Methyl 4-*O*-Acetyl-3-azido- and 3-Azido-4-*O*-methylsulfonyl-2,3,6,-trideoxyhex-5-enopyranosides in DFT-Level Conformational Studies

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Geometry optimizations at the B3LYP level of density functional theory (DFT) are reported for methyl 4-*O*-acetyl-3-azido- and 3-azido-4-*O*-methylsulfonyl-2,3,6-trideoxy-α,*β*-D-*threo*- and -*β*-D-*erythro*-hex-5-enopyranosides. The most stable conformers for each compound are presented, along with the corresponding enthalpies and Gibbs free energies. The influence of the exocyclic double bond on the chair conformation is discussed. Conformations of the 1-OMe, 3-N_3, and 4-OAc groups were examined, and delocalization in the OAc and N_3 groups was demonstrated. The contributions of particular conformers to the total number of structures found for each hex-5-enopyranoside were calculated. The theoretical results are compared with assignments based on ^{1}H NMR studies.

1. Introduction

3-Azido-2,3,6-trideoxyhex-5-enopyranosides are compounds of great interest as they are intermediates in the synthesis of 3-amino-2,3,6-trideoxyhexopyranosides,[1−5] the carbohydrate constituents of anthracycline antibiotics.[6] Some of these antibiotics exhibit impressive activities against a broad range of solid tumors and soft-tissue sarcomas.[7] Additionally, 6-deoxyhex-5-enopyranosides are substrates in Ferrier carbocyclization, the most common reaction for preparing chiral-substituted cyclohexanones from aldohexoses.[8,9] Many important compounds have been synthesized using Ferrier carbocyclization and its modifications.[10−22]

Conformational characteristics of the pyranose ring are important and have been investigated in considerable depth because the biological and chemical functions of carbohydrates are intimately related to their conformational properties.[23−26] The conformations of 6-deoxyhex-5-enopyranosides undoubtedly play a significant role in the stereochemistry of the ring-closure reaction during carbocyclization.[27,28]

The synthesis of methyl 4-*O*-acetyl-3-azido- and 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxyhex-5-enopyranosides with the α-*threo*, *β*-*threo*, and *β*-*erythro* configurations of the D[29] and L[30] series was described earlier (Figure 1). Conformational analysis of these hex-5-enopyranosides based on ^{1}H NMR studies enabled the discovery of interesting relationships with respect to the influence of the 5-methylene substituent on the pyranose ring. The geometry optimizations for methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-D-*threo*- (**1**), -*β*-D-*threo*- (**3**), and -*β*-D-*erythro*-hex-5-enopyranosides (**4**) and for 3-azido-4-*O*-methylsulfonyl-2,3,6-trideoxy-α-D-*threo*- (**2**) and -*β*-D-*erythro*-hex-5-enopyranosides (**5**) using the B3LYP density functional and the 6-31+G** basis set are presented here to encourage the discussion of hex-5-enopyranoside conformations. Because the DFT level of theory has been successfully applied to geometry optimizations of simple aldohexoses and aldohexosides,[31−34] it was decided to use this approach for the 3-azido-2,3,6-trideoxyhex-5-enopyranosides. The D series compounds were chosen as the representative group for the calculations. To simplify the theoretical calculations, the methylsulfonyl (mesyl) group was introduced in place of the *p*-tolylsulfonyl (tosyl) group used in our synthesis.

2. Methods

Taking into account rotation about the three single bonds attached to the pyranose ring and the additional single bond in the OAc or OMs groups, 34 structures for both $^4C_1$ and $^1C_4$ conformations and for each compound (**1**−**5**) were prepared in the MOLDEN program.[35] These prepared structures were initially optimized in the MOPAC93 package[36] with the PM3 method.[37,38] During the optimization procedure, the number of structures was significantly reduced because many were converted to the same optimized structure. It also became obvious during the optimization procedure that some of the examined rotamers are extremely unfavorable. Next, the B3LYP nonlocal exchange correlation functionals and the 6-31+G** basis set were used to conduct a full geometry optimization. Optimization was considered satisfactory if the energy difference between optimization cycles was $<1 \times 10^{-6}$ Hartree and a gradient of $<1 \times 10^{-4}$ au was achieved. The convergence of all of the systems studied was checked by harmonic vibrational analysis. No imaginary frequencies were observed. All calculations were done under default conditions (without any modifications or additional parameters) using the Gaussian 03 program.[39]

As the result of geometry optimization, the total electronic energies, E_{tot}, were obtained. Then, the thermochemical analysis was performed based on the harmonic vibrational frequencies. In this way, the zero-point energy, ZPE, and thermal correction to the energy, $E_{(0-298)}$, were obtained. The sum of the total energy (E_{tot}) and the ZPE gave the zero-point-corrected total energy, E_0. Calculation of the enthalpy at 298.15 K was based on the equation $H_{298} = E_{298} + RT$, where E_{298} is the sum of the electronic energy and the thermal correction to the energy ($E_0 + E_{(0-298)}$). Calculation of the Gibbs free energy (sum of the electronic and thermal free energies) at 298.15 K was based on the equation $G_{298} = H_{298} - TS_{298}$.

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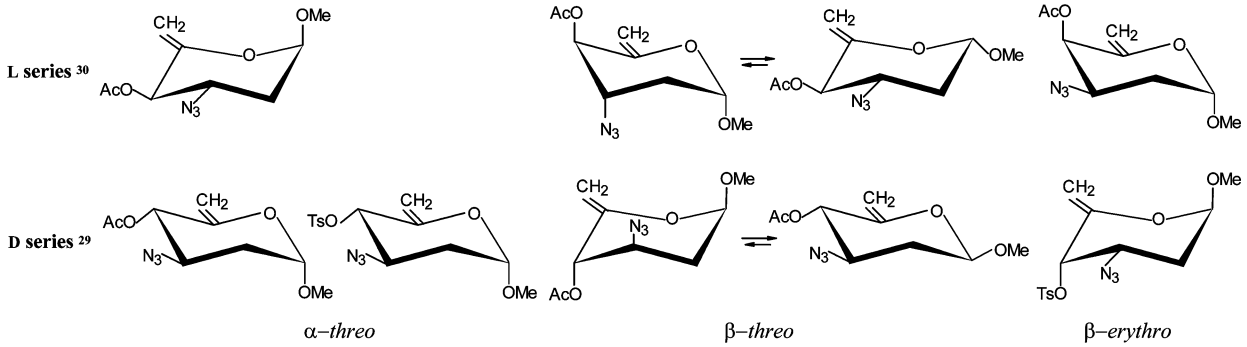


Figure 1. Previously reported conformations of 3-azido-2,3,6-trideoxyhex-5-enopyranosides in solution.

The contribution of each conformer to the equilibrium was calculated using the equation

$$\frac{e^{-\Delta G_i/RT}}{\sum_N e^{-\Delta G_i/RT}} \quad (1)$$

3. Results

Geometry optimization of 3-azido-2,3,6-trideoxyhex-5-enopyranosides of the D series (**1**−**5**) using the B3LYP/6-31+G** level yields 28 relatively stable structures, i.e., those with the lowest energy. Two of the most stable $^4C_1$ conformers (**1a**,**b**, **2a**,**b**, **3a**,**b**, and **4a**,**b**) and two of the most stable $^1C_4$ conformers (**1c**,**d**, **2c**,**d**, **3c**,**d**, **4c**,**d** and **5c**,**d**) were chosen from these 28 structures (Figure 2). In the case of **5**, only one stable $^4C_1$ conformer (**5a**) was found; in the case of **3**, an additional, relatively stable $^2S_0$ conformer (**3s**) was also found. The enthalpies and Gibbs free energies corresponding to these structures are listed in Table 1.

4. Discussion of Geometry

With the exception of structure **3s**, the lowest-energy structures of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides are not deformed chair conformations. This means that the addition of an sp^2-hybridized carbon atom to the pyranose ring does not prevent this ring from adopting the chair form. Although ring-puckering parameters are usually applied to assess the "quality" of a chair conformation,[40] visualizing the sugar geometry on the basis of these parameters is problematic. To assess qualitatively the effect of the presence of an exocyclic double bond on the ring conformation of the optimized structures, a set of three improper dihedral angles was adopted.[41,42] Their definition and values are presented in Table 2. The suggested ideal chair conformation requires that these three dihedral angles be ±35°. Thus, any flattening of the ring should result in a decrease of these angles. Although the DFT geometry-optimized chair conformers of D-glucopyranose differ from the ideal improper dihedral angles by about 4° on average, owing to the inherent asymmetry of glucose and its intramolecular interactions, it seems that more accurate assessments are unavailable among the glucopyranose chairs.[41] Our results show that the improper dihedral angles for chair conformers of the 5-enoglycosides are additionally decreased by ca. 1° relative to those of D-glucopyranose. The 1° difference in the DFT geometry-optimized chair conformers of D-glucopyranose and 3-azido-2,3,6-trideoxyhex-5-enopyranosides indicates a small flattening of the chair conformers, probably as a result of the sp^2 hybridization of the C5 carbon atom.

For comparison, values of the improper dihedral angles for the chair conformers of methylenecyclohexane (**enhex**) and 2-methylenetetrahydropyrane (**enpyr**) are included in Table 2. The results of the DFT geometry optimizations of these two compounds show that the ring oxygen atom exerts a significant influence on the flattening of the chair conformers.

To study the conformation of particular groups in optimized methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides, some of the dihedral angles were generated from the structures presented in Figure 2. These angles are listed in Table 3, and the numbering system used to describe these angles is illustrated in Figure 3.

All of the lowest-energy structures found are rotamers with the methyl group oriented in an antiperiplanar fashion with respect to the C2 carbon atom (C7−O1−C1−C2 torsion angle = ±170.3−173.1°), in both the axial and the equatorial orientations of the methoxy group. Stabilization of this O1−C1 rotamer results from the *exo*-anomeric effect, an important factor affecting the geometry of *O*-glycosides.

Rotation about the N3−C3 bond, which results in different arrangements of the 3-N_3 group relative to the ring, is not typical, because the N3 nitrogen atom is sp^2-hybridized whereas the C3 carbon atom is sp^3-hybridized. Such a hybridization of the N3 nitrogen atom is due to the resonance structures of the azide group and is confirmed by the N4−N3−C3 valence angle of 115.3−121.0° (average 116.5°). The effect of the different hybridizations of the N3 and C3 atoms is that the antiperiplanar orientation of the N4 nitrogen atom to each of the atoms bound to the C3 carbon atom results in repulsion between the lone pair of electrons on N3 and the electrons of the respective bonds (Figure 4). It seems that the most stable N3−C3 rotamers should be those with the N4−N3−C3−H3, N4−N3−C3−C2, or N4−N3−C3−C4 torsion angle equal to ±30°. In fact, these torsion angles lie within the range of ±25−48° for all of the structures of the methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides presented here, except for **2b**. It is likely that such a range is the result of a compromise between unfavorable steric (van der Waals repulsion) and electronic (electrons repulsion) interactions. Steric interactions are the probable cause for the rotamers with the N4−N3−C3−H3 torsion angle equal to 25−48° being the most favorable: this is demonstrated for all the $^4C_1$ (**1a**,**b**−**4a**,**b**, and **5a**), $^2S_0$ (**3s**), and some $^1C_4$ (**1c**,**d**, **2c**,**d**, **4c**) conformations (Figure 4). The other stable N3−C3 rotamers (Figure 4) are those with the N4−N3−C3−C4 torsion angle of about 40° (**3c**, **5c**) or the N4−N3−C3−C2 torsion angle in the 42−45° range (**3d**, **4d**, **5d**). A small exception to this rule is the 3-azido glycoside **2b**, for which the N4 nitrogen atom is eclipsed by the H3 hydrogen atom with a N4−N3−C3−H3 torsion angle of about 7°; this is probably due to the relatively large van der Waals radius of the 4-OMs group.

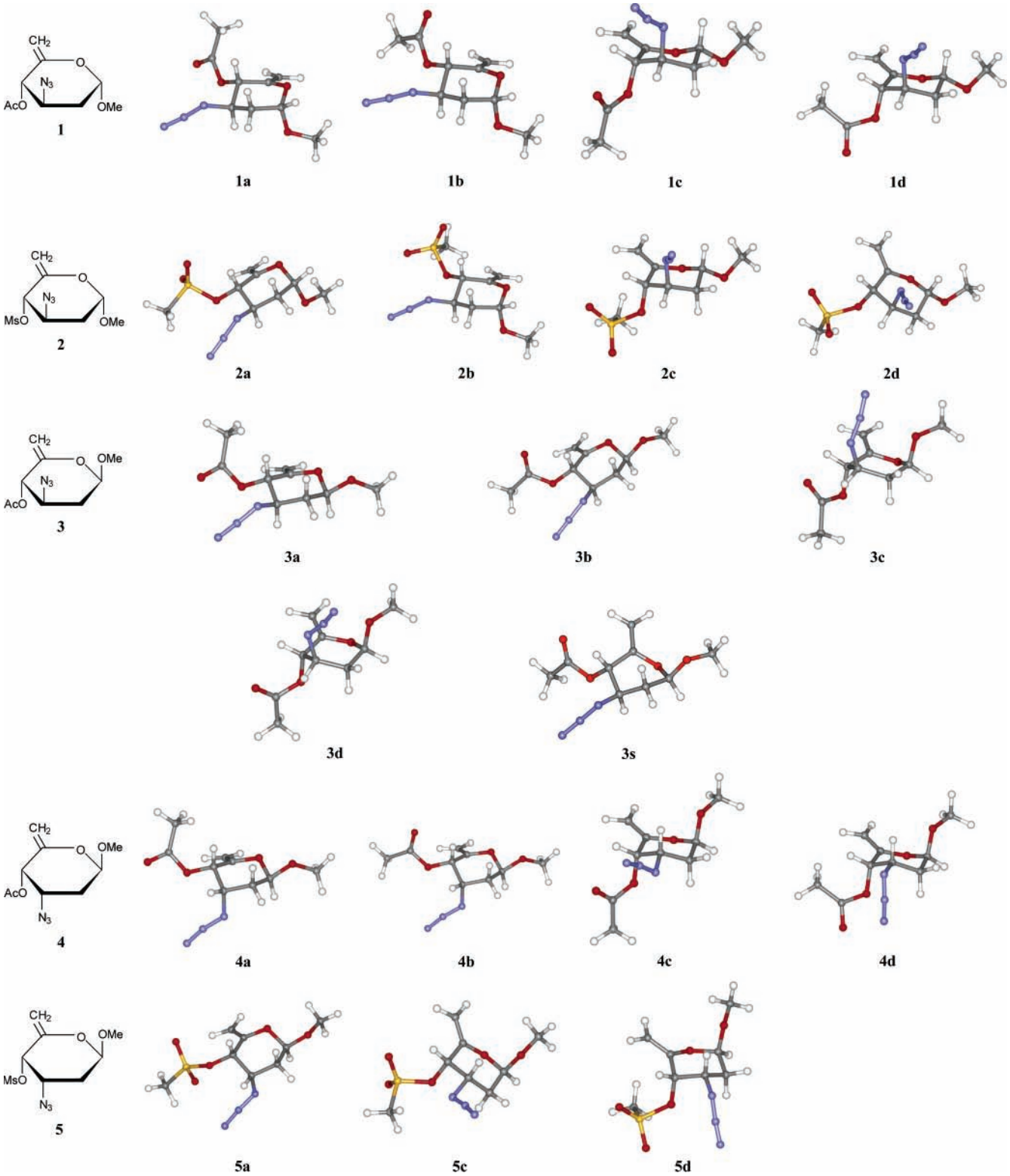


Figure 2. Most stable structures of geometry-optimized methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides **1**−**5**.

In the case of the 4-OAc group, the C8−O4 rotamers, unlike the N3−C3 rotamers, adopt only two conformations, in which the carbonyl oxygen (O5) or the methyl group is oriented in antiperiplanar fashion with respect to the C4 carbon atom (Figure 5). These two conformations are strongly preferred, despite the eclipsed orientation of the CH_3 group and the C4 atom (**1a**,**d**, **3a**, **4a**,**d**) or the O5 and C4 atoms (**1b**,**c**, **3b**,**c**,**d**,**s**, **4b**,**c**), because only they enable the *O*-acetyl group to delocalize the O4 oxygen lone pair of electrons onto the carbonyl oxygen. Such a delocalization stabilizes these rotamers and increases the C8−O4 rotational barrier. Rotations about the analogous S4−O4 bond in **2** and **5** are not so much in evidence.

Rotation of the 4-OAc group about the O4−C4 bond (Figure 6) does not give preference to any of the typical staggered conformations. The most stable O4−C4 rotamers are those with C8−O4−C4−C3 torsion angles ranging from 130° to 154° (**1a**,**b**,**d**, **3a**−**s**, **4a**,**d**) or from 90° to 109° (**1c**, **4b**,**c**). This recalls the above-mentioned rotation about the bond with the sp^2- and

TABLE 1: Energy Parameters of the Most Stable Conformers of Methyl 3-Azido-2,3,6-trideoxyhex-5-enopyranosides 1−5

structure	*H* (au)	*G* (au)	Δ*H* (kcal/mol)	Δ*G* (kcal/mol)
1a	−815.638 395	−815.700 827	6.8842	7.3590
1b	−815.649 372	−815.712 473	0	0.0552
1c	−815.645 761	−815.709 503	2.2646	1.9178
1d	−815.632 762	−815.695 292	10.4170	10.8302
2a	−1250.876 205	−1250.941 693	0	0
2b	−1250.874 14	−1250.940 27	1.2951	0.8924
2c	−1250.873 233	−1250.938 899	1.8639	1.7522
2d	−1250.872 524	−1250.939 738	2.3085	1.2261
3a	−815.636 678	−815.699 203	7.9610	8.3775
3b	−815.647 236	−815.710 516	1.3396	1.2825
3c	−815.642 781	−815.705 832	4.1335	4.2201
3d	−815.644 912	−815.707 809	2.7971	2.9802
3s	−815.644 701	−815.708 265	2.9294	2.6942
4a	−815.634 375	−815.696 144	9.4054	10.2959
4b	−815.647 011	−815.709 574	1.4807	1.8733
4c	−815.648 114	−815.712 561	0.7889	0
4d	−815.635 66	−815.697 91	8.5995	9.1884
5a	−1250.873 749	−1250.939 41	1.5403	1.4318
5c	−1250.875 301	−1250.940 847	0.5669	0.5306
5d	−1250.874 983	−1250.939 94	0.7664	1.0994

TABLE 2: Improper Dihedral Angles[a] for Geometry-Optimized Methyl 3-Azido-2,3,6-trideoxyhex-5-enopyranosides 1−5

structure	C4−O5−C2−C1	O5−C2−C4−C3	C2−C4−O5−C5
1a	−29.43	−33.18	−30.56
1b	−29.29	−34.42	−28.87
1c	31.93	31.11	24.73
1d	30.81	30.97	28.9
2a	−29.80	−33.70	−29.63
2b	−29.76	−33.85	−28.52
2c	31.66	30.54	26.64
2d	32.23	29.94	25.55
3a	−30.34	−30.90	−34.26
3b	−30.67	−32.07	−32.2
3c	29.3	26.9	26.2
3d	27.2	29.9	26.0
4a	−30.1	−32.2	−32.5
4b	−31.1	31.9	−29.8
4c	29.3	35.6	24.6
4d	27.8	36.5	27.3
5a	−31.5	−31.2	−29.0
5c	29.2	36.5	23.9
5d	29.4	35.0	26.1
enhex	−32.2	−32.2	−30.3
enpyr	−31.9	−32.9	−26.1

[a] Values in degrees.

sp^3-hybridized atoms (N3−C3 rotamers). This evidence again confirms the delocalization of the O4 oxygen lone pairs of electrons in the OAc group, which causes the O4 oxygen atom to be sp^2-hybridized. Otherwise, the O4−C4 rotamers should be similar to the O1−C1 rotamers with typical staggered conformations. It is worth noting that the C8 carbonyl atom prefers the neighborhood of the C5 carbon atom.

In the case of the sulfur analogs, the S4−O4−C4−C3 torsion angles resemble the C8−O4−C4−C3 torsion angles, which is indicative of the delocalization of the O4 oxygen lone pairs of electrons onto the S═O oxygen atom.

All of the O4−C4−C5−C6 torsion angles are divided into three groups depending on the conformation of the pyranose ring. When the methyl 3-azido-2,3,6-trideoxy-D-hex-5-enopyranosides adopt the $^4C_1$ conformation, the O4−C4−C5−C6 dihedral angles vary from 7° to 12°; this is due to the equatorial orientation of the group bound to the C4 carbon atom and the almost planar orientation of the O4, C4, C5, and C6 atoms.

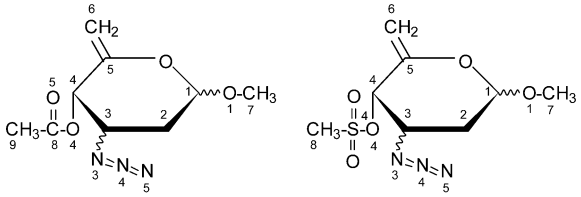


Figure 3. Numbering system used to describe the dihedral angles listed in Table 3.

This unfavorable coplanar orientation of the 4-OAc or 4-OMs and 5═CH$_2$ groups, known as allylic strain,[43] is one of the factors affecting the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium of the 3-azido-2,3,6-trideoxyhex-5-enopyranosides.[30] The O4−C4−C5−C6 torsion angles in the 103−113° range are the consequence of the axial orientation of the 4-OAc or 4-OMs groups, which corresponds to the $^1C_4$ conformation of the compounds under discussion. The O4−C4−C5−C6 torsion angle for **3s** is different (77.5°) because of the $^2S_0$ conformation.

5. Discussion of the Pyranose Ring Conformations

Our previous findings, based on ^{1}H NMR spectra, indicate that an exocyclic double bond introduced onto the C5 carbon atom causes the conformations of 3-azido-2,3,6-trideoxyhex-5-enopyranosides to become much more flexible in comparison with those of 3-azido-2,3-dideoxyhexopyranosides or 3-azido-6-iodo-2,3,6-trideoxyhexopyranosides.[29,30] The latter always adopt the $^4C_1$ conformation in solution, but the former adopt the $^4C_1$ or $^1C_4$ conformation or remain in $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium, depending on the configuration of the C1, C3, and C4 carbon atoms.

The most stable $^4C_1$ conformers (**1a**,**b**, **2a**,**b**, **3a**,**b**, **4a**,**b**, and **5a**) and the most stable $^1C_4$ conformers (**1c**,**d**, **2c**,**d**, **3c**,**d**, **4c**,**d**, and **5c**,**d**), along with the one stable $^2S_0$ conformer (**3s**), of 3-azido-2,3,6-trideoxyhex-5-enopyranosides (Figure 2) found during the DFT geometry optimizations were used to calculate (eq 1) the contribution of a particular conformer to the total number of stable structures for each compound. The results of these calculations (Table 4) show that there is one preferred stable conformation for each **1** (α-D-*threo*-) and **4** (-*β*-D-*erythro*-)—$^4C_1$ and $^1C_4$, respectively—with a total population of 96%. In the cases of **2** (-α-D-*threo*-), **3** (-*β*-D-*threo*-), and **5** (-*β*-D-*erythro*-), the energy differences between particular conformers found during the DFT geometry optimizations are not as significant as in **1** and **4**; this results in 87.3% (**2**), 86.5% (**3**), and 13.9% (**5**) contributions of the $^4C_1$ form to the total number of structures. With regard to *O*-acetyl derivatives (**1**, **3**, **4**), these findings agree with our previously reported results based on ^{1}H NMR analysis.[29,30] The ^{1}H NMR spectra indicate beyond any doubt that **1** and **4** adopt the $^4C_1$ and $^1C_4$ conformations, respectively, in $CDCl_3$ solution. The $^4C_1$ conformation is optimal for **1** because the 3-N$_3$ group is equatorially oriented and the anomeric effect is favorable (without a 1,3-diaxial interaction between the 1-OMe and 3-N$_3$ groups). For exactly the same reasons, **4** adopts the $^1C_4$ conformation, which is demonstrated by the ^{1}H NMR spectra and the DFT calculations. The conclusion drawn from the respective coupling constants of **3** was that conformational equilibrium exists between the $^4C_1$ and $^1C_4$ forms of this compound in solution. The adoption by **3** of one of the skew-boat forms was also taken into account. The findings presented in this article confirm previous statements, as the 86.5% contribution of $^4C_1$ to the total number of stable conformers of **3** suggests a conformational equilibrium in which

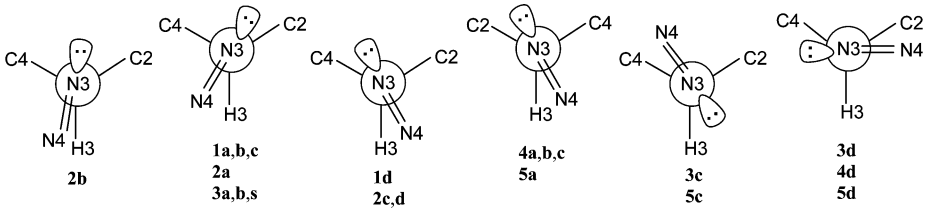


Figure 4. N3−C3 rotamers of the geometry-optimized structures of **1**−**5**.

TABLE 3: Selected Dihedral Angles[a] Generated from the Geometry-Optimized Structures of 1−5

structure	C7−O1−C1−C2	N4−N3−C3−C2	O5−C8−O4−C4[b] or C8−S4−O4−C4[c]	C8−O4−C4−C3[b] or S4−O4−C4−C3[c]	O4−C4−C5−C6
1a	−171.9	−145.5	175.9	142.0	10.7
1b	−172.4	−155.1	2.1	130.5	12.5
1c	−171.7	−166.2	−2.4	89.8	103.8
1d	−172.4	−72.0	177.9	152.4	113.2
2a	−173.1	−149.6	−136.0	142.9	12.7
2b	−172.1	−127.4	138.2	106.8	11.6
2c	−171.2	−76.4	98.5	152.3	108.9
2d	−172.3	−79.5	160.2	86.9	105.3
3a	171.9	−147.4	175.0	144.7	7.1
3b	172.9	−155.3	2.0	131.6	9.6
3c	172.8	80.3	−3.4	145.9	104.1
3d	172.6	−44.9	−3.6	145.2	105.2
3s	170.3	−156.6	1.2	146.9	77.5
4a	171.1	157.9	176.8	146.5	7.3
4b	171.7	159.8	−1.3	89.8	9.7
4c	171.8	154.2	2.0	108.9	105.5
4d	172.0	−41.7	174.3	151.8	112.6
5a	171.8	160.3	−171.6	98.3	12.1
5c	172.7	78.6	−111.8	128.9	105.4
5d	171.3	−42.1	99.9	154.4	108.7

[a] Values in degrees. [b] For compounds **1**, **3**, and **4**. [c] For compounds **2** and **5**.

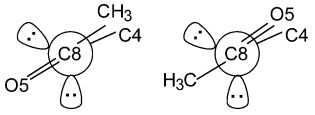
TABLE 4: Contributions of the Various Conformers to the Total Number of Stable Structures Found for 1−5

structure	conformation	$\Delta G°_{298}$[a]	$\exp(-\Delta G/RT)$	contribution[b]	total contribution of the $^4C_1$ conformer[b]
1a	$^4C_1$	7.30	4.33×10^{-6}	0.0	96.0
1b	$^4C_1$	0.00	1.00	96.0	
1c	$^1C_4$	2.28	0.04	4.0	
1d	$^1C_4$	10.93	1.22×10^{-8}	0.0	
2a	$^4C_1$	0.00	1.00	71.5	87.3
2b	$^4C_1$	0.89	0.22	15.8	
2c	$^1C_4$	1.75	0.05	3.7	
2d	$^1C_4$	1.23	0.13	9.0	
3a	$^4C_1$	7.10	6.17×10^{-6}	0.0	86.5
3b	$^4C_1$	0.00	1.00	86.5	
3c	$^1C_4$	2.94	6.97×10^{-3}	0.6	
3d	$^1C_4$	1.70	0.06	4.9	
3s	$^2S_0$	1.41	0.09	8.0	
4a	$^4C_1$	10.30	2.76×10^{-8}	0.0	4.0
4b	$^4C_1$	1.87	0.04	4.0	
4c	$^1C_4$	0.00	1.00	96.0	
4d	$^1C_4$	9.19	1.79×10^{-7}	0.0	
5a	$^4C_1$	0.89	0.22	13.9	13.9
5c	$^1C_4$	1.00	1.00	62.3	
5d	$^1C_4$	0.38	0.38	23.8	

[a] Relative Gibbs free energies in kcal/mol. [b] Values in percent.

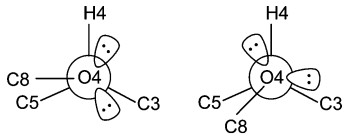
the $^2S_0$ form (**3s**) is intimately (8%) involved. This equilibrium results from the relatively small energy difference between the $^4C_1$ and $^1C_4$ conformations of **3**. This is because the *endo*-anomeric effect in the $^1C_4$ conformation of **3** is not as favorable as it is in the $^4C_1$ conformation of **1** or the $^1C_4$ conformation of **4**, because of the unfavorable diaxial interactions of the 1-OMe and 3-N_3 groups. The change of conformation into the $^4C_1$ form allows **3** to avoid these unfavorable diaxial interactions, and by the same token, the *endo*-anomeric effect is also avoided. The contribution of $^4C_1$ (86.5%) to the $^4C_1 \rightleftarrows {}^2S_0 \rightleftarrows {}^1C_4$ conformational equilibrium of **3** indicates that the more important of these two competitive factors are the 1,3-diaxial interactions between the 1-OMe and 3-N_3 groups. Also, comparison of the Gibbs free energies of **1c** and **3d** suggests that the decrease in stability resulting from the 1,3-diaxial interactions between the 3-N_3 and 1-OMe groups (**3d**) is greater than that resulting from the avoidance of the *endo*-anomeric effect (**1c**).

Comparison of the Gibbs free energies of the $^4C_1$ conformation of **1** and the $^1C_4$ conformation of **4** indicates that the above-



1a,d **1b,c**
3a **3b,c,d,s**
4a,d **4b,c**

Figure 5. C8−O4 rotamers of geometry-optimized structures of **1**, **3**, and **4**.



1a,b,d **1c**
3a-s **4b,c**
4a,d

Figure 6. O4−C4 rotamers of geometry-optimized structures of **1**, **3**, and **4**.

mentioned allylic strain has no evident influence on the chair conformation of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides. This unfavorable strain in the $^4C_1$ conformation probably competes with the 1,3-diaxial interactions of the 4-OAc group and the axial H-2 proton in the $^1C_4$ conformation. These two factors are therefore of the least importance with regard to the conformational analysis of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides.

For the *O*-methylsulfonyl derivatives **2** and **5**, our theoretical studies differ slightly from the ^{1}H NMR findings, which were obtained for the analogous *O*-*p*-tolylsulfonyl compounds. On the basis of the DFT calculations, it can be stated that **2** remains in $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium with a preference for the $^4C_1$ conformation (87.3%). ^{1}H NMR spectra of the analogous *O*-tosyl derivative indicate that 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*threo*-hex-5-enopyranoside (Figure 1),[29] like its *O*-acetyl analog **1**, unequivocally adopts the $^4C_1$ conformation in solution. Similarly, the theoretical calculations performed for **5** point to a $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium with a preference for the $^1C_4$ conformation (86.1%); the results of ^{1}H NMR studies indicate that 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (Figure 1),[29] like its *O*-acetyl analog **4**, undoubtedly adopts the $^1C_4$ conformation in solution. The observed differences between the conformational analysis of **2** and **5** based on DFT theory studies and conformational analysis of the *O*-tosyl derivatives of **2** and **5** (Figure 1) based on ^{1}H NMR studies probably result from the different *O*-protective groups. The *O*-mesyl group used here for geometry optimization, though very similar to the *O*-tosyl group for a number of reasons, can have quite a different influence on the conformational energy, because the shapes and van der Waals radii of these two groups are different.

6. Conclusions

Geometry optimizations at the B3LYP level of density functional theory permit an in-depth discussion of the conformations of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides. Studies of the optimized structures yield interesting findings concerning the *exo*-anomeric effect and the geometry of the N_3 and OAc groups. Both groups have been extensively explored in sugar and organic chemistry. With regard to the flexibility and conformational preferences of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides, the results of calculations based on DFT theory agree with our previous findings based on ^{1}H NMR studies. The most important factors affecting the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium in the case of methyl 3-azido-2,3,6-trideoxyhex-5-enopyranosides are the equatorial orientation of the 3-N_3 group and the axial orientation of the 1-OMe group. Competition between these two factors causes methyl 3-azido-2,3,6-trideoxyhex-5-enopyranoside **3** to remain in $^4C_1 \rightleftarrows {}^2S_0 \rightleftarrows {}^1C_4$ conformational equilibrium.

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References and Notes

(1) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.
(2) Bovin, J.; Païs, M.; Monneret, C. *Carbohydr. Res.* **1978**, *64*, 271.
(3) Cheung, T.-M.; Horton, D.; Sorenson, R. J.; Weckerle, W. *Carbohydr. Res.* **1978**, *63*, 77.
(4) Pelyvas, I.; Sztaricskai, F.; Szilagyi, L.; Bognar, R.; Tamas, J. *Carbohydr. Res.* **1979**, *68*, 321.
(5) Pelyvas, I.; Sztaricskai, F.; Szilagyi, L.; Bognar, R.; Tamas, J. *Carbohydr. Res.* **1979**, *76*, 79.
(6) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.
(7) Suarato, A.; Angelucci, F.; Bargiotti, A. *Chimicaoggi* **1990**, *8*, 9.
(8) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455.
(9) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.
(10) Pelyvas, I. F.; Madi-Puskas, M.; Toth, Z. G.; Varga, Z.; Batta, G.; Sztaricskai, F. *Carbohydr. Res.* **1995**, *272*, C5.
(11) Wang, L.-X.; Sakairi, N.; Kuzuhara, H. *Carbohydr. Res.* **1995**, *275*, 33.
(12) Chung, S.-K.; Yu, S.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1461.
(13) Thum, O.; Chen, J.; Prestwich, G. D. *Tetrahedron Lett.* **1996**, *37*, 9017.
(14) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1997**, *38*, 5933.
(15) Dubreuil, D.; Cleophax, J.; Viera de Almeida, M.; Verre-Sebrié, C.; Liaigre, J.; Vass, G.; Gero, S. D. *Tetrahedron* **1997**, *53*, 16747.
(16) Amano, S.; Takemura, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Tetrahedron* **1999**, *55*, 3855.
(17) Takahashi, H.; Kittaka, H.; Ikegami, S. *Tetrahedron Lett.* **1998**, *39*, 9707.
(18) Van Hooft, P. A. V.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 1769.
(19) Hladezuk, I.; Olesker, A.; Tchertanov, L.; Cleophax, J. *Carbohydr. Res.* **2001**, *330*, 257.
(20) Ko, K.-S.; Zea, C. J.; Pohl, N. L. *J. Am. Chem. Soc.* **2004**, *126*, 13188.
(21) Imuta, S.; Ochiai, S.; Kuribayashi, M.; Chida, N. *Tertahedron Lett.* **2003**, *44*, 5047.
(22) Jia, C.; Pearce, A. J.; Blériot, Y.; Zhang, Y.; Zhang, L.-H.; Sollogoub, M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **2004**, *15*, 699.
(23) Tang, T. H.; Whitfield, D. M.; Douglas, S. P.; Krepinsky, J. J.; Csizmadia, I. G. *Can. J. Chem.* **1992**, *70*, 2434.
(24) Martin, X.; Moreno, M.; Lunch, J. M. *Tetrahedron* **1994**, *50*, 6689.
(25) Bérces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460.
(26) Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765.
(27) Laszlo, P.; Pelyvas, I. F.; Sztaricskai, F. *Carbohydr. Res.* **1988**, *175*, 227.
(28) Machado, A. S.; Dubreuil, D.; Cleophax, J. *Carbohydr. Res.* **1992**, *233*, C5.
(29) Liberek, B.; Dabrowska, A.; Frankowski, R.; Smiatacz, Z. *J. Carbohydr. Chem.* **2004**, *23*, 425.
(30) B. Liberek *Carbohydr. Res.* **2005**, *340*, 2039.
(31) Tvaroška, I.; Taravel, F. R.; Utille, J. P.; Carver, J. P. *Carbohydr. Res.* **2002**, *337*, 353.
(32) Momany, F. A.; Appell, M.; Strati, G.; Willett, J. L. *Carbohydr. Res.* **2004**, *339*, 553.
(33) Nyerges, B.; Kovacs, A. *J. Phys. Chem. A* **2005**, *109*, 892.
(34) Momany, F. A.; Appell, M.; Willett, J. L.; Bosma, W. B. *Carbohydr. Res.* **2005**, *340*, 1638.
(35) Schaftenaar, G; Noordik, J. H. *J. Comput.-Aided Mol. Design* **2000**, *14*, 123.
(36) Stewart, J. J. P. *MOPAC93*; Fujitsu: Tokyo, Japan, 1993.
(37) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
(38) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.;

Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2004.

(40) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc*. **1975**, *97*, 1354.

(41) Joshi, N. V.; Rao, V. S. R. *Biopolymers* **1979**, *18*, 2993.

(42) Appell, M.; Strati, G.; Willett, J. L.; Momany, F. A. *Carbohydr. Res.* **2004**, *339*, 537.

(43) Ferrari, Ch.; Kleinpeter, E.; Taddei, F. *J. Mol. Struct. (THEOCHEM)* **2001**, *548*, 93.