Carbohydrate Research, 180 (1988) 129–135
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CONFORMATIONAL CALCULATIONS FOR THE α AND β ANOMER OF 2,3,4-TRI-*O*-ACETYL-D-ARABINOPYRANOSYL AZIDE

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(Received May 23rd, 1985; accepted for publication in revised form, July 7th, 1987)

ABSTRACT

The 2,3,4-tri-*O*-acetyl-α- and -β-D-arabinopyranosyl azide anomers were studied by the semiempirical quantum-chemical PCILO method. Rotational energy maps for the azide group and the three acetyl groups established the lowest energy minima for the two anomers. Two minima each were found for the azide group setting. The geometry around the anomeric carbon atom was optimized for each conformer. It was observed that the lowest minima found were in the range showing the exo-anomeric effect.

INTRODUCTION

There is considerable interest in the conformation of carbohydrates because of their biological importance. Several investigations have focused on the effect of substitution of polar groups on the geometry around the anomeric carbon atom in a pyranosyl ring. The anomeric effect, first postulated by Lemieux[1], manifests itself in the preference of a partially negatively charged substituent to lie *gauche* to C-5 of the pyranosyl ring, whereas a partially positively charged substituent prefers the *trans* conformation, a phenomenon called inverse anomeric effect. Paulsen, Györgydeák, and Friedman[2] proposed a sequence of groups having decreasing anomeric effect where the azide group falls between the OAc and the $NHCOCF_3$ group.

The exo-anomeric effect for a $^4C_1$(D) chair conformation points to the preference of the anomeric torsion angle (O-ring–C-1–O-1–X in aldopyranoses) to be between 60 and 70° when O-1 is axial, and between $-70°$ and $-80°$ when it is equatorial. Molecular orbital theory gives $-90°$ as ideal value[3]. For a $^1C_4$(D) chair conformation, torsion angles of the same magnitude but of opposite sign are expected. Systematic studies of the anomeric and exo-anomeric effects were carried out by Jeffrey and Taylor[3] with the Molecular Mechanics method and by Tvaroška and Kožar[4] with the semiempirical quantum-chemical method[5] PCILO. They investigated the axial and equatorial forms of 2-methoxyoxane.

In the study reported herein, the anomeric and exo-anomeric effects for a

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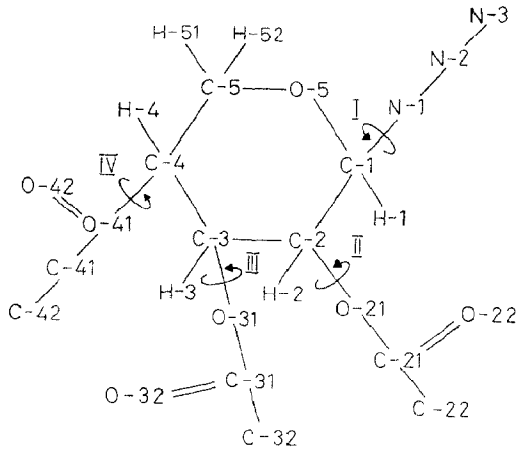

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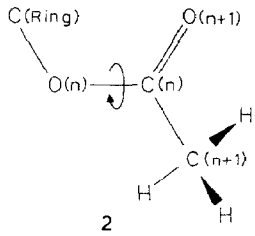

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molecule having an azide substituent at C-1, 2,3,4-tri-*O*-acetyl-α- and -β-D-arabino-pyranosyl azide, was examined. The calculations were carried out for the $^1C_4$(D) ring, where the azide group is equatorial and *trans* to the neigboring acetyl group in the α anomer, and axial *cis* to the neigboring acetyl group in the β anomer. The azide group is thereby *gauche* to the ring carbon atom C-5 in the β form, and it is *trans* in the α form. The crystal structure of 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl azide was determined by Luger and Paulsen[6]. Although the β form is energetically almost equivalent to the α form, it could not be synthesized so far[7] because both α and β starting compounds gave the α-azide. It is assumed that an acetoxonium intermediate opened into groups in *trans* position in both cases according to the Tipson–Baker "trans" rule[7].

The model and the applied method. — Structure **1** shows the atom numbering for 2,3,4-tri-*O*-acetyl-α- and -β-D-arabinopyranosylazide and the definition of the four rotation axes. The acetyl groups are referred to by the Roman numerals of the corresponding rotation axes. The starting geometry for the α anomer was taken from the X-ray investigation[6]. The starting coordinates for the β anomer were constructed by exchanging the axial and the equatorial substituents at C-1. The acetoxy groups were considered as planar rigid groups. In the crystal structure, the maximum deviation from exact planarity (0° or 180°) of the torsion angles ϕ and θ (see **2**) was 6°. Another set of calculations was carried out on 2,3,4-trideoxy-α- and -β-pentopyranosyl azide in order to eliminate the influence of substituents other than the azide group.

The calculations were carried out on a CRAY-1M computer with the PCILO (Perturbation Configuration Interaction using Localized Oribitals) semiempirical quantum-chemical method[5]. This method allows the calculation of the electronic ground-state energy of molecules containing elements up to Ne. The ground state of a molecule is built up from the interaction of localized orbitals that extend over

two bonded atoms and contain the valence electrons. *Ab initio* methods, on the other hand, extend the quantum-chemical treatment with fewer approximations to all orbitals, and therefore are more exact but also much more time-consuming. Molecular mechanics calculations use potential terms, whose equilibrium values are determined by measurements. These are less time-consuming, but they are seriously influenced by the parameters used. A potential term that includes the exo-anomeric effect might influence the result to show exactly this effect. The PCILO method is not biased by such assumptions. The program PCILO can perform energy calculations for stepwise rotations and geometry optimizations in order to minimize the energy of a molecule. Both features were used in the present investigation.

First a rotation about axis I (bond C-1–N-1) was carried out for all four molecules under investigation, to find low energy conformations for the azide group. The similarity in the locations of the minima on the substituted and unsubstituted pyranosyl azides showed that the calculations for the azide group and three acetoxy groups are separable. The geometric parameters around the azide group for the rotational minima were optimized for all four molecules. Consequently, the fine rotation around axis I gave more exact values for the rotational-torsion angles. Optimal conformations for the acetoxy groups were obtained after both PCILO and CHEMGRAF[8] energy calculations (see discussion below). For all torsion angles, the usual convention by Klyne and Prelog was used[9].

RESULTS AND DISCUSSION

In the energy diagrams with 10° rotation steps for axis I (rotation about the C-1–N-1 bond) for the arabinosyl compound (Fig. 1a) and for the oxane compound (Fig. 1b), two minima were observed for each curve. Optimization was performed only for the lower minima for each molecule under investigation. For each molecule, six parameters were optimized around C-1, the bond length C-1–N-1; the bond angles O-5–C-1–N-1, O-5–C-1–H-1, and C-1–N-1–N-2; and the torsion angles C-5–O-5–C-1–H-1 and C-5–O-5–C-1–N-1 (see Table I which also includes the starting values from the X-ray structure).

For the study of the minimal conformation of the side groups, rotation axes II, III, and IV (see structure 1) were defined by the torsion angles θ_{II} = C-3–C-2–O-21–C-21, θ_{III} = C-4–C-3–O-31–C-31, and θ_{IV} = C-5–C-4–O-41–C-41. Instead of well defined minima for these rotations, low energy ranges were found surprisingly near to places of steric hindrances, where two acetyl groups collide. Plots and distance calculations showed that these were false minima, where close contact of neighboring acetyl groups produced pseudo rings. This unfortunate characteristic of the PCILO program to arrive at unrealistically low energy values in the case of substantial steric overlap was also noticed by Froimowitz and Kollman[10]. In order to avoid these false minima, we used the CHEMGRAF[8] program system to produce two-dimensional rotational maps. The feature selected uses Coulomb and van der

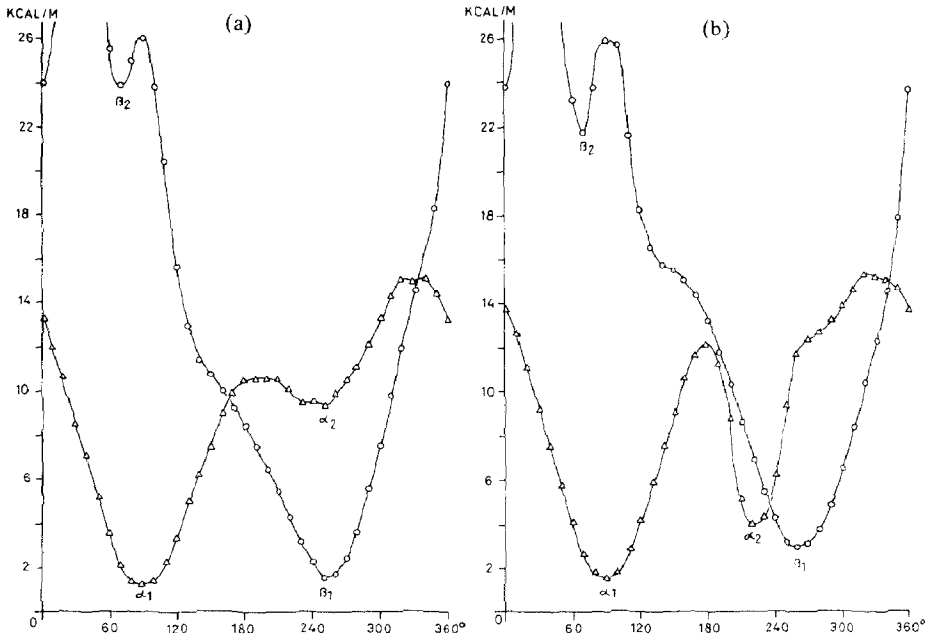

Fig. 1. Rotational energy diagrams for 2,3,4-tri-*O*-acetyl-α- and -β-D-arabinopyranosyl azide (a) and 2,3,4-trideoxy-α- and -β-D-pentopyranosyl azide (b). The rotation is about axis 1, *i.e.*, the azide group is rotated with respect to the sugar ring. The zero point on the energy coordinate corresponds to the lowest energy after optimization.

TABLE I

CHANGE OF INTERNAL COORDINATES THROUGH OPTIMIZATION[a]

International coordinates optimized	*Starting values*		*Values after optimization*			
	α-Anomer	*β-Anomer*	*α-Anomer*		*β-Anomer*	
			Arabinosyl cpd.	*Trideoxy cpd.*	*Arabinosyl cpd.*	*Trideoxy cpd.*
C-1–N-1	1.499(5)		1.425	1.426	1.425	1.429
O-5–C-1–N-1	107.9(3)		106.4	105.6	111.0	111.0
O-5–C-1–H-1	105 (1)		109	109	105	104
C-1–N-1–N-2	113.3(4)		121.3	121.4	121.7	122.9
C-5–O-5–C-1–N-1	−179.6	−58.6	+177.6	+177.8	−54.7	−54.3
C-5–O-5–C-1–H-1	−58.6	−179.6	−61.2	−61.2	−175.4	−174.7

[a]The bond lengths are given in Ångstrom units, the angles in degrees.

Waals potentials for determining the relative energies of conformations (see Fig. 2 for maps of rotations about axes II–III, III–IV, and II–IV). Each axis appeared on two maps, and the good three-way correlation of the minima proved that the two-dimensional maps are sufficiently good approximations for the three-dimensional rotation problem. The conformational settings, corresponding to the X-ray

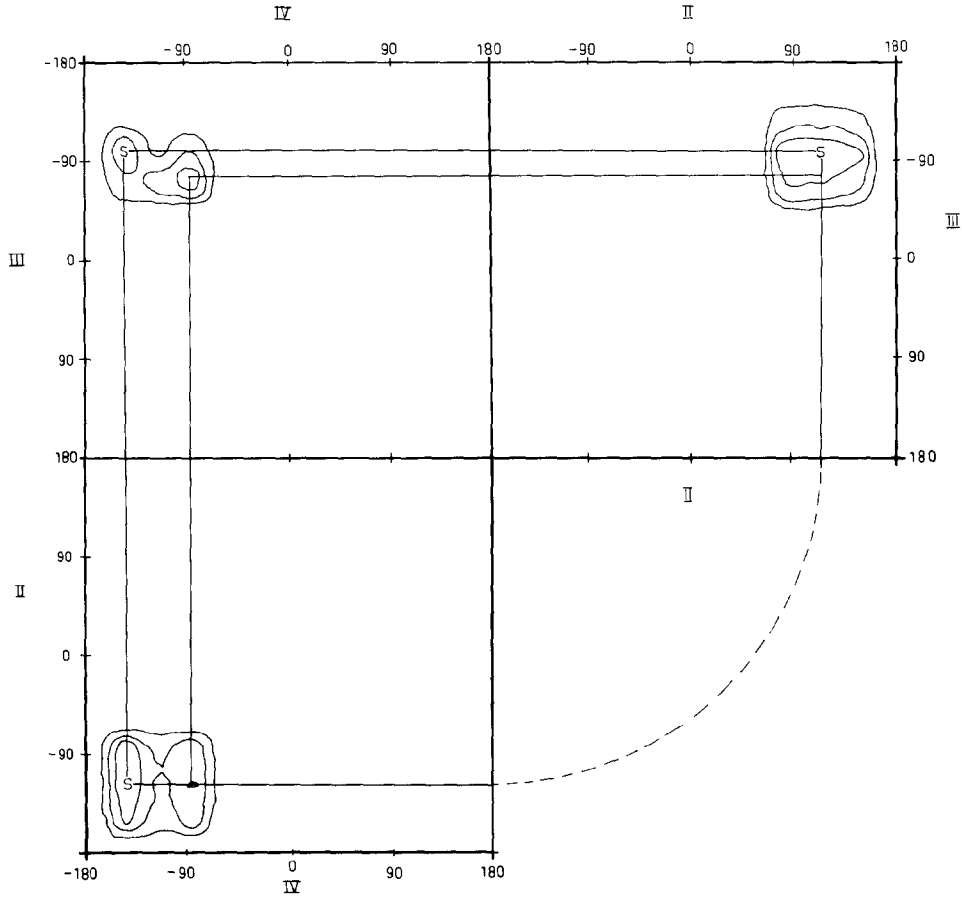

Fig. 2. Energy contour maps for pairwise rotation of the acetoxy groups. The roman numerals designate rotation axes defined in structure **1**. Divisions on the axes express the corresponding torsion angles in degrees. The contours are 1 kcal/mol (4.185 kJ/mol) apart.

TABLE II

ANOMERIC TORSION ANGLES (O-5–C-1–N-1–N-2) AND RELATIVE ENERGIES FOR THE LOWEST ENERGY CONFORMATIONS

	α Anomer		*β Anomer*	
	Arabinosyl cpd.	*Trideoxy cpd.*	*Arabinosyl cpd.*	*Trideoxy cpd.*
Rotation axis I (degrees)	80.0 87.5	82.5 90.0	−87.5	−90.0
Relative energy (kJ/mol)	1.2 0.0	0.9 0.0	5.5	0.5

structure of the α-arabinosyl azide, are denoted by S. It is clearly centered in one of the minima found by calculations. The other one is $-60°$ away in rotation IV.

Near the minima depicted in Fig. 2, three-dimensional rotations in 10° steps around II, III, and IV were carried out with the PCILO method. Local minima were found within 10–30° away from both CHEMGRAF minima for the α and β anomers. Although the map depicted in Fig. 2 was obtained for the α anomer, the corresponding map for the β anomer is so similar that it is not included. In the final energy table and figures, the setting "S" of Fig. 2 is adopted for both the α and β anomers.

Anomeric and exo-anomeric effect. — The presence of the anomeric effect could be examined by comparing the optimized parameters of the α and β anomers. The anomeric effect would predict a preference for the β anomer in which the azide group is attached axially. Since we found a difference of only 0.5 kJ/mol for the oxane derivative and since it favors the α anomer, one cannot make a definite statement in either direction. Tvaroška and Kožar[4] found a difference of 3.1 kJ/mol in favor of the axially attached methoxyoxane. A weaker effect would be expected for the azido compound[2].

Table II lists the values for rotation angle I and the relative energies for the lowest energy conformers. The absolute energies of the arabinosyl and unsubstituted oxane molecules differ by orders of magnitude, because the larger molecule contains 12 more "heavy atoms" (6 C and 6 O). Therefore, two relative scales have been adopted, and $E = 0$ for the lowest energy conformer for both molecules.

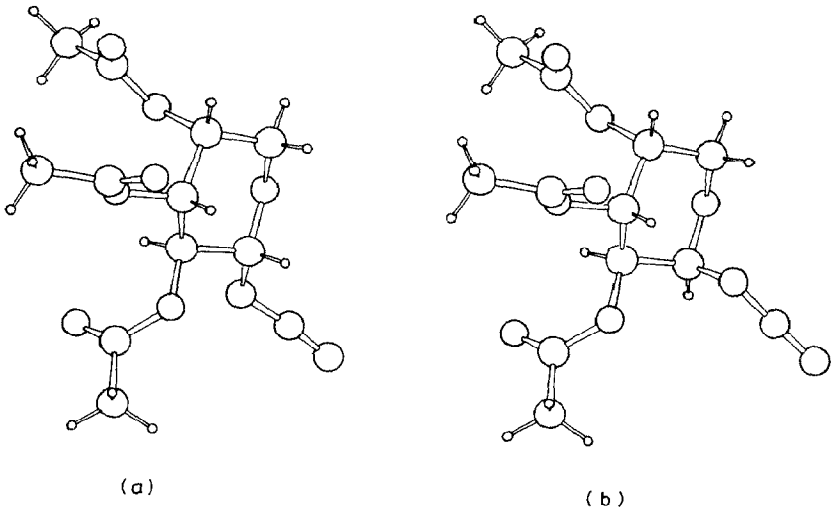

Fig. 3. The lowest energy conformations for the α (a) and for the β anomer (b) of 2,3,4-tri-*O*-acetyl-D-arabinopyranosyl azide. These plots were prepared with the molecular illustration program SCHAKAL[11].

The α-D-arabinosyl compound showed two minima, 7.5° and 1.2 kJ/mol apart (see Table II). The minimum at 80° is 5° away from the azide group conformation in the X-ray structure. The azidooxane also showed two similarly spaced minima that points to the conclusion that the double minimum is not caused by the presence of the substituents.

The β anomer showed one minimum for both the arabinosyl and for the unsubstituted oxane molecule (see Table II). We found no X-ray structure in the literature for a comparison with a molecule having an axial azide group at C-1 of a pyranosyl ring.

These results are close to the predicted and observed values for the exo-anomeric effect. The smaller absolute value for the anomeric torsion angle for an axial group was not found by these PCILO calculations. Here, the anomeric torsion angles are equal in magnitude (but have the expected opposite sign). The magnitudes reproduce closely the values given by Jeffrey and Taylor[3]. The lowest energy conformation for the α and β anomers are shown in Fig. 3.

ACKNOWLEDGMENT

The authors are grateful to the Deutsche Forschungsgemeinschaft for the financial support of this work.

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