



The origin of the generalized anomeric effect: possibility of CH/ n and CH/ π hydrogen bonds

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ABSTRACT

Ab initio MO calculations were carried out at the MP4/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) level to investigate the conformational Gibbs energy of a series of methyl ethers CH₃O–CH₂–X (X = OH, OCH₃, F, Cl, Br, CN, C≡CH, C₆H₅, CHO). It was found that the Gibbs energy of the *gauche* conformers is lower in every case than that of the corresponding *anti* conformers. In the more stable *gauche* conformers, the interatomic distance between X and the hydrogen atom was shorter than the sum of the van der Waals radii. The natural bonding orbital (NBO) charges of group X were more negative in the *gauche* conformers than in the *anti* conformers. We suggest that the CH/ n and CH/ π hydrogen bonds play an important role in stabilizing the *gauche* conformation of these compounds.

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1. Introduction

The anomeric effect refers to the tendency of an electronegative substituent X at C–1 of pyranose glycosides and halides to assume an axial rather than equatorial conformation (Fig. 1; X = OR, F, Cl, and Br). Since its discovery in 1955, the anomeric effect has attracted the interest of numerous researchers.¹

Edward proposed that this effect is caused by the unfavorable interaction between lone pairs of the oxygen and the dipole of the C–X bond of a pyranoside.² This proposal has been accepted in view of its consistency with experimental data on the solvent effect. In 1994, Perrin et al. presented data favoring the mechanism by dipole interaction, on the basis of their conformational study of 2-methoxy-1,3-dimethylhexahydropyrimidine.³

Another explanation has focused on orbital interaction; that is, the overlap between a nonbonding electron pair on the oxygen atom and the vacant σ^* orbital of the C–X bond.⁴ In 1971, Wolfe et al.⁵ and Radom et al.⁶ studied the issue using theoretical calculations. A number of researchers have since studied the conformation of simple aliphatic molecules by MO calculations.^{7,8}

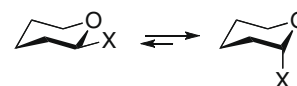


Figure 1. Anomeric effect.

The phenomenon is not limited to carbohydrate chemistry but extends to acyclic molecules such as R–Y–CH₂–X **1** (Y = O, S; X = OH, OCH₃, F, Cl, Br, etc.). The *gauche* conformer is preferred to the *anti* conformer, irrespective of the nature of the electronegative group, X (Fig. 2). This is called the ‘generalized anomeric effect’. Jeffrey et al. examined the conformational energy of methanediol,⁹ methoxymethanol,¹⁰ dimethoxymethane,¹¹ and methoxymethyl halides,¹² and discussed the results on the basis of the $n\text{--}\sigma^*$ mechanism.

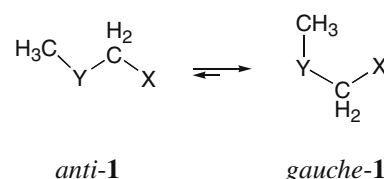


Figure 2. Generalized anomeric effect.

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Figure 3. Explanation of the anomeric effect in terms of the CH/ n hydrogen bond.

In a previous paper, we presented an alternative interpretation of the anomeric effect in which the five-membered CH/ n hydrogen bond, occurring between axial hydrogens and the electronegative atom X, is important.¹³ This proposal was based on high-level ab initio MO calculations of 2-substituted oxanes **2** and 1,3-dioxanes **3**; short interatomic distances have been found between H and group X (Fig. 3).

It remains to be settled to what extent the dipolar, $n-\sigma^*$, and hydrogen bond mechanisms are responsible for the anomeric effect. Here we examined, by ab initio calculations at the MP4/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) level, the conformational Gibbs energy of a series of methyl ethers $\text{CH}_3\text{--O--CH}_2\text{--X}$ **1** (X = OH, OCH_3 , F, Cl, Br, CN, $\text{C}\equiv\text{CH}$, C_6H_5 , and CHO). We present a hypothesis that the mechanism underlying the generalized anomeric effect involves contributions from the CH/X^{14,15} (X = O, F, Cl, and Br) and CH/ π hydrogen bonds¹⁶ (X = CN, $\text{C}\equiv\text{CH}$, C_6H_5 , and CHO). The CH/ π hydrogen bond is the weakest extreme of hydrogen bonds to occur between a soft acid (CH) and a soft base (π -group) in the context of Pearson's HSAB principle; the importance of this molecular force has been reviewed in several treatises.¹⁷

2. Methods

The GAUSSIAN 03 program¹⁸ was used. Electron correlation energies were calculated by applying the second-order Møller–Plesset (MP2) perturbation theory. The first geometry optimizations of the compounds $\text{CH}_3\text{--O--CH}_2\text{--X}$ (X = OH, OCH_3 , F, Cl, Br, CN, $\text{C}\equiv\text{CH}$, C_6H_5 , and CHO) were performed at the MP2/6-311G(d,p) level of approximation, and vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer in order to obtain the thermal energy corrections at 298.15 K and 1 atmosphere of pressure. The second geometry optimizations were performed at the MP2/6-311++G(3df,3pd) level using the previous geometries, and the single-point energy calculations at the MP4/6-311++G(3df,3pd) level were performed at the obtained geometries. The Gibbs energies were obtained by adding the thermal energy corrections. Natural bond orbital (NBO) calculations were performed with the NBO code¹⁹ included in GAUSSIAN 03.

3. Results and discussion

3.1. Gibbs energies of the *gauche* and *anti* conformers of **1**

Table 1 summarizes the relative Gibbs energies of the *anti*- and *gauche* conformers ($\Delta G_{\text{anti-gauche}}$) of $\text{CH}_3\text{--O--CH}_2\text{--X}$ **1** (X: OH, OCH_3 , F, Cl, Br, CN, $\text{C}\equiv\text{CH}$, C_6H_5 , and CHO), calculated at the MP4/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) level of approximation. Data for methyl *n*-propyl ether (X = CH_3) are included for comparison.

In every case, except for X = CH_3 and CHO, the *gauche* conformer was more stable than the *anti* conformer. This is consistent with the concept of the generalized anomeric effect. The result for methoxyacetaldehyde (X = CHO, $\Delta G_{\text{anti-gauche}}$ -0.83 kcal mol⁻¹) is anomalous, but we think that this is a consequence of the unfavorable

Table 1

Difference in the Gibbs energy between the *anti*- and *gauche* conformers of $\text{CH}_3\text{--O--CH}_2\text{--X}$ **1** (X: OH, OCH_3 , F, Cl, Br, CN, $\text{C}\equiv\text{CH}$, C_6H_5 , CHO, and CH_3)

X	1 $\Delta G_{\text{anti-gauche}}^a$	1 (Previous work) $\Delta E_{\text{anti-gauche}}$	2 $\Delta G_{\text{eq-ax}}$	3 $\Delta G_{\text{eq-ax}}$
OH	2.35	3.65 ^d	1.35	1.27
OCH_3	2.86	2.39 ^e	1.25 ^l	2.05 ^l
F	4.02 ^b	4.83 ^f	2.47 ^l	3.45 ^l
Cl	4.00 ^b		2.57 ^l	4.30 ^l
Br	4.46 ^b		3.08 ^l	5.47 ^l
CN	1.68 ^b	1.26 ^g	1.22	1.90
$\text{C}\equiv\text{CH}$	0.98 ^b	1.34 ^h	0.68	0.97
C_6H_5	1.09 ^{b,c}	-0.25^i		
CHO	-0.83^j	-0.99^j		
CH_3	-0.87^b	-1.38^k	-3.27^l	-5.18^l

Data for 2-substituted oxanes **2** and 1,3-dioxanes **3** ($\Delta G_{\text{eq-ax}} = G_{\text{equatorial}} - G_{\text{axial}}$) are included for comparison. Relevant data (ΔE) reported by other workers are also given.²⁰

^a $\Delta G_{\text{anti-gauche}} = G_{\text{anti}} - G_{\text{gauche}}$ (in kcal mol⁻¹).

^b This work. Corrected by entropy of mixing ($RT \ln 2 = 0.41$ kcal mol⁻¹, 298 K) for the *gauche* conformers.

^c MP2/6-311G(d,p).

^d Ref. 21, HF/4-31G.

^e Ref. 22, G2 theory.

^f Ref. 23, MP2/6-31G*.

^g Ref. 24, Raman spectroscopy.

^h Ref. 25, MP2/6-31++G**.

ⁱ Ref. 26, Matrix-isolation infrared spectroscopy.

^j Ref. 27, B3LYP/aug-cc-pVTZ.

^k Ref. 28, MP2/6-31G*.

^l Ref. 13.

interaction between the aldehyde CH and the methoxy CH_3 group in the *gauche* conformer (Fig. 4).

An interesting point is that the difference in the Gibbs energy between the *anti*- and *gauche* conformers $\Delta G_{\text{anti-gauche}}$ is smaller, generally, in compounds bearing a π -group (0.98 – 1.68 kcal mol⁻¹) than in compounds with an electronegative group (2.35 – 4.46 kcal mol⁻¹). Similar results have also been observed for **2** and **3**. At present we do not know the reason for this phenomenon, but it should be kept in mind that the genesis of the CH/ π hydrogen

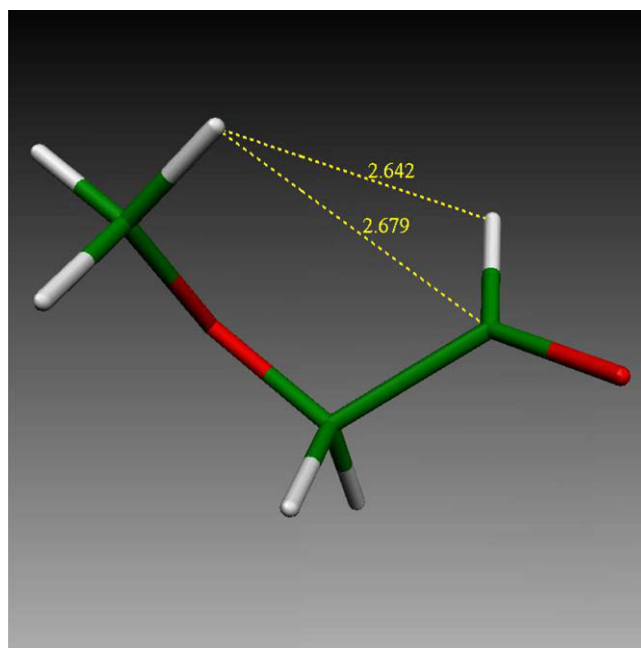


Figure 4. Calculated structure of the *gauche* conformer of methoxyacetaldehyde (**1**, X = CHO). Distances between the relevant atoms are given in Å.

bond is different from that of the CH/ π hydrogen bond. The energy of the CH/ π hydrogen bond comes mostly from the dispersion force,²⁹ while the Coulombic contribution is more important in the CH/ π hydrogen bond.³⁰

3.2. Nonbond distances

We thought that five-membered intramolecular CH/ π and CH/ π hydrogen bonds, as shown in Figure 5, are involved in bringing about the *gauche* conformation of **1** stable. In these geometries, a five-membered CH/ π or CH/ π hydrogen bond is possible between a CH hydrogen and X. The importance of the five-membered CH/O,^{31,32} CH/F,^{33,34} CH/Cl,¹³ CH/Br,¹³ OH/ π ,^{35,36} NH/ π ,³⁷ and CH/ π hydrogen bonds^{38–40} in conformational issues of organic molecules is well known.⁴¹ To test our hypothesis, we examined the interatomic distances between a C–H and X in the *gauche* conformers. Table 2 lists the results. The dihedral angles τ defined by atomic sequence H–C¹–C²–X and bond angles θ ($\angle$ OC²X) are also given. The interatomic distance, $d_{\text{H/X}}$, has been shown in every *gauche* conformer to be shorter than the sum of the van der Waals (vdW) radii of the relevant atoms.[†]

Table 2 shows that Δd is larger when X is a group bearing π -electrons (C $\equiv$ N, C $\equiv$ CH, C₆H₅, and CHO). This may imply the importance of the contribution from dispersion force in the CH/ π hydrogen bond.

3.3. Natural bonding orbital (NBO) charges

To obtain support to our hypothesis, we examined natural bonding orbital (NBO) charges of the X atoms. Table 3 lists the results. The NBO charge of X is more negative in the *gauche* conformer than in the *anti* conformer; the difference in the NBO charge ($\Delta_{\text{anti-gauche}}$) is always positive, accordingly. Table 3 also gives the difference in the NBO charge of the terminal methyl group. In every case, $\Delta_{\text{anti-gauche}}$ for CH₃ (average value)[‡] was negative, except for X = CHO. We think these findings show the hydrogen-bonding nature of this interaction.

3.4. Covalent bond lengths related to the anomeric effect

Tables 4 and 5 list the covalent bond lengths d_1 and d_2 relevant to the anomeric effect (see Figure 6).

It is noted that the covalent bond length dO–C is shorter than the standard value, 1.47 Å,^{44,8} irrespective of the conformation and the nature of group X (Table 4). This is consistent with the expectation from the current theory of the anomeric effect based on the $n-\sigma^*$ interaction considerations.¹

With respect to the C–X bond length (Table 5), however, $d_{\text{C}^2-\text{X}}$ has been shown to be shorter than the standard values (except for X = Cl and Br: italicised). This is incompatible with the orbital interaction theory. The bond length of the *gauche* conformer ($d_{\text{C}^2-\text{X}_{\text{gauche}}}$) is longer, in every case, than that of the *anti* conformer ($d_{\text{C}^2-\text{X}_{\text{anti}}}$).

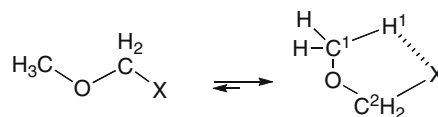


Figure 5. Intramolecular CH/ π or CH/ π hydrogen bonds.

Table 2

Interatomic distances $d_{\text{H/X}}$ and differences between $d_{\text{H/X}}$ and the van der Waals distance d_{vdW} ($\Delta d = d_{\text{vdW}} - d_{\text{H/X}}$), calculated at the MP2/6-311++G(d,p) level of approximation

X	$d_{\text{H/X}}^{\text{a}}$	τ^{b}	θ^{c} (°)	$X_{\text{vdW}}^{\text{d}}$	$H_{\text{vdW}}^{\text{e}}$	$d_{\text{vdW}}^{\text{f}}$	Δd^{g}
(a) Data calculated with the vdW radii by Bondi ⁴²							
OH	2.58	−5.7	113.4	1.52	1.2	2.72	0.14
OCH ₃	2.59	−2.5	109.9	1.52	1.2	2.72	0.13
F	2.57	−1.6	111.5	1.47	1.2	2.67	0.10
Cl	2.85	−3.4	113.4	1.75	1.2	2.95	0.10
Br	2.93	−2.9	113.8	1.85	1.2	3.05	0.12
CN	2.61	−0.74	111.9	1.77	1.2	2.97	0.36
C≡CH	2.63	−0.04	113.8	1.77	1.2	2.97	0.34
C ₆ H ₅	2.63	−3.3	113.0	1.77	1.2	2.97	0.34
CHO	2.68	−11.6	112.1	1.77	1.2	2.97	0.29
X	X_{vdW}		H_{vdW}		d_{vdW}		Δd
(b) Data calculated with the vdW radii by Rowland and Taylor ⁴³							
OH	1.58		1.1		2.68		0.10
OCH ₃	1.58		1.1		2.68		0.09
F	1.46		1.1		2.56		−0.01
Cl	1.76		1.1		2.86		0.01
Br	1.85		1.1		2.95		0.02
CN	1.77		1.1		2.87		0.26
C≡CH	1.77		1.1		2.87		0.24
C ₆ H ₅	1.77		1.1		2.87		0.24
CHO	1.77		1.1		2.87		0.19

^a Distance between H and X in the *gauche* conformer (Å).

^b Dihedral angle defined by the atomic sequence H–C¹–C²–X (°).

^c $\angle$ OC²X

^d van der Waals radius of X.

^e van der Waals radius of H.

^f Sum of the van der Waals radii (X + H).

^g $d_{\text{vdW}} - d_{\text{H/X}}$.

Table 3

Natural bonding orbital (NBO) charges of X and CH₃ in the *anti*- and *gauche* conformers and the difference in the NBO charges

X	NBO(X) _{anti} ^a	NBO(X) _{gauche} ^b	Δ NBO(X) _{anti-gauche} ^c	Δ NBO(CH ₃) _{anti-gauche} ^d
OH	−0.748	−0.769	0.021	−0.005
OCH ₃	−0.620	−0.640	0.021	−0.006
F	−0.417	−0.446	0.029	−0.006
Cl	−0.080	−0.149	0.069	−0.006
Br	−0.027	−0.117	0.090	−0.007
CN	0.327	0.299	0.028	−0.005
C $\equiv$ CH	−0.023	−0.050	0.027	−0.005
C ₆ H ₅	−0.043	−0.063	0.020	−0.005
CHO	0.542	0.519	0.023	+0.001

^a NBO charge of X for the *anti* conformer.

^b NBO charge of X for the *gauche* conformer.

^c Difference in the NBO charges of X between the *anti*- and *gauche* conformers.

^d Difference in the NBO charges of CH₃ between the *anti*- and *gauche* conformers.

3.5. NBO second-order perturbation analysis

In order to investigate the reason for the above irregularity observed in the halogenated derivatives, we carried out calculations of the so-called NBO second-order perturbation method. According to this theory, the conformational stability is affected by two kinds of hyperconjugative effects: the AP effect (antiperiplanar interactions between C–H bonds and C–X bonds: $\sigma_{\text{C-X}}, \text{C-H} \rightarrow \sigma_{\text{C-X}}^*, \text{C-H}^*$) and the LLP effect (long-range delocalization of lone-pair electrons on the oxygen atom to the antibonding orbital of the C–X or C–H bond: $n \rightarrow \sigma_{\text{C-X}}^*, \text{C-H}^*$).

[†] The shortening of interatomic distance is marginal for X = F, Cl, and Br when the vdW radii by Rowland and Taylor are considered. We do not know why this is the case, but the concept of the vdW radius is not without ambiguity; the shape of a group is nonspherical, and vdW radii depend on the direction of measurements. The vdW radii reported by Rowland and Taylor may be more reliable, since these values were obtained by an extensive CSD study, but Bondi's values are customarily used in this kind of argument.

[‡] The average values were used, since it was difficult to specify which hydrogen in the *anti* conformer corresponds to the interacting hydrogen in the *gauche* conformer.

[§] In calculating the C–O bond length in various conformers of methanediol (RHF/4-31G), Jeffray et al. used 1.437 Å for the standard value (Ref. 11).

Table 4

Bond lengths $d\text{O}-\text{C}^2$ (d_1) and differences between d_1 and the standard $\text{O}-\text{C}$ length Δd_1 , calculated at the MP2/6-311++G(3df,3pd) level

X	$\text{O}-\text{C}_{\text{std}}^a$	$d\text{O}-\text{C}_{\text{gauche}}^b$	$d\text{O}-\text{C}_{\text{anti}}^c$	$\Delta d_{\text{gauche}}^d$	Δd_{anti}^e
OH	1.47	1.398	1.407	0.072	0.063
OCH_3	1.47	1.382	1.381	0.088	0.089
F	1.47	1.372	1.388	0.098	0.082
Cl	1.47	1.373	1.394	0.097	0.076
Br	1.47	1.369	1.393	0.101	0.077
CN	1.47	1.402	1.406	0.068	0.064
CCH	1.47	1.411	1.413	0.059	0.057
C_6H_5	1.47	1.414	1.414	0.056	0.056
CHO	1.47	1.408	1.404	0.062	0.066

^a Standard $\text{O}-\text{C}$ bond length (in Å, Ref. 44).

^b $\text{O}-\text{C}^2$ bond length in the *gauche* conformer.

^c $\text{O}-\text{C}^2$ bond length in the *anti* conformer.

^d $\text{O}-\text{C}_{\text{std}} - d\text{O}-\text{C}_{\text{gauche}}^b$.

^e $\text{O}-\text{C}_{\text{std}} - d\text{O}-\text{C}_{\text{anti}}^c$.

Table 5

Bond lengths $d\text{C}^2-\text{X}$ (d_2) and differences between d_2 and the standard $\text{C}-\text{X}$ length Δd_2 , calculated at the MP2/6-311++G(3df,3pd) level

X	$\text{C}-\text{X}_{\text{std}}^a$	$d\text{C}^2-\text{X}_{\text{gauche}}^b$	$d\text{C}^2-\text{X}_{\text{anti}}^c$	$\Delta d_{\text{gauche}}^d$	Δd_{anti}^e
OH	1.47	1.406	1.388	0.064	0.082
OCH_3	1.47	1.406	1.408	0.064	0.062
F	1.45	1.386	1.361	0.064	0.089
Cl	1.76	1.812	1.767	−0.052	−0.007
Br	1.91	1.989	1.931	−0.079	−0.021
CN	1.54	1.481	1.469	0.059	0.071
CCH	1.54	1.474	1.464	0.066	0.076
C_6H_5	1.54	1.514	1.506	0.026	0.034
CHO	1.54	1.522	1.517	0.018	0.023

^a Standard $\text{C}-\text{X}$ bond length (Ref. 44).

^b C^2-X bond length in the *gauche* conformer.

^c C^2-X bond length in the *anti* conformer.

^d $\text{C}-\text{X}_{\text{std}} - d\text{C}^2-\text{X}_{\text{gauche}}^b$.

^e $\text{C}-\text{X}_{\text{std}} - d\text{C}^2-\text{X}_{\text{anti}}^c$.

Table 6 summarizes the results of our NBO analysis. The AP and LLP energies were estimated at the HF/6-311++G(3df,3pd) level because the NBO perturbation analysis was not possible at the MP2/

6-311++G(3df,3pd) level. It is difficult, therefore, to directly compare these data with the results that include the electron correlation. It is interesting, however, to see the orbital interaction's effect in relation to the mechanism underlying the anomeric effect.

The energy of the hyperconjugative effects ($\Delta E_{\text{AP}} + \Delta E_{\text{LLP}}$) agrees with that of the ab initio MO calculation ($\Delta E_{\text{Total energy}}$) only when $\text{X} = \text{F}$, the most electronegative group in the series. For $\text{X} = \text{Cl}$ and Br , where the correlation effect is dominant, the LLP energy is more positive in the *gauche* conformer than in the *anti* conformer, while the AP energy in the *gauche* conformer is less positive than in the *anti* conformer. Namely, the present NBO analysis of the Cl and Br derivatives suggests that the so-called hyperconjugative effect does not play a noticeable role. The values of $\Delta E_{\text{Total energy}}$ compares well with the Gibbs energy reported in Table 1. This shows that the orbital interaction does not play an important role in the anomeric effect.

4. Conclusions

Ab initio MO calculations were carried out at the MP4/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) level to investigate the conformational energy of a series of methyl ethers $\text{CH}_3\text{OCH}_2\text{X}$ ($\text{X} = \text{OH}, \text{OCH}_3, \text{F}, \text{Cl}, \text{Br}, \text{CN}, \text{C}\equiv\text{CH}, \text{C}_6\text{H}_5$, and CHO). In every case except for $\text{X} = \text{CHO}$, the Gibbs energy of the *gauche* conformers was lower than that of the corresponding *anti* conformers. In the *gauche* conformers, the interatomic distance between X and a hydrogen atom, separated by four covalent bonds, was shorter than the van der Waals distance, suggesting the importance of five-membered CH/π and CH/π hydrogen bonds. The NBO charge of X is more negative in the *gauche* conformer than in the *anti* conformer. It remains to be explored, however, to what extent the hydrogen-bond mechanism contributes to the anomeric effect as compared to the $n-\sigma^*$ and dipole mechanisms.⁴⁵ In any event, reconsideration of the theory of the anomeric effect is required, as argued by Perrin and his coworkers.^{3,45}

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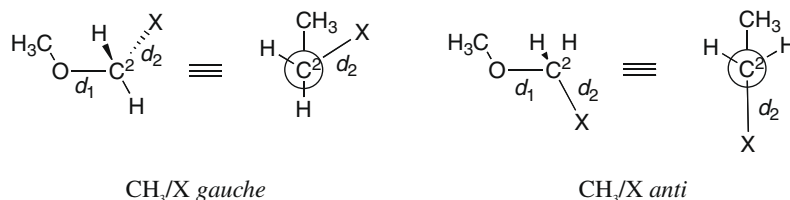


Figure 6. Covalent bond lengths ($d_1 = d\text{O}-\text{C}^2$; $d_2 = d\text{C}^2-\text{X}$) relevant to the anomeric effect.

Table 6

NBO second-order perturbation analysis^a of the *anti*- and *gauche* conformers

X		AP		LLP		$\Delta E_{\text{AP}}^{\text{b}} + \Delta E_{\text{LLP}}^{\text{b}}$	$\Delta E_{\text{Total energy}}^{\text{c}}$
			$\Delta E_{\text{AP}}^{\text{b}}$		$\Delta E_{\text{LLP}}^{\text{b}}$		
F	<i>gauche</i>	12.78		85.10		−5.52	4.16
	<i>anti</i>	11.77	−1.01	80.59	−4.51		
Cl	<i>gauche</i>	15.04		80.59		−9.07	4.10
	<i>anti</i>	15.43	0.39	71.13	−9.46		
Br	<i>gauche</i>	10.50		79.91		0.54	4.60
	<i>anti</i>	15.35	4.85	75.60	−4.31		

^a HF/6-311++G(3df,3pd) level.

^b $\Delta E = E_{\text{anti}} - E_{\text{gauche}}$ (kcal mol^{−1}).

^c $\Delta E_{\text{Total energy}} = E_{\text{anti}} - E_{\text{gauche}}$ (kcal mol^{−1}).

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Supplementary data

Supplementary data (atomic coordinates of methyl ethers $\text{CH}_3\text{OCH}_2\text{X}$ ($\text{X} = \text{OH}, \text{OCH}_3, \text{F}, \text{Cl}, \text{Br}, \text{CN}, \text{C}\equiv\text{CH}, \text{C}_6\text{H}_5$, and CHO) calculated at the MP2/6-311++G(d,p) level of approximation) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.04.011.

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