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Carbohydrate Research 341 (2006) 2224–2232
Carbohydrate RESEARCH

Fluoro-substitution effects in deoxyfluoro-D-glucose derivatives: random conformational search and quantum chemical calculation

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Received 30 October 2005; received in revised form 19 May 2006; accepted 23 May 2006
Available online 12 July 2006

Abstract—The effect of substitution by the fluorine atom at different positions of D-glucose was investigated by quantum chemical calculation of the low-energy conformers. These were obtained through the Random conformational search method. The geometries of conformers were optimized at the RHF/6-31(d) level, then reoptimization and vibrational analysis were performed at the B3LYP/6-31+G(d) level. Single-point energies were calculated at the B3LYP/6-311++G(2d,2p) level. The free energies of solvation in water were calculated utilizing the AM1-SM5.4 solvation model. For all substitution positions, the ring conformation does not change much, and the pyranoid $^4C_1$ conformers are dominant, while variations in the substitution site result in different effects in the network of hydrogen bonds, anomeric effect, the solvation free energy, and the ratio of α- and β-anomers.

Keywords: Fluoro-substitution; Fluorodeoxyglucoses; Low energy conformer; Random conformational search; B3LYP

1. Introduction

The fluorine atom and the hydroxyl group are isoelectronic, and they have similar polarity as well as close steric effect, therefore, F is considered to be a good substitute for OH both in biology and in drug design.[1–4] Once introduced, the high carbon–fluorine bond energy renders the substituent relatively resistant to metabolic transformation.[1,5] Thus, fluorinated analogues are potentially useful in studies of metabolism and clinical diagnostics.[2,6] Especially for carbohydrates, there are a number of successful examples where substitution of an F atom for an OH group results in a compound, which possesses biochemical and biological activities.

Nucleotides containing carbohydrates in which OH groups are replaced by F atoms serve as potential therapy in medicine for their anticancer[7–9] or antiviral activity.[10–12] Oligonucleotides whose sugar residues are modified by replacement of OH groups by F atoms were shown to be useful in gene therapy.[13–16] 3-Deoxy-3-fluoro-D-glucose can be used as molecular probe in studies of the metabolism of sugars in muscle, liver, and eyes with the ^{19}F NMR technique;[17–19] ^{18}F-deoxy-2-fluoro-D-glucose is the most important PET imaging agent to diagnose cancer and coronary heart diseases.[20–22]

The effect of substituting an F atom for an OH group has been widely studied by Hoffmann et al. using the quantum chemical calculation.[23–25] In the case of L-tartaric acid, replacement of an OH group by an F atom results in important conformational changes and ends up with greater conformational diversity,[23] while for D-glucose, substitution of an F atom for an OH group does not change much the shape and the electrostatic properties of the molecule. Hence, potential drugs obtained by replacing an OH group by an F atom are more

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doi:10.1016/j.carres.2006.05.020

likely to be discovered with cyclic compounds than aliphatic ones.[24] Since carbohydrates have multiple OH groups, there are several positions, which can be replaced by fluorine. It may be of interest to check whether there are significant differences for different positions of substitution. In this paper, the low-energy conformers of 2-, 3-, 4-, and 6-deoxyfluoroglucoses are studied in detail. As a result, it is shown that differences in substitution site have somehow different effects on the low-energy conformers of fluoroglucoses. Differences in the site of substitution may also bring different effects to the network of hydrogen bonds, in the anomeric effect, the solvation free energy, and the ratio of α- and β-anomers as well.

2. Results

2.1. The low energy conformation of deoxyfluoroglucoses

Substitution by fluorine at different positions results in a different number of low-energy structures. For 2-deoxy-2-fluoro-D-glucose, the number of low-energy conformers is 16, comparable to that of glucose (14). However, substitution at C-3 or C-4 may cause more low-energy structures (23 or 24, respectively). This is mainly due to the fact that replacement of the OH group by an F atom may destroy the cooperative network of intramolecular hydrogen bonds, which will gain more complex conformational space. Substitution at C-6 leads to much less low-energy structures (8) as the substituted OH group may play an important role in low energy conformational space. For all positions of substitution, the ring conformation does not change much, and pyranoid conformers are dominant. While for 2-deoxy-2-fluoro-D-glucose and 6-deoxy-6-fluoro-D-glucose, there are 2 furanoid conformers involved, for 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose, there is no furanoid conformer involved. The resultant pyranoid conformers adopt the $^4C_1$ conformation and it seems that substitution by the F atom does not change much the ring conformation compared to D-glucose.

The relative energies and population proportion of low-energy structures, both in gas phase and in aqueous phase of D-glucose and fluoro-substituted D-glucoses, are presented in Tables 1–5, respectively, and only when the equilibrium population is not less than 1% of total, the data of the corresponding low-energy structures are listed.

2.2. The network of intramolecular hydrogen bonds

The network of intramolecular hydrogen bonds plays an important role in the stability of the conformers. Therefore, the effect of replacing the OH group by an F atom on the network of intramolecular hydrogen bonds was evaluated. As shown in Table 6 for 2-deoxy-2-fluoro-D-glucose, all resulting low-energy structures have a counterclockwise network of intramolecular hydrogen bonds. For 3-deoxy-3-fluoro-D-glucose, the proportion of counterclockwise network and clockwise network, and crosswise network is 54%, 1%, and 45%, respectively. For 4-deoxy-4-fluoro-D-glucose, the proportion of counterclockwise network, clockwise network, and crosswise network is 67%, 20%, and 13%, respectively. For 6-deoxy-6-fluoro-D-glucose, the proportion of counterclockwise network and clockwise network is 97% and 3%, respectively, and no crosswise network is found. A further analysis of the results for 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose indicates that the structures with crosswise-oriented hydrogen bonds are about 3.8 kJ/mol higher in energy than those with counterclockwise-oriented hydrogen bonds. Structures with clockwise-oriented hydrogen bonds are about

Table 1. D-Glucose: relative energies (kJ/mol)[a] and proportion of low-energy structures in the gas phase and in aqueous solution

Conformer	MMFF94	B3LYP/6-31+G(d)	B3LYP/6-311++G(2d,2p)	TCG[b]	ΔG^0/gas	% Gas	$\Delta G_s^{0\,c}$	G_{sol}^0	% Aq
α G+g−/cc/g+	0.00	0.68	0.00	4.87	0.67	22	6.15	1.76	17
α Tg+/cl/g+	4.36	0.00	0.63	6.59	3.11	9	10.63	8.59	1
α G−g+/cc/g+	4.88	1.47	0.34	4.73	0.00	20	8.20	4.01	7
α Tt/cl/t	6.59	5.48	6.25	4.98	5.02	2	12.47	14.44	0
α G+t/cc/g+	10.23	10.71	8.82	2.80	9.46	2	3.81	6.17	3
α G−g+/cl/t	10.42	5.56	4.10	4.27	3.95	5	8.87	7.98	1
α Tg−/cl/t	11.52	4.85	5.20	6.13	6.59	2	10.71	12.78	0
α G+g+/cc/g+	12.08	11.31	9.08	2.95	2.85	1	2.43	5.20	4
β G+g−/cc/g−	0.55	4.93	3.47	2.61	6.01	14	3.18	0.00	35
β Tg+/cc/g−	5.78	4.59	4.59	4.18	1.97	5	8.07	7.58	2
β G−g+/cc/g−	5.91	5.35	3.73	2.52	5.71	13	7.11	4.10	7
β G+g−/cc/g+	8.07	7.69	5.99	2.39	1.21	5	3.35	2.47	13
β G+t/cc/g−	10.02	15.36	12.68	0.00	4.65	1	0.00	3.42	9

[a] Relative energies; the lowest value of total energy is −687.196281 hartree for B3LYP/6-31+G(d), and −687.426682 hartree for B3LYP/6-311++G(2d,2p).
[b] Thermal correction to Gibbs free energy at 298 K; the lowest value is 0.158003.
[c] The free energy of solvation in water; the lowest value is −66.86 kJ/mol.

Table 2. 2-Deoxy-2-fluoro-D-glucose: relative energies (kJ/mol)[a] and proportion of low-energy structures in gas phase and in aqueous solution

Conformer	MMFF94	B3LYP/6-31+G(d)	B3LYP/6-311++G(2d,2p)	TCG[b]	ΔG^0/gas	% Gas	$\Delta G_s^{0\,c}$	G_{sol}^0	% Aq
α G+g−/cc/g+	0.00	2.88	0.39	4.43	0.57	19	9.53	2.83	14
α G−g+/cc/g+	3.42	2.91	0.00	4.25	0.00	24	11.92	4.65	6
α Tg+/cc/g+	4.72	2.91	1.55	5.95	3.25	7	13.8	9.78	1
α G−t/cc/g+	10.59	13.67	9.61	2.16	7.52	1	8.11	8.36	1
α G+t/cc/g+	11.33	13.2	9.42	2.24	7.41	1	6.56	6.70	3
α G+g+/cc/g+	11.47	13.62	9.53	2.38	7.66	1	5.31	5.70	4
β G+g−/cc/g−	3.54	6.35	3.07	2.47	1.29	14	5.98	0.00	43
β G−g+/cc/g−	8.74	6.5	3.20	2.61	1.56	13	10.16	4.45	7
β Tg+/cc/g−	9.10	6.53	4.72	4.03	4.5	4	11.25	8.48	1
β G+g−/cc/g+	9.82	7.74	4.30	2.57	2.62	8	8.99	4.34	7
β G+t/cc/g−	13.25	16.48	12.07	0.00	7.82	1	3.3	3.85	9
β G−g+/cc/g+	13.53	9.34	5.61	2.27	3.63	6	9.82	6.18	3
Furα GTGG	7.06	21.77	19.04	1.88	16.67	0	0.00	9.40	1
Furβ GGGG	−5.06	0.00	2.66	9.68	8.09	1	29.21	30.03	0

[a] Relative energies; the lowest value of total energy is for −711.216705 B3LYP/6-31+G(d), and −711.447732 hartree for B3LYP/6-311++G(2d,2p).
[b] Thermal correction to Gibbs free energy at 298 K; the lowest value is 0.145632.
[c] The free energy of solvation in water; the lowest value is −65.89 kJ/mol.

Table 3. 3-Deoxy-3-fluoro-D-glucose: relative energies (kJ/mol)[a] and proportion of low-energy structures in the gas phase and in aqueous solution

Conformer	MMFF94	B3LYP/6-31+G(d)	B3LYP/6-311++G(2d,2p)	TCG[b]	ΔG^0/gas	% Gas	$\Delta G_s^{0\,c}$	G_{sol}^0	% Aq
α G+g−/cc/g+	0.00	0.58	0.84	4.63	0.89	14	7.46	2.02	12
α G−g+/cc/g+	2.91	0.00	0.00	4.58	0.00	20	10.34	4.01	5
α G+g−/cr/g+	3.79	7.25	6.48	3.2	5.10	3	4.36	3.13	8
α G+g−/cr/t	4.37	3.23	3.18	3.38	1.98	9	9.63	5.28	3
α G−g+/cr/g+	4.79	5.65	4.67	3.02	3.11	6	8.13	4.91	4
α Tg+/cc/g+	5.52	0.71	2.13	6.35	3.9	4	11.22	8.79	1
α Tg+/cr/g+	10.11	8.22	8.43	4.86	8.71	1	7.42	9.80	1
α G+t/cc/g+	10.33	10.48	9.48	2.41	7.31	1	5.07	6.05	2
α G−t/cc/g+	10.4	10.48	9.53	2.79	7.74	1	6.75	8.16	1
α Tt/cl/t	11.25	8.09	9.37	4.24	9.03	1	10.39	13.09	0
α G−g+/cr/t	4.79	0.92	0.84	3.8	0.06	19	13.44	7.17	2
α Tg+/cr/t	12.01	5.20	6.12	4.84	6.38	2	10.97	11.02	0
α G+g+/cc/g+	12.34	11.32	9.95	2.56	7.93	1	3.44	5.04	4
β G+g−/cc/g−	2.38	6.12	5.25	2.43	3.10	6	3.23	0.00	27
β G−g+/cc/g−	6.11	5.38	4.54	2.76	2.72	6	7.83	4.22	5
β Tg+/cc/g−	8.63	6.43	6.93	4.31	6.66	1	7.46	7.79	1
β G+g−/cr/t	9.86	11.79	10.90	1.68	8.00	1	4.78	6.45	2
β G+g−/cr/g−	11.01	11.79	10.16	0.95	6.53	1	1.77	1.97	12
β G+t/cc/g−	11.59	16.25	14.18	0.00	9.60	0	0.01	3.28	7
β G−g+/cr/t	11.74	10.74	9.82	1.55	6.79	1	8.59	9.05	1
β G−g+/cr/g−	14.01	10.56	9.06	1.11	5.59	2	7.04	6.30	2

[a] Relative energies; the lowest value of total energy is for −711.216692 B3LYP/6-31+G(d), and −711.448801 hartree for B3LYP/6-311++G(2d,2p).
[b] Thermal correction to Gibbs free energy at 298 K; the lowest value is 0.145663.
[c] The free energy of solvation in water; the lowest value is −65.94 kJ/mol.

2.9 kJ/mol higher in energy than those with counter-clockwise-oriented hydrogen bonds, except for the conformer α G−g+/cl/t of 4-deoxy-4-fluoro-D-glucose, which is extremely stable.[24]

2.3. Hydrogen bonds involving the F atom

The F atom serves as a proton acceptor in hydrogen bond interactions, and the hydrogen bonds involving the F atom were examined for each fluoroglucose and are shown in Table 7. For all positions of substitution, the F atom can serve as a proton acceptor and form F–H–O hydrogen bond interactions based on the analysis of the geometry parameters and the electron densities between proton and acceptor according to the Mulliken scheme.[23] Compared to D-glucose, it seems that the oxygen atom is a better hydrogen bond acceptor than the F atom, which is consistent with the results obtained by Hoffmann and Rychlewski.[24] For 2-deoxy-2-fluoro-D-glucose, the replacement of an F atom results in much weaker hydrogen bond interactions. For 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose, the strength of hydrogen bonds does not change much when the OH group is replaced by an F atom. For

Table 4. 4-Deoxy-4-fluoro-D-glucose: relative energies (kJ/mol)[a] and percent of low-energy structures in the gas phase and in aqueous solution

Conformer	MMFF94	B3LYP/6-31+G(d)	B3LYP/6-311++G(2d,2p)	TCG[b]	ΔG^0/gas	% Gas	$\Delta G_s^{0\,c}$	G_s^0	% Aq
α G+g−/cc/g+	2.47	3.84	3.58	3.33	3.53	9	6.15	0.84	11
α G+g−/cl/g+	2.78	8.22	7.44	2.17	5.97	4	7.95	5.08	2
α G−g+/cc/g+	6.15	3.34	2.77	3.31	2.86	12	7.16	1.18	9
α G−t/cl/t	8.91	11.35	10.3	1.51	7.88	2	9.84	8.88	0
α G+g−/cr/g+	11.1	8.96	7.94	2.60	6.81	2	3.68	1.65	8
α G+t/cc/g+	11.53	13.34	11.8	1.88	9.45	1	3.27	3.88	3
α G−t/cc/g+	12.03	13.45	11.75	2.17	10.00	1	3.06	4.22	3
α G−g+/cr/g+	12.78	7.96	6.73	2.54	5.71	4	5.69	2.56	5
α Tg+/cc/g+	13.44	9.17	8.65	3.39	8.87	1	4.19	4.22	3
α G−g+/cl/t	0.00	0.00	0.00	3.00	0.00	39	11.13	2.29	6
β G+g−/cc/g−	4.6	8.43	7.41	1.50	4.83	5	5.19	1.18	9
β G+g−/cl/t	8.86	12.22	11.35	1.20	8.57	1	6.91	6.64	2
β G−g+/cc/g−	9.14	7.73	6.15	1.73	4.07	7	7.74	2.97	4
β G−g+/cl/t	10.03	10.93	10.12	1.27	7.51	2	9.25	7.92	1
β G+g−/cc/g+	12.18	11.69	10.38	1.33	7.66	2	5.23	4.05	3
β G+t/cc/g−	13.18	18.12	15.89	0.00	10.96	0	1.59	3.71	3
β G+g−/cl/g−	14.03	13.11	11.4	1.05	8.21	2	2.81	2.18	6
β G−g+/cl/g−	16.15	11.56	10.06	1.06	7.09	2	6.95	5.2	2
β Tg+/cc/g−	16.62	14.24	13.19	1.53	10.92	0	3.35	5.43	2
β G−g+/cc/g+	16.67	12.48	10.96	1.38	8.35	1	4.27	3.78	3
β G−g+/cr/g−	16.84	14.45	12.35	0.92	8.84	1	0.00	0.00	15

[a] Relative energies; the lowest value of total energy is −711.218031 for B3LYP/6-31+G(d), and −711.449925 hartree for B3LYP/6-311++G(2d,2p).
[b] Thermal correction to Gibbs free energy at 298 K; the lowest value is 0.145769.
[c] The free energy of solvation in water; the lowest value is −64.06 kJ/mol.

Table 5. 6-Deoxy-6-fluoro-D-glucose: relative energies (kJ/mol)[a] and proportion of low-energy structures in the gas phase and in aqueous solution

Conformer	MMFF94	B3LYP/6-31+G(d)	B3LYP/6-311++G(2d,2p)	TCG[b]	ΔG^0/gas	% Gas	$\Delta G_s^{0\,c}$	G_s^0	% Aq
α G+/cc/g+	0.00	0.00	0.00	5.87	0.67	38	15.40	2.32	13
α G−/cc/g+	0.36	0.89	0.24	6.31	3.11	29	12.56	0.16	32
α T/cl/t	10.41	5.36	5.72	6.00	0.00	3	18.08	10.85	0
β G+/cc/g−	1.22	4.80	4.17	3.24	5.02	20	13.18	1.64	18
β G−/cc/g−	4.35	6.59	5.49	3.62	9.46	10	9.84	0.00	34
Furα GTTG	19.42	16.43	16.29	0.07	2.85	0	9.41	6.82	2
Furβ GTTG	28.87	28.41	27.58	0.00	1.97	0	0.00	8.63	1

[a] Relative energies; the lowest value of total energy is −711.219111 hartree for B3LYP/6-31+G(d), and −711.450591 hartree for B3LYP/6-311++G(2d,2p).
[b] Thermal correction to Gibbs free energy at 298 K; the lowest value is 0.145410.
[c] The free energy of solvation in water; the lowest value is −59.71 kJ/mol.

Table 6. Proportion (%) of network of intramolecular hydrogen bonds: counterclockwise (cc), clockwise (cl), crosswise (cr), according to the results of Tables 1–5

Compound	cc (%)	cl (%)	cr (%)
2-Deoxy-2-fluoro-D-glucose	99	0	0
3-Deoxy-3-fluoro-D-glucose	54	1	45
4-Deoxy-4-fluoro-D-glucose	39	54	7
6-Deoxy-6-fluoro-D-glucose	97	3	0
D-Glucose	82	18	—

6-deoxy-6-fluoro-D-glucose, the Mulliken population of hydrogen bond S(5)[$O^4H \rightarrow F$] of the α Tt/cl/t structure is 0.0253, higher than that of hydrogen bond S(5)[$O^4H \rightarrow O^6H$] of α Tt/cl/t in D-glucose (0.0084), which seems to be somehow odd because the geometry parameters of hydrogen bond in S(5)[O(4)H → O(6)H] indicate that it should be stronger than S(5)[O(4)H → F]. Further analysis using AIM[26] indicates that the electronic density of the critical point of hydrogen bond S(5)[O(4)H → O(6)H] is 0.0243, while that of hydrogen bond S(5)[O(4)H → F] is 0.0178, which indicates that hydrogen bond S(5)[O(4)H → O(6)H] is stronger.

2.4. Anomeric effect

The anomeric effect is known to provide the stabilization of the axial OR conformer to override the inherent steric bias of the substituent. As a result of intramolecular dipole–dipole interaction, it plays an important role in the determination of the proportion of α- and β-anomers of carbohydrates. The anomeric effect can be achieved through calculation of the energy difference ($E_\beta - E_\alpha$) between the α- and β-anomers, which differ only by the axial or equatorial orientation of OH groups on the anomeric carbon.[27] In our study, there are several pairs of α- and β-anomers for each compound, so the

Table 7. Hydrogen bonding parameters for hydrogen bonds involving an F atom in fluoroglucoses and the corresponding hydrogen bonds involving an oxygen atom in D-glucose

Compound	Structure	Hydrogen bond type	D–A	H–A	D–H–A	Population
2-Deoxy-2-fluoro-D-glucose	α G+g−/cc/g+	S(5)[3-OH → F]	2.890	2.610	96.6	0.0101
D-Glucose	α G+g−/cc/g+	S(5)[3-OH → 2-OH]	2.910	2.509	105.0	0.0172
3-Deoxy-3-fluoro-D-glucose	α G+g−/cc/g+	S(5)[4-OH → F]	2.860	2.486	103.2	0.0112
D-Glucose	α G+g−/cc/g+	S(5)[4-OH → 3-OH]	2.840	2.390	107.3	0.0123
4-Deoxy-4-fluoro-D-glucose	α G−g+/cr/g+	S(5)[3-OH → F]	2.885	2.540	100.8	0.0123
D-Glucose	α G−g+/cl/t	S(5)[3-OH → 4-OH]	2.850	2.461	104.0	0.0155
6-Deoxy-6-fluoro-D-glucose	α T/cl/t	S(6)[4-OH → F]	2.815	2.060	131.4	0.0253
D-Glucose	α Tt/cl/t	S(5)[4-OH → 6-OH]	2.764	1.950	137.1	0.0084

average of the individual energy differences is an evaluation of the anomeric effect. The results are listed in Table 8. Considering 2-deoxy-2-fluoro-D-glucose, 3-deoxy-3-fluoro-D-glucose, 4-deoxy-4-fluoro-D-glucose, and 6-deoxy-6-fluoro-D-glucose, the α-anomers are favored by about 2.93, 4.36, 3.93, and 4.71 kJ/mol, respectively, compared to their corresponding β-anomers, while for D-glucose, α-anomers are favored by about 3.67 kJ/mol. Therefore, 2-deoxy-2-fluoro-D-glucose is more populated in β-anomers than D-glucose, while other substitution sites may result in less population of β-anomers than D-glucose. As summarized by Juaristi and Cuevas,[28] the anomeric effect may be understood as the resonance of a lone pair of electrons in the ring oxygen trans to the anomeric OH group, which means that the C–O bond within the ring becomes more double in character and is shortened, while the other C–O bond becomes less bonded and is lengthened. The bond lengths of both C–O bonds of conformer G+g−/cc/g+ of D-glucose and fluoroglucoses are listed in Table 9. For D-glucose and its fluoro-analogues, the bond length of the anomeric C–O bond of the α-anomer is longer than that of the β-anomer, and the bond length of the heterocyclic C–O bond of the α-anomer is shorter than that of the β-anomer, which indicates the occurrence of the anomeric effect. For 2-deoxy-2-fluoro-D-glucose, the change in bond length is weaker, which indicates that the anomeric effect in 2-deoxy-2-fluoro-D-glucose is much less, and is consistent with the result in energy difference analysis. 6-Deoxy-6-fluoro-D-glucose experiences the largest bond length change, therefore, it has the biggest anomeric effect, and this is also consistent with the result of energy difference analysis.

Table 8. Comparative evaluation of the anomeric effect ($E_\beta - E_\alpha$) in fluoroglucoses and D-glucose

Compound	$E_\beta - E_\alpha$ (kJ/mol)
2-Deoxy-2-fluoro-D-glucose	2.93
3-Deoxy-3-fluoro-D-glucose	4.36
4-Deoxy-4-fluoro-D-glucose	3.93
6-Deoxy-6-fluoro-D-glucose	4.71
D-Glucose	3.67

2.5. The free energies of solvation in water

The free energies of solvation of fluoroglucoses and D-glucose were calculated using the AM1-SM5.4 solvation model. The results (ΔG_s^0) are listed in Tables 1–5. Since the OH group can interact with solvent molecules as both proton acceptor and donor, while the F atom can only act as proton acceptor, D-glucose is better solvated than its deoxyfluoro analogues. Besides, the different positions of substitution by fluorine may result in different solvation effects. 2-Deoxy-2-fluoro-D-glucose has an unfavorable average solvation free energy of about 4.2 kJ/mol compared to D-glucose; 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose have an unfavorable average solvation free energy of about 1.7 kJ/mol relative to D-glucose; while 6-deoxy-6-fluoro-D-glucose has an unfavorable average solvation free energy of about 11.7 kJ/mol relative to D-glucose. The solvation energy is also correlated to the hydrogen bond network of the conformers, the conformers with cc and cr hydrogen bond network being possibly more solvated than the conformers with a cl hydrogen bonds network. The β-anomer is more solvated than the α-anomer, and the solvated energy gap between β and α-anomer of D-glucose

Table 9. Bond length of anomeric C–O bond (former) and C–O bond within the ring (latter) in D-glucose and fluoroglucoses: the conformers α G+g−/cc/g+, α G−g+/cc/g+, β G+g−/cc/g−, and β G−g+/cc/g− are examined

Compound	α G+g−/cc/g+	α G−g+/cc/g+	β G+g−/cc/g−	β G−g+/cc/g−
D-Glucose	1.421/1.411	1.422/1.410	1.399/1.424	1.399/1.423
2-Deoxy-2-fluoro-D-glucose	1.404/1.420	1.406/1.418	1.389/1.420	1.389/1.420
3-Deoxy-3-fluoro-D-glucose	1.419/1.412	1.420/1.411	1.398/1.422	1.398/1.422
4-Deoxy-4-fluoro-D-glucose	1.418/1.413	1.419/1.412	1.397/1.426	1.398/1.425
6-Deoxy-6-fluoro-D-glucose	1.421/1.410	1.423/1.408	1.398/1.422	1.398/1.423

and its fluoro-analogues is about 3–5 kJ/mol, which makes the β-anomer more populated than the α-anomer in aqueous solution. This is mainly caused by the fact that the anomeric OH group in the β-anomer is better solvated than that of the α-anomer in aqueous solution.

2.6. Ratio of α- and β-anomers

The population of α- and β-anomers both in gas phase and in solution is shown in Table 10. Replacement of an OH group by an F atom at C-2 results in a decrease in the proportion of α-anomers both in gas phase and in solution relative to D-glucose, while substitution at C-3, C-4, or C-6 results in an increase of the amount of α-anomers. As a comparison, the ratios of α- and β-anomers of D-glucose and its fluoro-analogues in solution are in agreement with the experimental ratios, which were obtained through NMR method in D_2O solution.[29–33] As shown in Table 10, the ratios of α- and β-anomers are basis set dependent, but not very sensitive, and results by 6-311++G(2d,2p) basis set are more reasonable than that by 6-31+G(d).

3. Discussion

3.1. Calculation details

The conformational space of glucose has been widely studied.[34–38] It is reasonable to study the effect of substitution of an OH group by a fluorine atom for each conformer according to the substitution site.[39] However, because fluoro-substitution may result in some change in conformational space and properties of the compound are mainly determined by the low-energy conformations, in our study, we performed a series of conformational searches and selected the conformers within 5 kcal/mol above the global minimum for further analysis.

There are many conformational search methods, however, in the case of small molecules like D-glucose and its analogues, the random search method is a suitable choice. It was proved to be an efficient way to find the low energy conformation in our study. The relative energies obtained by the MM method for D-glucose and its fluoro-analogues are listed in Tables 1–5. The MM method is comparable to the DFT method, and the average difference in relative energy between the MM method and the DFT method is about 3 kJ/mol. Therefore, an energy window of 5 kcal/mol (about 20 kJ/mol) in the MM method is enough to ensure the low-energy conformers within an energy window of 3 kcal/mol (about 13 kJ/mol) in DFT method to be studied. For carbohydrates, previous studies indicate that introduction of a diffuse function into the basis set is essential.[40] Therefore, the 6-31+G(d) basis set was applied in geometry optimization for the optimal carbohydrate geometry.

Calculation of the solvation free energy for carbohydrates in aqueous solution is rather difficult as these molecules can experience strong hydrogen bond interactions with water molecules, and the conventional PCM model is not suitable. The QM/MM method, which implies the explicit water molecules seems to be a more suitable method;[41] however, it is rather time consuming and complex for building models, and it seemed an impossible task for us to calculate so many conformers by QM/MM. Therefore, the AM1-SM5.4 solvation model was used in our study because rather reasonable results were gained when the solvation free energy of glucose was calculated with it,[24] and the results in our study are also rather reasonable compared to the experimental data.

In comparison with the results of Hoffmann and Rychlewski[24] for D-glucose, it was found that most low-energy conformers are identical, but several new low-energy conformations are involved such as α Tg−/cl/t, α G+g+/cc/g+, and β G+t/cc/g− taking into

Table 10. Ratio of α- and β-anomers both *in vacuo* and in solution for fluoro-D-glucose and D-glucose

Compound	Anomer	6-31+G(d)		6-311++G(2d,2p)	
		Gas phase (%)	Aqueous solution (%)	Gas phase (%)	Aqueous solution (%)
D-Glucose	α	70	40	63	34 (36)
	β	30	60	37	66 (64)
2-Deoxy-2-fluoro-D-glucose	α	60	34	53	30 (33)
	β	40	66	47	70 (67)
3-Deoxy-3-fluoro-D-glucose	α	84	44	82	43 (47)
	β	16	56	18	57 (53)
4-Deoxy-4-fluoro-D-glucose	α	66	55	75	50 (42)
	β	35	45	25	50 (58)
6-Deoxy-6-fluoro-D-glucose	α	75	52	70	47 (43)
	β	25	48	30	53 (57)

Experimental data in aqueous solution are given in brackets.[29–33]

account in the conformational search that the lowest energy conformation in gas or in aqueous solution as well as the ratio of α- and β-anomers is the same as that reported by Hoffmann and Rychlewski. For 4-deoxy-4-fluoro-D-glucose, a number of new low-energy conformers result from the conformational search, especially the rather stable conformers with the crosswise hydrogen bonds network, and the 1:1 ratio of α- and β-anomers in 4-deoxy-4-fluoro-D-glucose differs in some extent of that found by Hoffmann and Rychlewski (29:21), which is mainly due to the involvement of the new conformers. Compared to the experimental data (ratio 21:29), our results seem to be more reasonable.

3.2. The effect of the site of substitution

For all positions of substitution, the ring conformation does not change much, and pyranoid $^4C_1$ conformers are predominant. However, the position of substitution may affect the network of hydrogen bonds, the anomeric effect, the solvation free energy, and the ratio of α- and β-anomers both in the gas and aqueous phases. For 2-deoxy-2-fluoro-D-glucose, a similar number of low-energy conformations compared to D-glucose is found; however, the anomeric effect of 2-deoxy-2-fluoro-D-glucose is weaker than that of D-glucose, which results in more β-anomers both in gas and in aqueous phase. 3-Deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose have more low-energy conformations, which involve a clockwise, counterclockwise, and crosswise network of cooperative hydrogen bonds and they experience a somehow stronger anomeric effect as compared to D-glucose, which results in less β-anomers proportion. For 6-deoxy-6-fluoro-D-glucose, the number of low-energy conformers is much less and the anomeric effect is also stronger than that of D-glucose.

Because the fluorine atom serves as a proton acceptor rather than as a proton donor, the F atom, unable to donate a hydrogen bond, acts as a stopper of the cooperative hydrogen bond. For 3 and 4 substitutions, the hydrogen bonds network is broken, which reduces the energy gaps between the clockwise, crosswise, and counterclockwise network conformers and results in the stable clockwise and crosswise network of conformers. Differences in substitution site also result in distinct difference in solvation energy. This indicates that the OH group at different positions may have different solvation patterns, especially in the situation where the OH group acts as hydrogen bond donor. From the result, we can see that the hydroxyl at C-2 of D-glucose is less solvated, while OH-6 is best solvated.

4. Computational methodology

4.1. Nomenclature

Capital letter G−, G+, or T corresponds to the torsion angle (O(6)–C(6)–C(5)–O5) of about −60°, 60°, or 180°. Letter g−, g+, or t corresponds to the torsion angle H–O(6)–C(6)–C(5) of about −60°, 60°, or 180° as shown in Chart 1. The following designator cc, cl, or cr describes the cooperative network of intramolecular hydrogen bonds running counterclockwise, clockwise, or crosswise, respectively as shown in Chart 2. The last letter g−, g+, or t corresponds to the torsion angle H–O(1)–C(1)–O(5) of about −60°, 60°, or 180°, respectively, as shown in Chart 2.[24] For furanose forms, four letters are used to describe the conformers in the order of torsional positions O(6)–C(6)–C(5)–O(5), O(6)–C(6)–C(5)–C(4), O(5)–C(5)–C(4)–O(4), and O(5)–C(5)–C(4)–C(3) as described by Buyong Ma et al.[38]

4.2. Conformation search

The search for stable conformations in conformational space for deoxyfluoroglucoses was carried out using the Random Search method, which is implemented in the Sybyl 6.9 software package from Tripos Inc., and the MMFF94 force field[42] was used. The parameters of conformation search were set as follows: Maximum Cycles 3000, Convergence Threshold 0.05,

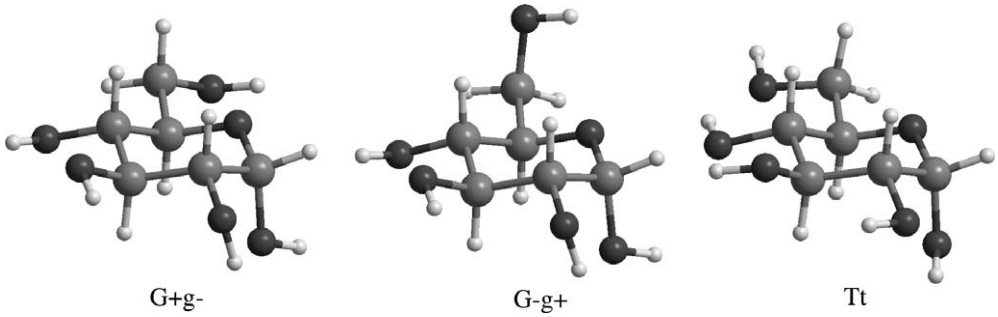

Chart 1. Description of the stereochemistry of the hydroxylmethyl group of glucopyranoses: the first capital letter G−, G+, and T corresponds to the torsion angle O(6)–C(6)–C(5)–O(5) of about −60°, 60°, and 180°, respectively. The following letter g−, g+, and t corresponds to the torsion angle H–O(6)–C(6)–C(5) of about −60°, 60°, and 180°.

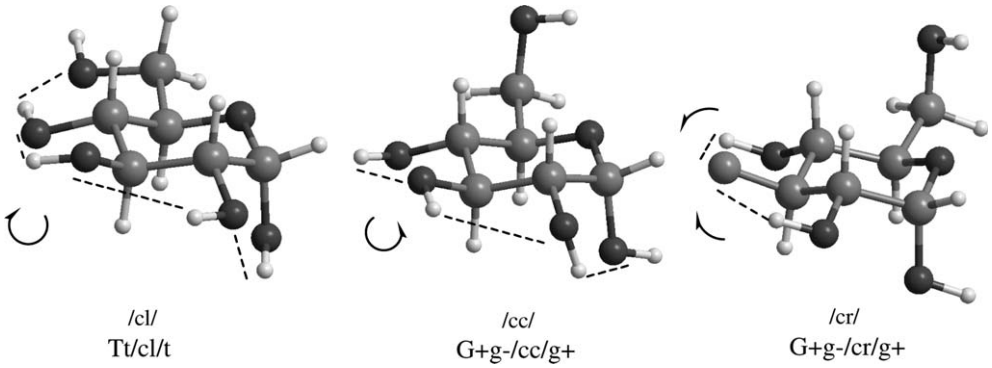

Chart 2. Description of the cooperative network of intramolecular and torsion angle of H–O(1)–C(1)–C(2): designators cc, cl, and cr describe the cooperative network of intramolecular hydrogen bonds as running counterclockwise, clockwise, and crosswise, respectively. The last letter g−, g+, and t corresponds to the torsion angle H–O(1)–C(1)–O(5), respectively.

Energy Cutoff 5 kcal/mol, Minimum Hits 10, RMS Threshold 0.1, and Check Chirality yes. Each search was performed 10 times, and the resulting low-energy conformers were combined. For each fluoroglucose, the pyranoid α-anomer, pyranoid β-anomer, furanoid α-anomer, and furanoid β-anomer were searched, respectively. For pyranoses, the initial conformer for search was built by substituting an F atom for an OH group based on the G+g−/cc/g+ geometry of glucose described by Barrows et al.[43] For furanoses, initial conformer for search was built by substituting an F atom for an OH group based on the GGGG geometry of glucofuranose described by Hoffmann and Rychlewski.[24] The resulting conformers were then minimized by the MMFF94 force field, and conformers within an energy window of 20 kJ/mol above the global minimum were selected for further quantum chemical calculation.

4.3. Quantum chemical calculation

After each search, the selected low-energy structures obtained by the Random Search method were fully optimized at the HF/6-31G(d) level. The re-optimization of the resulting geometries and vibrational analysis were performed at the B3LYP/6-31+G(d) level. Finally, the single-point energies were calculated at the B3LYP/6-311++G(2d,2p) level. The free energies of solvation in water ΔG_s^0 were calculated using the AM1-SM5.4 solvation model, which is included in the AMSOL6.8 program.[44] All ab initio and DFT calculations were carried out with the Gaussian98 program suite.[45]

4.4. Calculation analysis

Analysis of the calculation refers to the work of Hoffmann and Rychlewski.[24] The relative Gibbs free energies in the gas phase were obtained by combining the results of single-point energies and vibrational analysis, and TCG means thermal correction to Gibbs free energy at 298 K (Eq. 1).

$$G_{298}^0 = E(\text{B3LYP/6-311} + +\text{G(2d, 2p)//B3LYP/6-31} + \text{G}^*) + \text{TCG(B3LYP/6-31} + \text{G}^*) \quad (1)$$

The Gibbs free energies in solution were obtained by adding the free energies of solvation to the Gibbs free energies in the gas phase (Eq. 2).

$$G_{\text{sol}}^0 = G_{298}^0 + \Delta G_{\text{s}} \quad (2)$$

The usual Boltzmann equation was used in assessing the equilibrium population of conformers both in gas and in aqueous phase.

5. Conclusion

For cyclic compounds, substitution of an F atom for an OH group is considered as a feasible strategy to find potential drugs. In this paper, the effect of substitution at different positions of glucose by a fluorine atom was investigated by studying the low-energy conformers of the fluoroglucoses. When an OH group is replaced by a fluorine atom, besides the difference in C–F and C–OH bond, the conformational diversity is an important factor, which should affect the bioactivity of the fluorosugar. Compared to glucose, fluoroglucoses can keep the overall shape of the molecule (pyranoid $^4C_1$), which ensure matching of active binding sites as well as glucose. Otherwise, the different positions of fluoro-substitution result in a variety of low-energy conformers and different ratios of α- and β-anomers, which may improve the capability for fluoroglucoses to bind more tightly with the receptor. Therefore, unless the OH group plays an important role in binding with the receptor, its replacement by a fluorine atom is worth to attempt.

Acknowledgments

This investigation received financial support from the Innovation Project Foundation of SIOC (Shanghai

Institute of Organic Chemistry). We thank Professor D. G. Truhlar for his kindness in providing the AMSOL soft package, and we also thank Dr. M. Hoffmann for his kind help in calculating the solvation free energy using the AMSOL soft package.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.05.020.

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