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

Osamu Takahashi,*, Katsuyoshi Yamasaki, Yuji Kohno, Kazuyoshi Ueda, Hiroko Suezawa, Motohiro Nishio

Department of Chemistry, Graduate School of Science, Hiroshima University, Kagamiyama, Higashi-Hiroshima-shi 739-8526, Japan
Department of Materials Science, Yokohama National University, Hodogaya-ku, Yokohama-shi 240-8501, Japan
Ministry of Education, Culture, Sports, Science, and Technology, Kasumigaseki, Chiyoda-ku, Tokyo 100-8959, Japan
The CHPI Institute, 705-6-338 Minamiyo, Machida-shi Tokyo 194-0031, Japan

Article info
Article history:
Received 26 August 2008
Received in revised form 8 April 2009
Accepted 13 April 2009
Available online 17 April 2009

Keywords:
Ab initio calculation
CH/n hydrogen bond
CH/π hydrogen bond
Gauche conformation
Nonbonded distance
NBO charge

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.

© 2009 Elsevier Ltd. All rights reserved.

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

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, methoxymethanol, dimethoxymethane, and methoxymethyl halides, and discussed the results on the basis of the n–σ* mechanism.
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. 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 atom X (Fig. 3).

It remains to be settled to what extent the dipolar, n–σ′, 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 CH3–O–CH2–X 1 (X = OH, OCH3, F, Cl, Br, CN, C6H5, and CHO). We present a hypothesis that the mechanism underlying the generalized anomeric effect involves contributions from the CH/n hydrogen bond (X = F, Cl, Br, CN, C6H5, and CHO). The CH/n 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 treatments.

2. Methods

The Gaussian 03 program was used. Electron correlation energies were calculated by applying the second-order Möller–Plesset (MP2) perturbation theory. The first geometry optimizations of the compounds CH3–O–CH2–X (X = OH, OCH3, F, Cl, Br, CN, C6H5, 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 code 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 (ΔG_{anti-gauche}) of CH3–O–CH2–X 1 (X = OH, OCH3, F, Cl, Br, CN, C6H5, 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 = CH3) are included for comparison.

In every case, except for X = CH3 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 methoxymaldehyde (X = CHO, ΔG_{anti-gauche} = −0.83 kcal mol⁻¹) is anomalous, but we think that this is a consequence of the unfavorable interaction between the aldehyde CH and the methoxy CH3 group in the gauche conformer (Fig. 4).

An interesting point is that the difference in the Gibbs energy between the anti- and gauche conformers ΔG_{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 bond is more complex than previously thought.
bond is different from that of the CH/n hydrogen bond. The energy of the CH/n hydrogen bond comes mostly from the dispersion force,\textsuperscript{29} while the Coulombic contribution is more important in the CH/n hydrogen bond.\textsuperscript{30}

3.2. Nonbonded distances

We thought that five-membered intramolecular CH/n and CH/\pi 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/n or CH/\pi hydrogen bond is possible between a CH hydrogen and X. The importance of the five-membered CH/\pi, CHF, CHCl, CHBr, OH/\pi, and CH/\pi hydrogen bonds\textsuperscript{38–40} in conformational issues of organic molecules is well known.\textsuperscript{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 \( \tau \) defined by atomic sequence H–C\textsubscript{1}–C\textsubscript{2}–X and bond angles \( \theta \ (\angle \text{OC}X \text{X}) \) are also given. The interatomic distance, \( d \), has been shown in every gauche conformer to be shorter than the sum of the van der Waals (vdW) radii of the relevant atoms.\textsuperscript{1}

Table 2 shows that \( \Delta d \) is larger when X is a group bearing \( \pi \)-electrons (C\textsubscript{2}N, C\textsubscript{6}H\textsubscript{5}, and CHO). This may imply the importance of the contribution from dispersion force in the CH/n 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 CH\textsubscript{3} (average value)\textsuperscript{1} 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 \( d \) 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\( \text{Å} \),\textsuperscript{44,45} 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.\textsuperscript{1}

With respect to the C–X bond length (Table 5), however, \( d \) 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 (\( d \text{gauche} \)) is longer, in every case, than that of the anti conformer (\( d \text{anti} \)).

\[ \Delta d = d \text{gauche} - d \text{anti} \]

\textsuperscript{1} 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 by Rowland and Taylor 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.

\textsuperscript{2} 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.

\textsuperscript{3} In calculating the C–O bond length in various conformers of methanediol (RHF/4-31G), Jeffrey et al. used 1.437 \( \text{Å} \) for the standard value (Ref. 11).

\textsuperscript{4} Difference in the NBO charges of X 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: \( \sigma \text{C}X \rightarrow \sigma \text{C}X^* \rightarrow \sigma \text{C}X \rightarrow \sigma \text{C}X^* \) ) 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: \( n \rightarrow \sigma \text{C}X^* \rightarrow \sigma \text{C}X \rightarrow \sigma \text{C}X^* \)).
Table 4
Bond lengths d0–C–C(1) (d1) and differences between d1 and the standard O–C length Δd1, calculated at the MP2/6-311++G(3df,3pd) level

<table>
<thead>
<tr>
<th>X</th>
<th>O–Cstd</th>
<th>d0–C–C1</th>
<th>d0–C–C1</th>
<th>Δd1</th>
<th>ΔΔd1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>1.47</td>
<td>1.398</td>
<td>1.407</td>
<td>0.072</td>
<td>0.063</td>
</tr>
<tr>
<td>OCH3</td>
<td>1.47</td>
<td>1.382</td>
<td>1.381</td>
<td>0.088</td>
<td>0.089</td>
</tr>
<tr>
<td>F</td>
<td>1.47</td>
<td>1.372</td>
<td>1.388</td>
<td>0.098</td>
<td>0.082</td>
</tr>
<tr>
<td>Cl</td>
<td>1.47</td>
<td>1.373</td>
<td>1.394</td>
<td>0.097</td>
<td>0.076</td>
</tr>
<tr>
<td>Br</td>
<td>1.47</td>
<td>1.369</td>
<td>1.393</td>
<td>0.101</td>
<td>0.077</td>
</tr>
<tr>
<td>CN</td>
<td>1.47</td>
<td>1.402</td>
<td>1.406</td>
<td>0.068</td>
<td>0.064</td>
</tr>
<tr>
<td>CCH</td>
<td>1.47</td>
<td>1.411</td>
<td>1.413</td>
<td>0.059</td>
<td>0.057</td>
</tr>
<tr>
<td>C2H5</td>
<td>1.47</td>
<td>1.414</td>
<td>1.414</td>
<td>0.056</td>
<td>0.056</td>
</tr>
<tr>
<td>CHO</td>
<td>1.47</td>
<td>1.408</td>
<td>1.404</td>
<td>0.062</td>
<td>0.066</td>
</tr>
</tbody>
</table>

a Standard O–C bond length (in Å, Ref. 44).

Table 5
Bond lengths dC2–X (d2) and differences between d2 and the standard C–X length Δd2, calculated at the MP2/6-311++G(3df,3pd) level

<table>
<thead>
<tr>
<th>X</th>
<th>C–Xstd</th>
<th>dC2–Xgauche</th>
<th>dC2–Xanti</th>
<th>ΔΔd2</th>
<th>ΔΔd2</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>1.47</td>
<td>1.406</td>
<td>1.388</td>
<td>0.064</td>
<td>0.062</td>
</tr>
<tr>
<td>OCH3</td>
<td>1.47</td>
<td>1.406</td>
<td>1.408</td>
<td>0.064</td>
<td>0.062</td>
</tr>
<tr>
<td>F</td>
<td>1.45</td>
<td>1.386</td>
<td>1.361</td>
<td>0.064</td>
<td>0.089</td>
</tr>
<tr>
<td>Cl</td>
<td>1.76</td>
<td>1.812</td>
<td>1.767</td>
<td>–0.052</td>
<td>–0.007</td>
</tr>
<tr>
<td>Br</td>
<td>1.91</td>
<td>1.589</td>
<td>1.931</td>
<td>–0.079</td>
<td>–0.021</td>
</tr>
<tr>
<td>CN</td>
<td>1.54</td>
<td>1.481</td>
<td>1.469</td>
<td>0.059</td>
<td>0.071</td>
</tr>
<tr>
<td>CCH</td>
<td>1.54</td>
<td>1.474</td>
<td>1.464</td>
<td>0.066</td>
<td>0.076</td>
</tr>
<tr>
<td>C2H5</td>
<td>1.54</td>
<td>1.514</td>
<td>1.506</td>
<td>0.026</td>
<td>0.034</td>
</tr>
<tr>
<td>CHO</td>
<td>1.54</td>
<td>1.522</td>
<td>1.517</td>
<td>0.018</td>
<td>0.023</td>
</tr>
</tbody>
</table>

a Standard C–X bond length (Ref. 44).
b dC2–X bond length in the gauche conformer.
c dC2–X bond length in the anti conformer.
d C–Xstd = dC2–Xgauche.
e C–Xstd = dC2–Xanti.

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 (ΔEAP + ΔELLP) agrees with that of the ab initio MO calculation (ΔE1 total energy) only when X = F, the most electronegative group in the series. For X = 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 ΔE1 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 CH3OCH2X (X = OH, OCH3, F, Cl, Br, CN, C6H5, and CHO). In every case except for X = 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/n and CH/n 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-δ+ and dipole mechanism.45 In any event, reconsideration of the theory of the anomeric effect is required, as argued by Perrin and his coworkers.4,45

Acknowledgments

The authors thank the Information Media Center at Hiroshima University for the use of a grid with high-performance PCs, and