DFT STUDY ON 3-SUBSTITUTED TETRAHYDROPYRAN-2-YL RADICALS

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A series of tetrahydropyran-2-yl radical (**1**) analogs was studied using density functional theory (DFT) to model conformational behavior of glycopyranosyl radicals. Calculations of the structure and stability of the $^4C_1$, $^1C_4$, $B_{2,5}$, $^{O,3}B$, and $^4H_3$ ring conformers for tetrahydropyran-2-yl radical (**1**) and for 3-fluoro- (**2**, **7**), 3-hydroxy- (**3**, **8**), 3-methoxy- (**4**, **9**), 3-acetoxy- (**5**, **10**), and 3-(benzyloxy)tetrahydropyran-2-yl (**6**, **11**) derivatives showed that conformational behavior of the 3-substituted radicals depends on both the electronic character and orientation of the C3 substituent. The calculations show that radical **1** is slightly pyramidal and exists as an equilibrium mixture of the $^4C_1$ and $^1C_4$ conformers. Substituents at the C3 position force **2**–**11** radicals to adopt a chair conformation with the substituent in the axial orientation. Thus radicals **2**–**6** prefer the $^1C_4$ conformer though there are several ring conformers in equilibrium whereas for radicals **7**–**11** the $^4C_1$ conformer predominates. The calculated preferences are consistent with available ESR data. These results provide further support for the importance of quasi-homoanomeric interactions on stability of anomeric radicals.

Keywords: Carbohydrates; Radicals; Tetrahydropyrans; Conformational analysis; Quasi-homoanomeric effect; Molecular modeling; DFT calculations; Ab initio; ESR spectroscopy.

Anomeric carbohydrate radicals[1] play an important role in the stereoselective synthesis of carbohydrate derivatives. For example, free radical reactions have been successfully applied in synthesis of *C*-glycosides[2–4] and preparation of 2-deoxy-β-glycosides[5]. Radical-mediated halogenations[6] as well as generation of anomeric carbanions also involve anomeric radicals as key intermediates[3,7]. Most of these reactions may be carried out under non-polar conditions. A preference to the axial bond formation at the radical center was observed. The highly stereoselective outcome of tetrahydropyran-2-yl radical reactions was interpreted using the greater stability of the intermediate axial radicals than of the equatorial radicals[8]. The anisotropic interactions of the radical center with lone pair orbitals of the adjacent oxygen atom were used to interpret the preference to the axial radical conformation. This stabilization, as an analogy with the anomeric

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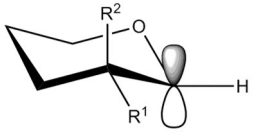
effect[9], was called the "quasi-anomeric effect"[10]. Later on also interactions of the unpaired electron with the antibonding orbital of the adjacent C–O bond were considered and termed[11] as the "quasi-homoanomeric effect". ESR studies on per-*O*-alkylated and per-*O*-acetylated glycopyranosyl radicals demonstrated that pyranosyl radicals exist as almost planar π-type radicals[10]. Experimental data on glycopyranosyl radicals were discussed in terms of various conformations of the pyranosyl ring; the analysis of hydrogen hyperfine splittings reveals that radicals from glucosyl-type parent compounds prefer a twisted $B_{2,5}$ conformation. Galactosyl-type pyranosyl radicals most likely exist in a $^4H_3$ half-chair conformation, while mannosyl-type radicals retain the $^4C_1$ conformation. The ESR spectra of the parent radical **1** were interpreted as a rapid equilibrium of two chair forms of a slightly pyramidal radical[12,13] and the ESR spectra of both 3-hydroxy- and 3-(acetoxy)tetrahydropyran-2-yl radicals indicated the preference for the $^4C_1$ conformation with the C3 substituent in the axial orientation[14–16]. Ab initio calculations[17] on tetrahydropyran-2-yl radical **1** showed a small pyramidalization at the radical center revealing that this radical prefers a chair form and that the axial radical is more stable than the equatorial radical. In this paper, we have carried out the structural analysis of several 3-substituted tetrahydropyran-2-yl radicals using the density functional method (DFT) calculations to shed more light on the factors that influence the structure and conformational behavior of anomeric glycopyranosyl radicals.

METHODOLOGY

The schematic representations and the labeling of the atoms for 3-fluoro- (**2**, **7**), 3-hydroxy- (**3**, **8**), 3-methoxy- (**4**, **9**), 3-acetoxy- (**5**, **10**), and 3-(benzyloxy)tetrahydropyran-2-yl (**6**, **11**) radicals together with the parent tetrahydropyran-2-yl radical (**1**) are given in Fig. 1. For each of the five 3-substituted derivatives, two possible positions of the 3-substituent group with respect to the $^4C_1$ conformation of a pyran ring were studied: the equatorial **2**–**6** and axial **7**–**11** orientations. The equatorially oriented group at the C3 position models the position found in *gluco* and *xylo* derivatives and the axially oriented substituent corresponds to the orientation in *manno* and *lyxo* derivatives. Thus, altogether the conformational properties of 11 compounds have been investigated. To develop a better understanding of conformational behavior of the anomeric radicals we have examined five different ring conformations, namely $^4C_1$, $^1C_4$, $B_{2,5}$, $^{O,3}B$, and $^4H_3$, which have been used in the interpretation of ESR spectra for carbohydrate

radicals with substituents[10,11]. The starting structures of these conformers were generated from the corresponding idealized ring conformations[18]. The conformation abound the C3–O3 bond (Fig. 2a) is defined by a dihedral angle Ψ = Ψ(C6–O3–C3–C2). Conformational analysis of dimethoxytetrahydropyrans using ab initio methods[19] revealed the existence of three staggered conformers for the methoxy group at the C3 atom. Therefore, three staggered rotamers about the C3–O3 bond were considered as possible starting orientations for the groups studied.



	R^1	R^2
1	H	H
2	F	H
3	OH	H
4	OMe	H
5	OAc	H
6	OBn	H
7	H	F
8	H	OH
9	H	OMe
10	H	OAc
11	H	OBn

FIG. 1
Schematic representation of tetrahydropyran-2-yl radical (**1**) and its 3-acetoxy (**2**, **5**), 3-methoxy (**3**, **6**), and 3-benzyloxy (**4**, **7**) derivatives and labeling of atoms

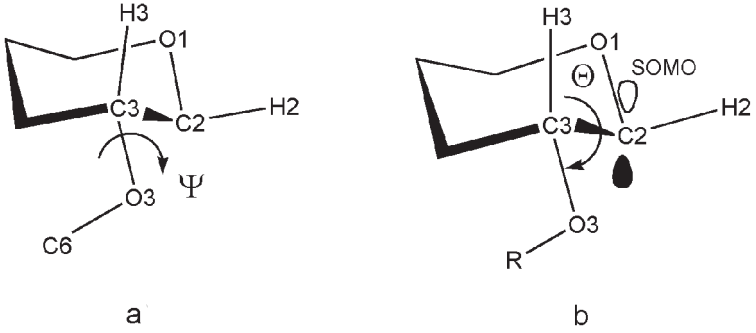


FIG. 2
Schematic representation of a dihedral angle Ψ = Ψ(C6–O3–C3–C2) (a) defining the orientation around the C3–O3 bond and a dihedral angle Θ = Θ(H3–C3–C2–SOMO) (b) between the β-C3–H3 bond and the half-occupied orbital (SOMO), which is used for calculations of the β-hydrogen coupling constant using Eq. (*1*)

For a comparison of the calculated structures with experimental ESR coupling constants we have estimated dihedral angle Θ = Θ(H3–C3–C2–SOMO) between the β-C3–H3 bond and the half-occupied orbital (SOMO) (Fig. 2b) for all optimized conformers. For this purpose, the direction of the SOMO orbital was associated with a vector directed to the remaining vertex of a tetrahedron and determined from the positions of the three atoms linked to the anomeric C2 carbon, namely O1, H2, and C3. The Θ dihedral angle was then used to compute β-hydrogen coupling constants *a*(H3) by means of the commonly used equation[20]

$$a(\mathrm{H3}) = 0.3(\pm 0.2) + 4.9(\pm 0.5)\cos^2\Theta\ . \qquad (1)$$

Calculations have been performed using the Amsterdam density functional (ADF) program system, ADF 2004.01[21–23] on QS8-2800C[24]. The atomic orbitals were described as an uncontracted triple-ζ Slater function basis sets with a single-ζ polarized function on all atoms (TZP), which were taken from ADF library. The local part of the V_{xc} potential (LDA) was described using the VWN parametrization[25], in combination with the gradient-corrected (CGA) Becke's functional[26] for exchange and Perdew's function for correlation (BP)[27]. All geometries were optimized using unrestricted DFT method and default optimization criteria were used for optimization in ADF. Geometries were optimized in the gas phase, and the influence of solvent has been estimated as single-point calculations using Cosmo solvation model[28–30] with dielectric permittivity constant ε = 2.28, 7.58, 10.34, 32.7, and 78.4 for benzene, tetrahydrofuran, octan-1-ol, methanol, and water, respectively, as solvent. Some calculations on the tetrahydropyran-2-yl radical and on 3-fluoro and 3-hydroxy radicals were carried out using the Jaguar program[31]. In this case, the optimization of geometry was performed using the B3LYP density functional method[32] with the 6-311++G** basis set. The conformer probability was computed for each compound separately using the Boltzmann distribution equation.

RESULTS AND DISCUSSION

Previous ab initio calculations[17] showed that radical **1** is pyramidal and the axial radical is more stable than the equatorial with the energy difference depending on the basis set used for calculations. The energy differences of 2.18 and 2.70 kcal/mol were calculated at the HF/3-21G and HF/6-31G* level, respectively. However, when correlation was taken into account at the MP2/6-31G*//6-31G* level, it appeared that the equatorial radical was

not a minimum on the energy surface. We have explored the influence of the method used on the structure of both the forms of the radical **1** using several different methods. The axial and equatorial radicals in the $^4C_1$ conformation were optimized at the HF/6-31G*, HF/6-31++G**, MP2/6-31G*, B3LYP/6-31G*, and BP/TZP levels and the results revealed that optimization using the HF/6-31++G**, MP2/6-31G*, and B3LYP/6-31G* methods led only to the axial radical of **1**. At the HF/6-31G* level, the axial radical was preferred by 2.70 kcal/mol; the BP/TZP method provided both forms of radical **1** with almost the same energy.

To further enhance our knowledge about conformational behavior of the anomeric radical **1**, we have examined six ring conformers, namely $^4C_1$, $^1C_4$, $B_{2,5}$, $^{1,4}B$, $^{O,3}B$, and $^4H_3$. Optimization of six idealized ring conformers[18] led to five minima of the axial radical. In the case of the initial ring conformation $^4H_3$, the final conformation corresponded to the chair form. The relative energies of the chair and boat conformers of the tetrahydropyran-2-yl radical **1** in vacuum and aqueous solution together with the calculated dihedral angle Θ and β-hydrogen coupling constants *a*(H3) are given in Table I. Our calculations show that the chair conformations are more stable than the boat conformations. Of two chair conformations, the $^4C_1$ form is predicted to be more stable by 0.04 kcal/mol in vacuum, while in aqueous solution the stability order is reversed by the same amount. The $B_{2,5}$, $^{1,4}B$, and $^{O,3}B$ conformers have higher energy than the $^4C_1$ form by 3.2, 2.5, and 1.9 kcal/mol, respectively. It can be seen that solvent effects influence the

TABLE I
The BP/TZP relative energies (kcal/mol) in vacuum (ΔE_{gas}) and aqueous solution (ΔE_{water}) and values of the β-hydrogen coupling constant[a] *a*(H3) calculated for the axial tetrahydropyran-2-yl radical **1** in various ring conformers

Conformation	ΔE_{gas}	ΔE_{water}	H-2-eq		H-2-ax	
			Θ	*a*(H-2)	Θ	*a*(H-2)
$^4C_1$	0.04	0.0	3.9	5.2	–113.2	1.1
$B_{2,5}$	3.28	3.58	–110.8	0.9	130.9	2.4
$^{1,4}B$	2.48	3.03	–57.8	1.7	–173.2	5.1
$^{O,3}B$	1.94	3.17	–20.4	4.6	–137.3	2.9
$^1C_4$	0.00	0.04	–66.1	0.4	176.9	5.2

[a] β-Hydrogen coupling constant was calculated from the torsional angle Θ estimated from the BP/TZP optimized geometries using Eq. (*1*).

stability of various forms of radical **1** and, generally, solvent effects stabilize the chair forms. These calculations clearly indicate that radical **1** exists as an equilibrium mixture of two chair forms of a slightly pyramidal radical, which is in good agreement with the ESR spectra of **1** [13]. An inspection of the optimized structures of the conformers of radical **1** that are given in Fig. 3 shows the structure around C2 to be slightly non-planar. The sum of the three valence angles around the C2 atom (O1–C2–C3, O1–C2–H2, and C3–C2–H2) is 350, 353, 352, and 350° for the $^{4}C_{1}$, $^{1}C_{4}$, $B_{2,5}$, and $^{1,4}B$ ring forms of **1**, respectively. The smallest deviation from the planarity is seen for the $^{O,3}B$ form, where the sum of the three valence angles around this atom is 356°. The geometrical parameters around the C2 atom are influenced by the hyperconjugation interactions between the half-filled SOMO orbital on the C2 carbon and the lone-pair orbitals of the ring oxygen O1; e.g. the C2–O1 bond length is shorter than the averaged bond length between the anomeric carbon and ring oxygen in carbohydrates[9]. The extent of these interactions results in a delocalization of SOMO and is illustrated also in Fig. 3, where the SOMO are superimposed on the calculated structures of radical conformations.

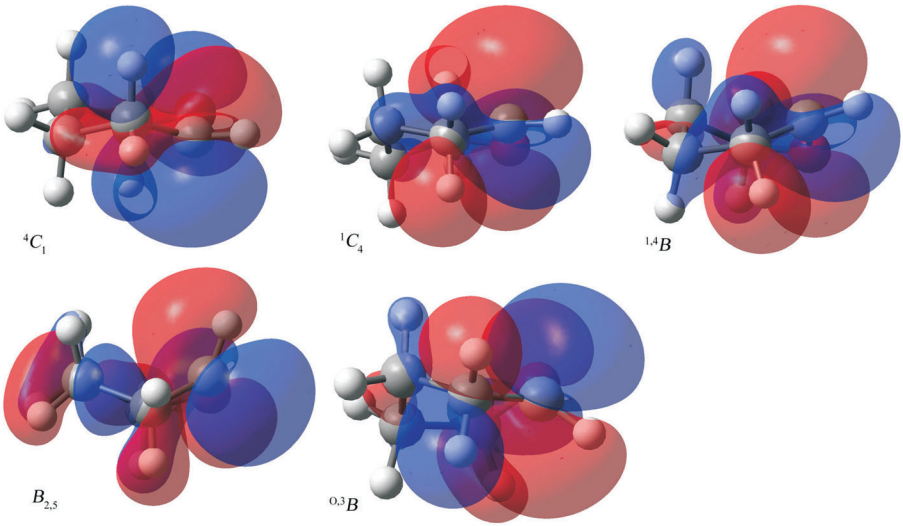


FIG. 3
Delocalized SOMO orbitals are superimposed on the optimized structures of the conformers of radical **1** to illustrate the extent of hyperconjugation interactions between the half-occupied orbital SOMO on the C2 carbon and the antibonding orbital σ_{CO}* of the C3–O3 bond

It has been observed that C3 substituent plays an important role in determining the structure and stability of the carbohydrate anomeric radicals[1,2,10,11]. To model the effects of a C3 substituent, we have examined the two chair ($^1C_4$ and $^4C_1$) and two boat ($B_{2,5}$ and $^{O,3}B$) conformations of the axial and equatorial 3-substituted tetrahydropyran-2-yl radicals **2**–**11**. The calculated relative energies of the chair and boat conformers of these radicals in vacuum and aqueous solution are listed in Table II. For each radical structure of **3**–**5** and **7**–**11** these data correspond to the lowest energy rotamer about the C3–O3 bond. Table III gives the predicted populations of the chair and boat conformers in vacuum and aqueous solution. Selected geometrical parameters together with the predicted values of β-hydrogen coupling constants are shown in Tables IV and V.

It has been recently shown[7] that, at the UMP2/6-31G*//6-31G* level, both the 3-fluoro-substituted tetrahydropyran-2-yl radicals and the unsubstituted radical **1** prefer the $^4C_1$ chair form to the $B_{2,5}$ form. Moreover, introducing a fluorine atom into the axial position stabilized the chair conformation by 2.09 kcal/mol compared with the unsubstituted radical. On the other hand, introducing an equatorial fluorine substituent stabilized the boat conformation by 2.79 kcal/mol compared with **1**. Our calcu-

TABLE II
The BP/TZP relative energies (kcal/mol) in vacuum (ΔE_{gas}) and aqueous solution (ΔE_{water}) for the lowest-energy conformers of **2**–**11** in various ring forms

Compd	ΔE_{gas}				ΔE_{water}			
	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$
2	2.9	2.0	[a]	0.0	2.4	1.8	[a]	0.0
3	2.0	1.9	[a]	0.0	0.3	2.4	[a]	0.0
4	1.3	0.9	2.8	0.0	0.4	0.0	2.6	0.4
5	1.8	1.6	3.2	0.0	0.8	0.9	2.1	0.0
6	2.0	1.1	3.0	0.0	0.8	0.6	2.4	0.0
7	0.0	[a]	2.0[b]	2.9	0.0	[a]	1.9[b]	2.5
8	0.0	5.6	1.9[b]	2.0	0.0	4.2	2.4[b]	0.3
9	0.0	4.6	2.9	1.1	0.0	3.9	2.3	1.0
10	0.0	5.8	3.5	2.0	0.0	5.5	3.0	2.2
11	0.0	4.7	4.2	1.8	0.0	4.8	4.2	1.7

[a] No local minimum was found. [b] The final local minimum conformation is $^{2,5}B$.

lated results on 3-fluorotetrahydropyran-2-yl radicals **2**, **7** show similar trends (Tables I–III) and chair conformers with the fluorine atom axially oriented were found as the most stable structures. The second chair conformer with the fluorine atom in the equatorial orientation has energy in vacuum and aqueous solution 0.1 and 1.0 kcal/mol higher, respectively. Thus, the lowest energy minimum for **2** is the chair $^{1}C_{4}$ conformer and the boat $B_{2,5}$ conformer has the relative energy 3.3 kcal/mol in vacuum and 2.9 kcal/mol in aqueous solution, respectively. On the contrary, for **7** the $^{4}C_{1}$ conformer was found to be dominant and the relative energy of boat conformer in vacuum and aqueous solution was calculated as 3.3 and 3.0 kcal/mol, respectively. It is noteworthy that the $^{O,3}B$ form was not found as a local minimum for **2** and **7**. The preference of a chair form with the axially oriented fluorine atom at C-3 is consistent with the "quasi-homoanomeric effect"[11].

The **3**–**6** radicals show similar conformational behavior with an equivalent lowest energy conformer found for vacuum. The global minimum corresponds to the chair $^{1}C_{4}$ (C3 substituent in the *sc* orientation) conformer, the next minimum is the boat $B_{2,5}$ (*sc*) conformer, and the chair $^{4}C_{1}$ (*sc*) conformer is the third low-energy minimum. The energy differences be-

TABLE III
The BP/TZP-calculated population for the ring conformers of **2**–**11** in vacuum (x_{gas}) and aqueous solution (x_{water})

Compd	x_{gas}				x_{water}			
	$^{4}C_{1}$	$B_{2,5}$	$^{O,3}B$	$^{1}C_{4}$	$^{4}C_{1}$	$B_{2,5}$	$^{O,3}B$	$^{1}C_{4}$
2	0.7	3.4	[a]	95.9	1.6	4.2	[a]	94.2
3	3.3	3.6	[a]	93.1	39.2	1.1	[a]	59.7
4	10.2	14.5	0.6	74.7	29.2	39.0	0.6	31.2
5	5.3	5.7	0.5	88.5	23.8	16.3	2.0	57.9
6	6.4	11.6	0.5	81.5	26.4	21.3	1.0	51.3
7	95.9	[a]	3.4[b]	0.7	94.5	[a]	4.0[b]	1.5
8	93.1	0.0	3.6[b]	3.3	60.1	0.1	1.0[b]	38.8
9	87.1	0.0	0.5	12.4	84.1	0.1	1.4	14.4
10	95.8	0.0	0.3	3.9	97.6	0.0	0.5	1.9
11	90.6	0.0	0.1	9.3	94.1	0.0	0.1	5.8

[a] No local minimum was found. [b] The final local minimum conformation is $^{2,5}B$.

TABLE IV

Comparison of the selected bond lengths C2–C3, C2–X3, and C2–O1 (Å) in various ring conformers of **2–11** calculated at BP/TZP level

Compd	C1–C2				C2–X2				C1–O5			
	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$
1	1.503	1.499	1.499	1.502					1.382	1.376	1.380	1.382
2	1.496	1.465	[a]	1.476	1.411	1.470	[a]	1.456	1.362	1.354	[a]	1.356
3	1.497	1.481	[a]	1.493	1.431	1.469	[a]	1.460	1.363	1.358	[a]	1.360
4	1.501	1.468	1.474	1.486	1.432	1.517	1.481	1.494	1.370	1.365	1.363	1.360
5	1.502	1.465	1.472	1.477	1.454	1.545	1.535	1.525	1.374	1.367	1.365	1.370
6	1.504	1.476	1.491	1.487	1.442	1.496	1.472	1.478	1.373	1.368	1.368	1.369
7	1.476	[a]	1.465[b]	1.486	1.457	[a]	1.471[b]	1.412	1.356	[a]	1.354[b]	1.362
8	1.493	1.498	1.482[b]	1.497	1.460	1.429	1.467[b]	1.431	1.359	1.368	1.358[b]	1.364
9	1.484	1.525	1.499	1.505	1.498	1.427	1.456	1.425	1.360	1.364	1.359	1.369
10	1.479	1.496	1.483	1.502	1.520	1.456	1.505	1.461	1.369	1.378	1.372	1.374
11	1.489	1.498	1.496	1.503	1.479	1.442	1.455	1.437	1.369	1.377	1.372	1.373

[a] No local minimum was found. [b] The final local minimum conformation is $^{2,5}B$.

TABLE V

Comparison of dihedral angles Ψ and Θ and values of the β-hydrogen coupling constant[a] *a*(H3) calculated at BP/TZP level for **2**–**11** in various ring conformers

Compd	Ψ				Θ				*a*(H-2)			
	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$	$^4C_1$	$B_{2,5}$	$^{O,3}B$	$^1C_4$
2					–9.6	–73.1	[b]	–57.1	5.06	0.71	[b]	1.75
3	161.9	48.9	[b]	45.8	–3.4	–72.6	[b]	–56.3	5.18	0.74	[b]	1.81
4	157.5	55.8	159.6	67.7	–6.1	–76.8	–59.2	–61.0	5.14	0.56	1.58	1.45
5	154.4	80.8	–38.1	85.2	–6.4	–71.3	–48.5	–60.6	5.14	0.80	2.45	1.48
6	62.0	57.2	65.3	59.0	–6.7	–74.8	–61.5	–59.4	5.13	0.64	1.42	1.57
7					–122.8	[b]	–106.7[c]	–169.6	1.74	[b]	0.70[c]	5.04
8	–45.6	–65.4	–51.9[c]	–162.4	–123.7	170.0	–107.8[c]	–176.5	1.81	5.05	0.76[c]	5.18
9	–67.4	–82.7	–68.6	–150.2	–117.7	179.9	–143.4	179.5	1.36	5.20	3.46	5.20
10	–63.6	–151.5	–76.5	–84.4	–121.7	173.1	–144.1	–169.5	1.65	5.13	3.51	5.03
11	–70.3	–80.5	–159.3	–80.5	–120.4	174.1	–162.8	–179.3	1.56	5.15	4.78	5.20

[a] β-Hydrogen coupling constant was calculated from the torsional angle Θ estimated from the BP/TZP optimized geometries using Eq. (*1*). [b] No local minimum was found. [c] The final local minimum conformation is $^{2,5}B$.

tween the most stable conformer and other two low-energy conformers in **3**–**6** are less than 4.5 kcal/mol and are influenced by medium. Similarly as for 3-fluoro derivatives, the $^{O,3}B$ form was not found as a local minimum for **3** and **8**. Populations of four ring conformations are $^1C_4 : {}^4C_1 : B_{2,5}$ = 93.1 : 3.3 : 3.6 for 3-hydroxy derivative **3**, $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 74.7 : 10.2 : 14.5 : 0.6 for 3-methoxy derivative **4**, $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 88.5 : 5.3 : 5.7 : 0.5 for 3-acetoxy derivative **5**, and $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 81.5 : 6.4 : 11.6 : 0.5 for 3-benzyloxy derivative **6**. When solvent is taken into account using the COSMO solvation method[28–30], an increase in permittivity constant decreases population of the $^1C_4$ conformer at the expense of other ring conformers and significant populations of the $^4C_1$ and $B_{2,5}$ ring forms occur in solution. The most significant shift in population of conformers can be seen for aqueous solution (Tables II and III) where the equilibrium mixtures change to: $^1C_4 : {}^4C_1 : B_{2,5}$ = 59.7 : 39.2 : 1.1 for 3-hydroxy derivative **3**, $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 31.2 : 29.3 : 39.0 : 0.6 for 3-methoxy derivative **4**, $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 57.9 : 23.8 : 16.3 : 2.0 for 3-acetoxy derivative **5**, and $^1C_4 : {}^4C_1 : B_{2,5} : {}^{O,3}B$ = 51.2 : 26.4 : 21.3 : 1.0 for 3-benzyloxy derivative **6**. In the case of 3-methoxy derivative **4**, the $B_{2,5}$ (*sc*) ring conformation becomes the global minimum, whereas for 3-hydroxy (**3**), 3-acetoxy (**5**), and 3-benzyloxy (**6**) derivatives the chair $^1C_4$ conformer remains to be the preferred ring form in aqueous solution. It is interesting to note that in aqueous solution the orientation about the C3–O3 bond is *ap* ($\Psi \sim 180°$) for 3-acetoxy (**5**) and 3-benzyloxy (**6**) compounds, whereas it is *sc* ($\Psi \sim 60°$) for 3-hydroxy (**3**) and 3-methoxy (**4**) derivatives, respectively.

The **8**–**11** radicals show different conformational behavior. The calculations predicted that conformational equilibrium of these radicals mainly consists of two chair conformers with a negligible contribution from boat conformers, which was less than 1.5%. The $^4C_1$ conformer was found to be the dominant conformer in vacuum for all **8**–**11** radicals with populations $^4C_1 : {}^1C_4$ = 93.1 : 3.3 for 3-hydroxy derivative **8**, $^4C_1 : {}^1C_4$ = 87.1 : 12.4 for 3-methoxy derivative **9**, $^4C_1 : {}^1C_4$ = 95.8 : 3.9 for 3-acetoxy derivative **10**, and $^4C_1 : {}^1C_4$ = 90.6 : 9.3 for 3-benzyloxy derivative **11**. In aqueous solution, the determined equilibrium is similar for 3-acetoxy (**10**) and 3-benzyloxy (**11**) derivatives with a little higher preference for the $^4C_1$ conformer, $^4C_1 : {}^1C_4$ = 97.6 : 1.8 and $^4C_1 : {}^1C_4$ = 94.0 : 5.8, respectively. The 3-hydroxy (**8**) and 3-methoxy (**9**) derivatives behaves slightly differently, solvent effects increases the contribution of the $^1C_4$ conformer $^4C_1 : {}^1C_4$ = 60.1 : 38.8 and $^4C_1 : {}^1C_4$ = 84.4 : 14.4, respectively. The global minimum for **8**–**11** radicals corresponds to the $^4C_1$ (*sc*) chair conformer. The ESR spectra of the 3-hydroxytetrahydropyran-2-yl (**9**), 3-acetoxytetrahydropyran-2-yl (**10**),

and 3-(butanoyloxy)tetrahydropyran-2-yl and 3-(trimethylacetoxy)tetrahydropyran-2-yl radicals[14–16] show very small values of β-hydrogen coupling indicating that the ester groups adopt the axial position and ring the $^4C_1$ conformation in agreement with the predicted conformation for **8**–**11** radicals.

The calculations revealed that all radicals prefer a chair conformation where the C3 substituent is in the axial position, which is the $^1C_4$ conformation for radicals **2**–**6** and the $^4C_1$ conformation for radicals **7**–**11**. The pseudorotation of the $^4C_1$ conformation into the $^1C_4$ conformation in radicals **2**–**6** involves an interconversion of the substituent on the C3 carbon from the equatorial to the axial position. The axial orientation in the $^1C_4$ conformation of these radicals is stabilized by interactions between the unpaired SOMO and the σ_{CX}* antibonding orbital of the C3–X3 bond favored by their coplanar arrangement in the $^1C_4$ conformer. A preference to the $^1C_4$ ring conformer implies that the delocalization interactions outweigh steric interactions imposed by an axially oriented electronegative substituent in **2**–**6**. Similarly, the $^4C_1$ conformation in **7**–**11** is favored by stabilizing interactions between the SOMO and the σ_{CX}* antibonding orbital of the C3–X3 bond in the axial position. The importance of a good overlap between electronegative substituent at the C3 position and the radical has been emphasized and attributed to a quasi-homoanomeric effect[11]. There appears to be a similarity between the above-described behavior of radicals with the observed effect of the electronegative substituent at the C3 position on the magnitude of the anomeric effect in hexopyranoses[9] where the anomeric effect was found to be substantially larger in *manno* derivatives compared with *gluco* derivatives.

The analysis of the optimized structures of radicals **2**–**11** revealed that these radicals are quasi-axial and the anomeric hydrogen H2 atom adopts always a quasi-equatorial orientation. The sum of the three valence angles about the C3 atom in **2**–**11** is within 353–357° and shows that the calculated structures of 3-substituted radicals **2**–**11** are more planar than corresponding unsubstituted tetrahydropyran-2-yl radical **1**, in agreement with the experimentally observed trends[10,11]. Selected structural parameters of radicals **1**–**11** given in Tables IV and V show several interesting trends and illustrate how delocalization interactions influence the structure around the radical center. A comparison of the C2–O1 bond length in **1**–**11** revealed that this bond varies from 1.354 to 1.378 Å in various ring forms of **2**–**11** and is considerably shorter than the standard C–O bond length (1.425 Å) or the average length of C2–O1 bond (1.422 Å) in glycosides[9]. The C2–O1 bond length calculated for conformers of the tetrahydropyran-2-yl radical **1**

is slightly larger (1.376–1.382 Å), compared with this bond length in **2**–**11**. The shortening of the C2–O1 bond length reflects delocalization of the lone-pair orbitals of the ring oxygen into the SOMO of the anomeric carbon. The calculated differences in the C2–O1 bond length between the radical **1** and 3-substituted radicals **2**–**11** show that this delocalization increases due to the presence of the C3 substituent. In analogy with the anomeric effect[9], this stabilization was called[10,11] the "quasi-homoanomeric effect".

Delocalization from the single occupied orbital SOMO into the properly oriented antibonding orbital of the C3–X3 bond σ_{CX}* is reflected in the C3–X3 bond length. These interactions are more profound when the C3–X3 bond is in the axial position. As a result, there is a small but clear difference in both the C2–C3 and C3–X3 bond length, respectively, between various ring conformers. For radicals **2**–**6**, the C2–C3 bond lengths are shorter (1.476–1.493 Å) in the $^1C_4$ conformations that have antiperiplanar orientation of the SOMO and σ_{CX}* orbitals compared with the $^4C_1$ conformation (1.496–1.504 Å) where these orbitals are oriented almost perpendicularly. For radicals **7**–**11**, the antiperiplanar orientation of the two orbitals occurs in the $^4C_1$ conformation and reflects in shorter C2–C3 bond lengths (1.476–1.493 Å), whereas in $^1C_4$ conformation the SOMO and σ_{CX}* orbitals are oriented almost perpendicularly and the C2–C3 bond length is longer (1.486–1.505 Å). Similar consequences of these hyperconjugative interactions have been found for the C3–X3 bond length. In this case, delocalization into the σ_{CX}* antibonding orbital of the C3–X3 bond elongates this bond. For example, for **2**–**6** radicals in the $^1C_4$ conformers, where the C3–X3 bond is in the axial orientation, the C3–X3 bond length is longer (1.456–1.525 Å) compared with those conformers where this bond is in the equatorial orientation (1.411–1.454 Å). This pattern is reversed in radicals **7**–**11**. These trends in the C2–C3 and C3–X3 bond lengths support an important role that delocalization from the single-occupied orbital SOMO into the properly oriented antibonding orbital σ_{CX}* of the C3–X3 bond plays in stabilization of radical conformers. They also suggest that better orbital overlap between the SOMO and σ_{CX}* orbital is responsible for the preference of the $^1C_4$ conformation over the $^4C_1$ in radicals **2**–**6** and, vice versa, for the preference of the $^4C_1$ conformer over the $^1C_4$ in radicals **7**–**11**.

Conformations of anomeric radicals were usually inferred[1,2,10,11,14–16] from the angular dependence of the β-hydrogen coupling constant (Eq. (*1*)) and using ideal values of dihedral angles between the direction of the singly occupied orbital (SOMO) and the C3–H3 bond (Θ). An inspection of the

estimated values of Θ angles in Table V shows that the Θ angle is close to 60° for all ring conformers except for the $^4C_1$ conformer where magnitude of this angle is near 0° for **2**–**6** and near 120° for **7**–**11**. A comparison of estimated values of the Θ angle for different ring conformations revealed a variation between –122 and 178°; values of the associated β-hydrogen coupling constants are predicted in the interval from 0.6 to 5.2 mT. Since radicals **2**–**11** exist in solution as a mixture of several ring conformers, measured values of the β-hydrogen coupling constants represent ensemble averages. Therefore, we have calculated the average values of the β-hydrogen coupling constants for equilibrium mixtures of 3-substituted tetrahydropyran-2-yl radicals **2**–**11** in different solvents; these values are given in Table VI. For radicals **2**–**6**, the average values of the β-hydrogen coupling constants vary with solvent in the interval 1.67–3.12 mT. In contrast, the average values of the β-hydrogen coupling constants predicted for radicals **7**–**11** remain almost constant reflecting the dominance of the $^4C_1$ conformer. Slight variation of the β-hydrogen coupling constant is predicted for 3-methoxy radical **10** in aqueous solution as a result of the 16% contribution from the $^1C_4$ form.

The most extensive studies of anomeric radical conformations come from ESR studies on glycopyranosyl radicals[1,2,10,11]. The ESR spectra obtained at several temperatures and solvents by different methods were interpreted on

TABLE VI
Comparison of the average values of the β-hydrogen coupling constant *a*(β-H) calculated for radicals **2**–**11** in various environment

Compd	Vacuum	Benzene	THF	Octan-1-ol	Methanol	Water
2	1.74	1.75	1.75	1.75	1.75	1.76
3	1.88	2.16	2.78	2.88	3.01	3.12
4	1.79	1.91	1.98	1.97	2.00	2.44
5	1.67	1.72	1.76	1.73	1.78	2.36
6	1.73	1.86	1.94	1.95	1.95	2.52
7	1.73	1.74	1.74	1.74	1.75	1.75
8	1.88	2.19	2.83	3.00	3.05	3.11
9	2.05	2.26	2.36	2.39	2.38	2.45
10	1.81	1.85	1.88	1.88	1.91	1.74
11	1.94	1.98	1.96	2.02	1.92	1.82

the basis of the observed hyperfine splitting due to the vicinal hydrogen. Here we want to emphasize that a comparison of experimental data for the persubstituted carbohydrate radicals with the calculated results for the 3-*O*-substituted tetrahydropyran-2-yl radicals can be only qualitative and any agreement or disagreement should be taken very cautiously since carbohydrate radicals carry many substituents, the steric interactions of which may considerably modify the ring structure and energy of conformers. For example, the β-hydrogen coupling constant values 1.172–1.407 mT were measured[10,11] for the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl radical and interpreted in terms of the slightly twisted $B_{2,5}$ boat conformation. The $B_{2,5}$ boat conformation was assigned to the 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl radical based on the β-hydrogen coupling constant values 1.058–1.274 mT measured for the temperature interval from –22 to 44 °C. Similarly, the β-hydrogen coupling constants 1.189–1.221 and 1.250 mT measured for the 2,3,4-tri-*O*-acetyl-D-glucopyranosyl radical and its benzoylated analog, respectively, led to the $B_{2,5}$ boat conformation. However, since the measured β-hydrogen coupling constants exhibit temperature variations, the possibility of ring pseudorotation and the presence of various radical conformers in an equilibrium mixture was not excluded[1]. The observed difference between the calculated values for radicals **2**–**6** and experimental data for glycopyranosyl radicals is quite understandable to the preference to the $^1C_4$ conformer in the calculated conformational equilibrium for radicals **2**–**6**. In particular, the $^1C_4$ conformer with all substituents in axial orientation is considerably destabilized in glucopyranosyl radical by steric interactions compared with the situation in 3-substituted tetrahydropyran-2-yl radicals **2**–**6**. As a result, glucopyranosyl radicals do not adopt the $^1C_4$ conformation and prefer the boat conformation. Therefore, we have calculated the ensemble average using the calculated values of the β-hydrogen coupling constant (Table V) and taking into account only the contribution of the $B_{2,5}$ and $^4C_1$ conformers. The predicted value 1.1–1.5 mT, using 85 ± 5% of the $B_{2,5}$ and 15 ± 5% of the $^4C_1$ conformer, is in good agreement with experimental data on the above mentioned glucopyranosyl radicals. This qualitative comparison supports the preference of the $B_{2,5}$ conformer to glucopyranosyl radicals.

The ESR spectra of the corresponding 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl radical with the β-hydrogen coupling constants 0.353 and 0.424 mT measured at 20 and 95 °C, respectively, implies a dominant preference of the $^4C_1$ conformer. This is in excellent agreement with the calculated preference for the $^4C_1$ conformer in the radicals **7**–**11**. On the other hand, it is evident that calculated average values *a*(H3) for

3-substituted tetrahydropyran-2-yl radicals **7**–**11** are larger than the corresponding ESR values measured for mannopyranosyl radicals. This difference is not that clear since both the calculated equilibrium for **7**–**11** and the preference to *manno* carbohydrate radicals indicated by the ESR experiment imply predominance of the same $^4C_1$ chair form. One can envisage several factors that could be brought for an explanation of found differences. First, one can expect that a different number of ring substituents affect the structure of conformers. Second, values of the Θ dihedral angle are very approximate and we assume that uncertainty of its estimates could be in some case as large as 20–30°. Moreover, an inherent accuracy of the couplings determined by Eq. (*1*) might be as large as ±0.7 mT and also the presence of electronegative substituents may considerably affect the values of coupling constant. Because the angular dependence of the β-hydrogen coupling constant in Eq. (*1*) is very steep for relevant regions of the Θ dihedral angle, a change in Θ dihedral angle by 20° around 60° changes the value of the β-hydrogen coupling constant by 1.1–1.6 mT. Similarly, the same variation around the Θ dihedral angle 180° changes *a*(H3) value by 0.6 mT. We can only hypothesize that all these factors contribute to the observed differences, but to which extent remains to be investigated. Though the results of calculations on 3-substituted tetrahydropyran-2-yl radicals are consistent with the ESR experiments on glycopyranosyl radicals, it is evident that ring substituents present in anomeric carbohydrate radicals significantly perturb conformational behavior of the radicals compared with 3-substituted tetrahydropyran analogs.

CONCLUSIONS

We have investigated conformational properties of tetrahydropyran-2-yl radical **1** and its 3-fluoro- (**2**, **7**), 3-hydroxy- (**3**, **8**), 3-methoxy- (**4**, **9**), 3-acetoxy- (**5**, **10**), and 3-(benzyloxy)tetrahydropyran-2-yl (**6**, **11**) derivatives at various levels of theory. The calculated geometries and energies of the $^4C_1$, $^1C_4$, $B_{2,5}$, and $^{O,3}B$ ring conformers show that 3-substituted radicals are predicted to be pyramidal and to show a clear preference to ring conformers with the axial orientation of the substituent at the C3 position and are consistent with available ESR data. The conformational patterns observed for the C2–C3 and C3–O3 bond lengths provide further support for the role of quasi-homoanomeric interactions on stability of anomeric radicals. Several factors were proposed to explain the apparent discrepancy between the average values of β-hydrogen coupling constants calculated for

3-alkoxy radicals and those obtained from ESR experiments on glycopyranosyl radicals.

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