Origin of the Anomeric Effect Revisited. Theoretical Conformation Analysis of 2-Hydroxypiperidine and 2-Hydroxyhexahydropyrimidine

Ulrike Salzner

*Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115*

Received October 17, 1994[⊗]

In a recent publication[1] NMR spectroscopic conformation analysis of 2-methoxy-1,3-dimethyl-hexahydropyrimidine was reported. The results were interpreted in terms of dipole repulsions and the author's claim to have proven that anomeric effects are in general not due to hyperconjugation. Various conformers of hexahydropyrimidine (**1**), 2-hydroxypiperidine (**2**), and 2-hydroxy-hexahydropyrimidine (**3**) were therefore optimized at the HF/6-31G* level, and the wave functions were analyzed with the NBO method. In agreement with experiment, theoretical results predict that anomeric effects are attenuated when compared to oxygen systems. This, however, is due to repulsions between parallel O−H and N−H bonds which destabilize the axial conformer with the strongest hyperconjugative interactions. Relative energies do not correlate with total dipole moments and are inconsistent with the dipole repulsion model. We thus confirm earlier conclusions that anomeric effects are due to charge back donation from lone pairs rather than dipole repulsions.

Introduction

The discussion about the origin of the anomeric effect is nearly as old as the term anomeric effect itself.[2−6] The first explanation for the anomeric effect, namely the unexpected preference of sugars for the sterically more crowded axial anomer, was offered by Edward in 1955.[7] He pointed out that electrostatic repulsive forces between the dipole due to the ring oxygen lone pairs and the exocyclic oxygen might be responsible for axial preferences (Scheme 1). This rationalization became to be known as "rabbit ear effect"[8] and is still favored by several research groups.[1,9]

In 1964 Altona and Romers[10,11] came up with an entirely different rationalization. They observed that 2,5-dichloro-1,4-dioxanes (Scheme 2) have unusually long exocyclic C−Cl bonds and unusually short endocyclic C−O bonds and suggested that in axial, and only in axial conformations, oxygen lone pairs may delocalize into antibonding C−Cl* orbitals (Scheme 3). This was assumed to account for the observed geometry distortions and for stabilizations of axial conformers. This interpretation is supported by analyses of ab initio wave functions such as the PMO,[11] NBO,[12−14] and Bader analysis.[12] Later Altona et al.[13−16] favored a different
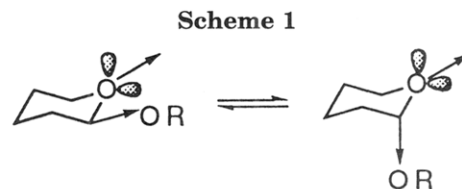
Scheme 1
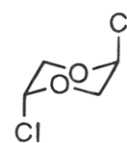
Scheme 2

Scheme 3

interpretation. They constructed anomeric systems from transferable group orbitals and discovered that the correct SCF-energies could only be reproduced by allowing for interactions between the nonorthogonal group orbitals. The resulting nonadditive energy contributions, however, were absorbed in interference rather than charge transfer terms. We are content that PMO, NBO, and Altona's analyses reflect the same physical effect. Whatever type of orbitals is employed to represent the electronic distribution, quantum chemical mixing results which leads to a slight double bond character of the C−O donor bond and a weakening of the acceptor bond.

[⊗] Abstract published in *Advance ACS Abstracts*, February 1, 1995.

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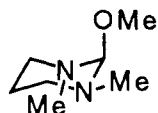
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Scheme 4

Scheme 5
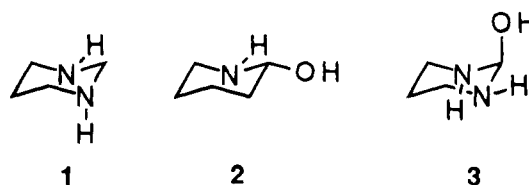
Scheme 6

1   2   3
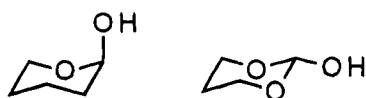
In order to test the dipole repulsion model and the hyperconjugation hypothesis independent of energy decomposition schemes, we optimized axial and equatorial conformations of 2-hydroxy-1,3-dioxane and compared them to the corresponding structures of 2-hydroxytetrahydropyran (Scheme 4).[13] The idea was that the presence of a third oxygen might attenuate axial preferences due to hyperconjugation since the ring oxygen can now also engage in $p_O \rightarrow \sigma^*_{C-O}$ interactions within the ring and the exo-anomeric effect which favors equatorial conformations might be increased. Dipole repulsions, however, would still favor the axial form. At HF/6-31G* 2-hydroxy-1,3-dioxane actually prefers the equatorial conformation by 0.5 kcal/mol. At the same level of theory 2-hydroxytetrahydropyran favors the axial form by 1.3 kcal/mol. The equatorial preference of 2-hydroxy-1,3-dioxane thus provides evidence against the dipole repulsion model. NBO analysis confirms that the equatorial preference of 2-hydroxy-1,3-dioxane is due to hyperconjugation, i.e. an enhanced exo-anomeric effect in the equatorial conformer compared to 2-hydroxytetrahydropyran. (Theoretical and experimental investigations show that 2-methoxy-1,3-dioxane prefers the axial conformation. NBO analysis, however, indicates that this axial preference is not due to hyperconjugation.)

In a recent experimental study Perrin et al.[1] attempted to assess the relative importance of hyperconjugative effects and dipole repulsions by replacing the ring oxygen by nitrogen (Scheme 5). This leads to a decrease of dipole repulsions while $n_N \rightarrow \sigma^*_{C-O}$ interactions are expected to be stronger than $p_O \rightarrow \sigma^*_{C-O}$ interactions. Therefore these authors argue that if dipole repulsions are more important, the anomeric effect should decrease, and if hyperconjugation is more important, the anomeric effect should increase compared to 2-methoxy-1,3-dioxane. Since no increase in axial preference was observed, they concluded that hyperconjugation is not responsible for anomeric effects.

Unfortunately, Perrin et al. employed 2-methoxy-1,3-dimethylhexahydropyrimidine for their investigation rather than a 2-substituted piperidine. Since hyperconjugative interactions in the oxygen analogs 2-hydroxy- and 2-methoxy-1,3-dioxanes favor equatorial conformations, the hexahydropyrimidine system might not be the ideal model for that kind of investigation. Furthermore, significant steric interactions are to be expected in 2-methoxy-1,3-dimethylhexahydropyrimidine. Perrin et al. discuss steric interactions and state that van der Waals repulsion in the axial conformation is relieved by rotation about the C–O bond. C–O bond rotation, however, attenuates the (exocyclic) $p_O \rightarrow \sigma^*_{C-N}$ interactions. Such a competition between steric and hyperconjugative effects actually leads to the equatorial preference of 2-aminotetrahydropyran.[13] Although it is an interesting proposal to test the relative importance of hypercon-

jugative and electrostatic effects by replacing oxygen with nitrogen, the evidence presented by Perrin et al. that anomeric effects are due to dipole repulsions is not convincing. We therefore reinvestigated conformational equilibria of nitrogen systems theoretically and tried to avoid excessive steric effects by employing hexahydropyrimidine (1), 2-hydroxypiperidine (2), and 2-hydroxyhexahydropyrimidine (3) (Scheme 6).

Methods

All geometry optimizations and energy evaluations were carried out at HF/6-31G* with GAUSSIAN 92.[14] Gas phase calculations are appropriate for this study since anomeric effects are intrinsic molecular properties and since axial–equatorial equilibria are hardly influenced by unpolar solvents.[9] In polar solvents anomeric effects decrease.[9] This, however, is not of interest in the present context. It has been shown in numerous studies that experimental results for anomeric equilibria are reproduced quite accurately at the HF/6-31G* level while smaller basis sets tend to overestimate axial preferences.[4,9–11,13,15–51] We have shown for a large range of systems[13] that basis set improvement beyond 6-31G* and

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inclusion of ZPE corrections together decrease axial (increase equatorial) preferences by 0.5–1 kcal/mol. Correlation effects at the MP2 level were shown to vanish with sufficiently large basis sets whereas MP2 corrections with the 6-31G* basis set increase axial preferences.[13] Correlation effects with the 6-31G* basis set are thus artifacts and were not included in the present study.

NBO analyses were also carried out with Gaussian 92. Hyperconjugative energy contributions were computed with the NBO deletion procedure.[52–54] We designated total SCF energies as E_{tot}, energies obtained after deletion of all off-diagonal Fock matrix elements with E_{Lew}, and delocalization energies as E_{del} ($E_{del} = E_{tot} - E_{Lew}$). E_{del} thus incorporates all possible orbital interactions. Although the familiar $n_Y–\sigma^*_{C-X}$ interactions are the dominant terms, smaller interactions of lone pairs with C–H and C–C antibonds as well as bond–antibond interactions also contribute. These smaller interactions lower the energy differences due to the absence and the presence of $n_Y–\sigma^*_{C-X}$ interactions considerably. In addition $n_Y–\sigma^*_{C-X}$ interactions depend crucially on the overlap between donor and acceptor and are thus influenced by subtle geometry differences between the various conformers. Counting the number of interactions of a certain type and adding up stabilizing energy contributions therefore provides a very crude guess only and can well be off by several kcal/mol. The interplay between various orbital interactions was discussed in more detail previously.[34]

E_{Lew} includes all energy contributions apart from delocalization effects. These are, in particular, steric, and electrostatic effects which cannot be separated with the NBO method. Note that electrostatic contributions to the Lewis energy are explicitly calculated electron–electron repulsions, nuclear–electron attractions, and nuclear-nuclear repulsions. These have to be distinguished from electrostatic repulsions as obtained from the dipole repulsion model which evaluates repulsions between bond dipoles classically. In addition Lewis energies are influenced by geometry changes induced by orbital interactions since geometries are not relaxed after the deletion procedure. Large individual orbital interactions which cause, for instance, a certain bond angle to widen lead to higher Lewis energies. We did not reoptimize the geometries after the deletion procedure since these energy increases have to be overcome to achieve larger stabilizition and should therefore be included. Interpretation of the Lewis energies is thus not completely straightforward.

Since it has been proposed that gas phase energies are lower for conformers with lower dipole moments,[1,44] we also cite dipole moments for all structures.

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Table 1. Relative Energies (E_{rel}), Relative Energies after Removal of Hyperconjugative Interactions (E_{Lew}), Contributions from Hyperconjugation (E_{del}) to the Total Energy Differences, and Dipole Moments (Dip) for ea, aa, and ee Conformers of Hexahydropyrimidine (1)

	E_{rel}	E_{Lew}	E_{del}	Dip
1ea	0.0	0.0	0.0	1.33
1aa	0.16	4.07	−3.91	1.78
1ee	2.95	1.20	1.74	2.03

Results

Hexahydropyrimidine (1). Hexahydropyrimidine, **1**, was optimized in three conformations which differ by the orientation of N–H bonds: axial/axial (aa), equatorial/axial (ea), and equatorial/equatorial (ee) (Figure 1). Conformation 1ea was fully optimized in C_1 symmetry and 1aa and 1ee in C_s. Relative energies and NBO results for **1** are summarized in Table 1. The 1ea and the 1aa conformers are close in energy and significantly more stable than the 1ee form. This ordering is contrary to what would be expected according to the VSEPR model. Since lone pairs require more space than bond pairs according to VSEPR, the relative energies are predicted to increase in the ordering 1aa < 1ea < 1ee. The dipole repulsion model correctly places 1ee with two axial nitrogen lone pairs highest in energy. If it is assumed that the polar N–H bonds also cause dipole repulsions but that these are smaller than those between the lone pairs, 1aa were lowest in energy. The similar energies of 1ea and 1aa can thus be rationalized by additional 1,3-diaxial steric repulsions between the axial N–H bonds in 1aa. The relative energies also correlate roughly with the total dipole moments. However, the dipole moments increase smoothly by about 0.5 D for 1ea < 1aa < 1ee while the total energies of 1ea and 1aa are almost identical and much lower than that of 1ee.

The NBO energy decomposition suggests a different interpretation. In the 1ee conformation the nitrogen lone pairs are antiperiplanar with the adjacent axial hydrogen. In the 1aa conformation both nitrogen lone pairs are antiperiplanar with the adjacent C–N bonds. Since $n_N–\sigma^*_{C-N}$ interactions are stronger than $n_N–\sigma^*_{C-H}$ interactions, a preference due to hyperconjugation for 1aa over 1ea and 1ee results. This is borne out in the NBO deletion energies (E_{del} in Table 1). E_{Lew} in line 2 of Table 1 shows that after removal of the hyperconjugative energy contributions 1aa is highest in energy. This points to repulsions between the N–H bonds. Thus, according to NBO analysis dipole repulsions between the lone pairs are much smaller than repulsions between the N–H bonds and do not explain the relative energies of **1**. The similar energies of 1aa and 1ea then result as a compromise between avoiding repulsions and maximizing hyperconjugative stabilization. The high energy of 1ee is due to attenuated hyperconjugative effects.

2-Hydroxypiperidine (2). For 2-hydroxypiperidine, **2**, twelve conformations arise due to combination of different O–H rotamers in axial and equatorial forms with axial and equatorial conformations of the N–H bond. Eleven of these conformations could be optimized and are shown in Figure 2. We designate the axial and equatorial orientations of the O–H group with capital letters (A and E), and the conformation of the N–H bond with small letters (a and e). The indices specify the C–O bond rotamers. The missing structure ($2A_3a$) is not a stationary point on potential energy surface. All conformers of **2** are optimized in C_1 symmetry. Table 2 summarizes the results.
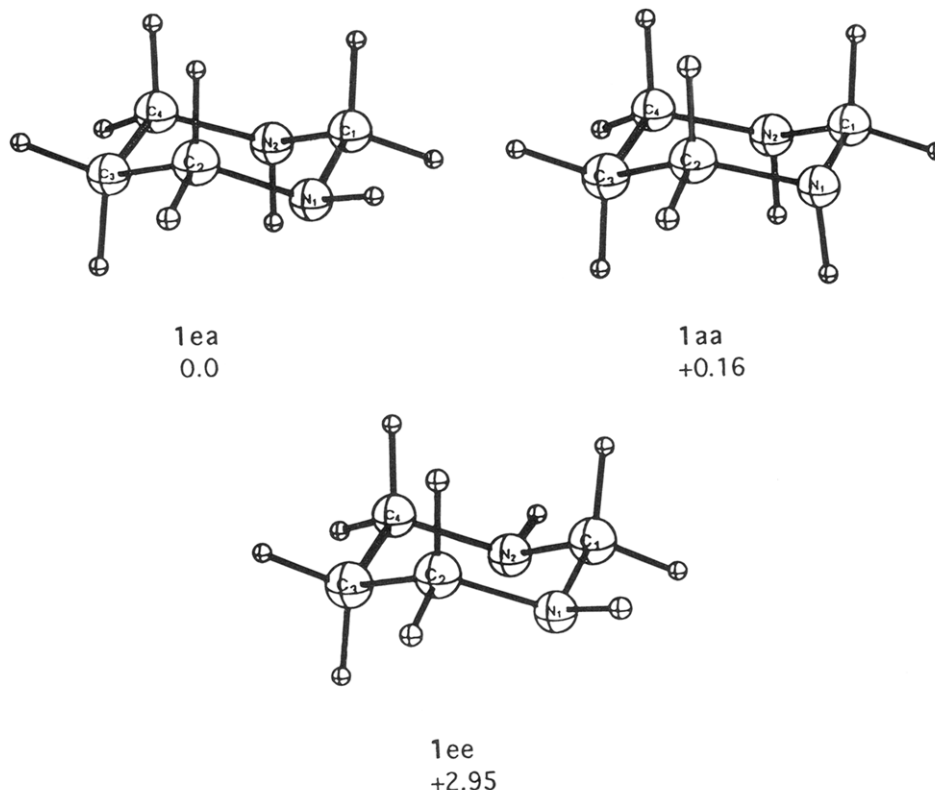
1ea
0.0

1aa
+0.16

1ee
+2.95

Figure 1. HF/6-31G* optimized structures and relative energies (in kcal/mol) of hexahydropyrimidine (**1**) conformers.

Table 2. Relative Energies (E_{rel}), Relative Energies after Removal of Hyperconjugative Interactions (E_{Lew}), Contributions from Hyperconjugation (E_{del}) to the Total Energy Differences, and Dipole Moments (Dip) for Various Conformers of 2-Hydroxypiperidine (2)

	E_{rel}	E_{Lew}	E_{del}	Dip
2E₃e	0.0	0.0	0.0	1.60
2E₁a	0.69	0.19	0.50	1.49
2A₁e	0.84	4.43	−3.60	1.58
2A₁a	0.99	0.78	0.19	1.67
2A₂e	0.99	1.67	−0.69	1.19
2A₃e	1.52	7.86	−6.34	1.69
2E₂e	3.46	2.33	1.13	2.27
2E₁e	3.78	2.55	1.23	2.48
2E₂a	4.84	4.17	0.66	2.61
2E₃a	5.20	6.33	−1.14	2.94
2A₂a	5.64	3.97	1.66	2.63

Two equatorial conformers, **2E₃e** and **2E₁a**, are lower in energy than the most stable axial form, **2A₁e**. Thus in contrast to 2-hydroxytetrahydropyran, 2-hydroxypiperidine **2** does not show an anomeric effect! The relative energies for **2** do not correlate with total dipole moments. On that basis **2A₁e** would be lowest in energy. Dipole repulsions are larger in equatorial structures than in axial forms. However, dipole repulsions between equatorial lone pairs and equatorial OH are expected to be larger than between axial lone pairs and equatorial OH as indicated in Scheme 7.

Thus the dipole repulsion model predicts equatorial structures with axial N−H (Ea) bonds to be higher in energy than equatorial forms with equatorial N−H (Ee). Neither an axial preference nor a preference for **2E₁a** over **2E₃e** is computed for **2**. Thus, dipole repulsions involving N are either greatly attenuated compared to those involving O¹ or they are not related to conformational preferences.

The **2A₁e** and **2E₁e** conformers correspond to the lowest energy structures A₁ and E₁ of 2-hydroxytetrahydropyran

Scheme 7

Ae

Aa

Ee

Ea
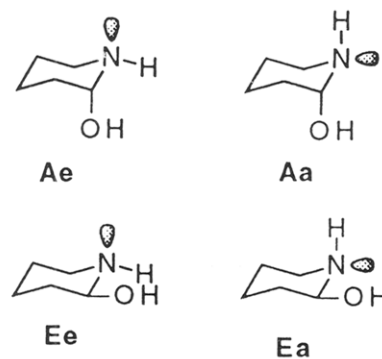
(2-OH-THP). The energy difference between these two conformers amounts to 2.94 kcal/mol in favor of the axial conformer. The axial preference of 2-OH-THP is only 1.3 kcal/mol at the same level of theory.[13] Comparison between the **2A₂e** and **2E₂e** pair also shows a substantial axial preference, 2.47 kcal/mol. Thus energy differences between corresponding conformers of **2** and the oxygen analog show that axial preferences are increased when the ring oxygen is replaced by nitrogen. The lowest energy structure, **2E₃e**, however, differs from **2A₁e** not only in the conformation at the anomeric carbon, it also differs in the orientation of the N−H bond. This will be discussed below. When the N−H bond is in the axial position and the lone pair is thus no longer antiperiplanar with the C−O bond, no axial preference is computed: **2E₁a** is 0.30 kcal/mol more stable than **2A₁a** and **2E₂a** is 0.80 kcal/mol more stable than **2A₂a**.

Rotating the OH bond by −120° (**2A₁e** → **2A₂e**) attenuates the exo-anomeric effect but increases the energy only by 0.15 kcal/mol. This finding corresponds to the "reverse anomeric effect" in 2-(methylamino)tetrahydropyran[55] and 2-aminotetrahydropyran[13] and to the absence of
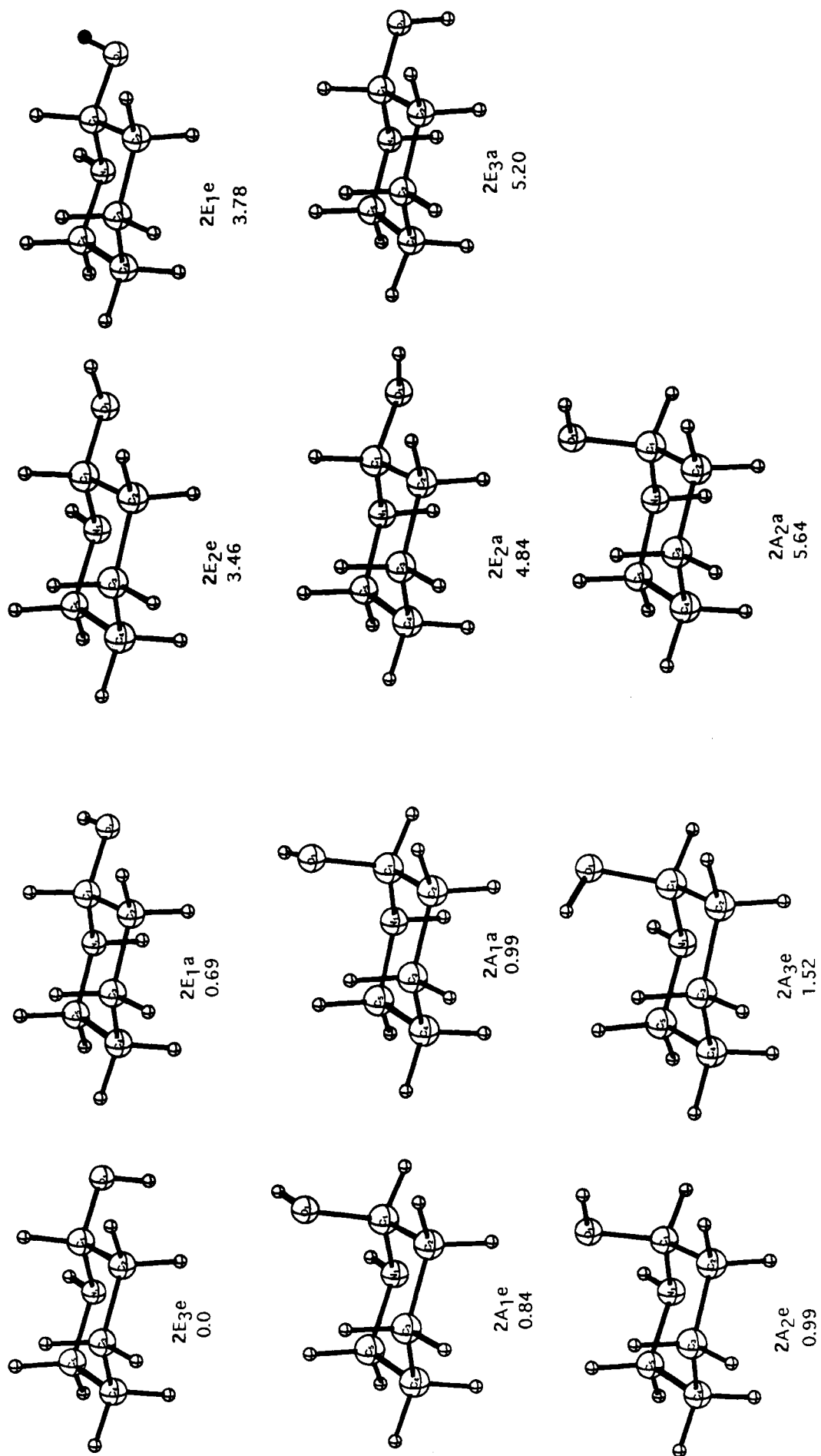
Figure 2. HF/6-31G* optimized structures and relative energies (in kcal/mol) of 2-hydroxypiperidine (**2**) conformers.

gauche preferences of the OH group in aminometha-nol[51,56] and of the OMe group methoxymethylamine.[57] Carballeira[15,16] found normal anomeric effects in the N−C−O moiety, but these authors employed unpolarized basis stets which overestimate anomeric effects. Booth and Khedhair[55] attributed the "reverse anomeric effect" in 2-(methylamino)tetrahydropyran to a competition between N and O for the electronegativity of the anomeric carbon atom. Krol et al.[57] concluded that it remains unclear whether the "reverse anomeric effect" is a result of electronic or steric interactions or both. Figure 2 shows that the O−H and the N−H bonds are aligned in the $2A_1e$ conformer. In the $2A_2e$ conformer O−H is aligned with a C−H bond. Since the C−C bond is longer than the C−N bond (1.527 Å vs 1.438 Å), smaller repulsions are expected. Thus the absence of an exo-anomeric effect for the $2Ae$ conformers might well be due to a relief of steric strain at the expense of hyperconjugative stabilization in $2A_2e$ compared to $2A_1e$. The presence of repulsions in $2A_1e$ is also indicated by the distortion of the N−C−O−H dihedral compared to that in $2A_1a$ ($-61.7°$ vs $-46.2°$). In agreement with prior investigations[51,56,57] $2A_1a$ shows a normal exo-anomeric effect. The energy difference between $2A_1a$ and $2A_2a$ is actually quite large, 4.65 kcal/mol.

The difference between the $2A_1e/2A_2e$ and $2A_1a/2A_2a$ pairs can be rationalized in two ways: Firstly, since there is no endo-anomeric effect in $2A_1a$ because the N−H bond is oriented axial, there is no competition between endo- and exo-anomeric effects in this conformer. The preference for $2A_1a$ is thus in line with the exo-anomeric effect. Secondly, in contrast to the $2A_1e/2A_2e$ pair, $2A_1a$ is favored over $2A_2a$ since no repulsions exist between O−H and N−H in $2A_1a$ but between O−H and C−H in $2A_2a$. The large energy difference between $2A_1a$ and $2A_2a$ probably results as a sum of decreased hyperconjugative stabilization and repulsions between O−H and C−H bonds in the latter.

Comparison of the energy differences between the equatorial structures $2E_1e$ and $2E_2e$ as well as $2E_1a$ and $2E_2a$ finally allows one to decide whether a competition between hyperconjugative interactions exists or whether the "reverse anomeric effect" is simply due to repulsions between O−H and N−H bonds. In equatorial conformations there is no competition between endo-anomeric and exo-anomeric effects since the C−O bond is not anti-periplanar to the nitrogen lone pair. Nonetheless, as for the axial form there is no exo-anomeric effect when repulsions are relieved by rotation around the C−O bond ($2E_1e \rightarrow 2E_2e$). $2E_2e$ is actually 0.32 kcal/mol more stable than $2E_1e$. When the exo-anomeric effect is attenuated and repulsions are built up at the same time ($2E_1a \rightarrow 2E_2a$), a substantial energy difference, 4.15 kcal/mol, results. The similar energy differences for these bond rotations in axial and equatorial conformations thus show that the "reverse anomeric effect" is due to repulsions rather than due to a competition between endo- and exo-anomeric effects.

Repulsions between aligned O−H and N−H bonds in $2A_1e$ not only explain the reverse anomeric effect, they also rationalize the equatorial preference of 2. $2A_1e$ is

the lowest lying axial structure and the only of the five low lying conformers in which both endo- and exo-anomeric effects are operative. In the other four low lying conformers either the exo-anomeric effect ($2A_2e$) or the endo-anomeric effect ($2E_3e$, $2E_1a$, $2A_1a$) is attenuated. These structures, however, are favorable since O−H and N−H are not parallel.

Assuming that $n_N-\sigma^*_{C-O}$ are stronger than $lp_O-\sigma^*_{C-N}$ orbital interactions, we expect that the hyperconjugative stabilization decreases in the order $2A_1e > 2A_2e > 2A_1a \approx 2E_3e \approx 2E_1a$. The NBO results for the hyperconjugative stabilizations in these conformers (E_{del}) in Table 2 are in perfect agreement with this prediction. The values relative to $2E_3e$ are -3.6, -0.69, 0.19, 0.0, and 0.5, respectively. Thus hyperconjugation would lead to an axial preference of 2. The Lewis energy, that is the energy in absence of orbital interactions, of $2A_1e$, however, is high. This is to be expected if steric and electrostatic repulsions are present. Thus NBO analysis confirms that the equatorial preference of 2 is not due to the absence of hyperconjugative stabilization but due to the presence of repulsions between N−H and O−H in the $2A_1e$ conformation.

The energies of the remaining structures can also be rationalized by considering hyperconjugative stabilizations and repulsions between O−H and N−H bonds. Next in energy is the $2A_3e$ conformer. Although the O−H bond is placed above the ring, the energy of $2A_3e$ is only 1.52 kcal/mol above the global minimum! For such an orientation steric effects have to be huge. However, both $p_o-\sigma^*_{C-N}$ and $n_N-\sigma^*_{C-O}$ interactions are at maximum. The NBO energy decomposition in Table 2 shows that the low energy of $2A_3e$ is indeed due to a compensation of large repulsions by strong hyperconjugative stabilization. That the hyperconjugative stabilization of $2A_3e$ is larger than that of $2A_1e$ is in line with results for dihydroxymethane, where the C_s form is stronger stabilized than the C_2 structure. The electrostatic model does not offer an explanation for the low energy of $2A_3e$. All of the remaining conformers have parallel O−H, N−H, and C−H bonds. These structures are between 3.5 and 5.6 kcal/mol higher in energy than the global minimum. Since these structures also lack $n_N-\sigma^*_{C-O}$ hyperconjugation, the high energies are due to unfavorable Lewis energies plus lower hyperconjugative stabilizations compared to $2A_3e$ and $2A_1e$.

To summarize, the equatorial preference as well as the absence of an exo-anomeric effect for 2 is due to repulsions between O−H and N−H bonds in $2A_1e$. That hyperconjugative stabilizations are present is indicated by substantial axial preferences within pairs of axial and equatorial structures with identical orientations of N−H and O−H bonds. Hyperconjugative stabilizations are also responsible for the low energy of the $2A_3e$ conformer which suffers severe steric repulsions and would otherwise be high in energy. This reasoning is borne out quantitatively in the NBO analysis.

2-Hydroxyhexahydropyrimidine (3). For 2-hydroxyhexahydropyrimidine (3), 14 different conformers arise with respect to different orientations of the O−H and the two N−H bonds. Twelve of these structures were found to be stationary points (Figure 3). The A_3 orientation of the O−H bond is only stable when both N−H bonds are equatorial. Thus only one out of three A_3 conformers could be located. All structures of 3 were optimized without symmetry constraints.

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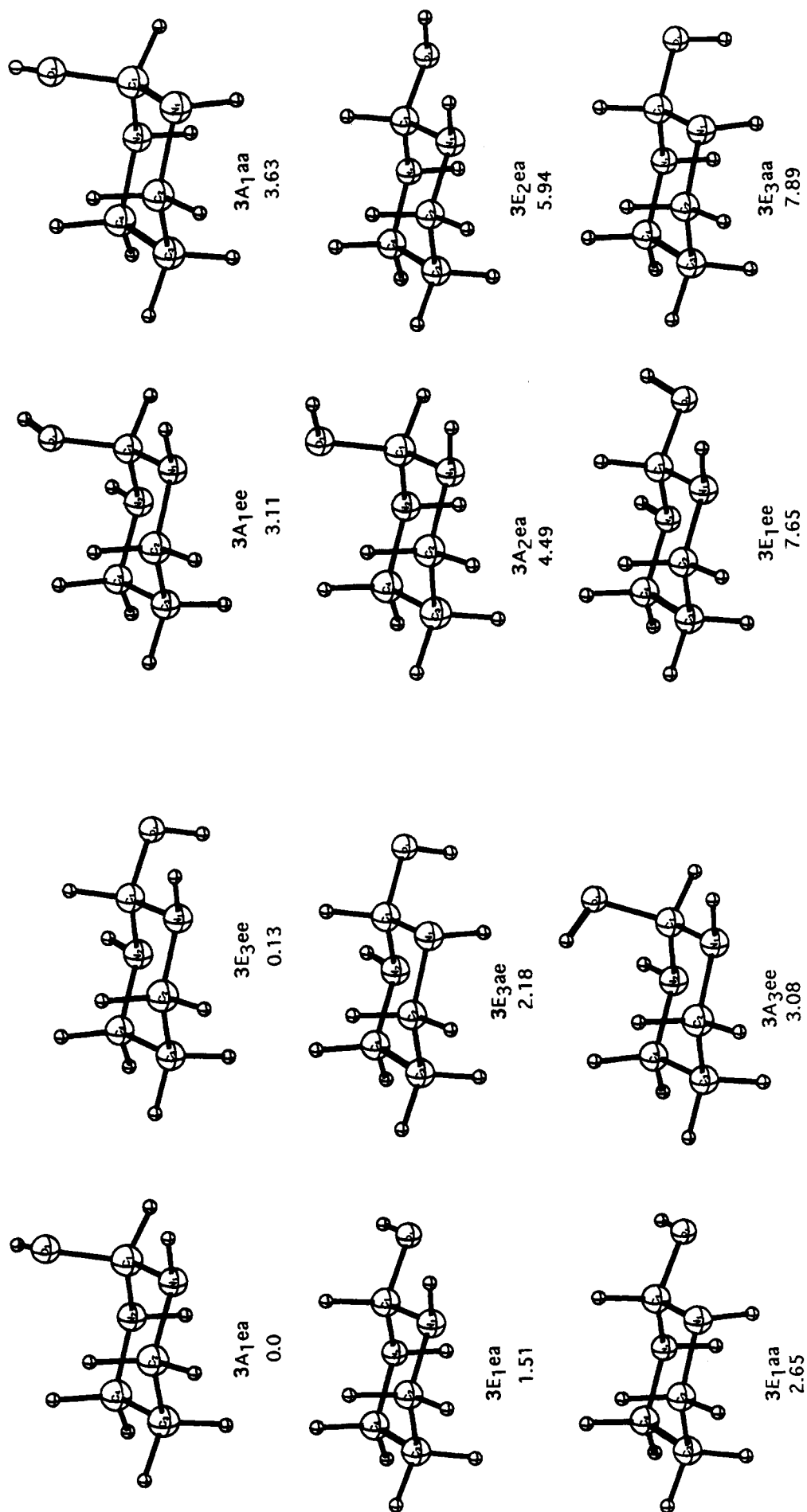
Figure 3. HF/6-31G* optimized structures and relative energies (in kcal/mol) of 2-hydroxyhexahydropyrimidine (3) conformers.

Table 3. Relative Energies (E_{rel}), Relative Energies after Removal of Hyperconjugative Interactions (E_{Lew}), Contributions from Hyperconjugation (E_{del}) to the Total Energy Differences, and Dipole Moments (Dip) for Various Conformers of 2-Hydroxyhexahydropyrimidine (3)

	E_{rel}	E_{Lew}	E_{del}	Dip
3A₁ea	0.0	0.0	0.0	0.74
3E₃ee	0.13	0.24	−0.12	1.89
3E₁ea	1.51	0.74	0.78	1.81
3E₃ae	2.18	1.92	0.27	2.72
3E₁aa	2.65	4.40	−1.75	2.45
3A₃ee	3.08	12.41	−9.33	2.17
3A₁ee	3.11	5.54	−2.42	1.83
3A₁aa	3.63	4.69	−1.05	2.89
3A₂ea	4.49	5.20	−0.71	2.52
3E₂ea	5.94	4.21	1.73	2.96
3E₁ee	7.65	6.40	1.25	3.47
3E₃aa	7.89	10.43	−2.53	3.55

The lowest energy structure of **3** is **3A₁ea**, but **3E₃ee** is only 0.13 kcal/mol higher in energy (Table 3). This axial preference will most likely disappear after inclusion of ZPE corrections especially if larger basis sets are employed since axial preferences are somewhat overestimated at HF/6-31G*.[13] Thus it can be concluded that **3** does not show an anomeric effect. The oxygen analog 2-hydroxy-1,3-dioxane (2-OH-DIOX) favors the equatorial conformation E_3 by 0.5 kcal/mol over A_1 at the same level of theory.[13] Thus the anomeric effect in **3** is increased by 0.63 kcal/mol compared to the oxygen system. A comparison with 2-OH-DIOX, however, is not straightforward since **3A₁ea** and **3E₃ee** differ in the N−H bond orientations in the ring systems. Such a complication is not present in 2-OH-DIOX.

Comparison of axial and equatorial structures with identical ring systems and corresponding orientations of the O−H group leads to interesting insights. The hyperconjugative stabilization of the axial structure is strongest when both N−H bonds are equatorial. For the **3A₁ee/3E₁ee** pair an axial preference of 4.54 kcal/mol results. When one of the N−H bonds is oriented axial, the endo-anomeric effect is attenuated. The energy difference between **3A₁ea** and **3E₁ea** amounts to 1.51 kcal/mol and between **3A₂ea** and **3E₂ea** to 1.45 kcal/mol. When both N−H bonds are axial there is no endo-anomeric effect and the **3E₁aa** form is 0.98 kcal/mol more stable than **3A₁aa**. Thus, when axial and equatorial structures with corresponding O−H and N−H bond orientations are compared, substantial axial preferences result in the presence of the endo-anomeric effect. The situation is very similar in **3** and in **2**.

Rotating the O−H group from **3A₁ea** to **3A₂ea** costs 4.49 kcal/mol and from **3E₁ea** to **3E₂ea** 4.43 kcal/mol. This exo-anomeric effect is not due to hyperconjuagtion since all conformers are stabilized by $p_O−\sigma^*_{C-N}$ orbital interactions. The energy differences have thus to be attributed to N−H/O−H bond repulsions.

As in **2** the relative energies of **3** are mainly determined by repulsions between O−H and N−H bonds. Of the six lowest energy structures of **3** none has aligned O−H and N−H bonds. The structures with aligned O−H and N−H bonds are at least 3 kcal/mol above the global minimum. Again NBO analysis confirms the qualitative considerations. The sterically favorable conformers have low Lewis energies. All conformers with high hyperconjugative stabilizations suffer repulsions and are unfavorable because of high Lewis energies. **3A₃ee**, for instance, is most strongly stabilized by hyperconjugation. This is

because the N lone pairs and the oxygen p and sp lone pairs are in optimal positions for stabilizing interactions. In addition the N−C−O bond angle widening induced by the steric repulsions reinforces hyperconjugative stabilization since bond angle widening increases the total overlap between donor and acceptor.[58] The Lewis energy of this structure with O−H above the ring, however, is prohibitively high.

When the N−H bonds are equatorial, the nitrogen lone pairs are antiperiplanar with the axial substituent at the anomeric carbon. When the N−H bonds are axial, the nitrogen lone pairs are antiperiplanar with the ring C−N bonds involving the anomeric carbon. The similar hyperconjugative stabilizations of **3A₁ee**, **3E₁aa**, and **3E₃aa** show that it does not make a big difference whether the nitrogen lone pairs engage in $n_N−\sigma^*_{C-O}$ or in $n_N−\sigma^*_{C-N}$ interactions. The stabilization of **3A₁ee** is only 0.67 kcal/mol larger than that of **3E₁aa**. The **3E₃aa** structure has a stronger exo-anomeric effect and is slightly favored (0.11 kcal/mol) over **3A₁ee** due to the hyperconjugative term. This confirms the findings for 2-OH-DIOX and 2-OMe-DIOX, where NBO analysis shows that hyperconjugation favors equatorial structures.[13] Like **3A₃ee**, **3E₃ee** is sterically unfavorable. The difference in hyperconjugative stabilization between **3A₁ee** and **3E₁aa** (0.67 kcal/mol) can be compared to that between the corresponding conformers of **2**, **2A₁e**, and **2E₁a** (4.10 kcal/mol). Thus due to the possibility of $n_N−\sigma^*_{C-N}$ interactions within the hexahydropyrimidine ring, the axial preference due to hyperconjugation is greatly attenuated compared to the piperidine system. Even in absence of repulsions between O−H and N−H bonds, large anomeric effects are not to be expected in the hexahydropyrimidine system.

We thus conclude that the conformational preferences of **3** even more so than those of **2** are governed repulsions between N−H and O−H bonds. Hyperconjugative effects are present but are strongest in conformations with severe steric hindrance. Hyperconjugative stabilization of the remaining forms does hardly favor axial structures since $n_N−\sigma^*_{C-O}$ interactions can be replaced by $n_N−\sigma^*_{C-N}$ interactions within the hexahydropyrimidine ring.

Discussion

NBO analysis shows that hyperconjugative stabilizations are present in the N−C−O moiety and that $n_N−\sigma^*_{C-O}$ interactions are stronger than $p_O−\sigma^*_{C-O}$ interactions. Parallel N−H and O−H bonds appear to repel each other by about 3-3.5 kcal /mol. The NBO method does not allow to determine the nature of this repulsion. One reviewer pointed out that these interactions are too large to be solely due to steric effects. Another reviewer emphasized that the relative energies of the different conformers are likely to be influenced by different numbers of 1,3-steric repulsions. Although NBO analysis shows that repulsions between N−H and O−H bonds are severe, it does not give any indication that 1,3-diaxial repulsions are of significance. The energy difference between **2E₁a** and **2A₁a** which has two additional 1,3-diaxial interactions amounts to 0.3 kcal/mol only, the Lewis energy difference to 0.6 kcal/mol. This is in agreement with results for 2-OH-THP where the Lewis energy actually favors the axial conformation.[13] Since the Lewis energy includes steric and electrostatic effects,

(58) Reed, A. E.; Schleyer, P. v. R. *Inorg. Chem.* **1988**, *27*, 3969.

Scheme 8
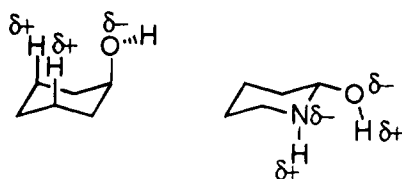
a possible explanation for this surprising result is that steric effects are indeed similar but that the electrostatic components of both interaction types have different signs. It seems likely that electrostatic interactions are attractive between axial oxygen and axial hydrogens but repulsive between aligned O−H and N−H bonds as indicated in Scheme 8. This might rationalize why bond−bond repulsions seem to be so much more important than 1,3-diaxial repulsions according to NBO.

NBO analyses thus indicates that the relative energies of the conformers of **1−3** are determined by a competition between O−H and N−H bond repulsions and hyperconjugative stabilizations. But even without employing the NBO method the same conclusion can be derived from comparison of pairs of structures with the same N−H bond orientations. The dipole repulsion model does not account for the relative energies and total energies do not correlate with total dipole moments as proposed by Wiberg[44] and Perrin.[1]

Perrin et al.[1] examined the conformational equilibrium of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3′**) NMR spectroscopically and found an axial conformer to be favored by 0.4−0.5 kcal/mol. It could not be determined which axial structure was observed but it was suggested that **3′** chiefly exists as **3′Aee**. This is in disagreement with Eliel's NMR results[8] that one of the methyl groups in N,N-dimethylhexahydropyrimidines tends to be in the axial position unless this conformation is sterically hindered by further axial ring substituents. Our theoretical results confirm Eliel's findings. Figure 3 indicates that the observed axial structure of **3′** almost certainly was **3′A₁ea**. Since the **3A₁ee** with parallel O−H and N−H bonds is already 3.11 kcal/mol higher in energy in the unsubstituted case, this structure will not be adopted when both nitrogens and oxygen carry methyl groups. The calculated energy difference between **3A₁ea** and the most stable equatorial conformation **3E₃ee** is slightly smaller, 0.13 kcal/mol, than that observed for **3′**. Considering the differences in substitution and medium, the agreement between theory and experiment is satisfactory. Perrin's and our interpretations of this result, however, could hardly disagree more.

Perrin et al. argue that since dipole repulsions decrease and hyperconjugative stabilization increases by replacing O with N, an enhanced anomeric effect has to be observed for **3′** compared to 2-methoxy-1,3-dioxane if orbital interactions were responsible for the anomeric effect. Since no such enhancement was found, these authors claim to have proven that anomeric effects are due to electrostatic effects and that hyperconjugation in general does not account for anomeric effects. This argument has two major problems. Firstly, the choice of the model system is unfortunate since in contrast to 2-hydroxytetrahydropyran and 2-hydroxypiperidine, hyperconjugation does not favor axial structures of 2-substituted-1,3-dioxanes and favors axial structures of 2-substituted-hexahydropyrimidines only slightly (when the sterically unfavorable A₃ structures are left out of consideration).

Secondly the conformational equilibrium of the N,N,O-three methyl derivative of 2-hydroxyhexahydropyrimidine is undoubtedly greatly affected by steric effects. The theoretical analysis of **2** and **3** shows that the axial−equatorial equilibria of nitrogen systems are governed by a complicated interplay between repulsive and hyperconjugative effects and that the absence of anomeric effects does not exclude the presence of hyperconjugative stabilizations.

Perrin et al. conclude that their results should stimulate a rethinking of the origins of the anomeric effect and that more attention should be paid to electrostatics. We would like to comment on this. According to the Hellmann−Feynman theorem[59] the forces exerted on a nucleus by the electrons and the other nuclei can be obtained from classical electrostatics provided that the exact wave function is known. There is thus no doubt that forces in anomeric systems can, in principle, be interpreted electrostatically. However, the required exact wave functions can only be obtained by quantum mechanics. Thus, even if an electrostatic model were available to provide correct structure and energy data using exact wave functions this would by no means prove that the origin of the anomeric effect is electrostatic. The Hellmann−Feynman theorem, however, holds for exact wave functions only. It was shown that electrostatically calculated forces based on approximate wave functions are totally unreliable.[59] From that point of view it would be rather surprising, if an electrostatic approximation employing a charge distribution as crude as the one based on point charges and bond dipoles were capable of yielding reliable results.

Conclusions

The RNCOR moiety does not prefer structures in which both N and O lone pairs are antiperiplanar with the adjacent C−O or C−N bonds at the same time. This is due to the fact that this orientation leads to aligned O−H and N−H bonds. The resulting repulsions offset the energy gain due to hyperconjugation. If either the NR₂ or the OR substituent is rotated, the other one strongly prefers to place its lone pair antiperiplanar to the acceptor bond. Thus the absence of anomeric effects in 2-substituted piperidines and hexahydropyrimidines as well as the reverse anomeric effects of 2-aminotetrahydropyran[25] are due to the competition between O−H/N−H bond repulsions and hyperconjugative stabilizations. There is no competition between exo- and endo-anomeric effects, and the dipole repulsion model does not satisfactorily explain the relative energies of the conformers of **2** and **3**. We thus confirm earlier conclusions that anomeric effects are due to quantum chemical stabilizations rather than dipole repulsions.

The conformational equilibrium of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3′**) which was investigated by Perrin et al.[1] is not suitable to assess the relative importance of hyperconjugative stabilizations and dipole repulsions for two reasons. Firstly, in the presence of two heteroatoms within the ring, hyperconjugation hardly favors axial structures because exo-anomeric effects are increased and endo-anomeric effects are decreased compared to systems with only one heteroatom in the ring. Secondly, the axial−equatorial equilibrium of **3′** is strongly influenced by steric effects which are already severe in

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3 but are enhanced in **3′** due to the presence of three methyl substituents in the NCOHN moiety.

We would like to emphasize finally that hyperconjugation is just a model for the quantum mechanical stabilization effect. Hyperconjugative interactions arise when localized orthogonal atomic orbitals are used to construct the wave function. Altona et al.'s analysis, for instance, which employs nonorthogonal group orbitals represents the charge back donation by interference terms. Wolf's analysis shows that stabilizing effects can also be found when canonical orbitals are employed. The advantage of the concept of hyperconjugation is simply that it corresponds to the chemists view of molecules in terms of Lewis structures.