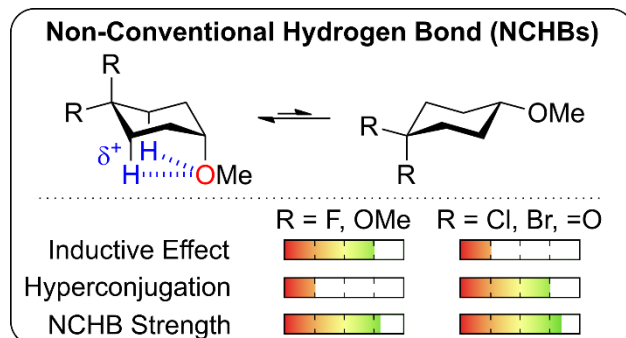


The Contribution of Hyperconjugation and Inductive Effects to the *Pseudo*-Anomeric Effect in 4-Substituted Methoxycyclohexanes

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ABSTRACT: The importance of electrostatic non-conventional hydrogen bonds (NCHBs) to the *pseudo*-anomeric effect of 4-substituted methoxycyclohexanes is evaluated using theory (NBO) to deconvolute electrostatic from other contributing effects. There is an interesting interplay between $\sigma_{\text{CH}} \rightarrow \sigma_{\text{C}^*_{\text{CX}}}$ hyperconjugation and the electropositive charge on the 3,5-axial hydrogens (H_{ax}). In essence better $\sigma_{\text{C}^*_{\text{CX}}}$ (or π_{CO}) acceptors increase the charge on 3,5- CH_{ax} , which in turn strengthens $\text{C}^{\delta+}\text{H}_{\text{ax}}\cdots\delta^-\text{OMe}$ NCHB interactions.



The anomeric effect was coined after Edward and Lemieux observations with carbohydrates, where an electronegative alpha- substituent (eg OMe, OH) on a six-membered pyran ring tends to adopt an axial rather than the equatorial orientation favored with cyclohexanes.^{1,2} How stereoelectronics influence conformation is fundamental to organic chemistry,^{3,4} and of course the origin of the anomeric effect has been the focus of much attention over many years. The interactions governing anomeric preferences have been extensively reviewed,⁵⁻⁹ and most notably hyperconjugation^{10,11} and minimization of dipolar repulsions¹² are among the most accepted effects. In this sense, we have previously demonstrated, using Natural Bond Orbitals (NBO) analysis, that *pseudo*-anomeric effects observed in selectively fluorinated methoxycyclohexanes arise mainly due to Non-Conventional Hydrogen Bonds (NCHBs) between the electropositive 3,5- CH_{ax} atoms and the electronegative axial OMe group ($\text{CH}_{\text{ax}}^{\delta+}\cdots\delta^-\text{OMe}$).^{13,14} The addition of highly electronegative groups (CF_2) into the ring, even at the most remote C-4 position, polarizes the axial hydrogens through inductive effects, thus strengthening through space NCHBs. However, for analogous ring oxygenated (4-O for 4- CH_2) cyclohexanes the *pseudo*-anomeric preference was either much more attenuated compared to fluorinated (eg. 4- CF_2 for 4- CH_2) analogues or the equatorial *pseudo*-anomers emerged as more energetically favored (Figure 1). This suggests that the strength of NCHBs in some fluorinated methoxycyclohexanes arises from the interplay between electrostatics and hyperconjugative effects¹⁵ and how those effects influence the atomic charge on 3,5- CH_{ax} ; either the presence of vicinal low energy acceptor orbitals (eg. σ_{CF}^*) interact to increase the atomic charge on 3,5- CH_{ax} through $\sigma_{\text{CH}_{\text{ax}}} \rightarrow \sigma_{\text{CF}}^*$ hyperconjugation and consequently increases NCHBs stabilization, or donor orbitals (eg. *endo* oxygen lone pair) decrease the atomic charge on 3,5- CH_{ax} through $n_{\text{O}} \rightarrow \sigma_{\text{CH}}^*$ hyperconjugation and therefore weakens NCHBs.

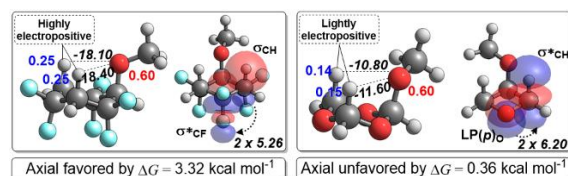


Figure 1. Natural population analysis (NPA) atomic charges (positive values in blue, negative values in red, in atomic units) and NBO derived 3,5- $\text{CH}_{\text{ax}}\cdots\text{OMe}$ electrostatic and $\sigma_{\text{CH}_{\text{ax}}} \rightarrow \sigma_{\text{CF}}^*$ // $n_{\text{O}} \rightarrow \sigma_{\text{CH}}^*$ hyperconjugative interaction energies (in kcal mol^{-1}) for 1,1,3,3,5,5-hexafluoro-2-methoxycyclohexane (left) and 2-methoxy-1,3,5-trioxane (right) calculated at the M06-2X/aug-cc-pVTZ theoretical level.¹⁴

We describe in the present study a deconstructive analysis of the *pseudo*-anomeric effect in 4-substituted methoxycyclohexanes to further assess the role of hyperconjugative interactions and their influence on the atomic charge of the 3,5-diaxial hydrogens. The study highlights the importance of both electrostatic and hyperconjugative effects in observed *pseudo*-anomeric effects. For this, several 4-substituted methoxycyclohexanes **1-10** were

computationally studied using DFT. Figure 2 shows the gas-phase ring interconversion Electronic Energy (ΔE) differences calculated at the M06-2X/aug-cc-pVTZ theoretical level for all of the compounds **1-10**.

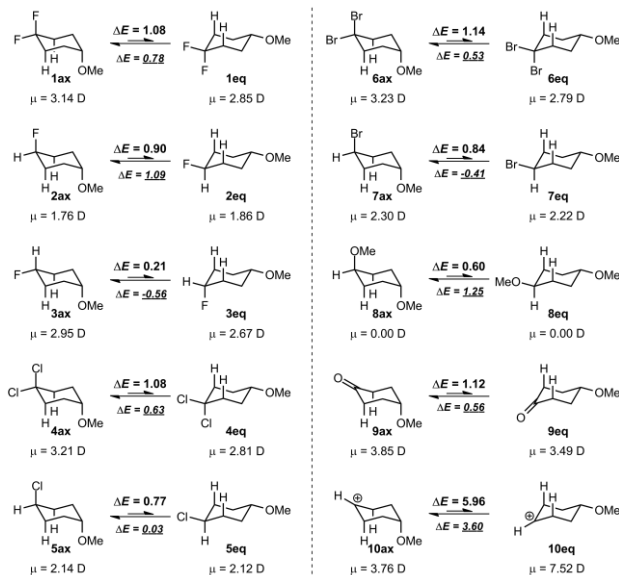


Figure 2. Ring interconversion Electronic Energies (ΔE) in kcal mol⁻¹ for compounds **1-10** calculated in the gas-phase at the M06-2X/aug-cc-pVTZ theoretical level. Underlined/italic values of ΔE represent ring interconversion energies after deletion of σ^* or π^* orbitals at position 4 of the ring. Molecular dipoles (μ) are given for each conformer in Debye units (D).

NBO analysis was used to deconvolute ring interconversion electronic energy differences, into hyperconjugative, electrostatic and steric contributions. The NBO program first deletes all “unfilled” (acceptor) orbitals from the molecule, leading essentially to an idealized Natural Lewis Structure (NLS), where all Lewis (bonding) NBOs necessarily get 2.0000 electrons, and each of the non-Lewis NBOs gets occupancy 0.0000. An evaluation of the energy of this new and modified density matrix corresponds to the Lewis energy [$\Delta E(L)$], i.e., the energy of a molecule without electron delocalization. Subtracting $\Delta E(L)$ from the total electronic energy [$\Delta E(T)$] of the molecule results in the non-Lewis energy component [$\Delta E(NL)$], which represents the total contribution of hyperconjugation to molecular stabilization. Those energies are summarized in Table 1 for compounds **1-10**. Also tabulated are Natural Electrostatic Energies [$\Delta E(NCE)$], which consider atom-atom interactions as interacting point charges derived from the Natural Population Analysis (NPA) according to the classical Coulomb equation, $E_{NCE} = \sum_{A,B} Q_A Q_B / R_{AB}$, where Q_A and Q_B = NPA atomic charges of atoms A and B and R_{AB} their internuclear distance. Natural Steric Analysis energies [$\Delta E(NSA)$] are recorded too for **1-10**, values which provide the energies associated with intramolecular steric hindrance in each system.

Table 1. NBO analysis relative energies (in kcal mol⁻¹) obtained at the M06-2X/aug-cc-pVTZ theory level for compounds **1-10**, where $\Delta E(T)$ is the electronic, $\Delta E(L)$ the Lewis, $\Delta E(NL)$ the non-Lewis, $\Delta E(NCE)$ the electrostatic and $\Delta E(NSA)$ the steric energies. Positive values favor the axial conformer and negative ones the equatorial conformer.

	$\Delta E(T)$	$\Delta E(L)$	$\Delta E(NL)$	$\Delta E(NCE)$	$\Delta E(NSA)$
1	1.08	3.73	-2.65	3.50	-3.38
2	0.90	4.55	-3.65	-1.07	-4.76
3	0.21	1.57	-1.36	1.42	-0.92
4	1.08	3.25	-2.17	-0.11	-3.48
5	0.77	3.52	-2.75	1.16	-5.40
6	1.14	3.03	-1.89	-1.33	-3.02

7	0.84	2.78	-1.93	1.59	-5.58
8	0.60	4.68	-4.09	-2.43	-5.62
9	1.12	3.43	-2.31	2.66	-2.99
10	5.96	7.31	-1.36	2.96	-3.17

In overview the outcomes were similar to what was observed previously where the strength of the NCHBs is the driving force dictating the most stable *pseudo*-anomer. For instance, compounds **1** and **9**, with a CF₂ and a carbonyl group at position 4, respectively, effectively withdraw electron density from the 3,5-CH_{ax} atoms both through the inductive effect as well as $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CF}}^*$ and $\sigma_{\text{CH}} \rightarrow \pi_{\text{CO}}^*$ hyperconjugative interactions. This results in a very similar average stabilizing energy of -16.8 kcal mol⁻¹ in **1** and **9** from NCHBs, with comparable preferences for the axial isomers by 1.08 and 1.12 kcal mol⁻¹, respectively. Compounds **3**, **5** and **7** show similar behavior, however the anomeric preference in these compounds are attenuated. While σ_{CBr}^* shows higher hyperconjugative stabilization than σ_{CCl}^* ($\sigma_{\text{CH}} \rightarrow \sigma_{\text{CCl}}^* = 7.34$ kcal mol⁻¹ vs $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CBr}}^* = 8.26$ kcal mol⁻¹) and can more effectively increase the atomic charge of the 3,5-CH_{ax} atoms through hyperconjugation, Cl is more electronegative and exhibit a stronger inductive effect. This results in very similar NCHB strength in **5** and **7**, which average -16.44 and -16.58 kcal mol⁻¹ respectively, leading to a similar axial conformer preference of 0.77 kcal mol⁻¹ in **5** and 0.84 kcal mol⁻¹ in **7**. For **3**, where the F atom is *cis* to the methoxy group, the acceptor orbital at position 4 is σ_{CH}^* for the axial conformer, and in this case the 3,5-CH_{ax} hydrogens are mainly polarized due to the inductive effect from the vicinal fluorine, which weakens the NCHB (15.98 kcal mol⁻¹) by 0.8 kcal mol⁻¹ relative to **1_{ax}** and the axial and equatorial isomers become virtually isoenergetic. Curiously, **1_{ax}** has an axial preference of 1.08 kcal mol⁻¹, exactly the NCHB energy difference between **1_{ax}** and **3**, highlighting the importance of NCHB stabilization for the axial preference in **1_{ax}**. For prototype **10**, the carbocation at position 4 of the ring strongly polarizes the 3,5-CH_{ax} hydrogens both by inductive effects and by $\sigma_{\text{CH}} \rightarrow p_{\text{C}^+}$ and $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ hyperconjugation. In this case the NCHBs stabilize the axial isomer by -20.51 and -22.35 kcal mol⁻¹, resulting in an impressive 5.96 kcal mol⁻¹ preference for the axial conformer.

Compounds **2**, **4**, **6** and **8** also display strong NCHBs, with values in the order of 16.17 kcal mol⁻¹ in **2**, 17.32 kcal mol⁻¹ in **4**, 17.43 kcal mol⁻¹ in **6** and 16.02 kcal mol⁻¹ in **8**, as the electronegative groups and σ_{CX}^* acceptor orbitals at position 4 effectively polarize the diaxial hydrogens. Nevertheless, electrostatic interactions $\Delta E(\text{NCE})$ stabilize the equatorial *pseudo*-anomer overall, and more so than in the axial anomer in these compounds. This counterintuitive outcome can be rationalized in terms of 1,4- $\delta^- \text{F} \delta^- \text{C}$ (19.61 kcal mol⁻¹) and 1,6- $\delta^- \text{F} \delta^- \text{O}$ (18.45 kcal mol⁻¹) electrostatic repulsions in **2** and 1,4- $\delta^- \text{O} \delta^- \text{C}$ (28.22 kcal mol⁻¹) and 1,6- $\delta^- \text{O} \delta^- \text{O}$ (26.44 kcal mol⁻¹) electrostatic repulsions in **8**, which overcome the stabilizing energies provided by the NCHBs and the interconversion equilibria toward the equatorial conformer is favored. Even though those repulsive interactions are also present in compounds which display an axial preference, in the 4-disubstituted **1**, **4** and **6** methoxycyclohexanes they equally destabilize the axial and equatorial conformers, so they do not play a role in ring interconversion energies. In addition, the axial 4-substituent in the axial conformers of **3**, **5** and **7** is either positive – resulting in stabilizing 1,4- $\delta^+ \text{X}_{\text{ax}} \delta^- \text{C}$ interactions – or slightly negative – resulting in weaker and negligible repulsive interactions compared to the NCHBs stabilization.

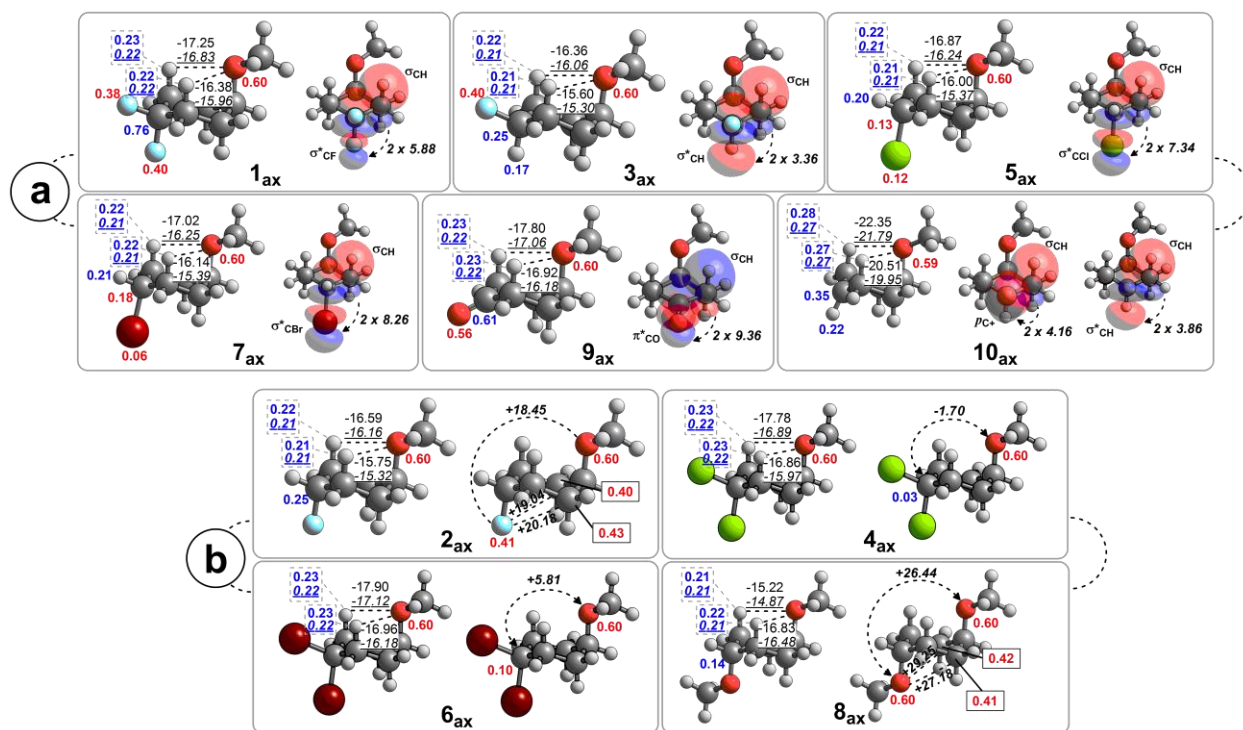


Figure 3. NPA derived atomic charges for selected atoms (positive values in blue, negative values in red, in atomic units) and selected electrostatic and hyperconjugative interactions (in kcal mol⁻¹) obtained from NBO analysis, calculated at the M06-2X/aug-cc-pVTZ theoretical level, for axial *pseudo*-anomers stabilized (a) and destabilized (b) by electrostatic effects [$\Delta E(\text{NCE})$]. Underlined/italic values represent charges/interaction energies calculated after deletion of σ^* and π^* orbitals in position 4 of the ring.

In general, the C4 carbon atoms in methoxycyclohexanes **1-10** are highly positively charged due to the inductive effect of their attached electronegative substituents, giving rise to strong charge-charge electrostatic attraction between the OMe group and C4, and that interaction contributes more to an axial stabilization. However, the lower electronegativity of CCl₂ and CBr₂ in compounds **4** and **6** respectively, only slightly polarizes C4, and the $\delta^+\text{C4}^{\delta-}\text{OMe}$ electrostatic interaction becomes either weakly attractive (-1.70 kcal mol⁻¹ in **4**) or repulsive (+5.81 kcal mol⁻¹ in **6**), resulting in a negative value of $\Delta E(\text{NCE})$, i.e., overall electrostatic stabilization of the equatorial isomers (see SI for full atom-atom electrostatic interactions). Considering that the Lewis energy $\Delta E(\text{L})$ is calculated over an idealized molecule without any hyperconjugation, $\Delta E(\text{L})$ can be used to qualitatively predict the importance of electrostatic and steric interactions to molecular stabilization. Since it is anticipated that steric effects will be stronger in the axial isomers due to repulsions between the OMe substituent and the ring atoms, a positive $\Delta E(\text{L})$ indicates that electrostatic interactions are still energetically favoring the axial isomers in all of the studied compounds, including **2**, **4**, **6** and **8**. Finally, it is important to note that the hyperconjugative $\Delta E(\text{NL})$ and steric $\Delta E(\text{NSA})$ contributions collectively promote equatorial conformer stability, and this reinforces the importance of the electrostatic NCHB interactions in determining the overall axial preference in these systems.

To further assess the importance of hyperconjugation on NCHB capacity, NBO calculations were carried out on hypothetical molecules where only the $\sigma^*\text{CX}$ (or $\pi^*\text{CO}$) antibonding orbitals of the different substituents at position 4 were deleted. With this constraint $\sigma_{\text{CHax}} \rightarrow \sigma^*\text{CX}$ (or $\pi^*\text{CO}$) hyperconjugations are not possible, resulting in weaker NCHBs and therefore smaller *pseudo*-anomeric preferences (Figure 2, underlined values). Interestingly, the 3,5-CH_{ax} atoms become less electropositive after this deletion, which indeed weakened the NCHBs interaction energies (Figure 3, underlined values). In fact, the positive charge increase on 3,5-CH_{ax} associated with hyperconjugation arises predominantly because of the overlap of σ_{CH} with the back lobe of $\sigma^*\text{CX}$ (Figure 3). It follows that the back lobe volume is bigger when bulky atoms are attached to C4, resulting in a better overlap with σ_{CH} and a concomitant increase in 3,5-CH_{ax} positive charges. Naturally, the stronger the $\sigma_{\text{CH}} \rightarrow \sigma^*\text{CX}$ (or $\pi^*\text{CO}$) interaction, then the 3,5-CH_{ax} atomic charges will become less positive after the antibonding orbital deletions. Accordingly compounds **1-3** and **8** experience a small charge decrease (~ 0.004 - 0.005 au) with this deletion due to the poor overlap between σ_{CH} and $\sigma^*\text{CF}$, $\sigma^*\text{CH}$ or $\sigma^*\text{CO}$ (σ_{CH}

→ σ^*_{CX} ; range of 3.36-5.88 kcal mol⁻¹), whereas compounds **4-7**, **9** and **10** experience a significant charge decrease (-0.008-0.012 au) due to more stabilizing hyperconjugative interactions ($\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CX}}$ or π^*_{CO} , range of 7.34-9.36 kcal mol⁻¹). It follows for compounds **1-3** and **8** that the NCHB strength is mainly controlled by the inductive effect of the substituent located at position 4, while for compounds **4-7** and **9** NCHB interactions are highly dependent on $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CX}}$ hyperconjugation. On the other hand, the empty *p* orbital and the σ^*_{CH} antibonding orbital at C4 in **10** are strong acceptors and the carbocation also exhibits a strong inductive effect, therefore the NCHB strength is controlled by a synergic interplay between hyperconjugation and inductive effects.

Finally, in order to further support the important role that NCHBs play in dictating an axial preference, the average stabilization energy of the NCHBs vs $\Delta E_{(\text{eq-ax})}$ was plotted for compounds **1-10** (Figure S1). An excellent linear correlation is apparent between NCHB strength and axial stabilization ($R^2 = 0.84$), which further supports the role that NCHBs play in the *pseudo*-anomeric effect, certainly among the compounds studied here.

In conclusion this study reinforces the dominant contribution played by electrostatic interactions, and more specifically the $\text{CH}_{\text{ax}} \cdots \text{OMe}$ NCHB interaction, to the *pseudo*-anomeric effect observed in an array of 4-substituted methoxycyclohexanes. The 3,5- CH_{ax} polarization, and thus the NCHB strength, can be modulated by either the introduction of vicinal electronegative groups, such as the difluoromethylene in **1**, which draws electron density mostly through inductive effects, or the introduction of substituents of moderate electronegativity, such as the dibromomethylene in **6**, which will mostly increase the electropositive nature of the H_{ax} atoms through hyperconjugation. This study highlights a strategy by which to deconvolute the various contributions to the origin of conformational preferences of small organic compounds and in this case to rationalize the counterintuitive observation that many C-4 substituted methoxycyclohexanes can display a *pseudo* anomeric preference.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <>.

Computational details, atom-atom electrostatic interactions decomposition, and geometric coordinates.

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