Structures of Furanosides: A Study of the Conformational Space of Methyl α-D-Lyxofuranoside by Density Functional Methods

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A search of the gas phase conformational space of methyl α-D-lyxofuranoside was carried out at the B3LYP/cc-pVDZ level. Relative energies of the local minima were computed using the larger aug-cc-pVDZ basis set and the recent mPW1LYP exchange-correlation functional. Local minima include structures with zero, one, two, three, or four internal hydrogen bonds and conformational energies of 12−2 kcal/mol relative to the "strain-free" methyl α-D-lyxopyranoside. The two most stable structures, with three and four internal hydrogen bonds, have conformational energies of approximately 2 kcal/mol. The relevance of these results to the conformational behavior of furanosides in the crystalline state and in solution is discussed. An efficient and accurate general procedure for searching the conformational space of furanosides is proposed.

Introduction

Furanosides are five-membered ring forms of carbohydrates. They are encountered throughout nature as components of bacterial and fungal cell walls, antibiotics, proteoglycans, messengers, and nucleic acids. In this last case, the conformation of the ribofuranosyl ring determines the overall structure of DNA or RNA and this can have a decided influence on their biological functions.

The five-membered ring is strained in all conformations, unlike the six-membered ring, which is most often encountered as a strain-free "chair" form. As a consequence, a five-membered ring (e.g., cyclopentane) fluctuates among a large number of conformational states, each of which is an uneasy compromise among bond-length, bond-angle, and nonbonded strains. The effect of exocyclic substituents on the conformational behavior of the furanoside ring is thus far more complex than the readily predictable substituent effects on the six-membered ring conformation.

In the previous paper of this series[1] and in a crystallographic paper currently in preparation[2] we reported highly accurate and precise low-temperature X-ray and neutron crystal structures of five of the eight methyl D-pentofuranosides and the results of gas-phase energy minimization of these structures. It was demonstrated that acceptable minimized geometries of the methyl pentofuranosides are obtained by means of density functional theory with a hybrid exchange-correlation functional such as B3LYP and a basis set of at least double-ξ plus polarization quality such as Dunning's cc-pVDZ.[13]

Minimization of the experimentally determined crystal structures led to structures in which intermolecular hydrogen bonds were replaced by intramolecular hydrogen bonds. For four of the methyl pentofuranosides there was little or no change in ring conformation, but for methyl α-D-lyxofuranoside, minimization led to a completely different ring conformation. This observation has prompted us to study the gas-phase conformation space of methyl α-D-lyxofuranoside in greater detail.

Computational Methods

Density functional theory (DFT) calculations were carried out by means of the Gaussian 98 program package[3] running on a DEC Alpha 500/500 workstation and on a SGI Origin 2000 supercomputer at the Weizmann Institute of Science. Two exchange-correlation functionals were used. The first, the popular B3LYP functional,[4] combines the Lee−Yang−Parr (LYP) correlation functional[5] with Becke's three-parameter hybrid exchange functional.[4] The second exchange-correlation functional we considered, mPW1LYP, combines the LYP correlation functional with the modified Perdew-Wang 1-parameter hybrid (mPW1) exchange functional proposed by Adamo and Barone.[6] The latter is a nonempirical[7] linear combination of the Hartree−Fock exchange and the Perdew-Wang generalized gradient approximation[8,9] exchange, but with the semi-arbitrary constants in the enhancement factor modified[6] in such a way as to reproduce the differential exchange energy of the rare gas dimers near their van der Waals minima. The mPW1 exchange functional appears to yield improved results for long-range interactions; in particular, it was shown[10] that mPW1LYP with sufficiently large basis sets yields essentially exact energies and geometric parameters for the water dimer, the prototype O−H···O hydrogen-bonded system. It was found previously[1] that the cc-pVDZ (correlation consistent polarized valence double-ζ) basis set of Dunning,[11] which is of [3s2p1d] quality for C and O and of [2s1p] quality for H, was the smallest basis set that yielded reliable geometries for flexible systems with internal hydrogen bonds. However, for accurate energetics, the addition of diffuse functions to the basis set is necessary since they dramatically reduce basis set superposition error (BSSE) for hydrogen bond interaction energies.[10,12] Thus we considered the augmented cc-pVDZ (aug-cc-pVDZ) basis set of Kendall et al.,[13] which is of [4s3p2d] quality for C and O and of [3s2p] quality for H.

Several tests revealed that mPW1LYP/aug-cc-pVDZ optimizations yielded essentially the same geometry as their computationally much less expensive B3LYP/cc-pVDZ counterparts. Hence we settled on B3LYP/cc-pVDZ geometry optimizations

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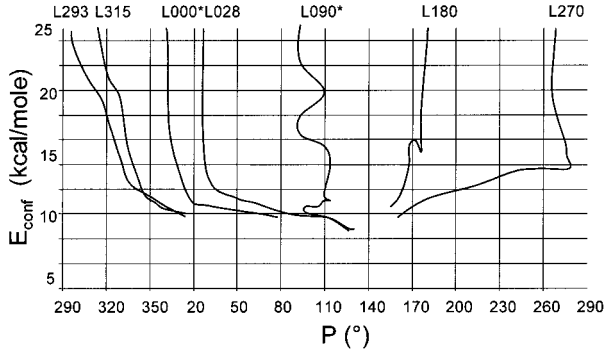


Figure 1. Minimization trajectories of some of the starting models. Conformational energy is on the vertical axis.

followed by mPW1LYP/aug-cc-pVDZ single point energy calculations at the final geometries.

After generation of the appropriate starting structures using the procedures to be detailed below, geometry optimizations were carried out with the Schlegel algorithm[14] in redundant internal coordinates.[15]

The energy of the structure of methyl α-D-lyxopyranoside, minimized by the same procedures as above, was used as a "strain-free" reference point. Thus, "conformational energy" is defined in this paper as the algebraic difference between the energy of formation of a given structure and that of methyl α-D-lyxopyranoside.

1. Generation of the Initial Set of Starting Models. 1.1. Ring Conformation. Five-membered ring conformations are represented numerically according to the exact four-parameter method of Marzec and Day,[16] an extension of the familiar Cremer−Pople two-parameter approximation.[17] Tetrahydrofuran rings used for starting models were generated with the program MAKERING (details of model generation will be published elsewhere[2]) for various values of P, with q set at 0.4 Å, s and Γ set to zero, and with average C−C and C−O bond lengths from highly accurate low-temperature X-ray and neutron crystal structures of five methyl pentofuranosides.[1,2] Exocyclic substituents were built onto the ring by means of the programs Insight II[18] or SPARTAN.[19] We have demonstrated[2] that this procedure regenerates ring coordinates of the crystal structures of all five methyl D-pentofuranosides within their small experimental uncertainties and is therefore suitable for construction of reasonable starting models for minimization.

During minimization, the conformation of the ring often traverses wide ranges of the pseudorotational phase angle, P. Thus, each intermediate structure can be regarded as a starting model in its own right and fine sampling of the pseudorotational cycle is accomplished with a rather small number of minimization trials. Indeed, trajectories starting from models with P = 0°, 90°, 180°, and 270° (starting models[20] **L000***, **L000**, **L090***, **L090**, **L180**, and **L270**) together cover a pseudorotational range of more than 270° (Figure 1). To cover the gap between 270° and 359° we have minimized two additional starting models with values of P = 315° and 293° (**L315**, **L293**).

1.2. Orientation of Ring Substituents. The orientation of ring substituents is defined as follows: for the O2−H and O3−H bonds, the orientation is "gauche +" (g+), "gauche −" (g−), or "trans" (t) relative to the C2−H2 and C3−H3 bonds, respectively. Descriptors of the C5−O5 bond were assigned with respect to the C4−H4 bond, whereas descriptors of the O5−H bond were assigned relative to the C5−O5 bond.

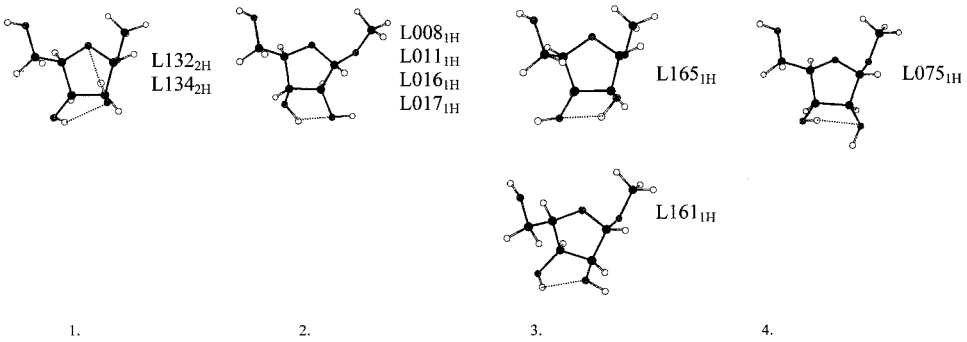
Since there are four independent exocyclic bonds, systematic investigation of all staggered rotamers of the exocyclics would require 3^4 = 81 starting conformations for each starting ring conformation. This large number of combinations was drastically reduced as follows: the methoxy group was always positioned in a (g−) orientation on the basis of steric hindrance considerations: O1−Me clashes with C2−H2 in the (g+) orientation and has multiple unfavorable interactions with the ring atoms in the (t) orientation. All crystal structures of the methyl pentofuranosides have the methoxy substituent in this (g−) orientation.[1,2]

At the outset, the C5−O5 bond was set as (g−), while both the (t) and (g+) rotamers of O5−H were explored with the O2−H and O3−H bonds eclipsed with their reference hydrogens, so as to impose no preference toward any particular rotamer or any particular hydrogen bonding pattern (See Table 1). Two additional starting models, with the O2−H and O3−H bonds set at (g−) and (g+), respectively, and initial P values of 0° and 90° (**L000*** and **L090***), were also minimized. Subsequently, we selected several additional combinations of

TABLE 1: Summary of Exocyclic Substituent Orientations for Starting Models and Minimized Structures

starting model	O2−H	O3−H	C5−O5	O5−H	minimized structure	O2−H	O3−H	C5−O5	O5−H
L000	e	e	g−	t	**L016**$_{1H}$**, L017**$_{1H}$	g+	g+	g−	t
L090	e	e	g−	t					
L315	e	e	g−	t	**L011**$_{1H}$	g+	g+	g−	t
L180	e	e	g−	g+	**L165**$_{1H}$	g−	g−	g−	g+
L270	e	e	g−	g+	**L161**$_{1H}$	g+	t	g−	g+
L165$_{O2-H>O3-H>O4}$	g−	t	g−	g+					
L161$_{O5-H>O4}$	g+	g−	t	g+	**L163**$_{1H}$	g+	g−	t	g−
L293	e	e	g−	t	**L008**$_{1H}$	g+	g+	g−	t
L000*	g−	g+	g−	t	**L075**$_{1H}$	g−	t	g−	t
L090*	g−	g+	g−	t	**L134**$_{2H}$	t	t	g−	t
L161$_{O5-H>O3}$	g+	g−	g+	e/g+	**L162**$_{2H}$	g+	t	g+	g+
L161$_{O2-H>O5-H>O4}$	t	g−	t	g+	**L157**$_{2H}$	t	g−	t	g+
L011$_{O2-H>O3}$	t	g−	g−	t	**L094**$_{2H}$	t	g+	g−	t
L028$_{C}$	t	t	g−	t	**L132**$_{2H}$	t	t	g−	t
L161$_{O3-H>O2-H>O4}$	t	t	g−	g+					
L075$_{O3-H>O2-H>O4}$	t	t	g−	t					
L011$_{O5-H>O3+\ O2-H>O3}$	t	t	e/g−	g+	**L058**$_{3H}$	t	t	g−	g+
L134$_{O5H>O3-H>O2-H>O4}$	t	t	g+	g+	**L137**$_{3H}$	t	t	g+	g+
L134$_{O5H>O4+O3-H>O2-H>O4}$	t	t	t	g+	**L161**$_{3H}$	t	t	t	g+
L161$_{O3-H>O2+\ O5-H>O4}$	g+	t	t	g+	**L148**$_{4H}$	g+	t	t	g+
L011$_{O2-H>O3-H>O5-H>O4}$	t	t/e	t/e	g+/e	**L137**$_{4H}$	g−	t	t	g+
L161$_{O2-H>O3+\ O5-H>O4}$	g−	g−	t	g+					
L011$_{nH}$**, L074**$_{nH}$**, L094**$_{nH}$	g+	g−	g−	t	**L005**$_{ØH}$	g+	g−	g−	t
L132$_{nH}$**, L161**$_{nH}$	g+	g−	g−	t	**L169**$_{ØH}$	g+	g−	g−	t

CHART 1: First-generation Minimized Structures. Hydrogen Bonding Is Represented by Dashed Lines. Plots Generated by XMol[24]



rotamers, with the goal of investigating as many possible hydrogen bonding patterns as possible, as described in section 2. In addition, the crystal structure of methyl α-D-lyxofuranoside[1,2] was used as a starting model, **L028**$_C$.

2. Generation of Starting Models with Predisposed Exocyclic Substituents. 2.1. Exocyclics Positioned to Favor Hydrogen Bonding. We found that, during minimization, rotation around an exocyclic bond is usually confined to a sector of 120° or less, defined by rather high energy barriers to rotation. This natural partitioning of conformational space prompted us to generate a second set of starting models based on the ring conformations of the local minima found in the first round of minimization. In these starting models, the exocyclics were initially rotated into positions that appeared to *favor* formation of additional hydrogen bonds. This principle is illustrated in the following examples:

To investigate a structure with two hydrogen bonds, O2−H···O3 and O3−H···O4, we modified **L165**$_{1H}$ (which has a single hydrogen bond, O2−H···O3, see Chart 1.3) to the model structure **L165**$_{O2-H>O3-H>O4}$ by rotating O3−H around the C3−O3 bond into a position that might favor the additional hydrogen bond, O3−H···O4.

L161$_{1H}$ (Chart 1.3) and **L075**$_{1H}$ (Chart 1.4) were modified by rotation around the C2−O2 bond, to favor formation of an additional hydrogen bond, O2−H···O4 (**L161**$_{O3-H>O2-H>O4}$ and **L075**$_{O3-H>O2-H>O4}$).

L134$_{2H}$ (Chart 1.1) was modified by rotation of the C5−O5−H group to provide the starting models **L134**$_{O5H>O3-H>O2-H>O4}$ and **L134**$_{O5-H>O4+O3-H>O2-H>O4}$ with suggested O5−H···O3 and O5−H···O4 hydrogen bonds, respectively. It should be noted that, in many cases, the additional hydrogen bonds did *not* form in the minimized structure.

2.2. Exocyclics Positioned to Hinder Hydrogen Bonding. We have used the same strategy to generate a third set of starting models with exocyclics positioned so as to allow the rotational energy barriers to *hinder* formation of hydrogen bonds, e.g., O2−H (g+), O3−H (g−), C5−O5 (g−), and O5−H (t) (See Table 1).

Results

Figure 1 illustrates how minimization of a small number of starting models can probe a wide range of ring conformation. The minima resulting from these trials have either one or two internal hydrogen bonds. Starting models **L090*** and **L028**$_C$ led to essentially the same minimized structure—**L132**$_{2H}$ or **L134**$_{2H}$ (Chart 1.1). **L000**, **L090**, **L293**, and **L315** led to geometrically and energetically similar structures **L016**$_{1H}$, **L017**$_{1H}$, **L008**$_{1H}$, and **L011**$_{1H}$ (Chart 1.2); whereas the models **L180** and **L270** led to two structures with similar ring conformation (**L165**$_{1H}$ and **L161**$_{1H}$) but different hydrogen-bonding patterns and somewhat different conformational energies (Chart 1.3). Minimization of **L000*** resulted in **L075**$_{1H}$ (Chart 1.4). The most stable structure at this stage was **L011**$_{1H}$ (or the similar structures **L016**$_{1H}$, **L017**$_{1H}$, and **L008**$_{1H}$) with one hydrogen bond and a conformational energy of approximately 6.8 kcal/mol. Geometrical and energetic parameters of these structures are summarized in Table 2.

A second set of models was generated by resetting certain exocyclic bond rotations so as to favor formation of additional hydrogen bonds, as described in Methods. Three of these starting models (**L075**$_{O3-H>O2-H>O4}$, **L165**$_{O2-H>O3-H>O4}$, and **L161**$_{O3-H>O2-H>O4}$) led back to two of the minima already found in the previous round (**L161**$_{1H}$, **L132**$_{2H}$). Minimization of three models derived from **L011**$_{1H}$ in order to test the possibility of alternative hydrogen bond patterns (**L011**$_{O2-H>O3}$, **L011**$_{O5-H>O3+O2-H>O3}$ and **L011**$_{O2-H>O3-H>O5-H>O4}$) resulted in three structures with completely different ring conformation—**L094**$_{2H}$ with *two* hydrogen bonds (Chart 2.1), **L058**$_{3H}$ with *three* (Chart 2.2), and **L137**$_{4H}$ with *four*[21] hydrogen bonds (Chart 2.3). **L137**$_{4H}$ is one of the two most stable minima found in this study, being only 1.6 kcal/mol more energetic than the "strain-free" reference compound, methyl α-D-lyxopyranoside.

Both models derived from **L132**$_{2H}$ led to new minima (**L137**$_{3H}$ and **L161**$_{3H}$, Chart 2.4 and .5), with ring conformations close to those of previously discovered minima but possessing *three* hydrogen bonds. **L161**$_{3H}$ is the second of the two most stable minima, having a conformational energy of 2 kcal/mol.

Minimization of five models, derived from **L161**$_{1H}$, **L161**$_{O5-H>O4}$, **L161**$_{O5-H>O3}$, **L161**$_{O2-H>O5-H>O4}$, **L161**$_{O3-H>O2+O5-H>O4}$, and **L161**$_{O2-H>O3+O5-H>O4}$ resulted in three structures of approximately the same ring conformation, **L163**$_{1H}$ (Chart 2.6), **L162**$_{2H}$ (Chart 2.7), and **L157**$_{2H}$ (Chart 2.8) and two of significantly different ring conformation, **L148**$_{4H}$ (Chart 2.9) and **L137**$_{4H}$ (Chart 2.3). Geometrical and energetic data for these structures are summarized in Table 2. Figure 2 is a schematic representation of the course of generation of a family of seven distinct structures for which *P* is approximately the same (165°).

A third set of models was generated by resetting the orientation of exocyclic substituents so as to disfavor formation of internal hydrogen bonds. The models generated from **L011**$_{1H}$, **L075**$_{1H}$, and **L094**$_{2H}$ all lead to **L005**$_{OH}$ (Chart 3.1) whereas the models generated from **L161**$_{1H}$ and **L132**$_{2H}$ lead to **L169**$_{OH}$ (Chart 3.2).Geometrical and energetic data for these hydrogen-bond-free local minima are summarized in Table 2.

Discussion

1. Ring Geometry. Average bond lengths and bond angles of all the minimized structures are within the averages of the

TABLE 2: Ring Conformations and Conformational Energies of Local Minima

			hydrogen bond lengths and angles			eclipsed angles (<30°)	
structure	*P*, deg	energy, kcal/mol	bond	length, Å H···O	angle, deg O−H···O	torsion angle	magnitude of torsion, deg
$L005_{ØH}$	5.2	11.7					
$L169_{ØH}$	169.2	12.1				O3−C3−C4−C5	28.4
$L008_{1H}$	8.1	6.8	O3−H···O2	2.05	118.3		
$L011_{1H}$	12.0	N/D	O3−H···O2	2.06	117.5		
$L016_{1H}$	16.1	N/D	O3−H···O2	2.05	118.1	O1−C1−C2−H2	26.5
						H1−C1−C2−O2	22.2
$L017_{1H}$	17.4	N/D	O3−H···O2	1.95	120.1	O1−C1−C2−H2	29.8
						H1−C1−C2−O2	25.5
$L075_{1H}$	75.0	7.3	O3−H···O2	2.19	107.7	H1−C1−C2−O2	13.4
						O1−C1−C2−H2	14.3
$L161_{1H}$	161.3	8.2	O3−H···O2	2.05	117.6	H3−C3−C4−H4	22.0
						O3−C3−C4−C5	23.0
$L163_{1H}$	163.2	9.6	O5−H···O2	1.91	151.2	H3−C3−C4−H4	25.6
						O3−C3−C4−C5	20.9
$L165_{1H}$	165.3	9.2	O2−H···O3	2.12	113.7	H3−C3−C4−H4	23.7
						O3−C3−C4−C5	19.6
$L094_{2H}$	93.7	7.4	O2−H···O3	2.37	91.7	O1−C1−C2−H2	26.6
						H1−C1−C2−O2	22.5
						O2−C2−C3−O3	1.1
						H2−C2−C3−H3	2.5
			O3−H···O2	2.19	102.8	O3−C3−C4−C5	23.4
						H3−C3−C4−H4	23.9
$L132_{2H}$	132.1	7.1	O3−H···O2	2.01	122.1	H3−C3−C4−H4	3.6
			O2−H···O4	2.41	107.9	O3−C3−C4−C5	4.2
$L134_{2H}$	134.4	N/D	O3−H···O2	2.02	123.3	H3−C3−C4−H4	5.0
			O2−H···O4	2.42	106.6	O3−C3−C4−C5	6.0
$L157_{2H}$	157.2	6.0	O2−H···O5	1.90	154.2	H3−C3−C4−H4	24.3
			O5−H···O4	2.26	107.3	O3−C3−C4−C5	22.7
$L162_{2H}$	162.1	7.9				H3−C3−C4−H4	22.4
			O3−H···O2	2.04	115.6	O3−C3−C4−C5	24.2
						H2−C2−C3−H3	29.3
			O5−H···O3	2.07	128.3	O1−C1−C2−H2	29.7
						O2−C2−C3−O3	28.1
$L058_{3H}$	58.2	6.1	O2−H···O3	2.01	122.3	O1−C1−C2−H2	1.1
						H1−C1−C2−O2	1.3
			O3−H···O4	2.52	105.5	O2−C2−C3−O3	25.1
			O5−H···O3	2.33	124.6	H2−C2−C3−H3	29.5
$L137_{3H}$	137.2	4.0	O2−H···O4	2.43	107.3	H3−C3−C4−H4	7.7
			O3−H···O2	2.02	121.9	O3−C3−C4−C5	8.7
			O5−H···O3	2.01	135.5		
$L161_{3H}$	161.2	2.1	O2−H···O5	1.83	163.6	H3−C3−C4−H4	23.0
			O3−H···O2	2.08	120.5	O3−C3−C4−C5	25.4
			O5−H···O4	2.26	104.5		
$L137_{4H}$	137.1	1.6	O2−H···O3	2.25	107.8	O3−C3−C4−C5	11.1
			O3−H···O5	1.84	145.1	H3−C3−C4−H4	7.9
			O5−H···O2[a]	2.34	124.8	H2−C2−C3−H3	28.3
			O5−H···O4[a]	2.45	103.4		
$L148_{4H}$	148.3	4.0	O3−H···O2[a]	2.46	97.6	O3−C3−C4−C5	20.9
			O3−H···O5[a]	1.98	136.1	H3−C3−C4−H4	18.2
			O5−H···O2[a]	2.00	134.1		
			O5−H···O4[a]	2.63	105.1		

[a] Three-center hydrogen bonds.

standard deviations of the crystallographic values[2] as shown in Table 3, suggesting that bond length and bond angle are indeed "hard" parameters that do not vary significantly as the ring conformation changes. The 20 unique minimized structures cluster mainly around three ring conformations represented by pseudorotational phase angles of 11 ± 6° (five structures), 134 ± 4° (four structures), and 165 ± 7° (seven structures). These ring conformations are represented by structures having from zero to four hydrogen bonds. Other ring conformations that are represented are $P = 58°$, 75°, 94°, and 148° with one structure each.

1.1. Structures with no Hydrogen Bonds. Two minima, at $P = 5°$ and 169° (**L005**$_{0H}$ and **L169**$_{0H}$) correspond to structures with no internal hydrogen bonds. They are characterized by minimal eclipsing of exocyclic substituents. Nevertheless, their energy is approximately 12 kcal/mol higher than that of the "strain-free" pyranoside. Neither the pyranoside nor the two furanosides have internal hydrogen bonds, therefore 12 kcal/mol approximates the total strain of bond-angle distortion and nonbonded repulsion in the two least strained conformations of methyl α-D-lyxofuranoside.

1.2. The Role of Hydrogen Bonds. Examination of the conformational energies of the minimized structures with increasing numbers of hydrogen bonds (Table 2) suggests that internal hydrogen bonding tends to stabilize the structures, as expected. This general trend is illustrated by the excellent linear regression of conformational energy on number of hydrogen bonds (Figure 3). On the basis of this analysis, each additional

CHART 2: Second-Generation Minimized Structures

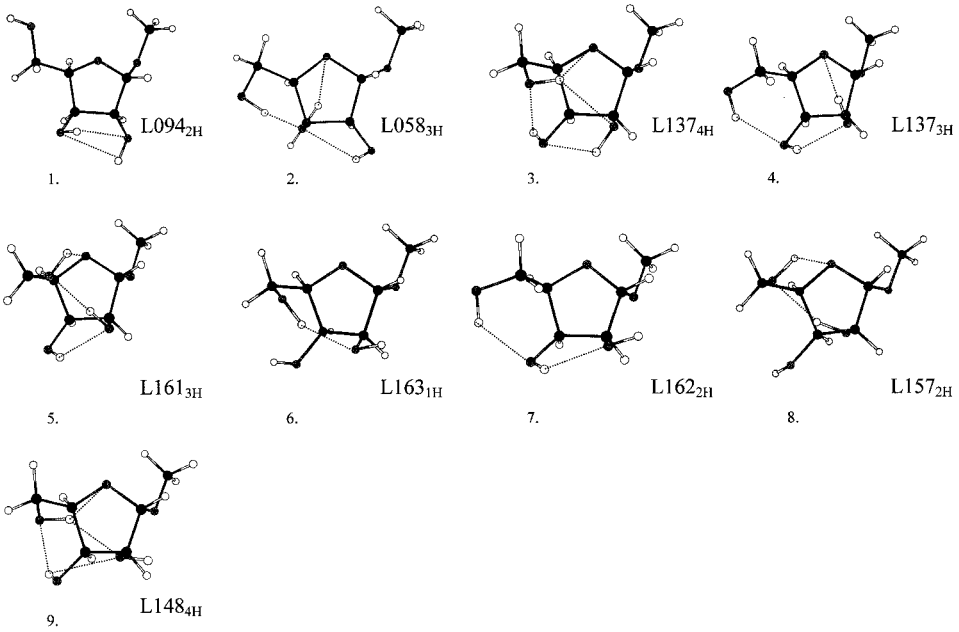


CHART 3: Minimized Structures with No Internal Hydrogen Bonds

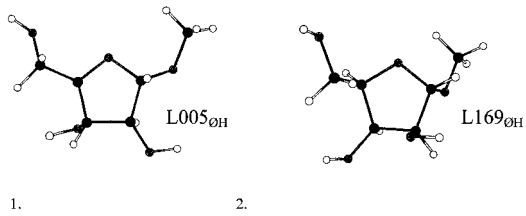


TABLE 3: Comparison of Ring Bond Lengths and Bond Angles of the 20 Minimized Structures of Methyl α-D-Lyxofuranoside and the Structures of the Five Crystalline Methyl Pentofuranosides

parameter	av for minimized struct	av for crystal struct[1,2]
C−C bond (Å)	1.54(1)	1.53(1)
C−O bond (Å)	1.43(1)	1.43(1)
C−C−C angle (deg)	101.9(0.7)	102.1(1.1)
C−C−O angle (deg)	105.5(0.9)	105.2(1.2)
C−O−C angle (deg)	109.0(1.0)	108.7(1.4)

hydrogen bond increases the stability of the furanoside by approximately 2.2 kcal/mol on average, a very acceptable numerical result (cf. 5.0 kcal for the water dimer[12]). Relative energies within the groups of structures having equal numbers of hydrogen bonds cannot, however, be rationalized in simple, intuitive terms such as "quality of hydrogen bond" or "severity of eclipsing". Indeed, there seem to be outright inconsistencies such as the case of **L161**$_{1H}$ compared to **L162**$_{2H}$—these two structures have the same ring conformation and differ by one hydrogen bond, yet their energies are nearly equal (8.2 vs 7.9 kcal/mol). This suggests that there may still be limitations in the accuracy of the energy calculations or that there are limits to our intuitive understanding of energetics or both. Minimization of these structures at even higher levels of theory, which might clarify this issue, is presently prohibitive to perform.

1.3. The Role of Eclipsing. The most severe cases of eclipsing of exocyclic substituents in the pseudorotational itinerary of a furanoside occur for the two symmetry-related ring conformations at $P = 90°$ and 270° (^{O}E and E_{O}). Despite this, we find that a highly eclipsed structure, **L094**$_{2H}$, is not significantly less stable than any of the less eclipsed structures

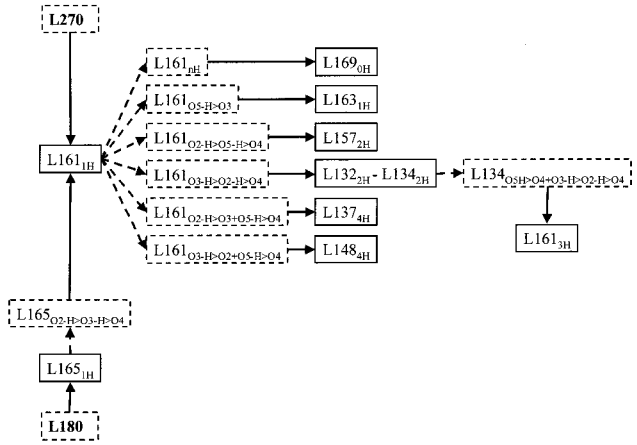


Figure 2. Chart of interconversion of starting models and minimized structures used to generate the minima. Starting models are in dashed boxes, minimized structures in solid boxes. First-generation starting models are in bold type. Dashed lines represent manual intervention; solid arrows represent minimization.

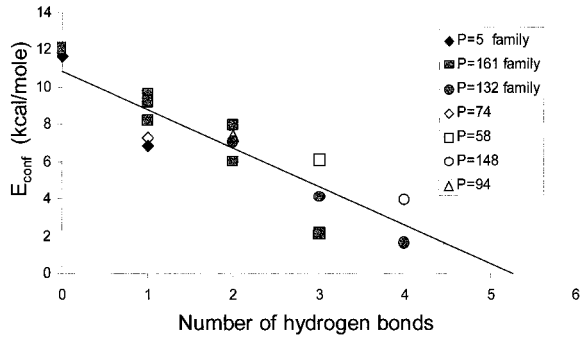


Figure 3. Least-squares fit of the energies of the minimized structures vs. the number of internal hydrogen bonds.

having two hydrogen bonds (Table 2). This suggests that eclipsing may play a relatively minor role in conformational energetics, at least for hydrogen-bonded furanosides. In the absence of internal hydrogen bonds, however, the effect of eclipsing is to preclude the existence of stable hydrogen-bond-free structures except in the two regions of minimal eclipsing,

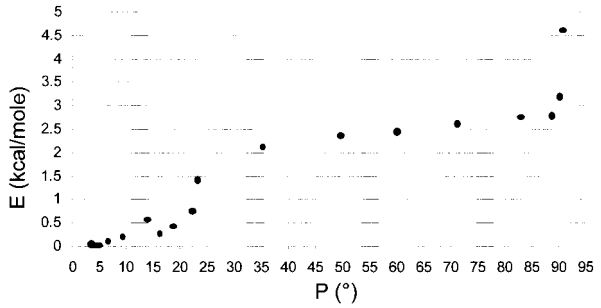


Figure 4. Trajectory followed by the starting model $\mathbf{L094}_{nH}$ during minimization. The vertical axis shows the difference in energy between each intermediate structure and that of the local minimum, $\mathbf{L005}_{\emptyset H}$.

i.e., near $P = 0°$ and 180°. Indeed, the only hydrogen-bond-free minima detected are $\mathbf{L005}_{OH}$ and $\mathbf{L169}_{OH}$.

A rough estimate of the energy associated with maximal eclipsing may be deduced from a plot of energy vs pseudorotational phase angle in the course of minimization of a hydrogen-bond-free model derived from $\mathbf{L094}_{2H}$ (Figure 4). The conformational energy at $P = 90°$ is only 3 kcal/mol greater than that of the hydrogen-bond-free minimum $\mathbf{L005}_{OH}$. This is approximately equivalent to the average stabilization associated with 1−1.5 internal hydrogen bonds (see Section 1.2.) and is not enough to preclude the existence of local minima with two or more hydrogen bonds even for highly eclipsed ring conformations. Cases in point are the family of minima near $P = 135°$ (Table 2), $\mathbf{L148}_{4H}$, and the maximally eclipsed $\mathbf{L094}_{2H}$. In the case of $\mathbf{L074}_{1H}$ a single hydrogen bond suffices to stabilize an eclipsed structure.

2. What Is the Global Minimum for Methyl α-D-Lyxofuranoside? On the basis of the analysis presented in sections 1.2. and 1.3, it is likely that the most stable structures in the gas phase are those with the largest number of hydrogen bonds. This general trend is illustrated by the linearity of the relationship between conformational energy and number of hydrogen bonds. Therefore, those ring conformations that are compatible with maximal internal hydrogen bonding, regardless of strain associated with eclipsing, are expected to be among the most stable structures. It is likely that our systematic procedure has allowed us to investigate all possible structures that are compatible with three and four hydrogen bonds; there seem to be no ring structures for methyl α-D-lyxofuranoside that are compatible with more than four hydrogen bonds. The two most stable structures detected are $\mathbf{L161}_{3H}$ and $\mathbf{L137}_{4H}$, with three and four hydrogen bonds, respectively, and conformational energy within approximately 2 kcal/mol of that of the "strain free" methyl α-D-lyxopyranoside. They are approximately 2 kcal more stable than the next lowest minima ($\mathbf{L137}_{3H}$ and $\mathbf{L148}_{4H}$) and thus they are the two most likely candidates for the "global minimum" gas-phase structure of methyl α-D-lyxofuranoside.

3. Relationship of the Calculated Gas-Phase Structures to the Crystal Structure of Methyl α-D-Lyxofuranoside and to Its Conformation in Solution. The experimentally determined crystal structure of methyl α-D-lyxofuranoside contains no internal hydrogen bonds and all three exocyclic hydroxyls participate in intermolecular hydrogen bonds that constitute important elements in stabilizing the crystal lattice.[1,2] At a pseudorotational phase angle of 28°, the ring conformation imposes no serious eclipsing of exocyclic substituents. Indeed, $\mathbf{L028}_{C}$ is quite similar to the hydrogen-bond-free gas-phase structure, $\mathbf{L005}_{OH}$. One important difference, however, is the C2−O2 rotamer which, in $\mathbf{L005}_{OH}$, orients O2−H away from O4 but in the crystal has O2−H predisposed for formation of an internal hydrogen bond with O4. This drives the minimization of $\mathbf{L028}_{C}$ to $\mathbf{L132}_{2H}$ with O2−H···O4 (and O3−H···O2) rather than to the nearby hydrogen-bond-free minimum at $P = 5°$. If we now consider the crystallization of methyl α-D-lyxofuranoside from polar solvents such as acetonitrile or ethyl acetate (these solvents are commonly used to grow crystals of methyl pentofuranosides),[1,2] we may imagine that the predominant conformers would be those having few or no internal hydrogen bonds, i.e., those with P near 10° and 165°, since external hydrogen bonding with the solvent molecules is likely to be preferred to internal hydrogen bonding. $\mathbf{L005}_{OH}$ and the family of structures $\mathbf{L008}_{1H}$−$\mathbf{L017}_{1H}$ are structurally very similar to $\mathbf{L028}_{C}$ and might well be precursors of the crystalline compound. In solvents with decreasing hydrogen bonding propensity (e.g., chloroform), one might expect to find structures with increasing numbers of internal hydrogen bonds, including those somewhat more seriously eclipsed, e.g., those with P near 75°, 135°, and even 95°, whereas in aqueous solution the two hydrogen-bond-free conformers, $\mathbf{L005}_{OH}$ and $\mathbf{L169}_{OH}$, would predominate.

4. An Efficient Procedure for Scanning the Conformational Space of Furanosides. It is evident that an exhaustive search of the conformational space of a single methyl pentofuranoside by systematic minimization of all possible starting models is a near-Sisyphean task. Even with a fast workstation such as our DEC Alpha500/500, a single minimization takes 24−48 h of CPU time and a single-point energy calculation with the larger basis set takes an additional 10 h. Our analysis, however, suggests a procedure for selection of a limited number of starting models with a very high probability of locating a complete set of the unique minima in the conformational space of a given methyl pentofuranoside. The procedure is based on the following observations:

1. Exocyclic bonds in all minimized structures are staggered or very close to staggered. Starting models where exocyclics are eclipsed always lead to minima where the exocyclics are staggered. Therefore, only starting models with staggered exocyclic bonds need be minimized. (But see point 4 below, where eclipsed exocyclics are used to good purpose in starting models.)

2. A staggered exocyclic bond in a starting model usually remains close to the original rotational angle throughout minimization. This allows partition of a conformational search into regions corresponding to predetermined combinations of staggered exocyclic rotamers. Specifically, rotamers can be chosen so as to probe the stability of structures containing selected hydrogen bonds.

3. Ring conformations with the least serious eclipsing of ring substituents are preferred for hydrogen-bond-free structures. These can be found by minimization of models where the exocyclic rotamers are chosen to avoid internal hydrogen bonds.

4. Eclipsed ring conformations can be stabilized by two or more internal hydrogen bonds. Such structures may be found by minimizing ring conformations in which the exocyclic rotamers of the starting models are eclipsed rather than staggered. This procedure may lead back to the same minimally eclipsed ring conformations as found by procedure 3 but can also lead to ring conformations in which increased eclipsing of ring substituents is balanced by multiple hydrogen bonding.

A viable systematic procedure based on the above observations might start with identification of the stable hydrogen-bond-free ring conformers according to 3 and proceed to investigation of one-, two-, and three-hydrogen bonded variants in these regions of pseudorotational space. The next step, based on 4,

would be to identify additional regions where increased ring eclipsing is balanced by hydrogen bonding.

Gas-phase DFT calculations at the B3LYP/6-31G* level for methyl α-D-ribofuranoside[22] and methyl α-D-arabinofuranoside[23] have been reported recently. In these studies the expedient of constraining one of the endocyclic torsion angles was adopted. It is difficult to assess the effect of this on the results. In any case, the present study shows that it is possible to achieve a highly comprehensive study of the conformational space of the methyl pentofuranosides without imposing artificial constraints on these systems.

Conclusion

A wealth of information about the conformational energetics of furanosides has come to light in the course of this DFT study of methyl α-D-lyxofuranoside. An economical method for constructing and selecting model structures for scanning conformational space has been devised, which facilitates systematic investigation of furanoside structures without introducing artificial constraints. Twenty local minima have been found for conformers of methyl α-D-lyxofuranoside having from zero to four internal hydrogen bonds. Regression analysis yields an average value of approximately 2.2 kcal/mol for the stabilization associated with formation of each internal hydrogen bond. The strain energy associated with eclipsing of the ring substituents is maximal for the conformers at $P = 90°$ and 270° (^{O}E and E_{O}) and is estimated to be approximately 3 kcal/mol. Consequently, avoidance of eclipsing is the dominant factor only for structures with no hydrogen bonds—in this group there are only two minima, one near the North pole of the pseudorotational itinerary (**L005**$_{0H}$) and one near the South pole (**L169**$_{0H}$). For structures with one hydrogen bond, in addition to the two regions of minimal eclipsing represented by **L008**$_{1H}$−**L017**$_{1H}$ and **L161**$_{1H}$−**L165**$_{1H}$, one local minimum in a region of moderately severe eclipsing, **L074**$_{1H}$, also appears, and for structures with two or more hydrogen bonds, conformers even in regions of the most severe eclipsing such as $P = 135°$ and 95° join the list of local minima. Of the 20 local minima, seven are in the region of $P = 165°$, five are in the region of $P = 10°$, and four cluster around $P = 135°$, suggesting that these may be preferred conformations of methyl α-D-lyxofuranoside. Closer inspection shows that the minima near $P = 10°$ have at most one hydrogen bond; minimization of models in the Northern region, around $P = 10°$, with exocyclic rotamers preoriented for formation of additional hydrogen bonds inevitably leads to large changes in ring conformation. Only structures in the Southern region, around $P = 165°$, have a natural predisposition to a large variety of stable hydrogen bonding patterns combined with minimal eclipsing. Although the neat description of the conformational energetics of methyl α-D-lyxofuranoside presented above is qualitatively appealing, discrepancies at the quantitative level suggest that our understanding of these systems is still somewhat limited. Analysis of the structures of the remaining seven methyl α-D-pentofuranosides and minimization at yet higher levels of theory might help resolve these problems.

In our previous paper,[1] we have described DFT energy minimizations of several methyl pentofuranosides using their accurate crystal structures as starting models. These minimizations resulted in final structures having *P* values very close to those observed in the crystal—with the notable exception of methyl α-D-lyxofuranoside. The present work explains this exceptional behavior and provides a link between the theoretical gas-phase structures and the conformation of the furanosides observed in the crystal.

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Supporting Information Available: Tables of atomic coordinates and anisotropic displacement factors of the neutron structure of partially deuterated methyl α-D-lyxofuranoside as well as Cartesian coordinates of all the final structures discussed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In the present paper we adopt the following nomenclature for starting models and final structures: all the names begin with the letter **L** (for lyxose), followed by the rounded value of *P*. Predisposed hydrogen bonds in the starting models are denoted in the subscript, e.g., **L165**$_{O3-H>O4}$ stands for a starting model with $P = 165°$ and a predisposed hydrogen bond O3−H···O4. If the starting model is predisposed to have no hydrogen bonds, it is designated with "nH" in the subscript. The number of observed hydrogen bonds in the final structures is denoted in the subscript, e.g., **L132**$_{2H}$ stands for a final structure with $P = 132°$ and two internal hydrogen bonds. **L028**$_{C}$ is the starting model derived from the crystal structure.

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