Effects of Substituting a OH Group by a F Atom in D-Glucose. Ab Initio and DFT Analysis

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Abstract: High-level ab initio and DFT methods up to MP2/6-311++G**//B3LYP/6-31G* and B3LYP/6-311++G**//B3LYP/6-31G* levels have been used to assess the relative energies of 17 different structures of D-glucose and 13 different structures of 4-deoxy-4-fluoro-D-glucose. The structures were confirmed to correspond to minima on the potential energy surface at the RHF/6-31G* level. Solvation Model 5.4/AM1 was used to calculate the effects of aqueous solution. The substitution of a OH group by a F atom does not much change the shape and electrostatic potential around corresponding conformers, but in the gas phase it destabilizes the cooperative network of intramolecular hydrogen bonds. This destabilization mostly affects structures with a chain of intramolecular hydrogen bonds oriented counterclockwise, as fluorine is unable to donate a hydrogen bond and therefore causes a gap in the chain. In contrast, for clockwise-oriented networks of hydrogen bonds, the fluorine can act as an acceptor at the end of a chain of cooperative hydrogen bonds. A slightly higher energy of anomeric and exo-anomeric stabilization is another effect of substituting the fourth hydroxyl group by a fluorine atom in D-glucose, observed both in the gas phase and in aqueous solution. For this reason, the α anomers contribute more to the equilibrium population of structures of 4-deoxy-4fluoro-D-glucose than D-glucose. In aqueous solution, both D-glucose and its 4-deoxy-4-fluoro analogue are present as a mixture of mainly three corresponding structures. This indicates that 4-deoxy-4-fluoro-D-glucose is a good substitute for D-glucose in terms of its biochemical and biological activity. Moreover, this suggests that, for molecules with limited conformational freedom, the substitution of a OH group by a F atom is very likely to lead to a potential new drug. In contrast, it had already been shown that, for conformationally labile aliphatic compounds, replacement of a hydroxyl by a fluorine increases conformational diversity, so the fluorine-containing aliphatic molecules were not likely to be an example of a successful drug design. On the other hand, this work shows that, among molecules with limited conformational freedom, such as cyclic compounds, one is very likely to find targets for a successful rational drug design.

Introduction

Fluorine-substituted analogues of naturally occurring and biologically active organic compounds have become the focus of increasing interest.[1−9,11−19] They are thought to provide insight into the interactions with enzymatic binding sites.[1,2] Thus, it has already become a common practice in bioorganic chemistry to replace a hydroxyl group for a fluorine to generate a fluorinated enzyme substrate or inhibitor in a given enzymatic process.[3−7] The rationale for such a strategy stems from similarities between a F atom and a OH group, with particular reference to polarity as well as the close isosteric relationship between fluorine and oxygen.[1,5,8] Consequently, a F atom is considered to be a good substitute of a OH group because it introduces a small steric disturbance.[9] Once introduced, the high carbon−fluorine bond energy[10] renders the substituent relatively resistant to metabolic transformation.[9] Therefore, fluorinated analogues are potentially useful in studies of metabolism[1,11] and some of them in clinical diagnostics.[12−15] Although several

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groups of compounds were studied,[2,15−19] carbohydrates seem to attract most of the attention. Among carbohydrates, there are a number of successful examples where substitution of a OH group by a F atom resulted in a compound which possessed biochemical and biological activity.

Carbohydrates, apart form being blood group determinants,[20] are important in many biological processes: cell adhesion,[21] hormone−receptor binding,[22] and lymphocyte homing and migration.[23] Especially D-glucose is involved in energy metabolism and storage[20] and thus is of utmost importance for all living organisms.[24]

Recently, nucleotides and nucleosides containing carbohydrates in which OH groups were substituted by F atoms attracted much attention. Some of these compounds are potential medicines, as they have anticancer activity.[25−30] Some are active against various viruses, including hepatitis B,[31−33] Epstein−Barr,[34] Varicella zoster,[35] and HIV.[36−39] Oligonucleotides whose sugar residues are modified by replacement of a OH group by a F atom were shown to be useful in gene therapy.[40−43] They may form triplexes with DNA, which can block unwanted genes.[40,41] They may also be used as ribozymes, eliminating unwanted RNA, and thus preventing synthesis of mutant or oncogenic proteins.[42,43]

Deoxyfluoro analogues of monosugars−glactose,[44] glucose,[1,45−48] fucose,[49] xylose,[50] and celobiose[51,52]−were utilized in studies on various enzymatic reactions. The ^{19}F NMR technique with 3-deoxy-3-fluoro-D-glucose as molecular probe is used in studies of metabolism of sugars[53−55] in muscles, the liver, and eyes. Positron emission tomography (PET) with [^{18}F]-2-deoxy-2-fluoro-D-glucose is widely utilized in studies on cancer cells,[56] in detection of cancer,[57−62] its diagnosis,[63−70] therapy planning,[71] predicting the prognoses,[72−74] and monitoring effects of treatment[75−81] in various types of cancer.

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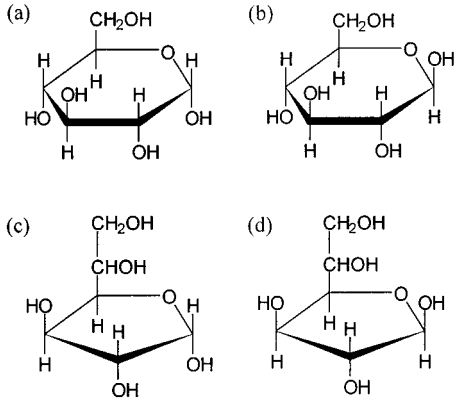

Figure 1. α and β annomers of D-glucopyranose and -furanose: (a) α-D-glucopyranose, (b) β-D-glucopyranose, (c) α-D-glucofuranose, and (d) β-D-glucofuranose.

Recently, due to its essential role in living organisms, D-glucose has attracted much attention from computational chemists.[82−95] On the basis of experimental results, it is commonly believed that the lowest energy form of D-glucose is the six-membered cyclic structure of D-glucopyranose. However, some computational studies, utilizing density functional theory (DFT) at B3LYP/6-31G** level,[93] performed by Ma et al., indicated that the lowest energy form of D-glucose is *fur GGGG*, the five-membered structure of D-glucofuranose[94] (see Figure 1). Later, those results were corrected by Lii et al., using the larger basis set 6-311++G(2d,2p).[95] With this basis set, the lowest energy structures possessed the usual for D-glucose, a six-membered ring of D-glucopyranose. Such a discrepancy was explained by Lii et al. as an effect of basis set superposition error[95] and by Hoffmann et al. as the result of the necessary inclusion of diffuse functions in energy calculations for structures with intramolecular hydrogen bonds with strong electrostatic components.[96]

Because sugars are of utmost importance for various biochemical and biological processes, and the usefulness of deoxyfluorosugars, we have decided to study the effects of substituting a OH group by a F atom for D-glucose, which is crucial for living organisms. This continues our efforts to study the effects of substituting a OH group by a F atom with the use of computational methods. In our previous study we examined aliphatic compounds—derivatives of (*R*,*R*)-tartaric acid, its ester, and its primary and tertiary amides.[97] It was shown that the substitution of a OH group by a F atom resulted in an increase of conformational freedom of the studied molecules. Therefore, it was concluded that potential new drugs are not likely to be found among deoxyfluoro analogues of aliphatic compounds.[97] The studied aliphatic deoxyfluoro analogues, in contrast to the parental compounds, were present at room temperature as a mixture of several conformers; thus, only a fraction of the mixture of deoxyfluoro analogues could mimic the biochemical and biological activity of molecules containing OH groups. Further, it was hypothesized that among molecules with limited conformational freedom, like cyclic compounds, the substitution of a OH group by a F atom should not lead to changes in shape and electrostatic potential around a molecule. Therefore, in this study, in the context of rational drug design, we focused on D-glucose to examine the effects of substituting a OH group by a F atom for cyclic compounds.

Computational Methods

In this study we utilized the geometries of lowest energy structures of D-glucose obtained by Barrows et al.,[90,92] Damm et al.,[91] and Ma et al.[94]—in all, 17 different structures of D-glucose. Further, to examine the effects of substituting a OH group by a F atom, we replaced the OH group attached to the fourth carbon by fluorine.

Geometry optimization and vibrational analyses were performed at the RHF/6-31G* level for all these structures. Further, the geometries were reoptimized at the B3LYP/6-31G* level in order to take into account effects of dynamic correlation of electrons on geometric parameters. Finally, single-point energies were calculated at the B3LYP and MP2 levels with the large and flexible 6-311++G** basis set—triple valence with two sets of diffuse and two sets of polarization functions. These results, together with the results of vibrational analysis, were combined in order to obtain relative Gibbs free energies in the gas phase (eqs 1a, 1b).

$$G^{\circ}_{298\,\mathrm{K}} = E(\mathrm{B3LYP/6\text{-}311{+}{+}G^{**}//B3LYP/6\text{-}31G^{*}}) + \Delta G_{\mathrm{vib-rot}}(T) \quad (1a)$$

$$G^{\circ}_{298\,\mathrm{K}} = E(\mathrm{MP2/6\text{-}311{+}{+}G^{**}//B3LYP/6\text{-}31G^{*}}) + \Delta G_{\mathrm{vib-rot}}(T) \quad (1b)$$

The usual Boltzman formalism was utilized in assessing equilibrium population of conformers in the gas phase (eq 2), and the percent of structure X was cacluated as

$$\%(\mathrm{X}) = \frac{\exp(-G^{\circ}_{\mathrm{X}}/RT)}{\sum_i \exp(-G^{\circ}_i RT)} \times 100\% \quad (2)$$

To assess free energies of solvation in water, a semiempirical, quantum chemical program AMSOL6.5.3[98] was utilized with the AM1-

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SM5.4 model, using the AM1[99] Hamiltonian. In the SM5.4 method,[100−103] solvation effects are included via two terms. The first accounts self-consistently for polarization of the solvent on the basis of a distributed monopole representation of solute charges with dielectric screening. The second term is proportional to the solvent-accessible surface area, with a set of proportionality constants which depend on the local nature of the solute for each atom's or group's interface with the solvent. To calculate the percent of a conformer X in a solution, eq 2 was also utilized, but the Gibbs free energy of solvation was added to the composite Gibbs free energy of the isolated molecule.

Ab initio and DFT calculations were carried out with the Gaussian94 program suite,[104] and semiempirical SM5.4 calculations were carried out with the AMSOL6.5.3 program.[98] All calculations were performed on a Cray J-916 at the Poznan Supercomputing and Networking Center.

Results and Discussion

Nomenclature. The conventional designations of α and *β* are used for specification of anomer stereochemistry (see Figure 1). For pyranose rings the next capital letter describes the stereochemistry of the hydroxymethyl group: *G*− corresponds to the torsion angle O(6)−C(6)−C(5)−O(5) of about −60°, *G*+ to the angle of about 60°, and *T* to the angle of about 180°. The following letter describes the relative position of the hydroxyl hydrogen of the hydroxymethyl group: *g*−, *g*+, and *t* correspond to the torsion angle H−O(6)−C(6)−C(5) of about −60°, 60°, and 180°, respectively (see Figure 2). These two letters are then separated by a slash, followed by either *cl* or *cc* designators, which describe the cooperative network of intramolecular hydrogen bonds as running clockwise or counterclockwise, respectively (see Figure 3). After the second slash comes the letter describing the relative orientation of the anomeric hydroxyl hydrogen, that is, *g*−, *g*+, and *t*, which corresponds to a torsion angle H−O(1)−C(1)−C(2) of about −60°, 60°, and 180°, respectively. The remaining four structures of D-glucose, possessing a disfavored five-membered furanose ring (see Figure 1), were designed as in the original work of Ma et al.[95]

(i) Gas Phase. The relative energies of various structures of D-glucose obtained during calculations up to the B3LYP/6-311++G**//B3LYP/6-31G* and MP2/6-311++G**//B3LYP/6-31G* levels[93] are summarized in Table 1. Rovibrational contributions to the free energies at 298 K, calculated at the RHF/6-31G* level, are also presented in Table 1. Table 2 presents the corresponding data for analogous structures of 4-deoxy-4-fluoro-D-glucose.

Furanose versus Pyranose Rings. It is clear that the relative energies of five-membered furanose rings of D-glucose are over 4 kcal/mol higher than energies of six-membered pyiranose rings at the B3LYP/6-311++G**//B3LYP/6-31G* and MP2/6-311++G**//B3LYP/6-31G* levels. But in the case of B3LYP/6-31G* calculations, the furanose rings are erroneously similar in energy to pyranose rings. This failure of B3LYP/6-31G* calculations had already been explained by basis set superposition error[95] or, alternatively, by necessity of inclusion of diffuse functions in the basis set when calculating relative energies of structures with strong hydrogen bonds, which were present in structures with furanose rings.[96]

The geometrical parameters of hydrogen bonds as well as electron densities between protons and acceptors calculated according to the Mulliken scheme, which can be used to asses the strength of hydrogen bond,[97] are presented in Table 3. For clarity, data for only three structures are presented: *fur GGGG* and α *Tg+/cc/g+* of D-glucose, and α *Tg+/cc/g+* of 4-deoxy-4-fluoro-D-glucose. For the bonding scheme of hydrogen bonds, we utilize the notation proposed earlier,[97] which indicates the hydrogen bond motif as proposed by Etter et al.[105] and also shows donor and acceptor groups.

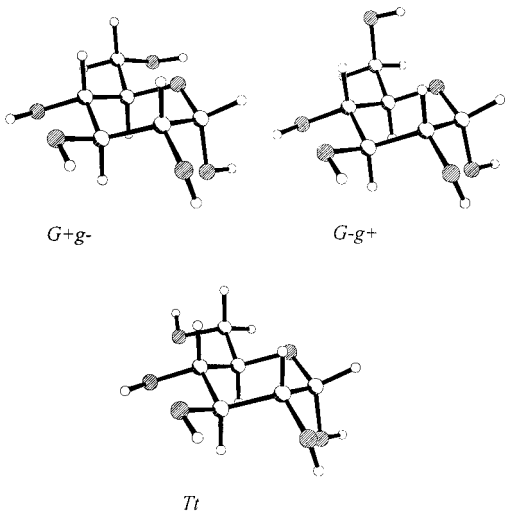

Figure 2. Perspective view of the α-D-glucopyranose structures, presenting the meaning of the two first letters used to characterize the pyranose structure. The first capital letter describes the rotation around the C5−C6 bond. The torsion angle O6−C6−C5−O5 is about 60° for the *G*+, −60° for the *G*−, and 180° for the *T* structure. The second letter describes the rotation around the C6−O6 bond. The torsional angle H−O6−C6−C5 is about 60°, −60°, and 180° for the *g*+, *g*−, and *t* conformers, respectively.

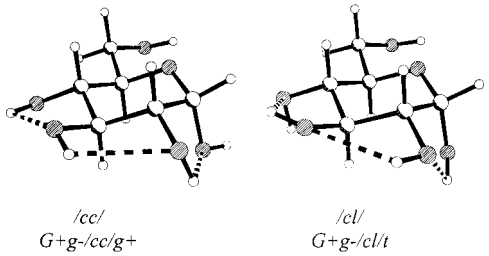

Figure 3. Perspective view of the *G*+*g*−*/cc/g*+ and *G*+*g*−*/cl/t* structures of α-D-glucopyranose, showing the cooperative network of intramolecular hydrogen bonds running counterclocwise, */cc/*, and clockwise, */cl/*.

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Table 1. D-Glucose: Relative Energies (kcal/mol)[a] and Percent of Low-Energy Structures of D-Glucose in the Gas Phase and in Aqueous Solution

structure	B3LYP 6-31G*	B3LYP 6-311++G**	MP2 6-311++G**	ZPE[b] (kcal/mol)	TCG[c] [kcal/mol]	ΔG^0_{B3LYP} (kcal/mol)	% gas B3LYP	ΔG^0_{MP2} (kcal/mol)	% gas MP2	G^0_{solv} (kcal/mol)	% aqua B3LYP SM5.4-AM1	% aqua MP2 SM5.4-AM1
α *G−g+/cc/g+*	0.55	0.11	0.00	0.52	0.89	0.19	19	0.00	30	−13.83	7	14
α *G+g−/cc/g+*	0.74	0.00	0.14	0.47	0.80	0.00	26	0.06	27	−14.38	25	32
α *Tg+/cc/g+*	0.00	0.06	0.48	0.68	1.14	0.40	13	0.73	9	−13.28	2	2
α *G−g+/cl/t*	1.45	1.11	0.87	0.48	0.79	1.09	4	0.77	8	−13.66	1	3
α *Tt/cl/t*	1.56	1.29	1.40	0.51	0.91	1.40	2	1.42	3	−13.09	0	0
α *Tt/cl/g+*	3.99	3.09	3.14	0.35	0.67	2.96	0	2.92	0	−14.47	0	0
β *G−g+/cc/g−*	2.31	0.95	1.19	0.13	0.36	0.50	11	0.66	10	−14.08	6	7
β *G+g−/cc/g−*	2.60	0.88	1.36	0.08	0.27	0.34	14	0.74	9	−15.06	45	32
β *Tg+/cc/g−*	1.95	1.05	1.79	0.26	0.57	0.82	6	1.48	2	−13.90	3	1
β *Tg+/cc/g+*	2.52	2.02	2.87	0.13	0.41	1.62	2	2.39	0	−14.37	2	1
β *Tt/cl/t*	4.81	3.75	4.15	0.05	0.28	3.23	0	3.55	0	−14.63	0	0
β *Tt/cl/g−*	5.22	3.90	4.63	0.00	0.18	3.27	0	3.92	0	−15.27	0	0
β *G−g+/cc/g+*	3.05	2.06	2.36	0.01	0.18	1.43	2	1.66	2	−15.10	7	7
Fur α *GGGG*	2.47	4.73	5.21	0.47	0.46	4.39	0	4.78	0	−11.28	0	0
Fur β *GGGG*	0.12	4.37	4.07	0.60	1.05	4.62	0	4.24	0	−12.54	0	0
Fur α *GGTG*	5.75	4.97	6.36	0.37	0.00	4.16	0	5.48	0	−14.00	0	0
Fur β *GGTG*	2.86	4.88	4.08	0.60	0.66	4.73	0	3.85	0	−12.64	0	0

[a] Relative energies calculated with respect to the lowest energy structure in a given method (for B3LYP/6-31G*, −687.153254; for B3LYP/6-311++G**, −687.404647; and for MP2/6-311++G**, −685.649073 Hartree). [b] Zero-point energy; the lowest value was equal to 0.214462 Hartree. [c] Thermal correction to Gibbs free energy at 298 K; the lowest value was equal to 0.177343 Hartree.

Table 2. 4-Deoxy-4-fluoro-D-glucose: Relative Energies (kcal/mol)[a] and Percent of Low-Energy Structures of D-Glucose in the Gas Phase and in Aqueous Solution

structure	B3LYP 6-311++G**	MP2 6-311++G**	ZPE[b] (kcal/mol]	TCG[c] (kcal/mol)]	ΔG^0_{B3LYP} (kcal/mol)	% gas B3LYP	ΔG^0_{MP2} (kcal/mol)	% gas MP2	G^0_{solv} (kcal/mol)	% aqua B3LYP SM5.4-AM1	% aqua MP2 SM5.4-AM1
α *G−g+/cc/g+*	0.69	0.75	1.05	1.62	0.75	15	0.81	16	−13.40	20	32
α *G+g−/cc/g+*	0.87	1.20	0.96	1.47	0.78	14	1.10	10	−13.67	30	32
α *Tg+/cc/g+*	2.30	3.06	1.01	1.59	2.32	1	3.08	0	−14.16	5	2
α *G−g+/cl/t*	0.00	0.00	0.96	1.57	0.00	54	0.00	65	−11.47	3	5
α *Tt/cl/t*	5.13	5.57	0.52	0.78	4.34	0	4.79	0	−13.36	0	0
α *Tt/cl/g+*	6.38	6.82	0.38	0.54	5.36	0	5.80	0	−14.34	0	0
β *G−g+/cc/g−*	1.64	2.03	0.63	1.07	1.14	8	1.53	5	−13.26	8	7
β *G+g−/cc/g−*	1.84	2.46	0.54	0.91	1.18	7	1.81	3	−13.89	22	14
β *Tg+/cc/g−*	3.40	4.47	0.56	0.99	2.82	0	3.89	0	−14.35	3	1
β *Tg+/cc/g+*	4.47	5.62	0.43	0.82	3.72	0	4.87	0	−14.83	1	0
β *Tt/cl/t*	7.68	8.41	0.05	0.12	6.23	0	6.96	0	−14.75	0	0
β *Tt/cl/g−*	7.41	8.51	0.00	0.00	5.85	0	6.95	0	−15.21	0	0
β *G−g+/cc/g+*	2.82	3.26	0.50	0.89	2.14	1	2.58	1	−14.24	8	7

[a] Relative energies calculated with respect to the lowest energy structure in a given method (for B3LYP/6-31G*, −711.171271; for B3LYP/6-311++G**, −711.4275000; and for MP2/6-311++G**, −709.644818 Hartree). [b] Zero point energy; the lowest value was equal to 0.200347 Hartree. [c] Thermal correction to Gibbs free energy at 298 K; the lowest value was equal to 0.162937 Hartree.

Table 3. Hydrogen Bonding Parameters for the *fur GGGG* and α *Tg+/pw/g+* Structures of D-Glucose and 4-Deoxy-4-fluoro-D-glucose

compound	structure	hydrogen bonding type	D−A	H−A	D−H−A	population
D-glucose	*fur GGGG*	S(7)[O^3 H → O^6 H]	2.725	1.782	160.1	0.0493
D-glucose	*fur GGGG*	S(6)[O^1 H → O^3 H]	2.789	1.965	140.5	0.0284
D-glucose	*fur GGGG*	S(5)[O^5 H → O^4 H]	2.672	2.082	117.3	0.0201
D-glucose	*fur GGGG*	S(5)[O^6 H → O^5 H]	2.624	2.104	111.7	0.0197
D-glucose	α *Tg+/pw/g+*	S(6)[O^6 H → O^4 H]	2.803	2.012	137.2	0.0178
4-deoxy-4-fluoro- D-glucose	α *Tg+/pw/g+*	S(6)[O^6 H → F]	2.818	2.049	134.8	0.0170
D-glucose	α *Tg+/pw/g+*	S(5)[O^2 H → O^1 H]	2.719	2.197	112.4	0.0160
4-deoxy-4-fluoro- D-glucose	α *Tg+/pw/g+*	S(5)[O^2 H → O^1 H]	2.733	2.224	111.3	0.0153
4-deoxy-4-fluoro- D-glucose	α *Tg+/pw/g+*	S(5)[O^3 H → O^2 H]	2.871	2.382	110.5	0.0132
D-glucose	α *Tg+/pw/g+*	S(5)[O^3 H → O^2 H]	2.909	2.471	107.3	0.0115
D-glucose	α *Tg+/pw/g+*	S(5)[O^4 H → O^3 H]	2.822	2.368	108.0	0.0105

From Table 3 it is clear that hydrogen bonds present in the *fur GGGG* structure of D-glucofuranose are strong hydrogen bonds. The proton acceptor distance for the S(7)[O(3)H → O(6)H] hydrogen bond, which closes a seven-membered ring, is only 1.782 Å, and the donor−proton−acceptor angle is over 160°. The Mulliken population analysis at the 6-31G* basis set shows that electron density between the hydrogen and oxygen is 0.049 e^-, which also proves that this hydrogen bond is a strong one. It should also be noted that the point charge of the accepting oxygen O(6) is −0.78 e^-, and that of the donating hydrogen +0.52 e^-. For other structures of D-glucose, in which weaker hydrogen bonds were present, the corresponding charges were of about −0.75 and +0.46 e^-, respectively. Thus, the S(7)-[O(3)H → O(6)H] hydrogen bond has a strong electrostatic component. Therefore, it is of no further surprise that for proper description of the relative energy of *fur GGGG* structure one must use a basis set augmented with diffuse functions (more detailed discussion is presented in ref 96).

Fluorine as Hydrogen Bond Acceptor. Table 3 shows that for the α *Tg+/cc/g+* structure the two hydrogen bonds, the S(6)-[O(6)H → O(4)H] present in D-glucose and the S(6)[O(6)H → F(4)] present in 4-deoxy-4-fluoro-D-glucose, are very similar with respect to geometrical parameters and the electron population between the proton and the acceptor. The electron population between the proton and the acceptor, obtained in Mulliken analysis, is equal to 0.018 and 0.017 e^- for H···O and H···F hydrogen bonds, respectively. Further, the proton−acceptor distance is 2.012 and 2.049 Å, and the donor−proton−acceptor angle is 137.2° and 134.8° for hydroxyl and fluorine accepting the hydrogen bond, respectively. It should also be noted that the other intramolecular hydrogen bonds present in the α *Tg+/cc/g+* structure of D-glucose and its deoxyfluoro analogue are weaker. Therefore, the answer to a question that has arisen lately, whether covalently bonded fluorine is capable of accepting hydrogen bonds,[5,106,107] is positive, but the accepting ability of covalently bonded fluorine is lower than that of oxygen. Our results are in line with the results of ab initio calculations for systems with intermolecular hydrogen bonds, which indicated that, although oxygen is a better acceptor, fluorine may accept hydrogen bonds.[5,108] The experimental evidence for whether a fluorine atom acts as an acceptor of hydrogen bonds is limited. Statistical analyses of the Cambridge Structural Database showed that short CF···H−X contacts are extremely rare.[5,106] On the other hand, some studies provide support for F···H bonding.[15,109−114] For example, it was suggested that a hydrogen bond with fluorine as an acceptor controls an enzymatic transformation of UDP-4-deoxy-4-fluoroglucose by UDP glucose dehydrogenase[1] and that the fluorine atom of 2-deoxy-2-fluoro-D-myo-inositol-1,4,5-triphosphate accepts the hydrogen bond from the cellular receptor.[2]

Cooperative Intramolecular Hydrogen Bonds. In the case of D-glucopyranose, the lowest energy structures have a counterclockwise network of intramolecular hydrogen bonds. Structures with cooperative intramolecular hydrogen bonds oriented clockwise are about 1 kcal/mol higher in energy. In contrast, in the case of 4-deoxy-4-fluoro-D-glucose, the lowest energy structure, the α *G−g+/cl/t*, has cooperative intramolecular hydrogen bonds oriented clockwise, and the structures with counterclockwise-oriented hydrogen bonds are 0.7 kcal/mol higher in energy. However, other */cl/* structures are much higher in energy—over 5.5 kcal/mol, which indicates that the α *G−g+/cl/t* structure constitutes an exception. Indeed, the α *G−g+/cl/t* structure of 4-deoxy-4-fluoro-D-glucose is the only structure which has four intramolecular hydrogen bonds—other structures of 4-deoxy-4-fluoro-D-glucose have three or two hydrogen bonds. Moreover, in the α *G−g+/cl/t* structure, the fluorine atom acts as an acceptor of a hydrogen bond at the end of a chain of three cooperative intramolecular hydrogen bonds (see Figure 4). Tables 1 and 2 present the relative free energies and populations of conformers of D-glucose and 4-deoxy-4-fluoro-D-glucose both in the gas phase and in solution. D-Glucose in the gas phase is present as a mixture of several structures, each constituting no more than 30%. In the case of 4-deoxy-4-fluoro-D-glucose, the lowest energy α *G−g+/cl/t* structure constitutes over 50% of the population. It is worth mentioning that this α *G−g+/cl/t* structure for D-glucose constituted less than 8%. Such a significant impact of replacement of the fourth OH by F is due to the fact that a cooperative network of intramolecular hydrogen bonds is much more destabilized for the counterclockwise */cc/* arrangement, where fluorine, unable to donate a hydrogen bond, acts as a stopper of the cooperative chain. For the clockwise */cl/* arrangement of intramolecular hydrogen bonds, the fluorine atom accepting a hydrogen bond is placed at the end of a system of cooperative hydrogen bonds.

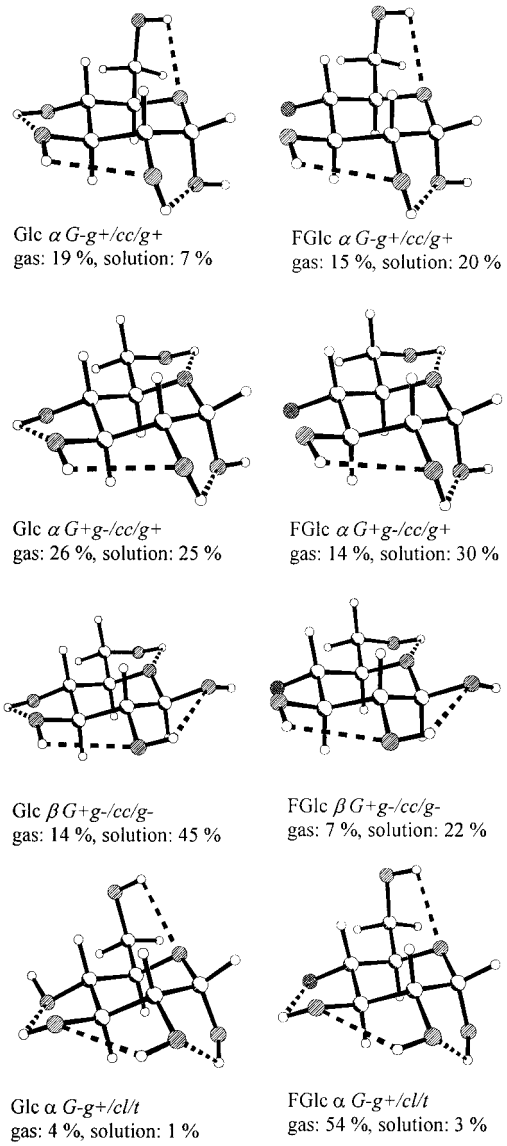

Figure 4. Structures of D-glucose and its deoxyfluoro analogue which contribute the most to the equilibrium population at room temperature in the gas phase or in aqueous solution. Glc stands for D-glucose and FGlc for 4-deoxy-4-fluoro-D-glucose.

Anomeric Effect. For pairs of structures (i) α *G−g+/cc/g+* and β *G−g+/cc/g−*, (ii) α *G+g−/cc/g+* and β *G+g−/cc/g−*, and (iii) α *Tg+/cc/g+* and β *Tg+/cc/g−*, one can observe the energetic consequences of the anomeric effect (see Tables 1

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Table 4. Mean Unsigned Error (kcal/mol) of Various Methods Compared to Composite Energies Obtained by Barrows et al.[90]

level of theory	mean unsigned error
RHF/6-31G(d)	0.2
B3LYP/6-31G(d)	0.9
MP2/6-31G(d)	1.0
CCSD/6-31G(d)//MP2/6-31G(d)	0.8
B3LYP/6-311++G(d,p)//B3LYP/6-31G(d)	0.1
MP2/6-311++G(d,p)//B3LYP/6-31G(d)	0.2
E composite[a]	0.0

[a] *E* composite = *E*(MP2/cc-pVTZ//MP2/cc-pVDZ) + [*E*(CCSD/6-31G(d)//MP2/6-31G(d) − *E*(MP2/6-31G(d))] + [*E*(RHF/cc-pVQZ//MP2/cc-pVDZ) − *E*(RHF/cc-pVTZ//MP2/cc-pVDZ)].

and 2). All of these structures possess the same number of intramolecular hydrogen bonds and gain stabilization from the exo-anomeric effect. Thus, for these structures of both D-glucose and its deoxyfluoro analogue, the only varying factor is the presence or absence of anomeric stabilization. For D-glucose at the B3LYP level, the α-anomers are favored over their corresponding *β*-anomers by about 0.9 kcal/mol, whereas at the MP2 level they are favored by 1.1 kcal/mol. Essentially the same energy of anomeric stabilization was found by Barrows et al.[90] In the case of 4-deoxy-4-fluoro-D-glucose, the anomeric stabilization is even greater. At the B3LYP level it accounts for up to 1.0 kcal/mol, and at the MP2 level it accounts for up to 1.3 kcal/mol. Therefore, slightly (by 0.1 kcal/mol) increased anomeric stabilization is a result of substituting a 4-OH group by a F atom in D-glucose.

Exo-Anomeric Effect. For D-glucose in a pair of *β Tt/cl/g*− and *β Tt/cl/t* structures, the *β Tt/cl/t* one has four intramolecular hydrogen bonds, whereas the *β Tt/cl/g*− one has only three but gains additional stabilization from the exo-anomeric effect. For D-glucose, the structure stabilized by the exo-anomeric effect is 0.3 kcal/mol higher in energy (see Table 1). That means that the energy of exo-anomeric stabilization is slightly lower (0.3 kcal/mol) than the energy of an additional intramolecular hydrogen bond. In contrast, for 4-deoxy-4-fluoro-D-glucose the *β Tt/cl/g*− structure, which has two hydrogen bonds and gains stabilization from the exo-anomeric effect, is 0.2 kcal/mol lower in energy than the *β Tt/cl/t* one with three hydrogen bonds (see Table 2). This means that the exo-anomeric effect for 4-deoxy-4-fluoro-D-glucose is 0.5 kcal/mol stronger than that for D-glucose, or that the additional hydrogen bond between OH groups is 0.5 kcal/mol weaker in 4-deoxy-4-fluoro-D-glucose than in D-glucose.

Reliability of Different Models. Table 4 provides a breakdown of model reliability ranked by mean unsigned error in predicted energies relative to the global minimum, compared to the composite, high level of theory, quantum mechanical energies obtained by Barrows et al.[90] That is, energy computed according to the equation

$$E_{\mathrm{comp}} = E(\mathrm{MP2/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ}) + [E(\mathrm{CCSD/6\text{-}31G^*//MP2//6\text{-}31G^*}) - E(\mathrm{MP2/6\text{-}31G^*})] + [E(\mathrm{RHF/cc\text{-}p^TVQZ//MP2/cc\text{-}pVDZ} - E(\mathrm{RHF/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ})] \quad (3)$$

The mean unsigned error for the 6-31G* basis set equals 1.0, 0.9, and 0.8 kcal/mol for the MP2, B3LYP, and CCSD methods. For energies calculated with the use of the 6-311++G** basis set for geometries optimized at the B3LYP/6-31G* level, the mean unsigned error is much lower: 0.1 and 0.2 kcal/mol for the B3LYP and MP2 methods, respectively. This demonstrates that the quality of the results obtained from the density functional theory (DFT) hybrid method, i.e., B3LYP, and from ab initio MP2 calculations is very similar. However, at the 6-31++G** basis set, the computational time needed to make single-point calculations for 4-deoxy-4-fluoro-D-glucose on the Cray J916 was 366 and 750 min for B3LYP and MP2 methods, respectively. This further proves the conclusion of Lozynski et al., that "B3LYP approach provides the shortest way to MP2 results".[115] Moreover, as was demonstrated earlier (vide supra), for proper description of relative energies of D-glucose structures, including glucofuranose structures, one must use a basis set augmented with diffuse functions. All in all, B3LYP/6-311++G**//B3LYP/6-31G* and MP2/6-311++G**//B3LYP/6-31G* levels of theory provide a description of relatives energies of structures of D-glucose almost as accurately as the very high quantum mechanics composite level employed by Barrows et al.[90]

Table 5. Point Charges Obtained via the CHELPG Procedure for the Fourth OH Group of D-glucose and the Fluorine Atom of 4-Deoxy-4-fluoro-D-glucose for Three Corresponding Structures of D-Glucose and Its Deoxyfluoro Analogue

structure	atom/group	charge
α *G+g−/pw/g+*	O(4)	−0.749
	H(O4)	0.488
	OH	−0.261
	F(4)	−0.269
α *Tg+/pw/g+*	O(4)	−0.760
	H(O4)	0.489
	OH	−0.271
	F(4)	−0.270
α *G−g+/zw/t*	O(4)	−0.755
	H(O4)	0.476
	OH	−0.279
	F(4)	−0.296

Electrostatic Potential. Table 5 presents point charges obtained by fitting to electrostatic potential by the CHELPG[116] method for three structures of D-glucose and 4-deoxy-4-fluoro-D-glucose. For clarity, the charges on the fourth OH group of D-glucose and the F atom of its 4-deoxyfluoro analogue are presented. The CHELPG method is thought to produce charges that successfully model the electrostatic potential field surrounding a molecule.[117] Therefore, this method is particularly suited for description of electrostatic interactions of the molecule with the outside world.

As is clear from Table 5, the sum of charges attributed to the oxygen and hydrogen of the fourth OH group is almost equal to the charge of the F atom in the corresponding structure of 4-deoxy-4-fluoro-D-glucose. Therefore, the substitution of a OH group by a F atom in the case of D-glucose does not much change the electrostatic potential around the corresponding molecules of D-glucose and its deoxyfluoro analogue.

(ii) Aqueous Solution. The Gibbs free energies and the percent of a structure in equilibrium population in aqueous solution are also presented in Tables 1 and 2 for D-glucose and its deoxyfluoro analogue, respectively. The aqueous solvation free energies (G^0_{auqa}) listed in these tables span a range of about 4.0 and 3.7 kcal/mol for D-glucose and its deoxyfluoro analogue, respectively. The weighted (by the percent in water solution) average solvation energy as calculated by the SM5.4/AM1

(115) Lozynski, M.; Rusinska-Roszak, D.; Mack, H.-G. *J. Phys. Chem. A* **1998**, *102*, 2899−2903.
(116) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.
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Table 6. Percent of α and *β* Anomers of D-Glucose and 4-Deoxy-4-fluoro-D-glucose As Calculated in the Gas Phase at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) Level and in Water Solution with the Use of the SM5.4/AM1 Model

compound	anomer	gas phase (%)	aqueous solution (%)
D-glucose	α	64%	36%
	β	36%	64%
4-deoxy-4-fluoro-D-glucose	α	83%	58%
	β	17%	42%

method is −14.6 kcal/mol for D-glucose and −13.7 kcal/mol for 4-deoxy-4-fluoro-D-glucose. That is, D-glucose is better solvated than its deoxyfluoro analogue by almost 1 kcal/mol.

Three structures, α *G−g+/cc/g+*, α *G+g−/cc/g−*, and *β G+g−/cc/g−*, contribute the most to the equilibrium population of D-glucose at room temperature (see Figure 4). An aqueous solution of D-glucose decreases the population of α anomers and favorably stabilizes *β* ones. Particularly, the percent of the α *G−g+/cc/g+* structure decreases from 19% to 7% and the percent of the *β G+g−/cc/g−* structure increases from 14% to 45%.

The same (as for D-glucose) three structures, α *G−g+/cc/g+*, α *G+g−/cc/g−*, and *β G+g−/cc/g−*, contribute the most to the equilibrium population of 4-deoxy-4-fluoro-D-glucose in solution. An aqueous solution most significantly affects the population of the α *G−g+/cl/t* structure, which is lowest in energy in the gas phase, mainly due to the fact that it has one intramolecular hydrogen bond more than other structures. This is also the reason this α *G−g+/cl/t* structure is solvated about 2 kcal/mol worse than other structures. Intramolecular hydrogen bonds in water solution must compete with intermolecular ones. Moreover, they interfere with intermolecular hydrogen bonds with water molecules. Therefore, the percent of the α *G−g+/cl/t* structure drops from 54% in the gas phase to only 3% in aqueous solution. The percent of the *β G+g−/cc/g−* structure of 4-deoxy-4-fluoro-D-glucose increases from 7% to 22%, but in an aqueous solution of D-glucose this structure constitutes up to 45%. The contribution of the α *G+g−/cc/g+* structure is 30% and 25% for 4-deoxy-4-fluoro-D-glucose and D-glucose, respectively.

α versus *β* Anomers. Table 6 presents the ratios of α to *β* anomers of D-glucose and its deoxyfluoro analogue as calculated in the gas phase at the B3LYP/6-311++G**//B3LYP/6-31G* level and in water solution with the use of the SM5.4/AM1 model.

The experimental ratio of α to *β* anomers of D-glucose in aqueous solution is 36%:64%,[118] exactly the same as the calculated value. However, such an excellent agreement between theory and experiment is most probably coincidental. If the SM5.4/PM3 model were used instead of the SM5.4/AM1 model, a ratio of 46%:54% would be obtained, which is still in good agreement with the experimental value. Although water solution favors *β* anomers, in the gas phase the α anomers constitute about 64% whereas *β* anomers constitute about 36%. These results are in line with other calculations.[90]

In the case of 4-deoxy-4-fluoro-D-glucose in the gas phase, the calculated ratio of α to *β* anomers is 83%:17%, and that in aqueous solution is 58%:42%. This means that the replacement of the fourth OH group of D-glucose by a F atom results in an increase in the amount of α anomers both in the gas phase and in solution. This effect may explain why 4-deoxy-4-fluoro-D-glucose is a better substrate for aldose reductase than D-glucose itself.[47,48] The shape and electrostatic potential around corresponding structures of both molecules are very similar, so if aldose reductase would preferably recognize α anomers as substrates, then 4-deoxy-4-fluoro-D-glucose should be a better substrate, as there are more α anomers in an equilibrium population of 4-deoxy-4-fluoro-D-glucose than D-glucose.

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Conclusions

Our studies showed that the substitution of a hydroxyl group by a fluorine atom for D-glucose does not much change either the shape of the corresponding structures of D-glucose and 4-deoxy-4-fluoro-D-glucose or the electrostatic potential around these molecules.

However, in the gas phase, it influences the cooperative network of intramolecular hydrogen bonds. Such a replacement of the fourth OH by F introduces a gap in the cooperative network of counterclockwise-oriented intramolecular hydrogen bonds and thus destabilizes these structures. In the case of some structures with a cooperative network of hydrogen bonds running clockwise, the fluorine atom is placed at the end of the chain of hydrogen bonds, and because it acts as an acceptor only, it does not obstruct the cooperativity. Therefore, for 4-deoxy-4-fluoro-D-glucose in the gas phase, the structure with a clockwise-oriented network of intramolecular hydrogen bonds, α *G−g+/cl/t*, is the most populated. This is a completely different picture than that obtained for D-glucose, where structures with hydrogen bonds arranged counterclockwise are definitely favored over the "clockwise" ones.

On the other hand, in aqueous solution, where intermolecular hydrogen bonds decrease stabilization from intramolecular ones—as they compete with them—for both D-glucose and 4-deoxy-4-fluoro-D-glucose the same three structures with a counterclockwise-oriented array of hydrogen bonds, α *G−g+/cc/g+*, α *G+g−/cc/g+*, and *β G+g−/cc/g−*, are undoubtedly favored. This means that in aqueous solution at equilibrium at room temperature, the same structures of D-glucose and 4-deoxy-4-fluoro-D-glucose are prevalent. In contrast, in the case of aliphatic compounds—deoxyfluoro analogues of (*R*,*R*)-tartaric acid—the substitution of a OH group by a F atom resulted in profound changes in the conformational preferences. That is, the fluorine-containing molecules were present as a mixture of several conformers, whereas for the parent compounds the conformational diversity was very limited—usually only one conformer predominated. This study shows that for cyclic compounds, D-glucose and 4-deoxy-4-fluro-D-glucose, the substitution of a OH group by a F atom should lead to a deoxyfluoro analogue which possesses biochemical and biological activity. Indeed, it was experimentally demonstrated that 4-deoxy-4-fluoro-D-glucose is a better substrate for aldose reductase than D-glucose.[47,48] This fact can be easily explained, providing aldose reductase recognizes α anomers as its substrates. For 4-deoxy-4-fluoro-D-glucose, α anomers constitute up to 58%, whereas for D-glucose they constitute only 36%.

All in all, for molecules with limited conformational freedom, such as cyclic compounds, the substitution of a OH group by a F atom does not much change the shape and the electrostatic properties of these molecules. However, as indicated previously, for conformationally labile aliphatic compounds the replacement of a OH by a F leads to profound changes in conformational preferences and to greater conformational diversity.[97] A fluorine atom, unlike a hydroxyl group, cannot donate hydrogen bonds, which stabilize the overall structure of the molecule, thus limiting its conformational freedom. In particular, this affects aliphatic compounds. In contrast, for cyclic compounds, covalent

bonds have already limited conformational freedom, so hydrogen bonds are not so important for determining the shape of a molecule. Moreover, a fluorine atom can substitute a hydroxyl group in its ability to accept hydrogen bonds. Thus, for molecules with limited conformational freedom, a fluorine atom is very likely to be a good substitute for a hydroxyl group. Therefore, potential drugs obtained by substituting a OH group by a F atom are much more likely to be discovered among molecules with limited conformational freedom (like cyclic compounds) than among conformational labile ones.

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Supporting Information Available: Computed data (Cartesian coordinates optimized at B3LYP/6-31G*, and energies in gas phase and solution) for the structures of the compounds described therein (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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