respect to the ring oxygen atom with an O-6-C-2-C-1-N torsion angle of 32.5(4)°. Since an intramolecular hydrogen bond is also found in the axial glycoside, this hydrogen bond cannot be the basis for the choice of the pyranosyl ring conformation ($^5C_2/^2C_5$).

CONFORMATIONAL ENERGY CALCULATIONS

Energy calculations employing semi-empirical potential functions[12,13] were carried out to determine the accessible conformations about the adjacent C-1-C-2 and O-3-C-8 bonds for 3. The total potential energy (V_{tot}) is the sum of van der Waals interactions (V_{nb}), electrostatic interactions (V_{es}) and the torsional potential for rotation about single bonds (V_t): $V_{tot} = V_{nb} + V_{es} + V_t$. V_{nb} are approximated using the Lennard-Jones potential function: $V_{nb}(r) = -A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12}$. The parameters A_{ij} are evaluated from the atomic polarizabilities and effective number of electrons by use of the Slater-Kirwood equation[14] and B_{ij} are chosen such that the Lennard-Jones potential function displays a minimum when $r_{ij} = r_i^o + r_j^o + 0.2\text{Å}$ where r_i^o and r_j^o are the van der Waals radii of the interacting pair of atoms.[15] V_{es} are measured in the monopole approximation employing the expression $V_{es} = 332e_ie_j/r_{ij}$ where e_i and e_j are the magnitudes of the partial electronic charges[16,17] and is the effective dielectric constant which was set to 4.[15] $V_t = V_o/2(1+3\cos\phi)$, which assumes a three fold potential function about both the C-1-C-2 and O-3-C-8 bonds, was used assuming a rotational barrier of 0.4 kcal/mol for C-1-C-2 and 1.2 kcal/mol for O-3-C-8.[12]

Potential energy maps for the $^5C_2$ conformation, where the orientation of the carbamoyl and C-3 acetoxy groups are axial, and the $^2C_5$ conformation, where the carbamoyl and C-3 acetoxy groups are equatorial, were computed by varying the torsion angles ϕ_1 (N-C-1-C-2-O-6) and ϕ_2 (C-3-O-3-C-8-O-8) over 360° at intervals of 10°. Prior to calculating the energy map for the $^2C_5$ conformation the value of the C-3-O-3 torsion angle was fixed at the value

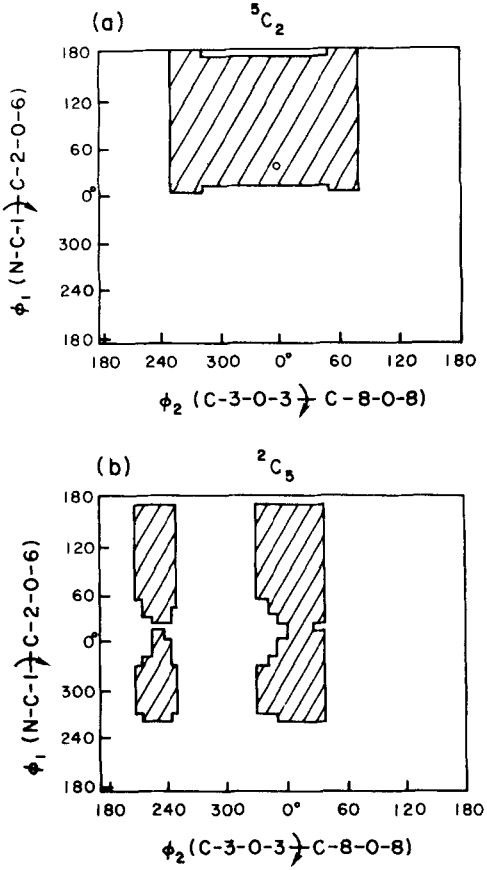

FIG. 4. The semi-empirical energy maps of 3,4,5,7-tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo-heptonamide in the (a) $^5C_2$ and (b) $^2C_5$ conformations. The conformation observed in the crystal structure is indicated by a circle.

where its minimum potential energy was observed. The shaded regions in figures 4a and 4b represent potential energies within 4 kcal/mol of the calculated minimum values. In the $^5C_2$ conformation (Fig. 4a) the rotational freedom around the C-1-C-2 bond, ϕ_1, is somewhat limited (170° range) compared to the $^2C_5$ conformation (270° range) (Fig. 4b). However, in the $^5C_2$ conformation the axial C-3 acetoxy

group exhibits a greater rotational freedom (190° ϕ_2 range) than the $^2C_5$ conformation (110° ϕ_2 range), which is also continuous, unlike that found in the $^2C_5$ conformation.

These semi-empirical energy calculations show that nonbonded interactions of the carbamoyl group are not the predominant factors which determine the pyranosyl ring conformation. However, the greater rotational freedom available to the axial C-3 acetoxy group may influence the conformational choice of the ring. In this structure and in the previously determined heptonamides the adopted ring conformation is such that the acetoxy groups on carbon atom C-3 are axial. It is not clear whether the axial orientation of this acetoxy group is dictated by steric, electronic and dipolar interactions of the carbamoyl moiety at the "anomeric" center.

CONCLUSIONS

In the crystalline state the conformation of the D-talo-heptonamide is $^5C_2$ which differs from that found for the D-ido-and L-gluco- heptonamides ($^2C_5$).[2] The endocyclic C-O bond distances are equal in all three heptonamides because of the lack of the anomeric effect.

ACKNOWLEDGEMENTS

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