

# Ab Initio Examination of Anomeric Effects in Tetrahydropyrans, 1,3-Dioxanes, and Glucose

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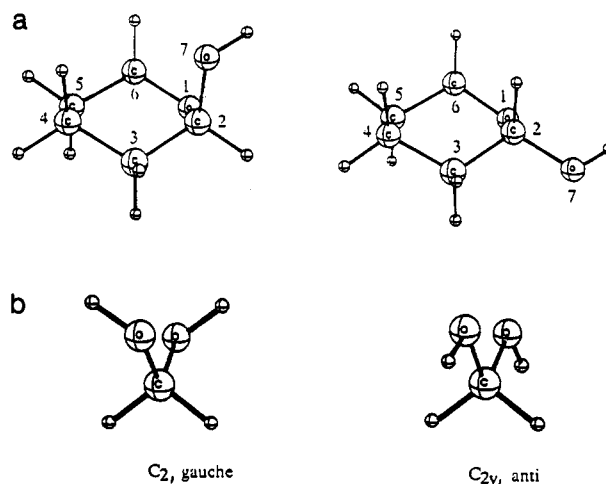
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Axial and equatorial structures of 2-methyl-, 2-hydroxy-, 2-methoxy-, 2-amino-, 2-fluoro-, and 2-chlorotetrahydropyran, of the 2-tetrahydropyranylammonium cation, of 2-methyl-, 2-hydroxy-, and 2-methoxy-1,3-dioxane, and of the corresponding cyclohexanes have been fully optimized at the HF/6-31G\* level. NBO analysis of the Hartree-Fock wave functions confirms that the anomeric effects of hydroxy-, methoxy-, fluoro-, and chloropyrans and of glucose and methyl glucoside are indeed due to hyperconjugation. In cyclohexane, tetrahydropyran, and glucose theoretical  $\Delta E$  values involving the OH and OMe substituents are nearly identical. The experimentally observed differences of about 1 kcal/mol in the  $\Delta H^\circ$  and  $\Delta G^\circ$  values of the OH and OMe compounds are very likely due to solvent interactions involving the OH group. In the gas phase, glucose orientates its ring hydroxy groups and the CH<sub>2</sub>OH group differently than in the crystal. The structures observed in the crystal lead to 7.9 kcal/mol higher energies. This might be rationalized by the fact that the isolated molecule tries to maximize the number of intramolecular hydrogen bonds. 2-Hydroxy-1,3-dioxane prefers an equatorial conformation. NBO analysis reveals that the exo-anomeric effect favoring the equatorial form dominates over the endo-anomeric effect in dioxanes. In contrast, 2-methoxy-1,3-dioxane shows an axial preference which is not due to hyperconjugation. The reverse anomeric effect in 2-aminotetrahydropyran is due to steric repulsions because the axial conformation with the largest hyperconjugation contribution requires one of the NH<sub>2</sub> hydrogens to point above the ring. The equatorial preference of NH<sub>3</sub><sup>+</sup> is a result of steric and other (probably electrostatic) contributions, since hyperconjugation strongly favors the axial conformation. For all cases for which the hyperconjugation contributions are overcompensated by the Lewis energies, steric repulsions are also indicated by significant ring distortions. Dipole moments correlate with relative energies qualitatively in some cases, but a quantitative relationship cannot be ascertained. Single point calculations with Huzinaga basis sets reveal that at the HF/6-31G\* level axial-equatorial energy differences of all compounds considered in this investigation are biased toward axial structures by 0.5–1 kcal/mol. Thus, the 6-31G\* basis set fails to reproduce the small equatorial preference of 2-fluorohexane at the HF as well as at correlated levels.

## Introduction

The axial preference of electronegative substituents at C2 in heterocycles is termed "the anomeric effect".<sup>1–4</sup> In such axial conformations the exocyclic C2–X7 bonds are orientated gauche with respect to the endocyclic C6–X1 bonds, while in the equatorial conformations the two bonds are orientated anti (Figure 1a). An additional gauche orientation of the exocyclic X7–R bond with respect to the endocyclic C2–X1 bond is designated "the exo-anomeric effect."<sup>5</sup> Gauche preferences also are observed in acyclic compounds, when two electronegative substituents are attached to the same center<sup>3</sup> (Figure 1b). The term "generalized anomeric effect" is used for such cases.<sup>3</sup> Since substituents larger than H tend to adopt equatorial placements in cyclohexanes, a driving force large enough to overcome the energy preference usually favoring the equatorial position must exist in axially-configured het-



**Figure 1.** (a) Illustration of gauche and anti orientations of C2 substituents with respect to the O–C6 bonds in axial and equatorial conformations of 2-substituted tetrahydropyrans. (b) Gauche and anti orientations of the O–H bonds with respect to the C–O bonds in the C<sub>2</sub> and the C<sub>2v</sub> conformers of HO–CH<sub>2</sub>–OH.

erocycles. This driving force must be larger than the axial-equatorial energy difference. Kirby suggested that the magnitude of the anomeric effect be evaluated as the difference ( $\Delta\Delta G^\circ$ ) between the  $\Delta G^\circ$  values of the axial-equatorial equilibria of the heterocycle and that of the

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corresponding cyclohexane.<sup>3</sup> Conversely, if a substituent favors the equatorial position in tetrahydropyran *more strongly* than in cyclohexane, the  $\Delta\Delta G^\circ$  value is negative. For such situations the term "reverse anomeric effect" is employed.<sup>6</sup>  $\Delta G^\circ_{(ax-eq)}$  values (see Table 3) have been determined experimentally for numerous cyclohexanes,<sup>7</sup> tetrahydropyrans,<sup>8</sup> and 1,3-dioxanes<sup>9</sup> mainly by NMR measurements of equilibria in solution,<sup>7,8</sup> but also in the gas phase by means of IR intensities,<sup>7e</sup> microwave rotational transition intensities,<sup>7e,10</sup> and electron diffraction.<sup>7e,11</sup> The experimental values are influenced by entropy contributions,<sup>8l,m</sup> solvent effects,<sup>7c,8i,n</sup> and other intermolecular interactions. The experimental  $\Delta G^\circ$  and  $\Delta\Delta G^\circ$  values vary considerably depending on the method and the conditions.<sup>7a,c,e,8i</sup> For instance, for 2-hydroxytetrahydropyran an equatorial preference,  $-0.63$  kcal, has been determined in terms of  $\Delta H^\circ$  (in  $\text{CFCl}_3\text{-CDCl}_3$  at 170 K). Under the same conditions  $\Delta G^\circ$  is  $0.21$  kcal/mol;<sup>8l,m</sup> however, in the neat liquid at 311 K a  $\Delta G^\circ$  value of  $0.75$  kcal/mol has been observed<sup>8c</sup> (compare also Table 3).

Theoretical calculations provide  $\Delta E$  values for isolated molecules at 0 K. Therefore, theoretical calculations are not expected, in principle, to quantitatively reproduce the experimental results. Nevertheless, it has been shown in numerous earlier studies<sup>12-29</sup> that *ab initio* calculations at the Hartree-Fock level do reproduce the energetic trends as well as all bond length and bond angle effects associated with the anomeric effect. Since the theoretical results are



**Figure 2.** Illustration of the lone pair repulsions in the equatorial structures of 2-substituted tetrahydropyrans and in the  $C_{2v}$  conformers of  $\text{RO-CH}_2\text{-X}$  systems.

free from intermolecular interferences, they are a valuable tool for a systematic study of substituents effects in cyclohexanes and tetrahydropyrans. Solvent effects on the equilibria also have been examined theoretically.<sup>29</sup> The experimentally observed reduction of the anomeric effect in more polar solvents is reproduced by theoretical investigations.

Although the anomeric effect has been studied extensively, its origin is still debated. The first explanation proposed by Edward<sup>1</sup> involves the repulsion between the ring oxygen lone pairs and the X atoms at C2 in the equatorial conformation and is known as "rabbit ear effect".<sup>30</sup> The resulting dipole due to the oxygen lone pairs points along the bisectrix of the angle between both lone pairs. Thus, the rabbit ear effect corresponds to dipole repulsions<sup>8d</sup> (Figure 2). The magnitude of the repulsion between two dipoles depends on their distance and on the angle between them. The repulsions are largest when the dipoles are parallel. The distance between the C-O and the C-X dipoles is approximately the same in the axial and the equatorial conformers of tetrahydropyrans. The nearly parallel orientation of these bond dipoles in the equatorial conformers, however, leads to larger dipole repulsions and to larger total dipole moments. Thus, stronger dipole repulsions are indicated by larger total dipole moments in sugars and tetrahydropyrans. The rationalization of the anomeric effect in terms of dipole repulsions is supported by the observation of Wiberg *et al.*<sup>23</sup> that in the gas phase the conformer with the larger dipole moment has the larger electrostatic energy and an increased total energy. Accordingly, anomeric effects decrease in more polar solvents.<sup>7c,8h,m,29</sup>

A different rationalization of the anomeric effect was given by Romers and Altona.<sup>31</sup> These authors suggested

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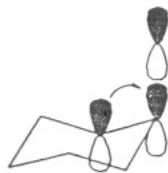
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**Figure 3.** Hyperconjugation in axial structures of 2-substituted tetrahydropyrans and dioxanes.

that the lone pairs of the electronegative substituents may delocalize (by quantum mechanical mixing) into the adjacent C–X antibond ( $n\text{-}\sigma^*$  hyperconjugation) (Figure 3) in gauche conformations. This orbital interaction model is capable of rationalizing the geometrical differences associated with the anomeric effect, namely the increase of the exocyclic and the decrease of the endocyclic C–X bond lengths as well as the X–C–X bond angle widening in axial conformations. Hyperconjugation is capable of rationalizing the exo-anomeric effect as well. However, Booth et al. claimed that it is possible to explain the exo-anomeric effect solely by steric effects.<sup>8m</sup>

Wolfe and his associates<sup>21</sup> examined the generalized anomeric effect by *ab initio* calculations, e.g., of fluoromethanol rotamers. The analysis of the components of the Hartree–Fock energy (nuclear repulsions, electron repulsions, nuclear electron attractions, and kinetic energy) showed that nuclear electron attractions are favored in the gauche conformations.

The above explanations for the anomeric effect imply enthalpic energy differences. In contrast, Booth et al.<sup>8k</sup> suggested that the axial preference of 2-methoxytetrahydropyran is due to entropy differences and that the enthalpies of the equatorial and the axial conformations are nearly identical.

Finally, Walkinshaw<sup>32</sup> suggested from a study on sugars that the dominant factor determining the anomeric equilibrium is the relative hydrophilicity of the two anomeric isomers. On this basis, the magnitude of the anomeric effect should depend on the hydrogen bridging ability of the solvent.

Since Hartree–Fock calculations do not include solvent and entropy effects, it is straightforward to decide whether enthalpic differences exist between axial and equatorial conformations. However, it is extremely difficult to quantify the effects employed in the other arguments. Radom et al.<sup>33</sup> studied the internal rotation in ethane, methylamine, methanol, hydrazine, hydroxylamine, and hydrogen peroxide and each of the monomethyl and monofluoro derivatives of these molecules. Calculated energies were analyzed in terms of a Fourier-type expansion of the potential function. One-fold ( $V_1$ ), 2-fold ( $V_2$ ), and 3-fold ( $V_3$ ) components were attributed to dipole repulsions,  $p_\gamma\text{-}\sigma^*\text{C-X}$  hyperconjugation, and steric effects, respectively. However, a formal proof that Fourier components correspond to physical properties has not been given. Indeed, such a correspondence is highly unlikely, whatever the didactic merits of the dissection may be.

We therefore prefer a different approach. Hyperconjugation can be regarded as the quantum mechanical mixing of localized orbitals. In a localized orbital basis, hyperconjugation makes a genuine contribution to the calculated total energy. NBO analysis<sup>34</sup> allows hyperconjugative effects to be quantified by comparing calcu-

lated total energies with Lewis energies, the latter corresponding to the energies of hypothetical molecules when hyperconjugation is absent. Since steric and electrostatic effects are included in the Lewis energies, NBO analyses separate the energy contributions due to hyperconjugative stabilizations and dipole repulsions.

We have carried out *ab initio* computations and have performed NBO analyses for the axial and equatorial conformers of methylcyclohexane (1), 2-methyltetrahydropyran (2), 2-methyl-1,3-dioxane (3), cyclohexanol (4), 2-hydroxytetrahydropyran (5), 2-hydroxy-1,3-dioxane (6), methoxycyclohexane (7), 2-methoxytetrahydropyran (8), 2-methoxy-1,3-dioxane (9), aminocyclohexane (10), 2-aminotetrahydropyran (11), the cyclohexylammonium ion (12), the 2-tetrahydropyranylammonium ion (13), fluorohexane (14), 2-fluorotetrahydropyran (15), chlorocyclohexane (16), 2-chlorotetrahydropyran (17), glucose (18), and the methylglucoside (19) (Figures 4–23). The compounds are chosen to span the whole range from anomeric effects to the reverse anomeric effects. Axial–equatorial equilibria are evaluated using the total Hartree–Fock energies and the Lewis energies in order to evaluate the influence of hyperconjugation. The relative energies of different conformers also are related to the corresponding dipole moments.

## Methods

All compounds have been fully optimized at the HF/6-31G\* level using the Gaussian 90 (G90)<sup>35</sup> and Gaussian 92 (G92) programs.<sup>36</sup> Methylcyclohexane (1) has also been optimized at the MP2-FC/6-31G\* level.

The axial preference computed for fluorocyclohexane 14 at HF/6-31G\* is in contradiction with experiment.<sup>7e,h</sup> Hence, 14 was studied in more detail and was reoptimized at the HF/6-31+G\*, HF/6-31G\*\*, and MP2-FC/6-31G\* levels. Single points have been calculated on the MP2 geometries of the axial and equatorial conformers at the MP4SDTQ/6-31G\* and the HF levels with larger basis sets first only for fluorine and then for all atoms. In these computations, Huzinaga's<sup>37</sup> 10s6p bases were contracted to 6s5p. For F the 6s5p basis was augmented by one s (expl 0.09), one p (expl 0.09), and 3d functions (expl 2.5, 0.8, and 0.25), for C the 6s5p basis was augmented by two d functions (expl 1.4 and 0.35). The Huzinaga<sup>37</sup> hydrogen 7s basis was contracted to 4s and augmented by two p functions (expl 1.3 and 0.33). The results are summarized in Table 1. Only the 6-31+G\* and the Huzinaga basis set (at least on fluorine) reproduce the correct equatorial preference of 14. Improvement of the F basis is essential, since augmentation of the 6-31G\* basis on C and H hardly influences the result. The diffuse function in the 6-31+G\* basis set only partly overcomes the deficiencies of 6-31G\*, but the accuracy achieved is sufficient for the present purposes. Note that the results with the 6-31G\* basis set are even worse at the correlated MP2 and MP4 levels!

Since it is not possible to improve the theoretical level significantly for all of these large systems uniformly, we checked the quality of the results for the oxygen compounds using methanediol, which is often used as model for the O–C–O moiety

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**Table 1. Energies of the Axial and Equatorial Conformers of Fluorocyclohexane (14), 2-Fluorotetrahydropyran (15), cyclohexanol (4), 2-Hydroxytetrahydropyran (5), 2-Hydroxy-1,3-dioxane (6), and Glucose (18) at Various Theoretical Levels. The Values for 14 Have Been Obtained by Single Point Calculations on the MP2/6-31G\* Optimized Geometries (the HF/6-31G\* Geometries Give Virtually Identical Results) and on the HF Geometries for 4-6**

compd	level	$E_a$	$E_e$	$\Delta E_{e-a}$
14	HF/6-31G*	-333.064 19	-333.063 78	0.26
14	HF/6-31G*	-333.071 47	-333.071 90	-0.27
14	HF/6-31G**	-333.081 09	-333.080 75	0.21
14	HF/6-311G*	-333.131 87	-333.141 81	0.03
14	HF/F:Huz, <sup>a</sup> C,H:6-31G*	-333.107 68	-333.108 35	-0.42
14	HF/Huz <sup>a</sup>	-333.172 89	-333.173 63	-0.46
14	MP2/6-31G*	-334.015 81	-334.014 69	0.70
14	MP2/6-31G**	-334.103 77	-334.102 82	0.60
14	MP4SDTQ/6-31G*	-334.112 58	-334.111 48	0.69
15	HF/6-31G*	-368.885 18	-368.880 36	3.72
15	HF/6-31+G*	-369.895 67	-368.891 19	2.81
15	HF/F:Huz, <sup>a</sup> C,H:6-31G*	-368.971 68	-368.967 93	2.35
4	HF/6-31G*	-309.059 83	-309.060 22	-0.24
4	HF/O:Huz, <sup>a</sup> C,H:6-31G	-309.091 13	-309.092 32	-0.75
5	HF/6-31G*	-344.883 36	-344.881 25	1.32
5	HF/O:Huz, <sup>a</sup> C,H:6-31G	-344.945 40	-344.944 33	0.67
6	HF/6-31G*	-380.704 49	-380.705 35	-0.54
6	HF/O:Huz, <sup>a</sup> C,H:6-31G*	-380.797 76	-380.798 92	-0.73

<sup>a</sup> For F, C, and O Huzinaga's<sup>37</sup> 10s6p bases were contracted to 6s5p. The F basis was augmented by 1s (exptl 0.09), 1p (exptl 0.09), and 3d functions (exptl 2.5, 0.8, and 0.25). The O and C bases were augmented by two d-functions (exptl 1.4 and 0.35). For H the 7s basis was contracted to 4s and augmented by two p-functions (exptl 1.3 and 0.33).

**Table 2. Conformational Energies of the Fully Optimized C<sub>2</sub>, C<sub>s</sub>, C<sub>1</sub>, and C<sub>2v</sub> Structures of Methanediol at Different Levels of Theory**

	6-31G*	6-31G**	6-31++G**	6-311++G**	Huzinaga <sup>a</sup>
	HF	HF/MP2	HF/MF2	HF/MP2	HF/MP2
C <sub>2</sub>	0.0	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0
C <sub>s</sub>	3.68	3.49/3.45	3.44/3.47	3.36/3.44	2.93/2.91
C <sub>1</sub>	3.93	3.80/4.27	3.52/3.98	3.36/3.71	3.19/3.21
C <sub>2v</sub>	8.70	8.35/9.19	8.06/9.00	7.73/8.57	7.08/7.02

<sup>a</sup> For C and O Huzinaga's<sup>37</sup> 10s6p bases were contracted to 6s5p and augmented by two d-functions (exptl 1.4 and 0.35). For H the 7s basis was contracted to 4s and augmented by two p-functions (exptl 1.3 and 0.33).

of pyrans and sugars.<sup>12,16,17,28</sup> The C<sub>2</sub>, C<sub>s</sub>, C<sub>1</sub>, and C<sub>2v</sub> structures of methanediol were optimized at different theoretical levels. Table 2 summarizes the conformational energies of these computations. The stability ordering is the same at all levels of theory. However, the energy differences decrease with the improvement of the basis sets. Significant differences between the 6-311++G\* and Huzinaga<sup>37</sup> basis results reveal that convergence is not yet achieved at the HF level. The influence of correlation decreases with improvement of the basis sets. With the large Huzinaga basis sets the relative energies are unaffected by correlation at the MP2 level. Thus, the correlation effects with the small Pople basis sets are artifacts due to basis set deficiencies. As for fluorocyclohexane 14 (see above), the results become worse with the Pople basis sets in Table 2 with correlation (MP2).

The bond angles and dihedral angles of methanediol do not change significantly by the improvement of theory. There is one exception. The H-O-C-O dihedral angle in the C<sub>1</sub> structure differs by 20° at the HF as compared to the MP2 level. All other dihedral angles are constant within 2°. While the bonds are uniformly longer at MP2 than at HF level, the relative values are consistent at both levels.

Single point calculations for cyclohexanol (4), 2-hydroxytetrahydropyran (5), and 2-hydroxy-1,3-dioxane (6) with the Huzinaga basis set for the oxygen atoms (Table 1) reveal that the energy differences between gauche and anti structures of hexanes, pyrans, and dioxanes are about 0.5–1.0 kcal/mol too positive with the 6-31G\* basis set. Since the anomeric effects are computed as differences between hexanes and pyrans or dioxanes, the

accuracy of the anomeric effects should be about 0.5 kcal/mol. For 5 and 14 the NBO analysis was compared at the HF/6-31G\* and at the HF/O,F:Huz,C,H:6-31G\* level. This basis set improvement does not affect the results of the NBO energy decomposition for 5 and 14. With 6-31G+G\*, however, the NBO energy components for 14 change sign. It seems likely that the addition of the diffuse functions to the relatively small 6-31G\* basis set leads to spurious charge transfer between F and the other atoms.

For nine compounds the IR frequencies were calculated at the HF level, and the zero point energy (ZPE) corrections were evaluated. In all cases the ZPE corrections are smaller for the equatorial structures, the contributions to the equilibria being 0.2 kcal/mol for compounds 1, 4, 8, and 9, 0.3 kcal/mol for 6, 0.1 kcal/mol for 7 and 14, and 0.4 kcal/mol for 5 and 11. Thus, uncorrected HF/6-31\* axial-equatorial energy differences are biased towards axial structures by about 1 kcal/mol due to basis set truncation and neglect of the ZPE correction.

The delocalization effects are evaluated using the NBO options<sup>34</sup> in G90<sup>35</sup> and G92.<sup>36</sup> The NBO method is discussed in detail by Reed et al.<sup>34</sup> Therefore, only a few qualitative features are outlined here. The NBO program orthogonalizes the atomic orbital basis set and transforms the canonical delocalized Hartree-Fock MOs into localized hybrids, the so-called natural bond orbitals (NBOs). These are designated as "core", "lone pair", and "bond orbitals" and comprise a hypothetical Lewis structure with strictly localized electron pairs. However, perfect Lewis structures do not exist for real molecules. Small delocalizations arise from interactions between the occupied orbitals and antibonds in the NBO description. Such orbital interactions are represented by off-diagonal elements in the Fock matrix in the NBO basis. (The Fock matrix is diagonal in the basis of the canonical MOs). Orbital interactions such as  $\rho_{O-\sigma^*C-X}$  and  $p_X-\sigma^*C-O$  (X = substituent at C2) are most important in pyrans. However,  $n-\sigma^*$  hyperconjugation includes interactions of both oxygen lone pairs, p and sp, and those of the X lone pairs with C-X and C-H antibonds. Thus,  $\rho_{O-\sigma^*C-H}$ ,  $sp_{O-\sigma^*C-X}$ , and  $sp_{O-\sigma^*C-H}$  as well as  $p_X-\sigma^*C-H$  interactions also have to be considered. The NBO Fock matrix further contains interactions between bonds (C-H, C-O, C-X) and adjacent antibonds such as  $\sigma_{C-H}-\sigma^*C-X$  hyperconjugation. The energy contributions of these orbital interactions are calculated by removing the corresponding off-diagonal elements from the Fock matrix and computing one SCF cycle. Simultaneous deletion of all off-diagonal Fock matrix elements results in the "Lewis energy" ( $E_{Lew}$ ) corresponding to a hypothetical molecule with strictly localized bonds.  $E_{del}$  is the  $E_{tot} - E_{Lew}$  energy difference, the effect of the sum of all orbital interactions in the system. Individual matrix elements also can be removed. Then the energy difference from the total Hartree-Fock energy gives the energy contribution of specific orbital interactions. However, we will not discuss the influence of  $\rho_{O-\sigma^*C-X}$  orbital interactions separately, since we showed in a recent investigation<sup>38</sup> that the neglect of the other hyperconjugative interactions (i.e., involving the sp orbital as donor and the C-H bonds as acceptors) results in unreliable predictions. Since the orbital basis is orthogonal, the deletion procedure conserves the total electron density. The Lewis energy includes steric and electrostatic effects (e.g., dipole repulsions) of hypothetical molecules in absence of hyperconjugation.

## Results

Table 3 summarizes the axial-equatorial energy differences  $\Delta E$  for compounds 1–19. The energy differences  $\Delta E$  and anomeric effects  $\Delta\Delta E$  ( $\Delta\Delta E = \Delta E_{hexane} - \Delta E_{pyran}$ ) are compared with experimental data. Table 4 gives the total ( $\Delta E_{tot}$ ), hyperconjugation ( $\Delta E_{del}$ ), and Lewis ( $\Delta E_{Lew}$ ) energy differences between axial and equatorial conformers and the corresponding dipole moments. The energy differences between the different rotamers of the OR and NH<sub>2</sub> compounds are listed in Table 5.  $\Delta E_{tot}$ ,  $\Delta E_{Lew}$ , and  $\Delta E_{del}$  as well as the dipole moments for the different rotamers are summarized in Table 6. In Table 7 endo-



**Table 3.** Calculated Total Energies  $E_{ax}$  and  $E_{eq}$  (in au) of the Lowest Axial and Equatorial Conformations,  $\Delta E_{ax-eq}$ , and Theoretical Anomeric Effects at the HF/6-31G\* Level (6-31+G\* for F Systems) as Well as Experimental  $\Delta H^\circ$  and  $\Delta G^\circ$  Values and Experimental Anomeric Effects (kcal/mol) for Methylcyclohexane (1), 2-Methyltetrahydropyran (2), 2-Methyl-1,3-dioxane (3), Cyclohexanol (4), 2-Hydroxytetrahydropyran (5), 2-Hydroxy-1,3-dioxane (6), Methoxycyclohexane (7), 2-Methoxytetrahydropyran (8), 2-Methoxy-1,3-dioxane (9), Aminocyclohexane (10), 2-Aminotetrahydropyran (11), the Cyclohexylammonium Cation (12), the 2-Tetrahydropyranammonium Ion (13), Fluorocyclohexane (14), 2-Fluoro-tetrahydropyran (15), Chlorocyclohexane (16), 2-Chlorotetrahydropyran (17), Glucose (18), and the Methyl Glucoside (19).

species	theory				expt		
	$E_{ax}$	$E_{eq}$	$\Delta E_{e-a}$	anomeric effect	$\Delta H^\circ$	$\Delta G^\circ$	anomeric effect
1	-273.240 00	-273.243 66	-2.3		-1.74 <sup>a</sup>		
2	-309.052 65	-309.057 96	-3.3	-1.0		-2.86 <sup>b</sup>	-1.12
3	-344.870 85	-344.878 43	-4.8	-2.5	<sup>c</sup>		
4	-309.059 83	-309.060 22	-0.2		-1.24 <sup>d</sup>	-0.3-1.5 <sup>e</sup>	
5	-344.883 36	-344.881 25	1.3	1.5	-0.63 <sup>d</sup>	0.12//+0.75 <sup>f</sup>	0.61
6	-380.704 49	-380.705 35	-0.5	-0.3			
7	-348.085 89	-348.086 25	-0.2		-0.71 <sup>d</sup>	-0.4-0.7 <sup>e</sup>	
8	-383.910 02	-383.907 68	1.5	1.7	0.04 <sup>d</sup>	0.58 <sup>f</sup>	0.75
9	-419.731 15	-419.729 54	1.0	1.2		0.62 <sup>h</sup>	1.33
10	-289.229 22	-289.230 34	-0.7		-1.78 <sup>d</sup>	-1.0-1.8 <sup>e</sup>	
11	-325.047 60	-325.052 00	-2.8	-2.1	-2.11 <sup>d</sup>	-1.57 <sup>i</sup>	-0.33
12	-289.605 58	-289.607 86	-1.4			-1.6-2.0 <sup>e</sup>	
13	-325.415 72	-325.420 44	-3.0	-1.6			
14	-333.071 47	-333.071 90	-0.3			-0.1-0.5 <sup>e</sup>	
15	-368.895 67	-368.891 19	2.8	3.1			
16	-693.113 06	-693.114 67	-1.0		-0.45 <sup>d</sup>	0.3-0.7 <sup>e</sup>	
17	-728.925 86	-728.911 90	2.5	3.5	1.67 <sup>d</sup>	2.18 <sup>j</sup>	2.12
18	-683.334 05	-683.332 19	1.2	1.4		-0.35 <sup>i</sup>	0.9 <sup>i</sup>
19	-722.355 62	-722.359 05	1.5	1.7			

<sup>a</sup> Reference 7g: low-temperature <sup>13</sup>C NMR, 172 K, in CFCl<sub>3</sub>-CDCl<sub>3</sub>. <sup>b</sup> Reference 8j: indirect determination of  $\Delta G^\circ$  using 2-, 3-, and 4-methyl- and -vinyltetrahydropyrans, mean value, CD<sub>2</sub>Cl<sub>2</sub>. <sup>c</sup> Reference 8e: "exclusively" equatorial. <sup>d</sup> Reference 8l <sup>13</sup>C and <sup>1</sup>H NMR spectroscopy: 4, in isooctane; 5, in CDCl<sub>3</sub>; 169-172 K; 7, in CFCl<sub>3</sub>; 8, in CFCl<sub>3</sub>-CDCl<sub>3</sub>, 169-172 K; 10, R = NHCH<sub>3</sub> in CFCl<sub>3</sub>-CDCl<sub>3</sub> integration 180 K and line broadening 190-230 K; 11, R = NHCH<sub>3</sub>, using the 4-methyl derivative, integration 174 K and line broadening 180-210 K; 16, in CFCl<sub>3</sub>; 17, <sup>1</sup>H NMR of the 4-methyl derivative, in CDCl<sub>3</sub>, 253-325 K. <sup>e</sup> Reference 7e. <sup>f</sup> Reference 8m: <sup>13</sup>C NMR, integration, in CFCl<sub>3</sub>-CDCl<sub>3</sub>, 300 K. <sup>g</sup> Reference 8c: neat liquid, 38 °C. <sup>h</sup> Reference 9b: calculated from dipole moment measurement in benzene at 25 °C. <sup>i</sup> Reference 3: in H<sub>2</sub>O.

**Table 4.** Total Energy ( $\Delta E_{tot}$ ), Lewis Energy ( $\Delta E_{Low}$ ), and Hyperconjugation Energy ( $\Delta E_{del}$ ) Differences between Equatorial and Axial Conformations in kcal/mol. Dipole Moments ( $D$ ) for Axial and Equatorial Structures and Dipole Moment Differences ( $\Delta D$ ) between Axial and Equatorial Conformations in D

compd	$\Delta E_{tot}$	$\Delta E_{Low}$	$\Delta E_{del}$	$D_a$	$D_e$	$\Delta D$
Hexanes						
1	-2.3	-0.2	-2.1	0.05	0.09	-0.04
4	-0.2	0.7	-0.9	1.55	1.70	-0.15
7	-0.2	0.4	-0.6	1.22	1.32	-0.10
10	-0.7	0.7	-1.4	1.34	1.34	0.0
12	-1.4	-2.6	1.2			
14	-0.3	-0.6	0.3	1.77	2.10	-0.33
16	-1.0	-1.5	0.5	2.49	2.77	-0.28
Pyrans						
2	-3.3	-3.3	0.0	1.51	1.45	0.06
5	1.3	-0.5	1.8	0.39	2.11	-1.72
8	1.5	-0.3	1.8	0.32	1.86	-1.54
11	-2.8	-6.4	3.6	1.37	1.27	0.10
13	-3.0	-15.0	12.0			
15	2.8	-1.2	4.0	2.03	3.29	-1.26
17	2.5	-5.4	7.9	2.86	3.74	-0.88
18	1.2	-2.5	3.7	2.77	2.93	-0.16
19	1.5	-1.6	3.0	2.82	3.31	-0.49
Dioxanes						
3	-4.8	-4.2	-0.6	2.10	2.03	-0.07
6	-0.5	1.8	-2.3	2.12	3.21	-1.09
9	1.0	1.3	-0.3	1.89	2.82	-0.93

and exo-anomeric effects are separated for 5 and 6. Geometry parameters for axial and equatorial conformations are printed in Table 8. The differences in the structural parameters between axial and equatorial conformations are listed in Table 9. If not stated otherwise, the values are obtained at the HF/6-31G\* level. For the fluorine compounds the HF/6-31+G\* level is employed. For the cyclohexanes and tetrahydropyrans the same numbering of the ring atoms will be used to facilitate the comparison. This means the exocyclic substituents in the cyclohexanes will be placed at C2 rather than C1.

**Methylcyclohexane (1), 2-methyltetrahydropyran (2), and methyl-1,3-dioxane (3).** In methylcyclohexane (1) (Figure 4) the equatorial conformation is favored by 2.3 kcal/mol (Table 3) at the HF/6-31G\* level. The MP2 value is slightly smaller, 1.9 kcal/mol. Since no heteroatoms are present in 1, the MP2/6-31G\* value may be reliable. The ZPE correction, 0.2 kcal/mol, increases the energy difference between equatorial and axial structures to 2.1 kcal/mol. The experimental  $\Delta H^\circ$  value, obtained by <sup>13</sup>C NMR measurements at 172 K in CFCl<sub>3</sub>-CDCl<sub>3</sub>, is 1.74 kcal/mol.<sup>7g</sup> Usually, steric effects are considered to be responsible for equatorial preferences of substituted cyclohexanes. According to NBO analysis, however, the equatorial preference of methylcyclohexane almost vanishes if the energy difference is calculated in the absence of orbital interactions. Bond-antibond interactions of the exocyclic C1-C7 bond with  $\sigma^*_{C-C}$  and  $\sigma^*_{C-H}$  bonds are mainly responsible for the 2.1 kcal/mol (Table 4) more favorable hyperconjugation in the equatorial structure. The energy difference between the equatorial and the axial conformation would only be ca. 0.2 kcal/mol for a hypothetical methylcyclohexane with strictly localized two-electron bonds. Since steric repulsions are included in this nonhyperconjugative energy contribution of 0.2 kcal/mol, the equatorial preference of methylcyclohexane is *not* due to steric effects according to the NBO analysis. Compared to cyclohexane, the geometry of the hexane ring is slightly distorted in 1, since the C6-C1-C2-C7 dihedral angle is increased by 7.6° (Table 9). Steric repulsions are avoided by an outward bending of the methyl group, and the 6-1-2-7 dihedral angle seems to be flexible enough to allow such a distortion without a significant increase of the steric energy.

The situation is quite different in 2-methyltetrahydropyran (2) (Figure 5). The equatorial preference, 3.3 kcal/mol (Table 3), is larger than in 1. But the hyperconjugation

**Table 5. Total Energies in au and Relative Energies in kcal/mol for Different Conformations of Cyclohexanol (4), 2-Hydroxytetrahydropyran (5), 2-Hydroxy-1,3-dioxane (6), 2-Methoxytetrahydropyran (8), 2-Methoxy-1,3-dioxane (9), Aminocyclohexane (10), and 2-Aminotetrahydropyran (11). Dihedral Angles (deg) Specifying These Conformations**

conformn	$E_{tot}$	$E_{rel}$	$\theta$ C6-O1-C2-O7	$\theta$ O1-C2-O7-R	
4	e <sub>1</sub>	-309.060 22	0.0	175.3	60.3
	e <sub>3</sub>	-309.059 91	0.2	170.0	-62.6
	a <sub>1</sub>	-309.059 83	0.2	-65.3	-58.9
	a <sub>3</sub>	-309.057 66	1.6	-72.0	+61.2
5	a <sub>1</sub>	-344.883 36	0.0	-65.3	-55.1
	e <sub>1</sub>	-344.881 25	1.3	-179.5	49.1
	e <sub>3</sub>	-344.880 17	2.0	-176.0	-50.1
	a <sub>2</sub>	-344.876 85	4.1	-65.0	-177.3
	a <sub>3</sub>	-344.876 77	4.1	-69.4	82.0
	e <sub>2</sub>	-344.873 59	6.1	-177.6	174.4
6	e <sub>3</sub>	-380.705 35	0.0	179.2	-60.4
	a <sub>1</sub>	-380.704 49	0.5	-68.0	-51.3
	a <sub>3</sub>	-380.697 95	4.6	-75.9	+51.7
8	a <sub>1</sub>	-383.910 02	0.0	-64.7	-64.4
	e <sub>1</sub>	-383.907 68	1.5	-179.2	63.5
	a <sub>2</sub>	-383.903 67	4.0	-64.4	-145.5
	e <sub>3</sub>	-383.903 04	4.4	-172.4	-54.7
9	a <sub>1</sub>	-419.731 15	0.0	-67.0	-65.0
	e <sub>3</sub>	-419.729 54	1.0	-179.5	61.0
	e <sub>1</sub>	-419.727 64	2.9	176.9	64.4
	a <sub>3</sub>	-419.716 61	0.0	-178.9	-60.3/-178.4
	e <sub>1</sub>	-289.230 03	0.2	-178.5	-59.1/58.8
	a <sub>3</sub>	-289.229 23	0.7	-67.3	-55.0/173.9
11	a <sub>1</sub>	-289.227 04	2.1	-71.1	-59.4/59.2
	e <sub>1</sub>	-325.052 00	0.0	-176.9	-59.5/57.9
	a <sub>1</sub>	-325.047 60	2.8	-70.9	-51.1/69.4
	a <sub>3</sub>	-325.046 96	3.2	-66.2	-59.3/-178.4
e <sub>3</sub>	-325.045 33	4.2	-178.9	55.0/173.9	
e <sub>2</sub>	-325.044 05	5.0	-174.3	-60.7/-179.8	

contribution to the equatorial-axial equilibrium is negligible because the endo-anomeric effect due to the ring oxygen, which favors the axial form, is equal and opposite to bond-antibond contributions favoring the equatorial conformation. The total energy difference is due entirely to the 3.3 kcal/mol Lewis energy difference (Table 4). Since the exocyclic C-C bond is not polar, the dipole moments of the axial and the equatorial structures are nearly equivalent. Thus, the higher Lewis energy of the axial conformer probably is due to steric effects. Indeed, the larger axial-equatorial C6-X1-C2 and X1-C2-X7 bond angle differences in 2 compared to 1, 2.1 and 4.8° vs 1.0 and 0.5° (Table 9), indicate an increased outward bending of the methyl group in the axial conformation. The distortion of the C6-X1-C2-C7 angle is only slightly smaller than in 1. Therefore, it seems reasonable to attribute the increased equatorial preference of 2 compared to 1 to increased steric repulsions between the methyl group and the axial hydrogens at C4 and C6, a consequence of the short C-O bonds.

The largest equatorial preference, 4.8 kcal/mol, of all compounds considered in this study is computed for 2-methyl-1,3-dioxane (3) (Figure 6). Experimentally, no axial isomer has been observed in solution.<sup>8a</sup> As in 2-methyltetrahydropyran (2), the energy difference is mainly due to the Lewis term. The C6-O1-C2 and O1-C2-C7 bond angles again are widened in the axial conformation of 3 (Table 9), and in addition, the C6-O1-C2-C7 dihedral angle is increased, 76°. Hence, the equatorial preference of methylidioxane can also be attributed to steric repulsions.

**Table 6. Relative Values for Total Energies, Hyperconjugation Contributions, and Lewis Energies for Different Conformations of Cyclohexanol (4), 2-Hydroxytetrahydropyran (5) 2-Hydroxy-1,3-dioxane (6), 2-Methoxytetrahydropyran (8), 2-Methoxy-1,3-dioxane (9), Aminocyclohexane (10), and 2-Aminotetrahydropyran (11) in kcal/mol. The Corresponding Dipole Moments (dip) Are Given in D**

		a <sub>1</sub>	a <sub>2</sub>	a <sub>3</sub>	e <sub>1</sub>	e <sub>2</sub>	e <sub>3</sub>
4	$E_{tot}$	0.2		+1.6	0.0		0.2
	$E_{del}$	0.9		-1.1	0.0		-1.6
	$E_{Lew}$	-0.7		+2.7	0.0		1.8
	dip	1.55		1.93	1.70		1.86
5	$E_{tot}$	0.0	4.1	4.1	1.3	6.1	2.0
	$E_{del}$	0.0	3.6	-3.3	1.8	2.8	1.4
	$E_{Lew}$	0.0	0.5	7.4	-0.5	3.3	0.6
	dip	0.39	2.40	2.97	2.11	3.20	2.49
6	$E_{tot}$	0.5		4.6			0.0
	$E_{del}$	2.4		-3.5			0.0
	$E_{Lew}$	-1.8		8.1			0.0
	dip	2.12		3.62			3.21
8	$E_{tot}$	0.0	4.0		1.5		4.4
	$E_{del}$	0.0	3.8		1.7		2.5
	$E_{Lew}$	0.0	0.2		-0.3		1.9
	dip	0.32	1.68		1.86		2.10
9	$E_{tot}$	0.0		9.1		2.9	1.0
	$E_{del}$	0.0		-8.6		-1.9	-0.3
	$E_{Lew}$	0.0		17.7		4.8	1.3
	dip	1.89		3.51		3.20	2.82
10	$E_{tot}$	2.1		0.7	0.2		0.0
	$E_{del}$	-0.5		1.4	-1.5		0.0
	$E_{Lew}$	2.6		-0.7	1.7		0.0
	dip	1.39		1.34	1.41		1.34
11	$E_{tot}$	2.8		3.2	0.0	5.0	4.2
	$E_{del}$	-3.6		5.0	0.0	1.3	4.7
	$E_{Lew}$	6.4		-1.8	0.0	3.7	-0.5
	dip	1.37		1.66	1.27	2.63	2.31

**Table 7. Contributions of the Endo- and the Exo-Anomeric Effects to the Equatorial-Axial Energy Differences in 2-Hydroxytetrahydropyran (5) and 2-Hydroxy-1,3-dioxane (6)**

compd	endo	exo	$\Sigma$
5	3.5	-2.1	1.4
6	3.0	-9.4	-6.4

Cyclohexanol (4), 2-Hydroxytetrahydropyran (5), and 2-Hydroxy-1,3-dioxane (6). Six different OH and OR rotamers may be expected for tetrahydropyrans (see Figure 8), three for the equatorial and three for the axial conformations. In cyclohexane and in 1,3-dioxanes only four conformers (Figure 7 and 9) are considered, since a<sub>1</sub> and a<sub>2</sub> as well as e<sub>1</sub> and e<sub>2</sub> (compare Figure 8) are enantiomers and have thus identical energies.

The most stable conformer of cyclohexanol (4) (Figure 7) is 4e<sub>1</sub>, followed by 4e<sub>3</sub> and 4a<sub>1</sub>. The energies of the three structures are very close at the HF/6-31G\* level; the relative values are 0.0, 0.2, and 0.2 kcal/mol (Table 5), respectively. The 4a<sub>3</sub> structure lies 1.6 kcal/mol above 4e<sub>1</sub>. Single point calculations employing the Huzinaga basis set (see above) for the oxygen atom on the 4e<sub>1</sub> and 4a<sub>1</sub> conformers result in an axial-equatorial energy difference of -0.8 kcal/mol. Including the ZPE correction of 0.2 kcal/mol, a 1.0 kcal/mol preference for the equatorial conformation 4e<sub>1</sub> results for cyclohexanol. The experimental preference for the equatorial structure ( $\Delta H^\circ$  value in isoctane)<sup>81</sup> is 1.24 kcal/mol. The calculated equatorial preference results from hyperconjugative influences, since the Lewis energy is slightly lower for the axial form 4a<sub>1</sub> than for the equatorial conformer 4e<sub>1</sub>.

The relative energies of the 2-hydroxytetrahydropyran (5) (Figure 8) conformers are 5a<sub>1</sub> 0.0, 5e<sub>1</sub> 1.3, 5e<sub>3</sub> 2.0, 5a<sub>2</sub> 4.1, 5a<sub>3</sub> 4.1, and 5e<sub>2</sub> 6.1 kcal/mol at the HF/6-31G\* level. The hyperconjugative terms decrease in the order 5a<sub>3</sub>

**Table 8. Selected Geometrical Parameters for the Lowest Axial (a) and the Lowest Equatorial (e) Conformations of Compounds 1–19. Bond Lengths Are Given in Å, Angles in Deg**

compd		$d_{1-2}$	$d_{2-7}$	$d_{2-8}$	$\theta_{6-1-2}$	$\theta_{1-2-7}$	$\Phi_{6-1-2-7}$	$\Phi_{1-2-7-R}$
1	a	1.539	1.534	1.088	113.2	112.5	-73.6	
1	e	1.535	1.520	1.091	112.2	112.0	179.1	
2	a	1.411	1.529	1.083	116.4	111.9	-72.9	
2	e	1.407	1.518	1.092	114.3	107.1	-176.4	
3	a	1.394	1.525	1.079	116.2	111.8	-76.0	
3	e	1.390	1.508	1.093	113.5	108.6	178.5	
4	a <sub>1</sub>	1.531	1.411	1.089	112.2	111.3	-65.3	-58.9
4	e <sub>1</sub>	1.528	1.407	1.091	111.5	111.7	175.3	60.3
5	a <sub>1</sub>	1.392	1.393	1.084	115.7	111.4	-65.3	-55.1
5	e <sub>1</sub>	1.398	1.378	1.093	114.0	108.4	-179.5	49.1
6	a <sub>1</sub>	1.382	1.386	1.079	115.5	110.7	-68.0	-51.3
6	e <sub>3</sub>	1.384	1.353	1.086	114.0	109.1	179.2	-60.4
7	a	1.533	1.408	1.090	111.8	111.9	-64.5	-77.9
7	e	1.530	1.404	1.092	111.4	112.2	174.9	78.3
8	a <sub>1</sub>	1.393	1.388	1.085	115.5	111.9	-64.7	-64.4
8	e <sub>1</sub>	1.398	1.372	1.095	114.1	109.0	179.2	63.5
9	a <sub>1</sub>	1.381	1.380	1.080	114.9	111.5	-67.0	-65.0
9	e <sub>3</sub>	1.384	1.351	1.087	114.0	110.0	-179.5	-61.0
10	a <sub>3</sub>	1.533	1.460	1.093	112.7	109.6	-67.3	-60.3/-178.4
10	e <sub>3</sub>	1.529	1.457	1.095	111.8	109.4	-178.9	55.0/173.9
11	a <sub>1</sub>	1.413	1.439	1.081	116.4	114.4	-70.9	-51.1/69.4
11	e <sub>1</sub>	1.442	1.428	1.089	114.1	110.0	-176.9	-59.5/57.9
12	a	1.529	1.534	1.081	113.1	108.8	-72.1	
12	e	1.525	1.528	1.083	109.8	108.9	177.7	
13	a	1.351	1.560	1.078	119.5	106.9	-81.6	
14	a	1.367	1.513	1.086	114.4	101.9	179.1	
14	e	1.521	1.385	1.084	111.7	108.0	-66.0	
14	e	1.519	1.378	1.085	110.9	108.9	176.6	
15	a	1.368	1.373	1.079	115.7	109.5	-64.4	
15	e	1.379	1.351	1.088	113.9	106.4	-179.0	
16	a	1.527	1.821	1.079	113.0	110.3	-72.4	
16	e	1.525	1.812	1.081	110.3	110.0	179.4	
17	a	1.364	1.839	1.075	117.1	111.0	-71.4	
17	e	1.383	1.789	1.084	113.2	107.2	-175.9	
18	a <sub>1</sub>	1.386	1.394	1.082	116.9	112.3	-61.9	-62.1
18	e <sub>1</sub>	1.394	1.377	1.090	114.5	109.1	-179.4	58.7
19	a <sub>1</sub>	1.388	1.386	1.084	116.8	112.8	-62.3	-65.0
19	e <sub>1</sub>	1.396	1.372	1.091	114.6	109.8	-60.4	68.8

**Table 9. Differences in Selected Geometrical Parameters between Axial and Equatorial Conformations. Differences in  $\theta_{6-1-2-7}$  Angles are Evaluated for Axial Structures and Refer to the Value of  $66^\circ$  in Cyclohexane. Bond Length Differences in Å, Bond Angle Changes in Deg**

compd	$\Delta d_{1-2}$	$\Delta d_{2-7}$	$\Delta d_{2-8}$	$\Delta \theta_{6-1-2}$	$\Delta \theta_{1-2-7}$	$\Delta \theta_{6-1-2-7}$
Hexanes						
1	0.004	0.014	-0.003	1.0	0.5	7.6
4	0.003	0.004	-0.002	0.7	-0.4	-0.7
7	0.003	0.004	-0.002	0.4	-0.3	-1.5
10	0.004	0.003	-0.002	0.9	0.2	1.3
12	0.004	0.006	-0.002	3.3	-0.1	6.1
14	0.002	0.007	-0.001	0.8	-0.9	
16	0.002	0.009	-0.002	2.7	0.3	6.4
Pyrans						
2	0.004	0.011	-0.009	2.1	4.8	6.9
5	-0.006	0.015	-0.009	1.7	3.0	-0.7
8	-0.005	0.016	-0.010	1.4	2.9	-1.3
11	-0.028	0.011	-0.008	2.3	4.4	4.9
13	-0.016	0.047	-0.008	5.1	5.0	15.6
15	-0.011	0.022	-0.009	1.8	3.1	-1.6
17	-0.019	0.050	-0.009	3.9	3.8	5.4
18	-0.008	0.014	-0.008	2.4	3.2	(116.5)
19	-0.008	0.014	-0.007	2.2	3.0	(113.9)
Dioxanes						
3	-0.004	0.017	-0.014	2.7	3.2	10.0
6	-0.002	0.033	-0.007	1.5	1.6	2.0
9	-0.003	0.029	-0.007	0.9	1.5	1.0

(endo- and exo-anomeric effects strongest), 5a<sub>1</sub> (endo-anomeric effect strong, exo-anomeric effect slightly reduced), 5e<sub>3</sub> (endo-anomeric effect small, exo-anomeric effect strong), 5e<sub>1</sub> (endo-anomeric effect small, exo-anomeric effect slightly reduced), 5e<sub>2</sub> and 5a<sub>2</sub> (exo-

anomeric effects absent). Despite the strong hyperconjugative stabilization, 5a<sub>3</sub> is unfavorable because in this rotamer the hydroxy substituent lies above the ring and suffers steric repulsions. Indeed, the Lewis energy difference between 5a<sub>1</sub> and 5a<sub>3</sub> is 7.4 kcal/mol (Table 6). The ordering of the structures which have similar Lewis energies 5a<sub>1</sub> < 5e<sub>1</sub> < 5e<sub>3</sub> < 5a<sub>2</sub> is determined by the hyperconjugative contribution. 5e<sub>2</sub> has unfavorable hyperconjugative and Lewis energy contributions.

The anomeric effect (energy difference between the most stable equatorial and axial structures 5e<sub>1</sub> and 5a<sub>1</sub>) of 1.3 kcal/mol at the HF/6-31G\* level (0.3 kcal/mol with the Huzinaga basis for the oxygen atoms and including the ZPE correction) is thus due to the 1.8 kcal/mol (Table 6) larger hyperconjugation contribution in 5a<sub>1</sub>. The Lewis energy favors 5e<sub>1</sub> over 5a<sub>1</sub>. Thus, if additional anomeric stabilizations actually arise due to dipole repulsions in the equatorial conformation, they are not large enough to overcome steric repulsions in the axial structure. The equatorial preference due to the Lewis term is in contradiction with the rationalization of the anomeric effect by dipole repulsions.<sup>1</sup>

NMR measurements suggest an equatorial preference, -0.63 kcal/mol ( $\Delta H^\circ$  value, in CDCl<sub>3</sub>, 169–172 K),<sup>81</sup> for 2-hydroxytetrahydropyran 5. A  $\Delta G^\circ$  value of +0.12 has been determined (in CDCl<sub>3</sub>-CFCl<sub>3</sub> at 300 K).<sup>8m</sup> However, in the neat liquid (311 K)  $\Delta G^\circ$  is 0.75 kcal/mol.<sup>8c</sup> Thus, a significant difference in  $\Delta G^\circ$  values is observed between measurements in solution and in the neat liquid. The equilibria involving the OH substituent may therefore be biased toward equatorial structures due to solvent interactions. By simulating aqueous solution in a combined *ab initio*/semiempirical AM1-SM2 study, Cramer<sup>29</sup> confirmed experimental observations that polar solvents tend to reduce the anomeric effect in the tetrahydropyranosyl system. Unfortunately, the effect of less polar solvents has not yet been probed theoretically.

A 0.5 kcal/mol preference (1.0 kcal/mol employing the Huzinaga basis set for oxygen and including the ZPE correction) for the equatorial structure 6e<sub>3</sub> over 6a<sub>1</sub> is calculated for 2-hydroxy-1,3-dioxane (6) (Figure 9). The 6a<sub>3</sub> conformer lies 4.6 kcal/mol above 6e<sub>3</sub>. No minimum exists for a 6e<sub>1</sub> conformation (compare Figure 8). During the geometry optimization the starting dihedral angle of +60° converted to -60.4° without any barrier.

As in 5, the endo-anomeric effect in 6 stabilizes axial over equatorial structures and the exo-anomeric effect favors the 6a<sub>3</sub> and 6e<sub>3</sub> over the 6a<sub>1</sub> and 6e<sub>1</sub> conformers. Again, the 6a<sub>3</sub> structure with the most favorable hyperconjugation contribution cannot be adopted because of the strong steric repulsions due to the hydrogen above the ring. The preference of 6e<sub>3</sub> over 6a<sub>1</sub>, however, is determined by the relative influences of the endo- and the exo-anomeric effects in 2-hydroxy-1,3-dioxane (6). In the 6a<sub>1</sub> structure the endo-anomeric stabilization is optimal, while the exo-anomeric stabilization is reduced, and in 6a<sub>3</sub> the exo-anomeric stabilization is optimal and the endo-anomeric stabilization is reduced. Table 7 shows the contributions of the endo- and the exo-anomeric effects to the axial-equatorial equilibria separately for 5 and 6. In both systems the endo-anomeric effect favors axial conformations (by 3.5 and 3.0 kcal/mol, respectively). The difference between the axial and the equatorial conformation due to the exo-anomeric effect, however, is much larger in the dioxane (9.4 kcal/mol in 6, 2.1 kcal/mol in 5) and outweighs the axial preference due to the endo-

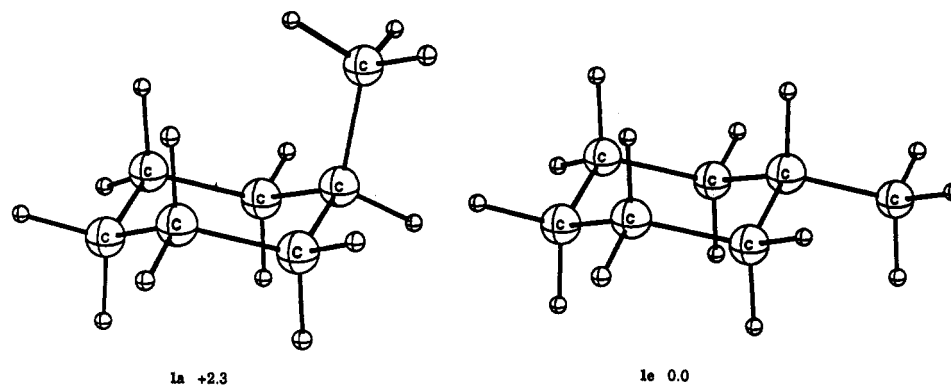


Figure 4. Different conformers of methylcyclohexane (1) (HF/6-31G\* relative energies in kcal/mol).

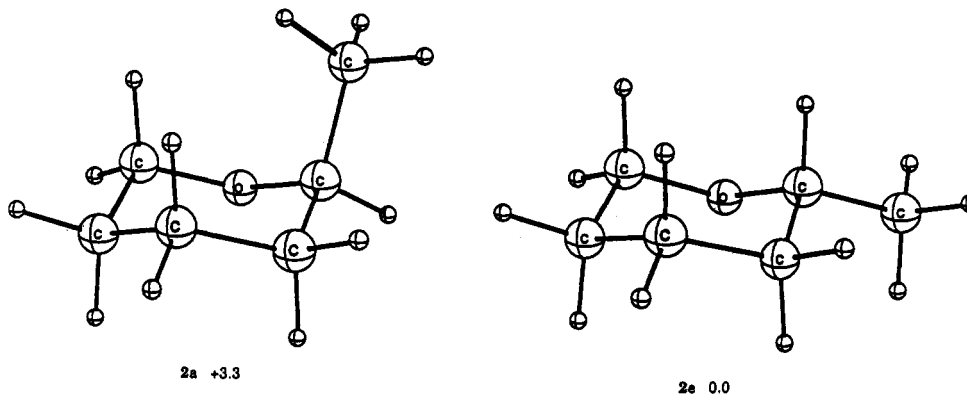


Figure 5. Different conformers of 2-methyltetrahydropyran (2) (HF/6-31G\* relative energies in kcal/mol).

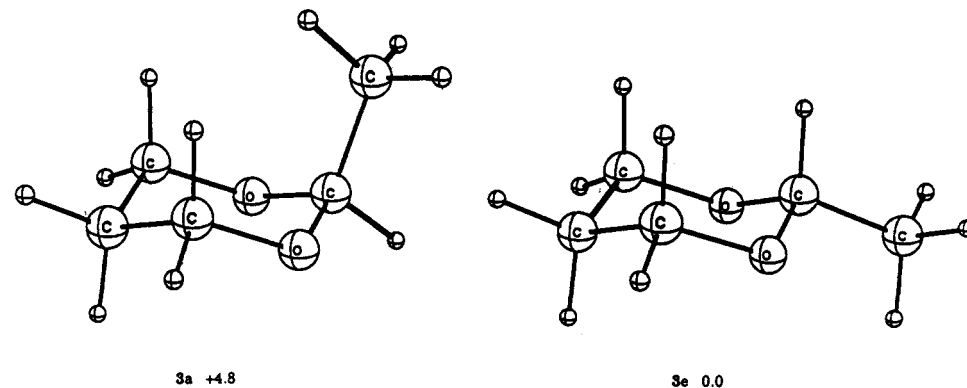


Figure 6. Different conformers of 2-methyl-1,3-dioxane (3) (HF/6-31G\* relative energies in kcal/mol).

anomeric effect. This increased preference for the  $6e_3$  structure is due to the presence of two oxygen atoms in the ring. Another consequence of this is that  $6e_1$  is not a minimum. Thus, due to the dominating *exo-anomeric effect*, hyperconjugation favors an equatorial structure in 2-hydroxy-1,3-dioxane! This is in disagreement with the suggestion of Kirby<sup>3</sup> that dioxanes may show strong axial preferences because they experience a double anomeric effect.

Since the dipole repulsions favor  $6a_1$  over  $6e_3$ , the equatorial preference of 2-hydroxy-1,3-dioxane clearly demonstrates that hyperconjugative effects rather than dipole repulsions determine the structures of electronegative substituted heterocycles.

**Methoxycyclohexane (7), 2-Methoxytetrahydropyran (8), and 2-Methoxy-1,3-dioxane (9).** Methoxycyclohexane (7) (Figure 10) prefers the equatorial conformation  $7e_1$  by 0.2 kcal/mol over the axial  $7a_1$  form. Other rotamers have not been optimized. The reduced axial-equatorial energy difference compared to methylcyclo-

hexane 1 is due to a less negative hyperconjugation term. As in cyclohexanol 4, the equatorial preference of the bond-antibond interactions is counteracted by the axial preference of the lone pair  $\sigma^*_{C-C}$  and  $\sigma^*_{C-H}$  interactions. The Lewis energy difference is small, favoring the axial form slightly.

NMR examinations of 2-methoxy-4-methyltetrahydropyran show that the  $a_1$  and  $e_1$  conformations are most important. Nuclear Overhauser enhancement (NOE) NMR spectra, however, indicate that the  $a_2$  and  $e_3$  conformations also are populated.<sup>80</sup> The relative abundances of  $a_2$  and  $e_3$  could not be calculated. The experimental  $\Delta G^\circ$  values range from 0.93 to 0.05 kcal/mol.<sup>81</sup> The enthalpic preference for the axial conformation of 2-methyltetrahydropyran (8) was determined to be only 0.04 kcal/mol.<sup>81,m</sup> Therefore, the anomeric effect of 8 was attributed to entropy effects.<sup>81,m</sup>

The relative energies of the 2-methoxytetrahydropyran (8) conformers (Figure 11) are  $8a_1$  0.0,  $8e_1$  1.5,  $8a_2$  4.0, and  $8e_3$  4.4 kcal/mol at the HF/6-31G\* level (Table 4). No



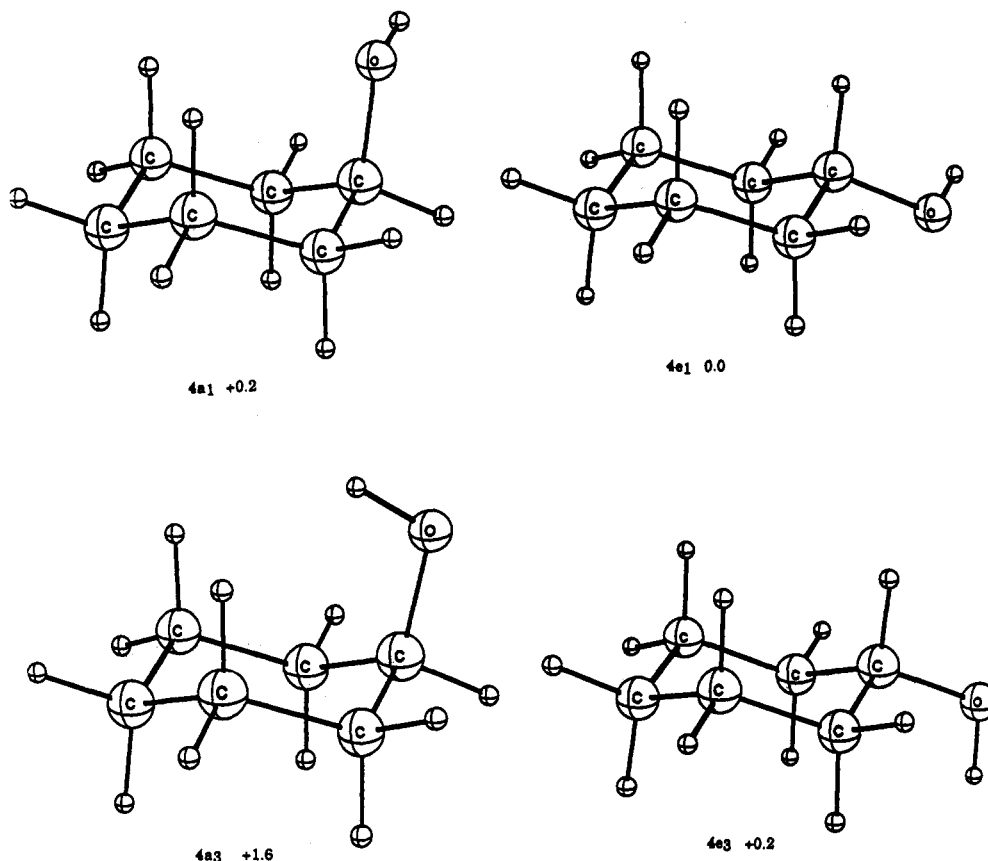


Figure 7. different conformers of cyclohexanol (4) (HF/6-31G\* relative energies in kcal/mol).

minima were found for  $8a_3$  and  $8e_2$  structures (compare Figure 8). Both would suffer severe steric repulsions between ring hydrogens and the bulky methyl group.

The axial preference, 1.5 kcal/mol (1.3 kcal/mol including the ZPE correction), as well as the hyperconjugation and Lewis energy contributions to the equilibrium, are almost identical for **8** and the OH-compound **5** (Table 4). The axial preference of **8** again is due to the hyperconjugation contribution, while the Lewis energy term which includes dipole repulsions is slightly more favorable for the equatorial structure. As in **5** no anomeric effect is computed in the absence of hyperconjugation.  $8a_1$  and  $8a_2$  have nearly identical Lewis energies, but because of a smaller hyperconjugative stabilization,  $8a_2$  is less stable. In  $8e_3$  hyperconjugative and Lewis energy contributions are unfavorable.

In contrast to 2-hydroxy-1,3-dioxane (**6**) and in agreement with experiment, 2-methoxy-1,3-dioxane (**9**) (Figure 12) favors the axial conformation  $9a_1$  by 1.0 kcal/mol (0.8 including the ZPE correction) over  $9e_3$ . The experimental axial preference ( $\Delta G^\circ$  value, in benzene at 25 °C) is 0.52 kcal/mol.<sup>8d</sup> The  $9e_1$  structure is a minimum for the methoxy in contrast to the hydroxy compound **6** but lies 2.9 kcal/mol higher in energy than  $9a_1$ . The sterically hindered  $9a_3$  conformer lies 9.1 kcal/mol above  $9a_1$ .

Hyperconjugation favors the  $9a_3 > 9e_1 > 9e_3$  conformations over the most stable axial  $9a_1$  form;  $9a_3$  has the most favorable hyperconjugative term but suffers severe steric repulsions. The 9.1 kcal/mol higher energy compared to  $9a_1$  is due to the 17.7 kcal/mol Lewis energy difference. The influence of steric repulsions in  $9a_3$  is obvious from the strong deformation of the ring, the C6–O1–C2–O7 dihedral angle being widened to 103°. The flattening of the ring and the outward bending of the C4 and C6 hydrogens as well as of the exocyclic C–O bond are

apparent in Figure 12. In contrast to pyrans, hyperconjugation favors equatorial structures  $9e_1$  and  $9e_3$  of 1,3-dioxanes over the  $9a_1$  form because of the dominance of the exo-anomeric effect.

The relative energies of the four conformers of **9**, however, are determined by the Lewis energy terms. Thus, the anomeric effect of 2-methoxy-1,3-dioxane has a different origin than that of the 2-hydroxy- and 2-methoxytetrahydropyrans (**5** and **8**).

**Aminocyclohexane (10) and 2-Aminotetrahydropyran (11)**. The optimized geometries of the amino compounds are presented in Figures 13 and 14. Aminocyclohexane (**10**) (Figure 13) shows a 0.7 kcal/mol preference for the equatorial  $10e_3$  over the axial  $10a_3$  conformation. A second equatorial conformation,  $10e_1$ , lies 0.2 kcal/mol above  $10e_3$ . One hydrogen is directed above the ring in the  $10a_1$  conformation. The 2.1 kcal/mol higher energy is due to the Lewis term (Table 6).

The room-temperature equilibrium of 2-(methylamino)-tetrahydropyran favors the equatorial conformer (93%) over the axial strongly.<sup>8e</sup> NOE effects<sup>8e</sup> show that the  $a_1$  and  $e_1$  forms are favored. In agreement with these data we calculate a 2.8 kcal/mol (3.2 kcal/mol including the ZPE correction) preference of 2-aminotetrahydropyran (**11**) (Figure 14) for the equatorial conformation  $11e_1$  over the axial form  $11a_1$ . Thus, **11** shows a reverse anomeric effect of 2.1 kcal/mol. The next stable conformer,  $11a_3$ , lies 3.2 kcal/mol higher in energy than  $11e_1$ . We also tried to optimize a third axial structure ( $11a_2$ ) obtained by +120° rotation of the NH<sub>2</sub> group in  $11a_1$ . But this conformation proved not to be a minimum on the energy hypersurface. The equatorial conformations  $11e_3$  and  $11e_2$  lie 4.2 and 5.0 kcal/mol above  $11e_1$ , respectively.

Figure 15 shows Newman projections along the exocyclic C–X bonds and relative energies of the three staggered

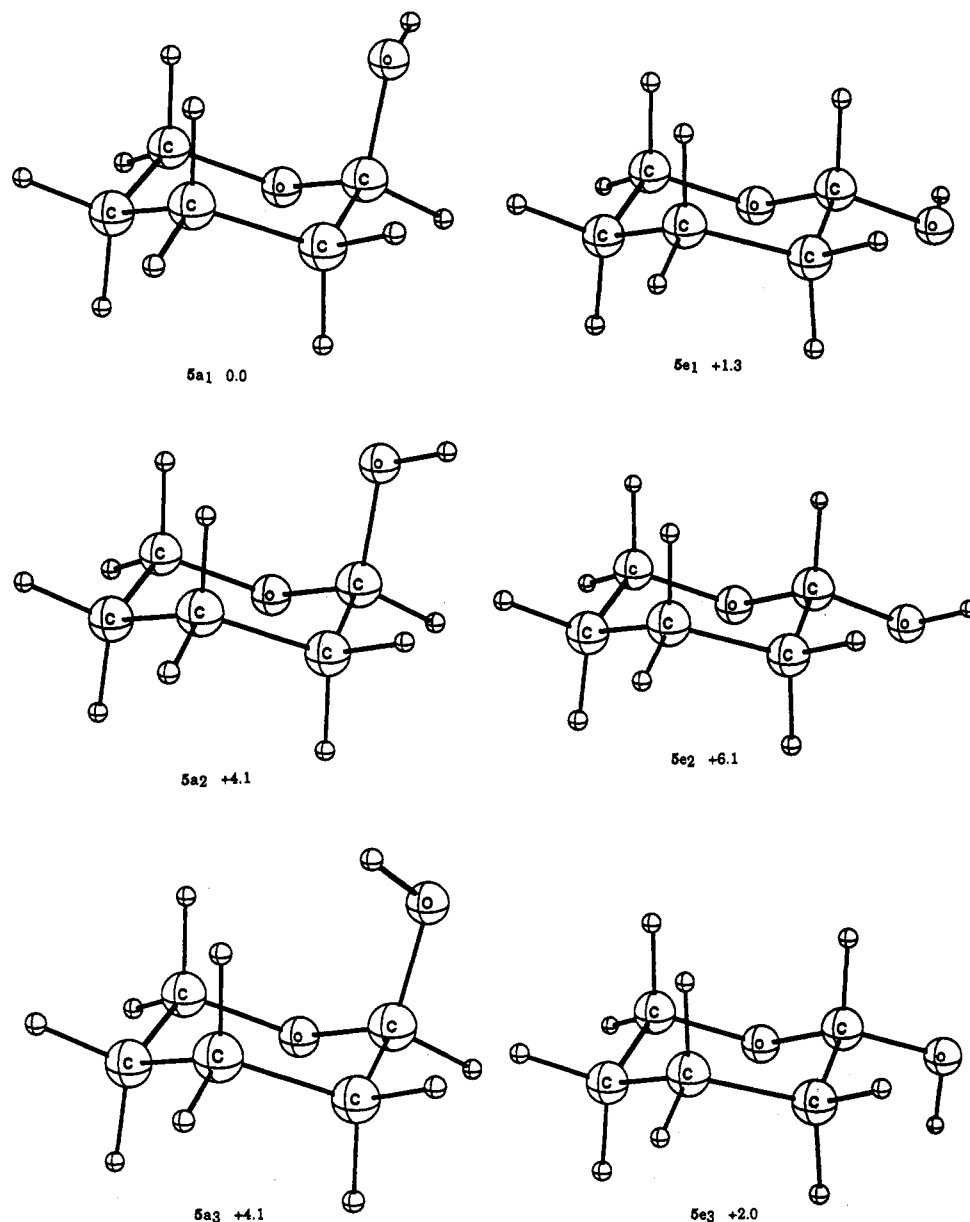


Figure 8. Different conformers of 2-hydroxytetrahydropyran (5) (HF/6-31G\* relative energies in kcal/mol).

axial structures of 2-hydroxytetrahydropyran (5) and 2-aminotetrahydropyran (11). Note the differences between the two systems. Since the hydroxy group carries only one hydrogen atom, two staggered conformations,  $5a_1$  and  $5a_2$ , exist which are favorable with respect to steric effects. For the  $\text{NH}_2$  group with two hydrogens only one conformation,  $11a_3$ , does not suffer steric repulsions. Furthermore, the p lone pair orbital of the oxygen atom is perpendicular with the OH bond and the angle between the nitrogen lone pair and the N-H bonds is  $120^\circ$ . In 5 the  $5a_1$  conformation allows effective overlap of the  $p_O$  with the  $\sigma^*_{\text{C-O}}$  orbital and is sterically favored. In contrast, the overlap between  $n_N$  and  $\sigma^*_{\text{C-O}}$  is maximal only in  $1a_1$  which suffers steric repulsions.

In agreement with the above considerations, NBO analysis shows that hyperconjugation favors the  $11a_1$  conformation by 3.6 kcal/mol over  $11e_1$  (Table 6). However, the Lewis energy of  $11a_1$  is very unfavorable, +6.4 kcal/mol compared to  $11e_1$ . Steric repulsions also are indicated by geometry distortions; namely, the C6-O1-C2 and O1-C2-N7 bond angles increase by 2.3 and  $4.4^\circ$ , respectively (Table 9), and the C6-O1-C2-N7 dihedral angle is widened ( $-70.9^\circ$  (Table 8)). The outward bending

of the  $\text{NH}_2$  substituent is apparent in Figure 14. This situation is similar to that in the  $a_3$  structures of OH compounds. In the  $11a_3$  conformation,  $n_N-\sigma^*_{\text{C-O}}$  hyperconjugation is not possible. However, since steric repulsions are small,  $11a_3$  is nearly as low in energy as  $11a_1$ . In  $11a_2$  the unfavorable influences from steric effects and hyperconjugation are combined. This is the reason why the  $11a_2$  conformer does not exist. In  $11e_2$  the hydrogens of the  $\text{NH}_2$  group are eclipsed with those at C3. Accordingly the higher energy of  $11e_2$  is mainly due to the Lewis term.  $11e_3$  is disfavored because  $n_N-\sigma^*_{\text{C-O}}$  hyperconjugation is minimal.

According to our analysis, the reverse anomeric effect of 11 is a consequence of the competition between exo-anomeric and steric effects in the axial conformation. In contrast, Booth and Khedhair<sup>81</sup> attributed the reverse anomeric effect of 11 to a competition between endo- and exo-anomeric effects. Due to the absence of the endo-anomeric effect in the equatorial conformation, the exo-anomeric effect is supposed to be larger because both donors compete for the electron deficiency of the anomeric carbon. Since N has a lower electronegativity than oxygen, the exo-anomeric effect may be more important than the

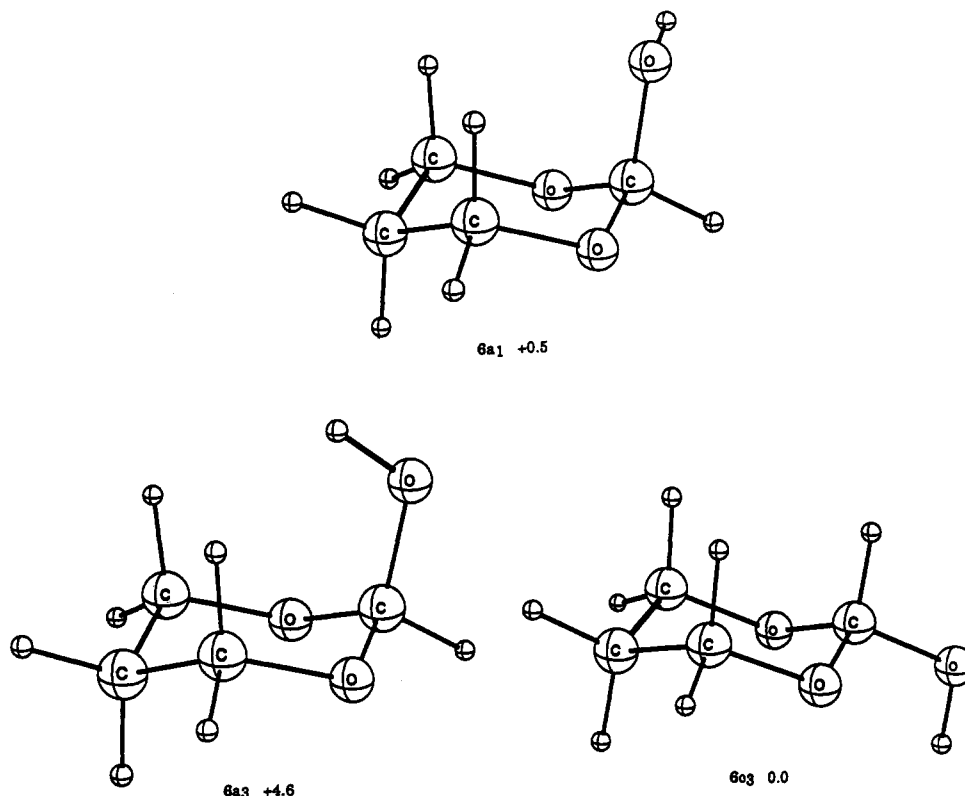


Figure 9. Different conformers of 2-hydroxy-1,3-dioxane (6) (HF/6-31G\* relative energies in kcal/mol).

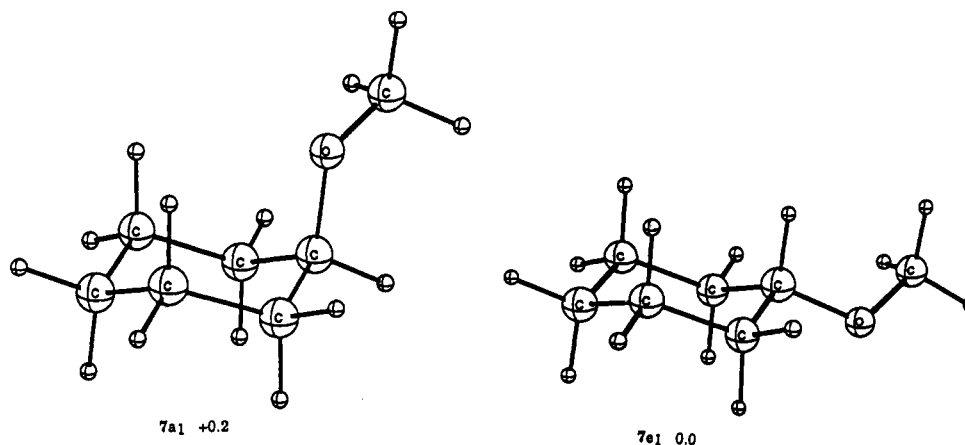


Figure 10. Different conformers of methoxycyclohexane (7) (HF/6-31G\* relative energies in kcal/mol).

endo-anomeric effect for nitrogen compounds and an equatorial preference results.<sup>8m</sup> Table 6, however, shows that these arguments are not valid, since the hyperconjugative term, which includes the endo- and the exo-anomeric effects favors the axial conformation 11a<sub>1</sub>.

The dipole moments of the 11e<sub>1</sub> and 11a<sub>1</sub> structures of aminotetrahydropyran are very similar, 1.27 and 1.37 D. This small difference cannot explain the 2.76 kcal/mol preference for the equatorial structure.

**Cyclohexylammonium Cation (12) and 2-Aminotetrahydropyranyl Cation (13).** Reverse anomeric effects are determined experimentally for quaternary nitrogen atoms.<sup>6b</sup> In agreement with these results, we calculate axial-equatorial energy differences for 12 (Figure 16) and 13 (Figure 17) of -1.4 and -3.0 kcal/mol (Table 3), respectively. Thus, the reverse anomeric effect for 13 is -1.6 kcal/mol. The equatorial preferences of NH<sub>2</sub> and NH<sub>3</sub><sup>+</sup> substituents are therefore almost identical (2.8 and 3.0 kcal/mol) and the reverse anomeric effect is larger for NH<sub>2</sub>. These data are in perfect agreement with the results

of an excellent recent experimental study on the reverse anomeric effect of glucopyranosylammonium ions by Perrin and Armstrong (PA).<sup>39</sup>

The preferences for equatorial conformations in 12 and 13 are entirely due to dominating Lewis energy contributions which outweigh the hyperconjugative preference for the axial form. As anticipated by PA,<sup>39</sup> 13 shows an extraordinary large axial preference due to the hyperconjugative term. The reason is that the lp<sub>O</sub>-σ\*<sub>C-N</sub> interaction (endo-anomeric effect) is about 50% stronger in the cation 13 compared to the amino compound 11. It is unlikely that the large Lewis energy difference is solely due to steric interactions. The NH<sub>3</sub><sup>+</sup> group may be expected to have steric interactions similar to CH<sub>3</sub>. Although the C-C and C-N lengths in 2 and 13 are similar (1.53 and 1.56 Å, respectively) the Lewis term contributes 15.0 kcal/mol for 13 compared to only 3.3 kcal/mol for 2. An inversion of the C-X bond dipole which as discussed

(39) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* 1993, 115, 6825.

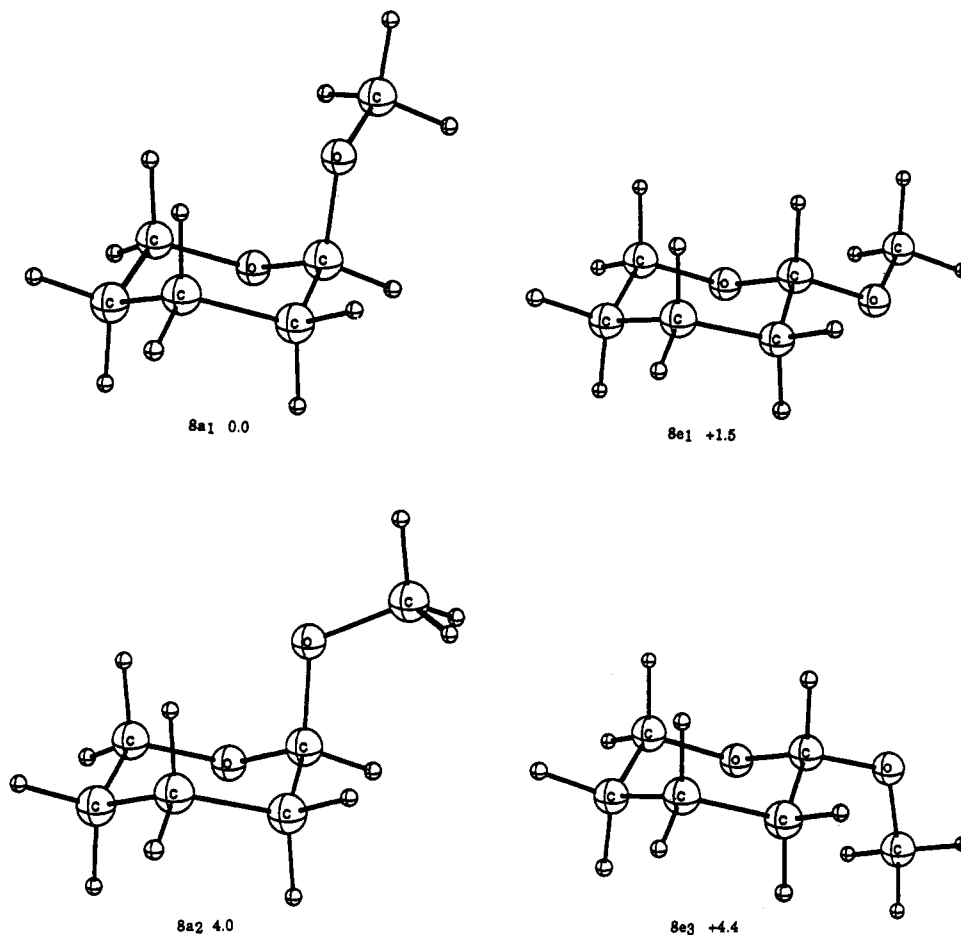


Figure 11. Different conformers of 2-methoxytetrahydropyran (8) (HF/6-31G\* relative energies in kcal/mol).

by Juaristi<sup>19</sup> leads to a destabilization of the axial conformation due to dipole repulsions cannot be invoked to explain the equatorial preference since the charge of the nitrogen atom is  $-0.83$ . The positive charge is distributed over the hydrogens. Thus, the C-X bond dipole moment has the same direction in 13 as in  $\text{NH}_2$  and OH compounds. Electrostatic repulsions between the bond from C2 to the positively charged  $\text{NH}_3^+$  substituent and the C6 to oxygen bond as proposed by Lemieux and Morgan<sup>6a</sup> are unlikely for the same reason.

Although our data agree with PA's experimental results we suggest a somewhat different interpretation. Firstly, PA conclude that there is no reverse anomeric effect in the charged species because the equatorial preference is not enhanced compared to the neutral analogs. We would like to propose a definition of the reverse anomeric effect in analogy to the normal anomeric effect. That is, a reverse anomeric is present if the preference for the equatorial form is increased in the tetrahydropyran compared to the cyclohexane, regardless of whether charged or neutral species are involved. According to this definition both the amino- and the ammoniotetrahydropyran show reversed anomeric effects. Secondly, PA argue that as for the glucopyranosylamines the anomeric equilibria of the conjugate acids can be accounted for almost entirely by steric effects. Our data support this interpretation for the glucopyranosylamines; however, NBO analyses suggest that the situation is more complicated for the charged species. There exists a strong stabilization of the axial conformation due to orbital interactions which is offset by another contribution. We can only say at the moment that this contribution is neither due to steric nor to dipole repulsions. However, an electrostatic origin is likely. The

nearly identical reverse anomeric effects of the amino- and ammoniumtetrahydropyrans are thus accidental and arise from a competition between hyperconjugative and steric effects in the former and between hyperconjugative and electrostatic effects in the latter.

**Fluorocyclohexane (14), 2-Fluorotetrahydropyran (15), Chlorocyclohexane (16), and 2-Chlorotetrahydropyran (17).** Fluorocyclohexane (14), (Figure 18) shows an equatorial preference, 0.3 kcal/mol, with the 6-31G+G\* basis set (Table 3). The ZPE correction increases this value to 0.4 kcal/mol. The geometry of the axial fluorocyclohexane is almost undistorted compared to that of cyclohexane. In fact, the 6-1-2 and the 6-1-2-7 angles are identical in cyclohexane and axial fluorocyclohexane, while the 1-2-7 angle is even slightly *contracted* in the latter! Thus, steric repulsions which are usually considered to be responsible for the equatorial preferences seem to be very small for the fluoro substituent. NBO results differ qualitatively with different basis sets for 14, since the equatorial preference is due to the Lewis term with the 6-31+G\* basis set but due to hyperconjugation with the 6-31G\* and the Huz,F:6-31G\* basis sets. The results with 6-31+G\* are probably not reliable, since improvement of small basis sets by diffuse functions leads to spurious charge transfer.

The  $\Delta E$  (6-31+G\*) value for 2-fluorotetrahydropyran (15) (Figure 19) is 2.8 kcal/mol. An anomeric effect of 3.1 kcal/mol results for 15 at the HF level. For the chloro compounds 16 (Figure 20) and 17 (Figure 21) the (6-31G\*)  $\Delta E_{\text{ax-eq}}$  values are  $-1.0$  and  $+2.5$ , respectively. The anomeric effect of 17 therefore amounts to 3.5 kcal/mol. The larger anomeric effect of 17 compared to 15, however, is therefore due to the stronger equatorial preference in

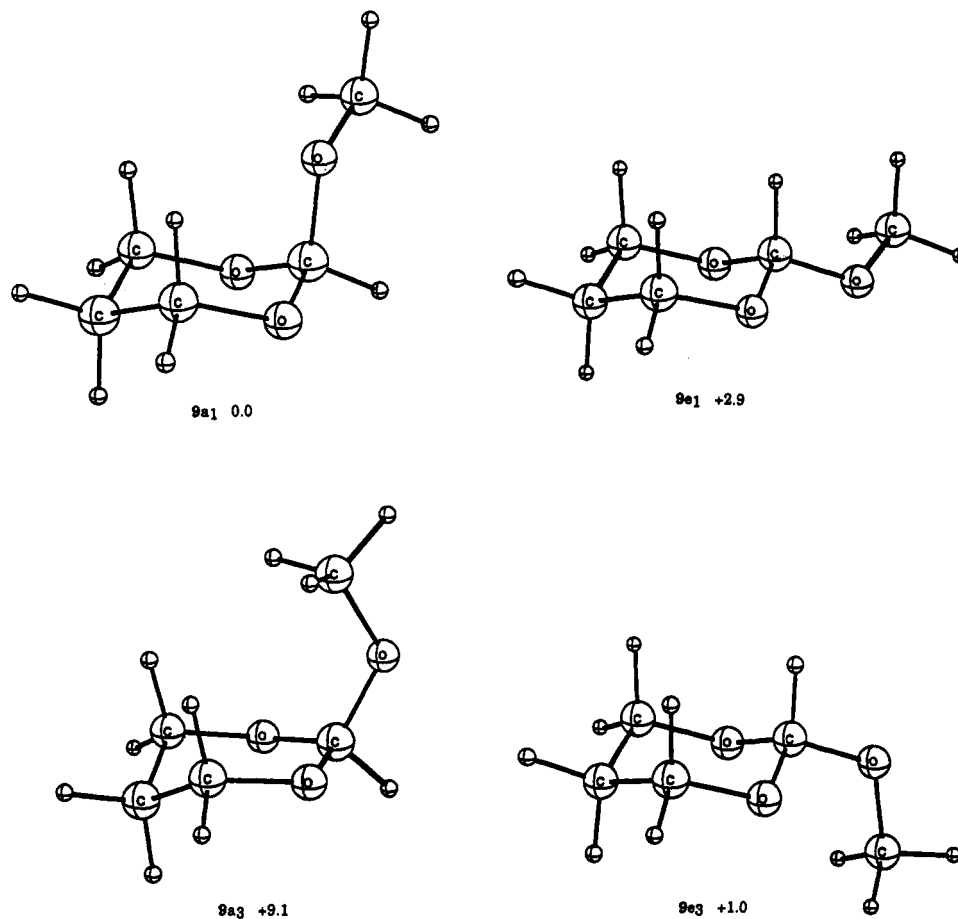


Figure 12. Different conformers of 2-methoxy-1,3-dioxane (9) (HF/6-31G\* relative energies in kcal/mol).

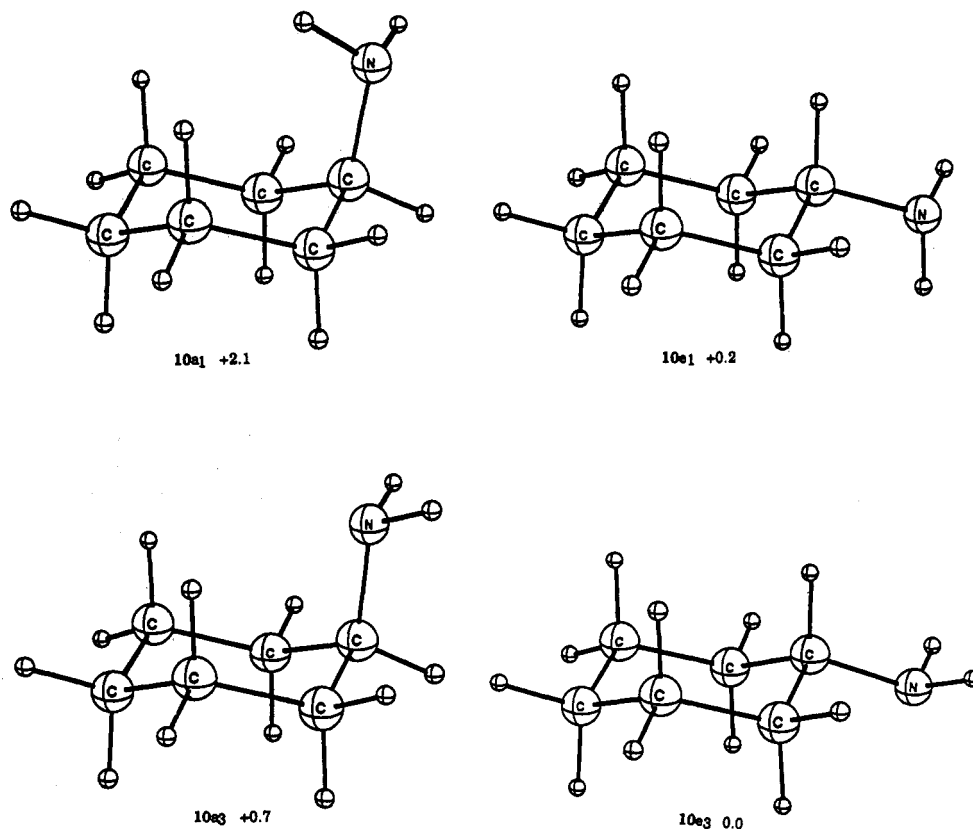


Figure 13. Different conformers of aminocyclohexane (10) (HF/6-31G\* relative energies in kcal/mol).

chlorocyclohexane rather than a larger axial preference in the chlorotetrahydropyran compared to fluorotetrahy-

dropyran. The Lewis energy contributions to the equilibria of fluorocyclohexane (14) and 2-fluorotetrahydropyran (15)



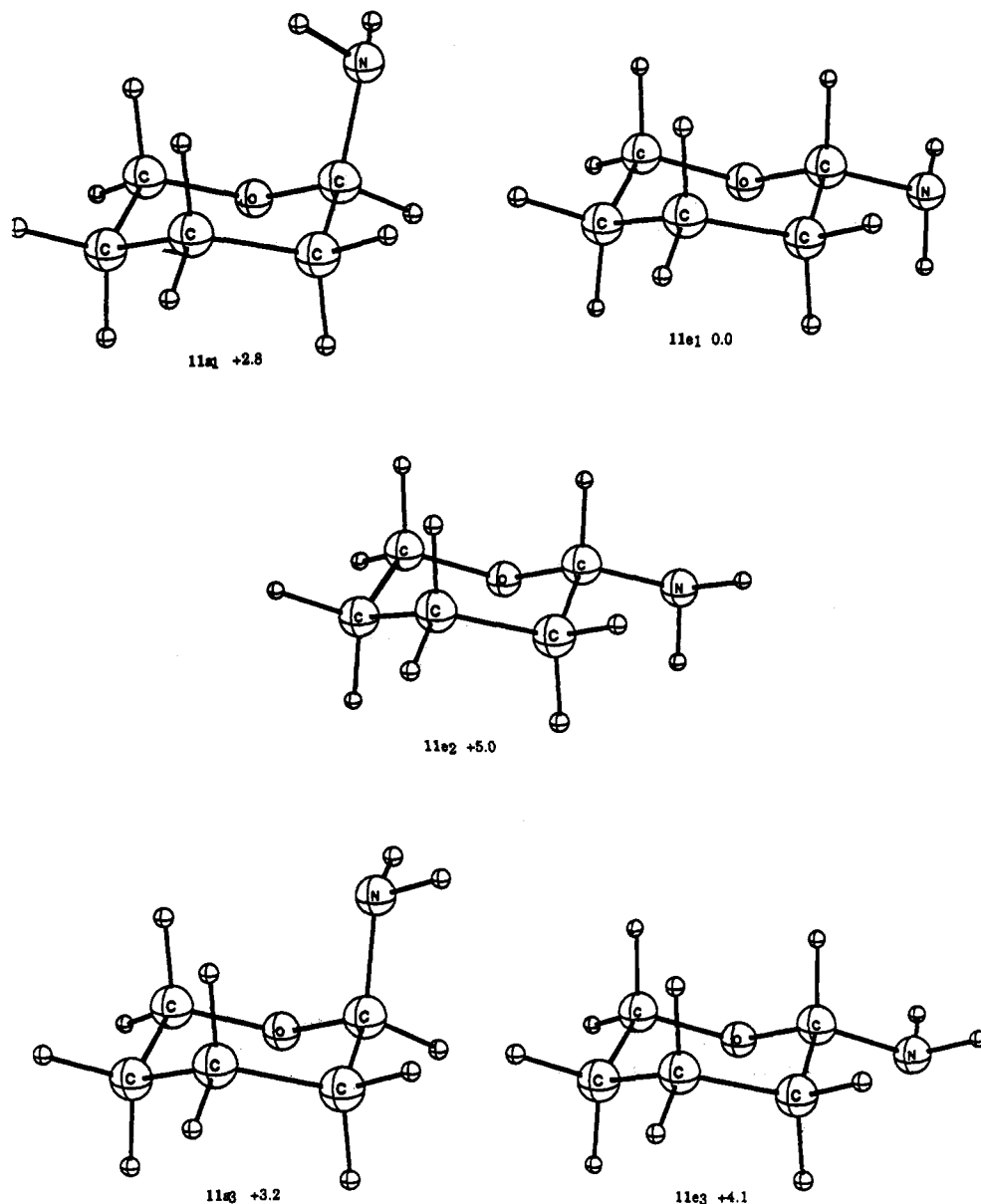


Figure 14. Different conformers of 2-aminotetrahydropyran (11) (HF/6-31G\* relative energies in kcal/mol).

are negative, and the axial preference is due to hyperconjugation. However, as for 14, the NBO analysis with the 6-31+G\* basis set is not very reliable.

In 2-chlorotetrahydropyran (16), Lewis and hyperconjugation contributions have opposite signs and are larger than for 15. Hyperconjugation is dominating. Large C6-O1-C2-Cl dihedral angles in the axial conformations of 16 and 17 indicate that the larger Lewis energy contributions are due to steric repulsions involving the bulky chlorine substituent. The difference in the hyperconjugative contributions compared to 2-fluorotetrahydropyran (15) is mainly due to the  $sp_0$  lone pairs.  $sp_0-\sigma^*_{C-F}$  interactions are significant in the equatorial form of 15 and partly compensate the axial preference of the  $p_0-\sigma^*_{C-F}$  interactions.  $sp_0-\sigma^*_{C-Cl}$  contributions to the equilibrium, however, are negligible. A larger axial preference due to hyperconjugation results. Note, however, that  $p_0-\sigma^*_{C-F}$  interactions are stronger than  $p_0-\sigma^*_{C-Cl}$  hyperconjugation.

**Glucose (18) and Methyl Glucoside (19).** The anomeric effect was originally discovered for sugars. However, glucose is the exception to the rule, showing a slight equatorial preference (0.33 kcal/mol in water<sup>3</sup>). For

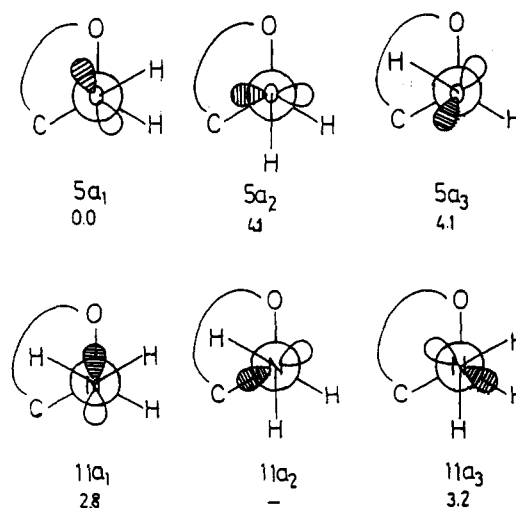


Figure 15. Newman projections and relative energies of three staggered axial structures of 2-hydroxytetrahydropyran (5) and 2-aminotetrahydropyran (11).

the substituted analogues axial preferences are usually observed.<sup>3</sup> This can hardly be explained with hypercon-

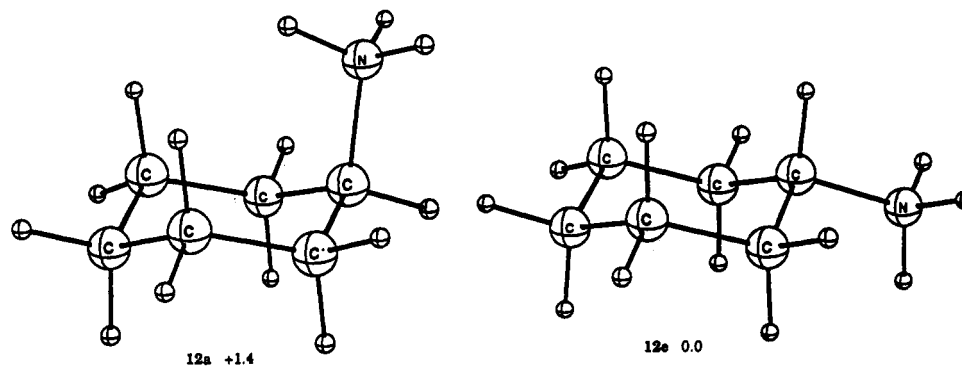


Figure 16. Different conformers of the cyclohexylammonium ion (12) (HF/6-31G\* relative energies in kcal/mol).

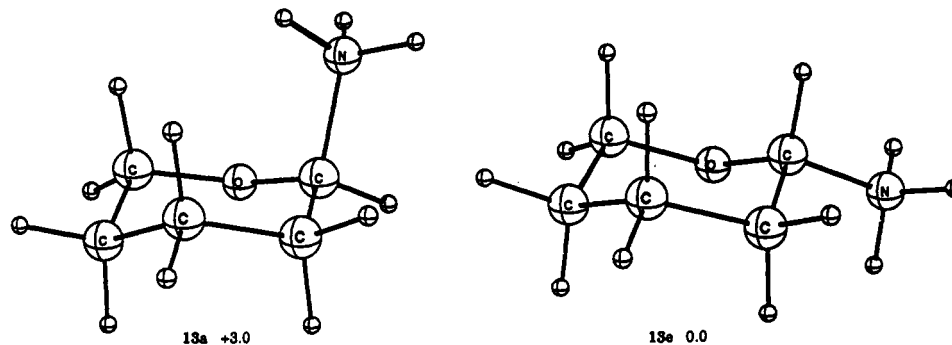


Figure 17. Different conformers of the 2-tetrahydropyranylammonium ion (13) (HF/6-31G\* relative energies in kcal/mol).

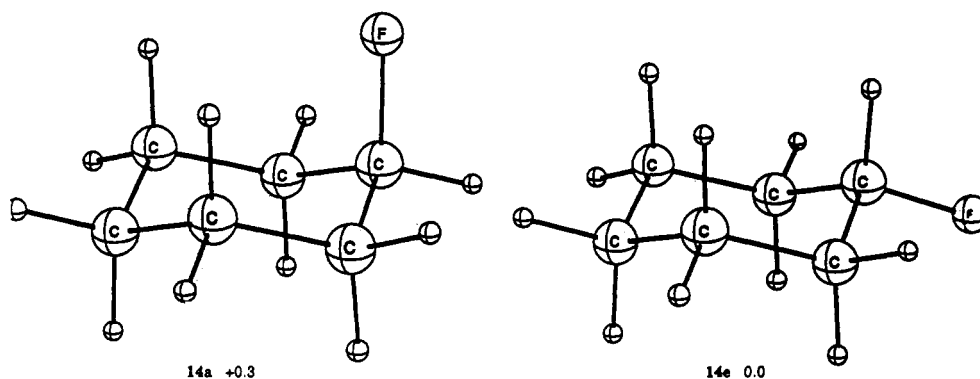


Figure 18. Different conformers of fluorocyclohexane (14) (HF/6-31+G\* relative energies in kcal/mol).

jugation and is in contradiction to steric influences. We therefore optimized glucose (18) and methyl glucoside (19) and carried out NBO analyses for both systems.

Polavarapu and Ewig (PE)<sup>40</sup> showed in a detailed study on various conformers of glucose (at the HF/4-31G level) that the conformation of the CH<sub>2</sub>OH group does not influence the *relative* energies of the  $\alpha$ - and  $\beta$ -anomers. Therefore, we made no attempt to locate the possible minima and only reoptimized PE's lowest energy conformers TG,G1 (18a in Figure 22) and GT,G1 (18b in Figure 22) at HF/6-31G\* level. Since the orientations of the ring hydroxy groups and of the CH<sub>2</sub>OH group differ from those observed in the crystal structure of  $\alpha$ -D-glucose<sup>41</sup> we also optimized the  $\alpha$ - and  $\beta$ -anomers in this conformation (18c in Figure 22). The conformations at the anomeric carbon correspond to either  $a_1$  or  $e_1$  (compare Figure 8). All three conformations lead to preferences for the  $\alpha$ -anomer of 1.1–1.3 kcal/mol (Table 3). These results are in contrast to the equatorial preference in water. However, one would expect that in the gas phase the  $\alpha$ -conformer would become

more favorable in relation to the  $\beta$ -conformer, since the polar solvent decreases the anomeric effect.<sup>8c,d,n,29,32</sup> In addition, basis set truncation and neglect of ZPE cause a bias of about 1 kcal/mol toward the axial conformation.

In the crystal structure of  $\alpha$ -D-glucose,<sup>41</sup> the orientation of the CH<sub>2</sub>OH and of the ring oxygen groups corresponds to the higher energy conformers 18c. These conformers lie 7.9 kcal/mol higher in energy than 18a and 18b, which are nearly equivalent in energy. Since this energy difference is identical for  $\alpha$ - and  $\beta$ -conformers the anomeric energy difference is not affected. The higher energies of these structures may be rationalized by hydrogen bonding. Since no *intermolecular* hydrogen bonds or hydrogen bridges with a solvent can be formed in the gas phase, glucose tends to maximize the number of *intramolecular* hydrogen bonds. In structures 18a and 18b the hydroxy groups at C3 point in the direction of the anomeric center. Hence, hydrogen bridges can be formed between the anomeric oxygen and the hydrogen at the adjacent carbon atom. Note that these OH groups prefer different

(40) Polavarapu, P. L.; Ewig, S. *J. Comput. Chem.* 1992, 13, 1255.

(41) Brown, G. M.; Levy, H. A. *Acta Crystallogr. Sect. B* 1979, 656.  
(42) Reference 40, supplementary material.

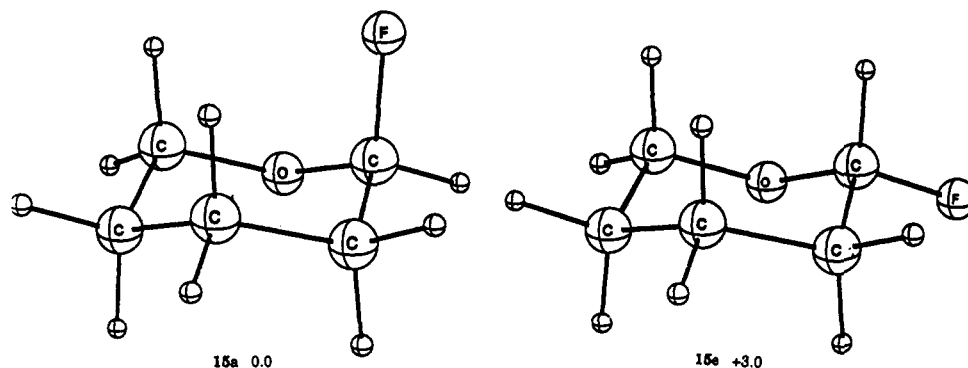


Figure 19. Different conformers of 2-fluorotetrahydropyran (15) (HF/6-31+G\* relative energies in kcal/mol).

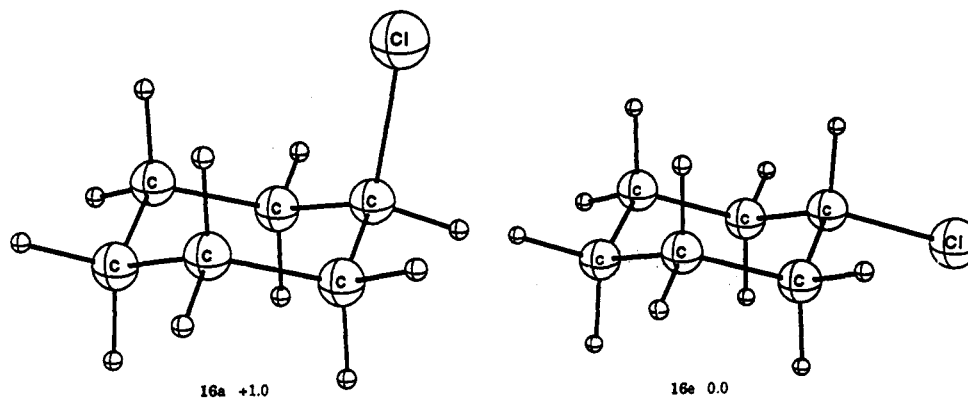


Figure 20. Different conformers of chlorocyclohexane (16) (HF/6-31G\* relative energies in kcal/mol).

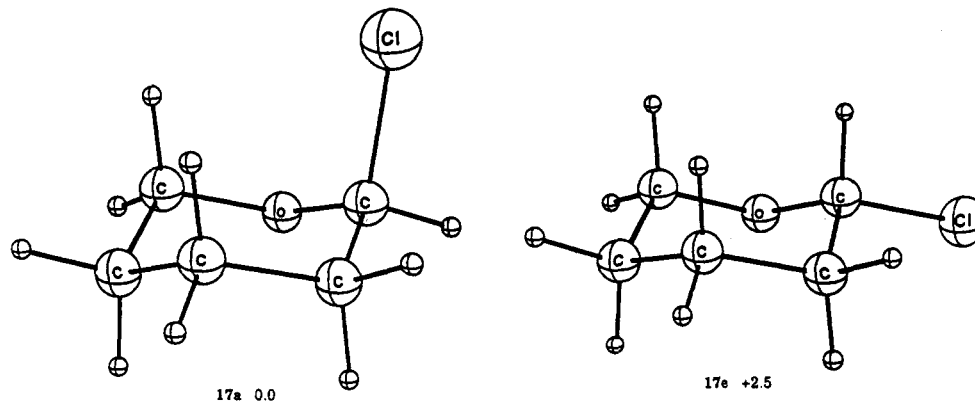


Figure 21. Different conformers of 2-chlorotetrahydropyran (17) (HF/6-31G\* relative energies in kcal/mol).

orientations in the  $\alpha$ - and  $\beta$ -anomers, the H-O-C3-C2 dihedral angles being  $-81^\circ$  and  $180^\circ$ , respectively. In 18 $\alpha$ c, 18 $\beta$ c, all three ring OH groups are orientated in a counterclockwise fashion and thus point away from the anomeric center. The same holds for the CH<sub>2</sub>OH conformation. In the crystal the OH group is directed away from the ring, and in the gas-phase structures the OH group is close either to the ring oxygen or to the oxygen at the adjacent carbon. These additional two hydrogen bonds probably account for the nearly 8 kcal/mol lower energies of 18a and 18b in the gas phase.

Methyl glucoside (19) (Figure 23) was optimized only in one conformation, corresponding to 18b. An axial preference of 1.5 kcal/mol results at HF/6-31G\*. This value hardly differs from the glucose results indicating that the experimentally observed differences between glucose and its derivatives may be related to solvent effects involving the anomeric hydroxy groups.

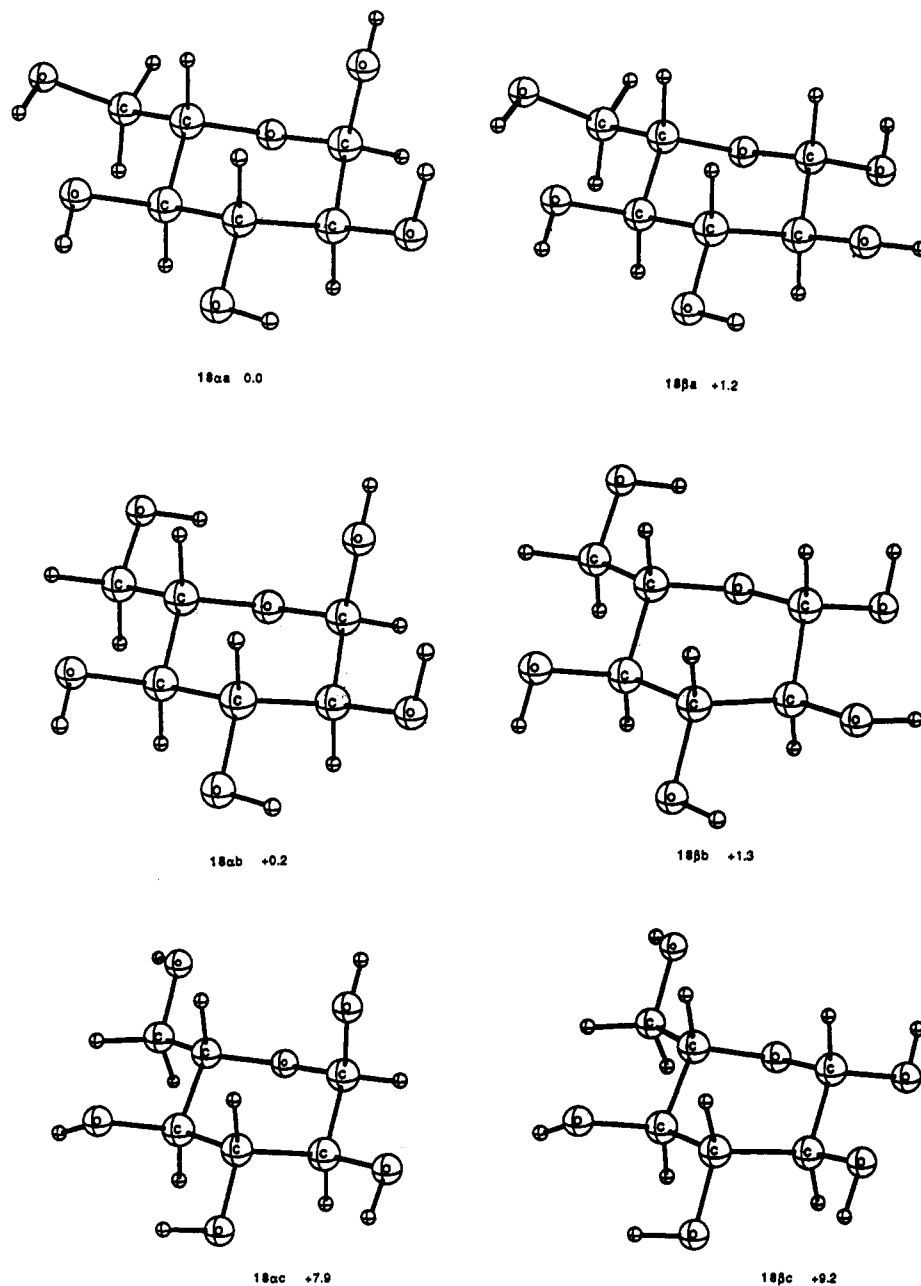
NBO analyses were carried out for 18a, 18b, 18c, and 19. The hyperconjugative contributions are 3.4, 3.7, 1.9, and

3.1 kcal/mol, respectively. The values for the hydrogen-bonded structures 18a, 18b, and 19 are larger than for 18c. The value for 18c is similar to those for hydroxy- (5) and methoxytetrahydropyran (8) (Table 4). This indicates that hydrogen bonding contributes to the Lewis and to the delocalization energies. In the absence of hyperconjugation, equatorial preferences result. The dipole moment differences are very small and cannot be responsible for the significant energy differences.

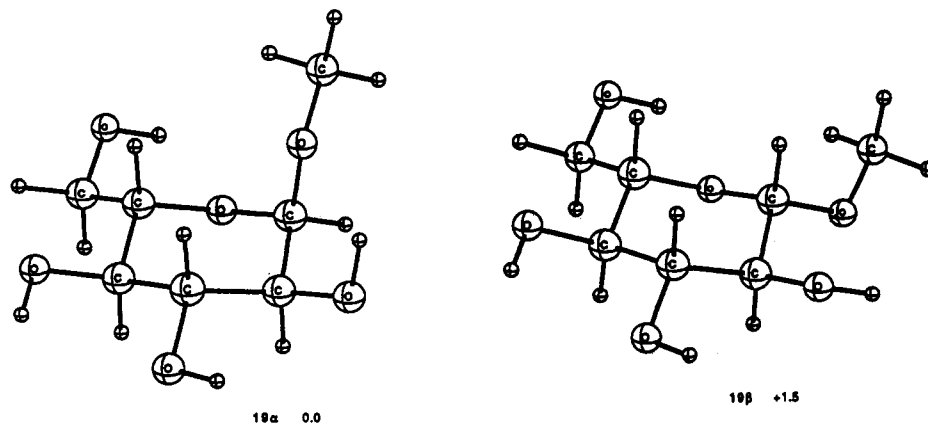
#### Geometries

Table 8 summarizes the calculated geometrical parameters for the lowest axial and the lowest equatorial structures of compounds 1-19. Table 9 gives the differences in bond lengths and bond angles between these conformations. Positive signs indicate larger values in the axial structures.

$\text{pO1-}\sigma^*\text{C2-X7}$  hyperconjugation (endo-anomeric effect) tends to shorten the O1-C2 bond and to lengthen the C2-O7 bond.  $\text{pX7-}\sigma^*\text{C2-O1}$  hyperconjugation (exo-anomeric



**Figure 22.** Different conformers of glucose (18) (HF/6-31G\* relative energies in kcal/mol).



**Figure 23.** Different conformers of methyl glucose (19) (HF/6-31G\* relative energies in kcal/mol).

effect) has the opposite influence. The latter is present in axial and equatorial structures, and the former is absent in the equatorial conformations. Thus, the orbital interaction model predicts the O1–C2 bonds to be shorter and

the C2–O7 bonds to be longer in the axial forms of tetrahydropyrans and dioxanes.

We note a general trend toward longer 1–2 bond lengths in the axial conformations of hexanes and in 2-meth-

oxytetrahydropyran (6). In contrast, the 1-2 bonds are uniformly shorter in the axial forms of tetrahydropyrans and dioxanes. The exocyclic 2-7 bonds are longer in the axial forms for all compounds, but the effect is more pronounced in the anomeric systems. Thus, for all compounds the trends are in line with the orbital interaction model.

The 6-1-2 angles are larger in the axial conformers of hexanes (0.4-3.3°), tetrahydropyrans (1.4-5.1°), and dioxanes (0.9-2.7°), indicating that the rings are less puckered than in the equatorial forms. The values increase for the individual substituents in the order hexanes < tetrahydropyrans < dioxanes. The largest differences in 6-1-2 angles between axial and equatorial structures are calculated for the bulky NH<sub>3</sub><sup>+</sup>, Cl, CH<sub>3</sub>, and NH<sub>2</sub> substituents. This indicates the influence of steric repulsions in agreement with large Lewis energy differences between axial and equatorial structures.

The 1-2-7 (X-C-X) angles in cyclohexanes are similar in axial and equatorial conformations. In contrast, the 1-2-7 bond angles in the axial conformers are significantly widened in the tetrahydropyrans and dioxanes. Similar O-C-O bond angle widening also is observed in methanediol. Theoretical examinations revealed that hyperconjugation is responsible.<sup>43</sup> Indeed, the O-C-O angle is even larger (112.4°) in the C<sub>2</sub> structure of methanediol than in hydroxytetrahydropyran (111.9°). Thus, 1-2-7 bond angle increases in axial tetrahydropyran conformers are probably due to hyperconjugation rather than to steric repulsions.

The 6-1-2-7 dihedral angles of the axial conformers of OH, OMe, and F compounds are between -65 and -68° for hexanes and pyrans. These values are almost identical to the 66° 6-1-2-7 dihedral angle in unsubstituted cyclohexane. CH<sub>3</sub>, NH<sub>2</sub>, NH<sub>3</sub><sup>+</sup>, and chlorine prefer larger 6-1-2-7 angles, -71 to -74°. The increases of the 6-1-2-7 dihedral angles lead to flattening of the rings and an outward bending of the hydrogens at C4 and C6. With the exception of methylcyclohexane such ring distortions are found in the systems which also display large 6-1-2 angle increases and large Lewis energy contributions to the  $\Delta E$  values. Thus, steric effects seem to be responsible.

### Conclusions

Although our theoretical calculations refer to isolated molecules at 0 K, calculated axial-equatorial energy differences and anomeric effects at the HF/6-31G\* level are in qualitative agreement with experimental data obtained in solution. However, comparison with higher level computations indicated that the HF/6-31G\* results are biased toward axial structures by about 1 kcal/mol. The largest deviations are observed for the fluoro compounds. The axial conformer of fluorocyclohexane is erroneously predicted to be more stable than the equatorial form with the 6-31G\* basis set at the HF as well as at the MP2 and MP4 levels. However, the 6-31+G\* and the larger Huzinaga basis sets reproduce the experimentally observed equatorial preference. Since the deviations due to basis set truncation seem to be similar for hexanes, tetrahydropyrans, and dioxanes, the accuracy of the calculated anomeric effects ( $\Delta\Delta E$  values) is about 0.5 kcal/mol.

In agreement with experiment, all our cyclohexanes favor equatorial structures. NBO analysis, however, suggests

that delocalization rather than steric effects are responsible for the equatorial preferences with all substituents, except NH<sub>3</sub><sup>+</sup> and Cl. This interpretation is supported by the fact that OH, OMe, NH<sub>2</sub>, and F causes very small distortions of the rings compared to the unsubstituted cyclohexane and small differences in the geometrical parameters between axial and equatorial conformers.

The contributions due hyperconjugation show regular trends. In methylcyclohexane hyperconjugation favors the equatorial structure by about 2 kcal/mol. In electro-negative substituted cyclohexanes, the equatorial preference due to hyperconjugation is decreased by about 1 kcal/mol. In 2-methyltetrahydropyran the differential contribution of hyperconjugation to the equilibrium is negligible but favors axial structures in all electronegative 2-substituted tetrahydropyrans.

The anomeric effects of 2-hydroxy-, 2-methoxy-, 2-fluoro-, and 2-chlorotetrahydropyran, of glucose, and of methyl glucoside are due to hyperconjugative stabilization. The reverse anomeric effects with the NH<sub>2</sub> and the NH<sub>3</sub><sup>+</sup> substituents are due to steric and electrostatic effects, respectively. Dipole repulsions in the axial structure of the 2-ammoniotetrahydropyran, because of a reversed C-X bond dipole compared to OR or halogen compounds, are not responsible for the equatorial preference, since the positive charge is on the hydrogens. The nitrogen atom charge is -0.8, leading to same orientation of the bond dipole as in OR and halogen compounds.

Hyperconjugation stabilizes the equatorial more strongly than the axial conformers of dioxanes. Axial forms of 2-hydroxytetrahydropyrans and 2-hydroxy-1,3-dioxanes cannot adopt the conformations with the largest exo-anomeric stabilizations because of steric repulsions. Therefore, exo-anomeric effects are usually stronger in equatorial conformations. Due to the presence of two oxygen atoms in the ring exo-anomeric effects are stronger in 1,3-dioxanes than in tetrahydropyrans and outweigh the endo-anomeric axial preference. 2-Hydroxy-1,3-dioxane actually adopts the equatorial structure. 2-Methoxy-1,3-dioxane prefers the axial conformation despite the hyperconjugative stabilization of the equatorial conformer. The anomeric effect of 2-methoxy-1,3-dioxane has thus a different origin than that of 2-hydroxy- and 2-methoxytetrahydropyrans.

The dipole repulsion model correctly predicts the axial preferences of the 2-OH, 2-OMe, 2-F, and 2-Cl tetrahydropyrans; however, it fails to account for equatorial preferences of 2-hydroxy-1,3-dioxane and of the NH<sub>2</sub> and NH<sub>3</sub><sup>+</sup> tetrahydropyrans. Furthermore, there is no correlation between dipole moment changes and Lewis energy differences between axial and equatorial structures. Lewis energies, however, include electrostatic terms. Since axial preference of the anomeric systems vanish when the axial-equatorial energy differences are calculated in absence of hyperconjugation, NBO analysis suggests that dipole repulsions are not responsible for the anomeric effect, even for 2-hydroxy-, 2-methoxy-, 2-fluoro-, and 2-chloro-tetrahydropyrans. Our general conclusions thus differ significantly with those proposed recently.<sup>44</sup>

**Acknowledgment.** We thank Dr. A. Dorigo for carefully reading the manuscript. This work was supported by the Stiftung Volkswagenwerk, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

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