Carbohydrate Research, 173 (1988) 197–204
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Ab initio SCF ENERGY CALCULATIONS OF THE ROTATIONAL ORIENTATION OF EACH OF THE EXOCYCLIC GROUPS OF 6-*O*-METHYL-β-D-TAGATOFURANOSE

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(Received March 1st, 1987; accepted for publication in revised form, August 10th, 1987)

ABSTRACT

Presented herein are potential-energy functions for the two side chains of a methyl ether of D-*lyxo*-2-hexulose, namely, 6-*O*-methyl-β-D-tagatofuranose, a model for β-D-tagatofuranose 6-phosphate. The methyl ether was chosen because, sterically, it is a good model of the phosphate, and yet it does not introduce the overwhelming complexity of phosphorus *d* orbitals into the calculations. The original minimum-energy structure for this molecule was obtained by using an empirical program, developed by Warshel, Lifson, and Karplus, which determined that the $^4T_3$(D) conformation is a minimum-energy structure; this was verified by our *ab initio* calculations. However, substantial differences were found in the minimum potential-energy structures of the two exocyclic groups. The equilibrium rotational orientation of each of these groups was then calculated. The results indicated that rotamers of angles 195° (for C-2) and 65° (for C-5) are very minor components. The calculations indicated that the molecule should mainly exist in two equal proportions as the two rotamers, one having angles of 295° (for C-2) and 290° (for C-5) and the other, angles of 75° (for C-2) and 290° (for C-5). All *ab initio* calculations were performed by using modified versions of the Gaussian-70 and Gaussian-76 programs at the STO-3G level.

INTRODUCTION

Ketohexose 6-phosphates are ubiquitous intermediates and regulators of carbohydrate metabolism[1] that exist in anomeric equilibria in solution[2,3]. Because

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0008-6215/88/$ 03.50

each anomeric form exists in a specific concentration and is capable of displaying different affinities and reactivities for catalytic and allosteric sites of enzymes (anomeric specificity), it is possible that ketohexose 6-phosphate anomerization may be the basis for a substrate-level regulation of antagonistic enzyme-pairs[4–6]. This possibility led us to determine the anomeric composition of ketohexose 6-phosphates *via* ^{13}C-n.m.r. spectroscopy[2,7], and to rationalize the observed anomeric equilibria through an analysis[2] of the furanose conformations of each sugar. Although this analysis was quantitatively successful, its empirical nature provided no real insight into the underlying physical forces that determine anomeric composition.

The recent development of *ab initio* techniques for the calculation of conformation energies of large molecular systems[8,9] has made this approach suitable for the analysis of complete monosaccharide structures without resorting to empirical or semiempirical compromise. Consequently, we have undertaken *ab initio* molecular orbital calculations of the conformational equilibria of 6-*O*-methyl-β-D-tagatofuranose (**1**), a model for β-D-tagatofuranose 6-phosphate. The methylated derivative was chosen because it is sterically a good model of the phosphate, and yet it does not introduce the overwhelming complexity of phosphorus *d* orbitals into the calculations. A similar analysis of the α anomer would allow calculation of the anomeric composition of 6-*O*-methyl-D-tagatofuranose, and its comparison with experimental values that are available from ^{13}C-n.m.r. studies[10].

Three conformational equilibria are possible for **1**. These are: (*1*), rotation of the 5-(methoxymethyl) group about the C-5–C-6 bond; (*2*), rotation of the 2-(hydroxymethyl) group about the C-1–C-2 bond; and (*3*), the pseudorotation of the furanose ring through an itinerary of ten envelope and ten twist conformations. We now report the results both of empirical and *ab initio* calculations of the rotational equilibria involving the two exocyclic groups.

METHODS

Specifically, the energy of a given conformation can be considered to consist of four parts: (*i*) intrinsic torsional potentials, (*ii*) van der Waals repulsions between nonbonded atoms and groups, (*iii*) dispersion attractions between nonbonded atoms, and (*iv*) energy of interaction of dipole moments between consecutive pairs of atoms or groups. The expression for the intramolecular energy associated with a rotation through the angle ϕ_i about the *i*th bond is[11–14]

$$E(\phi_i) = \tfrac{1}{2}E_0(1 - \cos 3\phi_i) + \sum_{k<l} (a_{kl}/r_{kl}^{12} - c_{kl}/r_{kl}^{6}) + 1389\ \delta_k\delta_l/\varepsilon r_{kl},$$

where $\tfrac{1}{2}E_0(1 - \cos 3\phi_i)$ represents the torsional term, with E_0 being the height of the potential barrier against internal rotation, $\Sigma(a_{kl}/r_{kl}^{12} - c_{kl}/r_{kl}^{6})$ are the nonbonded interactions of Lennard–Jones 6–12 form, and $1389\ \delta_k\delta_l/\varepsilon r_{kl}$ represent dipole inter-

actions in the point monopole approximation[15] (in kJ.mol^{-1}) for values of the partial electric charges, δ_j, and effective dielectric constant ε. The term r_{kl} represents the internuclear distance between atoms k and l for a given conformation. More-general expressions are sometimes used, and details of these and other empirical techniques have been published[11–14,16–18].

Until recently, the amounts of computational time needed to apply the foregoing equation to calculation of the conformational energies of intact hydrocarbons and carbohydrates has been prohibitive, and actual calculations have been limited to empirical and semiempirical approximations[11–13,19,20]. Although molecular mechanics programs incorporating these expressions have been useful for small systems[16–18], their major disadvantage has been that each different group of atoms must be individually parameterized. Often, adjustment of the required parameters has been done arbitrarily[13], so as to reproduce the energy differences observed between various conformations.

Recent improvements in computational capability brought about by current computer instrumentation and programming have allowed energy calculations based only on first principles. Consequently, *ab initio* techniques are now possible for the calculation of conformational energies of large molecular systems[8,9]. These *ab initio* programs have been used in the present study of the energies of the rotational forms of 6-*O*-methyl-β-D-tagatofuranose. The calculations were based upon Roothaan–Hartee–Fock self-consistent field theory[21]; they need no arbitrary parameters, and yield *ab initio* results, the accuracy of which can be made quite high. Usually, the only choice possible in these procedures is in the type of initial wave functions used. We have used the Slater type of orbitals approximated by three Gaussian functions (STO-3G). Additional details of these calculations have been published[8,22].

COMPUTATIONS

The *ab initio* calculations were performed by using modified versions of the Gaussian-70 and Gaussian-76 programs at the STO-3G level. These modifications were necessary in order to carry out calculations involving a more-complex molecule, to use more basic functions, and to help with convergence problems. The computers used were the IBM 370/3033 and the CYBER 180/830 instruments. The computational time for each point amounted to ~0.5 h. The total CPU time for this project was ~45 h.

RESULTS AND DISCUSSION

The study was begun by obtaining the structure of **1**, calculated to be an overall minimum-energy geometry using an empirical procedure. Subsequently, an exhaustive study of the various rotameric states of each "substituted methyl" group was carried out by using *ab initio* methods.

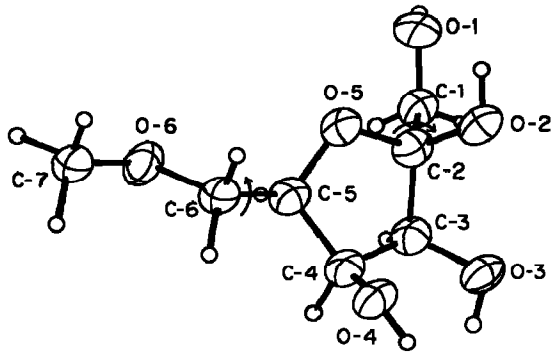

Fig. 1. Minimum energy conformation of 6-*O*-methyl-β-D-tagatofuranose (1), as calculated by empirical force-field calculations.

Empirical force-field calculations. — The structure depicted in Fig. 1 is that obtained by performing a total geometry optimization using a modified quantum chemical force field calculation of Warshel and Lifson[23] and Warshel and Karplus[24]. The geometry obtained is given in Table I. The first set of calculations was performed to determine if the furanose ring had the minimum-energy structure ${}^4T_3$(D). This was accomplished by adjusting the puckering of the various vertices of the

TABLE I

GEOMETRICAL PARAMETERS USED IN THE CALCULATIONS FOR 6-*O*-METHYL-β-D-TAGATOFURANOSE

Bond group	*Bond length*[a]	*Bond angle*[b]	*Dihedral angle*[c]
C-1–C-2–C-3–C-4	1.589	106.2	221.3
C-2–O-5–C-5–C-4	1.463	108.2	28.4
C-3–C-2–O-5–C-5	1.599	107.6	354.6
O-4–C-1–C-5–O-5	1.461	113.5	83.1
H–O-4–C-4–C-5	0.961	108.6	180.0
C-6–C-5–C-4–O-6	1.557	114.5	314.8
O-6–C-6–C-5–C-4	1.456	112.8	221.1
C-7–O-6–C-6–C-5	1.448	112.5	180.0
O-2–C-2–C-3–C-1	1.466	112.1	99.2
H–O-2–C-2–C-3	0.964	109.7	180.0
O-1–C-1–C-2–O-5	1.450	114.2	59.1
H–O-1–C-1–C-2	0.962	108.0	180.0
O-3–C-3–C-2–O-2	1.459	116.2	331.2
H–O-3–C-3–C-4	0.962	108.3	60.4
O-5–C-5–C-4	1.450	108.5	
C-4–C-5	1.567		

[a]The bond lengths, in Å units, correspond to the first two atoms of each group. [b]The bond angles, in degrees, correspond to the first three atoms of each group. [c]The dihedral angle, in degrees, corresponds to the four atoms of each group. These dihedral angles were used to begin the *ab initio* calculations.

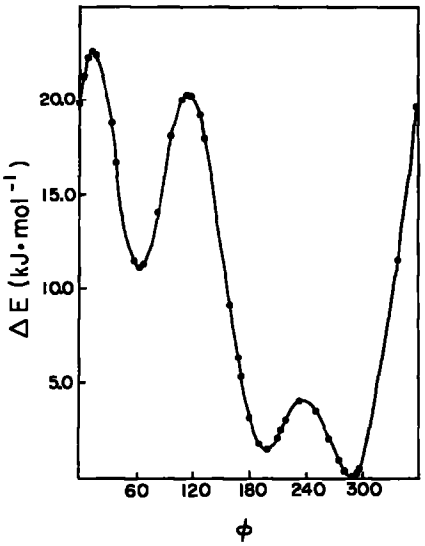

Fig. 2. Relative energy *vs.* dihedral angle for rotation about C-5–C-6 of 6-*O*-methyl-β-D-tagatofuranose.

ring. It was found that the $^4T_3$(D) conformation needed some slight adjustment, but it was calculated to be a minimum-energy structure for the furanose compound. It should be noted, however, that some improbable conformers in the itinerary were excluded from our calculations. Among the probable conformers calculated, the $^4T_3$(D) was found to have the lowest energy. The pertinent findings of the empirical calculation were that the lowest energy rotation for the 5-(methoxymethyl) group was at $\phi = \sim+221°$ and for 2-(hydroxymethyl), at $\phi = \sim+60°$.

A related molecule, namely, 2,5-anhydro-D-mannitol, was examined by X-ray diffraction[25], and it was found to have a slightly distorted $^4T_3$(D) conformation in the solid state. However, solution studies using n.m.r. spectroscopy had indicated that $^4T_3$(D) is actually the average conformation[26].

Ab initio *calculation of 5-(methoxymethyl) rotation*. — The next series of calculations was performed by rotation about the C-5–C-6 bond, where the dihedral angle is referenced with respect to C-4, *i.e.*, O-6 and C-4 are eclipsed at $\phi = 0°$. Rotation is considered positive for clockwise rotation, looking down the C-5–C-6 bond. Figure 1 shows the 5-CH_2OCH_3 group at a rotation of $\phi = \sim221°$. During rotation, all other geometric parameters were held fixed in their initial situations. The results of these *ab initio* calculations are shown in Fig. 2. As rotation begins, the energy increases to a maximum at $\phi = \sim15°$. This is the highest energy barrier for this rotation, with a relative value of 22.7 kJ.mol^{-1}. It may be noted that, at this dihedral angle, the O-6 and O-4 atoms are juxtaposed. A local minimum is obtained at $\phi = \sim65°$, and then it increases again to a maximum at $\phi \sim120°$. At the latter angle, O-6 eclipses the ring-oxygen atom (O-5). A second local minimum is obtained at $\phi \sim200°$, where O-6 approaches the hydrogen atom attached to C-5.

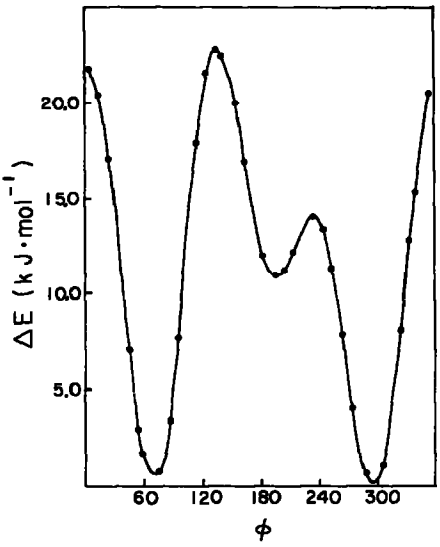

Fig. 3. Relative energy *vs.* dihedral angle for rotation about C-1–C-2 of 6-*O*-methyl-β-D-tagatofuranose.

The lowest energy structure is at $\phi = \sim 290°$, where O-6 is closest to the hydrogen atom attached to C-4.

It should be noted that the force-field calculations predicted a lowest energy orientation for this rotation at $\phi = \sim 221°$, whereas the *ab initio* results predict the minimum-energy rotameric orientation to be at $\phi = \sim 290°$. This is a difference of ~70°, which could be important in the interpretation of many experimental results.

Ab initio *calculation of 2-(hydroxymethyl) rotation.* — Rotation of the CH_2OH group about the C-1–C-2 bond is shown in Fig. 3. As may be seen, this rotation produces an energy plot more complex than that manifested by rotation about C-5–C-6. The dihedral angle is formed by the O-1–C-1–C-2–O-5 atoms, with positive rotation in the clockwise direction, looking down the C-1–C-2 bond. Figure 1 shows the 2-CH_2OH group at a rotation of $\phi = \sim 60°$.

It may be noted that, at $\phi = 0°$, the O-1 and O-5 atoms are eclipsed. As would be expected, this is an energetically unfavorable conformation, and this was confirmed by the calculations. As may be seen in Fig. 3, this is one of the higher energy conformations, with an energy barrier of ~22 kJ.mol^{-1}. As the rotation proceeds clockwise, the energy decreases to a relative energy of 0.682 kJ.mol^{-1} at $\phi = \sim 75°$. This is slightly displaced from $\phi = \sim 60°$, which would be expected on purely steric considerations. The reason for the slight displacement could be an attraction between O-1 and the hydrogen atom attached to O-2. In fact, this could be the beginning of hydrogen-bond formation.

A second barrier appears at an angle of $\phi = \sim 135°$. This is the highest energy barrier for this rotation, with a relative value of 22.8 kJ.mol^{-1}. The barrier is probably due both to steric hindrance and Coulombic repulsion of O-1 with O-2 and O-3.

TABLE II

CALCULATED RELATIVE ENERGIES AND EQUILIBRIUM COMPOSITIONS OF ROTATIONAL ORIENTATIONS (ROTAMERS) OF THE EXOCYCLIC GROUPS OF 6-*O*-METHYL-β-D-TAGATOFURANOSE

Group	*Rotamer*		*Composition (mole %)*[b]
	φ (degrees)	*Energy (kJ.mol^{-1})*[a]	
2-CH_2OH	75	0.682	43
	195	11.0	1
	295	0.0	56
5-CH_2OCH_3	65	11.2	1
	200	1.54	35
	290	0.0	64

[a]Relative to rotamer of lowest value for each group. [b]Calculated from the differences in the relative conformational free-energies, and assuming 35°.

A second local minimum, having a relative energy of 11.0 kJ.mol^{-1}, occurs at $\phi = \sim 195°$. This is probably due to a slight attraction between O-1 and the hydrogen atom attached to C-3. At $\phi = \sim 235°$, an additional local barrier, with a value of 13.9 kJ.mol^{-1}, is seen. This is not a very large barrier relative to the value at $\phi = \sim 195°$, and is probably due to steric interference of O-1 with C-3.

The global minimum-energy conformation, that is, the lowest energy conformation of all conformations studied, is found at $\phi \sim 295°$. This is a conformation in which O-1 is closest to the hydrogen atom attached to C-5.

It should be noted that the force-field calculations predicted the minimum-energy conformation at $\phi = \sim +60°$, whereas *ab initio* calculations predict this minimum at $\phi = \sim +295°$ ($= -65°$). However, *ab initio* results also predicted a very low energy conformation at $\phi = \sim +75°$. In fact, the difference between these two minimum-energy conformations is only 0.682 kJ.mol^{-1}, which indicates that both rotational conformers are about equally populated.

The equilibrium composition of the rotational orientations for each of the two exocyclic groups was calculated (see Table II). These results indicated that rotamers of angles 195° (for C-2) and 65° (for C-5) are very minor components. The calculations show that the molecule should exist in two equal amounts as the two rotamers, one with angles of 295° (for C-2) and 290° (for C-5), and the other with angles of 75° (for C-2) and 290° (for C-5).

CONCLUSIONS

In summary, we report that *ab initio* calculations predict a minimum-energy structure different from that produced by the simpler, force-field calculations. As this is an *ab initio* approach, it requires no additional input except the geometry of

the molecule. This eliminates the potential errors that are possible whenever techniques requiring extensive parameterization are used.

This report is the best *ab initio* energy calculation of this molecule attainable, considering the available program and minimal expenditure of time. It achieves the basic goals of this study.

ACKNOWLEDGMENTS

This investigation was supported in part by the Center for Energy and Mineral Resources of Texas A & M University and Donors of The Petroleum Research Fund administered by The American Chemical Society (J.A.D.), and in part by a grant to E.S.Y. and R.J.V. from The Office of Research and The College of Basic Sciences at Louisiana State University. The authors thank Drs. Neil R. Kestner, Michael A. Oliver, and William J. Colucci for their helpful comments, and a referee for making certain fruitful suggestions.

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