DFT calculations of the anomeric and exo-anomeric effect of the hydroperoxy and peroxy groups

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Abstract—DFT calculations were carried out on axially and equatorially oriented 2-hydroperoxy and 2-peroxy tetrahydropyran, cyclohexyl hydroperoxide, hydroperoxides of 2,3-unsaturated hexapyranoses, and hydroperoxides of *O*Me and *O*Bn substituted derivatives of 2-deoxy-glucopyranose and 2-deoxy-galactopyranose to investigate the anomeric and exo-anomeric effects of these groups. The structure and energy of the conformers were calculated at the B3LYP/6-311++G** level. Calculations showed that the peroxy anion group exhibits a strong anomeric effect, comparable in magnitude to the methoxy group, and that the anomeric effect of the hydroperoxy group is similar to the hydroxyl group. These results revealed that hydroperoxy and peroxy anion groups display an exo-anomeric effect, but the orientation around the C1–O1 bond is also affected by hydrogen bonding and electrostatic interactions.
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1. Introduction

The anomeric effect was originally defined as the preference of a polar substituent at the anomeric carbon of a monosaccharide to the axial position over the equatorial one.[1] Currently, the anomeric effect is generally recognized as being of more importance for molecules containing the R–X–C–Y moiety (where X = N, O, or S and Y = Br, Cl, F, N, O, or S) and describes the preference for synclinal (sc, gauche) over antiperiplanar (ap, trans) conformation.[2–4] The anomeric effect influences conformational equilibrium around the anomeric center of carbohydrates and affects the stereochemical output of many reactions occurring at the anomeric center. There are also practical consequences, because the conformation about the C1–O1 bond determines the overall conformation of oligo- and polysaccharides. To more fully understand the nature and magnitude of anomeric and exo-anomeric effects, we have investigated the

conformational behavior of various tetrahydropyran derivatives using ab initio methods.[5–9]

Previously, we reported the oxidation of 2,3-unsaturated hexopyranosides and 2-*C*-methylene glycosides with hydrogen peroxide, in the presence of a molybdenum trioxide catalyst, to give the corresponding anomeric hydroperoxides (Scheme 1) **1–6**.[10–14] Recently, we reported the synthesis of anomeric hydroperoxides **7–11**, which can be obtained from the corresponding 3,5-di-substituted-2-deoxy-D-erythropentofuranose, 3,4,6-tri-O-substituted-2-deoxy D-arabino and D-lyxohexopyranoses, or their glycosides using a treatment with hydrogen peroxide in the presence of an acid catalyst.[15] Hydroperoxides **1–11** are relatively stable, can be separated into pure anomers by column chromatography, and can be stored in a refrigerator without visible decomposition.[10–15] The easy formation of stable hydroperoxides from 2-deoxy- and from 2,3-unsaturated sugars, but not from fully hydroxylated sugars, demonstrates that the crucial issue in the formation of anomeric hydroperoxides is the readiness of the sugar to expel alkoxyl or hydroxyl from the anomeric center
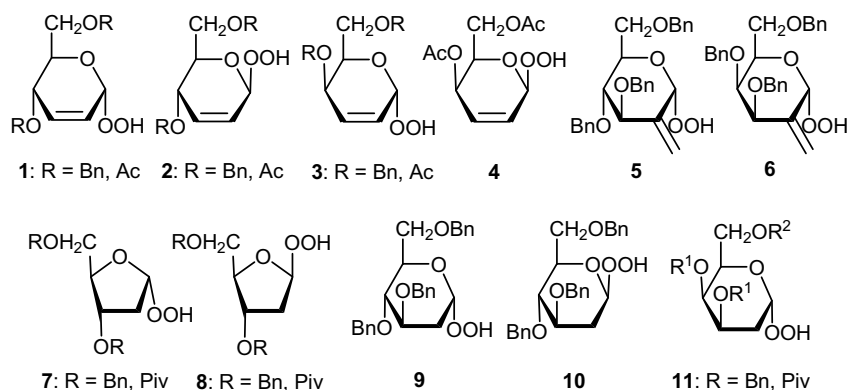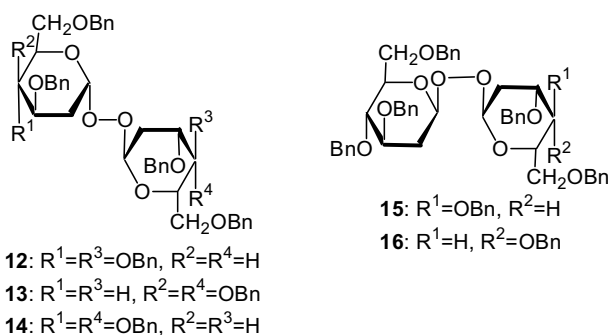

Scheme 1.

under mild acidic conditions and form a glycosyl cation to which hydrogen peroxide can be added.[15] 2-Deoxy- and 2,3-unsaturated sugars are known to undergo easy hydrolysis.[16] Hydroperoxides **1–6** have been used for enantioselective epoxidation of prochiral allylic alcohols and sulfides in the presence of Ti(O*i*Pr)$_4$, with stereoselectivities varying from about 10–50% ee.[12–14] 2,3-Unsaturated hydroperoxides related to compounds **1–6** have been used by Taylor and co-workers[17] for base-catalyzed enantioselective epoxidation of 2-methyl-1,4-naphtoquinone, and provide a corresponding epoxide with an ee from 40% to 78%. Moderate enantioselectivities, in the range of about 28–47% ee,[15] have been reported by us for the epoxidation of the same olefin under the same basic conditions using saturated hydroperoxides **7–11**. Similar enantioselectivities for the same olefin have also been achieved by Adam et al.[18] using 1-phenyl-ethyl-hydroperoxide, and by Lattanzi et al.[19] for asymmetric epoxidation using hydroperoxides derived from (+)-norcamphor derivatives. Recently, we reported on the synthesis of bis-glycoside peroxides (Scheme 2) **12–16** by the addition of peroxides **7–11** to glycals.[20] Compounds **12–16** display similar stabilities to those reported for glycosyl hydroperoxides **1–11**.

Based on the ring conformation in the 2,3-unsaturated sugar of β-*erythro* **2** (R = Ac) and β-*threo* **4** configura-
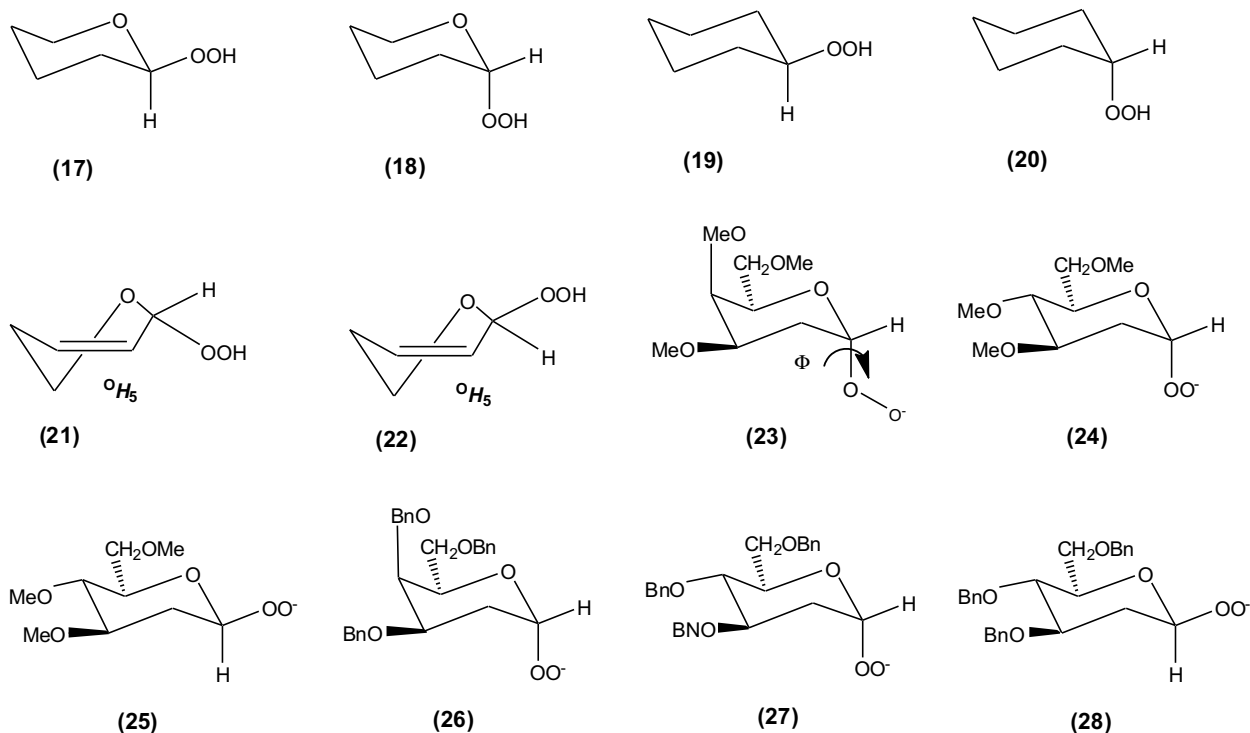
tion, it was suggested that the hydroperoxy group exhibits a strong anomeric effect.[11] This is supported by recent spectroscopy data and calculations on six-membered-ring peroxyl radicals[21] that showed that the axial orientation is the preferred conformation for the 2-peroxytetrahydropyran radical. However, the conformational behavior of the hydroperoxy group at the anomeric center was not investigated in spite of its importance. As a continuation of our efforts to understand the nature of the anomeric effect, we have undertaken a theoretical investigation of conformational behavior of the hydroperoxy and peroxy anion groups at the anomeric carbon using different models (**1–4, 17–28**, Schemes 1–3) and various levels of theory.
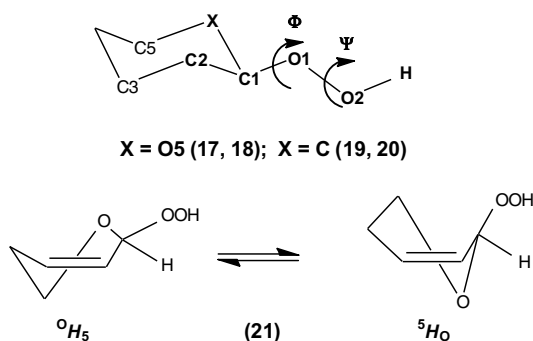
2. Models and methods

2-Hydroperoxides and 2-peroxides of tetrahydropyran (THP, **17**, **18**) and cyclohexane (CHX, **19**, **20**) were chosen as models to study the magnitude of the anomeric effect in hexopyranosides (Scheme 3). To distinguish between the hydroperoxyl group and peroxyl anion group, we add the **A** symbol as an identifier for the peroxy anion, for example, in the case of 2-hydroperoxytetrahydropyran and 2-peroxytetrahydropyran anion, we used **17** and **17A**, respectively. The rotation around the 'anomeric linkage' C1–O1 in **17–20** (Scheme 4) is described by the dihedral angle $\Phi = \Phi$[C2–C1–O1–O2] and the orientation around the O1–O2 linkage by the torsional angle $\Psi = \Psi$[C1–O1–O2–H]. To obtain a concise picture of the conformational preference around the anomeric C1–O1 bond, the available conformational space was monitored by a series of one-dimensional (Φ) potential energy surfaces (PES). The Φ torsional angle was varied by 30° increments, within the 0–360° range. For the hydroperoxy group derivatives, the starting orientation of the hydroperoxy proton was trans ($\Psi = 180°$). During the calculations, all the geometrical parameters except the dihedral angle Φ were optimized. As a result,

12: R^1=R^3=OBn, R^2=R^4=H
13: R^1=R^3=H, R^2=R^4=OBn
14: R^1=R^4=OBn, R^2=R^3=H

15: R^1=OBn, R^2=H
16: R^1=H, R^2=OBn

Scheme 2.

Scheme 3.

X = O5 (17, 18); X = C (19, 20)

Scheme 4.

each calculated point corresponds to the most stable geometrical conformation of the structure for the fixed value of Φ. The structure of all local minima identified on the PES was then refined, with no constraints on the Φ torsion angle and with the lowest energy orientation around the O1–O2 linkage. For 2,3-unsaturated glycosyl hydroperoxides (**1**–**3**, R = Ac; **4**, **21**, **22**), the structure and energy of the $^{O}H_5$ and $^{5}H_O$ forms (Scheme 4) were calculated for three stable conformations around the C1–O1 linkage.

The calculations were carried out using the JAGUAR program[22] on QS8-2800C.[23] The optimization of the geometry for points on PES was performed using the B3LYP density functional method[24] with the 6-31+G* basis set. The structure and energy of all the final minima of **1**–**3** (R = Ac), **4**, **17**–**22** were calculated using the B3LYP/6-311++G** basis set. For **17**–**20**, the solvent effect on the conformational equilibrium was investigated with a self-consistent reaction field method,[25] as implemented in the JAGUAR program[22] at the level B3LYP/6-311++G**, using the Poisson–Boltzmann solver. Solvation calculations were carried out for water ($\varepsilon = 80.37$). This approach correctly predicts the pK_a values for a large set of different molecules,[25] and we consider the solvation energies to be reasonably well predicted.

Finally, the geometry and energy of conformers around the C1–O1 linkage in **23**–**28** (Scheme 3) were calculated. The starting structures of **23**–**28** were built and optimized by the AMBER 9 program package[26] using the GAFF force field, antechamber and sander programs. For all the compounds, 500 ps standard vacuum molecular dynamic simulation at 350 K was performed. One hundred sampled structures from throughout the MD simulation were minimized and the lowest energy structure was selected for the next calculations. For each compound, three rotamers around the C1–O1 linkage were generated and their structure was calculated using the JAGUAR program.[22] Geometry optimizations for compounds **23**–**28** were performed at the B3LYP/6-311++G** level.

For all the minima of **1**–**3** (R = Ac), **4**, **17**–**28**, vibrational frequencies were calculated at the B3LYP/6-311++G** level and zero-point energy, thermal, and entropy corrections to 298 K were evaluated using

standard statistical thermodynamics methods based on the ideal-gas rigid-rotor model.[27]

The calculated conformational energy profiles for compounds **17–20** are shown in Figures 1 and 2. Tables 1–4 summarize the relevant geometrical parameters and the relative Gibbs free energies for the calculated minima of **1–3** (R = Ac), **4**, **17–28** compounds.

3. Results and discussion

3.1. The anomeric effect of the hydroperoxy group

The calculated energy profiles for **17–20** at the 6-31+G* level are shown in Figure 1. Three minima can be found on the energy profiles for each compound. The calculated profiles for the 2-hydroperoxy substituted tetrahydropyran (**17** and **18**) clearly differ from those calculated for cyclohexane (**19** and **20**) in the region at $\Phi \sim 180°$. For **17** and **18**, the deepest minimum appears in this region, the second minimum is at $\Phi \sim 60°$, and the third at $\Phi \sim -60°$. Examination of the data in Table 1 shows that in a vacuum the most stable conformation for 2-hydroperoxy substituted tetrahydropyran is gt
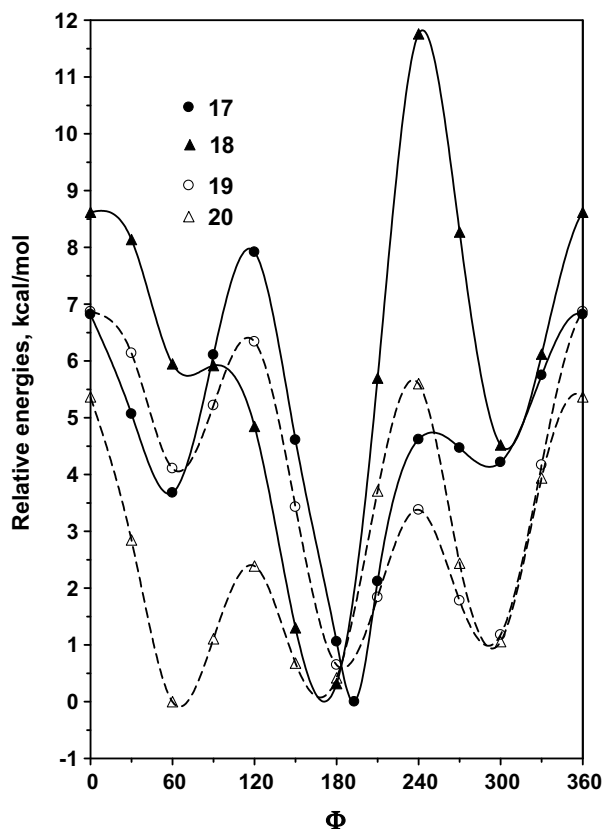

Figure 1. The B3LYP/6-31+G* potential energy of rotation about C1–O1 linkage for the axial (●, ○) and equatorial (▲, △) form of the hydroperoxy substituted tetrahydropyrans (full line) and cyclohexanes (dash line).
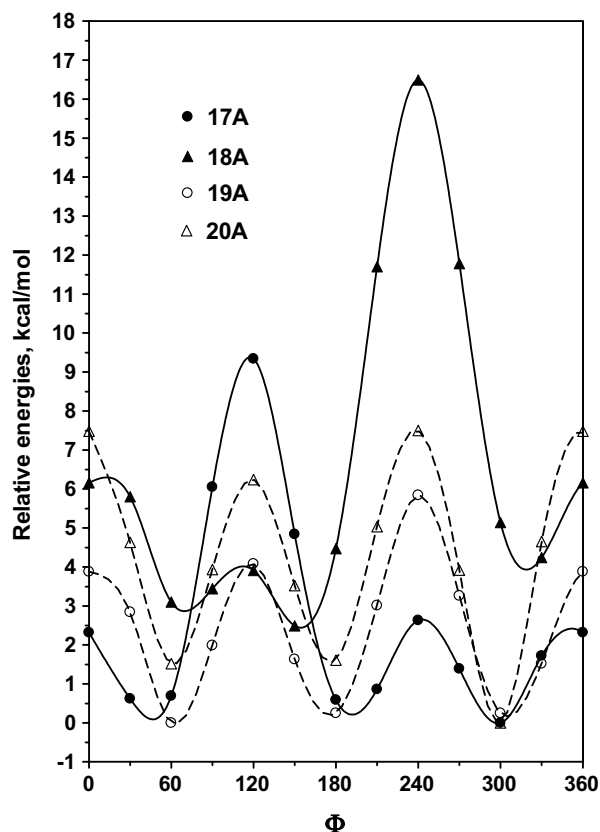

Figure 2. The B3LYP/6-31+G* potential energy of rotation about C1–O1 linkage for the axial (●, ○) and equatorial (▲, △) form of the peroxy (OO⁻) substituted tetrahydropyrans (full line) and cyclohexanes (dash line).

($\Phi = -167°$) of the axial form (**17**). In this notation,[6] the description of the torsion angle $\Phi_X = \Phi_X$ [X–C1–O2] is stated first, where X = O5 for THP derivatives (**17** and **18**) and X = C for CHX derivatives (**19** and **20**). The torsion angle $\Phi = \Phi$[C2–C1–O1–O2] states as the second. In this way, for example, gt means that the angles Φ_X and Φ are in close to those in synclinal or gauche (g) and antiperiplanar or trans (t) conformation, respectively (Scheme 5). The next most stable conformer is the gt orientation of the equatorial form (**18**). This conformer has Gibbs free energy of 0.15 kcal/mol higher than the energy of the tg conformer of the axial form (**17**). In an aqueous solution, the preferred minimum is the gt conformer of the equatorial form (**18**) and the Gibbs free energy of the gt conformer of the axial form (**17**) is 1.3 kcal/mol. For hydroperoxy substituted cyclohexane, the lowest energy conformer is the tg orientation around the C1–O1 linkage ($\Phi = 65°$) of the equatorial form (**19**). The lowest energy conformer of the axial form (**20**) is the gt orientation ($\Phi = -175°$). This conformer has an energy 0.59 kcal/mol higher than the gt conformer of the equatorial form. The calculated preference of the axial form over the equatorial one in compounds **17–20** is in agreement with

Table 1. The B3LYP/6-311++G** calculated geometrical parameters and the relative Gibbs free energy (kcal/mol) for the axially and equatorially oriented hydroperoxy substituted tetrahydropyran and cyclohexane (**17–20**)

	Min	Φ	r(C1–O1)	r(C1–X5)	α(O1–C1–C2)	α(O2–O1–C1)	Ψ	ΔG_{vacuum}	ΔG_{water}
17	gt	−166.7	1.413	1.423	106.5	108.2	−74.1	0.00[a]	1.32
	gg	55.9	1.403	1.426	114.1	109.8	127.1	3.06	3.50
	tg	−62.7	1.392	1.453	111.8	107.5	−116.8	3.78	4.88
18	gt	170.3	1.423	1.399	107.4	108.4	81.0	0.15	0.55
	gg	−58.1	1.419	1.406	114.6	109.6	−84.7	1.68	2.33
	tg	76.1	1.404	1.430	113.1	105.7	−129.2	5.52	0.00[c]
19	gt	−175.3	1.532	1.440	104.5	108.1	120.5	0.59	1.78
	gg	65.0	1.537	1.438	113.4	109.9	132.3	3.92	4.76
	tg	−70.2	1.533	1.441	112.3	107.6	126.5	0.85	2.07
20	gt	167.3	1.530	1.435	105.0	107.7	125.0	0.14	0.30
	gg	−66.8	1.530	1.438	113.0	108.8	122.9	1.11	0.96
	tg	65.1	1.530	1.434	112.3	107.9	123.1	0.00[b]	0.00[d]

[a] $E = -422.133555$.
[b] $E = -386.197227$ (in hartrees).
[c] $E = -422.156662$.
[d] $E = -386.207506$.

Table 2. The B3LYP/6-311++G** calculated geometrical parameters and the relative Gibbs free energy (kcal/mol) for the axially and equatorially oriented peroxy substituted tetrahydropyran and cyclohexane (**17A–20A**)

	Min	Φ	r(C1–O1)	r(C1–X5)	α(O1–C1–C2)	α(O2-O1–C1)	α(O1–C1–X)	ΔG_{vacuum}	ΔG_{water}
17A	gt	−167.5	1.469	1.358	107.9	110.1	114.7	0.43	2.09
	gg	46.5	1.462	1.367	115.8	111.1	108.2	0.10	7.75
	tg	−63.6	1.445	1.383	112.6	106.6	114.5	0.00[a]	4.94
18A	gt	154.6	1.482	1.342	110.2	109.7	111.4	2.35	0.00[c]
	gg	−40.5	1.486	1.350	115.5	112.2	111.0	2.67	3.11
	tg	70.5	1.455	1.368	113.8	104.7	106.4	3.61	3.78
19A	gt	−176.3	1.543	1.397	107.2	108.5	111.9	0.00[b]	2.60
	gg	64.6	1.551	1.398	114.3	109.8	107.2	3.00	8.59
	tg	−62.1	1.540	1.397	111.9	108.5	114.3	0.00[b]	2.60
20A	gt	171.4	1.540	1.391	108.5	107.8	112.9	0.58	0.00[d]
	gg	−62.8	1.542	1.402	112.1	108.8	112.1	1.51	2.56
	tg	66.1	1.537	1.391	112.9	107.8	108.5	0.58	0.00[d]

[a] $E = -421.552246$.
[b] $E = -385.612710$.
[c] $E = -421.685152$.
[d] $E = -385.739624$.

the axial preference based on the anomeric effect. The structural analysis of the calculated minima revealed that an intramolecular hydrogen bond between the ring oxygen and the hydrogen of the hydroperoxy group occurs in the gt conformers (Scheme 5). This suggests that hydrogen bonding also plays an important role in the conformational behavior of the hydroperoxy group. As a result, conformational stability of this conformer increases compared to other conformers. Thus, even though the preferred gt orientation around the C1–O1 linkage is in agreement with the exo-anomeric effect,[2] its stabilization is also affected by intramolecular hydrogen bonding. It is noteworthy that in the gt conformer the orientation of the proton is characterized by $\Psi \sim -80°$ for the axial form (**17**) and $\Psi \sim 80°$ for the equatorial form (**18**), respectively. In the case of cyclohexane, such a hydrogen bond is not

possible, and as a result the tg and gt conformers are preferred. To evaluate how hydrogen bonding affects the axial–equatorial equilibrium in substituted THP, we calculated the energy of the gt conformers with the proton orientation corresponding to the best orientation for the hydroperoxide,[28] namely $\Psi = 112°$. In this orientation of the proton, hydrogen bonding is not possible. The calculation showed that the hydrogen bonding prefers the equatorial form by 1.2 kcal/mol. Assuming this stabilization, a crude estimate of the axial preference over the equatorial one for the hydroperoxy group is 1.35 kcal/mol.

3.2. Conformational preferences of the peroxy anion

To provide additional insight into conformational behavior of the hydroperoxy group, we carried out

Table 3. The B3LYP/6-311++G** calculated geometrical parameters and the relative energy (kcal/mol) for the axially and equatorially oriented hydroperoxy and peroxy substituted saccharide derivatives (**1–4**, **21**, and **22**)

| Compound	Ring	Φ	$r(C1–O1)$	$r(C1–O5)$	$\alpha(O1–C1–C2)$	$\alpha(O2-O1–C1)$	$\tau(O1–C1–O5–C5)$	ΔG_{vacuum}
21	$^OH_5$	−163.6	1.426	1.408	105.9	108.0	79.9	0.00[a]
	^5H_O	−168.3	1.406	1.419	106.3	108.1	163.6	2.44
22	^5H_O	163.6	1.426	1.408	105.9	108.0	−79.9	0.00[a]
	$^OH_5$	168.3	1.406	1.419	106.3	108.1	−163.6	2.44
1, Ac	$^OH_5$	−161.9	1.424	1.410	105.7	108.0	78.7	0.00[b]
	^5H_O	−167.3	1.406	1.418	106.3	108.0	161.3	4.03
2, Ac	^5H_O	−172.0	1.427	1.404	104.5	108.5	−76.9	0.00[c]
	$^OH_5$	167.2	1.338	1.489	110.0	111.8	173.2	2.55
3, Ac	$^OH_5$	−162.7	1.424	1.406	106.3	108.0	80.2	0.00[d]
	^5H_O	−167.0	1.406	1.425	106.5	108.1	160.3	1.66
4	^5H_O	167.9	1.424	1.413	104.6	108.5	−78.6	0.00[e]
	$^OH_5$	173.2	1.403	1.418	106.5	108.0	−165.1	2.96
21A	$^OH_5$	49.3	1.365	1.427	113.6	108.6	88.2	0.00[f]
	^5H_O	−73.4	1.378	1.412	110.9	104.1	170.7	2.00
22A	^5H_O	−49.3	1.361	1.515	107.4	115.0	−88.2	0.00[f]
	$^OH_5$	73.4	1.378	1.412	110.9	104.1	−170.7	2.00
1A, Ac	$^OH_5$	−160.4	1.354	1.472	107.2	109.4	63.8	0.00[g]
	^5H_O	36.8	1.348	1.475	111.6	106.2	178.6	6.18
2A, Ac	^5H_O	−56.0	1.373	1.451	115.0	109.5	−55.1	0.00[h]
	$^OH_5$	−37.6	1.343	1.486	112.8	107.5	−173.2	3.33
3A, Ac	$^OH_5$	−164.0	1.360	1.465	107.2	109.7	59.0	0.00[i]
	^5H_O	38.4	1.346	1.487	112.5	107.4	176.0	3.76
4A	^5H_O	−37.7	1.358	1.481	112.4	108.9	−60.6	0.00[j]
	$^OH_5$	−47.8	1.354	1.453	112.9	106.4	−177.3	6.99

[a] $E = -420.924789$.
[b] $E = -916.048022$.
[c] $E = -916.045254$.
[d] $E = -916.035694$.
[e] $E = -916.040521$.
[f] $E = -420.342743$.
[g] $E = -915.481554$.
[h] $E = -915.475154$.
[i] $E = -915.465500$.
[j] $E = -915.481804$.

calculations on the anionic form of the hydroperoxy group that is more likely formed during the epoxidation reaction of electrophilic olefins in the presence of bases,[15,17–19] namely the peroxy anion substituted tetrahydropyran and cyclohexane. Calculated energy profiles for rotation around the C1–O1 bond in **17A–20A** (Fig. 2) differ significantly from those calculated for the hydroperoxy group (Fig. 1) but are rather similar to energy profiles calculated for peroxy radicals.[21] In the case of radicals, however, the calculated rotational barriers are lower and the minimum at the gg conformer is less pronounced compared to peroxy anions. The energy profiles also differ from energy profiles calculated for 2-methoxytetrahydropyran,[5,8] yet are surprisingly similar to profiles calculated for 2-methylammoniotetrahydropyranyl cation.[8] In the latter case, however, the equatorial form is preferred because of the reversed anomeric effect.[8]

Due to the lack of a proton, intramolecular hydrogen bonding is not possible in anionic forms (peroxy group) of **17A–20A**. On the other hand, electrostatic interactions between a negative charge on the peroxy group oxygen (O2) and the ring oxygen (O5) are more relevant in some conformations than for the hydroperoxy group. The role of these is reflected in the conformational energy profiles shown in Figure 2. For example, repulsive electrostatic interactions between the peroxy group oxygen and the ring oxygen are responsible for a large barrier at $\Phi = 120°$ and $\Phi = 240°$ for the axial and equatorial form, respectively. In these two structures, two electronegative atoms, the peroxy anion and ring oxygen, are in the eclipsed orientation. This suggests an important role of electrostatic interactions on the conformational behavior of the deprotonated hydroperoxy group. The calculated barriers for THP derivatives at $\Phi \sim 120°$ and $\Phi \sim 240°$ in **17A** and **18A**, respectively,

Table 4. The B3LYP/6-311++G** calculated geometrical parameters and the Gibbs free relative energy (kcal/mol) for compounds (**23A**–**28A**)

	Min	Φ	r(C1–O1)	r(C1–O5)	α(O1–C1–C2)	α(O2-O1–C1)	α(O1–C1–O5)	ΔG_{vacuum}
23A	gt	−169.93	1.362	1.463	107.63	109.54	114.60	2.06
	gg	48.54	1.370	1.458	115.57	110.68	114.61	0.0[a]
	tg	−59.89	1.386	1.443	112.59	106.59	107.89	1.32
24A	gt	−171.17	1.358	1.468	108.35	109.29	114.44	0.42
	gg	45.30	1.365	1.462	115.56	110.05	114.71	0.0[b]
	tg	−63.52	1.382	1.447	112.94	105.82	108.16	0.45
25A	gt	158.33	1.342	1.485	110.46	109.16	111.25	1.24
	gg	−40.40	1.349	1.490	115.79	111.78	110.85	2.68
	tg	69.01	1.369	1.451	113.11	104.04	106.76	0.0[c]
26A	gt	171.50	1.360	1.454	106.18	108.75	114.61	3.69
	gg	51.23	1.362	1.459	115.64	110.33	115.15	0.0[d]
	tg	−31.50	1.384	1.455	112.88	111.25	108.17	2.36
27A	gt	172.68	1.356	1.462	106.96	108.38	114.39	2.56
	gg	47.76	1.358	1.461	115.16	109.11	115.12	0.0[e]
	tg	−59.4	1.379	1.443	112.3	106.3	108.2	1.66
28A	gt	158.76	1.332	1.497	110.67	108.13	111.30	1.04
	gg	−41.87	1.340	1.500	114.19	110.72	110.37	1.40
	tg	67.14	1.356	1.464	112.80	101.37	107.68	0.0[f]

[a] $E = -804.427632$.
[b] $E = -804.423878$.
[c] $E = -804.420657$.
[d] $E = -1497.540394$.
[e] $E = -1497.537736$.
[f] $E = -1497.529873$.
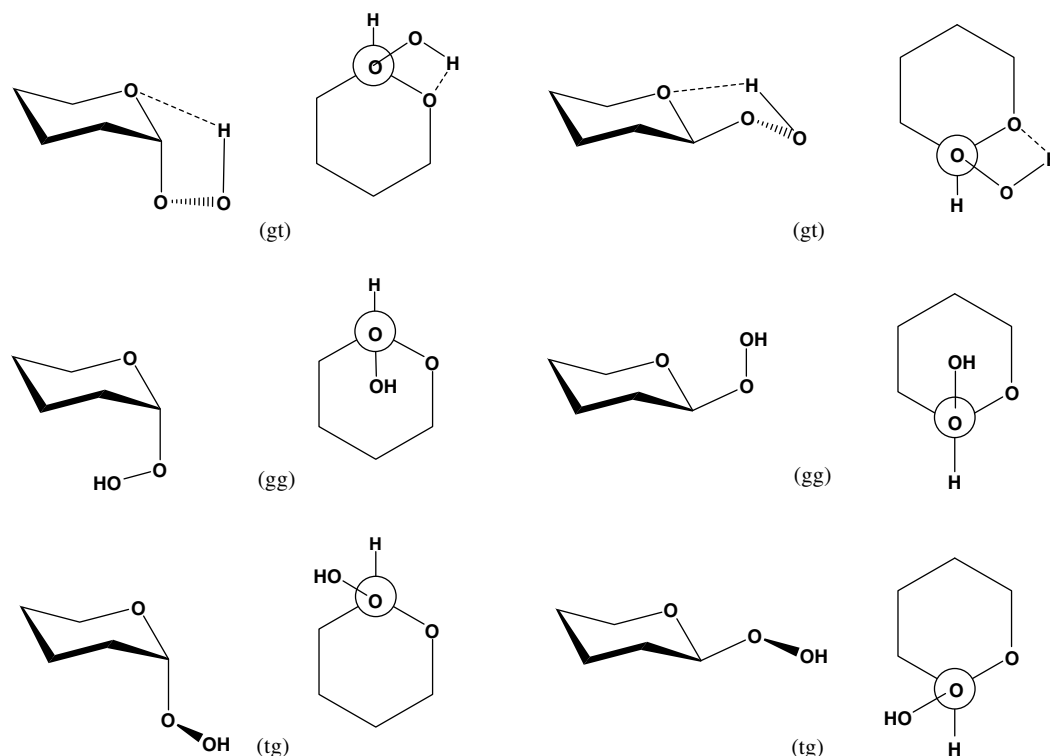
Scheme 5.

are considerably higher than those calculated for THX derivatives and for peroxy radicals.[21] This can be ascribed to the abovementioned electrostatic repulsion. For both anomeric forms of THP (**17A**, **18A**), the

calculations in a vacuum predict an approximately three-fold symmetry for torsional potential with minima at the staggered conformation. In the axial form, all the three minima are within 0.5 kcal/mol. Unexpectedly, and in contrast to all previously studied THP derivatives,[5–8] the tg and gg conformers of **17A** have a comparable Gibbs free energy in gas phase. In the gg conformation, the O5–C1–O1–O2 sequence is in the gauche conformation, and is, therefore, in agreement with the exo-anomeric effect. However, we assume that also the C3–H3···O2 and C5–H5···O2 hydrogen bonds contribute to the stability of the gg conformer. In this conformer, the distances C···O2 are approximately 3 Å, the distances H···O2 are ~2.3 Å, and the C–H···O2 angles are 120° and 115° for H3 and H4 atom, respectively. These values are in agreement with those reported for C–H···O hydrogen bonds in small molecules.[29] In the equatorial form, three minima are within 1.3 kcal/mol, and the deepest minimum appears at $\Phi = 155°$ (gt conformer). The effect of deprotonation of the hydroperoxy group also results in a large stabilization of the axial forms (**17A** and **19A**) relative to the equatorial (**18A** and **20A**) forms. Indeed, all the minima on the energy profile for the anionic axial form (**17A**) are lower in energy compared to the minima of the equatorial form (**18A**), and the calculated axial–equatorial Gibbs free energy difference is 2.35 kcal/mol (Table 2). For peroxy substituted cyclohexane, two conformers of the axial form (**19A**), having the gt ($\Phi = -176°$) and tg ($\Phi = -62°$) orientation around the C1–O1 linkage, are equal in Gibbs free energy for symmetrical reasons. Conformational equilibrium for the equatorial form (**20A**) is rather similar with two main minima equal in Gibbs free energy and located at the gt ($\Phi = 171°$) and tg orientation ($\Phi = 66°$), respectively. These conformers have a Gibbs free energy 0.58 kcal/mol higher than the lowest energy conformer of the axial form.

The previously published energy differences for methoxy, hydroxyl, thiomethyl, methylamino, methyl ammonio, ethyl, fluorine, and chlorine substituents calculated using the 6-31+G* basis set,[5–9] showed that the preference for the equatorial position in 2-substituted tetrahydropyrans decreases in the order $NH_2CH_3^+ > CH_3CH_2 > NHCH_3 > SCH_3 > OH > OCH_3 > F > Cl$ (−3.2, −3.9, −2.9, −0.6, 0.5, 0.9, 2.0, and 2.1 kcal/mol). A comparison of these values, with the calculated energy differences for the hydroperoxy and peroxy groups, shows that the hydroperoxy (OOH) and peroxy (OO⁻) groups exhibit larger preference for the axial orientation compared to the hydroxyl (1.4 vs 0.5 kcal/mol) and methoxy (2.4 vs 0.9 kcal/mol) groups, respectively. The magnitude of the anomeric affect is usually based on a comparison of the axial–equatorial equilibrium of a given substituent in a heterocyclic system and in cyclohexane (reference value). The calculations predict the axial–equatorial energy differences of −0.6 kcal/mol

and 0.6 kcal/mol for the hydroperoxy and peroxy anion groups in cyclohexane derivatives, respectively. Combining these values with the calculated values for tetrahydropyran derivatives, we estimated a 2.0 kcal/mol magnitude for the anomeric effect of the hydroperoxy group and 1.8.0 kcal/mol for the peroxy anion (OO⁻) group. Thus, the estimated magnitude of the anomeric effect is comparable to that estimated for the methoxy group (2.4 kcal/mol).[6,8]

3.3. The anomeric effect of the hydroperoxy group in 2,3-unsaturated hexopyranoses

NMR studies showed[11,14] that the 2,3-unsaturated α-D-erythro hydroperoxide (**1**, R = Ac) exists exclusively in the $^OH_5$ conformation, whereas the 2,3-unsaturated β-D-erythro hydroperoxide (**2**, R = Ac) occurs in the inverted ^5H_O conformation. It was also observed that the 2,3-unsaturated α-D-threo hydroperoxide (**3**, R = Ac) adopts the $^OH_5$ conformation. These results led to a suggestion[11] that the hydroperoxy group exhibits a strong anomeric effect. To evaluate the role of the anomeric effect on the conformational equilibrium of 2,3-unsaturated glycosyl peroxides, we have calculated the structure and energy of two ring forms for **1–3** (R = Ac) and **4**, having both hydroperoxy and peroxy anion groups, respectively. For each ring form of these compounds, calculations were carried out for three conformers around the C10-O1 linkage. For comparison, similar calculations for compounds without substituents at the 3, 4, and 5 positions (**21** and **22**) were performed. The relative energies of the ^5H_O and $^OH_5$ conformations, calculated at the B3LYP/6-311++G** level together with selected geometrical parameters, are given in Table 3. As shown in Table 3, for α-hydroperoxides the dominant conformation is the $^OH_5$ ring form, in agreement with the experimentally observed preference.[10] On the contrary, β-hydroperoxides prefer the ^5H_O ring form. Inspection of the three-dimensional structures of the 2,3-unsaturated derivatives revealed that in all the preferred ring forms the O1–C1–O5–C5 sequence of atoms exists in the gauche conformation, whereas in the second ring form the conformation of this segment is trans. This feature is documented by values of the τ dihedral angle listed in Table 3. Thus, for α-anomers (**1**, **3**, and **21**) in the preferred ring form ($^OH_5$) the values of the τ dihedral angle are in the interval of 59–88°. Similarly, the values of the τ dihedral angle in the preferred ring form (^5H_O) of the β-anomers (**2**, **4**, and **22**) are in the interval of −55° to −88°. The preference of the gauche conformation, over the trans conformation of the O1–C1–O5–C5 segment, represents a clear demonstration of the anomeric effect of the peroxy and hydroperoxy groups. The calculated energy differences between two ring forms from 1.7 to 6.9 kcal/mol suggest a dominance of only one ring form in **1–4**, **21**, and **22**.

As seen from the values of the Φ dihedral angle in Table 3, there is a clear difference in the conformational preference around the C1–O1 bond between the hydroperoxy and peroxy anion groups. The preferred orientation of the hydroperoxy group is gt. Similarly, as in **17–20**, this orientation is stabilized by a synergy between the exo-anomeric effect and hydrogen bonding. For the peroxy group (**1A–4A**, **21A**, and **22A**), there is a clear preference for the gg conformation, with the exception of two cases (see Table 3). Likewise, for the deprotonated hydroperoxy substituted THP we assume that electrostatic repulsive interactions between the negatively charged atoms O2 and O5 are responsible for this orientation. It is noteworthy that in the gg conformation the O5–C1–O1–O2 sequence is in the gauche conformation, and is therefore in agreement with the exo-anomeric effect. However, due to electrostatic interactions and C–H···O hydrogen bonds mentioned above, the preference is shifted from the gt to the gg conformation.

Finally, we have calculated conformational preference around the C1–O1 in **23A–28A** and the results are given in Table 4. The calculated results further support a large anomeric effect of the peroxy anion group. The role of the anomeric effect is documented by a preference of the α-anomer over the β-anomer in glucose derivatives (**24A**, **25A**, **27A**, and **28A**). This preference is approximately 2 kcal/mol for OMe derivatives (**24A** and **25A**) and 5 kcal/mol for OBn derivatives (**27A** and **28A**). Conformational behavior around the C1–O1 linkage shows a similar pattern in all peroxy derivatives. The preferred conformation, with the exception of **25A** and **28A**, is the gg conformation.

4. Conclusions

In this paper, we have calculated conformational properties of the hydroperoxy and peroxy groups at the anomeric carbon in compounds of various structural complexities. These results provide an essential set of data for the parameterization of molecular mechanical force fields. The calculated conformational equilibria have been used to estimate the magnitude of the anomeric effect. High level DFT calculations at the B3LYP/6-311++G** level demonstrated that the hydroperoxy and peroxy groups exhibit a strong anomeric effect with a magnitude comparable to the hydroxy and methoxy groups, respectively.

Acknowledgments

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