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

Bruno A. Piscelli,[a] David O'Hagan,[b] Rodrigo A. Cormanich[a,*]

[a] *University of Campinas, Chemistry Institute, Monteiro Lobato Street, Campinas, Sao Paulo, Brazil - 13083-862; Email: cormanich@unicamp.br;*
[b] *University of St Andrews, School of Chemistry, North Haugh, St Andrews, Fife, KY16 9ST, UK.*

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 $\sigma_{CH} \rightarrow \sigma^*_{CX}$ hyperconjugation and the electropositive charge on the 3,5-axial hydrogens (H_{ax}). In essence better σ^*_{CX} (or π^*_{CO}) acceptors increase the charge on 3,5-CH_{ax}, which in turn strengthens $C^{\delta+}H_{ax}\cdots^{\delta-}OMe$ NCHB interactions.

TOC Graph
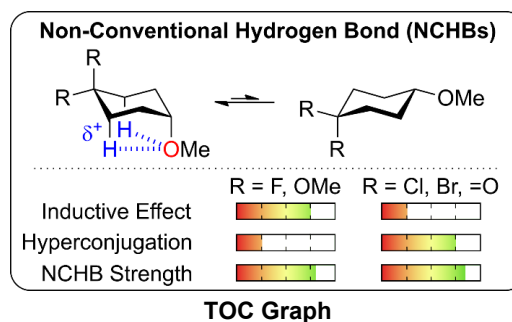
1. INTRODUCTION

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 repulsions[12] 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 ($CH_{ax}{}^{\delta+}\cdots^{\delta-}OMe$).[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 (e.g. 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 effects[15] 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 $\sigma_{CHax} \rightarrow \sigma^*_{CF}$ hyperconjugation and consequently increases NCHBs stabilization, or donor orbitals (e.g. *endo* oxygen lone pair) decrease the atomic charge on 3,5-CH_{ax} through $n_O \rightarrow \sigma^*_{CH}$ hyperconjugation and therefore weakens NCHBs.
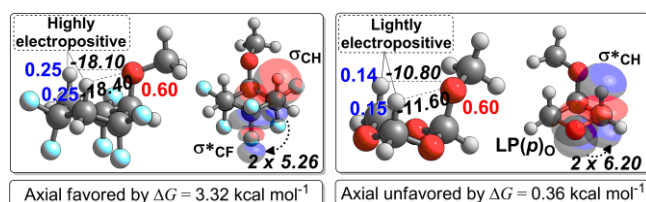

Figure 1. Natural population analysis (NPA) atomic charges (positive values in blue, negative values in red, in atomic units) and NBO derived 3,5-$CH_{ax}\cdots OMe$ electrostatic and $\sigma_{CHax} \rightarrow \sigma^*_{CF}$ // $n_O \rightarrow \sigma^*_{CH}$ hyperconjugative interaction energies (in 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-substitued 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**.
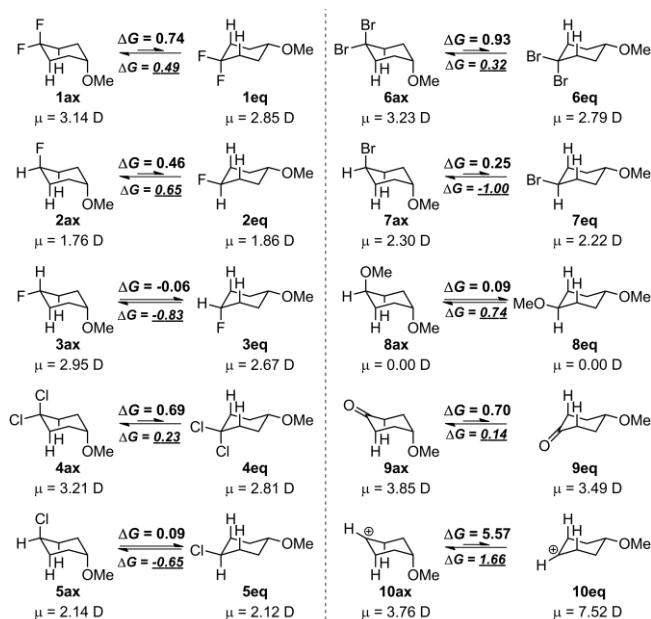

Figure 2. Ring interconversion Electronic Energies (ΔE) in kcal mol^{-1} for compounds **1-10** calculated in the gas-phase at the M06-2X/aug-cc-pVTZ theoretical level. Underlined/italic values of ΔE represent ring interconversion energies after deletion of σ^* or π^* orbitals at position 4 of the ring.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

2. COMPUTATIONAL METHODS

The axial and equatorial conformers of compounds **1-10** were optimized at the M06-2X/aug-cc-pVTZ theoretical level using the UltraFine integration grid, and harmonic frequency calculations were carried out at the same level in order to identify each geometry as true energy minima, showing no imaginary frequency, using Gaussian 16 Rev C.01 program.[16] Single point energies for all optimized geometries were calculated using the Domain-Based Local Pair Natural Orbital (DLPNO)[17] approximation for CCSD(T) and with the basis set extrapolated to completeness from Dunning's correlation-consistent polarized basis sets (cc-pVDZ/cc-pVTZ) as implemented in ORCA 5.0.3[18] with TightPNO and TightSCF settings. The good agreement between M06-2X/aug-cc-pVTZ and DLPNO-CCSD(T)/CBS single point energies indicate that the DFT functional and basis set chosen are suitable for the description of the molecular systems studied. Therefore, the M06-2X/aug-cc-pVTZ electronic energies were corrected with the thermal correction to Gibbs free energies obtained from the frequency calculations at the same theory level to afford the ring interconversion ΔG energy for compounds **1-10** equilibria. Molecular dipole moments and NBO analyses (using the NBO 7.0 program[19] implemented in Gaussian16) were also calculated at the M06-2X/aug-cc-pVTZ level of theory.

3. RESULTS AND DISCUSSION

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 (ΔE_L), i.e., the energy of a molecule without electron delocalization. Subtracting ΔE_L from the total electronic energy (ΔE_T) of the molecule results in the non-Lewis energy component (ΔE_{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 (ΔE_{NCE}),[20] which consider atom-atom interactions as interacting point charges derived from the Natural Population Analysis (NPA)[21] 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 (NSA)[22,23] considers steric exchange repulsion as the energy difference due to orbital orthogonalization, i.e. the energy difference between two molecular units separated to infinity and in the equilibrium geometry, and the total intramolecular steric hindrance as the sum of each pair-wise interaction energy (ΔE_{NSA}). In this way, NSA is in agreement with steric repulsions representing the effect of the Pauli exclusion principle in preventing electron pairs from "occupying" the same region in space.

Note that NCE and NSA are independent modules from the NBO program, each having thier own theoretical approaches. Therefore, ΔE_L, ΔE_{NCE} and ΔE_{NSA} are not quantitatively comparable, and their values should be evaluated separately from each other. In other words, one may evaluate the importance of electron delocalization from ΔE_L, because it represents a hypothetical molecule without electron delocalization, and the importance of electrostatic and steric repulsion from ΔE_{NCE} and ΔE_{NSA}, respectively. ΔE_L may be inaccurately considered to represent steric and electrostatic effects of a molecular system, since it represents a structure without electron delocalization and hence only these classical effects remain in the molecular system. However, care should be taken in this analysis, because ΔE_L is obtained after deletion of all antibonding orbitals of a molecular system and does not represent the steric and electrostatic energies in the original molecule. Thus, ΔE_{NCE} and ΔE_{NSA} may be considered the most reliable energies in evaluating electrostatic and steric effects from the NBO point of view.

Table 1. Gibbs Free Energy (ΔG) and NBO analysis relative energies (in kcal mol^{-1}) obtained at the M06-2X/aug-cc-pVTZ theory level for compounds **1-10**, where ΔE_T is the electronic, ΔE_L the Lewis, ΔE_{NL} the non-Lewis, ΔE_{NCE} the electrostatic and ΔE_{NSA} the steric energies. Positive values favor the axial conformer and negative ones the equatorial conformer.

	ΔG	ΔE_T	ΔE_L	ΔE_{NL}	ΔE_{NCE}	ΔE_{NSA}
1	0.74	1.08	3.73	-2.65	3.50	-3.38
2	0.46	0.90	4.55	-3.65	-1.07	-4.76
3	-0.06	0.21	1.57	-1.36	1.42	-0.92
4	0.69	1.08	3.25	-2.17	-0.11	-3.48
5	0.09	0.77	3.52	-2.75	1.16	-5.40
6	0.93	1.14	3.03	-1.89	-1.33	-3.02
7	0.25	0.84	2.78	-1.93	1.59	-5.58
8	0.09	0.60	4.68	-4.09	-2.43	-5.62
9	0.70	1.12	3.43	-2.31	2.66	-2.99
10	5.57	5.96	7.31	-1.36	2.96	-3.17

Table 1 indicates that the total electronic energy ΔE_T relative values among **1-10** has a similar trend in comparison to the Gibbs free energy ΔG given that enthalpic/entropic effects showed to have small influence in the conformational equilibria of **1-10** (see Table S32 in the ESI). Because NBO analysis relies on the electronic energy decomposition of ΔE rather than ΔG, the energetic discussion involving NBO analysis are given in terms of ΔE instead of ΔG in this paper.

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 CF$_2$ 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 $\sigma_{CH} \rightarrow \sigma^*_{CF}$ and $\sigma_{CH} \rightarrow \pi^*_{CO}$ 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} ($\sigma_{CH} \rightarrow \sigma^*_{CCl}$ = 7.34 kcal mol^{-1} *vs* $\sigma_{CH} \rightarrow \sigma^*_{CBr}$ = 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 $\sigma_{CH} \rightarrow p_{C+}$ and $\sigma_{CH} \rightarrow \sigma^*_{CH}$ 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 ΔE_{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-$^\delta$F$^\delta$-C (19.61 kcal mol^{-1}) and 1,6-$^\delta$F$^\delta$-O (18.45 kcal mol^{-1}) electrostatic repulsions in **2** and 1,4-$^\delta$O$^\delta$-C (28.22 kcal mol^{-1}) and 1,6-$^\delta$O$^\delta$-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-$^{\delta+}$X$_{ax}$$^\delta$-C interactions – or slightly negative – resulting in weaker and negligible repulsive interactions compared to the NCHBs stabilization.
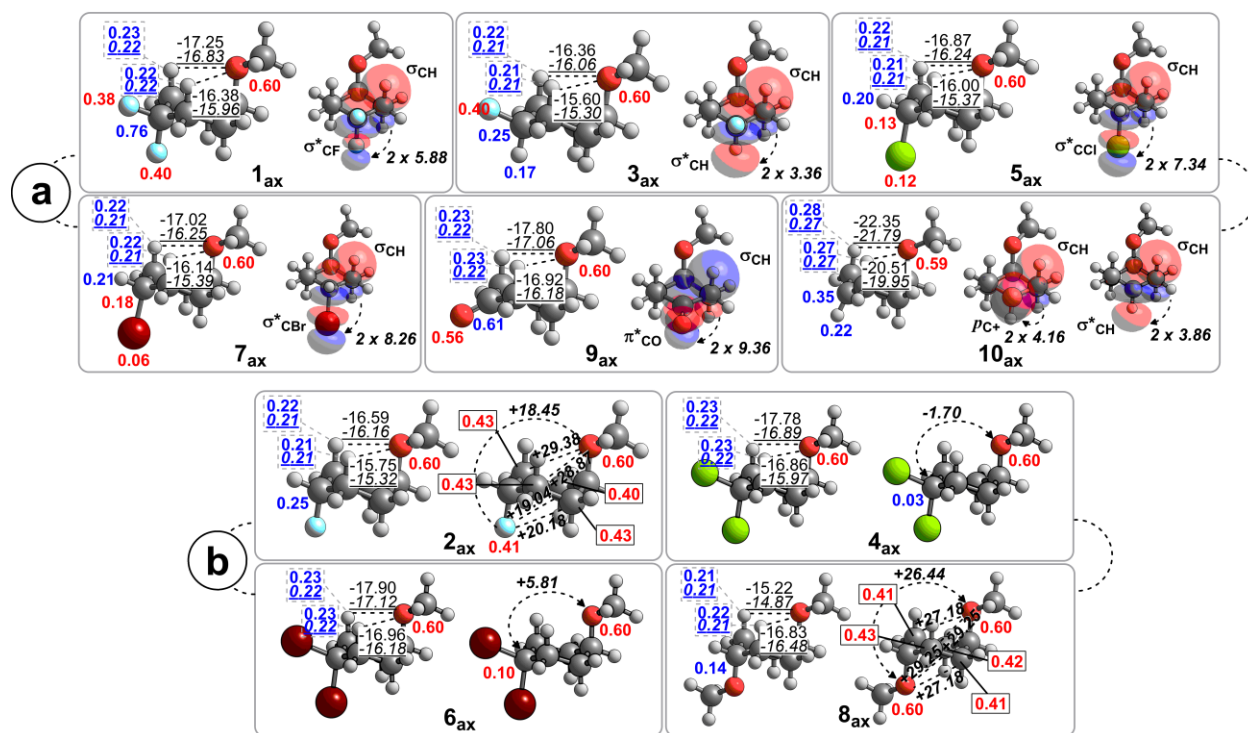

Figure 3. NPA derived atomic charges for selected atoms (positive values in blue, negative values in red, in atomic units) and selected electrostatic and hyperconjugative interactions (in kcal mol^{-1}) obtained from NBO analysis, calculated at the M06-2X/aug-cc-pVTZ theoretical level, for axial *pseudo*-anomers stabilized (**a**) and destabilized (**b**) by electrostatic effects (ΔE_{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 CCl$_2$ and CBr$_2$ in compounds **4** and **6** respectively, only slightly polarizes C4, and the $^{\delta+}$C4$^\delta$-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 ΔE_{NCE}, i.e., overall electrostatic stabilization of the equatorial isomers (see SI for full atom-atom electrostatic interactions). Considering that the Lewis energy ΔE_L is calculated over an idealized molecule without any hyperconjugation, ΔE_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 ΔE_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 ΔE_{NL} and steric ΔE_{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 σ^*_{CX} (or π^*_{CO}) antibonding orbitals of the different substituents at position 4 were deleted. With this constraint $\sigma_{CHax} \rightarrow \sigma^*_{CX}$ (or π^*_{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 increases on the 3,5-CH$_{ax}$ hydrogens and this is associated with hyperconjugation which arises predominantly because of the overlap of σ_{CH} with the back lobe of σ^*_{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 $\sigma_{CH} \rightarrow \sigma^*_{CX}$ (or π^*_{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 σ^*_{CF}, σ^*_{CH} or σ^*_{CO} ($\sigma_{CH} \rightarrow \sigma^*_{CX}$; 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 ($\sigma_{CH} \rightarrow \sigma^*_{CX}$ 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 $\sigma_{CH} \rightarrow \sigma^*_{CX}$ 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. ==Further details are presented in the ESI.==
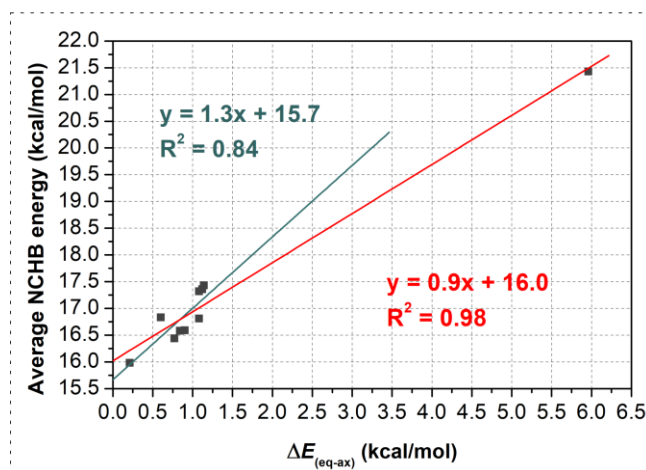

==**Figure 4.** Linear regression showing a positive correlation between NCHB stabilizing energy and axial isomer preference (without orbital deletion). In red, the linear regression considering all compounds **1-10**, and in green the linear regression considering only compounds **1-9**. Energies and atomic charges were calculated at the M06-2X/aug-cc-pVTZ theoretical level.==

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* $\Delta E_{(eq-ax)}$ was plotted for compounds **1-10** (==Figure 4==). 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.

5

4. CONCLUSIONS

In conclusion this study reinforces the dominant contribution played by electrostatic interactions, and more specifically the $CH_{ax}\cdots OMe$ 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.

AUTHOR INFORMATION

Corresponding Authors
 Rodrigo A. Cormanich - *University of Campinas, Chemistry Institute, Monteiro Lobato Street, Campinas, Sao Paulo, Brazil - 13083-862;*
E-mail: cormanich@unicamp.br.
Authors
 Bruno A. Piscelli – *University of Campinas, Chemistry Institute, Monteiro Lobato Street, Campinas, Sao Paulo, Brazil - 13083-862;*
 David O'Hagan - *University of St Andrews, School of Chemistry, North Haugh, St Andrews, Fife, KY16 9ST, UK.*

ACKNOWLEDGEMENTS

REFERENCES

(1) Edward, J. T. Stability of Glycosides to Acid Hydrolysis. *Chem. Ind. (London)* **1955**, 1102-1104.
(2) Lemieux, R. U. Effects of Unshared Pairs of Electrons and Their Solvation on Conformational Equilibria. *Pure Appl. Chem.* **1971**, *25*, 527-548.
(3) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Exeter, 1983.
(4) Alabugin, I. V. Stereoelectronic Effects: A Bridge Between Structure and Reactivity; John Wiley & Sons, Ltd.: New York, **2016**.
(5) Kirby, A. J. The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. Springer-Verlag: New York, 1983.
(6) Juaristi, E., Cuevas, G. The Anomeric Effect. CRC Press: Boca Raton, 1995.
(7) Filloux, C. M. The Problem of Origins and Origin of the Problem: Influence of Language on Studies Concerning the Anomeric Effect. *Angew. Chem. Int. Ed.* **2015**, *54*, 8880-8894.
(8) Wiberg, K. B., Bailey, W. F., Lambert, K. M., Stempel, Z. D. The Anomeric Effect: It's Complicated. *J. Org. Chem.* **2018**, *83*, 5242-5255.
(9) Alabugin, I. V., Kuhn, L., Krivoshchapov, N. V., Mehaffy, P., Medvedev, M. G. Anomeric Effect, Hyperconjugation and Electrostatics: Lessons from Complexity in a Classic Stereoelectronic Phenomenon. *Chem. Soc. Rev.* **2021**, *50*, 10212-10252.
(10) Freitas, M. P. The Anomeric Effect on the Basis of Natural Bond Orbital Analysis. *Org. Biomol. Chem.* **2013**, *11*, 2885-2890.
(11) Juaristi, E., Notario, R. Stereoelectronic Interactions Exhibited by $^1J_{C-H}$ One-Bond Coupling Constants and Examination of the Possible Existence of the Intramolecular α-Effect in Six-Membered Oxygen-Containing Heterocycles. *J. Org. Chem.* **2018**, *83*, 3293-3298.

(12) Mo, Y. Computational Evidence that Hyperconjugative Interactions are not Responsible for the Anomeric Effect. *Nat. Chem.* **2010**, *2*, 666-671.

(13) Piscelli, B. A., Sanders, W., Yu, C., Al Maharik, N., Lebl, T., Cormanich, R. A., O'Hagan, D. Fluorine-Induced Pseudo-Anomeric Effects in Methoxycyclohexanes Through Electrostatic 1,3-Diaxial Interactions. *Eur. J. Chem.* **2020**, *26*, 11989-11994.

(14) Piscelli, B. A., O'Hagan, D., Cormanich, R. A. The Contribution of non-Classical $CH_{ax}\cdots OC$ Hydrogen Bonds to the Anomeric Effect in Fluoro and Oxa-Methoxycyclohexanes. *Phys. Chem. Chem. Phys.* **2021**, *23*, 5845-5851.

(15) Afonso, M. A. S., Cormanich, R. A. The Preferred Geometry of Hydroperoxides is the Result of an Interplay Between Electrostatic and Hyperconjugative Effects. *Phys. Chem. Chem. Phys.* **2020**, *22*, 27173-27177.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H., *et al*. Gaussian 16, Revision C.01; Gaussian, Inc.: Wallingford, CT, 2016.

(17) Riplinger, C.; Neese, F. An Efficient and Near Linear Scaling Pair Natural Orbital Based Local Coupled Cluster Method. *J. Chem. Phys.* **2013**, *138*, 034106.

(18) Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152*, 224108.

(19) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Karafiloglou, P.; Landis, C. R.; Weinhold, F. NBO 7.0; Theoretical Chemistry Institute, University of Winsconsin: Madison, WI, 2018.

(20) Weinhold, F.; Landis, C. R. *Discovering Chemistry with Natural Bond Orbitals*. Wiley-VCH: Hoboken, 2012.

(21) Reed, A. E.; Weinstock, R. B.; Weinhold, F. Natural Population Analysis. *J. Chem. Phys.* **1985**, *83*, 730.

(22) Badenhoop, J. K.; Weinhold, F. Natural Bond Orbital Analysis of Steric Interactions. *J. Chem. Phys.* **1997**, *107*, 5406.

(23) Badenhoop, J. K.; Weinhold, F. Natural Steric Analysis of Internal Rotation Barriers. *Int. J. Quantum Chem.* **1999**, *72*, 269-280.