Ab Initio Molecular Orbital Calculation on Carbohydrate Model Compounds. 1. The Anomeric Effect in Fluoro and Chloro Derivatives of Tetrahydropyran

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Ab Initio Molecular Orbital Calculation on Carbohydrate Model Compounds. 1. The Anomeric Effect in Fluoro and Chloro Derivatives of Tetrahydropyran

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Ab initio calculations have been carried out on model compounds for the pyranose halides 2-fluoro- and 2-chlorotetrahydropyran with either an axially or an equatorially oriented halogen atom. Energy minimization has been carried out at the STO-3G, 3-21G, 6-31G, 6-31G*, 6-31+G*, and MP2/6-31G* levels. The optimized geometries were used to calculate the energy difference between the axial and equatorial conformers with STO-3G, 3-21G, 4-31G, 6-31G, 6-31G*, 6-31G**, 6-31+G*, 6-311G*, 6-31+G**, 6-311++G**, and MP2/6-31G* basis sets. Large differences in C–Hal bond lengths and O–C–Hal bond angles were found between the axial and equatorial conformers. After including the zero-point energy, thermal energy, entropy, and MP3 electron correlation corrections to energy differences calculated at 6-311++G**//6-31+G* basis set, these calculations favored the axial conformers by 2.4 and 2.5 kcal/mol. Solvent effects considerably reduce this energy difference; in the extreme case, in water, values of 0.5 and 1.5 kcal/mol were obtained for fluoro and chloro derivatives, respectively. The magnitude of the anomeric effect depends on the solvent and was estimated to be in the range 0.9-2.8 kcal/mol for the fluoro and 2.3-3.1 kcal/mol for the chloro forms. On the basis of these results, we suggest that the 6-31+G*//6-31G* procedure is suitable for calculations of the geometry and the conformational energies of carbohydrate molecules. The calculated energies and geometries provide additional data which should prove useful in the reparametrization of existing force fields to better reproduce the behavior of C–O–Hal systems.

Introduction

The determination of the ensemble of three-dimensional structures accessible to oligosaccharides is an essential step to understanding their biological function. Unfortunately, most experimental constraints are ensemble averages and hence cannot supply direct information about the discrete structures present in the ensemble. As a result, experimentalists must rely on models for the interpretation of the data. Conversely, theoretical approaches to the generation of three-dimensional structures for oligosaccharides rely on experimental data for their parameterization. When these data are averages, they cannot be used to directly parameterize the models, although they can subsequently provide useful tests of the validity of any given model. Because of the importance of the anomeric and exoanomeric effects in determining the three-dimensional structures of oligosaccharides,[1-6] particular care must be used in the parameterization of force fields for oligosaccharides.

Ab initio calculations provide a potential means of escaping from the circular problem outlined above. The results of such calculations can be used as a supplement to the limited experimental data available. Recently, we reported[7,8] the results of calculations at the semiempirical AM1 level for a set of models of monosaccharides. Although experimentally determined geometries were adequately reproduced, the calculated energies associated with the anomeric effect were significantly in error. In this paper we report the results of calculations aimed at determining the basis set which gives accurate geometries and energies for monosaccharide models. This is an essential first step before expending the considerable computer time necessary to perform calculations on monosaccharides themselves.

Halogen derivatives of pyranoses provide some of the most clear manifestations of the anomeric effect. The tendency toward the stabilization of the axial orientation in these derivatives is so pronounced that, for example, acetyl and benzoyl derivatives of β-D-xylopyranosyl halides exist in solution mainly in the ${}^{1}C_{4}$ conformation with all the substituents in axial positions.[9] In this case, the anomeric effect prevails over the unfavorable 1,3 diaxial interactions of bulky substituents. Detailed examination of the molecular geometry data available for pyranosyl halides and model compounds showed characteristic patterns of bond lengths and bond angles associated with particular conformations. In the fluoride the equatorial carbon–fluorine bond is shorter than the axial by ~2 pm and significantly shorter than the 143.2 pm found for nonanomeric carbon–fluorine bonds.[10-12] Therefore, halogen derivatives of tetrahydrofuran are particularly useful in the study of the anomeric effect in carbohydrates.

A number of theoretical studies[7,8,13,14] of the conformational properties of pyranosyl halides have been carried out using cyclic compounds, namely, 2-fluorotetrahydropyran (FTHP, 2-fluorooxane) and 2-chlorotetrahydropyran (CLTHP, 2-chlorooxane). The *ab initio* STO-3G calculation[13] for 2-chlorotetrahydropyran confirmed the stabilization of the axial orientation of the chlorine atom relative to the equatorial. An energy difference of 1.2 kcal/mol was found if a C–Cl bond length of 177 pm was assumed for both conformers and 3.7 kcal/mol if the axial C–Cl bond was lengthened to 182 pm. The axial preference of both the fluorine and chlorine derivatives of tetrahydropyran was also corroborated by the results of semiempirical PCILO, MNDO, and AM1 methods.[7,8,13] Though none of these methods completely describe all features of these compounds, it was suggested that the AM1 method might be more useful in calculations of carbohydrate geometries than *ab initio* calculations with the STO-3G basis set.[7,8]
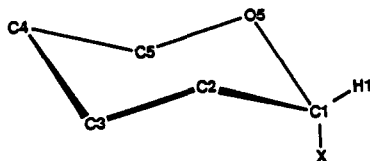
In this paper we have investigated the influence of basis set on the geometry and the conformational energy of conformers
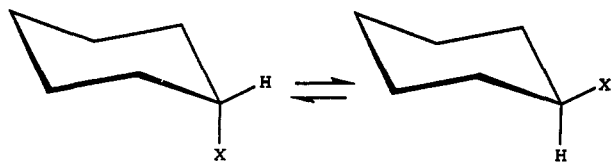
SCHEME 1

SCHEME 2

(Scheme 1) of 2-fluorotetrahydropyran and 2-chlorotetrahydropyran. The labeling of the atoms of interest is given in Scheme 2. The effect of electron correlation, zero-point energy and entropy corrections, and solvent on the calculated energies was also investigated. The aims of these calculations are the following: (*i*) to determine the *ab initio* procedure which is most suitable for the computation of the conformational energies of carbohydrate molecules in their equilibrium geometry; (*ii*) to estimate the magnitude of the anomeric effect for fluorine and chlorine substituents in different solvents; and (*iii*) to supplement experimental data with reliable estimates of the molecular stability and geometry of halide derivatives for the parameterization of force fields suitable for carbohydrates.

Calculations

The calculations were carried out using Gaussian 90[15] and Gaussian 92[16] with standard basis sets.[17] The geometries were fully optimized using gradient optimization routines in the program without any symmetry constraints. The electron correlation energy was included at the third-order Moller–Plesset perturbation (MP3) level.[18,19] Calculations of the effect of solvent upon the conformational energy differences in dilute solution were based on a model which has been used successfully to reproduce all the known solution data on 2-methoxytetrahydropyran[20] and to predict solvent effects on the conformational properties of carbohydrates.[14] In this model a cavity is formed in a polarizable dielectric continuum with the total solvation energy partitioned into three contributors: the cavity term, the electrostatic interactions, and the dispersion interactions. The model and relevant equations have been described in detail in our prevoius papers.[20,21] The calculations were carried out at the University of Toronto on HP370 and IRIS 4D/440 computers.

Results and Discussion

Geometrical Features. The optimized geometrical parameters and energies calculated at various theoretical levels are given in Tables 1–4. For comparison, the AM1 values previously calculated[7,8] are also included. The absolute values of the bond lengths, bond angles, and torsion angles depend on the level of calculation. The most pronounced geometric changes occur at the anomeric center. The STO-3G minimal basis set and the 3-21G and 6-31G split-valence basis sets predict significantly larger carbon–halogen and C–O bond lengths than those obtained at the 6-31G* level. Inclusion of p polarization orbitals on heavy atoms (i.e., 6-31G vs 6-31G*) has a dramatic effect on the carbon–halogen bond length; for example, the C–F bond length is decreased by 4.5 pm in the equatorial conformer and 5.3 pm in the axial. In CLTHP, the effect is even larger; the C–Cl bond length decreases 7.2 pm in the equatorial conformer and 10 pm in the axial one.

The geometry of conformers was also optimized at the 6-31+G* level to investigate the effect of further improvement of the basis

set on the optimized geometry. Inclusion of diffuse sp functions on non-hydrogen atoms (6-31G* vs 6-31+G*) had only a slight effect on the calculated geometry parameters.

The equilibrium geometry obtained at this level was found to be close to that obtained at the 6-31G* level; the maximum deviations of the bond lengths, bond angles, and torsion angles are 0.7 pm, 0.5°, and 0.6°, respectively. The calculated values at the 6-31G* level for the C1–F, C1–O5, C5–O5, and F–C1–O5 geometrical parameters of FTHP with an axially oriented fluorine atom were 138.1 pm, 136.7 pm, 141.7 pm, and 109.3°, which are close to the values of 138.5 pm, 136.2 pm, 142.4 pm, and 111.3°, respectively, previously reported from microwave spectra[12] of the fluorodimethyl ether and from the crystal structure of the acetyl derivative of D-xylopyranosyl fluoride[10,11] (138.9 pm, 136.2 pm, 145.8 pm, 107.5°). Similarly, for the equatorial conformer, the calculated values (135.6 pm, 137.8 pm, 140.9 pm, and 106.3°) are close to those from the crystal structure of the benzoyl derivative of D-xylopyranosyl fluoride where 136.7 pm, 140.6 pm, 142.8, and 109.8° values were observed.[10,11] In the case of CLTHP, the calculated values for C1–Cl, C1–O5, C5–O5, and C1–C1–O5 (183.9 pm 136.4 pm, 141.6 pm, and 110.9°) compare favorably with the values (182.2 pm, 136.2 pm, 142.1 pm, and 112.9°) reported for the axial conformer of the chlorodimethyl ether.[12]

The effect of electron correlation was investigated with MP2 using the 6-31G* basis set. MP2/6-31G* calculations confirm the differences in geometrical parameters between the axial and equatorial conformers calculated with the 6-31G* basis set. The effect of electron correlation on geometrical parameters is negligible, except for the C1–O5 and C1–H1 bond lengths which are about 2.5 pm longer than in the 6-31G* calculated structures. On the other hand, C1–Hal bond lengths are found to be about 1 pm different from that at the 6-31G* level. It is not possible to offer a clear explanation for this effect presently, but experimental data provide support for the 6–31G* values of these bond lengths.

Differences in geometric parameters between the axial and equatorial conformers calculated at the 6-31G* and 6-31+G* levels nicely reflect the influence of the anomeric effect. The carbon–halogen bond length in the axial conformer of CLTHP is 5 pm longer than that in the equatorial, and in FTHP this difference is 2 pm. This change is accompanied by a shortening of the C1–O5 and C1–H1 bond lengths. The Hal–C1–O5 bond angles in the equatorial conformers are smaller than in the axial conformations. The large differences in C1–Cl bond lengths observed for the chloro derivative show the important role of lone-pair delocalization interactions in the anomeric effect of the chlorine atom which have previously been suggested as one of the origins of this phenomenon.[1–4] According to this hyperconjugation model, the delocalization of the dominant lone pair of the oxygen atom into the antibonding σ*(C–Hal) orbital of the adjacent C–Hal bond is larger when the C–Hal bond is in an axial position. In the equatorial postion, the mutual orientation of both corresponding orbitals is less favorable for electron delocalization, and as a consequence, the C–Hal bond is shorter.

Electric dipole moments calculated using the 6-31++G**// 6-31G* basis set exhibit typical patterns. The axial conformers, where the dipole moment of the lone-pair orbitals on the ring oxygen atom is oriented antiparallel to the dipole moment of the carbon–halogen bond, exhibit smaller dipole moments than the equatorial conformers. In the latter, the dipole moment of the long-pair orbitals of the ring oxygen is oriented nearly parallel to the dipole moment of the carbon–halogen bond, yielding larger dipole moments. The calculated values are 2.357 vs 3.672 D for FTHP and 2.903 vs 3.848 D for CLTHP. It is interesting to note that for both systems the Mulliken charges of the halide atoms are more negative when they are in the axial position. In going from the axial to the equatorial conformer, the Mulliken charge

TABLE 1: Optimized Geometries and Energies (hartrees) of the Equatorial Conformer of the 2-Fluorotetrahydropyran[a]

	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/6-31G*
C1–F	137.24	137.76	138.22	139.63	135.12	135.61	137.84
C1–O5	142.75	143.77	141.05	140.48	137.87	137.83	140.45
C5–O5	142.27	143.69	144.69	144.26	140.70	140.89	143.27
C4–C5	151.90	154.95	153.17	152.42	152.40	152.36	152.21
C3–C4	151.48	154.28	154.19	153.61	153.14	153.10	152.88
C2–C3	151.27	154.22	153.96	153.66	153.22	153.26	153.05
C1–H1	112.90	110.92	108.28	108.22	108.77	108.71	110.35
F–C1–O5	100.65	105.70	107.01	106.35	106.41	106.31	105.80
C1–O5–C5	113.15	109.61	113.67	115.54	113.84	113.85	110.95
C4–C5–O5	112.15	112.35	110.13	110.32	111.03	111.08	109.86
C3–C4–C5	110.65	110.13	109.63	110.33	109.97	110.07	109.69
C2–C3–C4	110.49	109.83	109.66	110.51	110.00	110.08	109.94
H1–C1–O5	109.82	110.04	110.19	106.35	109.99	109.98	109.99
F–C1–O5–C5	182.82	177.23	179.58	182.17	179.00	179.01	177.67
H1–C1–O5–C5	66.62	59.44	62.08	67.05	63.11	63.84	61.69
C4–C5–O5–C1	56.92	61.81	60.14	57.68	60.58	60.16	62.38
C3–C4–C5–O5	–54.62	–56.98	–55.41	–53.26	–54.56	–54.33	–56.79
C2–C3–C4–C5	53.27	51.43	53.97	52.87	51.17	51.20	52.18
energy		–364.194557	–366.856213	–368.733236	–368.880363	–368.891239	–369.872926

[a] Bond lengths are given in picometers; bond angles and torsion angles are in degrees.

TABLE 2: Optimized Geometries and Energies (hartrees) of the Axial Conformer of the 2-Fluorotetrahydropyran[a]

	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/6-31G*
C1–F	137.78	138.26	140.56	142.62	137.35	138.10	140.59
C1–O5	141.57	143.34	139.94	138.97	136.81	136.65	139.10
C5–O5	142.58	144.05	145.45	144.97	141.50	141.65	144.15
C4–C5	151.79	154.83	153.14	152.35	152.26	152.19	152.00
C3–C4	151.47	154.27	154.29	153.64	153.08	153.03	152.85
C2–C3	151.27	154.19	154.01	153.49	153.05	153.04	152.78
C1–H1	113.06	110.50	107.46	107.34	107.89	107.81	109.32
F–C1–O5	105.29	109.89	109.16	108.77	109.40	109.23	109.58
C1–O5–C5	114.96	110.48	114.46	117.13	115.71	116.26	112.99
C4–C5–O5	111.95	112.38	110.15	110.38	111.30	111.38	111.30
C3–C4–C5	110.29	109.99	109.83	110.52	110.12	110.06	110.02
C2–C3–C4	110.69	109.75	109.47	110.32	109.61	109.66	109.44
H1–C1–O5	104.34	105.44	107.07	107.11	106.67	106.78	105.92
F–C1–O5–C5	72.01	63.48	58.59	64.70	64.34	64.60	62.64
H1–C1–O5–C5	187.47	180.93	175.39	179.16	179.64	180.94	177.56
C4–C5–O5–C1	55.66	61.01	58.00	54.78	57.02	56.29	57.96
C3–C4–C5–O5	–55.88	–57.57	–54.65	–53.07	–54.30	–54.49	–56.16
C2–C3–C4–C5	53.79	51.94	54.96	53.80	52.70	52.89	54.02
energy		–364.197063	–366.864093	–368.741317	–368.885178	–368.895782	–369.878493

[a] Bond lengths are given in picometers; bond angles and torsion angles are in degrees.

TABLE 3: Optimized Geometries and Energies (hartrees) of the Equatorial Conformer of the 2-Chlorotetrahydropyran

	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/3-61G*
C1–Cl	177.01	182.52	188.42	186.12	178.90	178.83	178.08
C1–O5	142.60	143.11	140.88	140.61	138.24	138.28	141.10
C5–O5	142.58	144.24	145.56	144.80	141.06	141.16	143.56
C4–C5	151.82	154.84	153.06	152.30	152.29	152.26	152.10
C3–C4	151.45	154.27	154.19	153.55	153.09	153.05	152.83
C2–C3	151.57	154.46	154.61	153.96	153.36	153.34	153.13
C1–H1	112.22	110.07	107.74	107.90	108.38	108.39	110.00
Cl–C1–O5	106.52	106.20	105.91	106.50	107.25	107.28	106.71
C1–O5–C5	112.47	108.84	112.81	114.72	113.18	113.37	110.37
C4–C5–O5	112.11	112.20	109.98	110.09	110.98	111.07	110.80
C3–C4–C5	110.58	110.18	109.84	110.41	109.99	110.07	109.71
C2–C3–C4	110.43	109.86	109.75	110.65	110.25	110.29	110.20
H1–C1–O5	109.63	111.20	112.08	110.88	110.32	110.11	110.07
Cl–C1–O5–C5	180.31	176.31	178.79	179.12	175.88	176.15	174.64
H1–C1–O5–C5	65.86	61.65	65.84	66.40	61.60	62.03	59.64
C4–C5–O5–C1	57.74	61.70	59.82	58.38	61.04	60.57	62.88
C3–C4–C5–O5	–54.44	–57.14	–55.61	–53.59	–54.68	–54.43	–56.93
C2–C3–C4–C5	52.52	51.56	54.56	53.12	51.37	51.36	52.23
energy		–720.739350	–725.245081	–728.780834	–728.921897	–728.927252	–729.878909

[a] Bond lengths are given in picometers; bond angles and torsion angles are in degrees.

at the MP2/6-31G* level decreases from –0.4427 to –0.4152 for a fluorine atom and from –0.1397 to –0.0626 for a chlorine atom. This implies that the electron delocalization is larger in the axial anomer in accordance with the hyperconjugation model.

Influence of Different Geometries and Basis Sets on the Calculated Energies. The importance of geometry optimization for the calculation of the conformational energies of carbohydrates has been stressed previously.[22] The differences in the calculated geometries of both the anomeric conformers clearly show that the rigid-rotor approximation leads to considerable errors in these cases. These results also suggest that split-valence basis sets are not adequate to represent the geometrical features of molecules

TABLE 4: Optimized Geometries and Energies (hartrees) of the Axial Conformer of the 2-Chlorotetrahydropyran

	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/6-31G*
Cl–Cl	179.47	185.06	196.72	193.97	183.96	183.91	182.97
Cl–O5	140.83	141.44	137.64	137.75	136.39	136.45	139.08
C5–O5	142.78	144.29	145.69	145.02	141.56	141.63	144.05
C4–C5	151.77	154.69	152.93	152.25	152.19	152.15	151.95
C3–C4	151.42	154.18	154.17	153.56	153.02	153.01	152.81
C2–C3	151.40	154.08	153.83	153.33	152.90	152.90	152.62
Cl–H1	112.36	109.75	107.08	107.06	107.53	107.51	109.04
Cl–Cl–O5	111.63	111.39	109.57	109.54	110.93	110.82	111.52
Cl–O5–C5	115.12	112.19	116.81	118.61	117.15	117.30	114.21
C4–C3–O5	111.95	112.67	110.43	110.52	111.49	111.51	111.42
C3–C4–C5	110.30	109.95	109.77	110.47	110.08	110.13	109.88
C2–C5–C4	110.34	109.46	109.48	110.33	109.57	109.63	109.43
H1–Cl–O5	104.38	106.46	109.02	108.12	107.01	106.96	105.83
Cl–Cl–O5–C5	72.78	69.56	68.78	71.75	71.49	71.79	68.95
H1–Cl–O5–C5	185.45	182.90	178.72	181.61	183.55	183.82	181.89
C4–C5–O5–C2	55.09	57.80	54.35	52.83	55.54	55.27	57.41
C3–C4–C5–O5	–55.15	–57.27	–55.63	–53.23	–54.37	–54.21	–56.32
C2–C3–C4–C5	53.62	53.04	55.77	54.02	52.94	52.88	53.97
energy		–720.744452	–725.254363	–728.788618	–728.925857	–728.931077	–729.883433

a Bond lengths are given in picometers; bond angles and torsion angles are in degrees.

TABLE 5: Energy Differences (kcal/mol) between the Equatorial and Axial Conformer of the 2-Fluorotetrahydropyran Calculated with Various Basis Sets and Geometries

	optimized geometry						
	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/6-31G*
AM1	1.92						
STO-3G	1.36	1.57					
3-21G	2.84	3.93	4.94				
4-31G	3.51	4.13	4.92				
6-31G	3.37	3.86	4.62	5.07			
6-31G*	2.65	2.78	2.78	3.00	3.02		
6-31G**	2.62	2.75	2.72	2.92	2.94		
6-31+G*	2.50	2.39	2.43	2.92	2.81	2.76	
6-311G*	2.60	2.56	2.54	2.91	2.81	2.72	
6-31+G**	2.51	2.36	2.41	2.80	2.66	2.74	
6-311++G**	2.59	2.34	2.31	2.80	2.66	2.62	
MP2/6-31G*							3.47
MP2/6-31G*						3.42	
MP3/6-31G*						3.31	

TABLE 6: Energy Differences (kcal/mol) between the Equatorial and Axial Conformer of the 2-Chlorotetrahydropyran Calculated with Various Basis Sets and Geometries

	optimized geometry						
	AM1	STO-3G	3-21G	6-31G	6-31G*	6-31+G*	MP2/6-31G*
AM1	3.62						
STO-3G	3.05	3.20					
3-21G	3.74	4.60	5.83				
4-31G	3.83	4.80	5.90				
6-31G	2.98	3.76	4.82	4.88			
6-31G*	1.87	2.47	2.45	2.41	2.48		
6-31G**	1.87	2.55	2.47	2.45	2.49		
6-31+G*	1.75	2.47	2.38	2.35	2.40	2.40	
5-311G*	2.27	3.02	3.05	3.01	2.98	2.98	
6-31+G**	1.79	2.51	2.45	2.41	2.44	2.44	
6-311++G**	1.79	2.74	2.68	2.65	2.69	2.67	
MP2/6-31G*							2.84
MP2/6-31G*						2.83	
MP3/6-31G*						2.57	

possessing 1,3-heteroatom sequences of atoms. The conformational energies of more complex molecules are often calculated for geometries optimized at a lower level, due to the large computation time required for geometry optimization. However, the effects of the use of geometries refined at a lower level cannot be predicted. Therefore, we have investigated the effect of using different geometries on the calculated energy difference between the axial and equatorial conformers as a function of increasing levels of sophistication in the basis set, namely, STO-3G, 3-21G, 4-31G, 6-31G, 6-31G*, 6-31G**, 6-31+G*, 6-311G*, 6-31+G**, and 6-311++G** basis sets[17] using six different sets of geometries optimized at the STO-3G, 3-21G, 6-31G, 6-31G*, and 6-31+G* level. To investigate whether AM1 geometries can be used as an aid in *ab initio* calculations of conformational energies of complex oligosaccharide molecules, the calculations with AM1 geometries were also performed.

Axial–Equatorial Energy Difference. The calculated relative energies are summarized in Tables 5 and 6. It is seen that the axial conformers are predicted to be preferred by all methods. However, there is a clear difference between the relative energies calculated by the minimal and split-valence basis sets and those calculated with the 6-31G* or larger basis sets. For the 6-31G* basis set, the relative energies are 1–2.5 kcal/mol lower than those obtained with basis sets without polarization or diffuse functions. A similar decrease of the relative energies between the split-valence basis sets and polarized split-valence basis sets was found in case of dimethoxymethane and methoxytetrahydropyran.[23,24] The energy differences calculated with the 6-31G*

and larger basis sets using the AM1 optimized geometries are always lower than the values calculated with other optimized geometries. The largest deviation is 0.9 kcal/mol. These results, together with our previous calculations,[7,8] show that the use of AM1 method for geometry optimization combined with single-point *ab initio* energy calculations will lead to significant errors. In the following we will focus on the results obtained with the 6-31G* and larger basis sets.

In the case of FTHP the calculated energy differences are 2.31–3.02 kcal/mol. Relative energies calculated using STO-3G and 3-21G geometries are slightly lower than those calculated with 6-31G, 6-31G*, and 6-31+G* geometries. For the same geometry, increasing the basis set decreases the energy difference. At the best level of theory, 6-311++G**//6-31+G*, the energy difference is 2.62 kcal/mol. In the case of CLTHP the calculated differences (2.38–2.69 kcal/mol) are almost the same, regardless of which geometry or basis is used. The energy differences calculated using 6-311G* and 6-311++G** basis sets are, in this case, generally larger than those calculated with other basis sets. The energy difference calculated using the 6-31++G**/6-31+G* basis set is 2.67 kcal/mol. The absolute energies calculated at the 6-31+G* level with optimized geometry obtained with the 6-31G* and 6-31+G* basis sets differ only by 0.0001 hartree. These results suggest that calculations using the 6-31+G*//6-31G* basis set represent the best practical method at present. This combination yields reliable geometries and conformational energies in molecules with 1,3-heteroatom segment of atoms, while still closely representing the results that could be obtained

with larger basis sets. For larger molecules larger basis sets are still prohibited due to their enormous requirements for CPU time.

The observation that the calculated energy differences are almost independent of the geometry used for calculation is rather surprising, considering the large differences found for the optimized geometrical parameters (Tables 1–4). It is likely that, although the energy hypersurfaces calculated with various basis sets differ, these deviations are similar in both anomers, and therefore, the errors are canceled.

Unfortunately, there are no experimental data available for a direct comparison of axial–equatorial energy differences. The instability of the 2-fluorotetrahydropyran compound precludes its isolation.[25,26] As a result, experimental estimates for the free energy difference between axial and equatorial orientations in solution have only been reported for the chloro derivative.[25-27] Based on ^{1}H NMR studies at 40° in acetone, a free energy difference of 2.15 kcal/mol was reported.[25,26] It was also estimated that for more polar solvents this value may be as low as 1.5 kcal/mol. For the bromo derivative, a free energy difference of more than 2.7 kcal/mol was found at 40°. This latter result implies that for the fluoro derivative the difference should be less than the 2.15 kcal/mol observed for the chloride. More recently, from variable temperature ^{1}H and ^{13}C NMR experiments in chloroform, a conformational free energy of difference of 2.18 kcal/mol was determined for the chloro derivative.[27]

Semiempirical molecular orbital calculations have also been applied to estimate this energy difference.[7,8,14] For the fluoro derivative both PCILO and MNDO methods predict an energy difference of 1.6 kcal/mol whereas the AM1 method gives 1.9 kcal/mol. For the chloro derivative, the PCILO, MNDO, and AM1 methods give energies of 1.8, 2.4, and 3.62 kcal/mol, respectively. These calculations[14] also showed a strong effect of solvent on this energy difference.

Molecular mechanics (MM) methods are known to perform poorly for moieties exhibiting the anomeric and exoanomeric effects in spite of the progress in this area during the past decade.[28] To illustrate this point, we have carried out MM calculations on the axial and equatorial forms of fluoro- and chlorotetrahydro-pyran using MM3[29] and CHARMM.[30] The CHARMM force field predicts an energy difference between the axial and equatorial forms of 1.38 and 0.16 kcal/mol for fluoro- and chlorotetrahydropyran, respectively. These results are in poor agreement with the *ab initio* calculations and experimental data. Since MM3 is not parametrized for an O–C–F segment of atoms, calculations were only performed with MM3 for chlorotetrahydropyran. In total disagreement with the above, MM3 predicts the equatorial form to be 1.25 kcal/mol more stable than the axial form. In addition to the poor estimation of energy differences, MM calculations do not predict the differences in geometry between axial and equatorial conformers. For example, CHARMM values for the C1–F and C1–Cl bonds for the equatorial orientations were 138.6 and 178.4 pm, respectively. For the axial orientation the corresponding values (139.0 and 179.1 pm) differ considerably from the *ab initio* values.

In molecular mechanics force fields, intramolecular forces are modeled in terms of potential energy as a function of the molecular internal coordinates. These functions contain adjustable parameters, which for a given class of molecules can be fitted to a body of experimental data. A crucial step in each parametrization process is the construction of a reliable and comprehensive test data set. The poor performance of the MM force fields with O–C–Hal segments is a direct result of the paucity of experimental data for these segments. The results of *ab initio* calculations on small model compounds can be used to overcome these short-comings in the test data set. A recent example is the parametrization of the O–C–F segment for MM2 using *ab initio* calculations.[31] The results presented in this paper provide

	2-fluorotetrahydropyran		2-chlorotetrahydropyran	
	axial	equatorial	axial	equatorial
zero-point energy	94.21	93.95	93.04	92.79
thermal energy	97.82	97.58	96.86	96.64
entropy	76.48	76.72	79.04	79.36
heat capacity	21.51	21.72	22.73	22.80

[a] Zero-point energy and thermal energy are given in kcal/mol; all other quantities are in cal/(mol K).

additional data that should prove useful in improving the parametrization of MM force fields.

Effect of Electron Correlation. To evaluate the effect of electron correlation on the calculated relative energies, MP3 single-point calculations at the 6-31G* level using the 6-31G* geometry were carried out. The calculated axial–equatorial energy differences increase by the incorporation of electron correlation. The energy differences obtained by MP2 are 3.42 kcal/mol for FTHP and 2.83 kcal/mol for CLTHP and are 0.14 and 0.26 kcal/mol, respectively, larger than the 3.31 and 2.57 kcal/mol values obtained at the MP3 level. A comparison of the MP3 results with the 6-31G* values of 3.02 and 2.48 kcal/mol gives the electron correlation corrections: 0.28 kcal/mol for FTHP and 0.09 kcal/mol for CLTHP.

Comparison of MP2/6-31G*//6-31G* results with the MP2/6-31G* values (Tables 5 and 6) is particularly interesting. The same energy differences between the axial and equatorial conformers would seem to indicate that the addition of the electron correlation into geometry optimization may not, in this case, be of great importance in determining the relative energies of these molecules.

Zero-Point Energy Correction. To see what effect zero-point energy and entropy differences between the axial and equatorial conformers might have on the calculated energy differences, we have calculated the vibrational frequencies using the 6-31G* basis set with Guassian 92.[16] These were used to estimate zero-point energies, thermal energies, and entropies, and the results are shown in Table 7. The entropies of both anomers are similar, and the entropy differences are 0.24 cal/(mol K) for FTHP and 0.32 cal/(mol K) for CLTHP. These correspond, at 300 K, to contributions to the free energy of 0.07 and 0.09 kcal/mol, respectively, which are clearly the least significant of all the corrections considered here.

The zero-point vibrational energies and thermal energies are found to be slightly higher for the axial conformer in both molecules. The differences in zero-point vibrational energies are –0.26 kcal/mol for FTHP and –0.25 kcal/mol for CLTHP; the differences in the thermal energis are –0.24 and –0.22 kcal/mol. Combining these corrections with *ab initio* energy difference values of 2.61 and 2.67 kcal/mol, MP3, and entropy corrections, this leads to the free energy differences of 2.47 kcal/mol for FTHP and 2.38 kcal/mol for CLTHP (see Table 8). It is interesting to note that, in the case of FTHP, the effect of zero-point energy correction (–0.26 kcal/mol) is as large as the effect of electron correlation at the MP3 level (+0.28 kcal/mol), but in the opposite direction.

Anomeric Effect. The magnitude of the anomeric effect is usually defined for tetrahydropyran derivatives relative to the corresponding cyclohexane derivatives since then the added effect due to the 1,3-heteroatom sequence can be extracted independent of other contributions. Thus, the formal definition is a double difference, i.e., the difference between the values of the free energy difference between axial and equatorial derivatives of tetrahydropyran and cyclohexane. There is, however, a well-recognized difficulty with the evaluation of the anomeric effect in this manner. The steric interactions of a group in the anomeric position of the

TABLE 8: Summary of Corrections to the Calculated Free Energy Differences between the Axial and Equatorial Conformers of 2-fluorotetrahydropyran and 2-Chlorotetrahydropyran Using the 6-31G* Basis Set[a]

	2-fluorotetrahydropyran	2-chlorotetrahydropyran
zero-point energy	−0.26	−0.25
thermal energy	−0.24	−0.22
electron correlation	+0.28	+0.09
entropy (300 K)	+0.07	+0.09
total correction	−0.15	−0.29
ab initio value	2.62	2.67
corrected value in vacuo	2.47	2.38
cyclohexane correction	+0.36	+0.76
anomeric effect in vacuo	2.83	3.14
solvation correction (chloroform)	0.35	0.15
corrected value (chloroform)	2.12	2.23
experimental value (chloroform)[27]		2.18
solvation correction (acetone)	0.48	0.26
corrected value (acetone)	1.99	2.12
experimental value (acetone)		2.15

a In kcal/mol.

TABLE 9: Calculated Effect of Solvent upon the Free Energy Difference (ΔG) between the Axial and Equatorial Conformers and upon the Anomeric Effect (AE) in 2-Fluorotetrahydropyran and 2-Chlorotetrahydropyran[a]

	2-fluorotetrahydropyran		2-chlorotetrahydropyran	
	ΔG	AE	ΔG	AE
vacuum	2.47	2.83	2.38	3.14
dioxane	2.56	2.92	2.41	3.17
carbon tetrachloride	2.41	2.77	2.41	3.17
chloroform	2.12	2.48	2.23	2.99
pyridine	1.99	2.35	2.13	2.89
acetone	1.99	2.36	2.12	2.88
methanol	1.55	1.91	1.88	2.64
dimethyl sulfoxide	1.85	2.21	2.03	2.79
water	0.50	0.86	1.51	2.27

a In kcal/mol.

heterocycle are different than those encountered in cyclohexane. For example, since the ring C–O bond is significantly shorter than a C–C bond, repulsive interactions of an axial group on a pyranoid ring are greater than those for the same group on a cyclohexane ring. Based on a comparison of the conformational preferences of various substituents found for cyclohexane and pyranoid rings, a correction factor of 1.53 has been estimated.[32] When this correction factor is applied, the magnitude of the free energy difference between the axial and equatorial derivatives of cyclohexane used for the calculation of the anomeric effect is 50% greater than the values from cyclohexane. For the cyclohexane halide derivatives, the equatorial orientation is favored by 0.36 and 0.76 kcal/mol for the fluoride and chloride,[4] respectively, after this correction. Thus, the *ab-initio*-derived differences in energy between the equatorial and axial orientations of the halide in the tetrahydropyran derivatives must be increased by these amounts to obtain an estimate of the anomeric effect. The various corrections are summarized in Table 8. The results for the fluoride and chloride derivatives in vacuum are 2.83 and 3.14 kcal/mol, respectively.

Solvent Effect. Finally, we have investigated the effect of the solvent upon the energy differences using a continuum dielectric model previously described.[20,21] The results for eight different solvents are given in Table 9. In both compounds, the free energy difference between the axial and equatorial conformers decreases with increases in the polarity of the solvent. However, in all solvents the axial form is favored. The values of 2.23 and 2.12

kcal/mol calculated for the 2-chlorotetrahydropyran in chloroform and acetone, respectively, satisfactorily reproduce the observed free energy differences[25–27] (2.2 kcal/mol) in these solvents. In more polar solvents than chloroform, the energy differences calculated for the fluorotetrahydropyran are smaller than for the chloro derivative. This is in qualitative agreement with the trend observed in experimental data for chloro and bromo derivatives.[26] The calculated values are also supported qualitatively by experimental data on the equilibria of more complex saccharide molecules. Tri-*O*-acetyl and tri-*O*-benzoyl β-D-xylopyranosyl derivatives in acetone have 80–90% in the axial form of the fluoride derivative and 90–98% for chloride form.[9–11]

The effect of solvent upon the conformational equilibrium was found to be more pronounced in FTHP than in CLTHP. The energy difference is decreased from vacuum to water by 1.97 kcal/mol in comparison with a decrease of 0.87 kcal/mol for CLTHP. Analysis of the results showed that the larger solvent effect with the fluoride is caused by solvent–solute electrostatic interactions which become larger whenever the dipole moment of the solute increases. This effect also becomes stronger on going to a medium with a higher dielectric constant. As has already been noted, the difference between the dipole moment of the equatorial and axial conformers is larger for FTHP (1.32 D) than for CLTHP (0.94 D), and as a result, the difference in the solute–solvent electrostatic interactions will be larger in FTHP. The values in Table 9 also reveal the stronger effect of chloroform compared with other solvents of similar polarity and, conversely, the relatively small effect of highly polar dimethyl sulfoxide compared with less polar solvents. This special behavior of chloroform has also been noted experimentally for glycosides.[4]

The calculated magnitudes of the anomeric effect in different solvents follow the trends in energy differences discussed above. The anomeric effect is maximized in the isolated molecule and gradually decreases in more polar solvents. The major differences appear between the effect in organic solvents, in water, and in the isolated molecule. The chloro substituent exhibits a larger anomeric effect than the fluoro one, and this difference between the magnitude of the anomeric effect for the two compounds increases with the polarity of solvents from 0.31 kcal/mol in the isolated molecule to 1.41 kcal/mol in water.

Conclusions

Geometries and conformational energies of the 2-fluorotetrahydropyran and 2-chlorotetrahydropyran have been obtained from various levels of *ab initio* molecular orbital calculations. These calculations show that the use of a polarized basis set, 6-31G*, is necessary to reproduce observed differences in valence geometrical parameters between axial and equatorial conformers. The energy differences are satisfactorily calculated at the 6-31G* level. The values of 2.76 kcal/mol for FTHP and 2.4 kcal/mol for CLTHP are barely altered on further improvement of the basis set. This leads us to believe that the 6-31+G*//6-31G* basis set is a good representation of the results that could be achieved by including higher basis sets and can be used for calculations of the conformational properties of more complex models for carbohydrate molecules. The agreement between the calculated and experimental data for fluoro- and chlorotetrahydropyran suggests that these results can be used as supplementary data for the parametrization of force fields for O–C–Hal segments. In addition, these results establish that *ab initio* calculations of cyclic carbohydrate models at the 6-31+G*//6-31G* level provide a promising source of data for the parametrization of force fields for carbohydrates.

Zero-point vibrational energy and thermal energy corrections decrease the energy difference by 0.5 and 0.47 kcal/mol whereas entropy and MP3 electron correlation corrections increase this difference by 0.37 and 0.18 kcal/mol. On the other hand, the solvent has a considerable effect on the equilibrium of conformers

and decreases *ab initio* calculated energy differences to values of 0.5 kcal/mol for FTHP and 1.5 kcal/mol for CLTHP in water. Thus, the calculated magnitude of the anomeric effect was found to be solvent dependent and is in the range 0.86–2.83 kcal/mol for the fluoro derivative and 2.27–3.14 kcal/mol for the chloro one.

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