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The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes

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Full geometry optimizations were carried out at the HF/6-31G** and B3LYP/6-31G** levels for methylcyclohexane, 2-, 3-, and 4-methyltetrahydropyran, 2-, 3-, and 4-methylpiperidine, 2-, 3-, and 4-methylthiane, 2-, 4-, and 5-methyl-1,3-dioxane, and 2-, 4-, and 5-methyl-1,3-dithiane and also for *S*-methyl thianium. Constrained geometry optimizations were carried out for methylcyclohexane, 2-methyl-1,3-dioxane, and the axial conformers of 2- and 3-methyltetrahydropyran and 2- and 3-methylpiperidine. The steric repulsion model, which is believed to account for the conformational energies of the cited compounds, was tested by stretching bonds and bending angles so that the axial methyl group is either forced to approach the ring γ methylenes or get farther away from them. The calculated energies show that the energy costs of these perturbations are not dependent on the distances between the axial methyl group and the ring γ methylenes and are not dependent on whether the methyl is axial or equatorial. It is shown that, besides the steric repulsion model, the conformational energies of the compounds studied are dictated by hyperconjugative interactions involving mainly the methine hydrogen. The C−C bond lengths of the axial and equatorial conformers of methylcyclohexane are shown to be related to hyperconjugation.

Introduction

The term "conformational analysis" usually covers two broad aspects: (1) the determination of the molecular geometric structures and the relative energies of conformers and (2) the attempts to find out which major forces control the relative conformational stabilities. The first aspect is more objective in nature and comprises a large body[1] of experimental and theoretical approaches, such as a number of spectrometric, difractometric, computational, and chemical methods. Modern ab initio calculations are an invaluable tool in this regard for their close reproduction of molecular structures and energies.[2] The second aspect is far more difficult to rationalize and can be exemplified by the various explanations and controversies regarding the origin of the anomeric effect.[3]

The conformational energy of methylcyclohexane has been frequently studied over the years and had been determined by ca. 14 methods by 1967.[4] Moreover, Beckett et al.[5] had explained its cause as early as 1947. The same rationale, namely, that 1,3-syn diaxial steric repulsion destabilizes the axial conformer, is still accepted today and found in many organic chemistry textbooks.[1,6−8] There appear to be two main points to support this view; first, an examination of the structure of axial methylcyclohexane and axial methylheterocyclohexanes shows that the methyl group is bending out of the ring, supposedly to relieve the 1,3-syn axial repulsions, and second, this view is consistent with the energetics of many methylheterocyclohexanes. Thus, for instance, 2-methyltetrahydropyran has a higher conformational free energy than methylcyclohexane because the shorter C−O bond length (compared to the C−C bond length) causes the axial methyl to be closer to the axial hydrogen at C-6. Moreover, in compounds that lack one or both of the syn-axial hydrogens, such as 3-methyltetrahydropyran, 3-methylpiperidine, 3-methylthiane, 5-methyl-1,3-dioxane, and 5-methyl-1,3-dithiane, the conformational free energies are smaller than that of methylcyclohexane.

The dioxane ring is very interesting because of the quite different conformational energies of the methyl group, 4.62, 3.29, and 0.68 kcal mol^{-1}, when in the 2, 4, or 5 position, respectively. This is nicely rationalized[9] by

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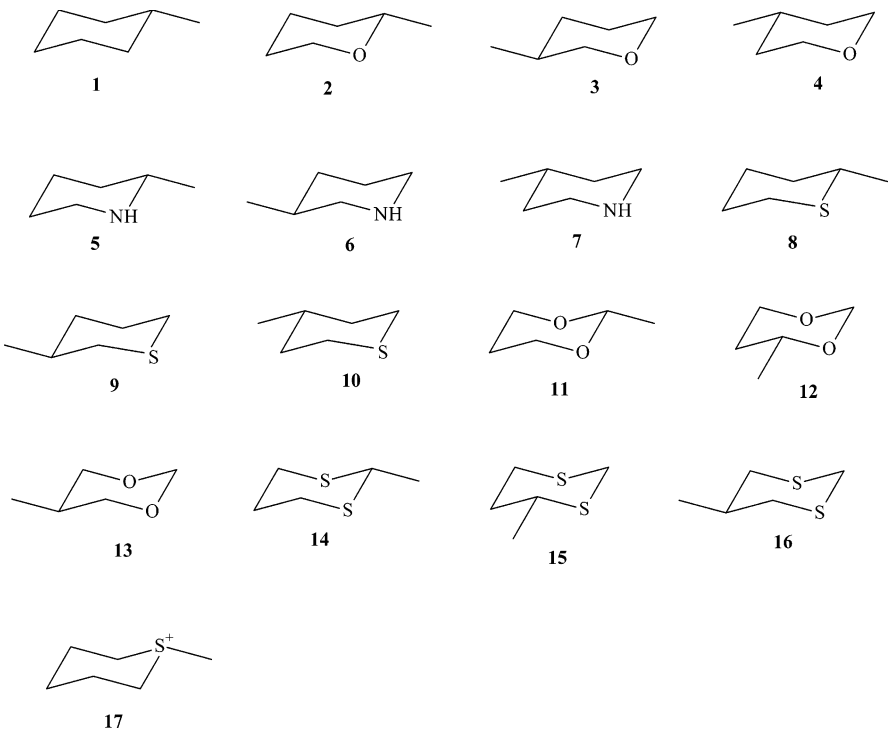

FIGURE 1. Structures of the equatorial conformers of methylcyclohexane (**1**), 2-methyltetrahydropyran (**2**), 3-methyltetrahydropyran (**3**), 4-methyltetrahydropyran (**4**), 2-methylpiperidine (**5**), 3-methylpiperidine (**6**), 4-methylpiperidine (**7**), 2-methylthiane (**8**), 3-methylthiane (**9**), 4-methylthiane (**10**), 2-methyl-1,3-dioxane (**11**), 4-methyl-1,3-dioxane (**12**), 5-methyl-1,3-dioxane (**13**), 2-methyl-1,3-dithiane (**14**), 4-methyl-1,3-dithiane (**15**), 5-methyl-1,3-dithiane (**16**), and *S*-methylthianium (**17**).

the steric repulsions of two close axial hydrogens for the 2-axial methyldioxane, two axial hydrogens with different distances for 4-methyldioxane, and the absence of any axial hydrogen for 5-methyl-1,3-dioxane. However, there are a few points that challenge this view. In a recent report[10] from our laboratory the conformational analysis of 2-methyl- and 4-methyl-1,3-dithiane has been discussed. For these compounds the conformational energies of the methyl group are very similar to that of methylcyclohexane, despite the greater separation between the axial methyl and the ring axial hydrogens located at C-4,6 and C-2,6, respectively. This finding, along with the suggestion of Wiberg et al.[11] that the syn axial interaction is not important in determining the conformational energy of methylcyclohexane, prompted us to carry out a series of calculations for a number of methyl-substituted six-membered rings.

This paper reports the results of ab initio calculations at the B3LYP/6-31G(d,p) and HF/6-31G(d,p) levels for the axial and equatorial conformations of methylcyclohexane, 2-, 3-, and 4-methyltetrahydropyran, 2-, 3-, and 4-methylpiperidine, 2-, 3-, and 4-methyl-thiane, 2-, 4-, and 5-methyl-1,3-dioxane, and 2-, 4-, and 5-methyl-1,3-dithiane. Calculations were also performed for *S*-methylthianium. The analysis of the fully optimized structures is presented for all compounds studied.

Geometry optimizations with constraints were performed for methylcyclohexane, 2-methyl-1,3-dioxane, and the axial conformers of 2- and 3-methyltetrahydropyran and 2- and 3-methylpiperidine.

The purpose of this paper is to present evidence that demonstrates the importance of hyperconjugative interactions in the conformational behavior of the title compounds.

Calculations

The theoretical calculations were carried out with the Gaussian 98 program,[12] using the computational facilities of CENAPAD-SP. The basis set was 6-31G** used with HF and DFT/B3LYP methods.

Results and Discussion

Analysis of the Fully Optimized Geometries. Figure 1 presents compounds **1**−**17** in their most stable equatorial conformation. Table 1 presents the calculated conformational energies from the fully optimized axial and equatorial conformations of **1**−**17**, using HF/6-31G** and B3LYP/6-31G** methods. The experimental conformational energies are also included for comparison. The conformational energies calculated through both methods are in reasonable agreement with each other. The HF

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TABLE 1. Relative Energies (Δ*E*, kcal mol^{-1}) Calculated by HF/6-31G and DFT/B3LYP/6-31G** for the Fully Optimized Axial and Equatorial Conformations of Compounds 1−17, and Experimental Conformational Energies (kcal mol^{-1})**

	Δ*E*		
compd	HF/6-31G**	B3LYP/6-31G**	exptl
1	2.31	2.15	1.74;[a] 1.93[b]
2	3.36	3.14	2.86[c]
3	1.46	1.38	1.43;[c] 1.50;[b] 1.60[d]
4	2.46	2.36	1.95[c]
5	3.07	2.93	2.50[e]
6	1.57	1.50	1.60[e]
7	2.46	2.34	1.90;[e] 2.30[b]
8	1.89	1.75	1.42[f]
9	1.92	1.72	1.40[f]
10	2.23	2.14	1.80[f]
11	4.78	4.62	3.6[g]
12	3.44	3.30	2.9[g]
13	0.65	0.68	0.80[g]
14	1.84	1.71	1.77;[h] 1.76;[i] 1.92[j]
15	1.95	1.83	1.69;[h] 1.75;[i] 1.55[j]
16	1.43	1.09	1.16[h]
17	1.00	0.68	0.3[k]

[a] Reference 22. [b] Reference 23. [c] Reference 24. [d] Reference 15. [e] Reference 25. [f] Reference 26. [g] Reference 27. [h] Reference 28. [i] Reference 10. [j] Reference 29. [k] Reference 30.

TABLE 2. Selected Bond Lengths (Å), Angles (deg), and Interatomic Distances (Å) for the Fully Optimized (B3LYP/6-31G) Axial and Equatorial Conformations for Methylcyclohexane (1), 4-Methyltetrahydropyran (4), 4-Methylpiperidine (7), 4-Methylthiane (10), 2-Methyl-1,3-dioxane (11), 5-Methyl-1,3-dioxane (13), 2-Methyl-1,3-dithiane (14), 5-Methyl-1,3-dithiane (16) and *S*-Methylthianium (17)**

compd	C_α-C_{Me}	C_α-C_β	C_β-C_γ	C_β-C_α-C_{Me}	Ha-C_γ-C_β	Ha-H	C_{Me}-C_γ
1a	1.538	1.545	1.538	112.4	109.9	2.381	3.211
1e	1.532	1.540	1.537	111.7	109.1		
4a	1.537	1.545	1.532	112.7	110.7	2.410	3.228
4e	1.531	1.539	1.531	112.3	109.8		
7a	1.537	1.545	1.533	112.6	109.7	2.397	3.224
7e	1.532	1.540	1.532	112.0	108.7		
10a	1.538	1.545	1.532	112.5	111.5	2.372	3.193
10e	1.533	1.540	1.531	111.0	110.7		
11a	1.531	1.419	1.427	112.6	111.0	2.314	3.073
11e	1.512	1.415	1.426	108.3	109.8		
13a	1.533	1.538	1.429	111.9			3.047
13e	1.530	1.535	1.426	112.1			
14a	1.531	1.846	1.837	113.3	109.6	2.476	3.412
14e	1.528	1.841	1.837	108.9	108.9		
16a	1.532	1.542	1.839	113.2			3.370
16e	1.538	1.538	1.836	109.6			
17a	1.823	1.851	1.529	104.1	110.3	2.393	3.392
17e	1.822	1.846	1.534	103.6	109.7		

calculations yielded energies roughly 0.15 kcal mol^{-1} greater than the DFT method, although the latter generally overestimates the experimental values by ca. 0.3 kcal mol^{-1}, with a few exceptions.

Methylcyclohexane (**1**), 4-methyltetrahydropyran (**4**), 4-methylpiperidine (**7**), and 4-methylthiane (**10**) show approximately the same behavior: calculated energies in the range 2.14−2.36 kcal mol^{-1} (DFT) and 2.23−2.46 kcal mol^{-1} (HF) versus 1.74−2.30 kcal mol^{-1} (experimental). This similarity is well-known and expected.[1,13]

3-Methyltetrahydropyran (**3**) and 3-methylpiperidine (**6**) present an excellent agreement between calculated and experimental energies. There is a drop of calculated energy of 1.0 and 0.8 kcal mol^{-1}, respectively, compared with the 4-methyl analogues (**4** and **7**). The experimental drop is 0.45 and 0.30 kcal mol^{-1} for tetrahydropyrans and piperidines, respectively. The usual explanation for this decrease in energy is the substitution of a syn axial H−H repulsion by a H/lone pair repulsion, which is thought to be less severe.[1,13]

The calculated conformational energy for 3-methylthiane (**9**) is larger than those of **3** and **6** and differs from the experimental value by 0.32 (DFT) and 0.52 kcal mol^{-1} (HF). Consequently, the decrease in energy from 4-methylthiane (**10**) to 3-methylthiane (**9**) is smaller, 0.31 kcal mol^{-1} (HF) and 0.42 kcal mol^{-1} (DFT).

As the conformational energies of these compounds are often discussed on the basis of bond lengths and distances between methyl hydrogens and ring axial hydrogens, as well as between the methyl group and the γ carbons, these geometrical parameters are presented in Table 2. The compounds were divided into three groups to facilitate the presentation. Those that possess a plane of symmetry passing through the methyl carbon and orthogonal to the plane of the ring are grouped in Table 2 and the remaining are grouped in Tables 5 and 6. All data refer to DFT/B3LYP/6-31G** calculations unless stated otherwise.

The distances Ha−H and C_{Me}−C_γ are within the range 2.372−2.410 and 3.193−3.228 Å, respectively, for compounds **1**, **4**, **7**, and **10**. These compounds also show similar conformational energies. Accordingly, **11a** (Table 2) presents the shortest Ha−H and C_{Me}−C_γ distances, 2.314 and 3.073 Å, respectively, and the greatest conformational energy, 4.62 kcal mol^{-1}.

The C_β−C_α−C_{Me} angle is (Table 2) 0.4−1.5° greater in the axial conformer of **1**, **4**, **7**, and **10** than it is in the equatorial one. This feature has been pointed out[14,15] as a consequence of the steric repulsion between the methyl group and the γ carbon atoms. Correspondingly, the Ha−C_γ−C_β angle is 0.8−1.0° greater in the axial conformation compared to the equatorial one. Thus, both the methyl carbon and the syn axial hydrogen seem to be bending out of the ring to relieve the steric strain. Compound **11a** shows a greater difference between the O_β−C_α−C_{Me} angle in the two conformations (4.3°), in perfect agreement with the purported stronger steric repulsion.

The conformational energies of **1**−**13** and **16** have been rationalized by the steric repulsion of the axial methyl group with the syn axial ring hydrogen and carbon atoms. The results for 2-methyl- (**14**) and 4-methyl-1,3-dithiane (**15**) have been discussed in a previous paper[10] and are not in agreement with this view. Their conformational energies are comparable to that of methylcyclohexane despite the greater distance between the methyl and the axial hydrogen and carbon atoms. *S*-Methylthianium (**17**) is also of interest because its conformational energy is very small and inconsistent with the steric repulsion model.

Testing the Steric Repulsion Model. It is often stated[1,13] that shorter C_α−C_β and C_β−C_γ bond lengths

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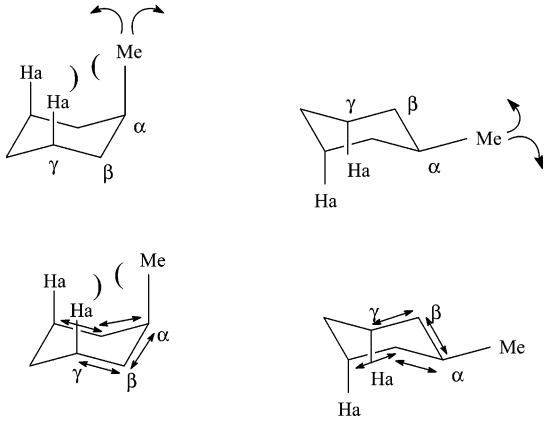


FIGURE 2. Illustration of the $C_\beta-C_\alpha-C_{Me}$ angle bending (top) and $C_\gamma-C_\beta$ and $C_\beta-C_\alpha$ bond stretching (bottom) for the axial and equatorial conformers of methylcyclohexane.

TABLE 3. Relative Energies (ΔE, kcal mol^{-1}) and Selected Bond Lengths (Å) and Angles (deg) of Optimized Structures of Methylcyclohexane with Constraints by DFT/B3LYP/6-31G**

entry	ΔE	C_α-C_β	C_β-C_γ	C_β-C_α-C_{Me}	Ha-C_γ-C_β	Ha-H	C_{Me}-C_γ
1ax	0	1.545	1.538	112.4	109.9	2.381	3.211
2ax	32.00	1.845[a]	1.521	112.2	109.8	2.507	3.402
3ax	16.03	1.534	1.738[a]	112.4	107.8	2.410	3.300
4ax	34.91	1.745[a]	1.738[a]	112.3	107.4	2.489	3.429
5ax	70.05	1.345[a]	1.338[a]	112.0	112.3	2.294	3.005
6ax	1.18	1.547	1.538	108.4[a]	110.3	2.266	3.135
7ax	0.30	1.546	1.538	110.4[a]	110.1	2.316	3.169
8ax	0.28	1.546	1.537	114.4[a]	109.8	2.446	3.252
9ax	1.14	1.547	1.538	116.4[a]	109.6	2.524	3.299
1eq	0	1.540	1.537	111.7	109.1		
2eq	32.46	1.840[a]	1.522	109.8	109.5		
3eq	16.08	1.530	1.736[a]	111.2	106.8		
4eq	35.16	1.740[a]	1.736[a]	111.8	106.8		
5eq	70.59	1.340[a]	1.336[a]	111.8	111.4		
6eq	1.21	1.540	1.538	107.7[a]	109.2		
7eq	0.30	1.540	1.537	109.7[a]	109.2		
8eq	0.30	1.541	1.536	113.7[a]	109.1		
9eq	1.22	1.543	1.535	115.7[a]	109.1		

[a] Fixed parameter.

bring the methyl group closer to the C_γ methylene, increasing the steric repulsion. Corresponding longer bond lengths obviously have an opposite effect. If this model is correct the required energy to stretch the $C_\alpha-C_\beta$, the $C_\beta-C_\gamma$, or both bonds simultaneously will be larger for the equatorial conformer than it would be for the axial one (Figure 2). The latter can relax because of the increased distances between the methyl and the C_γ group. Likewise, bending the $C_\beta-C_\alpha-C_{Me}$ angles in toward the ring in the axial conformer should not only require more energy than bending outward, but also, more energy than either bend in the equatorial conformer.

The results of the calculations involving longer, constrained bond lengths, and constrained bond angles are presented in Table 3 for the axial and equatorial conformers of methylcyclohexane and in Table 4 for 2-methyl-1,3-dioxane. The fixed geometrical parameter is indicated in each entry. The remaining parameters are free in the optimizations. The tabulated ΔE for each entry refers to the difference in energy between the constrained structures and the fully optimized ones, rather than to axial−equatorial equilibrium.

Methylcyclohexane. Stretching the $C_\alpha-C_\beta$ bonds by 0.3 Å increases the energy of the axial conformer by 32.00 kcal mol^{-1} compared to the fully optimized structure (Table 3, entries 1ax and 2ax). The corresponding value for the equatorial conformer is 32.46 kcal mol^{-1} (entry 2eq). The difference is only 0.46 kcal mol^{-1} while the Ha−H distance rises to 2.507 Å and the $C_{Me}-C_\gamma$ distance to 3.402 Å.

Stretching both the $C_\alpha-C_\beta$ and $C_\beta-C_\gamma$ bonds by 0.2 Å each (entries 4ax and 4eq) increases the energy of the axial and equatorial conformers by 34.91 and 35.16 kcal mol^{-1}, respectively. The difference in energy cost is only 0.25 kcal mol^{-1} and the distances Ha−H and $C_{Me}-C_\gamma$ in the axial conformation increase to 2.489 and 3.429 Å, respectively. The $Ha-C_\gamma-C_\beta$ angles decrease to 107.4° but the $C_\beta-C_\alpha-C_{Me}$ angles remain pratically unchanged. It would appear, after all, that there is some steric relief in the axial conformer with the elongation of these bonds, for the energy increase in the equatorial conformer is slightly higher. However, entries 5ax and 5eq present the energy cost of compressing the same bonds by 0.2 Å, 70.05 and 70.59 kcal mol^{-1} for the axial and equatorial conformers, respectively. In this case, the energy cost for the axial conformer is lower and the distances Ha −H and $C_{Me}-C_\gamma$ decrease to 2.294 and 3.005 Å, respectively. The angles $C_\beta-C_\alpha-C_{Me}$ actually decrease to 112.0°.

The energy cost of bending the $C_\beta-C_\alpha-C_{Me}$ angles by 4° inward is 1.18 kcal mol^{-1} for the axial and 1.21 kcal mol^{-1} for the equatorial conformers (entries 6ax and 6eq). The distances Ha−H and $C_{Me}-C_\gamma$ in the axial conformation decrease to 2.266 and 3.135 Å, respectively, and are now comparable to the analogous distances in 2-*ax*-methyl-1,3-dioxane. The $Ha-C_\gamma-C_\beta$ angles increase by a meaningless 0.4°. Conversely, increasing the $C_\beta-C_\alpha-C_{Me}$ angles by 4° (entries 9ax and 9eq) costs 1.14 and 1.22 kcal mol^{-1} and lengthen the distance of Ha−H and $C_{Me}-C_\gamma$ to 2.524 and 3.299 Å, respectively. The $Ha-C_\gamma-C_\beta$ angle relaxation is 0.3°.

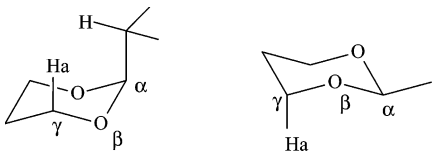
It is obvious from the preceding comparison of energy costs and the behavior of the $C_\beta-C_\alpha-C_{Me}$ and $Ha-C_\gamma-C_\beta$ angles that the steric repulsion between the axial methyl group and the axial ring hydrogens and C_γ in methylcyclohexane cannot be the sole origin of the known conformational energy.

2-Methyl-1,3-dioxane. This compound exhibits the greatest conformational energy of the molecules studied, supposedly because of the close approach of the syn axial hydrogens and the axial methyl group. Therefore, it should be the most likely compound to show a steric repulsion between the methyl group and the γ carbons.

Table 4 presents the energies and selected geometrical parameters for the fully optimized structures (entries 1ax and 1eq through HF and 3ax and 3eq through DFT) and for the optimized structures with constraints for the axial and equatorial conformers of 2-methyl-1,3-dioxane.

The energy cost (HF/6-31G** calculations) of stretching both the $C_\alpha-O_\beta$ and $O_\beta-C_\gamma$ bonds by 0.2 Å is 50.31 and 50.85 kcal mol^{-1} for the axial and equatorial conformers, respectively (entries 2ax and 2eq.). The difference in energy is only 0.54 kcal mol^{-1} and the distances Ha−H and $C_{Me}-C_\gamma$ rise from 2.350 to 2.401 Å and from 3.075 to 3.260 Å, respectively. The variations in the $O_\beta-C_\alpha-C_{Me}$ and $Ha-C_\gamma-O_\beta$ angles are very similar in both conform-

TABLE 4. Relative Energies (Δ*E*, kcal mol^{-1}) and Selected Bond Lengths (Å), Angles (deg), and Interatomic Distances (Å) for the Axial and Equatorial Conformations of 2-Methyl-1,3-dioxane Optimized with Constraints



entry	Δ*E*	C_α-O_β	O_β-C_γ	O_β-C_α-C_{Me}	Ha-C_γ-O_β	Ha-H	C_{Me}-C_γ
1ax[a]	0	1.395	1.405	112.5	110.7	2.350	3.075
2ax[a]	50.31	1.595[b]	1.605[b]	111.9	107.6	2.401	3.260
3ax	0	1.419	1.427	112.6	111.0	2.314	3.073
4ax	0.37	1.420	1.427	110.6[b]	111.0	2.277	3.052
5ax	0.37	1.420	1.428	114.6[b]	111.0	2.361	3.100
1eq[a]	0	1.391	1.404	108.6	109.7		
2eq[a]	50.85	1.591[b]	1.604[b]	107.6	106.9		
3eq	0	1.415	1.426	108.3	109.8		
4eq	0.33	1.415	1.427	106.3[b]	109.8		
5eq	0.35	1.415	1.425	110.3[b]	109.8		

[a] HF/6-31G**. [b] Fixed parameter.

ers. This result is inconsistent with such a large steric repulsion in the axial conformation.

The energy cost (B3LYP/6-31G** calculations) of bending the O_β−C_α−C_{Me} angle by 2° inward and outward with respect to the ring is 0.37 kcal mol^{-1} for the axial conformer and 0.33 and 0.35 kcal mol^{-1} for inward and outward bending for the equatorial conformer. The distances Ha−H and C_{Me}−C_γ vary from 2.277 to 2.361 Å and from 3.052 to 3.100 Å, respectively. Also, the Ha−C_γ−O_β angle remains unchanged for both conformers. Thus, it appears that the steric repulsion model cannot account entirely for these results.

α-Methyl Derivatives. 2-Methyltetrahydropyran (**2**), 2-methylpiperidine (**5**), 2-methylthiane (**8**), 4-methyl-1,3-dioxane (**12**), and 4-methyl-1,3-dithiane (**15**) are grouped under this heading.

Table 5 presents selected geometrical parameters for the fully optimized structures of the axial conformers of **2**, **5**, **8**, **12**, and **15**.

Compounds **2**, **5**, and **12** are said to have greater conformational energies than methylcyclohexane because one of the syn axial hydrogens is closer to the axial methyl group than the corresponding distances in methylcyclohexane. Correspondingly, compounds **8** and **15** show lower conformational energies due to the longer C−S bonds. The Ha−H(C6) distances are indeed smaller in **2**, **5**, and **12** and larger in **8** and **15** (the value of methylcyclohexane is 2.381 Å, Table 2).

The C_3−C_2−C_{Me}−H and X−C_2−C_{Me}−H dihedral angles are of interest. In **2**, **5**, and **12** there is a remarkable difference in these dihedral angles: they are smaller on the supposedly less hindered side and greater on the more hindered side. For **8** and **15** the difference between the dihedral angles is smaller but the same pattern is observed. This behavior suggests that the methyl group is rotating to relieve the steric repulsion with the closest ring axial hydrogen at C-6. To test if this is indeed the case, calculations were carried out in **2** and **5** by turning this dihedral angle by 5° in both directions. The results are presented in Table 5.

As the energy cost is very small and equal in both directions and the Ha−C_4−C_3, Ha−C_6−X, C_3−C_2−C_{Me}, and X−C_2−C_{Me} angles are insensitive to the Ha−H distances, it follows that the rationale of the increased conformational energy of **2**, **5**, and **12** compared to methylcyclohexane cannot rest on steric grounds alone.

3-Methyl Derivatives. 3-Methyltetrahydropyran (**3**), 3-methylpiperidine (**6**), and 3-methylthiane (**9**) show a decreased conformational energy compared to methylcyclohexane, which is attributed to the absence of one ring syn axial hydrogen. This is related to the 3-alkyl-ketone effect.[16]

Table 6 presents selected geometrical parameters for the fully optimized structures of **3**, **6**, and **9**. As observed in the 2-methyl analogues, the C_2−C_3−C_{Me}−H are smaller than the C_4−C_3−C_{Me}−H dihedral angles, suggesting an attempt to avoid a H−H steric interaction.

The geometric optimizations constraining the C_4−C_3−C_{Me}−H dihedral angle at 5° above and below its original value were carried out for the axial conformers of **3** and **6** and are presented in Table 6. By decreasing this angle, the methyl hydrogen moves closer to the axial hydrogen at C5, and by increasing it the hydrogens get farther away from each other. Yet, the energy cost is small and equal for both situations. Moreover, the Ha−C_5−C_4 angle is independent of the Ha−H distances. Thus, the same conclusions apply to these compounds.

Hyperconjugation. NMR coupling constants are discussed today on the basis of hyperconjugative interactions.[17,18] It is realized that the C−Hax bond in cyclohexane is longer and weaker than the C−Heq bonds because of the predominance of a $\sigma_{CH}/\sigma^*_{CH}$ hyperconjugative interaction.[19] Indeed, axial protons in cyclohexane are known to lead to a greater stability than do equatorial protons.[20]

Alabugin,[19] using NBO analysis, has given a quantitative estimate of the main stereoelectronic interactions for cyclohexane, 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane at the HF/6-31G** and B3LYP/6-31+G** levels. The author showed the relationship between hyperconjugative energies and C−H bond lengths. Three main types of hyperconjugative interactions were described for cyclohexane, a degenerate pair of $\sigma_{CH}/\sigma^*_{CH}$ for axial protons, and $\sigma_{CH}/\sigma^*_{CC}$ and $\sigma_{CC}/\sigma^*_{CH}$ for equatorial protons (Figure 3). The sum of individual deletion energies, which represents the increase in energy of the system by deleting all hyperconjugative interactions of a given C−H bond, is 13.5 and 10.7 kcal mol^{-1} (HF calculations) for a C−Hax and C−Heq bonds, respectively. By using DFT, these deletion energies are 20.4 and 14.6 kcal mol^{-1} for C−Hax and C−Heq bonds, respectively.

For heterocyclic systems, the $n_{(O)}/\sigma^*_{C-Hax}$ and $n_{(N)}/\sigma^*_{C-Hax}$ are not only more important than the $\sigma_{CH}/\sigma^*_{CH}$ hyperconjugative interactions, but also more important than any other of the remaining hyperconjugative interactions described. On the other hand, the donor ability of the sulfur lone pair is very small and the $n_{(S)}/\sigma^*_{C-Hax}$

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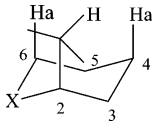
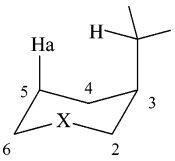
TABLE 5. Relative Energies (Δ*E*, kcal mol^{-1}) and Selected Geometrical Parameters for the Fully Optimized Structures of Axial 2-Methyltetrahydropyran (2), 2-Methylpiperidine (5), 2-Methylthiane (8), 4-Methyl-1,3-dioxane (12), and 4-Methyl-1,3-dithiane (15) and for the Optimizations with Constraints for 2 and 5



compd	Δ*E*	HaC_4C_3	H_aC_6X	$C_3C_2C_{Me}$	XC_2C_{Me}	$XC_2C_{Me}H$	$C_3C_2C_{Me}H$	Ha-H(C_6)	Ha-H(C_4)
2	0	110.2	110.9	113.9	112.0	69.8	56.8	2.332	2.400
2	0.06	110.2	110.9	113.9	112.0	65.0	61.8[a]	2.285	2.444
2	0.04	110.2	110.9	113.8	112.0	74.5	51.8[a]	2.374	2.368
5	0	110.1	113.7	112.8	114.7	64.2	60.4	2.358	2.399
5	0.05	110.1	113.7	112.9	114.6	59.2	65.4[a]	2.312	2.443
5	0.05	110.1	113.7	112.7	114.7	68.9	55.4[a]	2.404	2.361
8	0	110.0	109.5	113.7	112.5	63.5	63.7	2.515	2.394
12	0	111.1	110.7	114.3	112.0	69.7	55.4	2.339	2.425
15	0	111.6	110.4	113.9	112.5	63.7	65.4	2.438	2.382

[a] Fixed parameter.

TABLE 6. Relative Energies (Δ*E*, kcal mol^{-1}) and Selected Angles (deg) and Interatomic Distances (Å) for the Fully Optimized Axial Conformation of 3-Methyltetrahydropyran (3), 3-Methylpiperidine (6), and 3-Methylthiane (9) and for the Constrained C_4-C_3-C_{Me}-H Dihedral Angle for 3 and 6 As Calculated by DFT/B3LYP/6-31G**



compd	Δ*E*	$C_2C_3C_{Me}$	$C_4C_3C_{Me}$	HaC_5C_4	$C_2C_3C_{Me}H$	$C_4C_3C_{Me}H$	H-H(C_5)
3a	0	111.4	112.9	110.4	56.0	66.4	2.423
3a	0.041	111.5	112.8	110.4	60.9	61.4[a]	2.380
3a	0.047	111.2	113.0	110.4	51.0	71.4[a]	2.477
6a	0	111.7	112.9	110.3	56.3	66.8	2.430
6a	0.041	111.9	112.8	110.3	61.2	61.8[a]	2.382
6a	0.043	111.6	113.0	110.3	51.4	71.8[a]	2.482
9a	0	112.6	113.0	110.4	60.3	66.5	2.422

[a] Fixed parameter.

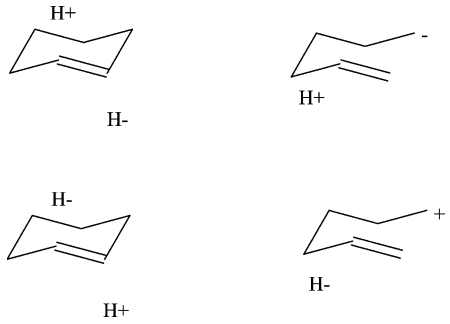


FIGURE 3. Illustration of the hyperconjugative interactions in cyclohexane: degenerate $\sigma_{CHax}/\sigma^*_{CHax}$ (top and bottom left), $\sigma_{C-Heq}/\sigma^*_{C-C}$ (top right) and $\sigma_{C-C}/\sigma^*_{C-Heq}$ (bottom right).

is even smaller than the $\sigma_{CH}/\sigma^*_{CH}$ hyperconjugative interaction.

Thus, the conformational energies of **1**, **2**, **4**, **5**, **7**, **8**, **10**, **11**, **12**, **14**, and **15** can be roughly understood, not on the basis of an axial or equatorial methyl group but because the methine hydrogen at the substitution site is either axial or equatorial (Figure 4).

This rationale may be summarized as follows:

Compounds **1**, **4**, **7**, and **10** prefer the equatorial conformation because the $\sigma_{CH}/\sigma^*_{CH}$ hyperconjugative

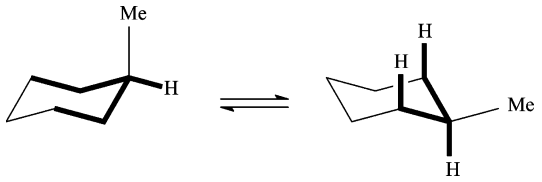


FIGURE 4. Bonds involved in the main hyperconjugative interactions which influence the conformational equilibrium of methylcyclohexane.

interaction for the axial methine hydrogen predominates over the $\sigma_{CH}/\sigma^*_{CC}$ interactions in the equatorial methine hydrogen.

Compounds **2**, **5**, and **12** have greater conformational energies compared to **1** because the axial methine hydrogen enjoys a large $n_{(X)}/\sigma^*_{C-Hax}$ hyperconjugative stabilization. Accordingly, **8**, **14**, and **15** have slightly lower conformational energies than **1** because the $n_{(S)}/\sigma^*_{C-Hax}$ is smaller than the $\sigma_{CH}/\sigma^*_{CH}$ interaction.

The low conformational energies of **13** and **16** are not so much related to the lack of 1,3-syn axial ring hydrogens, but to the small difference in the total deletion energies of the hydrogens at C5. The deletion energies for C5−Heq are actually slightly higher than the deletion energies for C5−Hax.

Salzner and Schleyer,[21] on the basis of NBO analysis at the HF/6-31G* level, showed that the conformational energy of **1** is almost totally accounted for by hyperconjugative interactions. Yet the authors found that, for **2** and **11,** hyperconjugation would not favor either conformer, i.e., the total deletion energies are balanced in the two conformations and, therefore, explained the conformational energies by classical steric repulsion.

The work of Alabugin[19] is enlightening because, while the HF deletion energies for the 2ax and 2eq hydrogens of **11** are equal, the DFT deletion energies for the 2ax hydrogen is 34 kcal mol^{-1}, whereas the energy for the 2eq hydrogen is 21.4 kcal mol^{-1}. Moreover, the so-called homoanomeric interaction described by the author can further stabilize the equatorial conformer of **11** but not the axial conformer. This interaction was said to occur between the axial lone pair of oxygen and the σ^*_{C5-Heq} of **13**. Two such interactions may occur between the oxygens axial lone pairs of **11** and the antiperiplanar $C_{Me}-H$ bonds in the equatorial conformation.

However, the drop in energy for **3**, **6**, and **9** relative to **4**, **7**, and **10** remains to be accounted for. We tentatively explain that resorting to the above cited homoanomeric interaction, proposed by Alabugin, would stabilize the axial conformation of **3**, **6**, and **9**, but not the equatorial conformation.

Finally, the low conformational energy of **17**, unexplained by the steric repulsion model, can be easily understood by noting that there is no methine hydrogen involved.

The concept of hyperconjugation can also aid in the interpretation of the high conformational energy (∼3.0 kcal mol^{-1})[31] of *N*-methylpiperidine. Its equatorial conformer enjoys two large $n_{(N)}/\sigma^*_{C-Hax}$ interactions. On protonation this energy decreases[25] to ∼2.0 kcal mol^{-1} as the lone pair is no longer available for hyperconjugation.

The much lower conformational energies of halocyclohexanes compared to methylcyclohexane can be understood by noting the hyperconjugative interactions present in these compounds. Alabugin and Zeidan[32] have recently published a theoretical study regarding general trends in hyperconjugative acceptor abilities of σ bonds using NBO analysis at the B3LYP/6-31G** level. Generally, the authors found that σ^*_{CX} bond orbitals are much better acceptors than σ^*_{CH}. Although the large sensitivity of the hyperconjugative energies on geometrical parameters has been pointed out, it seems safe to assume that the order of the acceptor abilities of the σ bonds found in substituted ethanes will hold approximately the same for substituted cyclohexanes.

TABLE 7. Data of the Multiple Regression Analysis of C-C Bond Lengths (Å) of Axial and Equatorial Methylcyclohexane versus the Number of Pairs of Atoms in an Antiperiplanar Relationship: H/H (*X*), H/C Edge (*Y*), and H/C Central (*Z*)

bond	bond length	X	Y	Z	calcd length[a]
C_{Me}-C_α (eq)	1.532	1	0	2	1.533
C_{Me}-C_α (ax)	1.538	1	2	2	1.538
C_α-C_β (eq)	1.540	1	3	1	1.540
C_α-C_β (ax)	1.545	0	3	3	1.545
C_β-C_γ (eq)	1.537	1	1	2	1.535
C_β-C_γ (ax)	1.538	1	2	2	1.538
C_γ-C_δ (eq)	1.536	1	2	2	1.538
C_γ-C_δ (ax)	1.537	1	2	2	1.538

[a] Calculated bond length through the equation $r_{C-C} = 1.5389 - 0.005476X + 0.002286Y - 0.000238Z$, $r^2 = 0.9257$, sd = 0.0013 Å.

The degenerate interactions $\sigma_{CH}/\sigma^*_{CH}$ (2 * 5.1 kcal mol^{-1} = 10.2 kcal mol^{-1})[19] in equatorial methylcyclohexane (Figure 4) predominate over the sum of $\sigma_{CH}/\sigma^*_{CC}$ (4.0 kcal mol^{-1})[19] and $\sigma_{CC}/\sigma^*_{CH}$ (3.3 kcal mol^{-1})[19] in axial methylcyclohexane leading to the observed relative stability of the equatorial conformer. The axial conformers of, inter alia, fluoro-, chloro-, and bromocyclohexane enjoy a larger stabilization due to the enhanced $\sigma_{CH}/\sigma^*_{CX}$ hyperconjugative interaction. This leads to the observed lower conformational energies of these compounds.

The hyperconjugative interactions as quantitatively probed by the NBO analysis can therefore explain the conformational behavior of a large number of compounds.

Hyperconjugation and C−C Bond Lengths. Figure 3 presents an ilustration of the three main types of hyperconjugative interactions of cyclohexane. As the structures suggest, a $\sigma_{CH}/\sigma^*_{CH}$ interaction lengthens the axial C−H bonds and shortens the central C−C bond. Interactions such as $\sigma_{CH}/\sigma^*_{CC}$ and $\sigma_{CC}/\sigma^*_{CH}$ shorten the central C−C bond and lengthen the C−C bonds at the edge.

A multiple regression analysis was carried out for the C−C bond lengths of the axial and equatorial conformers of methylcyclohexane and the results are shown in Table 7. The correlation obtained reads as follows: $r_{C-C} = 1.5389 - 0.005476X + 0.002286Y - 0.000238Z$, where X is the number of pairs of H/H atoms undertaking a $\sigma_{C-H}/\sigma^*_{C-H}$ interaction involving the C−C bond considered, Y is the number of H/C pairs undertaking $\sigma_{CH}/\sigma^*_{CC}$ and $\sigma_{CC}/\sigma^*_{CH}$ interactions involving the C−C bond considered at the edge, and Z is the number of H/C pairs involving the C−C bond at the center. $r^2 = 0.9257$ and sd = 0.0013 Å. The fit is only fair, but close enough to demonstrate that hyperconjugative interactions have a sizable effect over C−C bond lengths.

Conclusion

Calculations at the HF/6-31G** and B3LYP/6-31G** levels with constrained bond lengths and angles in which the axial methyl group is forced to either approach or get farther from the ring γ methylenes show that the energies involved are the same in both situations as well as when compared to the same perturbations carried out in the equatorial conformation.

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Dihedral angles constrained in the 2- and 3-methyl series so that the axial methyl hydrogen pointing into the ring is forced to move closer to or away from the supposedly more hindered direction result in the same energy cost for both directions. All these results demonstrate that the 1,3-syn diaxial steric repulsion is not the sole origin of the differences in energy between axial and equatorial conformations.

The conformational energies are also dictated by hyperconjugative interactions occurring mainly with the methine hydrogen, which is more stabilized in the axial position and, consequently, favors the equatorial methyl group. This latter rationale can explain all the observed trends, including the conformational energies of 2-methyl- and 4-methyl-1,3-dithiane and of *S*-methylthianium.

The hyperconjugative interactions also determine the observed differences in the C−C bond lengths in the axial and equatorial conformations of methylcyclohexane.

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Supporting Information Available: Cartesian coordinates for all optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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