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The anomeric effect revisited. A possible role of the CH/*n* hydrogen bond

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Abstract—Ab initio MO calculations were carried out at the MP2/6-311++G(d,p) level to investigate the conformational energy of 2-substituted oxanes and 1,3-dioxanes. It has been found that the Gibbs free energies of the axial conformers are smaller than those of the corresponding equatorial conformers in every case when the 2-substituent Z is electron withdrawing (OCH_3, F, Cl, Br). The difference in Gibbs energy between the equatorial and axial conformers $\Delta G_{\text{eq–ax}}$ increases from $Z = OCH_3$ to F, Cl, and then to Br. In the axial conformers, the interatomic distance between Z and the axial C–H, separated by four covalent bonds, has been found to be appreciably shorter than the van der Waals distance, suggesting the importance of the five-membered CH/*n* (CH/O or CH/halogen) hydrogen bond in stabilizing these conformations. Natural bonding orbital (NBO) charges of the relevant atoms have been shown to be different between the two conformers: more positive for H and more negative for C in the axial conformers than in the corresponding equatorial conformers. In view of the above findings, we suggest that the CH/*n* hydrogen bond plays an important role in stabilizing the axial conformation in 2-substituted oxanes and 1,3-dioxanes, and by implication, in the anomeric effect in carbohydrate chemistry.

Keywords: Ab initio calculation; Axial preference; Natural bonding orbital; Oxane; 1,3-Dioxane; Pyranose; CH/*n* hydrogen bond; CH/halogen hydrogen bond; ^{13}C γ-effect

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1. Introduction

The anomeric effect refers to the tendency of an electronegative substituent at C-1 of pyranosides, such as OCH_3 or halogen atoms, to assume the axial rather than the equatorial conformation, contrary to the expectation from ordinary steric considerations. Since its discovery in 1955,[1] the anomeric effect has been a subject of numerous studies, and the origin of the effect seems now to be settled on a firm theoretical basis.[2,3]

The phenomenon is not limited to carbohydrate chemistry but extends to stereochemistry of six-membered heterocyclic compounds such as 2-substituted oxanes (tetrahyropyrane) and 1,3-dioxanes. This effect extends also to acyclic molecules such as $R–X–CH_2–Z$ (X = O, S; $Z = OCH_3$, halogen, etc.). This is called the ‘generalized anomeric effect’. Figure 1 illustrates this for dimethoxymethane. In this case the GG conformer (model for the axial conformer of a 1-substituted pyranose), is preferred to the TG conformer (equatorial).

Several interpretations have been presented to explain the anomeric effect. Edward advanced an explanation in terms of unfavorable interaction between the lone pairs of the endocyclic oxygen and the dipole of the exocyclic C–O bond of a pyranoside. This reasoning seems sound

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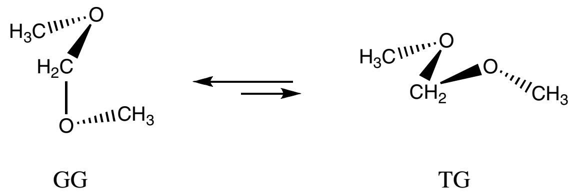


Figure 1. Conformation of dimethoxymethane.

and has been accepted in view of its consistency with experimental data of the solvent effect. Thus, a more polar solvent favors the equatorial conformer, the dipole moment of which is larger than that of the axial conformer. The size of the anomeric effect decreases in polar solvent accordingly. This dipolar mechanism, however, does not explain the variation of the bond lengths, X–C and C–Z, associated with the anomeric effect. Another explanation has been advanced on the basis of the orbital interaction.[4–11]

In 1971, Wolfe first studied the issue by theoretical calculations (STO-3G) and termed the effect as the Edward–Lemieux effect.[5] Jeffrey et al. examined, by the HF/4-31G level of approximation, the dependence of conformational energy of methanediol ($HOCH_2OH$),[6] methoxymethanol (CH_3OCH_2OH),[8] dimethoxymethane ($CH_3OCH_2OCH_3$),[9] and methoxymethyl halides (CH_3OCH_2F, CH_3OCH_2Cl).[11] Many workers have since estimated the conformational energy, GG versus TG, of dimethoxymethane.[12–14] In every case, the GG conformer has been found to be more stable, and the bond length O–CH_2 is appreciably shorter in the GG conformer than in the TG conformer. In the GG conformer, on the contrary, the bond length CH_2–Z (Z = OH, OCH_3, F, Cl) has been shown to be longer than that of the TG conformer. The result was argued in terms of the delocalization of the lone-pair electrons on the oxygen atom to the antibonding orbital of the O–CH_3 bond. The result obtained by the MO method was reported to be consistent with crystallographic data of many pyranosides,[15] by the analysis of the Cambridge Structural Database (CSD).[16] Very recently,[17] an explanation has been presented to the mechanism of the anomeric effect,[5–12,18,19] on the basis of the stabilizing $n \rightarrow \sigma^*$ interaction by the NBO analysis.

Here we examined, by ab initio calculations at the MP2/6-311++G(d,p) level, the conformational Gibbs energy of 2-substituted oxanes and 1,3-dioxanes. A hypothesis is presented that the mechanism of the anomeric effect includes a contribution from the CH/*n* hydrogen bond (*n*: lone pair electrons on an electronegative atom).

2. Methods

2.1. Computational method

The GAUSSIAN 03 program[20] was used. Electron correlation energies were calculated by applying the second order Møller–Plesset (MP2) perturbation theory. The geometry of axial and equatorial conformers of 2-substituted oxanes **1** and 1,3-dioxanes **2** was optimized at the MP2/6-311++G(d,p) level of approximation. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer. Using these results, the thermal energy corrections were added to the total Gibbs energy at 298.15 K and 1 atm of pressure. Natural bond orbital (NBO) calculations using the density by the Hartree-Fock (HF) calculations were performed with the NBO code[21] included in GAUSSIAN 03. We have confirmed that NBO charges at the HF level are nearly equal to those at the MP2 level by the test calculations using related compounds. The ^{13}C NMR chemical shifts were computed using tetramethylsilane (TMS) [calculated absolute chemical shift δ (C) = 198.98 ppm (MP2 GIAO magnetic shielding tensor)] as reference.

2.2. Crystallographic database search

The Cambridge Structural Database (CSD version 5.27, November 2005 release) was used. The relevant data were retrieved by using ConQuest version 6.0 and analyzed by VISTA version 2.0. Only organic crystal data with *R*-factor < 0.1 were considered.

3. Results and discussion

3.1. Gibbs free energies of the axial and equatorial conformers

Table 1 summarizes the relative ΔG of the equatorial and axial conformers of 2-substituted oxanes **1** (Fig. 2, X = O, Y = CH_2) and 1,3-dioxanes **2** (X = Y = O).

In every case, except for Z = CH_3, the axial conformer has been found more stable than the corresponding equatorial conformer, in agreement with the concept of the anomeric effect. The above results are consistent

Table 1. Difference in the Gibbs free energy ($\Delta G_{eq-ax} = G_{eq} - G_{ax}$, in kcal mol^{-1}), calculated at the MP2/6-311++G(d,p) level of approximation, between axial and equatorial conformers of 2-substituted oxanes **1** and 1,3-dioxanes **2**

Z	1	2
OCH_3	1.251	0.052[a] 1.939
F	2.466	3.422
Cl	2.569	4.311
Br	3.082	5.451
CH_3	−3.268	−5.220

[a] In 2-methoxy-1,3-dioxane two equatorial conformers were found: eq-I and eq-II. Eq-II is less stable than the axial conformer by 1.94 kcal mol^{-1}, while eq-I is relatively stabilized (ΔG_{eq-ax} = 0.05 kcal mol^{-1}) by the formation of CH/O hydrogen bonds, as illustrated in Figure 4 (vide infra).

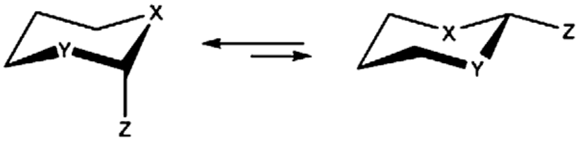


Figure 2. Conformation of 2-substituted oxanes **1** ($X = O$, $Y = CH_2$) and 1,3-dioxanes **2** ($X = Y = O$).

with Wolfe's computational results[10] that the magnitude of the anomeric effect is Cl > F > OH; however, these results do not agree with the conclusion of Jeffrey and Yates[11] that the sequence of anomeric energy for the anomeric substitution is F > OH > Cl > OCH_3. In the present case, the difference in the Gibbs energy between the equatorial and axial conformers ΔG_{eq-ax} has been shown to increase from $Z = OCH_3$ to F, Cl, and then to Br. This is contrary to the expectation from the orbital interaction considerations. The above result might, therefore, suggest that the negative charge of the halogen atom is built up around the axial proton. The size of the ion radius is Br > Cl > F.

Booth and Ouellette studied, by analyzing NMR spin-coupling constants, the conformational equilibrium of 2-halogenated oxanes (**1**, Z = Cl, Br).[22] They found that the preference for the axial orientation of the halogen group is so large that the equatorial conformer is hardly detected in the conformational equilibrium. The present result that ΔG_{eq-ax} of 2-halogenated **1** (2.47–3.08 kcal mol^{-1}) is compatible with their conclusion.

Eliel studied the acid-catalyzed equilibrium of substituted 2-oxanes and 1,3-dioxanes (Fig. 3).[23] In every case, the trans isomer, bearing the axial 2-alkoxy group, has been found to be more stable than the cis isomer (ΔG_{eq-ax} 0.35–0.83 kcal mol^{-1}). This compares with our calculated values, ΔG_{eq-ax} 1.25 kcal mol^{-1} for **1** and 1.94 kcal mol^{-1} for **2** ($R = CH_3$). Wiberg and Murcko reported 1.33 kcal mol^{-1} for ΔG_{eq-ax} of 2-methoxy oxane.[12] It is noted that ΔG_{eq-ax} is larger in 2-alkoxy-1,3-dioxanes (Y = O), as compared to those of 2-alkoxy-oxanes. The calculated geometry of one of the equatorial conformer of **2** ($Z = OCH_3$), eq-I: (ΔG_{eq-ax} 0.05 kcal mol^{-1}, O–C–O–CH_3 torsion angle 61.2°. See Fig. 4) shows that two C–H hydrogens in OCH_3 are in short contact (2.46 Å) with the ring oxygen atoms, thus making this conformation more stable than eq-II (ΔG_{eq-ax}1.94 kcal mol^{-1}).

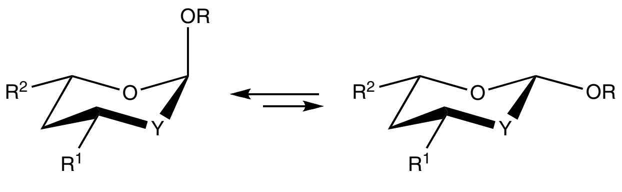


Figure 3. Equilibrium of 2-alkoxy oxanes ($Y = CH_2$) and 1,3-dioxanes (Y = O).

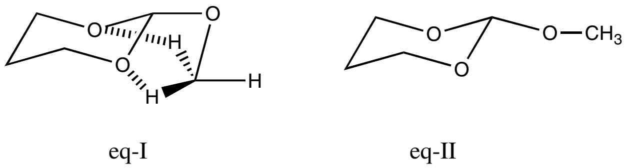


Figure 4. CH/O hydrogen bonds in an equatorial conformer (eq-I) of 2-methoxy-1,3-dioxane.

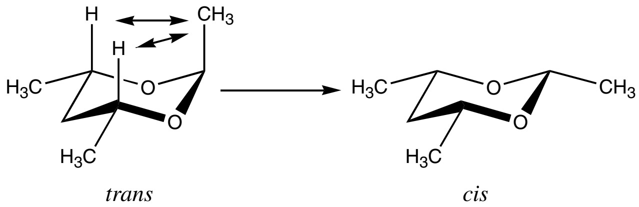


Figure 5. Equilibrium of 2,4,6-trimethyl-1,3-dioxane.

Eliel further reported that the trans isomer is very unstable in 2,4,6-trimethyl-1,3-dioxane ($\Delta G_{cis-trans}$ −3.55 kcal mol^{-1}).[24] This compares with the calculated value, −5.22 kcal mol^{-1} for 2-methyl-1,3-dioxane **2**. A severe unfavorable 1,3-diaxial interaction should occur in this case (Fig. 5).

To summarize, the present calculated results are consistent with the experimental data reported for 2-substituted oxanes and 1,3-dioxanes,[22–24] and provide a basis for the axial preference of the derivatives bearing an electron-withdrawing group.

3.2. Covalent bond lengths of the axial and equatorial conformers

Table 2 lists the bond lengths *d*X–C-2 and *d*C-2–Z calculated at the MP2/6-311++G(d,p) level of approximation. Bond lengths *d*C-6–X are also given for reference. In the last row of the table are included the calculated values by Momany et al. for glucose + $5H_2O$ by the DFT method.[25]

In every case, the endocyclic bond length *d*X–C-2 is shorter in the axial conformer than in the equatorial conformer. The inverse is true for the exocyclic bond length *d*C-2–Z. This is consistent with the accepted theory of the anomeric effect based on the orbital interaction.[5–14,17–19] Pinto and co-workers recently argued, by the NBO analysis,[17] that the anomeric and the exo-anomeric effect[10,5,26] are both important in understanding the orbital interaction.

The present data well compare with the calculated values by Momany et al. for the glucose pentahydrate, demonstrating that 2-methoxyoxane is a good model for the anomeric effect in carbohydrate chemistry. Difference in the bond-length shortening for X–C ($\Delta^{endo}d_{ax-eq} = d\text{X–C-2}_{ax} - d\text{X–C-2}_{eq}$) increases, in a constant manner, from $Z = CH_3O$ to F, Cl, and then

Table 2. Bond lengths $dC6–X$, $dX–C-2$, $dC-2–Z$, and differences (in Å) between the axial and equatorial conformers $\Delta d_{ax–eq}$ in 2-substituted oxanes **1** and 1,3-dioxanes **2**

	$dC-6–X_{ax}$	$dC-6–X_{eq}$	$dX–C-2_{ax}$	$dX–C-2_{eq}$	$\Delta^{endo}d_{ax–eq}$[a]	$dC-2–Z_{ax}$	$dC-2–Z_{eq}$	$\Delta^{exo}d_{ax–eq}$[b]
1								
CH_3O	1.430	1.422	1.414	1.420	−0.006	1.406	1.384	+0.022
F	1.434	1.434	1.385	1.398	−0.013	1.396	1.369	+0.027
Cl	1.433	1.428	1.384	1.404	−0.020	1.827	1.778	+0.049
Br	1.434	1.429	1.379	1.404	−0.025	2.012	1.946	+0.066
2								
CH_3O	1.432	1.425	1.384	1.389	−0.005	1.400	1.368	+0.032
F	1.434	1.428	1.376	1.386	−0.010	1.376	1.386	+0.047
Cl	1.433	1.430	1.373	1.391	−0.018	1.373	1.391	+0.090
Br	1.434	1.433	1.367	1.391	−0.024	1.367	1.391	+0.118
	$dC-5–O_{ax}$	$dC-5–O_{eq}$	$dO–C-1_{ax}$	$dO–C-1_{eq}$	$\Delta^{endo}d_{ax–eq}$	$dC-1–O_{ax}$	$dC-1–O_{eq}$	$\Delta^{exo}d_{ax–eq}$
Glucose[c]	1.434	1.429	1.415	1.425	−0.010	1.422	1.395	+0.028

[a] $dX–C-2_{ax} - dX–C-2_{eq}$.

[b] $dC-2–Z_{ax} - dC-2–Z_{eq}$.

[c] Bond lengths, calculated at the B3LYP/6-311++G**//B3LYP/6-31+G* level approximation, for glucose + $5H_2O$ (Ref. 25).

to Br. The corresponding value for C–Z bond length ($\Delta^{exo}d_{ax–eq} = dC\text{-}2–Z_{ax} - dC\text{-}2–Z_{eq}$) increases in the same order.

3.3. Consideration of the non-bond distance

Table 3 lists the non-bond distances H-4$_{ax}$/Z and H-6$_{ax}$/Z calculated for 2-substituted oxanes **1** and 1,3-dioxanes **2**. The data for substituted cyclohexanes, *cyclo*-$C_6H_{11}Z$ (**3**), are included for comparison (Fig. 6).

Table 3. Non-bond distances (in Å) between axial hydrogens and Z, calculated for 2-substituted oxanes **1**, and 1,3-dioxanes **2**, and cyclohexanes **3**[a]

	$dH-4_{ax}/Z$[b]	$dH-6_{ax}/Z$[c]	d_{vdW}[d]	$\Delta dH-4$[e]	$\Delta dH-6$[f]
Z = CH_3O					
1	2.63[g]	2.53[g]	2.72	−0.09	−0.19
2	2.54[g]	2.47[g]		−0.18	−0.25
3	2.65[g]	2.57[g]		−0.07	−0.15
Z = F					
1	2.64	2.49	2.67	−0.03	−0.18
2	2.50	2.50		−0.17	−0.17
3	2.62	2.62		−0.05	−0.05
Z = Cl					
1	2.89	2.75	2.95	−0.06	−0.20
2	2.76	2.76		−0.19	−0.19
3	2.88	2.88		−0.07	−0.07
Z = Br					
1	3.00	2.84	3.05	−0.06	−0.21
2	2.85	2.85		−0.20	−0.20
3	2.97	2.97		−0.08	−0.08

[a] $\Delta G_{eq–ax} = G_{eq} - G_{ax}$: −0.22 kcal mol^{-1} (Z = CH_3O), −0.18 (F); −0.49 (Cl), −0.69 (Br).

[b] Distance between H-4$_{ax}$ and Z (Å).

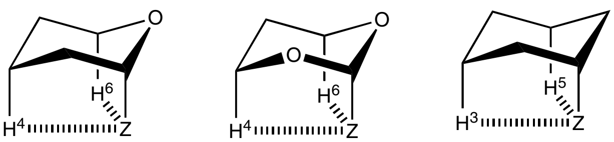
[c] Distance between H-6$_{ax}$ and Z (Å).

[d] Sum of the van der Waals radii of the relevant atoms (Å).[27]

[e] $dH-4_{ax}/Z-d_{vdW}$(Å); $dH-3_{ax}/Z - d_{vdW}$ (=$dH-5_{ax}/Z - d_{vdW}$) for **3**.

[f] $dH-6_{ax}/Z - d_{vdW}$ (Å).

[g] The methyl group in the O–CH_3 derivatives is dissymmetric.

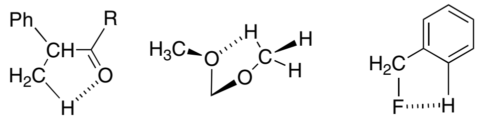


1 **2** **3**

Figure 6. Formation of a five-membered CH/*n* hydrogen bond is possible between axial hydrogens and Z in the axial conformers.

It is remarkable that in every case the interatomic distances are shorter than the sum of the van der Waals radii of the relevant atoms. In **1**, $dH-6_{ax}/Z$ is much shorter than $dH-4_{ax}/Z$; $|\Delta dH-6| > |\Delta dH-4|$, in other words. This is comprehensible since the C–O bond (1.38–1.43 Å, see Table 2) is shorter than the C–C bond (1.52–1.53 Å). Another plausible reason is that H-6 is more acidic than H-4. Consistent with the above observation, the absolute values for $\Delta dH-4$ are larger in **2** than in **1**. The values of ΔdH in **3** are comparable with $\Delta dH-4$ in **1**; this also is reasonable.

Notice that, in this molecular environment, a five-membered CH/*n* hydrogen bond is possible between the axial hydrogens and Z in the axial conformers. Importance of the CH/O[28] or CH/*n* hydrogen bond[29] in chemistry and biochemistry is well known. Importance of the five-membered intramolecular CH/*n* hydrogen bond has been demonstrated in various conformational issues in organic chemistry. A five-membered interaction in weak hydrogen bonds has been known to be effective in making a folded conformation of simple molecules. In Figure 7 are illustrated several examples: alkyl 1-phenylethylketones **4** (R = CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9),[30] dimethoxymethane **5**,[14,31] and benzyl fluoride **6**.[32] We suggest that the stabilizing CH/*n* hydrogen bond, which may occur between these hydrogens and Z, plays an important role in making these conformations favorable.



4 5 6

Figure 7. Conformation of simple organic molecules.

3.4. Database search

Next, we carried out a crystallographic database (CSD) search to see if the above short interatomic distances are found in the structure of carbohydrates. Table 4 summarizes the results obtained for methyl α-D-hexopyranosides. The calculated result for 2-methoxyoxane **1** is included for comparison. The result obtained by the CSD search is in good agreement with the calculated data for 2-methoxyoxane.

Table 5 summarizes the data retrieved from the CSD for 1-halogenated glycosides. The calculated values for 2-halogenated oxane **1** are included for comparison. The crystallographic data compare well with the calculated values, except for *d*H-3/Z in 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl fluoride (positive *d*H-3/F − d_{vdW}).[33] Inspection of the crystal structure of this compound (BIVTAR) has revealed that the interaction between molecules is the reason for this. Short F–H distances (2.621 and 2.648 Å) have in fact been disclosed between F and one of the methyl hydrogens in another molecule close to it.

To summarize, the five-membered CH/*n* (CH/O, CH/Z) hydrogen bond seems to play an important role in making the axial conformations of **1**–**3**, and pyranose glycosides stable, when the substituent Z is electron withdrawing.

3.5. NBO charges

In order to obtain support for this suggestion, we calculated the natural bonding orbital (NBO) charge of the atoms. Table 6 lists the NBO charges of atoms in 2-methoxyoxane (**1**, Z = OCH_3).

The NBO charge (average value of the both isomers) changes from ca. +0.54 to −0.37, −0.34, −0.36 and then to +0.05, respectively, for C-2 (α to Z), C-3 (β), C-4 (γ), C-5 (δ), and C-6 (γ). The positive value for C-6 is comprehensible since this is adjacent to the endocyclic oxygen. The above tendency is common to other compounds (data not shown) and seems reasonable in that the inductive effect decreases in this order, alternately, except for C-4, which is γ to Z. The NBO charges of the hydrogens are positive in every case. An interesting point is that the difference in the NBO charges between the axial and equatorial isomers (ΔNBO_{ax-eq}) are negative for C-4 and C-6 whereas it is positive for H-4_{ax} and H-6_{ax}. The value of ΔNBO_{ax-eq} is much larger in H-4_{ax} and H-6_{ax} than in the other hydrogens. In order to see whether this is a general phenomenon, we examined the relevant data for other compounds. Table 7 compares the difference in the NBO charges (ΔNBO_{ax-eq}),

Table 4. Results obtained by the CSD searches for methyl α-D-hexopyranosides

	*d*H-3/O	*d*H-5/O	d_{vdW}[a]	*d*H-3/O − d_{vdW}	*d*H-5/O − d_{vdW}
CSD[b]	2.645	2.533	2.72	−0.075	−0.187
	*d*H-4_{ax}/Z	*d*H-6_{ax}/Z		*d*H-4_{ax}/Z − d_{vdW}	*d*H-6_{ax}/Z − d_{vdW}
1, Z = OCH_3	2.626	2.526	2.72	−0.094	−0.194

[a] Sum of the van der Waals radii of H and O.

[b] Average values (Å) of 26 entries. CSD Refcode: FABYOW10, GAFTUC, HAHYEU, KAKPAO, KAPQAT, KAPQEX, KAPQIB, KAPQOH, KAPQUN, LIYRUG, MEMANP11, MGALPY, MGALPY01, MGLUCP11, MOGLPR, NUVTAZ, NUVTED, NUVTIH, OCEYAW, RAFHIQ, TEJHOF, WUXKUV, YODRUE, ZIZJEX, ZULPAX, ZULPEB.

Table 5. Distance data (in Å) retrieved from the CSD for halogenated glycosides

	Z	*d*H-3/Z	*d*H-5/Z	d_{vdW}[a]	*d*H-3/Z-d_{vdW}	*d*H-5/Z-d_{vdW}
BIVTAR01[b]	F	2.771	2.512	2.67	+0.101	−0.158
BIVTAR[c]	F	2.827	2.520		+0.157	−0.150
1	F	2.641	2.493		−0.029	−0.177
TBZMAC[d]	Cl	2.814	2.818	2.95	−0.136	−0.132
1	Cl	2.893	2.753		−0.057	−0.197
KATMEX[e]	Br	2.907	2.903	3.05	−0.143	−0.147
1	Br	2.995	2.843		−0.055	−0.207

[a] Sum of the van der Waals radii of the relevant atoms.

[b] 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl fluoride (295 K).

[c] 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl fluoride (115 K).

[d] 2,3,4,6-Tetra-*O*-benzoyl-2-chloro-α-D-mannopyranosyl chloride.

[e] 2,3,4,6-Tetra-*O*-acetyl-2-bromo-α-D-glucopyranosyl bromide.

Table 6. NBO charges in 2-methoxy oxane **1** ($Z = OCH_3$)

	ax-OCH_3	eq-OCH_3	ΔNBO_{ax-eq}
O-1	−0.67831	−0.68052	+0.00221
C-2	0.53634	0.54875	−0.01241
C-3	−0.36649	−0.36808	+0.00159
C-4	−0.33589	−0.33424	−0.00165
C-5	−0.35905	−0.35999	+0.00094
C-6	0.05164	0.05645	−0.00481
H-3$_{eq}$	0.18747	0.18509	+0.00238
H-3$_{ax}$	0.17367	0.18502	−0.01135
H-4$_{eq}$	0.17357	0.17936	−0.00579
H-4$_{ax}$	0.17921	0.16106	+0.01815
H-5$_{eq}$	0.17649	0.17583	+0.00066
H-5$_{ax}$	0.16765	0.17355	−0.00590
H-6$_{eq}$	0.15791	0.16245	−0.00454
H-6$_{ax}$	0.14181	0.12749	+0.01432
OCH_3	−0.67706	−0.65199	−0.02507

Table 7. Differences in the NBO charges between the axial and equatorial conformers of the relevant atoms, ΔNBO_{ax-eq}, in **1** and **2**

	H-4$_{ax}$	H-6$_{ax}$	C-4	C-6
1				
$Z = OCH_3$	+0.018	+0.014	−0.002	−0.005
F	+0.014	+0.020	−0.002	−0.002
Cl	+0.017	+0.022	−0.016	−0.001
Br	+0.019	+0.024	−0.001	−0.001
2				
$Z = OCH_3$	+0.023	+0.014	−0.002	−0.004
F	+0.019	+0.019	−0.001	−0.001
Cl	+0.022	+0.022	−0.006	−0.006
Br	+0.026	+0.026	−0.007	−0.007

in **1** and **2**, of the relevant atoms, H-4$_{ax}$, H-6$_{ax}$, C-4, and C-6.

The NBO charge is more positive in H-4$_{ax}$ and H-6$_{ax}$ and more negative in C-4 and C-6 for axial conformers than in the corresponding equatorial conformers, irrespective of the type of compound and the nature of the group Z. We think this to be a result of the through-space interaction of CH versus Z, namely the five-membered intramolecular CH/*n* hydrogen bond. This is possible only in the axial conformers.

3.6. ^{13}C NMR chemical shifts

We then examined whether the above NBO data are reflected in ^{13}C NMR chemical shifts. Table 8 lists the calculated ^{13}C NMR chemical shifts and the difference in the chemical shifts ($\Delta\delta = \delta_{ax} - \delta_{eq}$) for **1**. High-field ^{13}C chemical shifts have been calculated for C-4 and C-6, while such a remarkable effect has not been shown for the other carbons (data not shown). Notice that C-4 and C-6 are at position γ to Z. In view of this, we suggest that the well-known ^{13}C γ-effect[34] may find its origin in the CH/*n* hydrogen bond.

Table 8. Calculated ^{13}C NMR chemical shifts (in ppm) and the difference between the axial and equatorial conformers ($\Delta\delta = \delta_{ax} - \delta_{eq}$) for C-4 and C-6 in **1**

1	C-4$_{ax}$	C-4$_{eq}$	$\Delta\delta_{ax-eq}$(C-4)	C-6$_{ax}$	C-6$_{eq}$	$\Delta\delta_{ax-eq}$(C-6)
CH_3O	22.38	27.33	−4.95	63.55	71.02	−7.47
F	21.66	26.48	−4.82	65.46	71.16	−5.70
Cl	21.22	28.48	−7.26	64.81	74.01	−9.20
Br	21.77	29.35	−7.58	66.04	75.16	−9.11

3.7. Genesis of the axial preference

In view of the discussion raised as above, we suggest that the origin of the anomeric effect resides, at least in part, in the stabilization from the CH/*n* hydrogen bond occurring between the axial CHs and the electronegative atom Z at C-2. This mechanism is compatible with the NBO data that the charges in the atoms are more positive for the axial hydrogens and more negative for the γ carbons in the axial conformer, as compared to the corresponding values for the equatorial conformer, irrespective of the nature of the electronegative substituent. The short H$_{ax}$/Z interatomic distances can hardly be explained without invoking such an effect. Of note is that this mechanism is compatible with the effect of solvent; the anomeric effect has been known to decrease in polar solvents.[3,26] The nature of the CH/*n* interaction is largely electrostatic and therefore is amenable to the polarity of the solvent.

3.8. Explanation of the anomeric effect by the present hypothesis

The finding of Eliel that 2-alkoxy oxanes and 1,3-dioxanes are more stable in the axial OR conformation[23,24] may be explained in terms of the five-membered CH/O hydrogen bonds, as shown in Figure 8.

One of the impressive examples of the anomeric effect is found in chemistry of acetylated pyranosyl halides.[35] In the case of α anomers with the D-xylo and D-gluco configurations, the tendency for the $^4C_1$ conformation is so great that the alternate $^1C_4$ conformers are detected neither in solution nor in the crystal. Horton and co-workers studied the conformational equilibrium of various pyranose derivatives (α-xylose, α-lyxose, etc.)

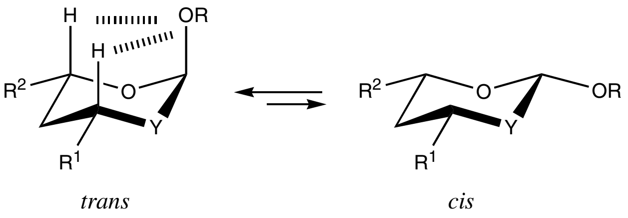


Figure 8. Explanation based on the five-membered CH/O hydrogen bonds for the axial preference of 2-alkoxy group in oxanes and 1,3-dioxanes.

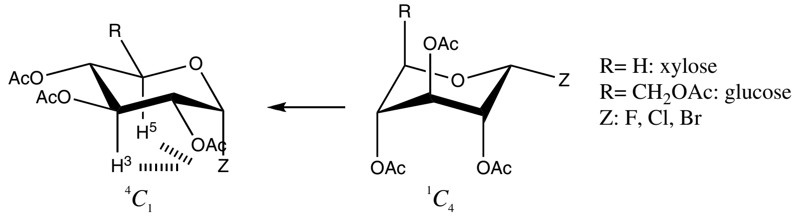


Figure 9. Explanation, in terms of the five-membered CH/O hydrogen bonds, for the axial preference of pyranosyl halides of α-anomers with the D-xylo and D-gluco configurations.

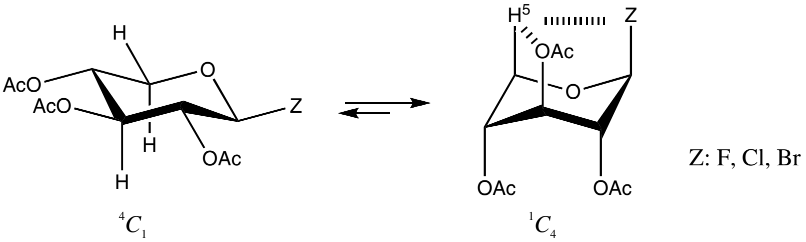


Figure 10. Explanation, in terms of the five-membered CH/O hydrogen bonds, for the axial preference of β anomers of xylosyl halides.

and reported that the preference of chlorine or bromine at C-1 for axial orientation is very large.[36] It seems the critical factor in the determination of conformational equilibrium. Our hypothesis is illustrated in Figure 9. Five-membered CH/Z hydrogen bonds (H-3 vs Z, H-5 vs Z) may occur only in the $^4C_1$ conformers.

Another noteworthy example of the anomeric effect is found in the β series of tri-*O*-acetyl-D-xylosyl halides (Fig. 10). Hall and Manville reported the axial preference for tri-*O*-acetyl-β-D-xylopyranosyl fluoride in solution.[37] With the bromide, every effort to synthesize the $^4C_1$ isomer has been reported unsuccessful. Our hypothesis is that this may be a consequence of the CH/*n* hydrogen bond. A bifurcated five-membered CH/*n* hydrogen bond, occurring between H-5 and Z and the C-3-acetoxy group, may stabilize the $^1C_4$ conformation. The present computational result ($\Delta G_{\text{eq-ax}} = 2.45$–$3.08\ \text{kcal mol}^{-1}$ for **1** and 3.42–$5.45\ \text{kcal mol}^{-1}$ for **2**) is consistent with the above findings.

4. Conclusions

High-level ab initio MO calculations have demonstrated that the Gibbs free energies of the axial conformers in 2-substituted oxanes and 1,3-dioxanes are smaller than those of the corresponding equatorial conformers, when the substituent Z is an electron-withdrawing group. The difference in Gibbs energy between the equatorial and axial conformers $\Delta G_{\text{eq-ax}}$ increases from Z = OCH$_3$ to F, Cl, and then to Br. The non-bonded distance between the 2-substituent and an axial C–H has been shown to be shorter than the van der Waals distance. Analysis of the NBO charge of the relevant protons and carbons has revealed an appreciable difference between the conformers: more positive for H and more negative for C in the axial conformer than in the corresponding equatorial conformer. We conclude that the CH/*n* hydrogen bond constitutes an important factor in stabilizing the axial conformations of cyclohexane derivatives, and by implication, glycosides. It remains to be explored, however, in what extent this factor is contributing to the anomeric effect, as compared to the orbital interaction. In any event, rethinking of the genesis of the anomeric effect is necessary.[38]

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References

1. Edward, J. T. *Chem. Ind. (London)* **1955**, 1102–1104.
2. Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527–548.
3. Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.
4. Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 39–97.
5. Wolfe, S.; Rauk, A.; Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B* **1971**, 136–145; Wolfe, S.; Shi, X. *Israel J. Chem.* **2000**, *40*, 343–355.

6. Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1972**, *25*, 117–131.
7. David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 3806–3807.
8. Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1974**, *38*, 81–95.
9. Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373–379.
10. Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979**, *69*, 1–26.
11. Jeffrey, G. A.; Yates, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 820–825.
12. Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821–4828.
13. Krol, M. C.; Huige, C. J. M.; Altona, C. *J. Comput. Chem.* **1990**, *11*, 765–790; Smith, G. D.; Jaffe, R. L.; Yoon, D. Y. *J. Phys. Chem.* **1994**, *98*, 9072–9077; Kneisler, J. R.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 757–766.
14. Favero, L. B.; Caminati, W.; Verino, B. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4776–4779.
15. Fuchs, B.; Schleifer, L.; Tartakovsky, E. *New J. Chem.* **1984**, *8*, 275–278; Schleifer, L.; Senderowitz, H.; Aped, P.; Tartakovsky, E.; Fuchs, B. *Carbohydr. Res.* **1990**, *206*, 21–39.
16. Allen, F. H. *Acta Crystallogr., Sect. A* **1998**, *54*, 758–771; Allen, F. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 380–388.
17. Trapp, M. L.; Watts, J. K.; Weinberg, N.; Pinto, B. M. *Can. J. Chem.* **2006**, *84*, 692–701.
18. Pinto, B. M.; Schlegel, H. B.; Wolfe, S. *Can. J. Chem.* **1987**, *65*, 1658–1662; Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051–1062.
19. Cramer, C. J. *J. Org. Chem.* **1992**, *57*, 7034–7043; Salzner, U.; von Raugé Schleyer, P. *J. Am. Chem. Soc.* **1993**, *115*, 10231–10236.
20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. GAUSSIAN *03, Revision C.02*; Gaussian: Wallingford CT, 2004.
21. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO (version 3.1).
22. Booth, G. E.; Ouellette, R. J. *J. Org. Chem.* **1966**, *31*, 544–546.
23. Eliel, E. L.; Giza, C. A. *J. Org. Chem.* **1968**, *33*, 3754–3758; Bailey, W. M.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798–1806.
24. Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444–3458.
25. Momany, F. A.; Appel, M.; Willett, J. L.; Bosma, W. B. *Carbohydr. Res.* **2005**, *340*, 1638–1655.
26. Praly, J.-P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213–223.
27. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
28. Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford Univ. Press: Oxford, 1999.
29. Nishio, M. Weak Hydrogen Bonds. In *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: New York, 2004; pp 1576–1585.
30. Zushi, S.; Kodama, Y.; Nishihata, K.; Umemura, K.; Nishio, M.; Uzawa, J.; Hirota, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3631–3640; Takahashi, O.; Yasunaga, K.; Gondoh, Y.; Kohno, Y.; Saito, K.; Nishio, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1777–1783; Takahashi, O.; Saito, K.; Kohno, Y.; Suezawa, H.; Ishihara, S.; Nishio, M. *New J. Chem.* **2004**, *28*, 355–360.
31. Yoshida, H.; Kaneko, I.; Matsuura, H.; Ogawa, Y.; Tasumi, M. *Chem. Phys. Lett.* **1992**, *196*, 601–606; Yoshida, H.; Tanaka, T.; Matsuura, H. *Chem. Lett.* **1996**, 637–638.
32. Penner, G. H.; Schaeffer, T.; Sebastian, R.; Wolfe, S. *Can. J. Chem.* **1987**, *65*, 1845–1852.
33. Luger, P.; Buschmann, J.; Schmidt, H.-J. *Acta Crystallogr., Sect. B* **1982**, *38*, 2732–2735.
34. Kroschwitz, J. I.; Winokur, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 5927–5928; Jackman, L. M.; Kelly, D. P. *J. Chem. Soc., B* **1970**, 102–110, 110–113; Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897–4901.
35. Lichtenthaler, F. W.; Rönninger, S.; Kreis, U. *Liebigs Ann. Chem.* **1990**, 1001–1006.
36. Horton, D.; Turner, W. M. *J. Org. Chem.* **1965**, *30*, 3387–3394; Durette, P. L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 57–80, and references cited therein.
37. Hall, L. D.; Manville, J. F. *Carbohydr. Res.* **1967**, *4*, 512–513.
38. Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715–722.