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Conformational Preferences of the O–C–C–C Unit in Acyclic and Cyclic Systems. The Exo-Deoxoanomeric Effect and Related Phenomena

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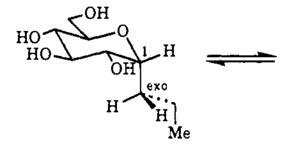
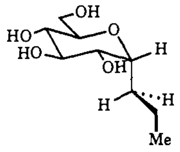
Abstract: The origin of the observation by Kishi et al. that C-glycosides have a gauche O–C_1–C_{exo}–C torsional arrangement was investigated by ab initio quantum mechanics. In propanol, 2-butanol, 2-ethyltetrahydropyran, and 2-ethyl-3-hydroxytetrahydropyran models for C-glycosides, the gauche O–C–C–C conformation is lower in energy than the anti. By contrast, in 3-methyltetrahydropyran and 5-methyl-1,3-dioxane, the equatorial forms (anti O–C–C–C) are more stable than the axial forms (gauche O–C–C–C). These apparently conflicting preferences are rationalized on the basis of electrostatic and steric arguments. The gauche O_1–C_2–C_3–C_4 preference of 0.3 kcal/mol in simple systems becomes an anti preference when C_2 and C_3 are part of a ring or when C_3 is alkyl substituted. The hypothesis was tested by developing bond dipole parameters for MM2; these parameters mimic experimental differences. A simple torsional parameter was developed and was also used in MM2 to predict the conformations of a series of acyclic alcohols. The results compare favorably with the experimental values derived from ^{13}C NMR spectra.

Introduction

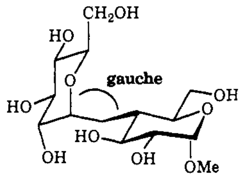
Kishi and co-workers have reported experimental studies of the conformations of C-glycosides such as **1A** and **1B**[1,2] and, more recently, 1,4-linked carbon disaccharides such as **2**, as well as carbon trisaccharides.[3] They discovered that these compounds exist in a gauche O–C_1–C_{exo}–C arrangement, **1A**, rather than the anti arrangement, **1B**.[1,2]



1A

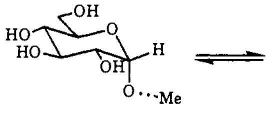


1B

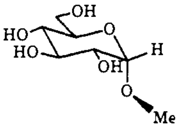


2

This is the same conformational preference displayed by glycosides such as **3**,[4] which exhibit the "exo-anomeric" effect.[5] This results in a gauche O–C–O–C dihedral angle, as in **3A**, rather than an anti angle, as in **3B**. This effect is on the order of 4 kcal/mol in glycosides.[6]



3A



3B

The observation of essentially only conformers such as **1A** in C-glycosides is puzzling. It implies that, even in the absence of the exocyclic oxygen, there is an effect which effectively locks the O–C_1–C_{exo}–C conformation into a gauche arrangement. Literature precedent suggests that **1A** should be only 0.4 kcal/mol more stable than **1B**,[7] a quantity too small to explain the large experimental preference for the exocyclic conformation. MM2 calculations on systems of this type predict a very slight preference for the exocyclic gauche conformer, again in disagreement with experimental results.

In this article we report a theoretical study of the origin of the effect—we call it the exo-deoxoanomeric effect—that causes C-glycosides to favor the same conformation as glycosides. We have also studied the conformers of a variety of acyclic and cyclic molecules containing the O–C–C–C group, and we report some differences between conformational preferences in acyclic and cyclic systems. We propose that both static and induced electrostatic effects, along with steric effects, explain these conformational preferences.

Background

The structural unit O–C–C–C is widely found in organic compounds. Traditionally, the conformational preference of this unit has been derived from cyclic systems as summarized in Figure 1. The axial conformation of methylcyclohexane (**4**) is less stable

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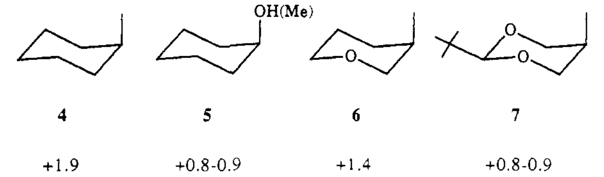

Figure 1. Axial conformers of methylcyclohexane,[8] hydroxy- and methoxycyclohexane,[9] 3-methyltetrahydropyran,[10] and 5-methyl-1,3-dioxane[11] and energies relative to the corresponding equatorial conformer. The results imply that a gauche C–C–C–C unit is +0.8–1 kcal/mol above an anti and a gauche O–C–C–C unit is +0.4–0.5 kcal/mol above an anti.

than its equatorial conformation by 1.9 kcal/mol in the gas phase.[8] This is the *A* value of a methyl group. Cyclohexanol and methoxycyclohexane (**5**) favor the equatorial conformations by 0.9 and 0.8 kcal/mol, respectively.[9] In these molecules the favored equatorial conformers have two anti O–C–C–C arrangements. The axial conformers, with two gauche O–C–C–C arrangements, are higher in energy. This indicates that a gauche O–C–C–C arrangement is about 0.4 kcal/mol above the anti in energy.

The equatorial conformations of 3-methyltetrahydropyran (**6**) and 5-methyl-1,3-dioxane (**7**) are more stable than their axial counterparts by 1.4 and 0.8–0.9 kcal/mol, respectively.[10,11] Since the equatorial and axial conformers of 5-methyl-1,3-dioxane differ by two O–C–C–C gauche to anti conversions, these results imply that a gauche O–C–C–C conformer is 0.4–0.5 kcal/mol higher in energy than an anti conformer. The conformational energies of **6** are consistent with this.

Therefore, it is often considered that each gauche C–C–C–C unit is destabilizing by about 0.8–1 kcal/mol and each gauche O–C–C–C unit is destabilizing by about 0.4–0.5 kcal/mol, primarily due to steric reasons. These conformational features have been used widely in conformational analysis.[7] The current MM2 and MM3 programs have been parameterized in such a way as to give 0.8 and 0.3 kcal/mol preferences for the anti conformations of butane and propanol, respectively, and reproduce the conformational preferences of **4**–**7** very well.[12]

The anti preference of the C–C–C–C unit is established both by experiments and ab initio calculations.[13,14] The conformational preference of the O–C–C–C unit has been studied widely in the case of propanol, and there is general agreement that the gauche conformation is favored.[15] Early electron diffraction work by Aziz and Rogowski only identified the trans form of propanol.[15a] Since then the gauche form has been determined to be the most stable. Most recently, Lotta et al. used IR and ab initio calculations to study the conformations in Ar, Kr, Xe, and N_2 matrices and found the gauche conformation to be favored.[15b] Krueger and Mettee[15c] and Shrindar and Chalakkal[15d] studied the IR spectra in dilute CCl_4 and determined the gauche conformation to be slightly favored. Richter and Schiel[15e] and Barnes and Whittle[15f] determined that there are three possible conformations of propanol. In microwave studies, Abdurakhmanov et al.[15g,h] and Driezler and Scappini[15i] have determined the gas-phase rotational barrier to be around 3 kcal/mol.

Table I. Total and Relative Energies for the Gauche O–C–C–Me, **8A**, and Anti O–C–C–Me, **8B**, Conformations of 2-Butanol[a]

conformation	3-21G	6-31G*	MP2/6-31G*[b]
gauche	−230.868 94	−232.150 09	−232.877 56
O–C–C–Me	(0.0)	(0.0)	(0.0)
anti	−230.867 11	−232.148 77	−232.876 19
O–C–C–Me	(1.15)	(0.83)	(0.86)

[a] Total energies are given in atomic units, and relative energies (in parentheses) are given in kilocalories/mole. [b] Single-point calculations on 6-31G* geometries.

Calculations by Wiberg et al. on methyl propyl ether predict that the gauche O–C–C–C conformation is more stable than the anti by 0.3–0.4 kcal/mol.[16] Kishi's observation of the exo-deoxoanomeric effect also challenges the correctness of the anti preference of the O–C–C–C unit deduced from **4**–**7**. Kishi's results can be rationalized only if the O–C–C–C unit has a significant gauche preference, at least in C-glycosides.

Two questions are raised by these observations: (1) What is the origin of the gauche preference of the O–C–C–C unit in C-glycosides and simpler analogs such as methyl propyl ether? (2) Why does the conformational preference of the O–C–C–C unit change to favor the anti conformation in cyclic systems? This research has led to resolution of both of these questions.

Computational Methods

Energies and structures were obtained using restricted Hartree–Fock theory with the 3-21G, 6-31G*, and 6-31+G* basis sets. Ab initio molecular orbital calculations were performed with the GAUSSIAN 88 program.[17] Electron correlation energy corrections were made using second-order Møller–Plesset theory.[18] Because systems of many different sizes were studied, a variety of different levels was used. The general approach was to increase the basis set size or the extent of correlation energy correction until the energy differences between conformers did not change. When the systems were too large, an attempt was made to carry out the calculations at a level which could be compared with higher level calculations on analogous systems.

Results and Discussion

(1) 2-Butanol, 2-Ethyltetrahydropyran, and 2-Ethyl-3-hydroxytetrahydropyran. We first investigated a very simple model for C-glycosides, 2-butanol. This molecule has the relevant O–C–C–Me and C–C–C–Me torsional angles that are present in C-glycosides. Calculations were performed on two conformers, **8A** and **8B**, representing the O–C–C–C gauche and anti conformations of the C-glycosides, respectively. Full geometry optimizations were performed with the 3-21G and 6-31G* basis sets, and energies were evaluated with MP2/6-31G* single-point calculations on the 6-31G* geometries. The results are presented in Table I.

Calculations indicate that **8A** is 0.8–0.9 kcal/mol more stable than **8B**. The 3-21G basis set results exaggerate the energy

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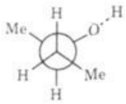
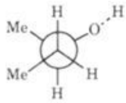


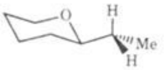
8A



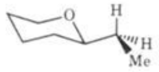
8B

difference. Conformer **8A** should be 0.8 kcal/mol more stable than **8B** because of the 0.8 kcal/mol preference for anti methyls alone. Thus, the gauche and anti O–C–C–C arrangements have about the same energy according to this result.

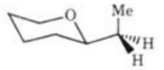
2-Ethyltetrahydropyran is a more complete model of a C-glycoside. Calculations were performed on the three rotamers of both the equatorial and axial conformers. In **9A** and **10A**, the methyl is gauche to the oxygen, in **9B** and **10B** the methyl is anti, and in **9C** and **10C**, the methyl is inside or over the ring. Full optimizations were done at the 3-21G level, and 6-31G* single-point energy calculations were performed on these geometries. The results are presented in Table II, and the optimized structures are shown in Figures 2 and 3.



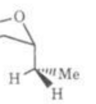
9A



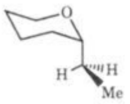
9B



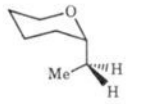
9C



10A



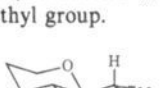
10B



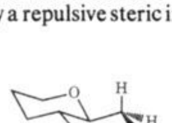
10C

The calculations show at least a 3 kcal/mol preference for the equatorial conformations (**9**) over the axial conformations (**10**). This very large energy difference is consistent with the findings of Eliel for the conformational energies of 2-alkyltetrahydropyrans and 2-alkyl-1,3-dioxanes.[10,11] For both ring conformations, the rotamer with O–C–C–Me gauche and C–C–C–Me anti (**9A** and **10A**) is calculated to be the most stable by at least 0.7 kcal/mol over the other rotamers. Earlier semi-empirical calculations by Tvaroska[19] indicated that rotamers **9A** and **9B** were close in energy while **9C** was slightly less stable. For the axial conformer, he calculated **10A** and **10B** to be close in energy, with **10C** considerably higher in energy.

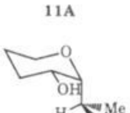
Calculations were also performed on 2-ethyl-3-hydroxytetrahydropyran to test the effects of a hydroxy group at position 3 (Table II). These calculations show a 3.3–3.6 kcal/mol preference for the equatorial conformations (**11**) over the axial conformations (**12**). For the equatorial and axial conformations, the gauche O–C–C–Me conformers (**11A** and **12A**) are more stable by 2.2 and 1.8 kcal/mol, respectively, than the anti O–C–C–Me conformers (**11B** and **12B**). The difference between the gauche and anti conformers is larger for **11** and **12** than it was for **9** and **10**. This larger energy difference indicates that the hydroxy group has a destabilizing effect on the anti O–C–C–Me conformers (**11B** and **12B**), caused by a repulsive steric interaction with the ethyl group.



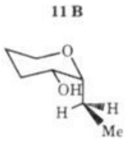
11A



11B



12A



12B

These calculations on C-glycoside models indicate a gauche preference for the O–C–C–C unit, the magnitude of which is dependent on other substituents on the ring such as the hydroxy group. Kishi's work on C-glycosides proves that this gauche preference is very significant.[1] From the ^{1}H NMR spectra of compounds **1** and **13**, Kishi determined the spin–spin coupling constants between a proton at C_1 and the diastereotopic protons at C_1':$J_{1,X}$ and $J_{1,Y}$. Using the monodeuterated C-glycoside **13**, Kishi specifically assigned the spin–spin couplings and determined the preferred conformation to be gauche. Determination of the coupling constants at different temperatures allows the estimation of the magnitude of the preference for the gauche O–C–C–C conformation over the anti O–C–C–C conformation.

Table II. Total and Relative Energies for Six Conformations of 2-Ethyltetrahydropyran and Four Conformations of 2-Ethyl-3-hydroxytetrahydropyran[a]

conformation	3-21G	6-31G*//3-21G
2-ethyltetrahydropyran		
eq gauche (**9A**)	–346.171 43 (0.0)	–348.089 78 (0.0)
equ anti (**9B**)	–346.169 67 (1.1)	–348.088 74 (0.7)
eq inside ring (**9C**)	–346.169 99 (0.9)	–348.087 78 (1.2)
ax. gauche (**10A**)	–346.167 68 (2.4)	–348.084 57 (3.3)
ax. anti (**10B**)	–346.165 69 (3.6)	–348.083 29 (4.1)
ax. over ring (**10C**)	–346.157 77 (8.6)	–348.076 71 (8.2)
2-ethyl-3-hydroxytetrahydropyran		
eq gauche (**11A**)	–420.608 74 (0.0)	–422.939 70 (0.0)
eq anti (**11B**)	–420.606 25 (1.6)	–422.936 25 (2.2)
ax. gauche (**12A**)	–420.604 83 (2.4)	–422.934 01 (3.6)
ax. anti (**12B**)	–420.602 35 (4.0)	–422.931 06 (5.4)

[a] Total energies are in atomic units, and relative energies (in parentheses) are given in kilocalories/mole.

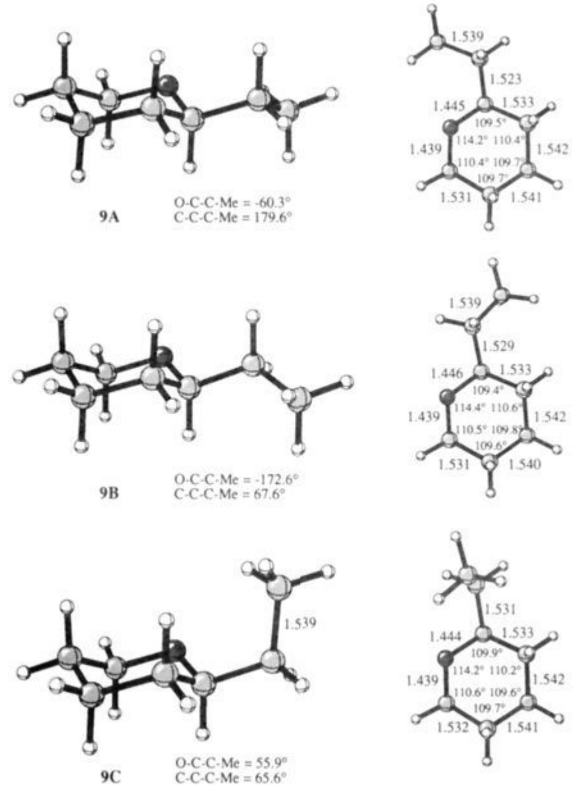


Figure 2. Side and top views of the 3-21G optimized structures of **9A**–**9C**.

The spin–spin coupling constants for **1** are as follows: $J_{1,X}$ and $J_{1,Y}$ are equal to 3.2 and 11.4 Hz, respectively, at 24 °C and 2.6 and 12.0 Hz at –33 °C. For **13**, the spin–spin coupling constant $J_{1,Y}$ is equal to 11.6 Hz at 24 °C, establishing that the preferred conformer has the O–C–C–C unit gauche. Application of the Karplus equation indicates that the preferred O–C–C–C torsional angle is about 55° for **1**.[1] Assuming that 2.6 and 12.0 Hz observed at –33 °C are the J values of the pure gauche conformer, we can

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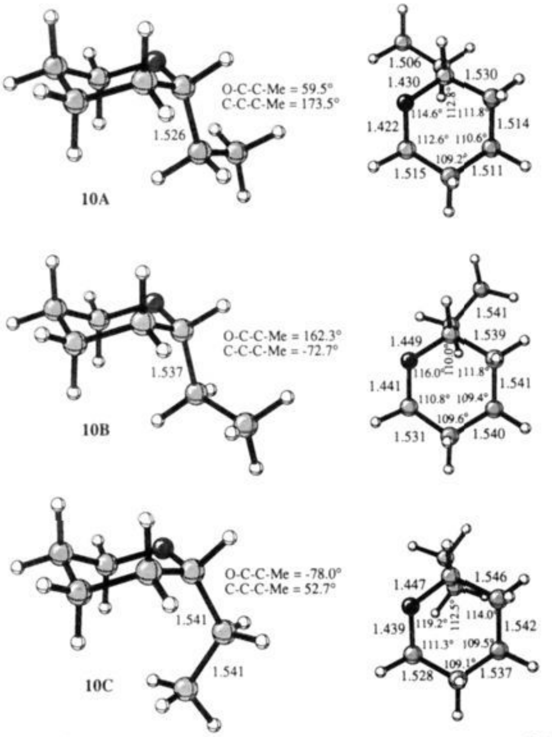
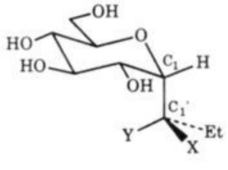


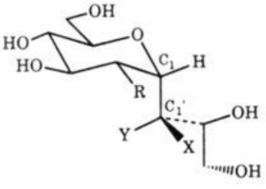
Figure 3. Side and top views of the 3-21G optimized structures of **10A**–**10C**.



1: X = Y = H
13: X = D, Y = H

estimate that the ratio of gauche to anti isomers is about 93:7 at 24 °C. This implies that **1A** (gauche O–C–C–C) is 1.6 kcal more stable than **1B** (anti O–C–C–C) at this temperature. Similar estimates for other compounds (axial and equatorial) give preferences of 1–2 kcal/mol.

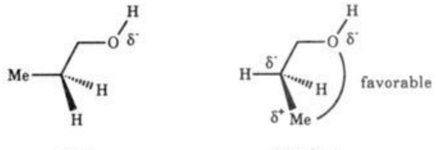
Kishi also investigated systems without the C_2 hydroxy, **14** and **15**, to determine whether this group has any effect. Experimentally, these molecules do show a preference for gauche O–C–C–C, but it appears to be slightly less than that of **1**. The spin–spin coupling constants for **14** are as follows: $J_{1,X}$ and $J_{1,Y}$ are equal to 3.5 and 11.2 Hz, respectively, at 24 °C. For **15**, $J_{1,Y}$ is equal to 11.3 Hz. The gauche preference of **14** is estimated to be a few tenths of a kcal/mol less than that of **1**.



14: X = Y = R = H
15: X = D, Y = R = H

In summary, the calculations on 2-ethyl-3-hydroxytetrahydropyran (**11** and **12**) show a significant preference for gauche O–C–C–C over anti O–C–C–C. This is in close agreement with Kishi's experimental results on the more thoroughly studied C-glycoside, **1**. The gauche O–C–C–C conformer is favored by 1–2 kcal/mol. However, our calculations on 2-ethyltetrahydropyran (**9** and **10**) indicate that, without the hydroxy substituent, the preference is only on the order of 1 kcal/mol. Experimentally, this gauche preference appears to be larger (**14**). The quantitative reconciliation of experiment and theory will require further investigations.

(2) Propanol, 2-Methyl-1-propanol, Propyl Fluoride, and Isobutyl Fluoride. To explore the factors which influence the conformational preference of the O–C–C–C unit, the gauche and anti conformations of propanol and the gauche/gauche and gauche/anti conformations of 2-methyl-1-propanol (Figure 4) have been optimized. The results are summarized in Tables III and IV. The gauche conformer of propanol, which has a O–C–C–C dihedral angle of 63°, is more stable than the anti conformer by 0.3 kcal/mol (MP2/6-31+G*). The results are quite sensitive to the type of calculation, although all predict the gauche to be essentially identical in energy or more stable than the anti conformer. This is in agreement with Wiberg's results for methyl propyl ether.[16] The gauche preference of propanol is caused by electrostatic and polarization interactions between the methyl group and oxygen. Since O is electronegative, the C_2–C_3 bond in the gauche conformer is polarized, as shown by charge distributions[20] in Figure 4. The oxygen causes the methyl group to become more positive in the gauche conformer compared to the anti, and at the same time the methylene group becomes more negative. This results in a stabilizing electrostatic (or dipole–induced dipole) interaction. In fact, it is the hydrogen of the methyl nearest the oxygen which becomes most positive, and the other methyl hydrogens become slightly negative. This induced electrostatic interaction is absent in the anti conformer. The gauche conformer is destabilized by steric interactions to some extent, but the induced electrostatic stabilization is larger. This explanation is the same as that given for the syn conformational preference of propanal proposed by Wiberg.[21] We have also invoked this effect to explain the conformations of the intermediates favored in the metal reduction of propanal.[22]



anti **gauche**

In nonpolar systems, the magnitude of the gauche versus anti preference for a single interaction is additive and can easily be used to determine the effects of multiple interactions. For example, the gauche/gauche conformer of 2-methylbutane is less stable than the gauche/anti conformation by 0.8 kcal/mol, which is the same as the anti preference of butane.[14] If the O–C–C–C gauche preferences were additive, then the gauche/gauche (G/G) conformation of 2-methyl-1-propanol would be 0.3 kcal/mol more stable than the gauche/anti (G/A) conformer. However, calculations indicate that the G/G conformer of 2-methyl-1-propanol is less stable than the G/A conformer by 0.2 kcal/mol (Figure 4). In the G/G conformer there are two induced dipoles; each methyl is at the positive end of an induced dipole. Only one induced dipole exists in the G/A conformer. The two induced geminal C–C dipoles in the G/G conformer interact in a destabilizing fashion. This cancels the stabilizing electrostatic interactions to some extent. There is no such repulsion in the G/A conformer. Thus, the repulsive steric interactions dominate in the G/G conformer and cause it to be less stable than the G/A conformer.

We have also calculated conformations of propyl fluoride and isobutyl fluoride. As shown in Figure 4, the gauche and gauche/

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(21) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

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Table III. Total Energies (au) for 1-Propanol, 2-Methyl-1-propanol, 3-Methyltetrahydropyran, and 5-Methyl-1,3-dioxane

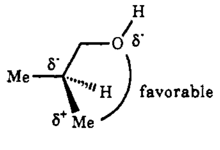
system	3-21G	6-31G*	6-31+G* [a]	MP2/6-31+G* [a]
propanol, anti	−192.042 70	−193.110 50	−193.116 58	−193.695 17
propanol, gauche	−192.043 71	−193.110 67	−193.116 47	−193.695 67
2-methyl-1-propanol, G/A	−230.865 69	−232.145 88	−232.152 02	−232.865 64
2-methyl-1-propanol, G/G	−230.866 04	−232.145 58	−232.151 44	−232.865 31
3-methyltetrahydropyran, eq	−307.347 69	−309.053 86	−309.059 21	−310.028 06
3-methyltetrahydropyran, ax.	−307.346 59	−309.051 57	−309.056 50	−310.025 98
dioxane, eq	−342.963 57	−344.870 83	−344.878 74	−345.890 50
dioxane, ax.	−342.964 29	−344.869 85	−344.877 00	−345.889 73

[a] Energies calculated on 6-31G* geometries.

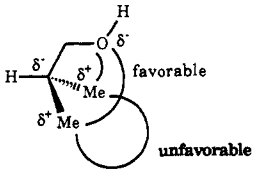
Table IV. Ab Initio and MM2 Relative Energies (kcal/mol) for 1-Propanol, 2-Methyl-1-propanol, 3-Methyltetrahydropyran, and 5-Methyl-1,3-dioxane

	1-propanol		2-methyl-1-propanol		3-methyltetrahydropyran		5-methyl-1,3-dioxane	
	anti	gauche	G/A	G/G	eq (**16A**)	ax. (**16B**)	eq	ax.
3-21G	0.0	−0.63	0.0	−0.22	0.0	0.69	0.0	−0.46
6-31G*	0.0	−0.11	0.0	0.19	0.0	1.44	0.0	0.62
6-31+G* [a]	0.0	0.07	0.0	0.36	0.0	1.70	0.0	1.09
MP2/6-31+G* [a]	0.0	−0.31	0.0	0.21	0.0	1.30	0.0	0.48
I (original MM2)	0.0	0.35	0.0	0.31	0.0	1.27	0.0	0.71
II[b]	0.0	0.19	0.0	0.16	0.0	1.12	0.0	0.40
III[c]	0.0	−0.31	0.0	0.13	0.0	1.15	0.0	0.78
IV[d]	0.0	−0.31	0.0	−0.15	0.0	0.73	0.0	−0.11

[a] Energies calculated on 6-31G* geometries. [b] The C–C–C–O torsional parameter is [0.0, 0.0, 0.18]. [c] The torsional parameter is used, the C–O dipole is set to 2.0 D, and each C–C bond gauche to a C–O bond has a bond dipole of 0.25 D. [d] The torsional parameter is used, and the C–O dipole is set to 2.0 D.



G/A



G/G

anti conformers are favored by 0.4 and 0.2 kcal/mol, respectively, over the anti and gauche/gauche conformers. A partial positive charge is induced on the methyl group when it is gauche to the electron-rich fluorine. In the G/G conformation, the two positively charged methyls repel each other. Although the individual charges are small, the methyls are very close, and there is no net favorable electrostatic interaction.

MM2 calculations with various altered dipoles were carried out to test the model of electrostatic effects on the conformational preference. These parameters are not intended to be used generally, but are tried out to test the induced dipole hypothesis. Table IV shows the results. Four sets of calculations were performed on propanol and 2-methyl-1-propanol. With the original MM2 parameters (I), the gauche conformer of propanol is less stable than the anti by 0.35 kcal/mol, which is in disagreement with the ab initio calculations. With the same parameters, the G/G conformer of 2-methyl-1-propanol is calculated to be less stable than the G/A conformer by 0.31 kcal/mol, which is in line with the ab initio calculations. For the second set of calculations, a torsional parameter of (V_1 = 0.0, V_2 = 0.0, V_3 = 0.18) for the dihedral angle C_3–C_2–C_1–O was used. In the third set of calculations, the C_1–O bond was assigned a dipole of 2.0 D, each C_3–C_2 bond gauche to the C_1–O bond was given a bond dipole of 0.25 D, and the revised C–C–C–O torsional parameters were used. This set of parameters gives a 0.31 kcal/mol preference for the gauche conformer of propanol and a 0.13 kcal/mol preference for the G/A conformer of 2-methyl-1-propanol, in good agreement with the ab initio relative energies. The fourth set of calculations involved the same parameters as the third set of calculations, but the geminal dipole–dipole interactions are excluded. This results in a 0.15 kcal/mol preference for the G/G conformer of 2-methyl-1-propanol. These model calculations support the proposal that interactions between induced dipoles can be quite important in the determination of conformational preferences.

(3) Methylcyclohexane, 3-Methyltetrahydropyran, and 5-Methyl-1,3-dioxane. The optimized structures for the axial and equatorial conformations of methylcyclohexane, 3-methyltetrahydropyran, and 5-methyl-1,3-dioxane are given in Figures 5–7. The calculated total and relative energies of these structures are collected in Tables III and IV. Overall, the relative energies of the conformers are in good agreement with the experimental observations for related systems cited earlier.

Figure 5 shows the optimized structures for axial and equatorial methylcyclohexane. The axial conformation, which contains two gauche C–C–C–Me units, is 2.3 kcal/mol higher in energy than the equatorial conformation (two anti C–C–C–Me units). Calculations by Wiberg on butane indicate that the anti conformer is 0.7–1.0 kcal/mol more stable than the gauche conformer, depending on the level of calculation.[14] In this case, in going from gauche butane (one C–C–C–Me unit) to axial methylcyclohexane (two C–C–C–Me units), the effect is roughly additive.

The optimized structures for equatorial and axial 3-methyltetrahydropyran are shown in Figure 6. The equatorial conformer, which contains one anti C–C–C–Me unit and one anti O–C–C–Me unit, is more stable than the axial conformer, which contains one gauche C–C–C–Me unit and one gauche O–C–C–Me unit, by 1.3 kcal/mol.

As shown below, the equatorial conformer of 3-methyltetrahydropyran, **16A**, resembles the G/A conformation of 2-methyl-1-propanol, and the axial conformer, **16B**, resembles the G/G conformer of 2-methyl-1-propanol. Therefore, an axial methyl should be destabilized by 0.2 kcal/mol as it is in G/G 2-methyl-1-propanol and by 0.8 kcal/mol as in gauche butane. Combination of these two effects gives a preference for equatorial 3-methyltetrahydropyran of a little more than 1 kcal/mol. The full calculation gives a 1.3 kcal/mol preference for the equatorial conformation. There is a 0.3 kcal/mol difference between the cyclic and acyclic systems.

The equatorial conformer of 5-methyl-1,3-dioxane (Figure 7) has two G/A units of 2-methyl-1-propanol, while the axial conformer has two G/G units. This should made the axial conformer 2 × 0.2 = 0.4 kcal/mol higher in energy than the equatorial. Calculations indicate that the axial conformer is 0.5

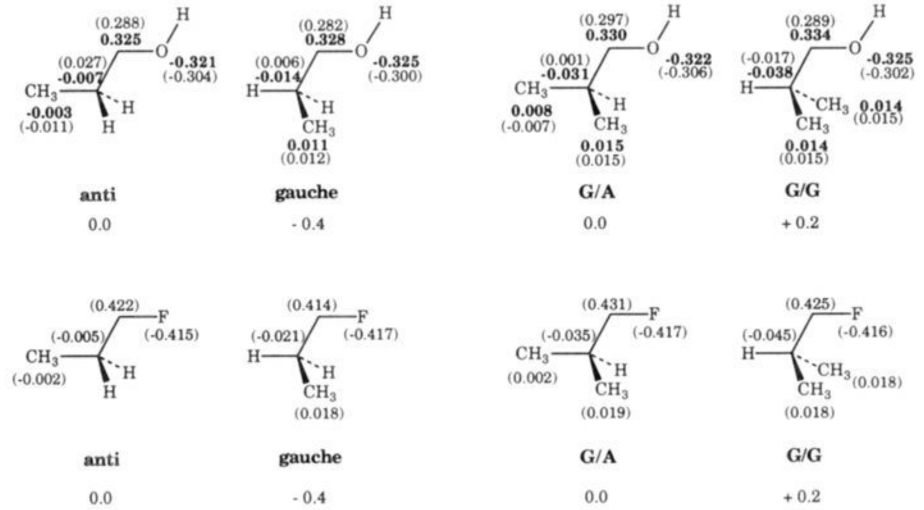


Figure 4. RHF/6-31G* natural bond orbital charge distributions and the Mulliken charges (in parentheses) for the anti and gauche conformations of propanol, the gauche/anti (G/A) and gauche/gauche (G/G) conformations of 2-methylpropanol, the anti and gauche conformations of propyl fluoride, and the gauche/anti (G/A) and gauche/gauche (G/G) conformations of isobutyl fluoride. The charges of the hydrogens are summed into those of the attached carbons. The MP2/6-31+G*//6-31G* relative energies (kcal/mol) of the conformers are also shown.

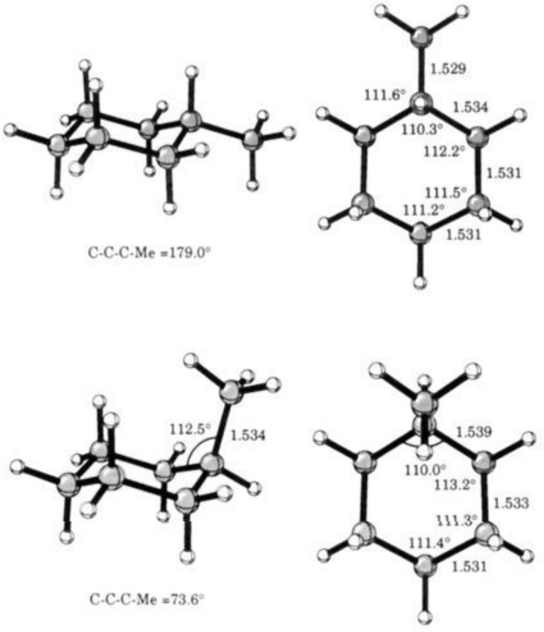


Figure 5. Side and top views of the 6-31G* optimized structures for the equatorial and axial forms of methylcyclohexane.

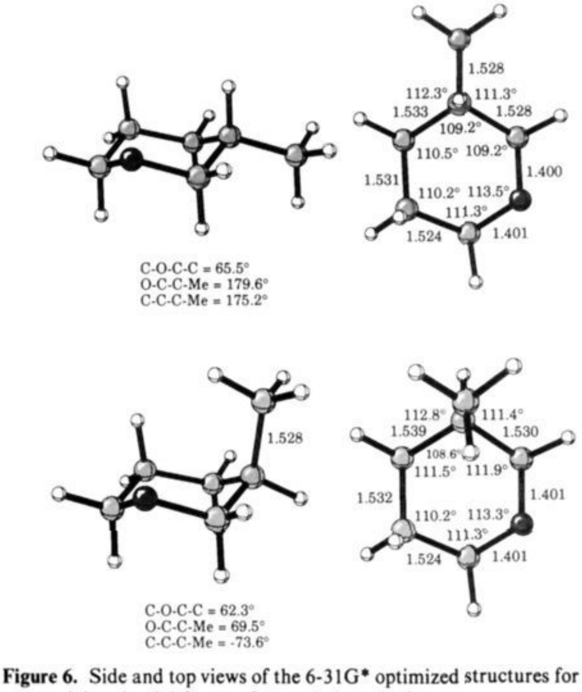
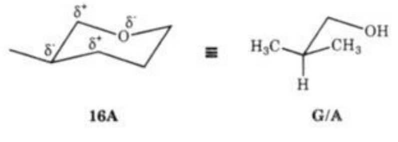


Figure 6. Side and top views of the 6-31G* optimized structures for the equatorial and axial forms of 3-methyltetrahydropyran.



16A G/A

16 B G/G

kcal/mol higher in energy than the equatorial conformer; here also, the effects are nearly additive.

We also applied the model MM2 parameters used earlier to 3-methyltetrahydropyran and 5-methyl-1,3-dioxane. As given in Table IV, when original MM2 parameters are used, the calculated relative energies of the two systems agree with the ab initio and experimental values quite well. These parameters, however, are the ones that predict the wrong conformational preference for propanol! The second set of calculations also agree well with the ab initio results. The third set, which works the best for propanol and 2-methyl-1-propanol, also does well for the cyclic systems. When the geminal dipole–dipole interactions were excluded (set IV), the calculated equatorial preference for 3-methyltetrahydropyran drops to 0.73 kcal/mol, while the equatorial conformation of 5-methyl-1,3-dioxane becomes less stable by 0.11 kcal/mol. These results are in poor agreement with the ab initio results and indicate the importance of the geminal dipole–dipole interactions. Overall, the parameters developed for set III are the most consistent in calculating the conformational preferences for both the acyclic and cyclic systems.

(4) Constrained Optimizations of Methyl Propyl Ether. In addition to electrostatic interactions, differences in dihedral angles accessible to cyclic systems as compared to acyclic systems might be important in causing differences in gauche energies. To further investigate the difference between the acyclic preference for

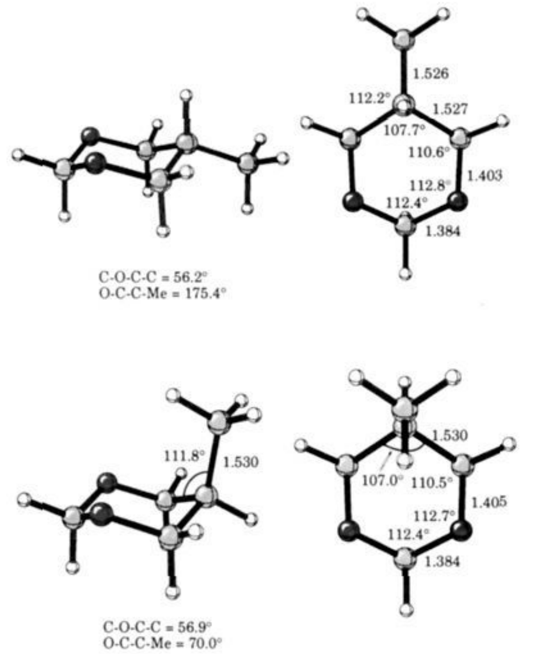


Figure 7. Side and top views of the 6-31G* optimized structures for the equatorial and axial forms of 5-methyl-1,3-dioxane.

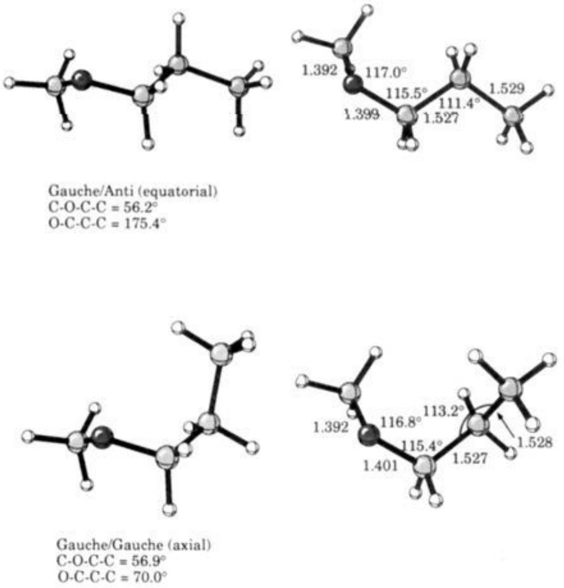


Figure 8. 6-31G* optimized structures of methyl propyl ether with fixed torsional angles.

Table V. Calculated and Observed ^{1}H NMR Shifts (ppm) for 1-Hexanol, 2-Hexanol, 3-Hexanol, and 4-Methyl-1-pentanol at 298 K

	Whitesell calcd shift[a]	new calcd shift[b]	obsd shift
1-hexanol			
C_1	61.3	62.8	62.6
C_2	33.6	33.6	32.8
C_3	27.3	26.8	25.9
C_4	31.3	32.8	32.0
C_5	23.4	23.4	22.9
C_6	14.4	14.5	14.1
2-hexanol			
C_1	22.4	22.2	23.5
C_2	67.0	67.1	67.3
C_3	39.5	39.6	39.2
C_4	28.9	28.4	28.2
C_6	23.1	23.2	22.9
C_6	14.0	14.1	14.3
3-hexanol			
C_1	10.4	10.0	10.0
C_2	28.9	29.0	30.4
C_3	72.7	72.7	72.9
C_4	38.6	38.6	39.4
C_5	19.8	19.1	19.1
C_6	14.3	14.3	14.2
4-methyl-1-pentanol			
C_1	61.7	62.8	63.0
C_2	29.6	30.5	30.7
C_3	36.5	36.1	35.2
C_4	27.6	28.6	28.0
C_5	22.0	22.0	22.6

[a] Whitesell's reported shifts were recalculated for 298 K (25° C). They were originally incorrectly calculated for 25 K.[23] [b] Shifts were calculated using the method outlined in the text and the new torsional parameter at 298 K.

gauche O–C–C–C and the cyclic preference for anti O–C–C–C, we performed some constrained optimizations on methyl propyl ether. Methyl propyl ether has the same two relevant torsional angles (O–C–C–C and C–O–C–C) as 5-methyl-1,3-dioxane. Wiberg has performed full optimizations on methyl propyl ether and has determined that the gauche/gauche conformer (O–C–C–Me = 58.4° and C–O–C–C = 77.1°) is favored over the anti/gauche conformer (O–C–C–Me = 175.7° and C–O–C–C = 79.6°) by 0.46 kcal/mol.[16]

In the RHF/6-31G* calculations on the axial conformation of 5-methyl-1,3-dioxane, the O–C–C–C torsional angle is larger (70°) for the dioxane than it is for propanol (63°) or methyl propyl ether (58°). In Figures 5–7, it can be seen that the axial substituents lean outward away from the center of the ring, and thus the torsional angles are larger. This is a result of the flattening of all six-membered rings as compared to the ideal staggered acyclic molecules.

In order to determine quantitatively the effect of this larger O–C–C–Me torsional angle in 5-methyl-1,3-dioxane, the torsional angles of methyl propyl ether were fixed at the optimized O–C–C–Me and C–O–C–C angles from the dioxane 6-31G* calculation; all other parameters were optimized. Figure 8 shows the 6-31G* partially optimized structures and geometries. Equatorial 5-methyl-1,3-dioxane (O–C–C–Me = 175.4° and C–O–C–C = 56.2°) corresponds to anti/gauche methyl propyl ether, and axial 5-methyl-1,3-dioxane (O–C–C–Me = 70.0° and C–O–C–C = 56.9°) corresponds to gauche/gauche methyl propyl ether. The calculations indicate that neither form is significantly favored over the other (gauche/gauche is more stable than anti/gauche by 0.02 kcal/mol). This is a net relative destabilization of the anti/gauche conformer by 0.4 kcal/mol from the optimal structures. The larger O–C–C–Me torsional angle in the G/G methyl propyl ether has pushed the methyl group farther away from the oxygen, lessening the favorable electrostatic interaction and contributing to the destabilization of the G/G form.

The constrained optimizations help to further explain the differences between the acyclic and cyclic systems. The molecules 2-butanol, 2-ethyltetrahydropyran, and 1-propanol all have a gauche O–C–C–C preference. This is because oxygen induces a dipole in the ethyl group for the gauche conformer, resulting in a stabilization. While 2-methyl-1-propanol is an acyclic molecule, the expected lowest energy conformer, G/G, is actually higher in energy than the G/A conformer. The two gauche interactions in the G/G conformer now have no stabilizing electrostatic effect. In the cyclic systems, 2-methyltetrahydropyran and 5-methyl-1,3-dioxane, the axial conformers are disfavored because of a combination of two effects: the unfavorable geminal dipole–dipole interactions and the larger torsional angles which result from the outward tilting of the axial substituents. The larger torsional angle decreases the electrostatic interactions of the methyl group and a gauche C–O bond in the ring.

(5) Development of MM2 Parameters. MM2 has been used to predict the ^{13}C NMR chemical shifts of alcohols.[23] However, as noted earlier, MM2 incorrectly predicts an anti preference for simple acyclic alcohols and ethers. We have developed an ad hoc reparametrized MM2 which gives the correct 0.3 kcal/mol preference for oxygen gauche to carbon. The torsional parameters were fit to ab initio calculations on 1-propanol at the MP2/6-31+G*//6-31G* level.[24] In this case, we determined $V_1 = 1.45$, $V_2 = -1.79$, and $V_3 = 1.19$ kcal/mol, as compared to the standard values of $V_1 = 0.10$, $V_2 = -0.10$, and $V_3 = 0.18$, respectively. To ascertain the validity of the parameters, we attempted to predict the ^{13}C NMR shifts in a series of acyclic alcohols studied earlier by Whitesell et al.[23] They used calculated MM2 conformational mixtures and empirical parameters for ^{13}C chemical shifts induced by substituents to predict measured ^{13}C chemical shifts. In this way, ^{13}C NMR shifts were predicted for a battery of acyclic alcohols. We expected to improve the predicted shift values of those carbons gauche to the hydroxyl oxygen the most, since Whitesell's calculations involved parameters which incorrectly favor the anti O–C–C–C conformation. The results of our calculations for some of these compounds are presented in Table V.

The procedure used is described in the following example. For 1-hexanol, the energies of all of the possible gauche and anti conformations about the four C–C bonds are calculated. The population of each conformer is found from a Boltzmann distribution at 298 K. In order to predict the ^{13}C NMR shift for a given carbon, a standard chemical shift, representative of the type of carbon, is adjusted by the Whitesell parameters for each gauche interaction. In hexanol, the predicted chemical shift of C-3 should be affected the most since it is gauche to oxygen. Those conformations with oxygen gauche should be more populated since they are lower in energy; the chemical shift weighting factor for the gauche conformer then contributes more to the adjusted shift value. From the results given in Table V, it can be seen that the new gauche parameter provides an improvement over the standard MM2 torsional parameter and gives further evidence for the preferred gauche O–C–C–C arrangement of alcohols in solution.

Conclusion

The different preferences for the O–C–C–C unit in acyclic and cyclic systems have been explained on the basis of electrostatic and steric arguments with the use of ab initio calculations. MM2 model calculations provide further evidence for the origin of these effects. The understanding of these effects should assist the successful prediction of the conformations of a variety of molecules.

Acknowledgment. We are grateful to Professor Yoshito Kishi for helpful discussions and to the National Institutes of Health for financial support of this research.

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[23] Whitesell, J. K.; La Cour, T.; Lovell, R. L.; Pojman, J.; Ryan, P.; Yamada-Nosaka, A. *J. Am. Chem. Soc.* **1988**, *110*, 991.

[24] In developing a parameter to be used for reproducing solution data, it would have been possible to calculate ZPE, thermal energy, and entropy contributions in the ab initio calculations to obtain $\Delta G°$. However, we expect these quantities to have little effect on the relative energies of the two closely related conformers, and these were neglected.