Anomeric Effect, Hyperconjugation and Electrostatics: Lessons from Complexity in a Classic Stereoelectronic Phenomenon.

Journal:	*Chemical Society Reviews*
Manuscript ID	CS-REV-06-2021-000564.R1
Article Type:	Review Article
Date Submitted by the Author:	11-Jul-2021
Complete List of Authors:	Alabugin, Igor; Florida State University, Chemistry and Biochemistry Kuhn, Leah; Florida State University, Chemistry and Biochemistry Krivoshchapov, Nikolai; Zelinsky Institute of Organic Chemistry RAS; Lomonosov Moscow State University Mehaffy, Patricia; Florida State University, Chemistry and Biochemistry Medvedev, Michael; Zelinsky Institute of Organic Chemistry RAS; A N Nesmeyanov Institute of Organoelement Compounds RAS

Anomeric Effect, Hyperconjugation and Electrostatics: Lessons from Complexity in a Classic Stereoelectronic Phenomenon.

Igor V. Alabugin,[a*] Leah Kuhn,[a] Nikolai V. Krivoshchapov[b,c], Patricia Mehaffy,[a] Michael G. Medvedev[b,d*]

[a]Department of Chemistry and Biochemistry, Florida State University, USA.

[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation

[c]Lomonosov Moscow State University, Leninskie Gory 1 (3), Moscow, 119991, Russian Federation

[d]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova St., 119991 Moscow, Russian Federation

Corresponding author: alabugin@chem.fsu.edu (I. V. Alabugin), medvedev.m.g@gmail.com (M. G. Medvedev).

Abstract

Understanding the interplay of multiple components (steric, electrostatic, stereoelectronic, dispersive, etc.) that define the overall energy, structure, and reactivity of organic molecules can be a daunting task. The task becomes even more difficult when multiple approaches based on different physical premises disagree in their analysis of a multicomponent molecular system. Herein, we will use a classic conformational "oddity", the anomeric effect, to discuss the value of identifying the key contributors to reactivity that can guide chemical predictions.

After providing the background related to the relevant types of hyperconjugation and a brief historic outline of the origins of the anomeric effect, we outline variations of its patterns and provide illustrative examples for the role of the anomeric effect in structure, stability, and spectroscopic properties. We show that complete hyperconjugative model remains superior in explaining the interplay between structure and reactivity.

We will use recent controversies regarding the origin of the anomeric effect to start a deeper discussion relevant to any electronic effect. Why are such questions inherently controversial? How to describe a complex quantum system using a model that is "as simple as possible, but no simpler"? What is a fair test for such a model? Perhaps, instead of asking "who is right and who is wrong?", one should ask "why do we disagree?".

Stereoelectronic thinking can reconcile quantum complexity with chemical intuition and build the conceptual bridge between structure and reactivity. Even when many factors contribute to the observed structural and conformational trends, electron delocalization is a dominating force when the electronic demand is high (i.e., bonds are breaking as molecules distort from their equilibrium geometries). In these situations, the role of orbital interactions increases to the extent where they can define reactivity. For example, negative hyperconjugation can unleash the "underutilized" stereoelectronic power of unshared electrons (i.e., the lone pairs) to stabilize a developing positive charge at an anomeric carbon. This analysis paves the way for the broader discussion of the omnipresent importance of negative hyperconjugation in oxygen-containing functional groups. From that point of view, the stereoelectronic component of the anomeric effect plays a unique role in guiding reaction design.

Introduction

The importance of delocalization and the nature of stereoelectronic effects

Chemical reactivity is complex. In order to rationalize and predict the net effect of multiple functional groups in a molecule, one has to consider, in addition to the obvious electrostatic and steric factors (the usual focus of an undergraduate organic chemistry class), the quantum effects associated with superposition of atomic wavefunctions. Of course, a variety of modern quantum mechanical methods can quantitatively model chemical reactivity, but their ever-increasing accuracy generally comes at the expense of conceptual clarity. As our approximations for solving the Schrodinger equation grow in complexity, the fundamental concept of chemical bonds and functional groups start to vanish into thin air.[1] One can argue if this trend is good or bad, but, at the moment, we still need humans to be able to understand and predict chemical reactivity. At least, before this job is taken over by the computer algorithms that may embrace the alternative logic and use it more efficiently.

Although chemists are comfortable with describing molecules as Lewis structures - bonds as lines, unpaired valence electrons as dots - molecules are nothing like lines and dots drawn on paper. They are complex quantum objects, constituted of electrons delocalized around the atomic nuclei. Conjugation, hyperconjugation, and σ-conjugation are manifestations of this delocalization, i.e., a refinement of the initial Lewis structure approximation by resonance (Figure 1). Such delocalizing interactions come in a variety of patterns, each of which can correspond to a stereoelectronic effect on stability or reactivity. [2] Generally, intramolecular delocalizing interactions are classified as conjugation, hyperconjugation, and σ-conjugation (Figure 1). Interactions that involve π-bonds and p-orbitals are referred to as conjugation. Based on IUPAC definition, interactions between σ- and π-orbitals are classified as hyperconjugation, whereas the interactions between two σ-orbitals are called σ-conjugation.[2-5] In practice, σ-conjugation is often treated as another pattern of hyperconjugation.

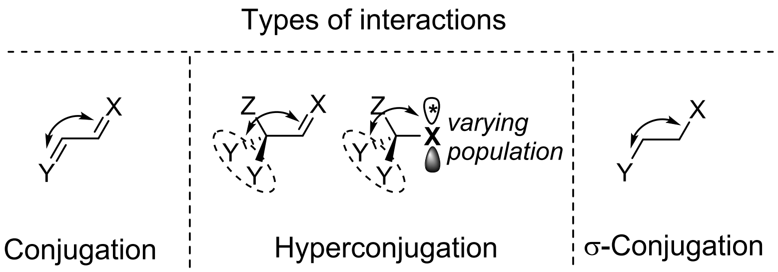


Figure 1. Common types of intramolecular delocalizing interactions.[2]

Herein, our focus will be on negative hyperconjugation, i.e., the interactions between lone pairs and σ^*-orbitals. Negative hyperconjugation involves the transfer of electron density from a good donor (usually, a lone pair) to an acceptor σ^*-orbital. The "opposite" delocalization pattern, positive hyperconjugation, involves the transfer of electron density from a donor σ-orbital to an empty orbital (often at a cationic center). The third type, neutral hyperconjugation, is balanced, so both molecular fragments act simultaneously as donor and acceptor towards each other via a pair of delocalizing interactions of opposite direction (i.e., $\pi_{CX}\rightarrow\sigma^*_{CY}$ and $\sigma_{CY}\rightarrow\pi^*_{CX}$ for a C=X/C-Y pair).

In order to calibrate our perception, Figure 2 provides Natural Bond Orbital (NBO) evaluation of the electronic stabilization provided by negative, neutral, and positive hyperconjugation in three parent H_3C-X systems of different electronic nature (X = NH_2, CH_3, BH_2). As a more detailed discussion of these trends can be found in the literature,[6] we will only provide a very short outline of the key chemical consequences of these delocalizing effects. Further details of the NBO method will be given in one of the following sections.

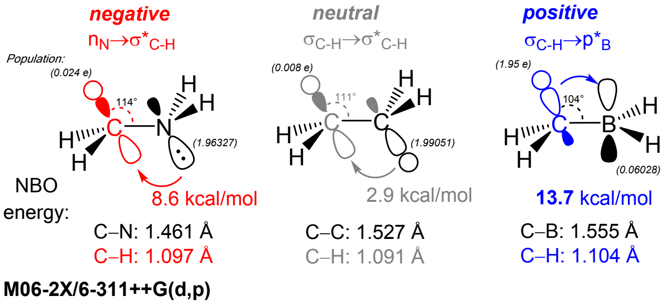


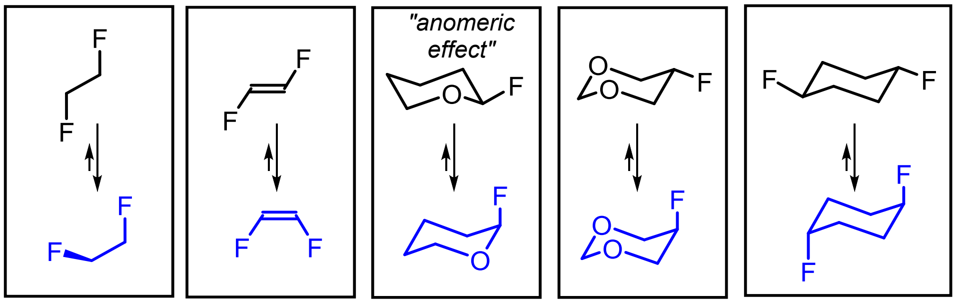
Figure 2. Examples of negative, neutral and positive hyperconjugation. Orbital interaction energies are evaluated using the 2nd order perturbation approach. Note that NBO orbital interaction energy for neutral hyperconjugation needs to be multiplied by two since this pattern is bidirectional (i.e., each C-H bond serves as a donor and an acceptor).

Positive hyperconjugation, associated with a strong $\sigma_{CH}\rightarrow p^*_B$ interaction (13.7 kcal/mol), is greater than the other two hyperconjugation types even in the absence of positive charge. Delocalization in methylborane is essential in partially compensating for the lack of an octet at the boron atom. Delocalization of charge through positive hyperconjugation plays an important role in stabilizing carbocations[7] and explains the well-known order of cation stability (tertiary>secondary>primary>methyl).[8, 9]

Negative hyperconjugation is smaller but still relatively large (note the $n_N \rightarrow \sigma^*_{CH}$ interaction of 8.6 kcal/mol in Figure 2). It is essential because it provides a way to involve non-bonding orbitals (lone pairs) in chemical bonding. A remarkable feature of negative hyperconjugation is that these strong delocalizing interactions are present in stable textbook molecules (amines, ethers, alcohols, ketones).

In addition, one can also separate orbital interactions into vicinal, geminal, and remote interactions, depending on whether the interacting orbitals are at the same atom (geminal), adjacent atoms (vicinal) and atoms that are not directly bonded (remote). Although both the geminal[10, 11,12, 13] and the remote[14,15] interactions are ubiquitous and provide important contribution to overall molecular stability,[3] it is the vicinal interactions that are especially interesting as a tool for control chemical reactivity as these interactions can be switch off and on by rotation around the bridging bond.

Although hyperconjugation is an omnipresent "foundational" force, essential for understanding many aspects of chemical structure and reactivity, there are chemical phenomena where the role of hyperconjugation is especially relevant. In particular, hyperconjugation provides simple and intuitively appealing explanations for the strikingly counterintuitive consequences for molecular structure, stability and reactivity associated with stereoelectronic effects.[2] Stereoelectronic effects, i.e., the stabilizing interactions of orbitals in space, are based on the quantum nature of molecular bonding but express this nature in a set of simple and intuitive practical rules that build a bridge between structure and reactivity.[2, 3] "Stereo" in "stereoelectronic" is not related to "steric repulsion" but, instead, highlights the directionality of orbital interactions in space. Stereoelectronic stabilization is only "switched on" when the geometry is favorable for orbital overlap. For example, in each of the five pairs in Figure 3, the more stable structure is the one that seems to be disfavored sterically (i.e., gauche, cis, or axial) but has the "best donor" orbital aligned with the "best acceptor" orbital.[16, 17] For those readers who would like to learn more about the foundations of stereoelectronic effects and the difference between NBOs and molecular orbitals, we have also provided addenda at the end of the Review .



In every case, the blue structure is more stable

Figure 3. Examples of stereoelectronic effects on stability of conformers and isomers.[2] In every case, a "sterically disfavored structure is more stable

Out of this illustrative selection of stereoelectronic effects, one of the oldest and historically important examples is the anomeric effect (AE), shown here is the preference for the axial conformer of 2-F-tetrahydropyran (2-F-THP).[18, 19] A well-accepted explanation for the anomeric effect is based on stabilizing hyperconjugative donor-acceptor interactions between the lone pair of oxygen and the acceptor $\sigma^*_{C\text{-}F}$ orbital (vide infra). As we will show below, this simple model has significant predictive power and, with a modest expansion, can explain a variety of unusual properties of anomeric systems, including their structure, stability, and reactivity.

However, even though the hyperconjugative model of the anomeric effect remains the most popular, a few literature reports offer a dissenting opinion and argue for the primary importance of electrostatic factors and the relative unimportance of hyperconjugation. For example, Wiberg and Rablen acknowledge the complexity of the anomeric effect but advocate for the greater importance of bond polarization and electrostatics.[20] Mo and coworkers developed Block Localized Wavefunction (BLW) analysis and used it "to disprove the hyperconjugation explanation for the anomeric effect".[21, 22] In several reports, Ferro-Costas, Mosquera and coworkers state that "QTAIM properties dissent from the view of the hyperconjugative model, but agree with an interpretation based upon electron–electron repulsions"[23-29] and conclude that hyperconjugation is less important than electrostatics.

Considering that the anomeric effect is the prototypical stereoelectronic effect, these conflicting opinions suggest that it is timely to reevaluate the role of hyperconjugation in this phenomenon. One of the goals of this review is to illustrate how stereoelectronic aspects of orbital interactions affect structure and reactivity in the anomeric systems.

Furthermore, we would like to go one step further and use this essential topic to start a deeper discussion that is relevant to any electronic effect and can be summarized by the following questions*. Can we describe a complex "full-blooded" quantum system with a model based on a single parameter? How would we choose such a parameter and what is a fair test for a model that tries to represent a reality that is not simple and is not clearly separable into completely independent components?*

In a situation where multiple effects combine to account for the observed trend in stability, conclusions from different studies often remind one of the old tale of blind men and an elephant. The story tells that when the men touch different parts of the elephant, they describe it in different ways: "a snake, a wall, a rope etc…", illustrating the danger of making conclusions based on limited information (or a limited point of view). The real situation for *theoretical* analysis of the anomeric effect is even worse. Here, a more suitable analogy would be men applying different senses (touch, smell, hearing - whatever corresponds to their preferred computational method of analysis) to perceive the different isolated aspects of "an elephant" and then discussing what the most important part of an elephant may be. Clearly, *both* the trunk and the ears have to be present in an elephant in the same way as *both* the electrostatic and hyperconjugative effects are present in anomeric systems. Furthermore, our perception of molecules is shaped by our methods of study, by our observation tools, by the focus of our attention, and by the underlying conceptual paradigm.

We will show that the conflicting literature descriptions of the anomeric effect, illustrate the general limitations of chemical models, a situation which is not unique but, rather, typical for stereoelectronic effects. Developing criteria for a good model that connects structure with reactivity will provide the general paradigm for analyzing *any* stereoelectronic effect. Understanding AE will set the stage for a broader discussion of reactivity of O-containing organic functional groups. The role of negative hyperconjugation in AE highlights the important role of oxygen lone pairs in molecular structure/stability/reactivity and illustrates that even though we usually refer to the lone pairs as "non-bonding" orbitals, these orbitals are not spectators but important players in a variety of chemical phenomena.

With these questions in mind, let us learn more about the anomeric effect.

The brief history of anomeric effect

Anomeric effect was discovered in 1955 by J. T. Edward in studies of carbohydrate chemistry. Originally called the "Edward-Lemieux effect", the phenomenon was dubbed the "anomeric effect" by Lemieux in

1958.[2, 3, 20, 30-33] Historically, this phenomenon was introduced to explain unusual conformational preferences in carbohydrates where the presence of an endocyclic oxygen in a glycoside leads to an "abnormal" axial conformational preference for certain substituents at the "anomeric" carbon (Figure 4). It was also found that this axial preference becomes more pronounced as acceptor character of the anomeric substituent increases.

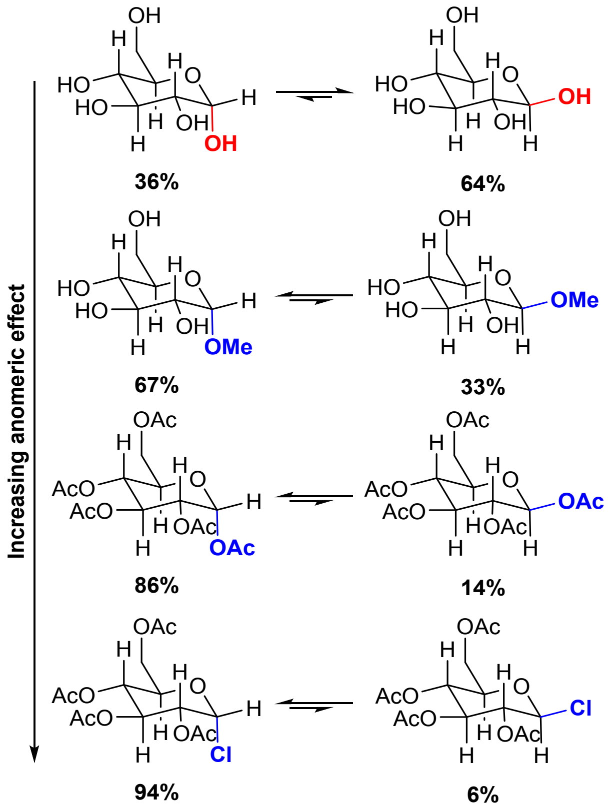


Figure 4. Anomeric effect leads to the "abnormal" conformational preference. The anomeric substituents are colored and bolded.

Although the effect of AE on the relative stability of conformers was "the smoking gun" leading to the discovery of this effect in carbohydrates, the magnitude of this effect in polysubstituted sugar molecules is not easy to evaluate — one should also keep in mind that many real molecules, including some of the classic examples where the anomeric effect was first recognized, are complex. In the presence of other steric or stereoelectronic interactions, the true importance of the anomeric effect can be not immediately obvious as it is the _balance_ of multiple effects that defines the overall preferences.[34] For example, the gauche effect (preference for the conformations with fewer antiperiplanar CX/CY arrangements for the bonds to electronegative elements X and Y[2]) can either enforce or oppose the anomeric effect for systems shown in Figure 5.

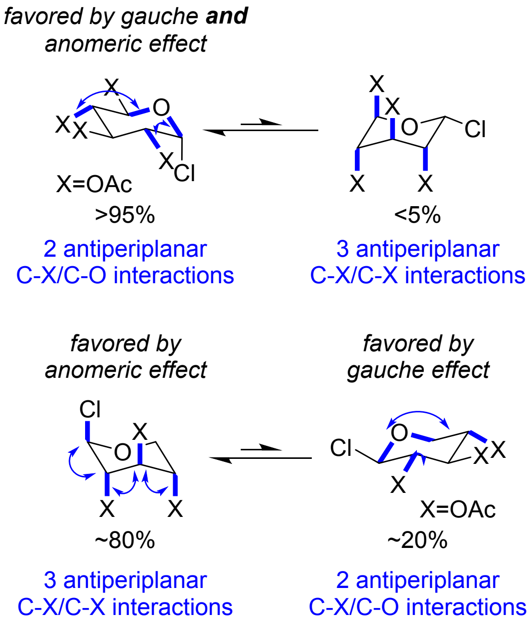


Figure 5. Combination of gauche and anomeric effects in sugar conformations.[30]

The true magnitude of anomeric stabilization is easier to quantify in the absence of additional substituents. For example, it is convenient to evaluate such stabilization by comparing the energy associated with the change from an axial to an equatorial conformer in cyclohexane and tetrahydropyran, (THP, Figure 6). Furthermore, the 1,3-diaxial repulsions in tetrahydropyran are potentially greater than in cyclohexane as C-O bonds are shorter than C-C bonds,.[35] It was proposed that the following equation can correct for this difference: $\Delta\Delta G(AE) = \Delta G(\text{heterocycle}) - 1.53 * \Delta G(\text{cyclohexane}) - 0.08$.[36]

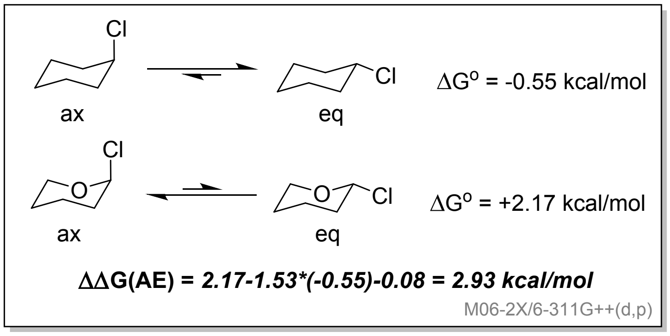
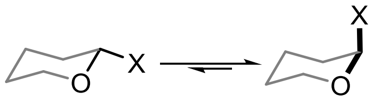


Figure 6. The equatorial preference is switched to axial when the anomeric effect is present.

Figure 7 illustrates how the axial/equatorial preferences in the anomeric systems depend on the σ-acceptor ability of substituent X at the anomeric position in the gas phase. Note that the conformational energies for the axial/equatorial flip in THP reflect loss of only exo-anomeric effect and *underestimate* the total anomeric stabilization in such systems by ~ half, *vide infra* (Figure 14).



X	ΔE	ΔG
Cl	–3.4	–3.0
F	–2.3	–2.0
OMe	–0.9	–0.6
OH	–0.5	–0.1

PBE0-D3BJ/aug-cc-pVTZ, kcal/mol

Figure 7. Conformational preferences illustrate the anomeric effect in 2-X-tetrahydropyranes (2-X-THP, gas phase, PBE0(D3BJ)/aug-cc-pVTZ, in kcal/mol).[37, 38]

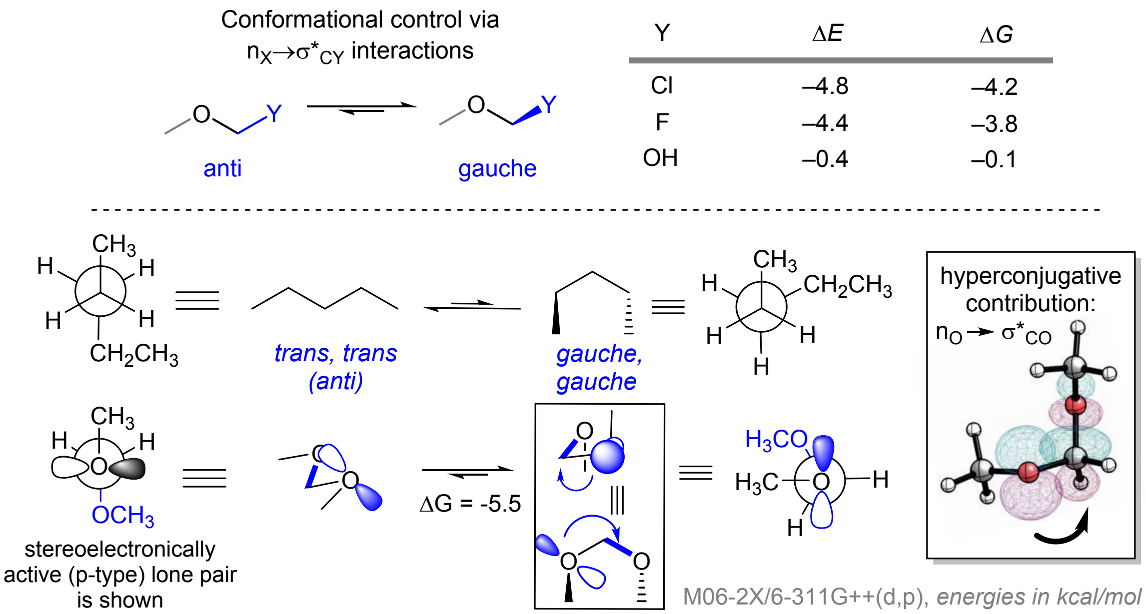
You may have noticed that the free energy difference between 2-chloro-THP conformers in Figure 6 and Figure 7 are slightly different. This “inconsistency” results from applying different sets of quantum chemical approximations (i.e., the “levels of theory”) to the same problem. A variety of quantum chemical methods are used in chemistry, among which density functionals (DFT methods) are most popular. There are several hundred DFT methods,[39] including such extremely popular ones as PBE0,[40] B3LYP,[41, 42] and M06-2X.[43] Recently Nam et al. have reported that errors of density functionals are proportional to the magnitude of electron delocalization in the molecule, so that some functionals make large errors in relative energies of species with significantly different extents of delocalization.[44] The two most accurate functionals in the Nam’s work are M05-2X[45] and PBE0, so we use M06-2X (an “improved successor” of the former) and PBE0 functionals throughout the review, when possible. Note, that although different levels of theory provide somewhat different numbers, the good ones usually lead to qualitatively similar pictures.

The generality of anomeric effect

The conformational preference embodied by the classic anomeric effect is not confined to cyclic systems. The analogous conformational preference, referred to as the *generalized anomeric effect*, is observed in a variety of non-cyclic systems where two heteroatoms are connected to the same central carbon (X-CR$_2$-

Y) or, even more generally, to the same atom A (X-A-Y)).[46, 47] It requires that a lone pair n_X at heteroatom X is aligned with the C-Y bond in a YCR_2X moiety.

This requirement influences the preferred conformations of many molecules including several ubiquitous functional groups such as esters, halogen-containing organics, acetals, peroxides, etc. A simple demonstration of this behavior is the comparison of pentane and dimethoxymethane ("2,4-dioxapentane"). In contrast to pentane, where the all-anti conformation is preferred (Figure 8), the g+,g- conformation fulfilling the alignment between n_O and C-O' bond is more favorable in dimethoxymethane (Figure 8).



Y	Δ*E*	Δ*G*
Cl	–4.8	–4.2
F	–4.4	–3.8
OH	–0.4	–0.1

Figure 8. Conformational control by generalized anomeric effect.[2] Top: Examples of conformational control with various C-Y bonds. Bottom: The main orbital contribution to the anomeric effect is shown in the insert.

Similar effects are observed in compounds with multiple fluorine substituents. Indeed, the increased thermodynamic stability of fluoroorganic moieties contributes to their wide abundance in pharmaceutical compounds and industrial applications.[48] It is also likely to contribute to the great persistence of polyfluorinated chemicals in the environment. AE manifests itself in the >12 kcal/mol greater stability of compounds with a CF_2 group in comparison to their 1,2-substituted isomers. Note the differences in polarity (evaluated via dipole moments) do not correlate with the trends in stability. Similarly, 1,1-difluoroethene is >9 kcal/mol more stable than cis- and trans-1,2-difluoroethenes (Figure 9).

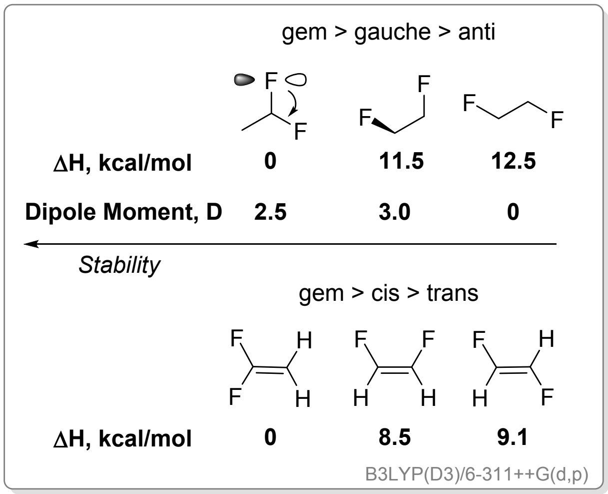


Figure 9. Evaluating anomeric stabilization in a CF_2 group by isomerization reactions involving difluoroethanes and difluoroethenes. Dipole moments of difluroethanes are given to evaluate the role of electrostatic effects.

The anomeric stabilization increases even further when additional fluorine atoms are connected at the same carbon. This effect can be evaluated by group separation reactions (Figure 10) that indicate the progressive increase in stability upon continuous fluorination of methane or its isoelectronic analogue, the BH_4-anion. Remarkably, CF_4 is stabilized relative to four CH_3F molecules by ~50 kcal/mol at the CBS-QB3 level of theory.[49]

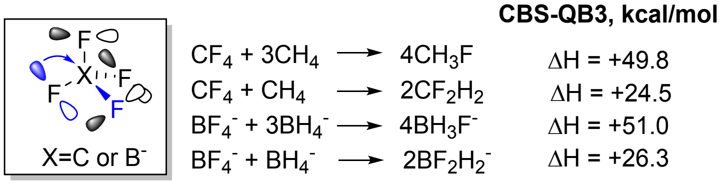


Figure 10. Group separation reactions illustrate that introduction of multiple fluorines at the same carbon or boron atoms has a great stabilizing effect. Four of the eight p-lone pairs on F-atoms are shown to illustrate the possibility of multiple $n_F \rightarrow \sigma^*_{C-F}$ interactions.

The similarity between carbon and boron compounds in Figure 10 suggest that the anomeric effect may have a broad role in the main group element chemistry. Indeed, the list of available examples continues to expand to include systems where the central atom is boron, phosphorus, nitrogen, sulfur, etc (Figure 11).[16, 17, 50-59] Furthermore, Zhu and Walczak[60] recently uncovered "the metalloanomeric effect", i.e. the axial conformational preference for many late transition metal substituents at the anomeric carbon of tetrahydropyran.

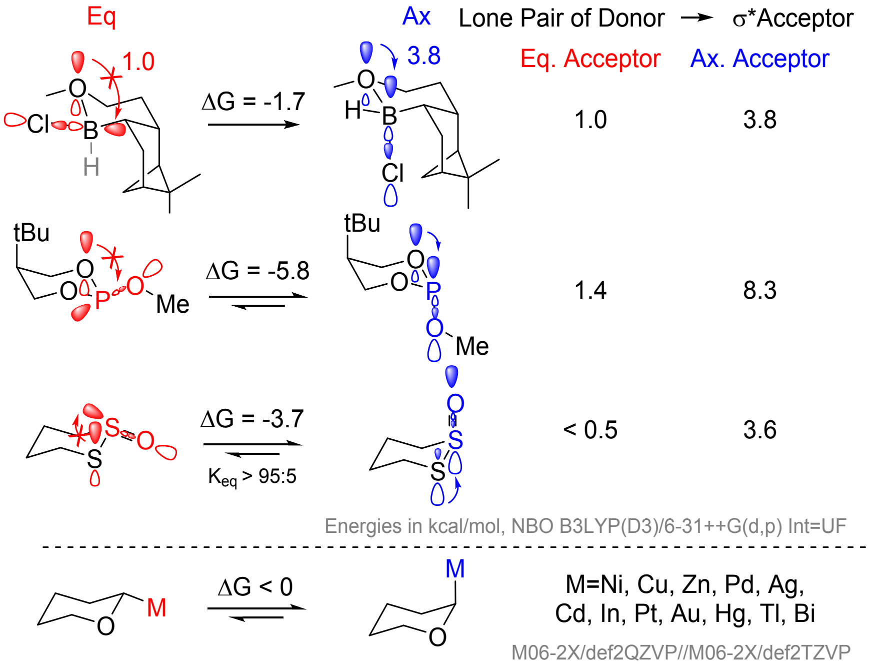


Figure 11. Selected examples of anomeric X-Y-Z systems where the central atom Y is different from carbon.

Explanations and models of anomeric effect

Several explanations have been proposed to rationalize the anomeric effect. Figure 12 presents four of these models: three based on electrostatics (dipole-dipole interactions, coulombic repulsion of point charges, non-classical hydrogen bond) and one based on stereoelectronics (hyperconjugative interactions).[20, 31, 32] Arguably, the most popular current explanation of the AE is a hyperconjugative interaction between the lone pair of the endocyclic heteroatom and the antibonding orbital of the axial substituent at the anomeric carbon (Figure 12, right). However, the discussion continues, and different variations of the electrostatic model continue to be offered, often when developing a new theoretical method. Although the relative contribution of classic (electrostatic) and quantum (hyperconjugation) components is still a matter of debate, it is clear that each of the above descriptions provides a physically relevant contribution to the phenomenon. Below, we will discuss these contributions in the context of the several historically important examples.

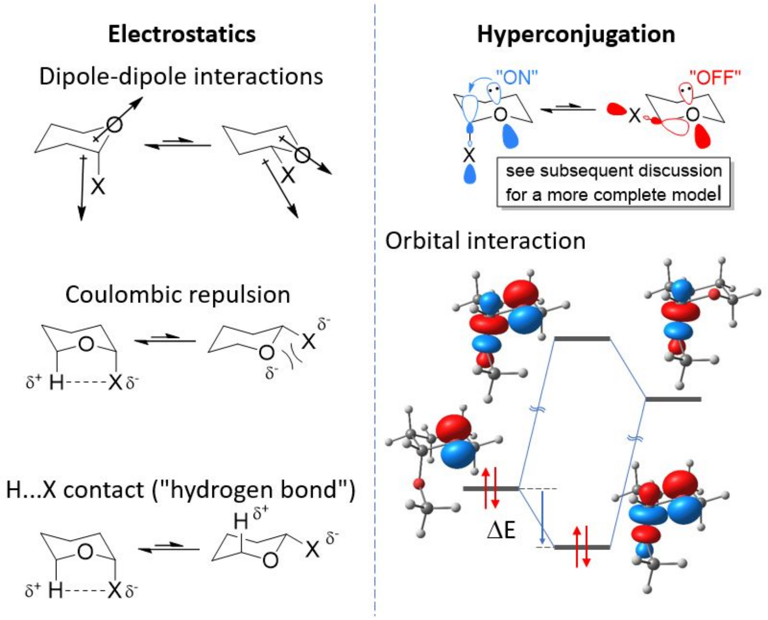


Figure 12. Most frequently considered models for the anomeric effect.[20] Note that the commonly used hyperconjugative model (shown here for 2-OMe-tetrahydropyran, 2-OMe-THP) is only half-complete (*vide infra, see* Figure 14). The lone pair stabilization energy is estimated with NBO approach at PBE0-D3BJ/aug-cc-pVTZ/CPCM(H2O) level of theory.

In the original 1955 publication, Edward proposed that the anomeric effect is caused by an interaction of the dipole moments of the exocyclic C-X bond and the endocyclic C-O bonds.[33] This repulsive dipole interaction causes the exocyclic bond to adopt the axial position in order to minimize the overall molecular dipole moment (Figure 12, top left). This concept was recast in a slightly different light by Lemieux[61] who instead described the repulsion as a Coulombic interaction between localized charges at each of the atoms (Figure 12, middle left). In this description, the partially negative exocyclic substituent prefers the axial position due to the increased distance from the partially negative endocyclic heteroatom. This model also benefits from accounting for attractive forces between the axial heteroatom and the slightly positively charged *syn*-axial hydrogens.[62, 63]

A more recent, conceptually related description focuses on the strongest of such Coulombic contacts: the CH···X interactions (Figure 12, bottom left).[20, 63, 64] This attractive Coulombic interaction was rebranded as a non-classical hydrogen bond between the heteroatom lone pairs and the *syn*-axial hydrogens (Figure 12, bottom left). Like a classic H-bond, it also benefits from the H…X Coulombic attraction but the C-H…O angle is far away from the 180° angle preferred by classic H-bonds. These three descriptions are closely related—each focuses on electrostatics as the conceptual origin from varying perspectives.

We will spend more time comparing electrostatic and hyperconjugative models in the following sections but will use a set of molecules in Figure 13 to illustrate that the non-classical H-bond description falls short as being the sole explanation for the traditional anomeric effect. On one hand, the charges at H (+ 0.2e) and O (-0.6e) for the methoxy-substituted six-membered rings shown in Figure 13 indicate clearly that electrostatic factors are favorable and the O...H contacts are stabilizing in each of the for examples. However, the trends in stability do not agree with the relative magnitude of this electrostatic stabilization. For example, the axial hydrogen atoms of CH_2-O fragments are *less positive* in methoxy cyclohexane than in 2-OMe-THP. Because the negative charge on the oxygen atom in these two systems is nearly the same, the greater positive charge at the hydrogens would suggest the greater axial preference for cyclohexyl methyl ether, which is not the case (Figure 13). Of course, the situation can change in more complex systems. For example, the importance of CH..O interactions can be increased as shown in the recent report of a "pseudo-anomeric effect" by Piscelli et al.[65] when a CF_2 group is introduced in the ring to increase the positive charge on axial hydrogens (Figure 13). Wiberg and coworkers also reported that the importance of similar C-H...O contacts increases in 1,3-dioxolanes where acceptor substituents at C5 polarize the C4-H axial bonds.[20]

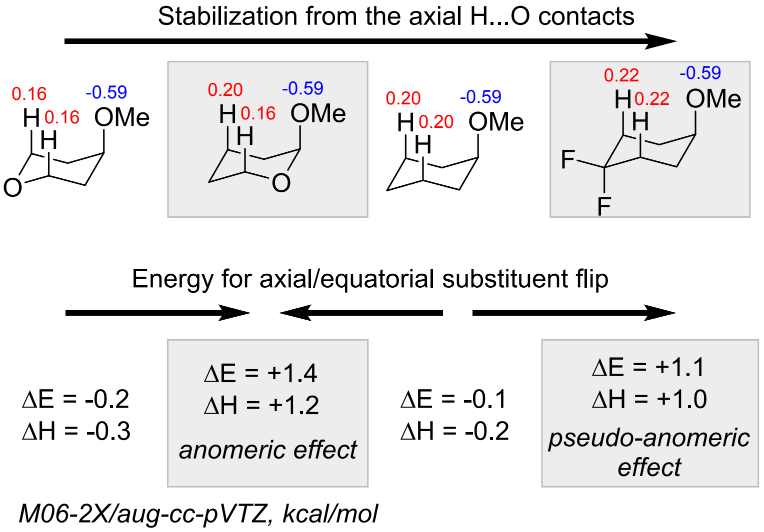


Figure 13. Comparison of Natural Population Analysis charges for the axial O...H contacts with the conformational preferences for systems exhibiting anomeric and pseudo-anomeric effects. Note that the endocyclic O atom decreases positive charge at the axial α-C-H atom (in agreement with a hyperconjugative donation from the oxygen lone pair and the C-H anti-bonding orbital).

The hyperconjugative model was first proposed by Altona et al. to explain the axial C-Cl bond lengthening observed in the X-ray geometries of chlorinated dioxanes, which could not be intuitively explained by the electrostatic model.[66, 67] This model is based on a stabilizing interaction between the antibonding σ^*_{C-X} orbital and the vicinal oxygen lone pair (LP) (Figure 12, right).[68] Since this interaction requires the LP to be coplanar to the substituent, it stabilizes the axial 2-X THP conformation where the C-X bond is aligned with the p-type lone pair of the endocyclic oxygen. The stabilizing effect of this interaction can be estimated using the Natural Bond Orbitals (NBO) approach[69], which constructs a set of orbitals corresponding to the localized molecular Lewis structure and evaluates all delocalizing orbital interactions with the second order perturbation theory. We will discuss the salient features of NBOs in one of the following sections. Here, it is helpful to compare the 13.4 kcal/mol NBO estimate for the highlighted $n_O \rightarrow \sigma^*_{CO}$ interaction in 2-methoxy-THP with the energies of the NBO interactions given earlier in Figure 2, i.e., the 8.6 kcal/mol energy for the $n_N \rightarrow \sigma^*_{CH}$ interaction in methyl amine. Clearly, negative hyperconjugation is greater when a stronger C-O σ-acceptor is present, i.e. at the anomeric carbon. This relatively strong interaction provides half of the anomeric stereoelectronic stabilization – we will tell where the 2nd half is when presenting a more complete model in Figure 14.

It is also worth pointing out that although increased delocalization is always stabilizing, the need for a good orbital alignment comes with an entropic penalty that can counterpoise the enthalpic gain. Such penalty is generally unavoidable in oxygen-containing organics where the presence of substituents on neutral oxygen shapes the conformational space “anisotropically”, so only a few geometries would have a stereoelectronically favorable arrangement of orbitals. In other words, stereoelectronic effects on oxygen are switchable “on” and “off” by conformational changes, e.g., rotation around single bonds. Although such sensitivity to the geometric changes is the essence of stereoelectronic control, achieving the right geometry comes with an entropic penalty. Such penalty can potentially lead to temperature dependence of anomeric effects.

However, there is an important exception from this tug-of-war between entropy and enthalpy, i.e., the anomeric effect in fluoroorganics that contain multiple fluorine atoms at the same carbon. Herein, the stabilizing $n_F \rightarrow \sigma^*_{CF}$ orbital interactions can come *without* entropic penalty because the combination of two p-type lone pairs of fluorine is “stereoelectronically promiscuous”. These lone pairs do not discriminate against any location for a vicinal acceptor - their interaction with the vicinal sigma acceptors is always “on”. No geometric adjustment is needed to achieve the anomeric effect in fluoroorganics, and no entropic penalty is present to offset the very large enthalpic stabilization. Besides the halogens, the only other common substituent that has the same stereoelectronic property is the anionic oxygen (alkoxide). We will discuss the unique properties of fluoroorganics and their connection with anomeric effect in one of the subsequent sections.

This stereoelectronic hyperconjugative model emphasizes the stabilizing role of electron delocalization which provide relief to “stereoelectronic frustration“.[2, 70] The non-bonding orbitals do not contribute to the primary bonding pattern described by the molecular Lewis structure but can contribute to the secondary stabilizing interactions, i.e., conjugation or hyperconjugation. Because lone pair delocalization depends on the nature of the accepting orbital and its relative location in space, organic functionalities prefer arrangements which allow their lone pairs to delocalize in geometrically favorable interactions with strong acceptors (i.e., “relieve stereoelectronic frustration”). Stereoelectronic frustration can be viewed as a driving force of many organic transformations discussed in ref. [71]**.**

The stereoelectronic model is also related to other theoretical chemistry concepts, e.g., the “chemical hardness” (η), $\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$,[72] an important chemical concept directly connected to the HOMO-LUMO gap. According to the “maximum hardness principle” (MHP) proposed by Pearson in 1987[47] and mathematically proven by Parr and Chattaraj,[48] any chemical process characterized by energy lowering (stabilization of the system) is accompanied by increase in chemical hardness.[72, 73] Since the high energy lone pairs (LPs) have large contributions into the Highest Occupied Molecular Orbital (“the HOMO”), LP stabilization often leads to HOMO energy lowering and widening of the HOMO-LUMO gap (energy difference between HOMO and the Lowest Unoccupied Molecular Orbital, LUMO). Thus, the MHP and anomeric effect reflect each other: orbital interaction leads to an increase in the HOMO-LUMO gap and, thus, in molecule’s hardness.[74, 75]

The anomeric effect provides an answer to one of the long-standing questions of the MHP: “how does the hardness of a given system vary under molecular rearrangements/transformations such as intra- and intermolecular reactions or internal rotations of a molecule?”.[76] The alignment of the right orbitals increases both stability and hardness of the axial conformer.

The complete hyperconjugative model: balancing exo- and endo-anomeric effects

So far, we have introduced the usual orbital explanation for the anomeric effect that involves hyperconjugative donation from the endocyclic non-bonding orbital (n_O) into the exocyclic C-X antibonding orbital (σ^*_{C-X}) (Figure 12). This interaction is activated in the axial conformer where the p-type lone pair of oxygen is aligned with the C-X bond but deactivated in the equatorial conformer where the p-lone pair and the σ^*_{C-X} orbital are misaligned. However, despite its popularity, *this description is inadequate* and leads to a number of misunderstandings.

The fault with the common hyperconjugative description (Figure 12) is not that it is wrong but that it is incomplete. One should not forget that donation to the axial σ-acceptor is *not* the only important orbital interaction that needs to be considered for a balanced description of hyperconjugation in anomeric systems. The other, often neglected, part of the equation is the exo-anomeric effect, the analogous $n_X \rightarrow \sigma^*_{C\text{-}O}$ interaction that transfers electron density in the *opposite* direction (from exocyclic heteroatom Y to the endocyclic heteroatom X). The exo-anomeric effect is present in *both* axial and equatorial conformers (Figure 14). If one considered only the classic (i.e., the endo-) anomeric effect, the picture would be incomplete.

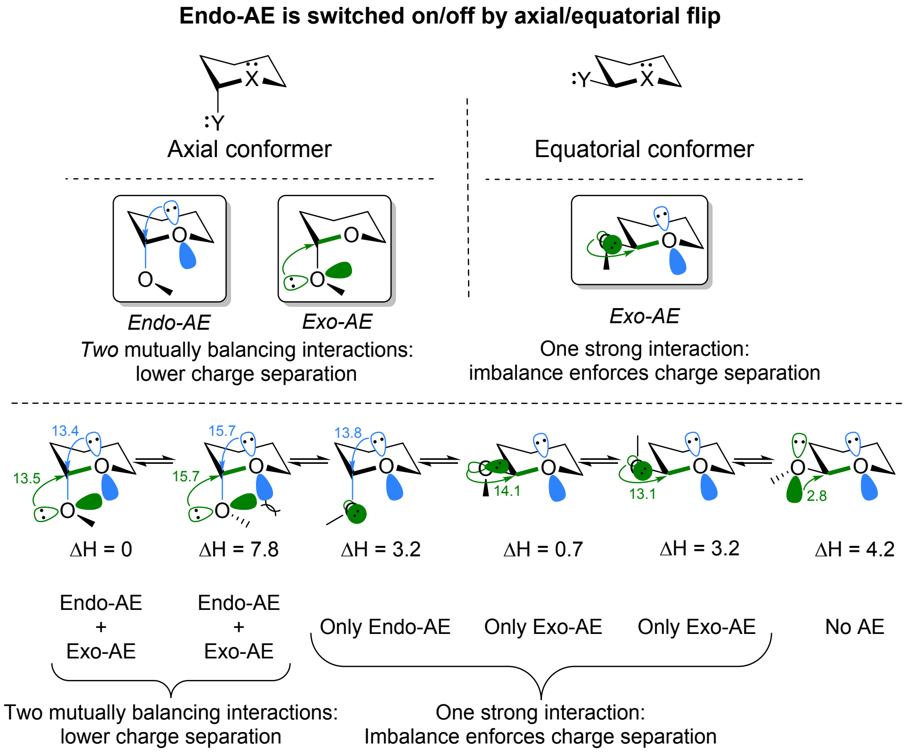


Figure 14. Top: A balanced description of the anomeric effect has to include both endo- and exo-anomeric effects.[2] Bottom: Conformational control of the endo-anomeric effect. Only the p-type lone pairs of oxygen atoms are shown.

A characteristic feature of the exo-anomeric effect is its sensitivity to the rotation of the substituent at the exocyclic group Y around the C-Y bond. This conformational change provides one more way to perturb the balance of anomeric interactions in addition to the axial/equatorial ring flip. Hence, either one (or both) component in the pair of (exo and endo) anomeric effects at a di-oxa-substituted carbon can be switched on and off.

Figure 14 illustrates that when the endo- and exo-AE operate together, the combination of *mutually compensating charge transfers in opposite directions* leads to the more balanced charge distribution in the axial conformer. On the other hand, when the endo-AE is removed in the equatorial conformer, it results in imbalanced, *unidirectional* electron density transfer (from the exocyclic substituent to the endocyclic heteroatom via the exo-AE). *Hence, negative hyperconjugation does not worsen but rather partially alleviates charge separation in the axial conformer while contributing to the greater polarity of the equatorial conformer.* Hence, there is no conflict between the electrostatic and hyperconjugative stabilization - instead they reinforce each other in stabilizing the axial conformer.

Presence of the exo-anomeric effect, which balances charge redistribution in the axial/gauche conformer explains the results of Mosquera[23, 25-27, 77-79] and Wiberg[20], who analyzed charge redistributions in systems exhibiting anomeric effect using QTAIM and Hirshfeld charges, respectively, and did not find a significant charge flow from the LP-donating atom to the accepting bond. We will show that these observations are consistent with the hyperconjugation model when we discuss this situation in detail later (Figure 41).

In summary, the axial conformer has ***two*** strong n→σ* interactions (endo-AE and exo-AE) and balanced bidirectional delocalization, whereas the equatorial conformer has only ***one*** unbalanced interaction (the exo-AE). Similar logic applies to acyclic systems where the general anomeric effect operates. From the stereoelectronic perspective, the main requirement for this conformational preference is that the partners (lone pairs and neighboring substituents) involved in the interaction have to be aligned in order to maximize the stabilizing interaction of the non-bonding lone pair and the adjacent antibonding orbital ($n_O \rightarrow \sigma^*_{C\text{-}O}$). From an electrostatic standpoint, the preference is caused by the minimization of repulsive Coulombic interaction between the lone pairs on the two heteroatoms.[2, 3]

Electrostatic contribution and solvent effects on the anomeric effect

From the very early studies of the anomeric effect (when this term was only applied to the epimerization of the anomeric position of carbohydrates)[80], it was known that its amplitude diminishes in polar solvents.[81, 82] Later, this behavior was shown to be general[16, 17, 83] and sometimes taken as a proof for the primary importance of electrostatic factors in anomeric effect. Herein, we will show that the full hyperconjugative model explains the effect of solvents on anomeric conformational equilibria.

The solvent effects are illustrated by the dependence of experimentally measured axial-equatorial equilibrium constants of two prototype molecules[84,83] from the relative permittivity (i.e., the dielectric constant) of the solvent (Figure 15). Although the effect of highly polar solvents like water and acetonitrile is clear, significant differences are observed for the solvents of similar polarity. This observation illustrates that solvent effects are not limited to simple electrostatic screening. The origin of these effects may be quite different for solvents of different types. For example, the deviation of the $CHCl_3$ energy (dark red) from the general trend may stem from its ability[85] to form hydrogen bonds with the solute oxygen atoms, while having relative permittivity in the range of non-H-bonding solvents. This deviation may be considered as evidence for the impact of hydrogen bonding on the anomeric effect.[71]

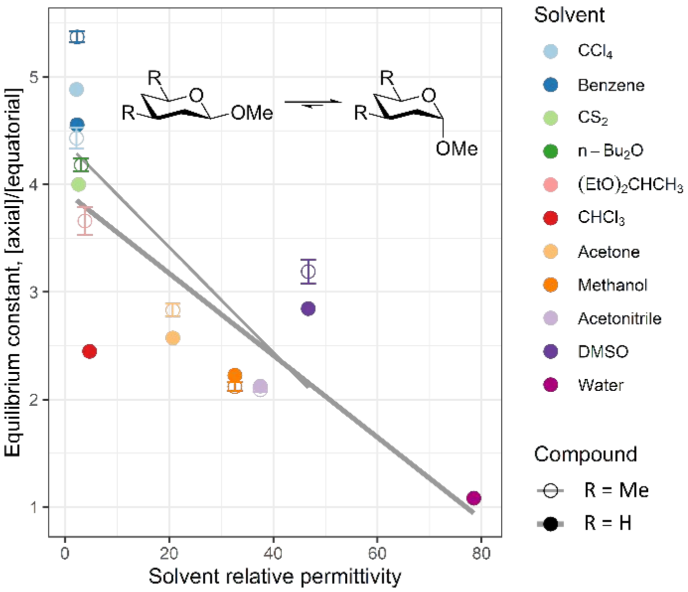


Figure 15. Experimentally measured solvent effects on conformational equilibrium in 2-methoxy-4,6-dimethiltetrahydropyran[84] (open dots) and 2-methoxytetrahydropyran[83] (solid dots). Grey lines denote linear fits; standard deviations for 2-methoxy-4,6-dimethiltetrahydropyran data are shown with error bars.

Although the anomeric conformational preference can weaken in water, it does not have to disappear. For example, the axial anomers are still preferred in the aqueous solutions of mannose and xylose (65% and 71%, respectively).[86]

Anomeric effect alleviation in polar solvents implies that the equatorial conformer is more polar than the more stable axial one and thus is stabilized preferentially as the medium's polarity increases. This behavior was considered, at some point, as the key evidence for the dipole-dipole model of the anomeric effect (Figure 12 left top). However, Fuchs et al.[87] showed that solvation effects mostly depend on the *overall* molecular dipole moment, so that the fraction of axial conformer in symmetric alkoxy-substituted dioxanes tend to *increase* in more polar solvents.

Furthermore, the hyperconjugative model itself is consistent with solvation effects because it is hyperconjugation that is, at least partially, *responsible* for making the axial anomers less polar. The balance between the endo and exo-anomeric effect (Figure 14) can lower the overall charge separation[88] and explain the perceived "weakening" of hyperconjugative effects in polar solvents.

In the axial conformer, where both the endo and exo-anomeric effect are active, they work in opposite directions minimizing charge separation and the overall polarity of the molecule. However, in the equatorial conformer only the exo-anomeric effect is active, resulting in an unbalanced delocalization of electron density and a more polar molecule. Hence, a more polar solvent would favor the equatorial conformer in polar solvents because the hyperconjugative effects are unbalanced in this geometry.

An instructive example of anomeric influence on the overall polarity and solubility is provided by the different solubility of two oxygen-rich polymers, polyethylene glycol PEG and polyoxymethylene POM, in water (Figure 16). Whereas PEG ($[–CH_2–CH_2–O–]_n$) is infinitely soluble, POM ($[–CH_2–O–]_n$) is completely insoluble in water, exactly the opposite of what one would expect from the C/O ratios of the two polymeric chains. Smaller cyclic and acyclic analogs behave in a similar way. The time-resolved (femtosecond) IR and GHz dielectric spectroscopy-based experiments[89] revealed that water molecules solvating POM (or trioxane) are less slowed down by interactions with the solute than water molecules solvating PEG (or dioxane). The authors concluded that the “chemical nature of O atoms…is different due to an electronic charge distribution that depends on the number of C atoms between the O atoms” and “the more negative O atoms in PEG are expected to form stronger hydrogen bonds to the hydrating water solvent than the less negative O atoms in POM.” This observation is fully consistent with the more balanced charge distribution in the anomeric systems.

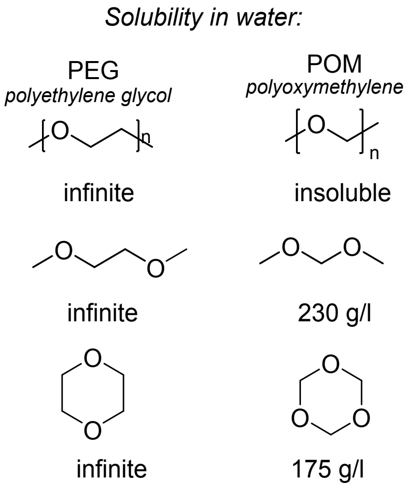


Figure 16. Balanced hyperconjugation in anomeric systems can decrease polarity and solubility in water

Another insight into the role of electrostatic effects via the solvent polarity effect was provided by the recent work of Juaristi, Gomes, et al.[90] who compared anomeric effects in ethers and peroxides. This comparison is instructive because the change from ether to peroxide nearly removes the electrostatic contribution from one of the C-O bond dipoles (by changing the polar C-O bond into a nearly non-polar O-O bond). The drastically different bond dipoles for the C-O and O-O bonds reverse the direction of the solvent effect on the axial/equatorial preference. As expected from the electrostatic model, polar solvents, such as DMSO, increase the anomeric preference in peroxides but decrease the anomeric preference in ethers (Figure 17). However, that the axial preference is still retained in the peroxide indicates that electrostatic factors, albeit important, do not fully explain the anomeric effect. The remaining differences between peroxides and ethers originate from a decrease in the hyperconjugative contribution caused by the lower donor ability of the peroxide lone pairs, i.e., *the inverse α-effect.* [91, 92, 93, 94]

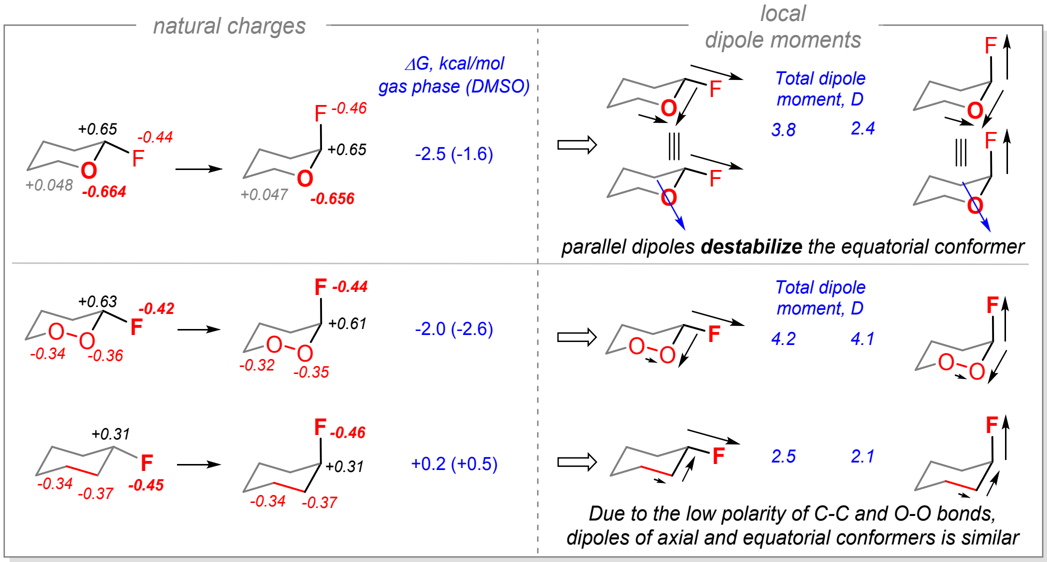


Figure 17. NBO charges for monofluorinated systems with zero, one and two oxygen atoms in a six-membered saturated cycle, estimated bond dipoles, and calculated molecular dipoles in the axial and equatorial conformers (MP2/6-311+G(d,p) level of theory).

H-bonding and Anomeric Effect: the tug-of-war between inter- and intra-molecular delocalization

Praly and Lemieux analyzed the effects of solvent on the conformational equilibria of 2-substituted tetrahydropyrans by NMR analysis.[95] In addition to evaluating the polarity effects, this work has provided evidence for specific H-bonded complexes with solvents such as CDCl$_3$ and D$_2$O.

Not only does H-bond formation favor the less stable (and more polar) equatorial conformers but it was also suggested that the solvent can change the relative magnitudes of the *endo*- and *exo*-anomeric effects by forming specific complexes with the oxygen functionalities. For example, the *exo*-anomeric effect of α-glycoside was proposed to be strongly enhanced by hydrogen bonding of solvent to the ring oxygen (Figure 18). For this reason, water is particularly effective in strengthening the *exo*-anomeric effect. On the other hand, the *endo*-anomeric effect can be weakened when the endocyclic oxygen lone pair is involved in a competing *intermolecular* $n_O \rightarrow \sigma^*_{H\text{-}X}$ donor-acceptor interaction (i.e., an H-bond). Experimental data indicated that the anomeric hydroxyl groups of free sugars dissolved in water tend to prefer the equatorial orientation because these provide stronger hydrogen bonds as proton donors to water. The role of this effect in increasing the conformational rigidity of glycosides was suggested to be essential for the formation of specific carbohydrate-protein complexes at the receptor sites of proteins. The enhanced *exo*-anomeric effect helps oligosaccharides to present well-defined rigid surfaces about which the protein becomes organized.

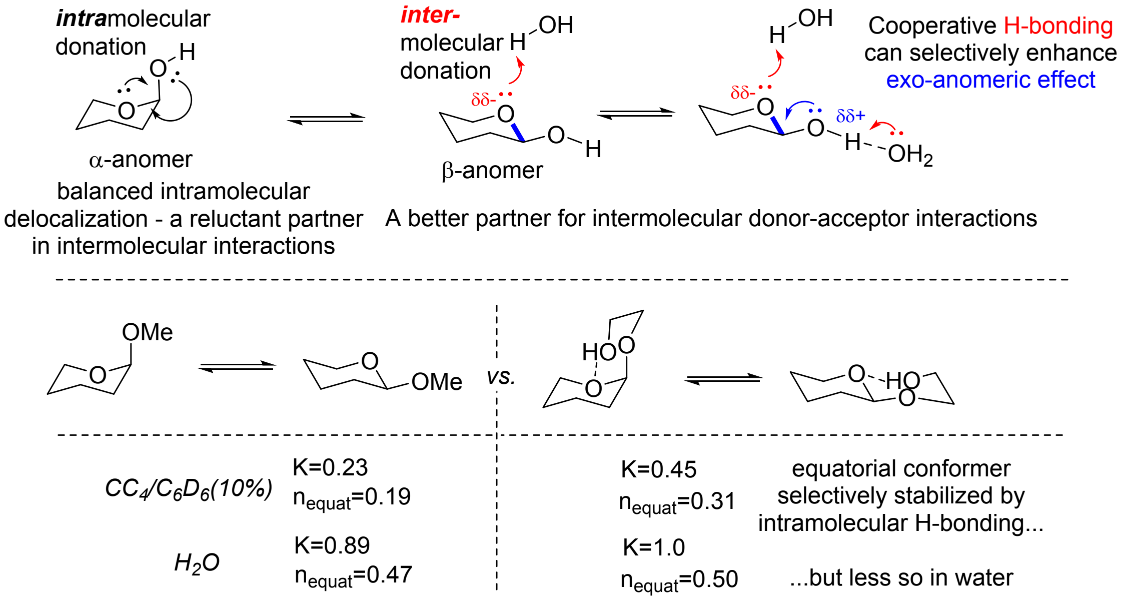


Figure 18. Top: H-bonding selectively stabilizes the equatorial conformer (β-anomer) of 2-hydroxy-THP, a glycoside model. Cooperative H-bonding interactions can also selectively enhance exo-anomeric effect in both conformers of 2-OH-THP. Bottom: An example of intramolecular H-bonding that selectively stabilizes equatorial conformer and leads to the apparent weakening of anomeric effect

An example of intramolecular H-bonding that selectively stabilizes equatorial conformer and leads to the apparent weakening of anomeric effect is provided by the increased abundance of equatorial conformer of the 2-hydroxyethyl THP (n_{eq}= 0.31 in CCl_4/C_6D_6) relative to 2-OMeTHP (n_{eq}= 0.19) although the OCH_2CH_2OH group is more electronegative than the OCH_3 group.[95] This apparent anomaly can be attributed to involvement of the ring oxygen in intramolecular H-bonding that favors the equatorial conformer. As expected, the difference nearly disappears in water.

Theoretical analysis by Mo and coworkers[142] also found that the conformational preference for the axial conformers in 2-X-THP molecules is reduced in solution, more so as the solvent polarity increases. In agreement with the above model, the relative stabilization of equatorial anomers mostly comes from their stronger solvent/solute interactions. For instance, while H-bond formation between water molecule and the oxygen atom of 2-F-THP decreases the α−β energy gap at the MP2 level by 1.0 kcal/mol (from 3.4 to 2.4 kcal/mol), most of this difference comes from the 0.8 kcal/mol increase in the H-bond strength in the β anomer.

The high proportion of E-carboxylic acids as compared to E-esters in the Cambridge Structural Database reflects the same phenomenon.[96] The distances between the C(O)**O**H oxygens and the H-bond-accepter suggest that the nature of the hydrogen bond acceptor can significantly affect conformational preferences of the carboxylic group.

These observations can be explained by analyzing the two H-bonded complexes of acetic acid in Figure 19. The difference between E- and Z-conformers of carboxylic acids[2, 3, 71] is controlled by an anomeric effect in a way that is analogous to the difference between axial and equatorial conformers in 2-substituted tetrahydropyrans. The stereoelectronic component of the Z-isomer's greater stability is the $n \rightarrow \sigma^*_{C=O}$ donation from the σ-type sp^n lone pair of oxygen to the carbonyl's σ^*_{CO} orbital. This is analogous to the $n \rightarrow \sigma^*_{C-O}$ hyperconjugative interaction in classic anomeric systems.

Interestingly, the Z-preference in carboxylic acids decreases independent of the choice of the H-bonding partner (an H-bond donor or an H-bond acceptor). This is because the less stable E-isomer is stereoelectronically unbalanced – the σ-lone pair is interacting with a weaker σ^*_{C-C} acceptor whereas the more electron-deficient $\sigma_{C=O}$ bond is aligned with another acceptor, i.e., the σ_{O-H} orbital. Hence, the σ–lone pair and the O-H bond of the E-isomer are, respectively, a better donor and a better acceptor than they are in the Z-isomer. Because of that, the E-isomer is a better partner in H-bonding interactions, both as a donor and as an acceptor. This example shows that the fully developed *intramolecular* anomeric orbital interactions can render the more stable conformer (i.e., the Z-carboxylic acid) to be a less stabilizing partner in *intermolecular* donor-acceptor interactions.

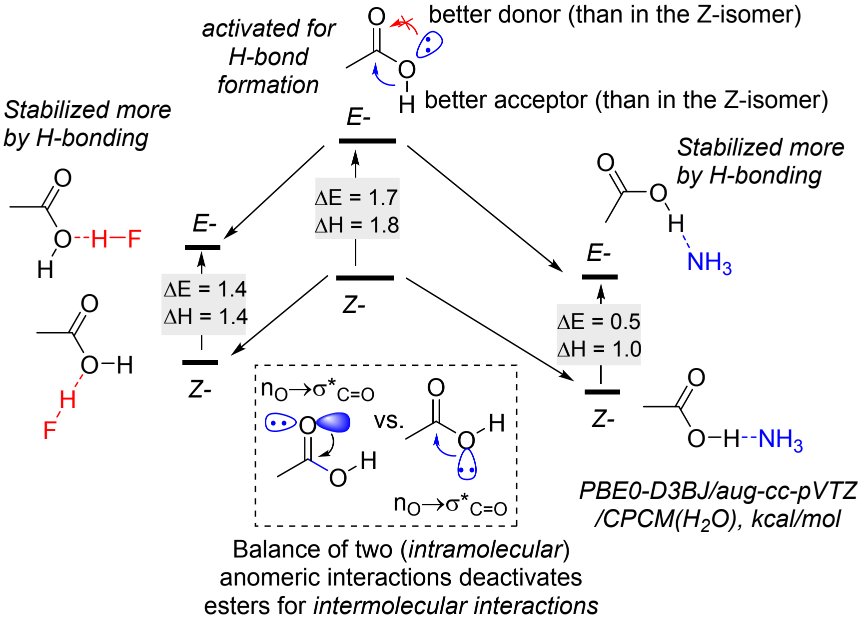


Figure 19. Influence of hydrogen bonding on the E/Z preference of acetic acid. Note the importance of n →σ*$_{C=O}$ interaction (insert at the bottom) that is analogous to n→σ*$_{C\text{-}O}$ interaction in classic anomeric systems.

These two examples are likely to illustrate a general principle: those conformers that are more stabilized by a "balanced" network of intramolecular delocalizing interactions (e.g., axial 2-X-THP or Z- carboxylic acid) have "less to offer" in the "external" intermolecular interactions and, as a consequence, are less stabilized by H-bonding or electrostatic interactions with the solvent. From this point of view, the hyperconjugative model readily explains the observed solvent effects in anomeric systems.

Structural consequences of AE

The structural effects of hyperconjugation are known to be large even in simple molecules. For example, if ethane's geometry is reoptimized in the absence of hyperconjugative interactions between the vicinal C-H bonds, the C-C bond elongates (from 1.53 to 1.64 Å).[97] Interestingly, this C-C bond length in the hypothetical "hyperconjugation-free" ethane is nearly identical to the length of the B-N bond of BH_3NH_3 (1.66 Å Å), an isoelectronic analog of ethane. In BH_3NH_3, the vicinal hyperconjugation is drastically weakened by the differences in the HBH and HNH valence angles that make alignment of all vicinal B-H and N-H bonds impossible.[98] In the absence of strong B-H/N-H hyperconjugation, the strongly polarized B-N bond is longer than the non-polar C-C bond.

An attractive feature of the hyperconjugative model is that it readily explains the structural changes associated with the anomeric effect. In particular, the presence of an acceptor group at the axial position is accompanied by a characteristic combination of geometric features that can be attributed to the increased contribution of $n_O \rightarrow \sigma^*_{CX}$ interactions. The O-C2 distance shortening in the axial conformer of 2-X-substituted tetrahydropyran is consistent with the increased O-C2 double bond character whereas C-X bond elongation reflects the transfer of additional electron density to the antibonding σ^*_{CX} orbital.

However, this simple picture is incomplete because exo- and endo-anomeric effects do not operate in isolation of each other (Figure 20). If both effects have the same magnitude, they should cancel each other out and no structural change will be observed.

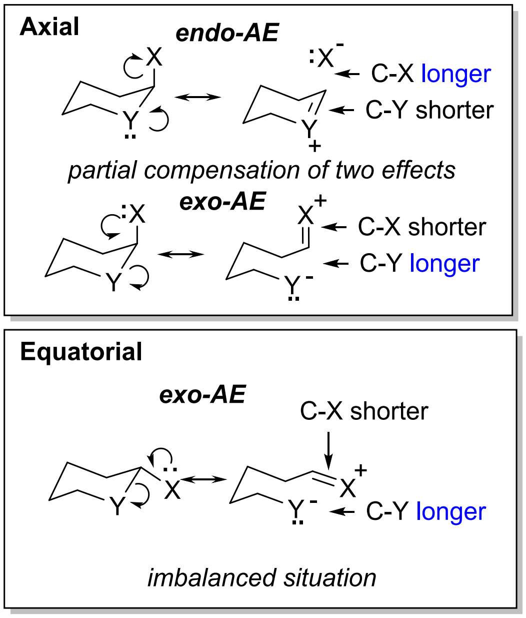


Figure 20. The expected structural effects of endo- and exo-anomeric hyperconjugation

Taking both effects into account is instructive because it provides a conceptually different explanation for the structural changes associated with the axial/equatorial flip—*it is not just the presence of an axial C-X acceptor that leads to the endocyclic C-Y bond contraction, but the presence of an equatorial substituent that is associated with the non-balanced C-Y bond elongation (and C-X contraction).*

Independent of the description, such structural effects are apparent when the relative geometries of similar axial and equatorial conformers or isomers are compared. For example, the axial C-Cl bond is considerably longer than the equatorial C-Cl bond in cis-2,3-dichloro-2,4-dioxane (Figure 21). Changes in the C-O bond lengths occur in the opposite direction. In a similar manner, shortening of the endocyclic bond C2-O and concomitant lengthening of the exocyclic bond C2-F are observed in the axial conformer of tri-OBz-2-fluorotetrahydropyran.[99] The axial and equatorial C-F bonds in 3,4,5,6-tetraOAc-2-desoxyglucopyranoses follow the same trend.[100, 101]

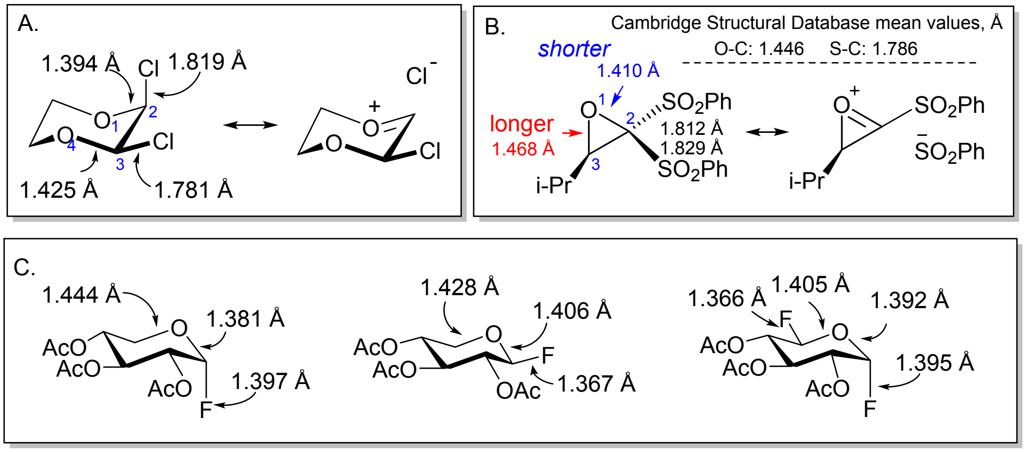


Figure 21. Selected structural consequences of anomeric effect. A: Selected bond lengths in *cis*-2,3-dichloro-1,4-dioxane. B: Bond lengths in 2,2-bis(phenylsulfonyl)-3-isopropyloxirane. C: Selected structural consequences of anomeric effect in OCF moiety.

An interesting example of anomeric effects on structure is reported for oxiranes.[102] In sulfonyl-substituted oxiranes, only the endo-anomeric effect operates—no *exo*-anomeric effect is possible as the sulfonyl sulfur atom has no lone pair. In crystal structures of these compounds, the endocyclic C2-O bonds are substantially shorter (1.410 Å) and both C2-S bonds are longer (1.812/1.829 Å) than the respective mean values in the Cambridge Structural Database (Figure 21, B). The large deviations (>0.03 Å) from the average lengths are consistent with an increase in the double bond character between C and O and with the decreased bonding between C and S—the two expected consequences of the $n_O \rightarrow \sigma^*_{CS}$ interactions.

The structural consequences of an interconnected network of anomeric interactions can be illustrated by X-ray geometry of a bicyclic ortho-carbonate, 3-methoxy-2,4,10-trioxaadamantane (Figure 22).[103] The exocyclic C–O bond has no vicinal p-lone pairs aligned with it. Hence, the exocyclic oxygen can act only as a donor in $n_O \rightarrow \sigma^*_{CO}$ interactions with two of the endocyclic C–O bonds, slightly elongating them. On the other hand, each of the *endo*cyclic C–O bonds has two aligned p-type lone pairs. Overall, the three endocyclic oxygens engage in a cyclic network of six $n_O \rightarrow \sigma^*_{CO}$ interactions. The imbalance between endo- and exo-anomeric leads to the noticeably different C-O bond lengths, with the exocyclic C–O bond being the shortest one.

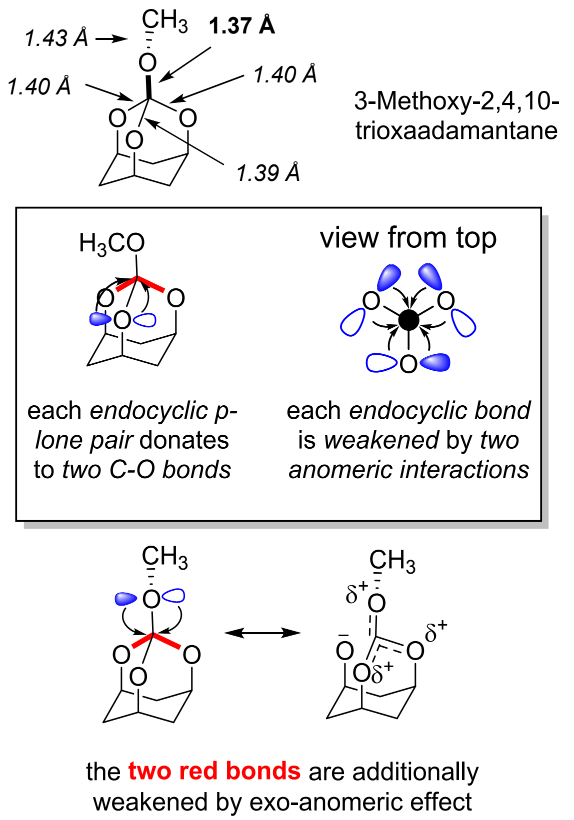


Figure 22. Effects of anomeric hyperconjugation on the C-O bond lengths in 3-methoxy-2,4,10-trioxaadamantane[103]

The consequences of delocalizing interactions with oxygen lone pairs can also be detected in functional groups that are not generally thought of as "anomeric" but are, in fact, stereoelectronically similar. An instructive example is provided by carbonyl compounds where the C=O bond length can be either shortened or lengthened depending on the donor/acceptor balance in the $n_O \rightarrow \sigma^*_{C\text{-}R}$ interactions. Such hyperconjugative interactions are surprisingly strong in ketones and aldehydes (even stronger than $n_O \rightarrow \sigma^*_{C\text{-}O}$ interactions in acetals) because the interacting donor and acceptor orbitals are brought much closer by the short C=O bond (see Figure 47 for additional information). Not only is this orbital interaction very important for reactivity (e.g., explaining the "anomalously" low C-H BDE in aldehydes) but it also contributes to the C=O bond elongation if the carbonyl oxygen lone pair is H-bonded or protonated (Figure 23, bottom).[104] In this situation, the anomeric effect is weakened. On the contrary, the anomeric effect is strengthened when the C-R bond becomes a better acceptor on route to the formation of acylium ion with a formal triple bond between the lone pair of oxygen and the cationic center.[105]

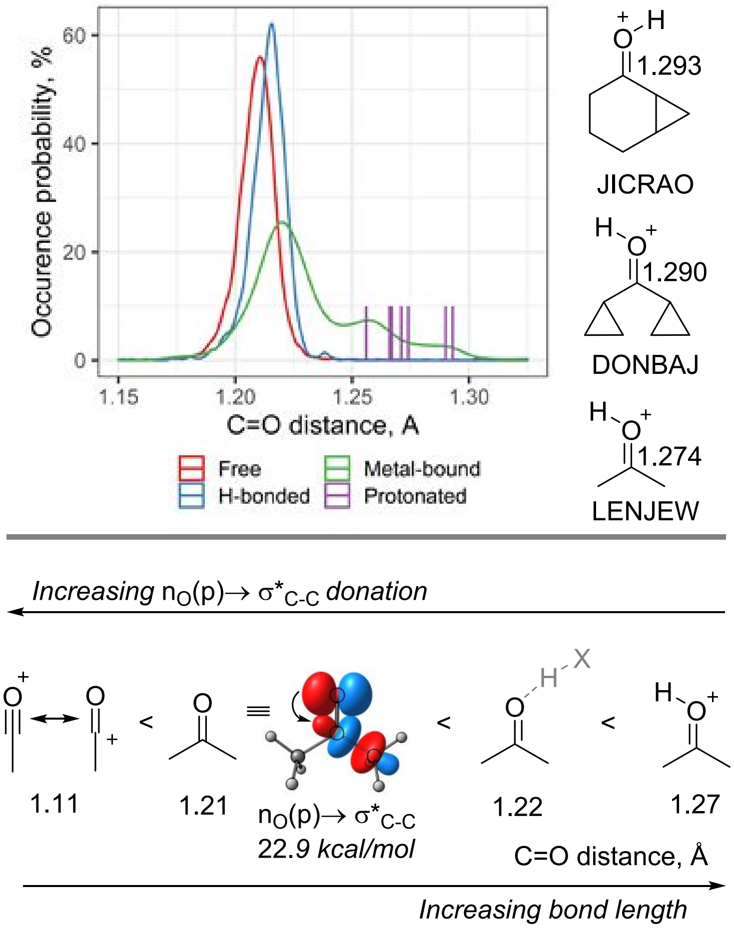


Figure 23. Top left: Cambridge Structural Database (CSD) data for the C=O distances in alkyl ketones in different situations: free, H-bonded (acting as H-bond acceptor), metal-bound and protonated (acting as H-bond donor)**.** Top right: Examples of protonated ketones[106-108] Bottom: increased donation from the carbonyl oxygen lone pair to the vicinal acceptor shortens the CO distance. NBO energy at the PBE0-D3BJ/aug-cc-pVTZ level (vacuum).

The geometric consequences of the anomeric effect emerge especially clearly from a well-defined set of model compounds where one of the parameters is changed systematically. From this point of view, it is instructive to analyze geometries of 2-X-substituted tetrahydropyrans (Figure 24).

The C-O bond shortening in the axial conformer is expected when one component in the pair of donor/acceptor anomeric interactions is stronger than the other. For example, this imbalance should be observed if X is a more electronegative element than O. This notion can be explored by comparing the bond lengths for the axial and equatorial 2-X-tetrahydropyran conformers where X includes atoms from the 2nd and 3rd period with varying electronegativities. As the electronegativity of the axial substituent X increases, one would expect the C2-O bond to shorten. However, the situation is not as simple as illustrated by the pronounced differences between the effect of two axial substituents X with similar electronegativity but from the different periods (NH_2 in 2nd vs. Cl in 3rd, Figure 24, left).

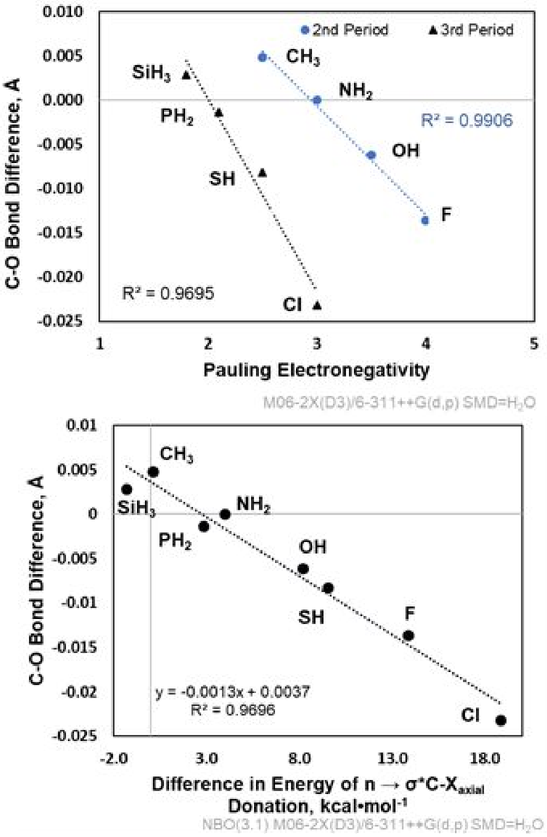


Figure 24. The anomeric C-O bond shortening for eight substituents X in 2-X substituted tetrahydropyrans does not show a universal correlation with electronegativity of substituents (and C-X bond polarity) (left) but does show such correlation with hyperconjugative acceptor ability of σ-bonds (right), clearly illustrating the geometric consequences of anomeric hyperconjugation, M06-2X(D3)/6-311++G(d,p) level of theory.

The presence of the two separate correlations of C-O bond contraction with Pauling electronegativity for the exocyclic substituents X from 2nd and 3rd periods is important. Although the C-O bond length correlates with electronegativity of X for *each* of the periods, the lack of a *common* correlation illustrates that C-X bond polarization and subsequent electrostatic effects *cannot* be the sole determining factor for this structural effect. The answer to this interesting observation is the known increase of hyperconjugative acceptor ability of σ* orbitals for the C-X bonds with the elements of the 3rd period.[18] This increase makes the C-X bonds to the heavier elements the better acceptors. Once this factor is taken into account, it is not surprising that the anomerically-induced C-O bond contraction is described very well by a single correlation with the energy of NBO $n_O \rightarrow \sigma^*_{CX}$ interactions (i.e., the hyperconjugative component of the anomeric effect). **The difference between the two correlations in Figure 24 clearly shows that it is *not* the C-X bond polarity (directly proportional to Pauling electronegativity)[49] but hyperconjugation that serves as the primary force in the anomeric C-O bond shortening.**

Furthermore, an alternative computational approach that can evaluate the effects of orbital delocalization, i.e., the block-localized wave function (BLW) method, found considerable elongation of C–X bonds in anomeric systems with several atoms X at the same carbon when the specific $n_X \rightarrow \sigma^*_{CX}$ orbital interactions are "turned off".[109]

Another clear experimental illustration of the role of anomeric delocalization in molecular geometries is provided by the work of Kirby and coworkers who analyzed structural changes in anomeric systems while changing electron demand in the exocyclic ("leaving") OAr-group.[110] As the axial OAr group becomes more electron deficient, as measured by the pKa's of the parent phenols, ArOH, in water, the geometries show a significant lengthening of the exocyclic C-OAr bond, coupled with a slightly less pronounced shortening of the endocyclic bond.

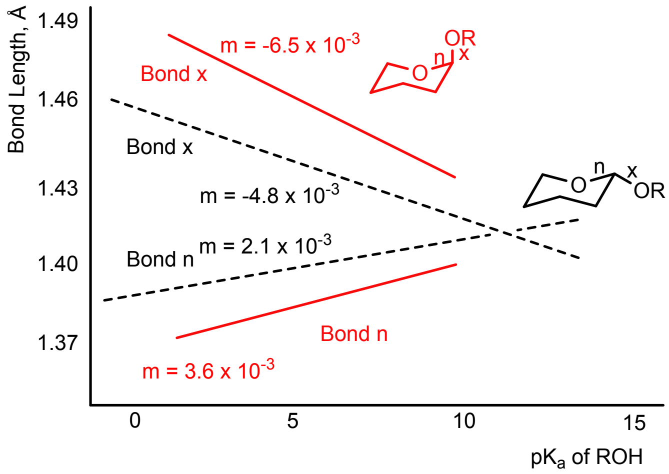


Figure 25. Plot of bond lengths vs. the pK$_a$ of ROH for the series of axial tetrahydropyranyl acetals. "x" stands for exocyclic OR bond, "n" stands for an endocyclic OR bond.

In these systems, where no other significant stereoelectronic effects are present, the trend is clear - there is a linear relationship between the length of the C-OAr bond and the pK$_a$ of the conjugate acid (ArOH) of the leaving group: $r_{C\text{-}OR}$(exo) = 1.493 - (6.495 X 10^{-3})pKa (R = 0.99). There is also a weaker correlation for the associated shortening of the endocyclic C-O bond constrained within a six-membered ring: $r_{C\text{-}OR}$ (endo) = 1.364 + (3.639 X 10^{-3})pKa (R = 0.94). For the series of equatorial tetrahydropyranyl acetals, the bond length vs. pKa correlations have smaller slopes and lower correlation coefficients: $r_{C\text{-}OR}(exo) = 1.456 - (4.76 \times 10^{-3})pKa$ (R = 0.95) and $r_{C\text{-}OR}(endo) = 1.394 + (2.14 \times 10^{-3})pKa$ (R = 0.91).

Remarkably, these effects on bond lengths nearly disappear in analogously substituted α-glucopyranosides, although the conformations at the acetal center are the same. The two acetal C-O bond lengths are similar for methyl α-D-glucoside and similar also for the 2,4-dinitrophenyl derivative (tetraacetate). Although statistical analysis reveals the presence of weak trends in the same direction as observed for axial aryl tetrahydropyranyl acetals, the sensitivity of the acetal bonds lengths to the pKa of ROH is lower by about an order of magnitude. Kirby et al. interpreted this observation to suggest that charge separation is greatly reduced in the glucosides by inductive destabilization of the oxocarbenium ion by the four oxygen substituents. Considering that alkyl and aryl glucosides are hydrolyzed 10^6-10^7 times slower than the corresponding tetrahydropyranyl acetals, it was also suggested that the much reduced reactivity at the acetal center of glucosides originates from the same electronic effects which inhibit the C-OR cleavage and suppress the bond length changes observed in the tetrahydropyranyl acetals.

This approach for detecting the presence of donor-acceptor interactions within an organic molecule by variations in the acceptor ability of OR-groups is known as the variable oxygen probe (VOP). White and coworkers used this approach to obtain important insights in many interesting donor/acceptor systems.[111-115] When interpreting trends provided by VOP, one should keep in mind that the slopes of distance/pKa correlations do not provide a measure of the donor-acceptor interactions directly but rather describe the *response* of these interactions to the increase in electron demand from the acceptor. The differences are similar to the difference between polarity and polarizability – these are clearly related but not identical concepts.

In summary, the importance of anomeric delocalization on geometry can be masked by other factors in multifunctional molecules where several effects can either compete or work together to amplify each other. However, in the well-defined substrates of Figure 24, the dominant role of anomeric effect on the structural changes is clear and this role is fully consistent with the expectations based on the double-bond/no-bond resonance description of negative hyperconjugation.

Spectroscopic manifestations of anomeric hyperconjugation

In this part, we provide a few examples of spectroscopic effects on N-H and C-X bonds but focus on the effects of lone pairs at the adjacent C-H bonds as this is where several spectroscopic techniques (IR, ^{1}H NMR) can provide complementary information. Although C-H bonds are weak acceptors and not generally considered to be part of anomeric systems, sensitive spectroscopic methods clearly support the importance of "anomeric-like" hyperconjugative donation even to such relatively weak acceptors. This is especially useful because C-H bonds are so ubiquitous in organic structures and their reactivity is currently explored in a variety of innovative C-H activation reaction designs.

IR-spectra – Bohlmann effects: A historically important connection between bond length, bond strength, and IR-stretching frequencies is the Bohlmann effect.[116-118] The characteristic red-shifted bands in conformationally confined amines (~2800–2700 cm^{-1}; as a reference point, the C-H stretching frequency in methane is ~3000 cm^{-1})[119, 120] are observed for the C-H bonds that are antiperiplanar to the lone pair of nitrogen and, thus, weakened and lengthened by the anomeric $n_N \rightarrow \sigma^*_{CH}$ hyperconjugative interaction. The IR stretching frequencies for the C-H bonds antiperiplanar to the nitrogen lone pair are also red-shifted in imines and related compounds where the presence of geometric isomers allows a particularly clear distinction between syn- and anti-periplanarity effects. [2,121]

Similar spectroscopic features are known for C-H bonds adjacent to the oxygen atom of alcohols, ethers, and carbonyl compounds. For example, the stretching frequencies for C-H bonds at the sp^2 carbons in aldehydes are significantly red-shifted in comparison to the C-H bonds of ethylene (Figure 26). The $n_O \rightarrow \sigma^*_{CH}$ interactions can be used to rationalize the IR-trends for the C-H bonds in formic acid derivatives. Here, the acceptor C-X bonds aligned with the in-plane p-type lone pair of the carbonyl oxygen weaken the Bohlmann effect for C-H bonds. As the anomeric $n_O \rightarrow \sigma^*_{CX}$ interactions get stronger, the competing $n_O \rightarrow \sigma^*_{CH}$ interactions get weaker, increasing the C-H stretching frequencies. In acyl halides, esters, and amides, the order of C-H blue-shift parallels the σ-acceptor ability of X (F>O>N).

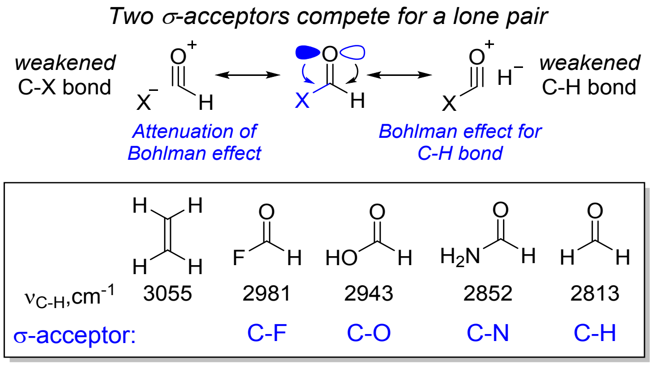


Figure 26. Bohlmann effect observed in C-H IR-stretching frequencies reflect stereoelectronic effects in the carbonyl containing compounds and their chemical relatives. Bond lengths calculated at B3LYP/6-311G++(d,2p) level. Values from reference.[121]

The effect of $n_O \rightarrow \sigma^*_{CH}$ interactions can be probed directly by switching them off via Lewis acid (LA) coordination at the carbonyl. After the O-LA bond is formed, there is no p-type lone pair left to participate in the $n_O \rightarrow \sigma^*_{CH}$ interaction. Hence, the C-H bond gets stronger as indicated by the 160 cm^{-1} increase in the C-H IR frequency (Figure 27, left).

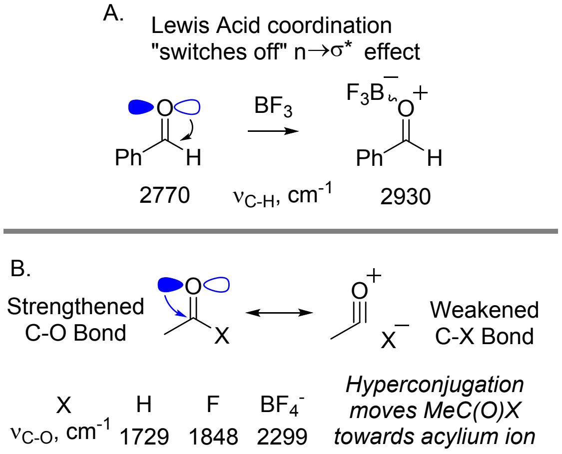


Figure 27. Probing stereoelectronic effects in carbonyl compounds. A: Lewis acid coordination removes $n_O \rightarrow \sigma^*_{CH}$ hyperconjugation and blue shifts the C-H stretching frequency. B: Increased electron demand of substituent X at the carbonyl strengthens $n_O \rightarrow \sigma^*_{CX}$ interaction and leads to the blue shift of the IR C=O stretching frequency in MeC(O)X

As the C=O group is also an IR-active functionality, it also can be used to monitor the same effects. However, the carbonyl properties are sensitive to the competition of two orthogonal sets of delocalizing effects: the in-plane $n_O \rightarrow \sigma^*_{C\text{-}X}$ and out-of-plane $p_X \rightarrow \pi^*_{C=O}$ interactions. As the two effects have opposite structural and spectroscopic consequences, the $n_O \rightarrow \sigma^*_{C\text{-}X}$ interactions become dominant only for highly electronegative substituents. In those cases, the donation from the lone pair to the $\sigma^*_{C\text{-}X}$ orbital leads to partial triple bond character and the blue shift of the C=O IR stretching frequencies (Figure 27, right).[122]

An interesting indirect method of probing electronic density in anomeric systems in the gas phase was developed by using IR-“sensors” based on small peptides.[123] The “reporting” N-H moiety of the peptide forms two hydrogen bonds involving both the endocyclic oxygen and the adjacent OH group of the two sugars anomers. Upon moving from the equatorial to the axial conformer, the N-H vibrational band of the sensor is red-shifted. By analyzing the secondary factors, Davis and coworkers interpreted this change as a combination of two effects: the weakening of the H-bond to the endocyclic oxygen and the concomitant strengthening of the H bond to a remote OH group (Figure 28, top). The former effect was attributed to the decreasing electron density on that oxygen when the endo-anomeric effect is switched on (Figure 18). The vibrational bands associated with the other hydroxyl groups remained in the same position in both spectra.

Subsequently, the difficulties in using such indirect methods were highlighted by a computational study of Mo and coworkers.[124] Mo systematically removed each of the H-bond participants from the sugar anomers and found that the red-shift in the N-H vibrational frequency is still observed even when the endo-anomeric effect is deactivated by replacing the endocyclic oxygen with a CH_2-group. (Figure 28, bottom). Because the anomeric effect cannot be responsible for the spectroscopic shift in the cyclohexane analog, Mo concludes that the spectroscopic changes are due to the variations of hydrogen-bonding distances in the two complexes.

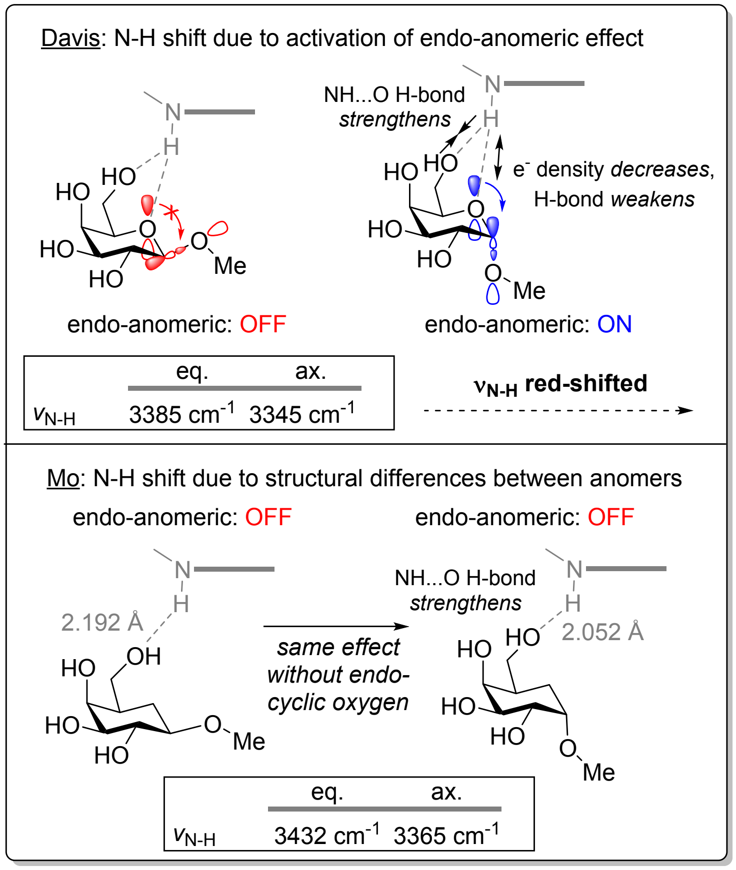


Figure 28. An illustration of the complexity of probing anomeric effects in experimental systems: IR and computational studies of α- and β- anomers of methyl D-galactopyranoside and their analogs

The spectroscopic signatures of anomeric effect and its modulations by intermolecular interactions can provide useful information about chemical behavior of O-containing macromolecules. For example, Hallinan and coworkers[125] reported that the spectroscopic consequences of anomeric effect weakening can be used to detect the structural effect of lithium cation doping in polystyrene (PS) – poly(ethylene oxide) (PEO) diblock copolymer electrolyte. In particular, a change from the uncoordinated PEO to the Li-coordinated gauche configuration is reflected in the IR C-H bond vibration frequencies. In the absence of Li-cation coordination, the lone pairs of oxygen are able to donate to the antibonding C-H orbitals, effectively weakening the C-H bonds. However, when the PEO backbone coordinates with the lithium cation, oxygen "gives up one of its lone pairs" to coordinate with lithium. In addition, the orbital overlap between the donor and acceptor is compromised by the conformational change associated with the Li-coordination. According to NBO analysis, the average donor ability of oxygen decreases from 6 kcal/mol in the uncoordinated configuration to 4.2 kcal/mol in the Li-coordinated complex. Due to the weaker $n_O \rightarrow \sigma^*_{C\text{-}H}$ donation, the IR peaks corresponding to C-H bond vibrations are blue-shifted in the Li-cation-doped polymer (Figure 29).

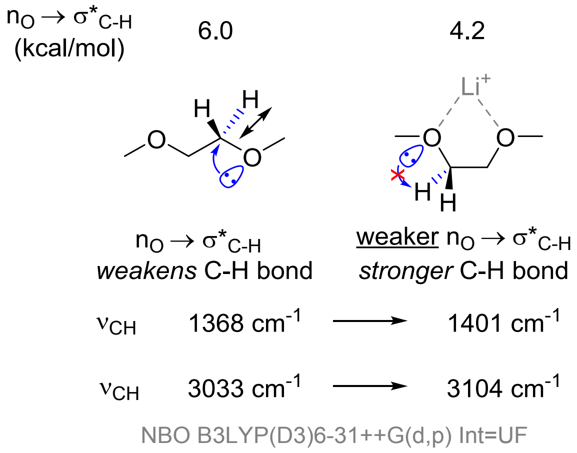


Figure 29. The calculated effect of anomeric effect weakening in the IR spectra of the model unit of poly(ethylene oxide) (PEO)/Li-cation system.

NMR Perlin Effect as a Measure of Anomeric Effects on C-H coupling: Spin–spin coupling constants or ''J values'' in NMR are widely used in structure determination and conformational analysis of organic and inorganic molecules.[126-128] In cyclohexane, the direct ^{1}H-^{13}C coupling constants are smaller for axial hydrogens. This observation, known as the normal Perlin effect[129], can be traced back to the elongation of the axial C-H bonds as a consequence of hyperconjugative $\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}H}$ interactions.[130] The role of negative hyperconjugation on the C-H coupling in six-membered saturated heterocycles was thoroughly investigated by Juaristi and coworkers (Figure 30).[131, 132] The axial lone pairs of O and N-atoms increase the magnitude of the Perlin effect by selectively weakening the axial C-H bond. The effect is clearly stereoelectronic because once the N-lone pair of azacyclohexane is oriented equatorially, the difference between axial and equatorial ${}^{1}J_{C\text{-}H}$ values decreases to its value in cyclohexane. Interestingly, the lone pair of an S atom does not impose a similar effect, revealing the existence of alternative delocalizing C-H/C-S interactions that selectively weaken and elongate the equatorial C-H bond.[131, 132]

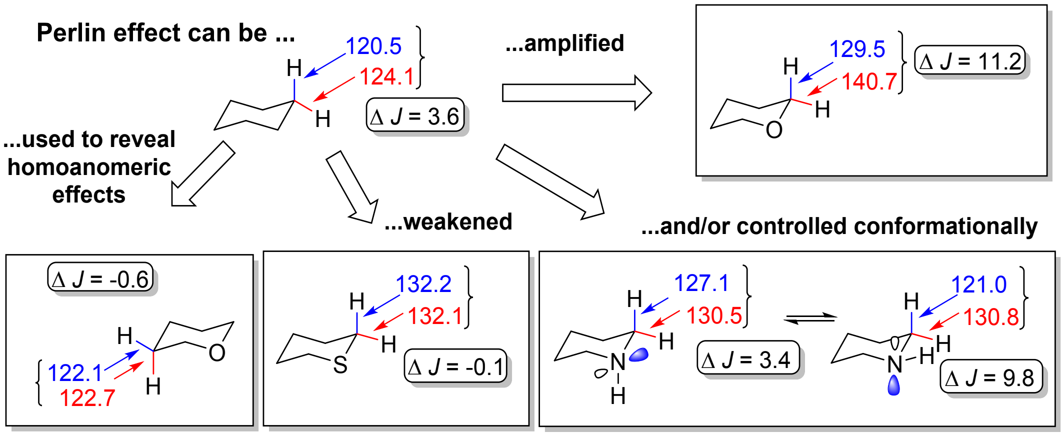


Figure 30. Selected direct ${}^{13}C$-${}^{1}H$ coupling constants (J) at B3LYP/6-31G(d,p) level for the axial and equatorial C-H bonds (note that the longer bonds generally correspond to the smaller coupling constants)[133]

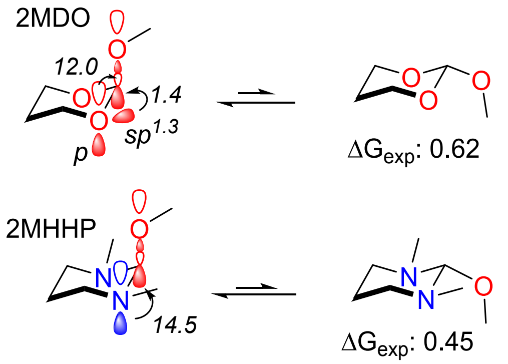
Because C-H bonds are weak acceptors, the correlation of hyperconjugation and one-bond C-H coupling constants can be overshadowed by other factors.[133] Computational analysis of structures with systematic variations in the H-C-O-C dihedral angle in acyclic ethers revealed that although the effects of $n_O \rightarrow \sigma^*_{CH}$ and $n_O \rightarrow \sigma^*_{CC}$ delocalization are not negligible, polarization effects associated with the local dipole-dipole interactions can be even more important for the observed NMR trends. Recently, a thorough analysis of Perlin effects in cyclohexane-derived compounds by Podlech and coworkers illustrated that the NMR coupling constants are also affected by other factors including the s-character in the respective hybrid carbon orbitals in the C-H bonds.[128] From these recent findings, NMR evidence of anomeric effects has to be considered critically and used in the conjunction with other experimental and computational data.

The use of model compounds in studying anomeric effects

A common approach is to compare anomeric systems with related model compounds designed to either remove or amplify one of the proposed factors, suspected of being important. A good example of this approach is the insightful work by Perrin et al.[134] who compared conformational preferences of 2-methoxy-1,3-dioxane (2MDO) and 2-methoxy-N,N'-dimethylhexahydropyrimidine (2MHHP). One could expect that due to the lower electronegativity of nitrogen, replacement of both cyclic oxygen atoms with

NMe groups would enhance orbital interactions and reduce local dipole moments. The authors also estimated that steric destabilization of axial-2MHHP would be lower than that of axial-2MDO, thus allowing a higher amount of the axial conformer in the case of 2MHHP.

However, 2MDO and 2MHHP were found to nearly identical equilibrium constants for the axial and equatorial conformer interconversion. In order to understand this finding, one should take into account a number of significant differences between oxygen and nitrogen. For example, even though nitrogen is less electronegative, the stereoelectronically important O and N lone pairs are similar in energy because the difference in electronegativity is offset by greater p-character in the stereoelectronically active oxygen's lone pair (see Addendum #2 at the end of the Review).[135] An additional difference is the longer C-N bond lengths (1.469 Å in C^{sp3}-N^{sp3} vs. 1.426 Å in C^{sp3}-O^{sp3} on average, according to Cambridge Structural Database).[136] These differences decrease the expected hyperconjugation in 2MHHP relative to 2MDO. Furthermore, each oxygen has two lone pairs and is much more stereoelectronically "forgiving" than nitrogen which has only one lone pair. As the result, the combined donation from both lone pairs of an oxygen atom in the axial-2MDO is comparable to donation from the lone pair of nitrogen in the axial 2MHHP (13.4 vs. 14.5 kcal/mol, Figure 31). Hence, the small difference between the N- and the O-systems does not disqualify hyperconjugative interactions as the important contributor to anomeric effect, although it does also illustrate that other factors, such as electrostatics, also play a role.



Energies in kcal/mol, NBO B3LYP(D3)/6-31+G(d,p) Int=UF

Figure 31. Comparison of the conformational preference of 2-methoxy-1,3-dioxane (2MDO) versus 2-methoxy-N,N'-dimethylhexahydropyrimidine (2MHHP)

In fact, many model substrates used in the similar studies of anomeric effect illustrate the elusive nature of "electronic effects" in chemistry. When making structural changes aiming to simplify stereoelectronic analysis, one has to be aware of an analog of the "Heisenberg uncertainty principle" that complicates clear dissections of coexisting factors. Often, the “tools”, (i.e., the structural modifications) used to make a particular phenomenon “obvious”, change the initial object of study so much that the “model system” is too different from the original system. In other words, when studying the balance of stereoelectronic and coulombic interactions, one should consider if a change from O to CF_2 or from O to NH may perturb the system so much that the observed trends are not really applicable to the original O-functionality. From that point of view, one can understand the appeal of theoretical approaches that hold a promise of a potentially “cleaner” analysis.

Theoretical tools used to study anomeric effects – an outline

Theoretical approaches for investigating the anomeric effect are numerous and are summarized in Figure 32. They can be roughly divided into two classes: (1) interaction-lockout-based and (2) chemoinformatic-based.

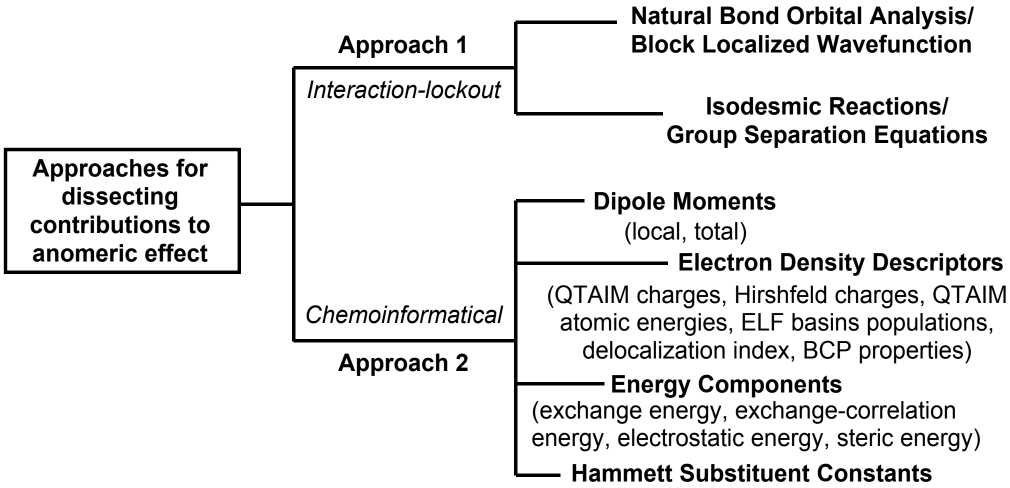


Figure 32. Computational approaches to studying anomeric effects. Acronyms: NBO – natural bonding orbitals; QTAIM – quantum theory of atoms-in-molecules; ELF – electron localization function; BCP – bond critical point (defined within the QTAIM framework).

Interaction-lockout-based approaches construct a hypothetical system where the “key” interactions causing the anomeric effect are switched off. Then, the difference in total energies of this interaction-free system and the original system can be taken as the anomeric effect strength. If such interaction energies correlate with the relative total energies of conformers, it provides an indication that the switched off interactions are indeed responsible for the anomeric effect in the given molecule.

The most popular interaction-lockout approaches are orbital- and valence-bond-theory based. These methods allow construction of a delocalization-free wavefunction, corresponding to the chosen Lewis structure. Orbital-based approaches include the very popular NBO- analysis[75, 88, 130, 137-143], as well as other methods, e.g., "bond model analysis"[144], "paired interaction orbital method"[145], etc. Valence-bond-theory approaches include the block-localized wavefunction (BLW) method[31, 146-148], developed by Mo, and other approaches such as "perfect-pairing generalized valence bond theory" (GVB-PP).[149] NBO analysis of Weinhold can estimate energies of specific orbital interactions. This feature is very useful as it allows a more detailed exploration of delocalization effects (see examples below). However, unlike the BLW method, NBO does not relax the wavefunction of the delocalization-free state by its variational reoptimization. This leads to a higher energy of the reference state, somewhat overestimating the delocalization energies.[150] Valence bond theory approaches, on the other hand, are often based on non-orthogonal orbitals and, thus, suffer from the "overlap dependency", which leads to ambiguities in assigning electronic overlap density to one site or another, thus complicating analysis of charge transfer.[69]

Finally, one can switch off a particular interaction by constructing an isodesmic reaction where all interactions, except for the one under investigation, are conserved.[151] An example of an isodesmic reaction is given in Figure 33. This approach presents, perhaps, the most direct way for measuring anomeric effect strength in a given molecule, without relying on a chosen model. From the very general point of view, a conformational change can be considered a special "perfect" isodesmic reaction, as it fully preserves all bond types, hybridizations etc.

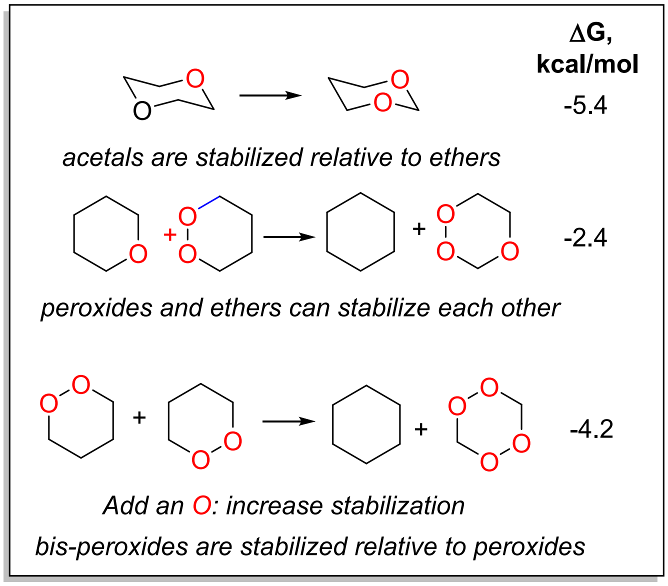


Figure 33. An isodesmic reaction can illustrate how the stabilization of bis-peroxides and peroxyacetals increases due to the introduction of $n_O \rightarrow \sigma^*_{CO}$ interactions.[152]

The chemoinformatic approaches do not attempt to estimate the interaction energy, but rather search for a correlation between the conformers' energies and a molecular property such as total or local dipole moments[142, 153], atomic charges (QTAIM[23, 25-27, 77-79] or Hirshfeld[20]), QTAIM atomic energies[25-27, 77, 79], electron localization function (ELF) basins populations[25], delocalization indexes[23, 26, 78], electron density properties at bond critical points (BCP)[139, 140], or even Hammett substituent constants[154]. If found, the correlation is often considered to imply causation. In other words, if a change in a property is associated with the observed change in the conformer energy, this property is viewed as the cause of the anomeric effect.

Another set of chemoinformatic approaches relies on correlating the energy components (kinetic, potential, exchange, correlation, etc) with the overall energy differences. It was shown that relative conformer energies correlate well with the exchange energy[155], but not with the correlation energy, leading the authors to conclude that anomeric effect arises from the Pauli principle. In another study[153], correlations were found between the conformers relative energies and (1) exchange-correlation, (2) electrostatic and (3) steric energies, showing that all of them participate in determining conformational equilibria in the anomeric systems.

One can easily see, that the interaction-lockout-based and, especially, the chemoinformatic approaches rely on the presence of a correlation to conclude that a particular interaction or property gives rise to the observed conformational properties, structural features, or reactivity patterns. When applying this logic, one should remember that correlation does not always imply causation (see ref.[156], and its TOC Figure). Not surprisingly, different approaches often disagree in underpinning the origin of anomeric effect.

Obviously, all approaches presented in Figure 12 were constructed to be useful as mental models. However, the reality is simultaneously much less and much more complicated: the molecules are combinations of positively charged nuclei held together by a "cloud" of negatively charged electrons which are delocalized in the potential field imposed by nuclei. All the participating particles (electrons and nuclei) interact with each other by the electroweak force, which determines the ground state electron density distribution and the preferred molecular geometry. This seemingly simple but intractable for human mind model intrinsically incorporates the anomeric effect (as well as all the other effects), so quantum chemical calculations reproduce it without the *a priori* knowledge of its existence.

Unlike the quantum chemical methods, molecular mechanics force fields require explicit parameterization of the anomeric effects to accurately describe molecules where such effects are present. For this reason, the search for unexpected anomeric effect manifestations remains important as such manifestations directly affect accuracies of force fields used to describe very large molecular systems (e.g. in computational biochemistry).

Let's analyze now how the different information provided by different methods can lead to misunderstandings and controversies.

"Conflicting" origins of anomeric effect: comparison of recent computational models

Because molecular properties originate from an interplay of multiple factors, the origin of AE remains a popular testing ground for the development of new theoretical models and computational techniques aimed at providing deeper insights into electronic structure. Following these discussions can be confusing because the overall conclusions keep changing and the results seem to conflict each other, especially when different criteria are used for evaluating the "same" electronic factor. Below, we will give a brief outline of selected recent findings. They can be separated into two parts a) based on dissection of electronic wavefunctions into individual components and b) analysis of secondary factors, such as the overall charge distribution, individual bond polarity etc.

Dissections of electronic wavefunctions:

A particularly helpful theoretical method for organic chemists is the Natural Bond Orbital (NBO) analysis of Weinhold. NBO analysis transforms the canonical delocalized Hartree-Fock or Kohn-Sham MOs and non-orthogonal atomic orbitals (AOs) into sets of localized "natural" atomic orbitals (NAOs), hybrid orbitals (NHOs) and bond orbital (NBOs). Each of these localized basis sets is complete, orthonormal, and describes the wavefunction with the minimal number of filled orbitals in the most rapidly convergent fashion. Foster and Boys[157], Edmiston and Ruedenberg[158], and Pipek and Mezey[159] reported alternative localization procedures for transforming delocalized MOs into the intuitive Lewis structure description that provides additional bridges between MO and VB theories (see Addendum #1 at the end of the Review for details).

In this review, we provide hyperconjugation energies computed within NBO approach on top of DFT calculations. Even in situations where steric and electrostatic interactions may play a more important role, the NBO energies can show the extent by which hyperconjugation changes upon a structural perturbation or a conformational change, providing a firm foundation for gedanken experimenting.

Filled NBOs describe the hypothetical, strictly localized Lewis structure where each NBO corresponds to either a bond, a lone pair, or an antibond. The interactions between filled and unfilled (antibonding) orbitals represent deviation from the localized Lewis structure and can be used as a measure of delocalization. When the occupancies of filled NBOs are highly condensed, the delocalizing interactions energies can be estimated using second order perturbation approach (Equation 1) where $<\sigma|F|\sigma^*>$, or F_{ij} is the Fock matrix element between orbitals (NBOs) i and j, ε_σ and ε_{σ^*} are the energies of the σ and σ* NBO's, and n_σ is the population of the donor orbital.[160]

Equation 1

$$E(2) = -n_\sigma \frac{<\sigma|F|\sigma^*>^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{i,j}^2}{\Delta E}$$

Alternatively, orbital interactions can be evaluated by deletion of the corresponding off-diagonal elements of the Fock matrix in the NBO basis and recalculating the energy (the "deletion energies", E_{del}).[160-162] The advantage is that an individual interaction or a group of interactions can be evaluated. Usually, there is a good linear correlation between deletion (E_{del}) and perturbation (*E(2)*) energies.[18] Deviation from such a correlation often reflects cooperativity or anticooperativity between the individual delocalizing interactions.

Because the NBO method can provide contributions from well-defined individual orbital interactions, it is very convenient for evaluating the role of specific stereoelectronic effects in organic reactivity. For example, Figure 34 illustrates the strength of two distinct interactions mediated by the same σ* acceptor (top) and the contribution of one orbital interaction to the anomeric effect in dimethoxymethane (bottom).

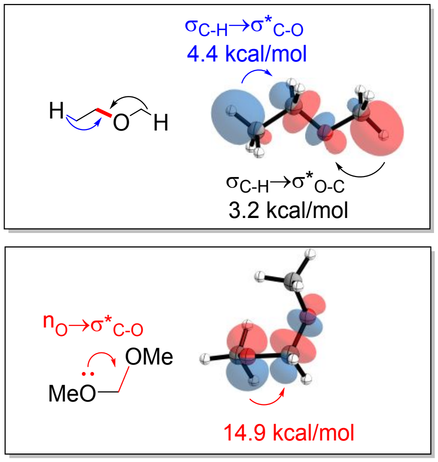


Figure 34. Two examples of NBO analysis of orbital interactions. Top: Anisotropy of orbital interactions at the opposite ends of same σ^* acceptor with two analogous σ_{CH} donors.[130] Bottom: the negative hyperconjugation contribution into anomeric effect in dimethoxymethane.

Detailed NBO studies by Freitas[88] found that NBO evaluations of hyperconjugative contributions to anomeric preferences agree well with the observed conformational trends in the gas phase and in solvents of different polarity. Recently, Nori-Shargh et al. have shown that, after NBO deletion of the hyperconjugative exo- and endo-anomeric interactions in 2-fluorotetrahydropyran, -thiopyran, -selenopyran, and their chloro- and bromo- analogs, the equatorial conformers become more stable than the axial conformers, supporting the hyperconjugative anomeric effect origins.[75]

Conceptually interesting, but in our opinion, less useful for the understanding of practical aspects of chemical reactivity are "global NBO delocalization energies" that combine contributions of ***all*** "non-Lewis" orbitals. In addition to vicinal hyperconjugation, such energies include geminal delocalization from orbitals at the same atom as well as contributions from interactions with empty atomic orbitals with higher quantum numbers (Rydberg orbitals). Geminal interactions include contributions that come from rehybridization and repolarization of orbitals at the same atom and are less intuitive to understand than the stereoelectronically controlled vicinal interactions. To complicate it further, the physical origin and chemical consequences of Rydberg interactions are not well-studied. Considering the possible influence of multiple effects, getting a practical insight from the global deletion energies is challenging.

Another interesting approach is the block localized wavefunction (BLW) method developed by Mo and coworkers.[148, 163-171] Like NBO, the BLW method can evaluate the contribution of orbital effects on the overall electronic energy. However, it does not separate vicinal and geminal hyperconjugation and, in general, lacks the flexibility needed for evaluating each individual orbital interaction separately. The localized reference Lewis structure in the BLW method is derived by "partitioning the system into several mutually interacting subgroups and restricting the expansion of each MO in only one subspace" (Figure 35). This separation into individual blocks must be done carefully so the same orbitals are not included in multiple blocks. An advantage of BLW over the current implementation of NBO is that the localized block-orbitals are variationally optimized. Reoptimization of orbitals stabilizes the localized state and, thus, decreases the apparent stabilization by delocalization effects.

Unfortunately, direct comparison between these methods is complicated because, unlike NBO, BLW starts with non-orthogonal orbitals as the basis for building the localized reference "free of delocalization". As a result of the above differences, NBO estimates of delocalization are generally larger than BLW estimates.

The differences between alternative wavefunction dissections can be traced back to assigning the overlap density to either the filled orbital (and counted toward steric effects) or to the unfilled orbital (and counted toward hyperconjugative charge-transfer).

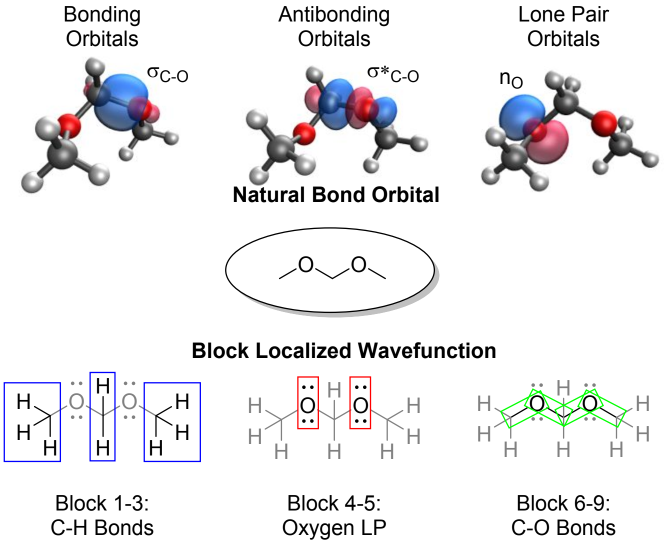


Figure 35. Comparison of reference states used in NBO and BLW interaction-lockout approaches.

Keeping these differences in mind, let's highlight the in-depth BLW analysis of the anomeric effect in dimethoxymethane.[31] To start, the localized blocks were constructed—the C-H bonds were localized within their own methyl or methylene groups while constraining the oxygen lone electron pairs to individual oxygen atoms. Finally, each C-O bond was strictly localized between the two bonding atoms (Figure 35). Nine blocks were defined, each containing an even number of electrons. Each MO was expanded within only one block or subgroup and was doubly occupied. The energy difference between BLW and HF was taken as the magnitude of the vicinal n/σ^* and σ/σ^* interactions as well as some of the geminal interactions of bonds sharing the same apex atoms. This BLW analysis found that this combination of hyperconjugative interactions is an important stabilizing force (on the order of 57-59 kcal/mol) for each of the three rotamers of dimethoxymethane. Interestingly, for this subset of hyperconjugative interactions (which combines vicinal hyperconjugation, geminal hyperconjugation and other delocalizing effects), hyperconjugation slightly favors the all-trans over all-gauche conformations. The 1.9 kcal/mol difference for the alternative conformations is small (~3% of the overall delocalization energy). The overall BLW data suggest that the anomeric effect is mostly derived from the "steric preference".

When considering this conclusion, one has to remember that steric energy was defined as the sum of the electrostatic interaction (stabilizing or destabilizing) and Pauli repulsion in the BLW approach whereas the

NBO approach (i.e., Natural Steric Analysis)[172, 173] treats sterics as the "kinetic energy pressure" that opposes interpenetration of matter.[174] In the latter case, the physically required orthogonalization of overlapping orbitals leads to additional oscillatory and nodal features which are associated with increased wavefunction curvature and kinetic energy of electrons.

This situation points to a typical problem. It is not uncommon that the "same component" is defined in a different way in alternative models of AE. In another example, da Silva and coworkers[155] use the energy terms that emerge directly from the application of the molecular Hamiltonian on the appropriate wavefunction. The energy terms that constitute the total energy (E_{tot}) were taken as the kinetic (T), electrostatic (V_{el}) and exchange (K) components.

Perhaps not surprisingly, da Silva and coworkers arrive to a different conclusion—in their model, the origin of AE is in repulsive exchange interactions, and electrostatic factors do not contribute to the anomeric preference. Not only is the definition of steric energy quite different from the earlier conventions, but orbital interaction effects are not explicitly discussed.

In summary, the answers obtained in new theoretical treatments of the anomeric effect often depend on the model design, such as the choice of the reference (i.e., delocalization-free) state, the inclusion of additional, sometimes conflicting effects in the analysis, and/or conceptually different definitions of individual contributions. Importantly, arriving to a consensus would require a suitable localized reference point that everybody agrees upon and theoretical approaches that define analogously named energy contributions from the same physical principles.

Furthermore, although the separation of the total energy into global contributions of a "different nature" (e.g., hyperconjugation + electrostatics + steric) may have conceptual value, it often offers limited guidance to a practicing synthetic organic chemist. Even if the combination of minor effects shows a slight preference one way, we argue, from our personal point of view, that such global pictures offer less *practical* value in guiding chemical intuition and reaction design than a single key electronic reorganization effect that closely follows the reaction path and defines the bond-breaking and bond-making steps.

Considering the abundance of theoretical approaches and conflicting conclusions discussed above, it is remarkable that chemists still generally prefer the hyperconjugative model of AE, even when acknowledging the electrostatic contributions. Let's keep that in mind while reviewing a few specific controversies related to anomeric effect.

Delocalization, polarity and electron density transfer in anomeric systems:

As discussed earlier, the thermodynamic consequences of anomeric effect can often be evaluated using isomerization or group separation reactions. For example, 1,4-dioxane is ~5 kcal/mol less stable than 1,3-dioxane. This difference indicates the presence of a stabilizing effect, specific to 1,3-dioxane. Note that this effect is larger than the 0.8-0.9 kcal/mol axial/equatorial difference in 2-OMe THP, [48] indicating that loss of two $n_O \rightarrow \sigma^*_{C\text{-}O}$ interactions involving the two endocyclic O atoms (in 1,4-dioxane) comes with the greater penalty than loss of one $n_O \rightarrow \sigma^*_{C\text{-}O(ax)}$ donation (in equatorial 2-OMe THP).

A corollary of these thermodynamic estimates - interesting in the context of the above electrostatic arguments - is that the greater stability of 1,3-dioxane reiterates that an increased dipole moment does not lead directly to a lower stability in a pair of isomers. Sometimes, the more polar isomer can be more stable: *polarization does not equal instability and vice versa.* On the other hand, the hyperconjugative model readily explains why 1,3-dioxane, where the vicinal anomeric $n_O \rightarrow \sigma^*_{CO}$ interactions are possible, is more stable than the 1,4-isomer.

A controversial opinion, related to the interplay between polarity and delocalization, is that hyperconjugative interactions within a symmetry-related donor/acceptor pair (such as CF_2) would “counteract each other” and, thus, provide net zero stabilizing effects. In particular, Wiberg makes the following point about negative hyperconjugation in a CF_2 group: “Since each fluorine is both a donor and an acceptor, it is not obvious why the energy should decrease.” Although he agrees that negative hyperconjugation “may well be operative in other cases in which there is an opportunity for charge transfer”,[32] the above statements also imply that negative hyperconjugation without such an opportunity is unimportant. This comment brings the question of whether delocalization should *always* be associated with charge transfer to be stabilizing.

The answer to the above question is clearly “No”. Figure 36 shows a selection of textbook symmetric delocalization patterns which are stabilizing in the absence of net charge transfer. Even when such systems include polar substituents (e.g., the C-F bonds in -CF_2-), the local polarization is cancelled out on the molecular scale.

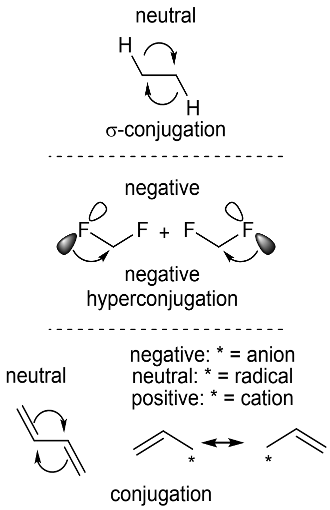


Figure 36. Delocalization without charge transfer: a selection of symmetry related pairs of delocalizing interactions

These examples also address another common misconception that it is impossible to "weaken a bond but stabilize a molecule". Here, both allylic radical and 1,3-butadiene illustrate that even though conjugative interactions may formally decrease the double bond character in the dominant Lewis structures describing these species, the added delocalization of the π electrons stabilizes each of these molecules as a whole.[49, 175] By increasing the "potential energy box" for electrons, delocalization decreases their kinetic energy. The same argument readily applies to the symmetric CF_2 fragment as well. In fact, the delocalization is at its best exactly when it does *not* separate charges, as illustrated readily by the "symmetry enforced neutral delocalization" in benzene that we refer to, for brevity, as "aromaticity". Of course, aromaticity is one of the best ways to stabilize a molecule by delocalization.

Anomeric effect in polyfluorinated organics

In a thorough study, Schleyer showed that the increased stabilization associated with additional fluorine atoms at the same carbon (Figure 10) is consistent with the greater number of possible anomeric orbital interactions. Each F atom has three lone pairs, two of which are p-type and can interact with the adjacent acceptor orbitals. These orbitals can give rise to 2, 6, and 12 $n_F \rightarrow \sigma^*_{CF}$ interactions in CH_2F_2, CHF_3, and CF_4 respectively. According to the NBO deletion calculations by Salzner and Schleyer[176], such interactions add up to ~131 kcal/mol in CF_4. The difference in the overall molecular stability and the NBO evaluation suggests that the stabilizing effect associated with anomeric delocalization is partially offset by structural distortions needed to reach the molecular geometries that provide the best compromise between the localized (Lewis) and delocalized wavefunctions.

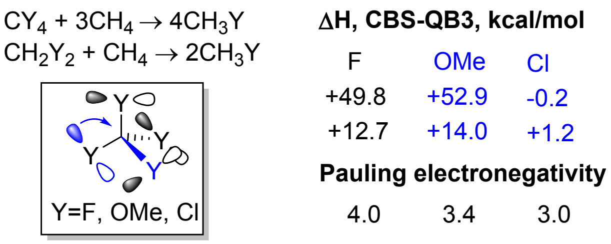


Figure 37. Group separation reactions that probe the effect of different substituents at the same carbon.

Alternatively, Wiberg and Rablen[32] emphasized the electrostatic contribution to the C-F bonds shortening as a consequence of the positive charge increase on the central carbon with increasing F substitution. Such increase should lead to significant polar contribution to the C-F bond strength, albeit with the partial loss of covalent bond order.

In this context, it is interesting that the calculations of Wiberg and Rablen find nearly the same strong anomeric stabilization for Y=F and OMe but the stabilization essentially disappears for Y=Cl (Figure 37). These authors, who attribute the increase in anomeric stabilization and the C-Y bond strength with the increased number of substituents Y = F, OR to the greater polarity of the C-Y bonds, suggest that the ~50 kcal/mol difference in the stabilization energies can be attributed to the lower electronegativity of Cl (3.2 on the Pauling's scale) in comparison to the electronegativity of O (3.4). When considering this argument, one should note that the even larger difference between O and F (4.0) does not decrease the extent of anomeric stabilization in a similar way. In fact, the stabilization is even larger for O, despite its lower electronegativity.

From the hyperconjugative model point of view, the difference between Y = F vs. Cl is readily explained by the fact that the much longer C-Cl bond length considerable weakens the $n_Y \rightarrow \sigma^*_{C-Y}$ interactions by separating the interacting orbitals further away in space (approximately by 50%). According to NBO analysis, the representative $n_Y \rightarrow \sigma^*_{C-Y}$ interaction energies are 15.0 (Y=F), 15.0 (Y=OH), and 7.5 (Y=Cl) (in kcal/mol, at the B3LYP/6-31G(d,p) level).

Importantly, the anomeric effect in fluorocarbons (mediated by $n_F \rightarrow \sigma^*_{CF}$ donation) greatly stabilizes each CF_2 moiety without introducing charge separation that could assist in the initiation of polar reactions (Figure 38). The charge on the F atoms doesn't change greatly. Although the central carbon becomes progressively more positively charged, the additional F atoms also create a negatively charged "armor" that shields the positively charged carbon atom from a nucleophilic attack. Together, these structural and electronic features offer protection from both reducing and oxidizing agents and explain why fluorocarbons are such a difficult target for common bio- and chemo-degradation mechanisms.[177]

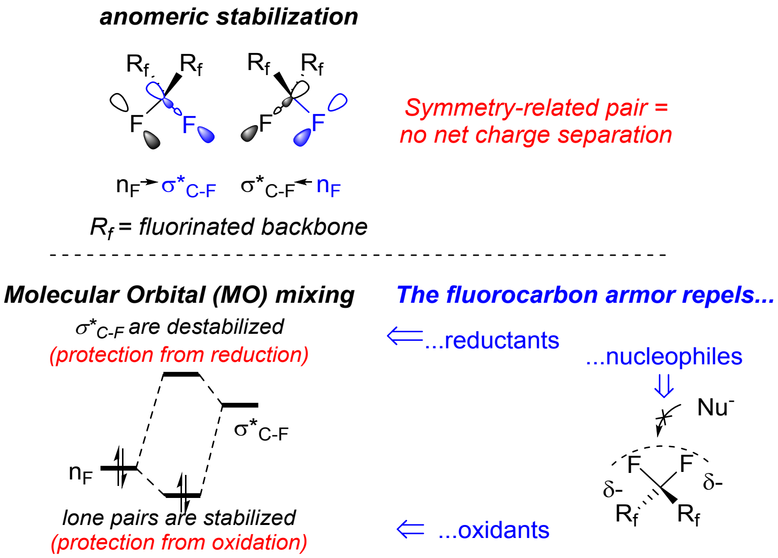


Figure 38. The "anomeric armor" of fluorocarbons: $n_F \rightarrow \sigma^*_{C-F}$ interactions as components of electronic stabilization of fluorocarbons.

The anomeric effect also contributes to the significant increase in the BDEs of the C-F bonds with the increasing degree of fluorination at the same carbon atom. Here, the apparent C-F bond strength increases greatly if the C-F bond in question is part of a CF_2 or a CF_3 group. Inspection of the individual resonance structures here is misleading since it suggests that the pair of symmetry related $n_F \rightarrow \sigma^*_{CF}$ interactions in each CF_2 moiety would, in turn, weaken and strengthen the C-F bond and, hence, have little effect (Figure 39). The confusion can be resolved once one realizes that *both* of the two symmetry related interactions will be lost if one of the C-F bonds is broken. Hence, the cumulative effect of double anomeric hyperconjugation should strengthen each of the two C-F bonds in the CF_2 moiety relative to that in CH_3F.

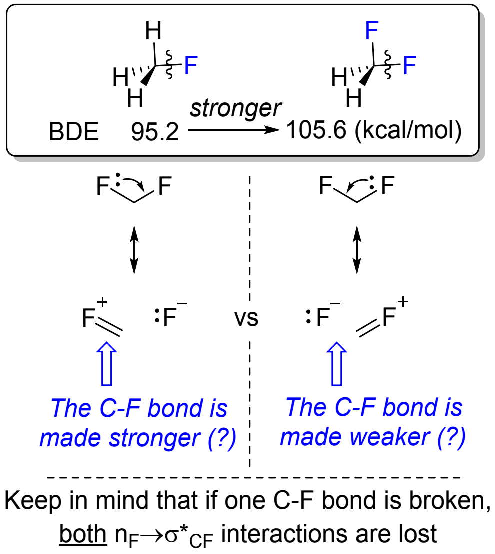


Figure 39. The seeming paradox of symmetric anomeric patterns: will the C-F bond be weakened or strengthened? The $n_F \rightarrow \sigma^*_{CF}$ interactions are clearly stabilizing but the overall effect on geometry cannot be readily predicted from the analysis of resonance structures. BDE from ref. 32.

Other conceptual controversies – puzzles originating from complexity:

Recently, Wiberg and co-workers[20] made several interesting observations when analyzing the Hirshfeld atomic charges of axial and equatorial 2-fluoro-1,3-dioxane at the MP2/aug-cc-pVTZ level. For example, they pointed out that, although both hydrogen and fluorine do gain additional electron density when they move from an equatorial to an axial position, the calculated charge at the oxygen changes to a lesser extent (Figure 40). This observation seems to disagree with the premise that hyperconjugative donation of electron density from the n_O orbital into the σ^*_{CF} orbital should decrease electron density at the endocyclic oxygen in the axial conformer and prompted the following comment: "The hyperconjugation model involving electron transfer from a ring heteroatom to an excited state (sic) of an axial C–G bond was shown to be, at most, a minor contributor because of the very small changes in charge density at the ring heteroatom(s): the main charge transfer is from hydrogen to G in the H–C–G unit".[20] The authors continue to suggest the following: "As a corollary to this study we suggest that proposals of hyperconjugative interactions in neutral closed shell systems should be checked by calculating the atomic charges to see if the proposed charge transfer is found".

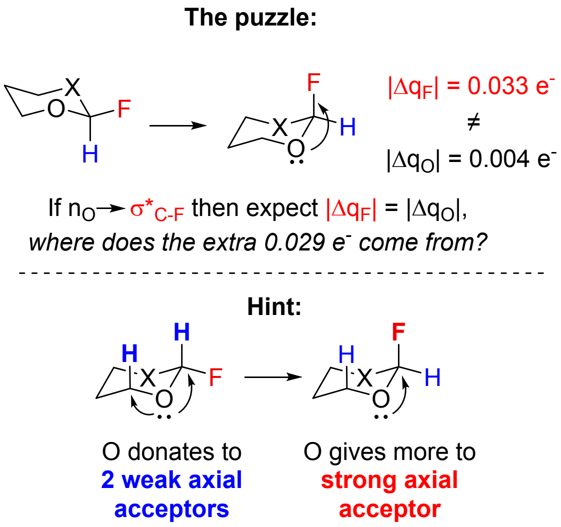
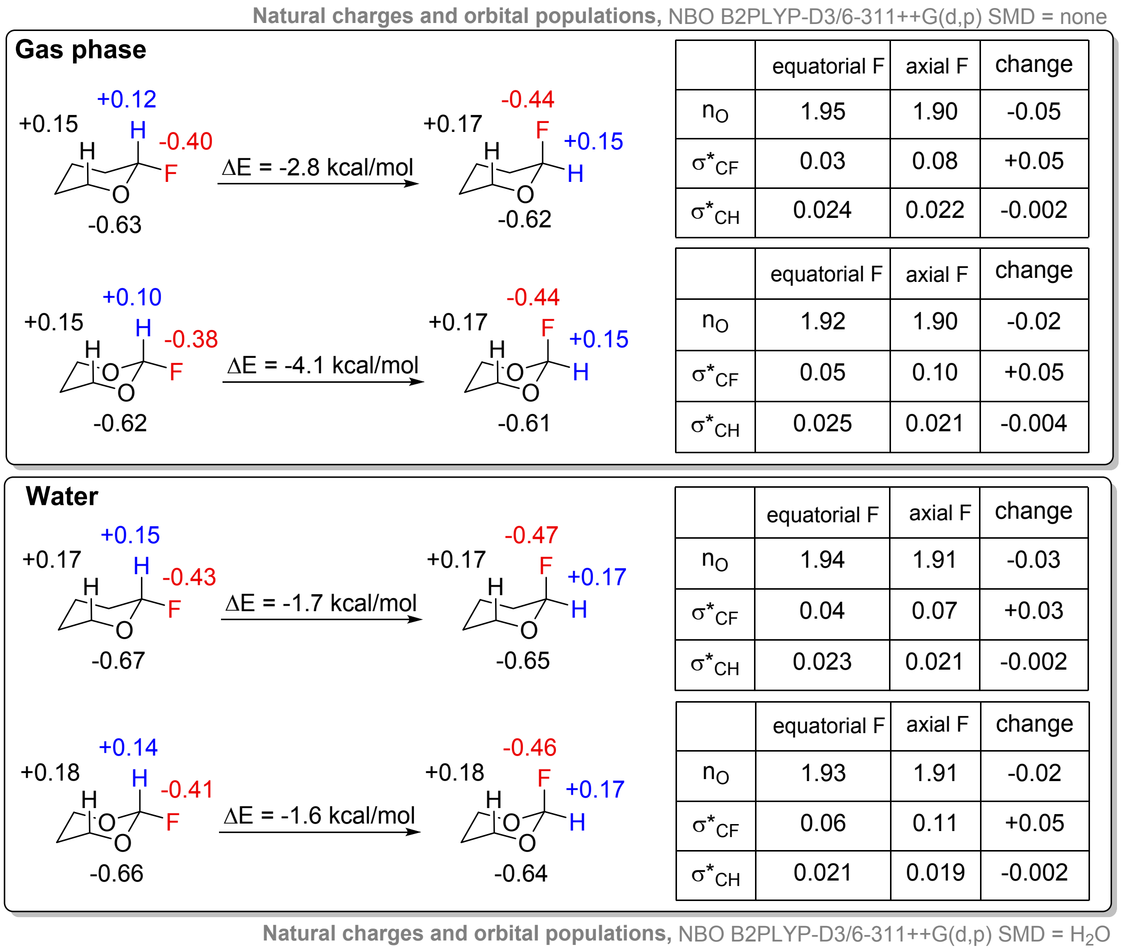


Figure 40. Left: The Wiberg's puzzle: is anomeric effect complicated? *Changes* in selected atomic Hirshfeld charges at MP2/aug-cc-pVTZ level upon axial/equatorial flip in 2-F-1,3-dioxane indicate that the axial fluorine gets electron density but it doesn't seem to come from the oxygen. Right: a hint for solving the puzzle (vide infra)

Indeed, the observation of oxygen not gaining electron density seems counterintuitive and warrants a more detailed analysis. We perform such analysis below for both 2-fluoro-1,3-dioxane and 2-fluoro-tetrahydropyran (2-F-THP). 2-F-THP is a more balanced test compound for analyzing charge density changes because anomeric charge delocalization in 2-fluoro-1,3-dioxane is unavoidably *diluted* by an imbalance between the number of donors and acceptors. To put it simply, since there are *two* oxygen donors per *one* C-F acceptor, *any* electronic effect (such as a charge decrease) at each of the two oxygens would be expected to be *half* of the related effect on the fluorine. For this simple symmetry-based reason, 2-fluorotetrahydropyran, that has one donor per one acceptor, serves as a better model for the analysis of electron density redistribution upon the equatorial-axial flip.

The advantage of NBO for such analysis is that we can look at the individual orbitals in addition to the total charge at each of the atoms. The observations are interesting and they illustrate that, indeed, the "anomeric effect is complicated", as suggested by Wiberg et al.[20] However, this complexity revolves around the hyperconjugative picture of the anomeric effect. The salient observations are summarized in Figure 41. These observations fully support the key role of hyperconjugation in charge density changes associated with AE.



Natural charges and orbital populations, NBO B2PLYP-D3/6-311++G(d,p) SMD = none

Gas phase

	equatorial F	axial F	change
n_O	1.95	1.90	-0.05
σ^*_{CF}	0.03	0.08	+0.05
σ^*_{CH}	0.024	0.022	-0.002

	equatorial F	axial F	change
n_O	1.92	1.90	-0.02
σ^*_{CF}	0.05	0.10	+0.05
σ^*_{CH}	0.025	0.021	-0.004

Water

	equatorial F	axial F	change
n_O	1.94	1.91	-0.03
σ^*_{CF}	0.04	0.07	+0.03
σ^*_{CH}	0.023	0.021	-0.002

	equatorial F	axial F	change
n_O	1.93	1.91	-0.02
σ^*_{CF}	0.06	0.11	+0.05
σ^*_{CH}	0.021	0.019	-0.002

Natural charges and orbital populations, NBO B2PLYP-D3/6-311++G(d,p) SMD = H_2O

Figure 41. Changes in the charge distribution in the axial and equatorial conformers of 2-fluoro-1,3-dioxane and 2-fluorotetrahydropyran. Numbers in the table correspond to orbital population, in electrons.

First, if one looks at the population of the individual NBO orbitals (tables in the left part of Figure 41), the key premise of the hyperconjugative model is reflected nearly perfectly in their relative populations. For example, as the σ^*_{CF} bond gains 0.05 e^- upon the equatorial-axial transition, the p-type lone pair of oxygen loses the same amount of charge (i.e., 0.05 electrons).

However, if one looks at the *total* charges at an atom, the situation is indeed similar to what is described by Wiberg et al.[20] The total negative charge at F increases by 0.04 e whereas the negative charge at O decreases by only 0.01 e. In other words, 0.03 electrons seem to be missing.

Interestingly, this "loss" is only observed in the gas phase. In water, the discrepancy with the charges on F and O is less alarming - fluorine gets 0.04 electron and oxygen loses just a bit less (0.02 e). This observation suggests that there is an intramolecular redistribution of charges in the gas phase that partially compensates for the charge transfer associated with the $n_O \rightarrow \sigma^*_{CF}$ interaction, activated in the axial conformer. But what can this compensating mechanism be?

An important piece of the puzzle is that the *oxygen lone pair participates at the same time in two anomeric interactions with the two axial substituents*, C2-F and C6-H. It is the second anomeric $n_O \rightarrow \sigma^*_{CH}$ interaction, where the axial C6-H bond serves as an acceptor, that provides the missing components of the puzzle. The positive charge at the axial hydrogen does show an increase by 0.03 e in the axial 2-F THP conformer, which is the exact missing difference in the charge changes for O and F. This observation is consistent with the overall charge redistribution as the competition between two anomeric delocalizations: $n_O \rightarrow \sigma^*_{CF}$ and $n_O \rightarrow \sigma^*_{CH}$. In this scenario, because oxygen gives more electron density to the axial C-F, it has to give less to the adjacent axial C-H. Once the electron checkbook is balanced, fluorine gets 0.04 electron more, hydrogen gets 0.03 electron less, and oxygen loses only 0.01 electron. *As happens in life, the weakest (i.e., the least electronegative) partner in this relay of anomeric interactions loses the most after the trade transaction is completed and electron density is redistributed.*

In the same work, Wiberg offers another puzzle (Figure 42, left).[20] The observation the hydrogen and the fluorine at C2 of 2-fluoro-1,3-dioxane gain nearly the same amount of electron density by switching from the equatorial to the axial position is also surprising in view of the different acceptor abilities of the C-H and C-F antibonding orbitals.[20]

This observation also results from an interplay of electronic effects that goes beyond the simple "one-interaction" model. NBO analysis shows that the mechanisms by which the electron density is increased at the axial (C2)-H and the axial (C2)-F atoms are different. Most of the gained electron density at the axial F is due to the σ^*_{CF} population increase - which is exactly as one would expect as a consequence of the $n_O \rightarrow \sigma^*_{CF}$ negative hyperconjugation! In contrast, the density increase at the axial H comes from two sources: an increase in the σ_{CH} population and an increase in the σ^*_{CH} population. The axial C-H bond has no vicinal hyperconjugative acceptors as it is aligned only with the three donor lone pairs at the three (O,O,F) heteroatoms. As all vicinal $\sigma_{CHeq} \rightarrow \sigma^*$ interactions, which deplete the σ_{CH} orbital of its electron density, are deactivated when the C-H bond is axial, the σ_{CH} population goes back to ~2.0 e (Figure 42). This, more nuanced, description further expands the hyperconjugative picture of anomeric effect.

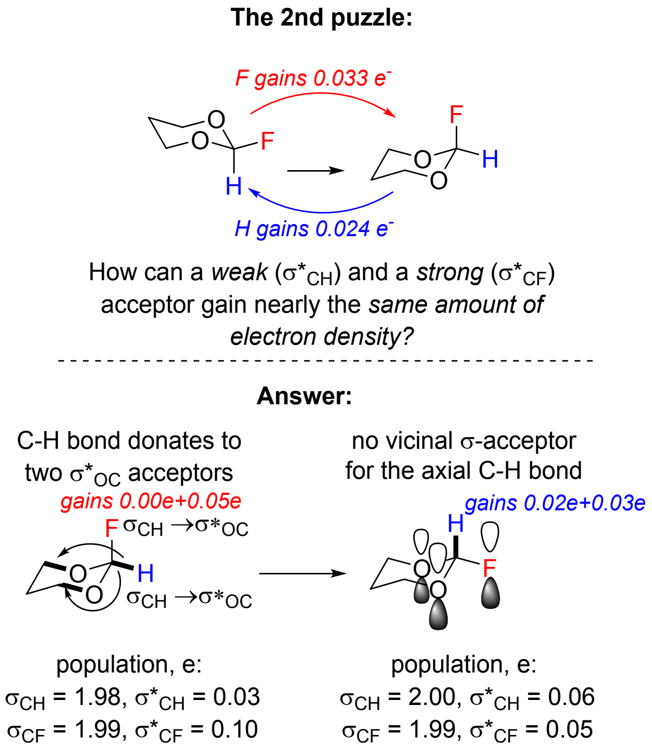


Figure 42. Left: The second Wiberg's puzzle. *Changes* in selected atomic Hirshfeld charges at MP2/aug-cc-pVTZ level upon axial/equatorial flip in 2-F-1,3-dioxane indicate that axial H and axial F get a similar amount of electron density. Right: The absence of vicinal σ-acceptors for the axial C2-H hydrogen in 2-fluoro-1,3-dioxane increases the bonding σ_{CH} NBO population to 2.0 electrons upon equatorial/axial C-H flip. The Hirshfeld and the NBO charges are slightly different but the trends are similar

Clearly, such fundamental discussions are interesting from the conceptual point of view. It is important to keep analyzing AE and other stereoelectronic effects from different perspectives. The above data and discussion reiterate that AE is a complex, multi-component phenomenon where several factors either combine or act against each other in setting up the conformational outcome. Although these alternative explanations do not put in doubt the key role of $n \rightarrow \sigma^*_{CX}$ interaction, they do raise the question whether one should surrender to this complexity and just accept that anomeric effect "is complicated" or whether one should try to distill it into a simpler picture that still retains both the descriptive and the predictive powers.

The individual answers to the above questions may be a matter of taste but they set up the stage for our subsequent discussion where we would like to look at the AE and its components from a practical point of view. Are such dissections into a multitude of small components useful to practicing organic chemists (especially if definitions of steric and electronic factors keep changing)? What model would be the most useful addition to the arsenal of practical tools for reaction design?

The criteria for a useful model: Hyperconjugation as a bridge between structure and reactivity

How important is it to settle these arguments? We think that, although the present discussions are valuable, the future theoretical scrutiny of the anomeric effect would benefit if the following points are considered and addressed.

In addition to quantifying the greatest energetic contributions for both individual and groups of components, is it also worth considering factors that contribute *the most* to the meaningful chemical observables such as structure, spectroscopic properties, and, especially, reactivity?

More generally, it would be helpful to agree on what are the criteria for a useful model. How complex or how simple should such a model be? Is complexity inherently preferable to simplicity or should it be the other way around? These questions are not trivial as illustrated by a quote attributed to Einstein - "Everything should be made *as simple* as possible, *but no simpler*".[178]

If one chooses a simplified model, then which properties of a model should be of primary importance? In addition to having a predictive power, should the model be physically realistic, related to chemical reactivity, describe structural features, etc? Asking the right questions may sometimes be as important as getting the right answers.

Can we describe a complex "full-blooded" quantum system with a model based on a single parameter? Why would a specific parameter be chosen instead of an alternative one? The question of "ambiguity" is a fair test for any model that tries to represent a reality that is not that simple and is not clearly separable into completely independent components. Furthermore, the difficulties in attributing a conformational preference to one specific phenomenon should not be a surprise because, in fact, any "electronic effect" of organic chemistry is a small perturbation on top of very large total electronic energies. Even though an energy contribution on the order of 3 kcal/mol can be quite important from a chemical point of view (e.g., leading to ~1:100 ratio of two products at equilibrium), the same 3 kcal/mol can be a very small *perturbation* on top of a very large overall electronic energies (hundreds of thousands to millions of kcal/mol, depending on the size of the molecules). In a way, isolating an individual effect is similar to determining a captain's weight by weighing the ship with and without him aboard. In order for this treatment to be useful, it has to be coupled with the logical approach to chemical reactivity.

From the literature discussions, one may conclude that for a situation where multiple effects combine to account for the observed trend in *stability*, all such effects are of equal value for predicting *reactivity*. To make it worse, our opinions and perception of molecules are shaped by our methods of study, by our observation tools, by the focus of our attention, and by the underlying conceptual paradigm. Although the conflicting literature descriptions of anomeric effect illustrate it particularly well, this situation is not unique but, rather, typical for stereoelectronic effects.

If the goal is to have an intuitive understanding of what a chemical system is capable of, then the key components of the overall puzzle are *those that can help predict molecular reactivity by responding to an external perturbation in a clear and logical way*. Even when many components add up to define the overall energy (which is always the case for any molecule in any conformation), the hyperconjugative contribution becomes *dominant* as the bonds stretch and angles distort from the equilibrium geometries, e.g., on a path to a transition state or a reactive intermediate!

The hyperconjugative $n_X \rightarrow \sigma^*_{CY}$ interactions are the single dominating effect with *a clear origin and useful predictive value* in the X-C-Y systems. In the following sections, we will show that these interactions can be amplified at key reaction stages where electron demand increases as bonds are stretched and broken. In these situations, focusing on the key stereoelectronic factor provides the greatest predictive power.

Evolution of hyperconjugative interactions in reactions at the anomeric position:

Figure 43 (top) highlights the electronic changes associated with leaving group departure in a typical anomeric system, 2-chloro-1,3-dioxane. As the C-Cl bond elongates, the role of the anomeric $n_O \rightarrow \sigma^*_{C\text{-}Cl}$ interaction increases as the molecule uses electron delocalization to compensate for C-Cl bond breaking and carbocation development. The NBO negative hyperconjugation increases by 4 kcal/mol when the C-Cl bond is stretched by 0.08 Å and by another 5 kcal/mol by one more 0.1 Å increase (total stretching from 1.92 Å to 2.1 Å). At the same time, the C-O distance shortens and the OCCl angle decreases to the Burgi-Dunitz angle as the system starts to resemble an oxacarbenium ion attacked by chloride. These changes illustrate the origin of TS stabilization for C-X scission at an anomeric position.

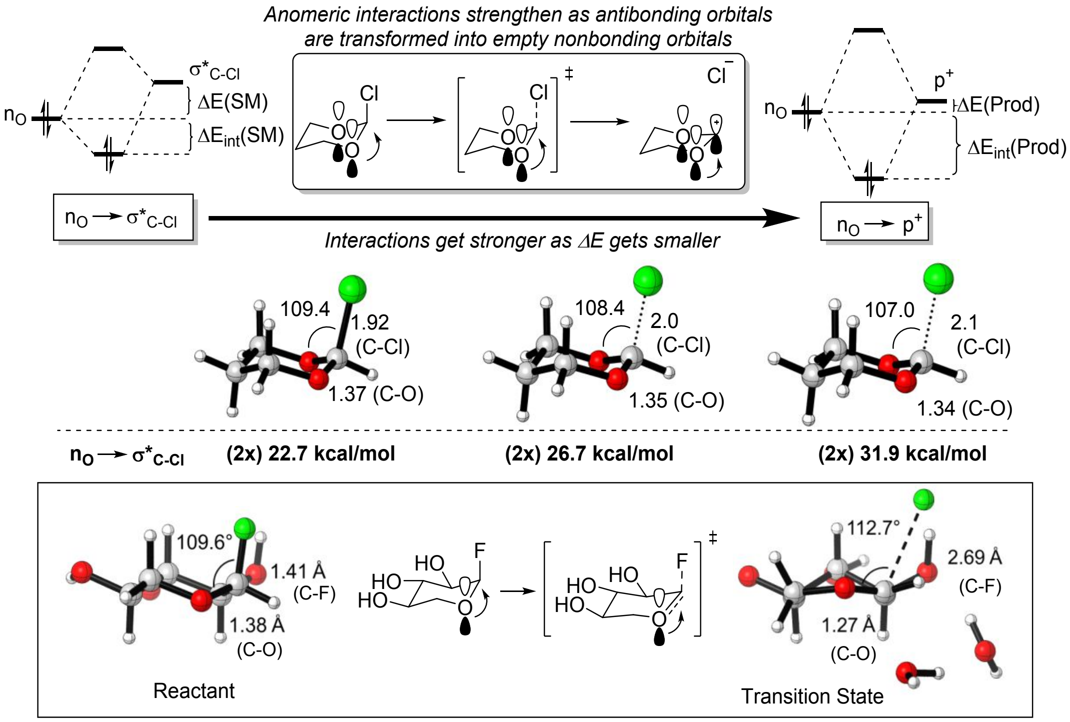


Figure 43. Top: Amplification of anomeric $n_O \rightarrow \sigma^*_{C\text{-}Cl}$ hyperconjugation upon stretching of the C-Cl bond in 2-chloro-1,3-dioxane. Orbital interaction energies are from a 2nd order perturbation NBO analysis. Bottom: structural changes in the TS for C-F bond ionization in a representative anomeric system.

Similar structural changes are apparent in a representative TS for solvolysis in an anomeric system (Figure 43, bottom).[101] As the C-F bond elongates from 1.41 to 1.69 Å in the TS, the C-O bond shortens from 1.38 to 1.27 Å and the C-O-O-C moiety planarizes due to the developing C=O+ character at the reacting carbon. All of these structural changes clearly illustrate the dramatically increasing role of $n_O \rightarrow \sigma^*_{C\text{-}F}$ hyperconjugation in the process of C-F bond ionization.

Relationship between thermodynamic and kinetic effects

The apparent paradox of the anomeric effect (shared by many other stereoelectronic effects) is that stabilization of a molecule is often accompanied by "destabilization" of a bond. In fact, stabilizing effects can amplify a weakness in the molecular armor and facilitate chemical transformations.

A few questions may immediately come to mind: *How can stabilization of a molecule lead to its increased reactivity? Is there a paradox? A breakdown in logic?* The answer is that the interactions which stabilize a molecule may also be active in a transition state that transforms this molecule into something else. If the interaction in the transition state is *enhanced* in comparison to the ground state, then the interaction activates the molecule toward transformations which proceed via this transition state (Figure 44).

This analysis explains how the AE, despite always being stabilizing, can be either activating or deactivating – the overall effect simply depends on where the AE is stronger, in the reactant or the TS. When AE is enhanced in the TS, it manifests itself as *kinetic anomeric effect (KAE).* Such TS stabilization is of primary importance for the control of reaction rate and selectivity, especially in catalysis.

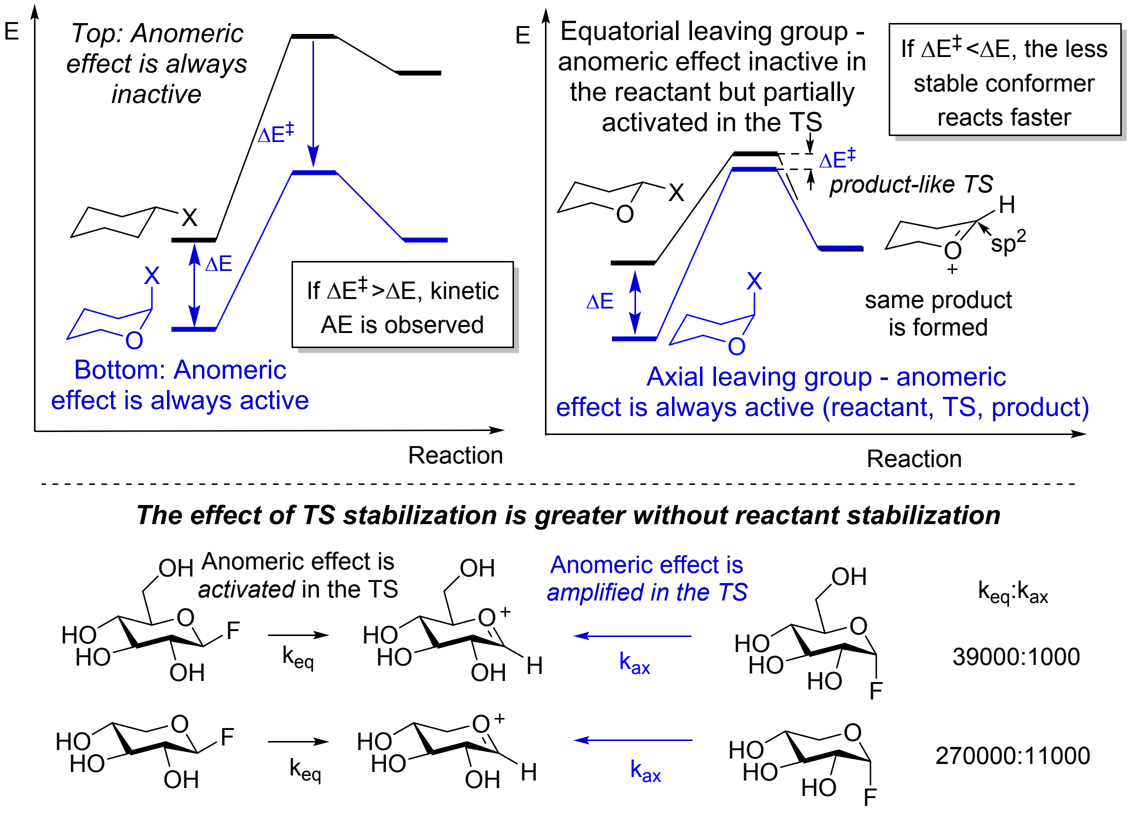


Figure 44. Origin of kinetic anomeric effect in systems that do not interconvert into each other. Top left: Two PES that compare a system with active anomeric stabilization (blue) with a hypothetical system where such interaction is absent (black). In the blue system, anomeric effect is always active (i.e., in the reactant, the TS and the product). Kinetic AE is observed when TS stabilization is greater than the reactant stabilization. Top right: Two PES that compare a system where the anomeric stabilization is active in the reactant and strengthened in the TS (blue) with a system where the anomeric stabilization is absent in the reactant and strengthened in the TS (black). Bottom: Kinetic anomeric effect accelerates reactions more in systems where the transition state stabilization is not partially compensated by reactant stabilization.

For reactants with activated AE, KAE occurs when anomeric stabilization is greater in the TS than in the reactant (Figure 44). However, KAE can also contribute to reactivity of systems where AE is absent in the ground state. In fact, the kinetic assistance from AE can be, paradoxically, stronger in such systems. In the absence of reactant stabilization, even relatively weak anomeric contribution to the TS stability will accelerate the reaction. The latter scenario explains the much faster solvolysis of carbohydrates with an equatorial leaving group in Figure 44, bottom. Such systems do not have significant anomeric stabilization in the reactant but gain such stabilization on the way to the product-looking TS, as the molecule distorts towards the product geometry. After the leaving group departs completely (i.e., the contact or solvent-separated ionic pair gives rise to free cation), the S_N1 product of both axial and equatorial group is the same sp^2-hybridized oxacarbenium cation (Figure 44) with no memory of the initial anomeric configuration.[179]

While Figure 44 illustrates KAE by comparing two systems that do not interconvert under the reaction conditions, the role of stereoelectronic effects in the common case of two rapidly interconverting conformers of different stability and reactivity can be analyzed through the prism of the Curtin-Hammett principle (Figure 45).

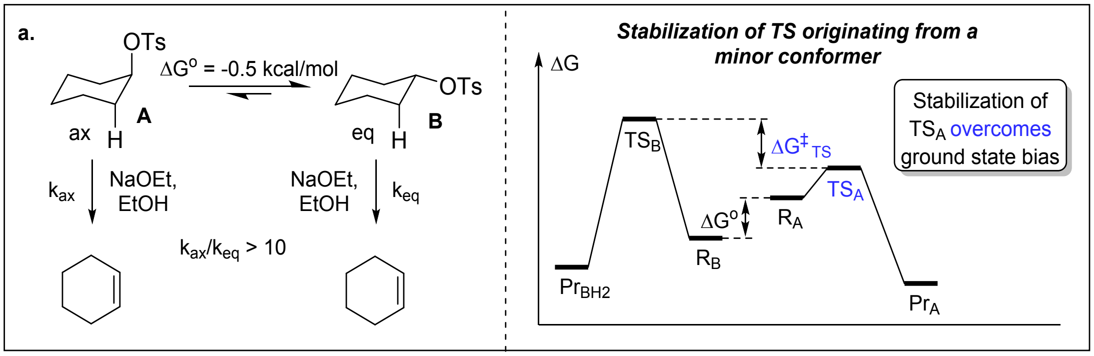
According to the Curtin-Hammett principle, the preferential reaction path is defined by the difference in free energy between the alternative transition states - as long as the reactive conformers can quickly equilibrate.[180] The relative TS energies do not always mirror the difference between the ground state conformers. A preferred molecular structure generally originates from the tug-of-war of multiple electronic, steric, and electrostatic effects. Because of this complexity, it is not unusual for even a potentially significant stereoelectronic interaction to be overridden by a combination of several other effects that, taken together, favor a geometry where this stereoelectronic interaction is either dormant or not fully activated. However, even such “hidden” stereoelectronic interactions can still impact reactivity and define the nature of reaction products as we will illustrate in Figure 45.

For the simple case of two conformers A and B, shown in Figure 45, TS_A may still be the more stable transition state even if B is the most stable reactant conformer. When TS_A is the rate- and product-determining TS, stabilization of B is, in fact, counterproductive. When such stabilization is lost upon the conversion of B to A and then to TS_A, the stabilization of reactant B will slow down the reaction.

Figure 45a shows a case where the reaction proceeds through a minor conformer, disfavored in the ground state. In this case, the stereoelectronic stabilization not available in the more stable of the two ground state conformers is amplified in the TS geometry to an extent where it can overcome the ground state disadvantage. More specifically, although the axial conformer of the OTs-substituted cyclohexane is ~0.5 kcal/mol *higher* in energy than the equatorial conformer, the E2 elimination from the axial conformer proceeds much faster due to the favorable antiperiplanar arrangement between the C-H and C-OTs bonds in the elimination transition state.[181, 182] In this scenario, a stereoelectronic effect (i.e., the $\sigma_{CH} \rightarrow \sigma^*_{CX}$

interaction) that is dormant in the ground state, becomes dominant in the TS as the power of hyperconjugation is enhanced when the two breaking bonds are antiperiplanar to each other.

TS stabilization overcomes the ground state preference



TS stabilization amplifies the ground state preference

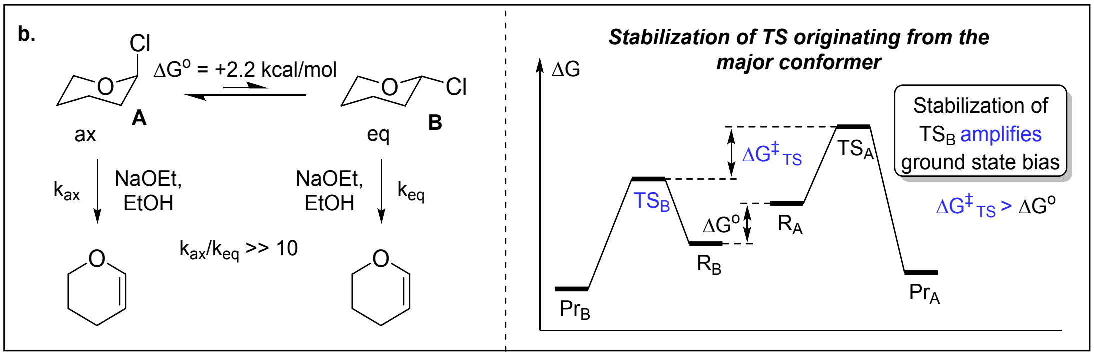


Figure 45. Two Curtin-Hammett scenarios where reacting conformers can quickly interconvert and the reaction can proceed through a TS with the lower absolute energy. In this situation, TS stabilization can: a) overcome unfavorable ground state properties which require a change in conformation to activate the stereoelectronic assistance, b) amplify a ground state stereoelectronic effect—where the more stable conformation allows the stereoelectronic assistance to operate

In an anomeric system (e.g., dehydrohalogenation of 2-chlorotetrahydropyran, Figure 45b), the situation is simpler as the reaction proceeds from the more stable conformer. In this case, the key stereoelectronic effect (the anomeric $n_O \rightarrow \sigma^*_{CCl}$) is already present in the most stable conformer of the reactant. This hyperconjugative interaction is "productive" because it is *amplified* in the TS in comparison to the ground state (i.e., the TS is more stabilized by this interaction than the reactant). This common caveat shouldn't be understated: stabilization of the TS originating from the major conformer by a stereoelectronic effect is only productive when it is *greater* than the stabilization of reactant by the same effect. If a delocalizing interaction stabilizes a ground state structure to a greater extent than the TS, then the reaction will be slowed down by this stabilizing effect ("reactant stabilization").

The classic story summarized in Figure 45 reiterates that even when a stereoelectronic effect is dormant, it can "wake up" and direct the symphony of electronic changes that culminates in a chemical transformation. In other words, even when negative hyperconjugation is not apparent in the ground state conformation, it can be greatly amplified in the TS to impose its defining influence on the observed reaction rate and selectivity. In these scenarios, even a “ghost” of a TS stabilizing interaction can be very helpful to an observer trained to detect stereoelectronic effects.

Conclusions: From anomeric effect to the broad role of hyperconjugation in O-containing organic functional groups

From the above discussion, it is clear that the magnitude of kinetic anomeric effects depends on the degree of “electron deficiency” of breaking bonds at the transition states. Because lone pairs are potent donors, they greatly assist chemical transformations that create an electron deficient center at an adjacent atom. For example, the development of anomeric stabilization continues after the TS on the way to the product, where the stabilizing effect of oxygen can develop fully in the oxarbenium ion. Comparison of hydride affinities of methyl and hydroxymethyl carbonium ions illustrates that, in the gas phase, this stabilization (69 kcal/mol) by an oxygen atom is greater than stabilization provided by allylic resonance (56 kcal/mol).[3] Considering the above, it is not surprising that anomeric effects play an important role in many oxygen-rich systems where electron-deficient intermediates are involved in reactivity.

In fact, this stereoelectronic component doesn’t disappear when its role on the conformational preferences is overridden by a combination of other factors, e.g., when an acceptor group displays an equatorial preference at the anomeric position (i.e., the reverse anomeric effect for the protonated amines).[142, 183]

Molecular stability always depends on multiple factors. Singling one out many can be misleading - unless there is a reason. The role of anomeric effect in reactivity addresses the concern of ambiguity (choosing a single orbital interaction in a complex molecule). It gives a logical reason to choose negative $n_O \rightarrow \sigma^*_{C\text{-}X}$ hyperconjugation out of many orbital interactions and electrostatic contacts that combine in a molecule. It also tells that even if there is no clear dominating effect in the ground state, the situation is likely to change dramatically in the transition state where a C-X bond can be broken near an oxygen atom.

One can consider an analogy to a star player in a hockey or soccer team. Like individual players combining their efforts in a team sport, several factors combine to account for the overall conformational trends. In a routine game (i.e., a stable ground state molecule), the overall balance may be tipped to the winning direction by the rest of the team. However, a true moment of brilliance, something nearly impossible in a difficult situation, more often comes from the star player. It is hyperconjugation that, like Gretzky or Pele, steps in the drastic situations when adjacent chemical bonds break and form. As the result, it is the hyperconjugative contribution that have the greatest predictive power in analyzing chemical reactivity. On a different day, electrostatics can help to nudge molecular energy towards one of the several possible local minima.

Of course, every analogy is imperfect and has its limits, but we hope that it provides a useful perspective for understanding the role of negative hyperconjugation in the diverse manifestations of anomeric reactivity. Of all individual contributions, the $n_X \to \sigma^*_{CY}$ negative hyperconjugation has a disproportionately large impact on chemical reactivity because it allows lone pairs (electron density not involved in the covalent bond formation) serve as a resource for compensating electron-deficiency at an adjacent atom.

When the electronic demand is high (bonds are breaking and molecules are distorted from their equilibrium geometries), the role of orbital interactions increases even when distribution of charges does not change significantly (Figure 46). From that point of view, stereoelectronic effects play a unique predictive power in guiding reaction design and reactivity studies.

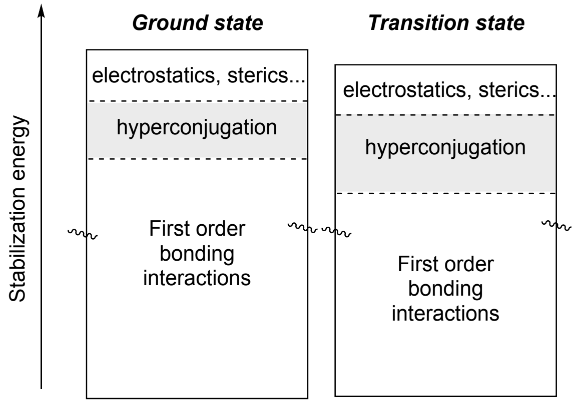


Figure 46. Molecular distortion needed to reach a transition state for a chemical reaction (e.g., stretching a bond) weakens first order (primary) bonding interactions (i.e., direct orbital overlap in chemical bonds) but partially compensates it by increase in secondary bonding interactions (delocalization including hyperconjugation). Such increase is generally larger than changes in the other contributors to the total energy (e.g., electrostatics, sterics, dispersion).

Of course, other components of intramolecular network of interactions can change too. For example, for reactions that are accompanied by shift of electron density, electrostatic contributions adjust as well. However, although the partial charge transfer is a frequent, it is not universal. Furthermore, such changes can proceed it either direction, i.e., either increase or decrease charge separation, so concomitant Coulombic interactions can become either less stabilizing or more stabilizing.

In the companion manuscript,[71] we concentrate on dynamic nature of AE and its role in the reactivity organic functional groups. We will discuss how negative hyperconjugation with the oxygen lone pairs manifests itself in chemical reactivity (Figure 47). The scope of this analysis will extend from simple alcohols and ethers to functionalities with multiple oxygen atoms and complex networks of anomeric interactions (esters, peroxides, carboxylic acid derivatives). The broad analysis of oxygen-containing functional groups will illustrate that the above observations are general and show how chemical structure and reactivity change when a lone pair is aligned with a good σ-acceptor.

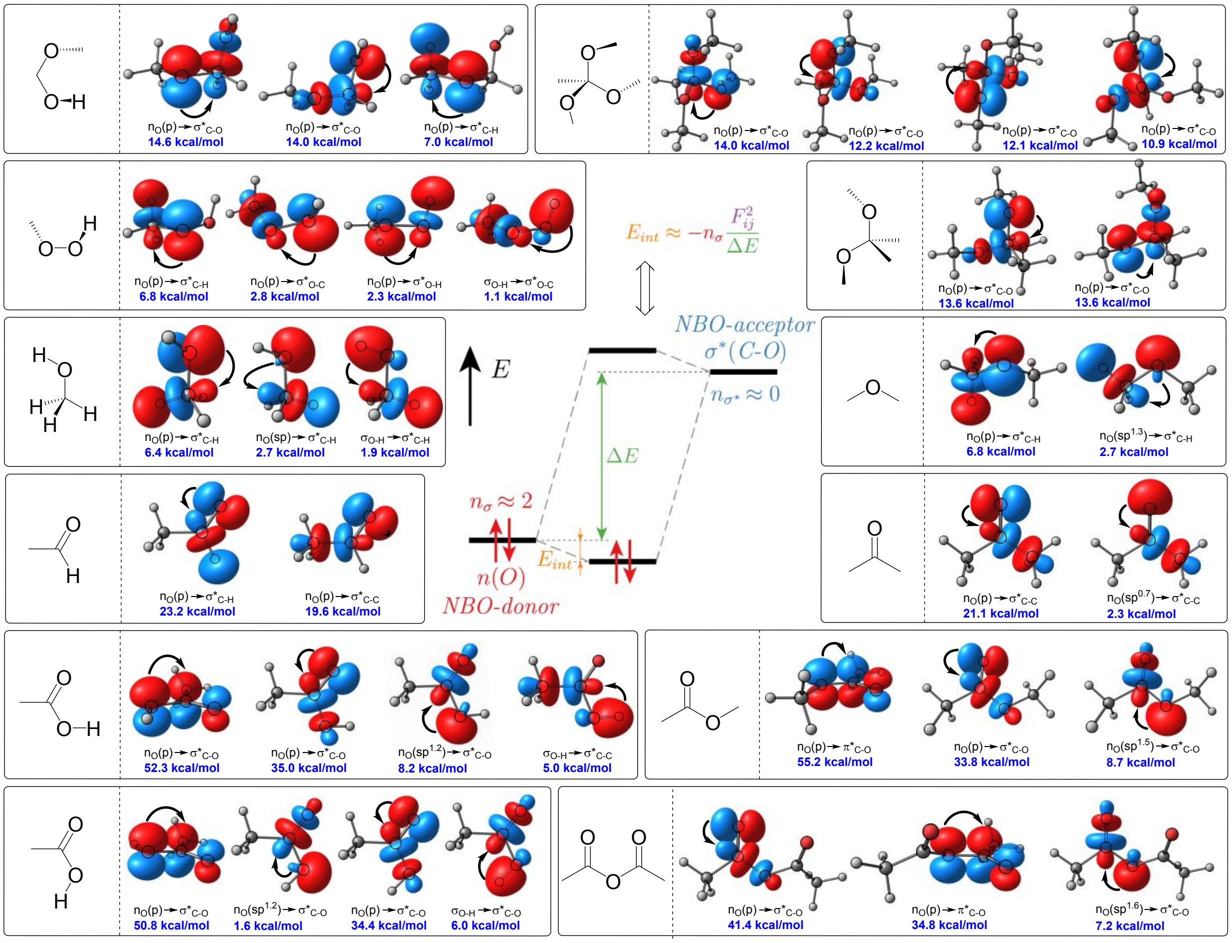


Figure 47. A selection of donor-acceptor anomeric interactions in organic O-functionalities. E_{int} values are computed in the second-order perturbation theory approximation.

Furthermore, the key observations from the classic anomeric systems have much greater implications. One can expand the main conclusions of this discussion from X-C-O- systems to a broad selection of O-containing groups including those that do not contain other heteroatoms (i.e., ethers and alcohols). From this perspective, it is useful to refer the reader to the insightful analysis of Filloux[80] who, when analyzing how language influences our understanding and interpretation of scientific phenomena, suggested to distinguish “anomeric effect” from “anomeric interactions”. It is useful to separate the “anomeric effect”, a cumulative phenomenon effect based on the interplay of orbital, electrostatic, and steric factors from “anomeric interactions”, i.e., stereoelectronic orbital interactions originating from negative hyperconjugation (i.e., the donation from oxygen lone pairs to the antibonding C-X orbitals).

Separating “anomeric effect” from “anomeric interactions” allows one to use the word “anomeric” in more general sense that transcends the historic definition of a conformational effect in the chemistry of carbohydrates.[80] This is useful because hyperconjugative “anomeric interactions” are found in many organic functionalities, both familiar and exotic, as donation from the oxygen lone pairs can affect chemistry of even relatively weak acceptors. In a sister paper,[71] we will illustrate how anomeric interactions assist in breaking C-O, C-C, and C-H bonds and explore more broadly why hyperconjugative anomeric interactions can serve as an indicator of latent reactivity.

Addendum #1: Difference between NBOs and molecular orbitals, or how to find LPs in a molecule

By definition, orbitals are one-electron wavefunctions describing behavior of each electron in the field of all other electrons and nuclei. Although orbitals are not directly measurable, the sum of their squares equals to electron density (Figure 1), which can be studied directly, e.g. via X-ray diffraction.[184] Thus, any unitary transformations which leaves the electron density intact provides a valid set of orbitals representing the system, giving rise to an infinite number of possible orbital sets.

The most common orbitals are the canonical molecular orbitals (usually referred to as molecular orbitals, i.e., the MOs) obtained during a Hartree-Fock calculation, or the Kohn-Sham orbitals derived from a DFT one.[185] The MOs have a nice feature that their energies estimate molecule’s ionization potentials according to the Koopman’s theorem.[186] Because canonical orbitals span the whole molecule, the individual bonds and lone pairs can be hard to see in these orbitals (Figure 1).

Various localization techniques allow construction of orbitals which describe local bonding features such as lone pairs or bonds. Natural Bond Orbitals (NBO)[69] are one of the localized orbitals sets, which correspond to the eigenfunction of the 1st-order reduced density operator[187] with the condition of maximum occupancy. Occupied NBOs represent a localized Lewis structure of the studied molecule. All deviations of the real system correspond to “electron delocalizations”. NBO analysis allows one to estimate delocalization energies – a feature we broadly employ in this review to understand how lone pairs interactions with the surrounding orbitals lead to anomeric effects. Another localized orbitals set can be obtained using Foster-Boys localization[157], which attempts to minimize the spatial extent of orbitals and leads to a drastically different pair of lone-pair orbitals (Figure 1). This symmetric variant of two identical ~sp^3-hybrids is known as “rabbit-ears” and it has been a natural lone pairs representation for many organic chemists.[17] The “p+sp^n“ (e.g., NBO) and the “rabbit-ears” lone pair orbitals are connected via a unitary transformation and lead to identical combined lone pair electron densities (Figure 1).[188-190]

Another approach for locating lone pairs consists in topological analysis of the Laplacian of the electron density[191]; it leads to two symmetric sites of local electron density concentration (Figure 1), which complement the localized orbitals pictures: sites of local concentration are located at each of the “rabbit-ears”, or, alternatively, at the regions in space where the NBOs overlap.

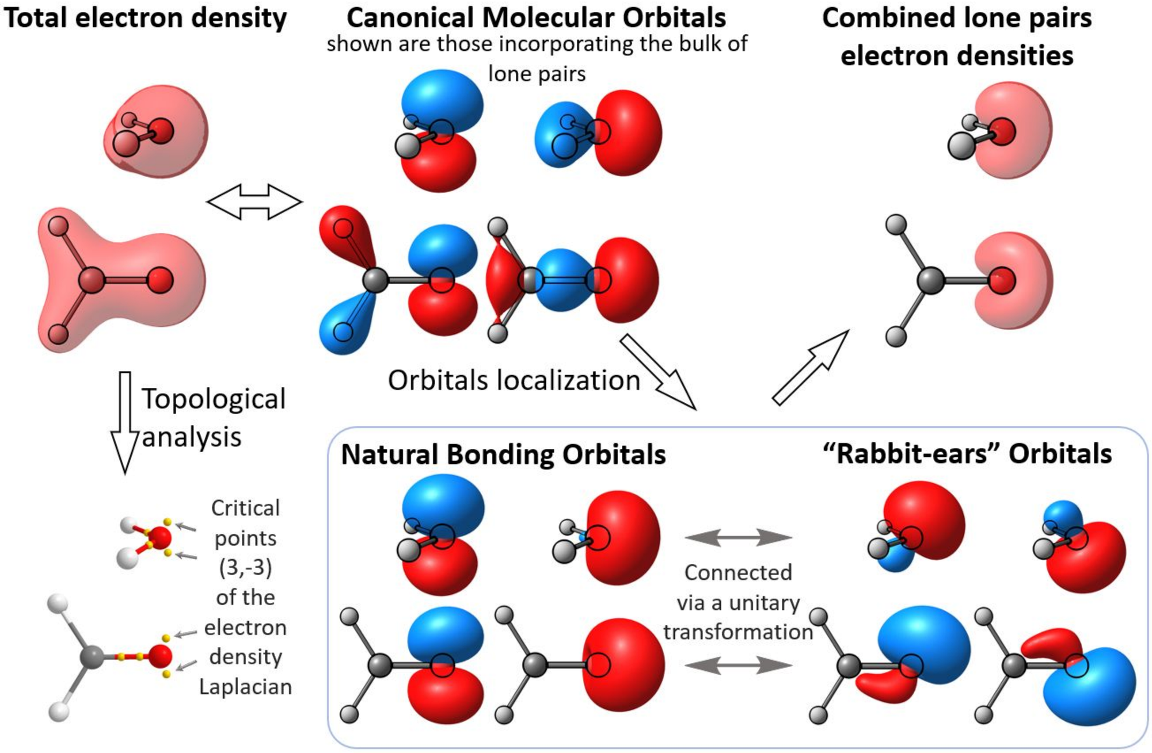


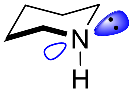
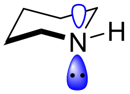
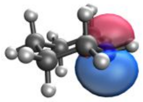
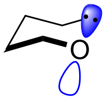
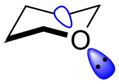
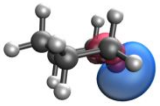
Figure 48. Two approaches to extract lone pairs from molecular wavefunction. NBO-style and “rabbit ears” localized orbitals of oxygen lone pairs along with their interconnection are shown in the rectangle. Electron densities are shown as translucent isosurfaces, and orbitals – as solid ones; all isosurfaces are drawn at the same isovalue. “Rabbit-ears” orbitals were obtained via Foster-Boys localization.

Addendum #2: Are lone pairs made equal?

Although the NBO and “rabbit-ears” lone pairs of oxygen are equivalent in the absence of other orbitals (Figure 48), the situation changes drastically ones we consider their interactions with other orbitals. For an atom with several lone pairs, their donor abilities are proportional to their p-characters: lone pairs with 100% p-character are intrinsically better donors than the respective sp^n hybrids. Thus, lone pairs proliferation into a pure p-orbital interacting strongly with the surrounding orbitals and an “idle” sp^n hybrid happens to be energetically favorable process. In fact, this is the reason why NBO, which searches for the best set of *interacting* orbitals, favors unequal LP orbitals.

Table 1 illustrates that a p-type lone pair of oxygen is comparable in energy to an ~$sp^{4.6}$ lone pair of nitrogen, despite the higher electronegativity and the greater nuclear charge of oxygen.

Table 1. The NBO s-character, hybridization and energy of oxygen and nitrogen lone pairs (X = N, O) in selected saturated heterocycles at the B3LYP/6-31G** level, and the NBO plots of the lone pairs.

	% s-character of Lone Pair	E(X) (in a.u.)	Lone Pair
 Equatorial	18.2 ($sp^{4.6}$)	-0.27	
 Axial	17.9 ($sp^{4.6}$)	-0.27	
 "Axial"	0.03 (p)	-0.27	
 "Equatorial"	44.2 ($sp^{1.3}$)	-0.55	

NBO B3LYP(D3)/6-31G** Int=UltraFine

In tetrahydropyran, the presence of a higher energy p-orbital parallel to the vicinal axial acceptors accounts for the presence of the strong hyperconjugative anomeric $n_O \rightarrow \sigma^*_{C\text{-}Y}$ interaction. NBO analysis, which determines “the best hybrids” describing a Lewis structure, finds two lone pairs of different hybridization in tetrahydropyran: a pure p-orbital and an $sp^{1.3}$ hybrid. The deviation from sp hybridization predicted by an idealized model is explained by the correlation of hybridization and electronegativity, known as Bent's rule.[192, 193]

The higher energy p-lone pair is more readily delocalized than the lower-energy one, so we use it as the 1st approximation in the stereoelectronic analysis of O-systems. Considering only this lone pair can often greatly simplify the stereoelectronic analysis by allowing one to concentrate on a single donor orbital per oxygen where multiple cooperative interactions coexist.[2, 32] There are situations, however, when both lone pairs should be considered, as, for example, in chemistry of esters. Usually, such situations occur when two adjacent functionalities engage in more than one stereoelectronic interaction.

Table 1 also illustrates the noticeable hybridization-imposed differences in the lone pair directionality for O- and N-heterocycles. In tetrahydropyran, the p-type lone pair overlaps noticeably not only with the C-H bond but with the C-C bond too. This is one of the reasons why 1,3-dioxane can benefit from anomeric effect and be more stable than its 1,4-isomer.

Note that due to the lone pair directionality and puckering of the tetrahydropyran, the overlap of the p-type lone pair with the axial C-R substituent is good but imperfect.[194] Several studies of enzyme catalysis highlighted the ability of the enzyme active site to distort the sugar substrates from their lowest energy geometries to the conformations where orbitals interactions that favor anomeric ionization are promoted.[195, 196]

Addendum #3: On the importance and acceptor ability of σ*-orbitals

In the bond-localized orbital description, every σ-bond consists of two orbitals: "bonding" σ and "antibonding" σ*, formed via the in-phase and out-of-phase overlap of atomic orbitals. In other words, the σ* orbitals are as important for the bond formation as σ orbitals - they are inseparable and "created" together as atomic orbitals mix to make a bond.

Even though the antibonding orbitals are not occupied in an idealized Lewis structure, they are crucial for the description of structures and reactivities of real molecules – the "empty orbitals" describe the capacity of molecules to change, e.g., to accept electron density from a donor, providing a basis for delocalizing donor-acceptor interactions, both inter- and intramolecular. Although the antibonding σ* orbitals also important for the ability to participate in photochemical excitation, referring to them as "excited bonds"[19] is inaccurate. We would like to reiterate that each chemical bond is a combination of σ and the σ* orbitals - even in the ground state.

According to NBO analysis, the relative order of acceptor ability of $\sigma^*_{C\text{-}X}$ bonds towards an antiperiplanar C-H bond is determined by the combination of two factors: electronegativity and $\sigma^*_{C\text{-}X}$ energy.[18] As the result, the acceptor ability of the C-X σ-bonds relative to the same donor (an antiperiplanar C-H bond) increases towards the end of a period and down a group as X becomes more electronegative. However, changes in the acceptor ability in groups are opposite to the changes in electronegativity of X and in the C-X bond polarization, following instead the decrease in the energy of $\sigma^*_{C\text{-}X}$ orbitals. Even when polarity of C-X bonds decreases, the C-X bond can still function as a good acceptor as long as the $\sigma^*_{C\text{-}X}$ has low energy (Figure 49).

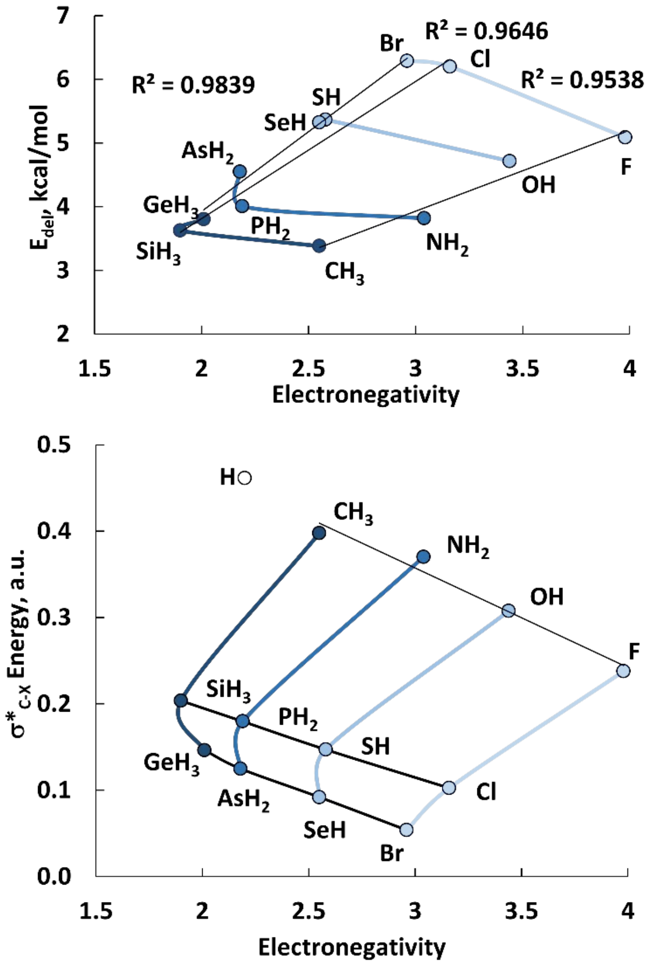


Figure 49. Top: Correlation of energy of $\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}X}$ interaction, E_{del} with electronegativity of element X in substituted ethanes, CH_3CH_2X. Bottom: Correlation of energy of $\sigma^*_{C\text{-}X}$ orbitals with electronegativity of element X in substituted ethanes, CH_3CH_2X. Adopted with permission from ref. [2].

Acknowledgement

I. A. thanks Prof. N. Williams for generous hospitality and fruitful discussions during a six-month stay at the University of Sheffield and to the US-UK Fulbright Fellowship that made this stay possible, to M. Abdo for his contributions to the preliminary version of this manuscript, and to Professors M. Yarie and M. A. Zolfigol (Bu-Ali Sina University) for helpful discussions and initiating this review. I.A. is also grateful to the National Science Foundation for the financial support of research at FSU (CHE-1800329 and CHE-2102579). M.G.M. thanks Dr. I. S. Bushmarinov for fruitful discussions. M.G.M. and N.V.K. are grateful to the Russian Science Foundation for financial support (grant #19-13-00238). Part of quantum chemical calculations were performed with the financial support from Ministry of Science and Higher Education of the Russian Federation. M.G.M. and N.V.K. also acknowledge computing resources provided by the Federal Collective Usage Center 'Complex for Simulation and Data Processing for Mega-science Facilities at NRC "Kurchatov Institute"' (http://ckp.nrcki.ru, accessed 11/15/2020) and by the shared HPC facilities at Lomonosov Moscow State University [V. Sadovnichy, A. Tikhonravov, V. Voevodin and V. Opanasenko, in Contemporary high performance computing: From petascale toward exascale, CRC Press, Boca Raton, USA, 2013, pp. 283–307]. L. K. is grateful to the National Science Foundation for the Graduate Research Fellowship.

References and Notes

1. Hoffmann, R.; Shaik, S.; Hiberty, P. C., A Conversation on VB vs MO Theory: A Never-Ending Rivalry? *Accounts of Chemical Research* **2003,** *36* (10), 750-756.

2. Alabugin, I. V., *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*. Wiley: 2016; p 392.

3. Alabugin, I. V.; Dos Passos Gomes, G.; Abdo, M. A., Hyperconjugation. *WIREs Computational Molecular Science* **2019,** *9* (2), e1389.

4. Mullins, J., Hyperconjugation: A More Coherent Approach. *Journal of Chemical Education* **2012,** *89* (7), 834-836.

5. Ferreira, R. C., Hyperconjugation: An elementary approach. *J. Chem. Educ.* **1952,** *29* (11), 554-555.

6. Gomes, G. d. P.; Alabugin, I., Stereoelectronic Effects: Analysis by Computational and Theoretical Methods. In *Applied Theoretical Organic Chemistry*, WORLD SCIENTIFIC (EUROPE): 2017; pp 451-502.

7. Mo, Y.; Jiao, H.; Schleyer, P. V. R., Hyperconjugation Effect in Substituted Methyl Boranes: An Orbital Deletion Procedure Analysis. *J. Org. Chem.* **2004,** *69* (10), 3493-3499.

8. Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry Part A: Structure and Mechanisms*. 5 ed.; Springer US: 2007; p 1199.

9. Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry Part B: Reaction and Synthesis*. 5 ed.; Springer US: 2007; p 1321.

10. Kemnitz, C. R., Electron Delocalization Explains much of the Branching and Protobranching Stability. *Chemistry – A European Journal* **2013,** *19* (33), 11093-11095.

11. Gronert, S., Electron Delocalization Is Not a Satisfactory Explanation for the Preference for Branching in the Alkanes. *Chemistry – A European Journal* **2013,** *19* (33), 11090-11092.

12. Wu, J. I. C.; Wang, C.; McKee, W. C.; von Ragué Schleyer, P.; Wu, W.; Mo, Y., On the large σ-hyperconjugation in alkanes and alkenes. *Journal of Molecular Modeling* **2014,** *20* (6), 2228.

13. Kemnitz, C. R.; Mackey, J. L.; Loewen, M. J.; Hargrove, J. L.; Lewis, J. L.; Hawkins, W. E.; Nielsen, A. F., Origin of Stability in Branched Alkanes. *Chemistry – A European Journal* **2010,** *16* (23), 6942-6949.

14. Lambert, J. B.; Ciro, S. M., The Interaction of π Orbitals with a Carbocation over Three σ Bonds. *The Journal of Organic Chemistry* **1996,** *61* (6), 1940-1945.

15. Windsor, I. W.; Gold, B.; Raines, R. T., An n→π* Interaction in the Bound Substrate of Aspartic Proteases Replicates the Oxyanion Hole. *ACS Catalysis* **2019,** *9* (2), 1464-1471.

16. Deslongchamps, P., *Stereoelectronic effects in organic chemistry*. Pergamon Press: Oxford Oxfordshire, 1983.

17. Kirby, A. J., *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*. Springer, Berlin, Heidelberg: 1983.

18. Alabugin, I. V.; Zeidan, T. A., Stereoelectronic Effects and General Trends in Hyperconjugative Acceptor Ability of σ Bonds. *Journal of the American Chemical Society* **2002,** *124* (12), 3175-3185.

19. Mulliken, R. S.; Rieke, C. A.; Brown, W. G., Hyperconjugation. *Journal of the American Chemical Society* **1941,** *63* (1), 41-56.

20. Wiberg, K. B.; Bailey, W. F.; Lambert, K. M.; Stempel, Z. D., The Anomeric Effect: It's Complicated. *The Journal of Organic Chemistry* **2018,** *83* (9), 5242-5255.

21. Wang, C.; Ying, F.; Wu, W.; Mo, Y., How solvent influences the anomeric effect: roles of hyperconjugative versus steric interactions on the conformational preference. *J Org Chem* **2014,** *79* (4), 1571-81.

22. Wang, C.; Chen, Z.; Wu, W.; Mo, Y., How the Generalized Anomeric Effect Influences the Conformational Preference. *Chemistry – A European Journal* **2013,** *19* (4), 1436-1444.

23. Ferro-Costas, D.; Mosquera, R. A., Excluding hyperconjugation from the Z conformational preference and investigating its origin: formic acid and beyond. *Physical Chemistry Chemical Physics* **2015,** *17* (40), 26946-26954.

24. Ferro-Costas, D.; Vila, A.; Mosquera, R. A., Anomeric Effect in Halogenated Methanols: A Quantum Theory of Atoms in Molecules Study. *The Journal of Physical Chemistry A* **2013,** *117* (7), 1641-1650.

25. Ferro-Costas, D.; Mosquera, R. A., Complementarity of QTAIM and ELF Partitions: Deeper Understanding of the Anomeric Effect. *Journal of Chemical Theory and Computation* **2013,** *9* (11), 4816-4824.

26. Ferro-Costas, D.; Otero, N.; Graña, A. M.; Mosquera, R. A., A QTAIM-based energy partitioning for understanding the physical origin of conformational preferences: Application to the Z effect in O=C-X-R and related units. *Journal of Computational Chemistry* **2012,** *33* (32), 2533-2543.

27. Vila, A.; Estévez, L.; Mosquera, R. A., Influence of the Solvent on the Charge Distribution of Anomeric Compounds. *The Journal of Physical Chemistry A* **2011,** *115* (10), 1964-1970.

28. Vila, A.; Mosquera, R. A., QTAIM explanation of the anomeric effect in the O–C–O unit II: 2-Methoxyoxane and 2,2-dimethoxypropane. *Chemical Physics Letters* **2007,** *443* (1), 22-28.

29. Vila, A.; Mosquera, R. A., Atoms in molecules interpretation of the anomeric effect in the O--C--O unit. *J Comput Chem* **2007,** *28* (9), 1516-1530.

30. Juaristi, E.; Cuevas, G., Recent Studies of the Anomeric Effect. *Tetrahedron* **1992,** *48* (24), 5019-5087.

31. Mo, Y., Computational evidence that hyperconjugative interactions are not responsible for the anomeric effect. *Nature Chemistry* **2010,** *2* (8), 666-671.

32. Wiberg, K. B.; Rablen, P. R., Origin of the stability of carbon tetrafluoride: negative hyperconjugation reexamined. *Journal of the American Chemical Society* **1993,** *115* (2), 614-625.

33. Edward, J., Chem. Ind.(London). **1955**.

34. Cramer, C. J.; Kelterer, A.-M.; French, A. D., When anomeric effects collide. *Journal of Computational Chemistry* **2001,** *22* (11), 1194-1204.

35. Deslongchamps, P., Intramolecular Strategies and Stereoelectronic Effects - Glycosides Hydrolysis Revisited. *Pure and Applied Chemistry* **1993,** *65* (6), 1161-1178.

36. Franck, R. W., A revision of the value for the anomeric effect. *Tetrahedron* **1983,** *39* (20), 3251-3252.

37. Schalley, C. A.; Harvey, J. N.; Schröder, D.; Schwarz, H., Ether Oxides: A New Class of Stable Ylides? A Theoretical Study of Methanol Oxide and Dimethyl Ether Oxide. *The Journal of Physical Chemistry A* **1998,** *102* (6), 1021-1035.

38. Passos Gomes, G. D.; Vera Vil'; Alexander Terent'Ev; V. Alabugin, I., Stereoelectronic source of the anomalous stability of bis-peroxides. *Chemical Science* **2015,** *6* (12), 6783-6791.

39. Jones, R. O., Density functional theory: Its origins, rise to prominence, and future. *Reviews of Modern Physics* **2015,** *87* (3), 897-923.

40. Adamo, C.; Barone, V., Toward reliable density functional methods without adjustable parameters: The PBE0 model. *The Journal of Chemical Physics* **1999,** *110* (13), 6158-6170.

41. Becke, A. D., Density-functional thermochemistry. III. The role of exact exchange. *The Journal of Chemical Physics* **1993,** *98* (7), 5648-5652.

42. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J., Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *The Journal of Physical Chemistry* **1994,** *98* (45), 11623-11627.

43. Zhao, Y.; Truhlar, D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theoretical Chemistry Accounts* **2008,** *120* (1), 215-241.

44. Nam, S.; Cho, E.; Sim, E.; Burke, K., Explaining and Fixing DFT Failures for Torsional Barriers. *The Journal of Physical Chemistry Letters* **2021,** *12* (11), 2796-2804.

45. Zhao, Y.; Schultz, N. E.; Truhlar, D. G., Design of Density Functionals by Combining the Method of Constraint Satisfaction with Parametrization for Thermochemistry, Thermochemical Kinetics, and Noncovalent Interactions. *Journal of Chemical Theory and Computation* **2006,** *2* (2), 364-382.

46. Reed, A. E.; Schleyer, P. v. R., The anomeric effect with central atoms other than carbon. 2. Strong interactions between nonbonded substituents in mono- and polyfluorinated first- and second-row amines, FnAHmNH2. *Inorganic Chemistry* **1988,** *27* (22), 3969-3987.

47. David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R., Superjacent orbital control. Interpretation of the anomeric effect. *Journal of the American Chemical Society* **1973,** *95* (11), 3806-3807.

48. Politanskaya, L. V.; Selivanova, G. A.; Panteleeva, E. V.; Tretyakov, E. V.; Platonov, V. E.; Nikul'shin, P. V.; Vinogradov, A. S.; Zonov, Y. V.; Karpov, V. M.; Mezhenkova, T. V.; Vasilyev, A. V.; Koldobskii, A. B.; Shilova, O. S.; Morozova, S. M.; Burgart, Y. V.; Shchegolkov, E. V.; Saloutin, V. I.; Sokolov, V. B.; Aksinenko, A. Y.; Nenajdenko, V. G.; Moskalik, M. Y.; Astakhova, V. V.; Shainyan, B. A.; Tabolin, A. A.; Ioffe, S. L.; Muzalevskiy, V. M.; Balenkova, E. S.; Shastin, A. V.; Tyutyunov, A. A.; Boiko, V. E.; Igumnov, S. M.; Dilman, A. D.; Adonin, N. Y.; Bardin, V. V.; Masoud, S. M.; Vorobyeva, D. V.; Osipov, S. N.; Nosova, E. V.; Lipunova, G. N.; Charushin, V. N.; Prima, D. O.; Makarov, A. G.; Zibarev, A. V.; Trofimov, B. A.; Sobenina, L. N.; Belyaeva, K. V.; Sosnovskikh, V. Y.; Obydennov, D. L.; Usachev, S. A., Organofluorine chemistry: promising growth areas and challenges. *Russ Chem Rev+* **2019,** *88* (5), 425-569.

49. Wiberg, K. B.; Rablen, P. R., Methoxymethane C–O Bond Strengths: Do Their Changes Result from Hyperconjugation or Polar Effects? *The Journal of Physical Chemistry A* **2018,** *122* (28), 6021-6025.

50. Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C., Synthesis and crystal structure of an optically active, internally coordinated alkylchloroborane. The boron-centered anomeric effect. *Journal of the American Chemical Society* **1985,** *107* (24), 7167-7172.

51. Wilcox, C. F.; Bauer, S. H., DFT calculations of thermochemical and structural parameters of tetracyanohydrazine and related tetrasubstituted hydrazines. *Journal of Molecular Structure: THEOCHEM* **2003,** *625* (1), 1-8.

52. Juaristi, E.; Cruz-Sanchez, J. S., Synthesis and conformation of 4,4,5,5-tetramethyl-1,2-dithiane mono-S-oxide. *The Journal of Organic Chemistry* **1988,** *53* (14), 3334-3338.

53. Taira, K.; Mock, W. L.; Gorenstein, D. G., Experimental tests of the stereoelectronic effect at phosphorus: nucleophilic reactivity of phosphite esters. *Journal of the American Chemical Society* **1984,** *106* (25), 7831-7835.

54. Ruben, E. A.; Plumley, J. A.; Chapman, M. S.; Evanseck, J. D., Anomeric Effect in “High Energy” Phosphate Bonds. Selective Destabilization of the Scissile Bond and Modulation of the Exothermicity of Hydrolysis. *Journal of the American Chemical Society* **2008,** *130* (11), 3349-3358.

55. Banavali, N. K.; MacKerell, A. D., Reevaluation of Stereoelectronic Contributions to the Conformational Properties of the Phosphodiester and N3‘-Phosphoramidate Moieties of Nucleic Acids. *Journal of the American Chemical Society* **2001,** *123* (28), 6747-6755.

56. Imperio, D.; Del Grosso, E.; Fallarini, S.; Lombardi, G.; Panza, L., Anomeric sugar boronic acid analogues as potential agents for boron neutron capture therapy. *Beilstein J Org Chem* **2019,** *15*, 1355-1359.

57. Leitz, D.; Bayer, M. C.; Morgenstern, Y.; Zischka, F.; Kornath, A. J., Tuning the Anomeric Effect in Sulfamide with Superacids. *Chemistry – A European Journal* **2018,** *24* (59), 15825-15830.

58. Scholl, K.; Dillashaw, J.; Timpy, E.; Lam, Y.-h.; DeRatt, L.; Benton, T. R.; Powell, J. P.; Houk, K. N.; Morgan, J. B., Quinine-Promoted, Enantioselective Boron-Tethered Diels–Alder Reaction by Anomeric Control of Transition-State Conformation. *The Journal of Organic Chemistry* **2018,** *83* (10), 5756-5765.

59. Lebedev, V. L.; Dolin, S. P., Anomeric effect and structure of Si(OH)4 and related molecular systems. *Theoretical and Experimental Chemistry* **1991,** *27* (4), 421-423.

60. Zhu, F.; Walczak, M. A., Stereochemistry of transition metal complexes controlled by the metallo-anomeric effect. *Journal of the American Chemical Society* **2020**.

61. Lemieux, R. U., Effects of unshared pairs of electrons and their solvation on conformational equilibria. *Pure and Applied Chemistry* **1971,** *25* (3), 527.

62. Cuevas, G., Hydrogen Bond Type Contributions to the Anomeric Effect in S−C−P(O) and S−C−P(S) Segments. *Journal of the American Chemical Society* **2000,** *122* (4), 692-698.

63. Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ohtaki, R.; Ueda, K.; Suezawa, H.; Umezawa, Y.; Nishio, M., The anomeric effect revisited. A possible role of the CH/n hydrogen bond. *Carbohydrate Research* **2007,** *342* (9), 1202-1209.

64. Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ueda, K.; Suezawa, H.; Nishio, M., The origin of the generalized anomeric effect: possibility of CH/n and CH/pi hydrogen bonds. *Carbohydr Res* **2009,** *344* (10), 1225-9.

65. Piscelli, B. A.; Sanders, W.; Yu, C.; Al Maharik, N.; Lebl, T.; Cormanisch, R. A.; O'Hagan, D., Fluorine induced pseudo-anomeric effects in methoxycyclohexanes through electrostatic 1,3-diaxial interactions. *Chemistry – A European Journal* **2020**.

66. Altona, C.; Knobler, C.; Romers, C., The conformation of non-aromatic ring compounds. VII. Crystal structure of trans-2,5-dichloro-1,4-dioxane at 125degreesC. *Acta Crystallographica* **1963,** *16* (12), 1217-1225.

67. Romers, C.; Altona, C.; Buys, H. R.; Havinga, E., Geometry and Conformational Properties of Some Five- and Six-Membered Heterocyclic Compounds Containing Oxygen or Sulfur. In *Topics in Stereochemistry*, 1969; pp 39-97.

68. Petillo, P. A.; Lerner, L. E., Origin and Quantitative Modeling of Anomeric Effect. In *The Anomeric Effect and Associated Stereoelectronic Effects*, American Chemical Society: 1993; Vol. 539, pp 156-175.

69. Glendening, E. D.; Landis, C. R.; Weinhold, F., Natural bond orbital methods. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2012,** *2* (1), 1-42.

70. Yaremenko, I. A.; Radulov, P. S.; Medvedev, M. G.; Krivoshchapov, N. V.; Belyakova, Y. Y.; Korlyukov, A. A.; Ilovaisky, A. I.; Terent'ev, A. O.; Alabugin, I. V., How to Build Rigid Oxygen-Rich Tricyclic Heterocycles from Triketones and Hydrogen Peroxide: Control of Dynamic Covalent Chemistry with Inverse α-Effect. *J Am Chem Soc* **2020**.

71. Alabugin, I. V.; Kuhn, L. R.; Medvedev, M. G.; Krivoshchapov, N. V.; Vil', V. A.; Yaremenko, I. A.; Mehaffy, P.; Yarie, M.; Terent'ev, A. O.; Zolfigol, M. A., Stereoelectronic power of oxygen in control of chemical reactivity: analysis through the prism of the anomeric effect. *Chemical Society Reviews* **2020, Submitted**.

72. Parr, R. G.; Chattaraj, P. K., Principle of maximum hardness. *Journal of the American Chemical Society* **1991,** *113* (5), 1854-1855.

73. Pearson, R. G., Recent advances in the concept of hard and soft acids and bases. *Journal of Chemical Education* **1987,** *64* (7), 561.

74. Hati, S.; Datta, D., Anomeric effect and hardness. *The Journal of Organic Chemistry* **1992,** *57* (22), 6056-6057.

75. Nori-Shargh, D.; Mousavi, S. N.; Tale, R.; Yahyaei, H., Hyperconjugative interactions are the main responsible for the anomeric effect: a direct relationship between the hyperconjugative anomeric effect, global hardness and zero-point energy. *Struct Chem* **2016,** *27* (6), 1753-1768.

76. Geerlings, P.; Chamorro, E.; Chattaraj, P. K.; De Proft, F.; Gázquez, J. L.; Liu, S.; Morell, C.; Toro-Labbé, A.; Vela, A.; Ayers, P., Conceptual density functional theory: status, prospects, issues. *Theoretical Chemistry Accounts* **2020,** *139* (2), 36.

77. Ferro-Costas, D.; Vila, A.; Mosquera, R. A., Anomeric Effect in Halogenated Methanols: A Quantum Theory of Atoms in Molecules Study. *J. Phys. Chem. A* **2013,** *117* (7), 1641-1650.

78. Vila, A.; Mosquera, R. A., QTAIM explanation of the anomeric effect in the O–C–O unit II: 2-Methoxyoxane and 2,2-dimethoxypropane. *Chemical Physics Letters* **2007,** *443* (1-3), 22-28.

79. Vila, A.; Mosquera, R. A., Atoms in molecules interpretation of the anomeric effect in the O—C—O unit. *J. Comput. Chem.* **2007,** *28* (9), 1516-1530.

80. Filloux, C. M., The Problem of Origins and Origins of the Problem: Influence of Language on Studies Concerning the Anomeric Effect. *Angewandte Chemie International Edition* **2015,** *54* (31), 8880-8894.

81. Lemieux, R. U., Some Implications in Carbohydrate Chemistry of Theories Relating to the Mechanisms of Replacement Reactions. In *Advances in Carbohydrate Chemistry*, Wolfrom, M. L., Ed. Academic Press: 1954; Vol. 9, pp 1-57.

82. Pigman, W.; Isbell, H. S., Mutarotation of Sugars in Solution.: Part I: History, Basic Kinetics, and Composition of Sugar Solutions. In *Advances in Carbohydrate Chemistry*, Wolfrom, M. L.; Tipson, R. S., Eds. Academic Press: 1968; Vol. 23, pp 11-57.

83. Lemieux, R. U.; Pavia, A. A.; Martin, J. C.; Watanabe, K. A., Solvation effects on conformational equilibria. Studies related to the conformational properties of 2-methoxytetrahydropyran and related methyl glycopyranosides. *Canadian Journal of Chemistry* **1969,** *47* (23), 4427-4439.

84. Wiberg, K. B.; Marquez, M., The Energy Components of the Anomeric Effect for 2-Methoxytetrahydropyran - an Experimental Comparison of the Gas-Phase and Solutions. *J Am Chem Soc* **1994,** *116* (5), 2197-2198.

85. Eckert, J.; Draznieks, C. M.; Cheetham, A. K., Direct Observation of Host−Guest Hydrogen Bonding in the Zeolite NaY/Chloroform System by Neutron Scattering. *Journal of the American Chemical Society* **2002,** *124* (2), 170-171.

86. Koichi Matsuo; Kunihiko Gekko, Vacuum-ultraviolet circular dichroism study of saccharides by synchrotron radiation spectrophotometry. *Carbohydrate Research* **2004,** *339* (3), 591-597.

87. Fuchs, B.; Ellencweig, A.; Tartakovsky, E.; Aped, P., Solvent Polarity and the Anomeric Effect. *Angewandte Chemie International Edition in English* **1986,** *25* (3), 287-289.

88. Freitas, M. P., The anomeric effect on the basis of natural bond orbital analysis. *Org Biomol Chem* **2013,** *11* (17), 2885-90.

89. Ensing, B.; Tiwari, A.; Tros, M.; Hunger, J.; Domingos, S. R.; Pérez, C.; Smits, G.; Bonn, M.; Bonn, D.; Woutersen, S., On the origin of the extremely different solubilities of polyethers in water. *Nat Commun* **2019,** *10* (1), 2893.

90. Juaristi, E.; Gomes, G. D.; Terent'ev, A. O.; Notario, R.; Alabugin, I. V., Stereoelectronic Interactions as a Probe for the Existence of the Intramolecular alpha-Effect. *Journal of the American Chemical Society* **2017,** *139* (31), 10799-10813.

91. Vil, V. A.; Gomes, G. D.; Bityukov, O. V.; Lyssenko, K. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O., Interrupted Baeyer-Villiger Rearrangement: Building A Stereoelectronic Trap for the Criegee Intermediate. *Angew Chem Int Edit* **2018,** *57* (13), 3372-3376.

92. Vil, V. A.; Barsegyan, Y. A.; Kuhn, L.; Ekimova, M. V.; Semenov, E. A.; Korlyukov, A. A.; Terent'ev, A. O.; Alabugin, I. V., Synthesis of unstrained Criegee intermediates: inverse α-effect and

other protective stereoelectronic forces can stop Baeyer–Villiger rearrangement of γ-hydroperoxy-γ-peroxylactones. *Chemical Science* **2020,** *11* (20), 5313-5322.

93. Yaremenko, I. A.; Radulov, P. S.; Medvedev, M. G.; Krivoshchapov, N. V.; Belyakova, Y. Y.; Korlyukov, A. A.; Ilovaisky, A. I.; Terent'Ev, A. O.; Alabugin, I. V., How to Build Rigid Oxygen-Rich Tricyclic Heterocycles from Triketones and Hydrogen Peroxide: Control of Dynamic Covalent Chemistry with Inverse α-Effect. *Journal of the American Chemical Society* **2020**.

94. Yaremenko, I. A.; Belyakova, Y. Y.; Radulov, P. S.; Novikov, R. A.; Medvedev, M. G.; Krivoshchapov, N. V.; Korlyukov, A. A.; Alabugin, I. V.; Terent'ev, A. O., Marriage of Peroxides and Nitrogen Heterocycles: Selective Three-Component Assembly, Peroxide-Preserving Rearrangement, and Stereoelectronic Source of Unusual Stability of Bridged Azaozonides. *Journal of the American Chemical Society* **2021,** *143* (17), 6634-6648.

95. Praly, J.-P.; Lemieux, R. U., Influence of solvent on the magnitude of the anomeric effect. *Canadian Journal of Chemistry* **1987,** *65* (1), 213-223.

96. Medvedev, M. G.; Bushmarinov, I. S.; Lyssenko, K. A., Z-effect reversal in carboxylic acid associates. *Chem Commun* **2016,** *52* (39), 6593-6596.

97. Goodman, L.; Gu, H.; Pophristic, V., Flexing analysis of ethane internal rotation energetics. *The Journal of Chemical Physics* **1999,** *110* (9), 4268-4275.

98. Alabugin, I. V.; Bresch, S.; Gomes, G. D., Orbital hybridization: a key electronic factor in control of structure and reactivity. *J Phys Org Chem* **2015,** *28* (2), 147-162.

99. Paulsen, H.; Luger, P.; Heiker, F., Anomeric Effect, Origin and Consequences. A CS Symposium Series, herausgegeben von WA SZAREK & D. HORTON, S. 63-79. Washington: American Chemical Society: 1979.

100. Leroux, F.; Jeschke, P.; Schlosser, M., α-Fluorinated Ethers, Thioethers, and Amines: Anomerically Biased Species. *Chem Rev* **2005,** *105* (3), 827-856.

101. Lee, S. S.; Greig, I. R.; Vocadlo, D. J.; McCarter, J. D.; Patrick, B. O.; Withers, S. G., Structural, Mechanistic, and Computational Analysis of the Effects of Anomeric Fluorines on Anomeric Fluoride Departure in 5-Fluoroxylosyl Fluorides. *Journal of the American Chemical Society* **2011,** *133* (40), 15826-15829.

102. Jackson, R. F. W.; Dunn, S. F. C.; McCamley, A.; Clegg, W., Synthesis and crystal structures of 2-substituted-2-phenylsulfonyloxiranes: evidence for a generalised anomeric effect in 2-phenylsulfonyloxiranes. *Organic & Biomolecular Chemistry* **2003,** *1* (14), 2527-2530.

103. Chandrasekhar, S.; Mukherjee, S., An encaged σ∗ orbital in 3-methoxy-2,4,10-trioxaadamantane. Preferred exo-anomeric effect as revealed by the crystal structure. *Journal of Molecular Structure* **2015,** *1083*, 426-429.

104. Allen, F., The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallographica Section B* **2002,** *58*, 380-388.

105. Davlieva, M. G.; Lindeman, S. V.; Neretin, I. S.; Kochi, J. K., Structural effects of carbon monoxide coordination to carbon centers. π and σ bindings in aliphatic acyl versus aromatic aroyl cations. *New J Chem* **2004,** *28* (12), 1568-1574.

106. Stuart, D.; Wetmore, S. D.; Gerken, M., Solid-State Structure of Protonated Ketones and Aldehydes. *Angewandte Chemie International Edition* **2017,** *56* (51), 16380-16384.

107. Childs, R. F.; Faggiani, R.; Lock, C. J. L.; Mahendran, M.; Zweep, S. D., Structures of two cyclopropylcarbinyl cations. *Journal of the American Chemical Society* **1986,** *108* (7), 1692-1693.

108. Childs, R. F.; Kostyk, M. D.; Lock, C. J. L.; Mahendran, M., The structure of cyclopropylcarbinyl cations: the crystal structures of protonated cyclopropyl ketones. *Journal of the American Chemical Society* **1990,** *112* (24), 8912-8920.

109. Lin, X.; Wu, W.; Wiberg, K. B.; Mo, Y., Role of Intramolecular Electron Delocalization in the C–X Bond Strength in CH4-nXn (n = 0–4, X = F, Cl, CN, OCH3). *The Journal of Physical Chemistry A* **2018,** *122* (38), 7716-7722.

110. Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P., Bond length and reactivity. Stereoelectronic effects on bonding in acetals and glucosides. *Journal of the American Chemical Society* **1984,** *106* (21), 6200-6206.

111. Spiniello, M.; White, J. M., Low-temperature X-ray structural studies of the ester and ether derivatives of cis- and trans-4-tert-butyl cyclohexanol and 2-adamantanol: application of the variable oxygen probe to determine the relative σ-donor ability of C–H and C–C bonds. *Organic & Biomolecular Chemistry* **2003,** *1* (17), 3094-3101.

112. Harris, B.; Savage, G. P.; White, J. M., Hyperconjugation involving strained carbon–carbon bonds. Application of the variable oxygen probe to ester and ether derivatives of cubylmethanol. *Organic & Biomolecular Chemistry* **2013,** *11* (19), 3151-3158.

113. Yeoh, S. D.; Skene, C. E.; White, J. M., Hyperconjugation Involving Strained Carbon–Carbon Bonds. Structural Analysis of Ester and Ether Derivatives and One-Bond 13C–13C Coupling Constants of α- and β-Nopinol. *The Journal of Organic Chemistry* **2013,** *78* (2), 311-319.

114. Fifer, N. L.; White, J. M., Determining the σ-donor ability of the cyclopropane C–C bond. *Organic & Biomolecular Chemistry* **2005,** *3* (9), 1776-1780.

115. Pool, B. R.; White, J. M.; Wolynec, P. P., X-ray structural studies on a series of oxygenated anthracene cycloadducts. Evidence for pi-sigma negative homohyperconjugation in the ground state. *J Org Chem* **2000,** *65* (22), 7595-601.

116. Bohlmann, F., Lupinen-Alkaloide, VIII. Zur Konfigurationsbestimmung von Chinolizidin-Derivaten. *Chemische Berichte* **1958,** *91* (10), 2157-2167.

117. Wolfe, S.; Kim, C., A theoretical study of conformational deuterium isotope effects and bond dissociation energies of diastereotopic hydrogens. *Canadian Journal of Chemistry* **2011,** *69*, 1408-1412.

118. Bohlmann, F., Zur Konfigurationsbestimmung von Chinolizin-Derivaten. *Angewandte Chemie* **1957,** *69*, 641-642.

119. McKean, D. C., Individual CH bond strengths in simple organic compounds: effects of conformation and substitution. *Chemical Society Reviews* **1978,** *7* (3), 399-422.

120. McKean, D. C.; Duncan, J. L.; Batt, L., CH stretching frequencies, bond lengths and dissociation energies. *Spectrochimica Acta Part A: Molecular Spectroscopy* **1973,** *29* (6), 1037-1049.

121. Bellamy, L. J.; Mayo, D. W., Infrared frequency effects of lone pair interactions with antibonding orbitals on adjacent atoms. *The Journal of Physical Chemistry* **1976,** *80* (11), 1217-1220.

122. Olah, G. A.; Kuhn, S. J.; Tolgyesi, W. S.; Baker, E. B., Stable Carbonium Ions. II.1a Oxocarbonium1b (Acylium) Tetrafluoroborates, Hexafluorophosphates, Hexafluoroantimonates and Hexafluoroarsenates. Structure and Chemical Reactivity of Acyl Fluoride: Lewis Acid Fluoride Complexes. *Journal of the American Chemical Society* **1962,** *84* (14), 2733-2740.

123. Cocinero, E. J.; Carcabal, P.; Vaden, T. D.; Simons, J. P.; Davis, B. G., Sensing the anomeric effect in a solvent-free environment. *Nature* **2011,** *469* (7328), 76-79.

124. Wang, C.; Ying, F.; Wu, W.; Mo, Y., Sensing or No Sensing: Can the Anomeric Effect Be Probed by a Sensing Molecule? *Journal of the American Chemical Society* **2011,** *133* (34), 13731-13736.

125. Kim, K.; Kuhn, L.; Alabugin, I. V.; Hallinan, D. T., Lithium Salt Dissociation in Diblock Copolymer Electrolyte Using Fourier Transform Infrared Spectroscopy. *Front. Energy Res.* **2020,** *8:569442*.

126. Tvaroska, I.; Taravel, F. R., Carbon-proton coupling constants in the conformational analysis of sugar molecules. *Adv Carbohydr Chem Biochem* **1995,** *51*, 15-61.

127. Church, T. J.; Carmichael, I.; Serianni, A. S., 13C−1H and 13C−13C Spin-Coupling Constants in Methyl β-d-Ribofuranoside and Methyl 2-Deoxy-β-d-erythro- pentofuranoside: Correlations with Molecular Structure and Conformation. *Journal of the American Chemical Society* **1997,** *119* (38), 8946-8964.

128. Jung, S. T.; Nickisch, R.; Reinsperger, T.; Luy, B.; Podlech, J., Stereoelectronic effects: Perlin effects in cyclohexane-derived compounds. *J Phys Org Chem* **2021,** *34* (4), e4165.

129. Perlin, A. S.; Casu, B., Carbon-13 and proton magnetic resonance spectra of D-glucose-13C. *Tetrahedron Lett* **1969,** *10* (34), 2921-2924.

130. Alabugin, I. V., Stereoelectronic Interactions in Cyclohexane, 1,3-Dioxane,

1,3-Oxathiane, and 1,3-Dithiane: W-Effect, σC-X T σ*C-H

Interactions, Anomeric EffectsWhat Is Really Important? *J Org Chem* **2000,** *65*, 3910-3919.

131. Juaristi, E.; Cuevas, G., Manifestations of Stereoelectronic Interactions in 1JC–H One-Bond Coupling Constants. *Accounts of Chemical Research* **2007,** *40* (10), 961-970.

132. Cuevas, G.; Juaristi, E., Manifestation of Stereoelectronic Effects on the Calculated Carbon−Hydrogen Bond Lengths and One Bond 1JC-H NMR Coupling Constants in Cyclohexane, Six-Membered Heterocycles, and Cyclohexanone Derivatives. *Journal of the American Chemical Society* **2002,** *124* (44), 13088-13096.

133. Perrin, C. L.; Erdélyi, M., One-Bond C−C Coupling Constants in Ethers Are Not Primarily Determined by n−σ* Delocalization. *Journal of the American Chemical Society* **2005,** *127* (17), 6168-6169.

134. Perrin, C. L.; Armstrong, K. B.; Fabian, M. A., The origin of the anomeric effect: conformational analysis of 2-methoxy-1,3-dimethylhexahydropyrimidine. *Journal of the American Chemical Society* **1994,** *116* (2), 715-722.

135. Alabugin, I. V.; Manoharan, M.; Zeidan, T. A., Homoanomeric effects in six-membered heterocycles. *Journal of the American Chemical Society* **2003,** *125* (46), 14014-14031.

136. Allen, F. H.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R., Typical interatomic distances: organic compounds. In *International Tables for Crystallography*, 1 ed.; Prince, E., Ed. International Union of Crystallography: Chester, England, 2006; Vol. C, pp 790-811.

137. Martins, F. A.; Silla, J. M.; Freitas, M. P., Theoretical study on the anomeric effect in α-substituted tetrahydropyrans and piperidines. *Carbohydrate Research* **2017,** *451*, 29-35.

138. Ghanbarpour, P.; Nori-Shargh, D., Exploring the origin of the anomeric relationships in 2-cyanooxane, 2-cyanothiane, 2-cyanoselenane and their corresponding isocyano isomers. Correlations between hyper-conjugative anomeric effect, hardness and electrostatic interactions. *RSC Adv.* **2016,** *6* (52), 46406-46420.

139. Roohi, H.; Ebrahimi, A.; Habibi, S. M.; Jarahi, E., NBO and AIM analyses of the anomeric effect in fluoromethanthiol. *Journal of Molecular Structure: THEOCHEM* **2006,** *772* (1), 65-73.

140. Roohi, H.; Ebrahimi, A., Anomeric effect and rotational barrier in fluoromethanol: A theoretical study. *Journal of Molecular Structure: THEOCHEM* **2005,** *726* (1-3), 141-148.

141. Cortés, F.; Tenorio, J.; Collera, O.; Cuevas, G., Electronic Delocalization Contribution to the Anomeric Effect Evaluated by Computational Methods. *The Journal of Organic Chemistry* **2001,** *66* (9), 2918-2924.

142. Salzner, U.; Schleyer, P. v. R., Ab Initio Examination of Anomeric Effects in Tetrahydropyrans, 1,3-Dioxanes, and Glucose. *The Journal of Organic Chemistry* **1994,** *59* (8), 2138-2155.

143. Petillo, P. A.; Lerner, L. E., Origin and Quantitative Modeling of Anomeric Effect. In *The Anomeric Effect and Associated Stereoelectronic Effects*, Thatcher, G. R. J., Ed. American Chemical Society: Washington, DC, 1993; Vol. 539, pp 156-175.

144. Hayashi, N.; Ujihara, T.; Ikeda, H., Interpretation of anomeric effect in 2-hydroxytetrahydropyrans based on extensive bond interactions. *Tetrahedron* **2020,** *76* (7), 130919.

145. Omoto, K.; Marusaki, K.; Hirao, H.; Imade, M.; Fujimoto, H., Theoretical Study of the Anomeric Effect in CH2ClOH. *The Journal of Physical Chemistry A* **2000,** *104* (27), 6499-6504.

146. Wang, C.; Ying, F.; Wu, W.; Mo, Y., How Solvent Influences the Anomeric Effect: Roles of Hyperconjugative versus Steric Interactions on the Conformational Preference. *The Journal of Organic Chemistry* **2014,** *79* (4), 1571-1581.

147. Wang, C.; Chen, Z.; Wu, W.; Mo, Y., How the Generalized Anomeric Effect Influences the Conformational Preference. *Chem. Eur. J.* **2013,** *19* (4), 1436-1444.

148. Mo, Y.; Peyerimhoff, S. D., Theoretical analysis of electronic delocalization. *The Journal of Chemical Physics* **1998,** *109* (5), 1687-1697.

149. Bitzer, R. S.; Barbosa, A. G.; da Silva, C. O.; Nascimento, M. A., On the generalized valence bond description of the anomeric and exo-anomeric effects: an ab initio conformational study of 2-methoxytetrahydropyran. *Carbohydr Res* **2005,** *340* (13), 2171-84.

150. F. Gonthier, J.; N. Steinmann, S.; D. Wodrich, M.; Corminboeuf, C., Quantification of "fuzzy" chemical concepts: a computational perspective. *Chemical Society Reviews* **2012,** *41* (13), 4671-4687.

151. Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D., A Hierarchy of Homodesmotic Reactions for Thermochemistry. *Journal of the American Chemical Society* **2009,** *131* (7), 2547-2560.

152. Gomes, G. D.; Vil', V. A.; Terent'ev, A. O.; Alabugin, I. V., Stereoelectronic source of the anomalous stability of bis-peroxides. *Chemical Science* **2015,** *6* (12), 6783-6791.

153. Huang, Y.; Zhong, A.-G.; Yang, Q.; Liu, S., Origin of anomeric effect: A density functional steric analysis. *The Journal of Chemical Physics* **2011,** *134* (8), 084103.

154. Dabbagh, H. A.; Naderi, M.; Chermahini, A. N., Linear free energy relationship for the anomeric effect: MP2, DFT and ab initio study of 2-substituted-1,4-dioxanes. *Carbohydrate Research* **2011,** *346* (8), 1047-1056.

155. Bauerfeldt, G. F.; Cardozo, T. M.; Pereira, M. S.; da Silva, C. O., The anomeric effect: the dominance of exchange effects in closed-shell systems. *Organic & Biomolecular Chemistry* **2013,** *11* (2), 299-308.

156. Johnson, S. R., The Trouble with QSAR (or How I Learned To Stop Worrying and Embrace Fallacy). *Journal of Chemical Information and Modeling* **2008,** *48* (1), 25-26.

157. Foster, J. M.; Boys, S. F., Canonical Configurational Interaction Procedure. *Reviews of Modern Physics* **1960,** *32* (2), 300-302.

158. Edmiston, C.; Ruedenberg, K., Localized Atomic and Molecular Orbitals. *Reviews of Modern Physics* **1963,** *35* (3), 457-464.

159. Pipek, J.; Mezey, P. G., A fast intrinsic localization procedure applicable for ab initio and semiempirical linear combination of atomic orbital wave functions. *The Journal of Chemical Physics* **1989,** *90* (9), 4916-4926.

160. Reed, A.; Curtiss, L.; Weinhold, F., Intermolecular Interactions from a Natural Bond Orbital, Donor-Acceptor Viewpoint. *Chem Rev* **1988,** *88*, 899-926.

161. Reed, A. E.; Weinhold, F., Natural localized molecular orbitals. *The Journal of Chemical Physics* **1985,** *83* (4), 1736-1740.

162. Weinhold, F.; Schleyer, P. v. R.; Allinger, N. L.; Clark, T.; Gasteiger, J.; Kollman, P. A.; III, H. F. S.; Schreiner, P. R., Natural Bond Orbital Methods. In *Encyclopedia of Computational Chemistry*, John Wiley & Sons: Chichester, UK, 1998; Vol. 3, pp 1892 - 1811.

163. Mo, Y.; Wu, W.; Song, L.; Lin, M.; Zhang, Q.; Gao, J., The Magnitude of Hyperconjugation in Ethane: A Perspective from Ab Initio Valence Bond Theory. *Angewandte Chemie International Edition* **2004,** *43* (15), 1986-1990.

164. Mo, Y.; Gao, J., Theoretical Analysis of the Rotational Barrier of Ethane. *Accounts of Chemical Research* **2007,** *40* (2), 113-119.

165. Mo, Y.; Zhang, Y.; Gao, J., A Simple Electrostatic Model for Trisilylamine: Theoretical Examinations of the n→σ* Negative Hyperconjugation, pπ→dπ Bonding, and Stereoelectronic Interaction. *Journal of the American Chemical Society* **1999,** *121* (24), 5737-5742.

166. Mo, Y.; Gao, J.; Peyerimhoff, S. D., Energy decomposition analysis of intermolecular interactions using a block-localized wave function approach. *The Journal of Chemical Physics* **2000,** *112* (13), 5530-5538.

167. Mo, Y.; Subramanian, G.; Gao, J.; Ferguson, D. M., Cation−π Interactions: An Energy Decomposition Analysis and Its Implication in δ-Opioid Receptor−Ligand Binding. *Journal of the American Chemical Society* **2002,** *124* (17), 4832-4837.

168. Mo, Y.; Song, L.; Wu, W.; Zhang, Q., Charge Transfer in the Electron Donor−Acceptor Complex BH3NH3. *Journal of the American Chemical Society* **2004,** *126* (12), 3974-3982.

169. Mo, Y.; Gao, J., An Ab Initio Molecular Orbital−Valence Bond (MOVB) Method for Simulating Chemical Reactions in Solution. *The Journal of Physical Chemistry A* **2000,** *104* (13), 3012-3020.

170. Mo, Y.; Gao, J., Ab initio QM/MM simulations with a molecular orbital-valence bond (MOVB) method: application to an SN2 reaction in water. *Journal of Computational Chemistry* **2000,** *21* (16), 1458-1469.

171. Mo, Y., Resonance Effect in the Allyl Cation and Anion: A Revisit. *The Journal of Organic Chemistry* **2004,** *69* (17), 5563-5567.

172. Badenhoop, J. K.; Weinhold, F., Natural steric analysis: Ab initio van der Waals radii of atoms and ions. *The Journal of Chemical Physics* **1997,** *107* (14), 5422-5432.

173. Badenhoop, J. K.; Weinhold, F., Natural steric analysis of internal rotation barriers. *International Journal of Quantum Chemistry* **1999,** *72* (4), 269-280.

174. Weisskopf, V. F., Of Atoms, Mountains, and Stars: A Study in Qualitative Physics. *Science* **1975,** *187* (4177), 605-612.

175. El-Issa, B. D.; Hinchliffe, A., SCF-Xα study of the electronic structure of CF4, CCl4, CBr4, CI4, SiF4, SiCl4, SiBr4 SiI4 and GeF4. *Journal of the Chemical Society, Faraday Transactions 2: Molecular and Chemical Physics* **1980,** *76* (0), 1375-1380.

176. Salzner, U.; von Raguè Schleyer, P., CH4−nXn: a comparison between the stabilized X ⍰ F series and the destabilized X ⍰ CN series. *Chemical Physics Letters* **1992,** *190* (5), 401-406.

177. Gardiner, J., Fluoropolymers: Origin, Production, and Industrial and Commercial Applications. *Australian Journal of Chemistry* **2015,** *68* (1), 13-22.

178. Albert Einstein. https://en.wikiquote.org/wiki/Albert_Einstein.

179. Greis, K.; Mucha, E.; Lettow, M.; Thomas, D. A.; Kirschbaum, C.; Moon, S.; Pardo-Vargas, A.; von Helden, G.; Meijer, G.; Gilmore, K.; Seeberger, P. H.; Pagel, K., The Impact of Leaving Group Anomericity on the Structure of Glycosyl Cations of Protected Galactosides. *Chemphyschem* **2020**.

180. Zefirov, N. S., Stereochemical studies—XXI: General equation of relationship between products ratio and conformational equilibrium. *Tetrahedron* **1977,** *33* (20), 2719-2722.

181. Winstein, S.; Holness, N. J., Neighboring Carbon and Hydrogen. XIX. t-Butylcyclohexyl Derivatives. Quantitative Conformational Analysis. *Journal of the American Chemical Society* **1955,** *77* (21), 5562-5578.

182. Schneider, H. J.; Hoppen, V., Carbon-13 nuclear magnetic resonance substituent-induced shieldings and conformational equilibriums in cyclohexanes. *The Journal of Organic Chemistry* **1978,** *43* (20), 3866-3873.

183. Perrin, C. L., Reverse anomeric effect: fact or fiction? *Tetrahedron* **1995,** *51* (44), 11901-11935.

184. Coppens, P., Electron Density from X-Ray Diffraction. *Annual Review of Physical Chemistry* **1992,** *43* (1), 663-692.

185. Stowasser, R.; Hoffmann, R., What Do the Kohn−Sham Orbitals and Eigenvalues Mean? *Journal of the American Chemical Society* **1999,** *121* (14), 3414-3420.

186. Duke, B. J.; O'Leary, B., Non-Koopmans' Molecules. *Journal of Chemical Education* **1995,** *72* (6), 501.

187. Löwdin, P.-O., Quantum Theory of Many-Particle Systems. I. Physical Interpretations by Means of Density Matrices, Natural Spin-Orbitals, and Convergence Problems in the Method of Configurational Interaction. *Physical Review* **1955,** *97* (6), 1474-1489.

188. Hiberty, P. C.; Danovich, D.; Shaik, S., Comment on "Rabbit-ears hybrids, VSEPR sterics, and other orbital anachronisms". A reply to a criticism. *Chem. Educ. Res. Pract.* **2015,** *16* (3), 689-693.

189. Clauss, A. D.; Ayoub, M.; Moore, J. W.; Landis, C. R.; Weinhold, F., Rabbit ears concepts of water lone pairs: a reply to comments of Hiberty, Danovich, and Shaik. *Chemistry Education Research and Practice* **2015,** *16* (3), 694-696.

190. Stewart, J. J. P., An examination of the nature of localized molecular orbitals and their value in understanding various phenomena that occur in organic chemistry. *Journal of Molecular Modeling* **2019,** *25* (1).

191. Popelier, P. L. A., On the full topology of the Laplacian of the electron density. *Coordination Chemistry Reviews* **2000,** *197* (1), 169-189.

192. Bent, H. A., An Appraisal of Valence-bond Structures and Hybridization in Compounds of the First-row elements. *Chem Rev* **1961,** *61* (3), 275-311.

193. Alabugin, I. V.; Bresch, S.; Manoharan, M., Hybridization Trends for Main Group Elements and Expanding the Bent's Rule Beyond Carbon: More than Electronegativity. *The Journal of Physical Chemistry A* **2014,** *118* (20), 3663-3677.

194. Mayes, H. B.; Broadbelt, L. J.; Beckham, G. T., How Sugars Pucker: Electronic Structure Calculations Map the Kinetic Landscape of Five Biologically Paramount Monosaccharides and Their Implications for Enzymatic Catalysis. *Journal of the American Chemical Society* **2014,** *136* (3), 1008-1022.

195. Davies, G. J.; Planas, A.; Rovira, C., Conformational Analyses of the Reaction Coordinate of Glycosidases. *Accounts of Chemical Research* **2012,** *45* (2), 308-316.

196. Walvoort, M. T. C.; van der Marel, G. A.; Overkleeft, H. S.; Codée, J. D. C., On the reactivity and selectivity of donor glycosides in glycochemistry and glycobiology: trapped covalent intermediates. *Chemical Science* **2013,** *4* (3), 897-906.