



Hyperconjugation

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This review outlines the ubiquitous nature of hyperconjugative interactions and their role in the structure and reactivity of organic molecules. After defining the common hyperconjugative patterns, we discuss the main factors controlling the magnitude of hyperconjugative effects, including orbital symmetry, energy gap, electronegativity, and polarizability. The danger of underestimating the magnitude of hyperconjugative interactions are illustrated by a number of spectroscopic, conformational, and structural effects. Through the use of advanced computational techniques, the true role of hyperconjugative effects, as it pertains to their influence on stereoelectronics, conformational equilibria, and reactivities relative to other electronic effects, continue to be uncovered. © 2011 John Wiley & Sons, Ltd. *WIREs Comput Mol Sci* 2011 1 109–141 DOI: 10.1002/wcms.6

HYPERCONJUGATION, CONJUGATION, AND σ -CONJUGATION

Stabilizing interactions between electronic orbitals in molecules can be displayed *via* one of three ubiquitous effects: conjugation, hyperconjugation, and σ -conjugation. Each of these effects describes the electronic consequences of delocalization and can be expressed as the difference between a perfectly localized, single Lewis structure, system and a real molecule. Although the interaction of π -orbitals, or conjugation, has been a prominent feature of theoretical organic chemistry for a long time, the importance of delocalizing interactions involving σ -bonds^{1,2} has not been equally recognized, even though Mulliken's pioneering papers on hyperconjugation date back to the early 1940s.^{3,4}

This situation has changed not only because σ -bonds are much more common than π -bonds and, thus, hyperconjugative interactions are ubiquitous in chemistry, but mostly due to the accumulation of significant theoretical and experimental evidences that these interactions lead to significant changes in geometry, electron density, molecular orbital (MO) energies, infrared (IR)-spectra, bond strengths (Bohlmann effect),^{5,6} and nuclear magnetic resonance (NMR) properties.⁷ In many cases, hyperconjugation influences conformational equilibria,^{8–22} modifies reactivity,^{23–32} and determines selectivity.³³

Their importance is enhanced dramatically in excited, radical, and ionic species.^{34–37} Two-electron/two-orbital hyperconjugative interactions are also proposed to be important components of intermolecular interactions, both in ground³⁸ and transition states (TSs).^{39–45} The separation of σ -conjugation, hyperconjugation, and conjugation into three different effects is based on an arbitrary decision to treat σ - and π -orbitals on a different basis. In the formalism, IUPAC defines hyperconjugation as an interaction between σ - and π -orbitals. The interaction of σ -orbitals is called sigma conjugation whereas the interaction of π -orbitals is referred to as conjugation. The latter term is also extended to the analogous interaction involving a p-orbital, for example, $\text{NH}_2\text{-Ph}$. Note that the interactions of π -bonds with lone pairs start to blur the line between hyperconjugation and conjugation because lone pairs are often hybridized and possess significant s-character.⁴⁶

Because the above mentioned effects describe the same fundamental phenomenon and are different only within the σ - π model, their separation has mostly historic value. Interestingly, Mulliken in his seminal 1941 paper titled 'Hyperconjugation'⁴⁷ emphasized that 'differences in conjugating power' among saturated and unsaturated groups are 'quantitative rather than qualitative'. He suggested to use terms 'second-order conjugation, or first-order hyperconjugation' for the σ - π interaction and 'third-order conjugation, or second-order hyperconjugation' for the σ - σ interaction. Mulliken's analysis remains valid—the basic stereoelectronic guidelines and orbital interaction patterns are similar as those for the three types of delocalizing interactions. In fact, σ -conjugation is often referred to as hyperconjugation

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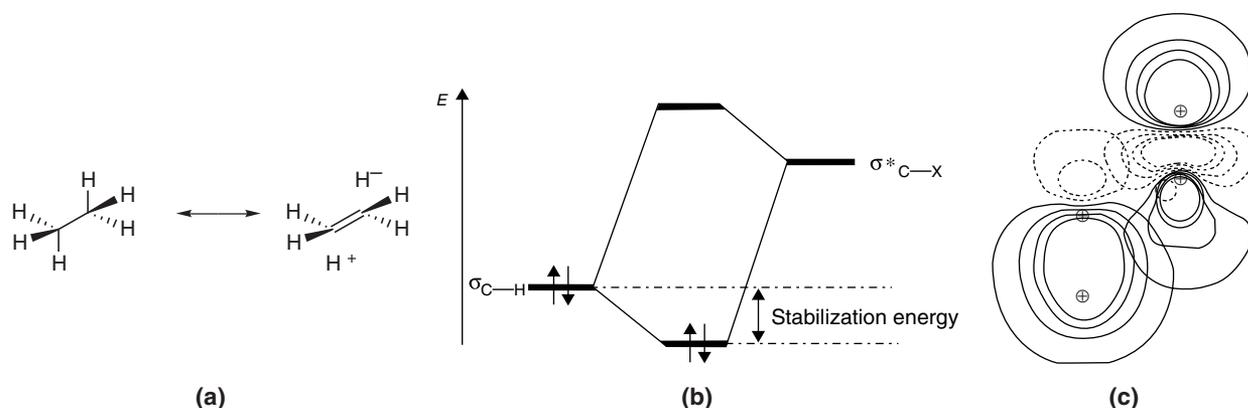


FIGURE 1 | (a) Description of the vicinal $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-H}}$ interaction in ethane in terms of resonance theory ('double bond/no bond resonance'). (b) Energy lowering due to hyperconjugative interaction between $\sigma_{\text{C-H}}$ and $\sigma^*_{\text{C-X}}$ orbitals. (c) Natural bond orbital plots illustrating overlap of vicinal $\sigma_{\text{C-H}}$ and $\sigma^*_{\text{C-H}}$ orbitals in ethane.

in modern scientific literature. In this review, we will follow the spirit of Mulliken's treatment and combine both types of interactions including σ -bonds under one title 'hyperconjugation'. Not only can hyperconjugation with strong σ -donors rival stabilization due to the conventional conjugation patterns, but the two effects are sometimes difficult to distinguish. For example, in the process of an allylic σ -bond stretching and breaking, hyperconjugation with the σ -bond is transformed into conjugation with the nonbonding orbital (radical in the case of homolytic bond cleavage, or cation/anion in the case of heterolytic bond cleavage). This transition further illustrates the inherent similarity between hyperconjugation and σ -conjugation.

DESCRIPTIONS OF HYPERCONJUGATION

In valence bond (VB) theory, hyperconjugation arises from the presence of additional resonance structures (the double bond/no bond resonance in Figure 1(a)). In MO theory, hyperconjugation is commonly described as the interaction between electronic orbitals, one of which corresponds to a σ -bond. In order for the interaction to be stabilizing, the higher energy orbital has to be at least partially empty (zero or one electron), and the lower energy orbital has to be at least partially filled. The most common scenario, illustrated in Figure 1, corresponds to a two-electron interaction where the lower energy orbital (a bond or a lone pair) is completely filled whereas the higher energy antibonding orbital is empty. Two-center/one-electron and two-center/three-electron hyperconjugation

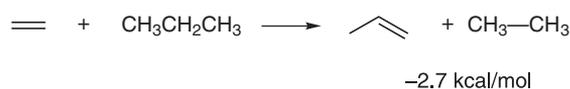


FIGURE 2 | A possible way to estimate hyperconjugation in propene through a bond separation reaction.

tion patterns are also possible and play important roles in odd-electron species such as radicals, radical ions, and excited states.^{48, 49}

Theoretical Approaches to Analysis of Hyperconjugation

Isodesmic Reactions and Conformational Energy Profiles

Very often, delocalization is estimated through thermochemical data and application of hypothetical reactions (isogyric, isodesmic, hypohomodesmotic, homodesmotic, or hyperhomodesmotic),⁵⁰ which are designed to isolate the desired effect. For example, the equation in Figure 2 can be used to evaluate the hyperconjugative stabilization of an alkene by a methyl group.⁵¹

The advantage of these equations is that, in many cases, the thermochemical data can be either obtained experimentally or calculated with a high degree of accuracy. The challenge is in isolating the key electronic effect without introducing additional structural and electronic perturbations. For example, the above equation suffers from an imbalance in the hybridization, such as a different number of sp^3 - sp^3 and sp^2 - sp^3 C-C bonds and vinyl C-H bonds in the reactant and product.

An 'ideal' reaction for the analysis of an electronic effect would involve no changes in

hybridization and the types of bonds. None of these parameters change upon conformational changes as a result of rotation around a single bond, whereas many hyperconjugative effects are stereoelectronic (depend on orbital overlap in space) and can be 'switched off and on' through conformational changes. Conformational analysis has played an important historical role in the development of theoretical organic chemistry and proved to be very useful for the understanding of hyperconjugative effects. However, such an analysis is complicated by the fact that conformational equilibrium is often controlled by a complex mixture of factors, of which hyperconjugation is only a single contributor.

Wavefunction Analysis

A different approach, which has a conceptual advantage over such conventional delocalization energy assessments, involves direct computational dissection of delocalized wavefunctions. In order to describe and quantify delocalizing interactions, one needs to evaluate the energy penalty, which occurs when this interaction is absent. The difference in energy between this state (sometimes called diabatic state) and the full state (sometimes called adiabatic) can be taken as the interaction energy. The main challenge lies in defining the appropriate correct localized state to serve as a reference point. Three approaches have emerged for dissecting delocalizing interactions: natural bond orbital (NBO) analysis, energy decomposition analysis (EDA),^{52–55} and block-localized wavefunction (BLW) method.⁵⁶

All of these methods share a conceptual similarity in comparing the full wavefunction with a hypothetical localized construct. However, an important difference between these methods lies in the starting basic set of orbitals used to describe delocalization. Whereas NBO utilizes orthogonal orbitals to describe the localized reference, the other methods start with nonorthogonal orbitals.⁵⁷ This difference leads to significant variations in the magnitude of delocalizing interactions obtained, and exaggerates the role of steric effects in methods based on non-orthogonal orbitals.

From the conceptual perspective, the non-orthogonal initial orbitals cannot be the eigenfunctions of any imaginable physical (Hermitian) Hamiltonian that can serve as the 'unperturbed system' for such an analysis. Although the overlap contamination effects do not change energies evaluated on the basis of the *overall* molecular wave functions (whether orbitals of a determinantal wavefunction are orthogonal or not does not affect the overall expectation value), orbitals (and charge density) attributed to one group have overlap with (and thus could equally

well be attributed to) orbitals of the other group. If the 'bond' of one group overlaps with the antibond of the other group, such overlap will automatically be labeled 'exchange repulsion' in a scheme based on nonorthogonal orbitals.⁵⁸

The observed differences between alternative computational dissections are due to the ambiguity about which non-orthogonal subunits receive credit for unaccounted density in the overlap region. The associated overlap density can be assigned to the filled orbital (and counted toward steric effects) or to the unfilled orbital (and counted toward hyperconjugative charge-transfer). All methods that harbor such overlap ambiguities are expected to differ sharply from NBO-based assessments of intramolecular or intermolecular interactions.

Figure 3(a) illustrates the origin of 'four-electron destabilization' between two non-orthogonal filled orbitals often taken as the physical origin of the steric destabilization. However, it is simply a mathematical artifact of nonorthogonality and does not, in fact, correspond to a physical interpretation of any imaginable physical process. Once orbitals are orthogonalized, the 'four-electron destabilization' disappears (Figure 3(b)). When at least one unoccupied orbital is added to the system, the overall interaction becomes stabilizing (Figure 3(c)).^{59–61}

Natural Bond Orbital (NBO) Analysis

The NBO analysis transforms the canonical delocalized Hartree–Fock (HF) MOs and non-orthogonal atomic orbitals (AOs) into the sets of localized 'natural' atomic orbitals, hybrid orbitals, and NBOs. Importantly, each of these localized basis sets is complete and orthonormal, and describes the wavefunction with the minimal amount of filled orbitals in the most rapidly convergent fashion. Unlike delocalized canonical MOs, filled NBOs describe the hypothetical, strictly localized Lewis structure. Natural population analysis (NPA) charge assignments based on NBO analysis correlate well with empirical charge measures.⁶²

The interactions between filled and antibonding (or Rydberg) orbitals represent the deviation of the molecule from the Lewis structure and can be used as a measure of delocalization. Because the occupancies of filled NBOs are highly condensed, the delocalizing interactions can be treated by a standard second-order perturbation approach (Eq. (1)) or by deletion of the corresponding off-diagonal elements of the Fock matrix in the NBO basis and recalculating the energy (referred to as E_{del} energies)^{63,64} where $\langle \sigma / F / \sigma^* \rangle$, or $F_{i,j}$ is the Fock matrix element between the orbitals (NBOs) i and j , ε_{σ} and ε_{σ^*} are the energies of the σ

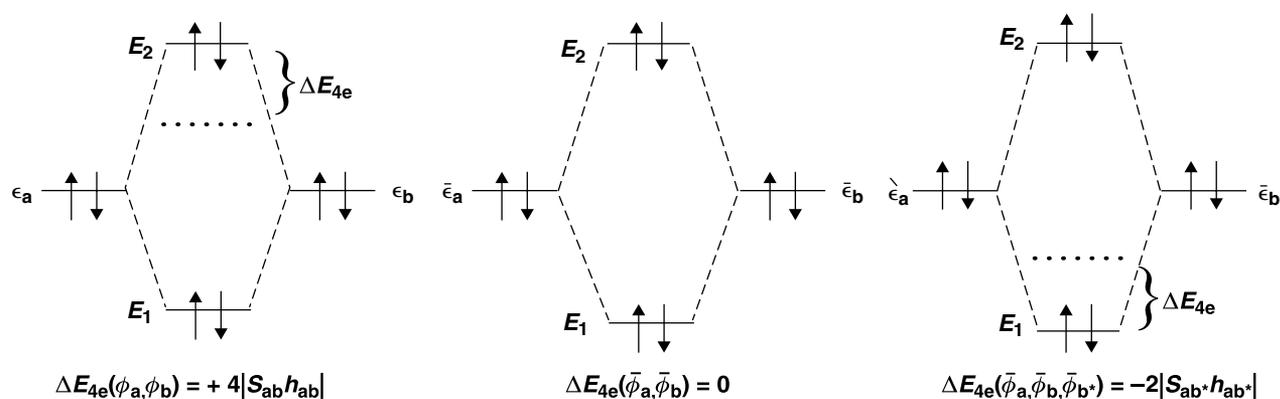


FIGURE 3 | (Left) Four-electron destabilizing interaction expressed in terms of nonorthogonal “unperturbed” orbitals (for which there is no imaginable Hermitian perturbation theory). (Middle) Four-electron nonstabilizing interaction expressed in terms of orthogonalized unperturbed orbitals (for which there exists a valid Hermitian). (Right) Four-electron stabilizing interaction for a proper three-term description of orbital energies in terms of Löwdin-orthogonalized basis orbitals (Reprinted with permission from Refs 59 to 61).

and σ^* NBOs, and n_σ is the population of the donor σ orbital.² Usually, there is a good linear correlation between the deletion (E_{del}) and perturbation [$E(2)$] energies.⁶⁵ One can also delete some or all of the virtual localized NBOs, thus eliminating all interactions involving these orbitals.

$$E(2) = -n_\sigma \frac{\langle \sigma / F / \sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{(F_{i,j})^2}{\Delta E} \quad (1)$$

Natural steric analysis⁶⁶ in the NBO procedure is based on the model of Weiskopff where orbital orthogonalization leads to the ‘kinetic energy pressure’ that opposes interpenetration of matter.⁶⁷ As the orbitals begin to overlap, the physically required orthogonalization leads to additional oscillatory and nodal features in the orbital waveform, which correspond to increased wavefunction curvature and kinetic energy, the essential ‘destabilization’ that opposes interpenetration. The overlap-type analysis of Pauli interactions can be introduced to the NBO framework through interactions of not orthogonalized pre-NBOs.

Energy Decomposition Analysis (EDA)

This analysis starts with ‘a zeroth-order’ wavefunction from the overlapping orbitals of the isolated molecular fragments.^{68–71} In EDA, the interactions between these fragments are divided into three steps. In the first step, the fragments, which are calculated with the frozen geometry of the entire molecule, are superimposed without electronic relaxation; this yields the quasiclassical electrostatic attraction ΔE_{elstat} . In the second step the product wavefunction becomes antisymmetrized and renormalized, which gives the repulsive term ΔE_{Pauli} , termed Pauli

repulsion. In the third step the MOs relax to their final form to yield the stabilizing orbital interaction ΔE_{orb} . The latter term can be divided into contributions of orbitals having different symmetry that is useful for separation of σ - and π -effects. The sum of the three terms $\Delta E_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{orb}}$ gives the total interaction energy ΔE_{int} .

Block-localized Wavefunction (BLW) Method

Mo et al.^{72–82} suggested that the electron delocalization to the cationic carbon and neutral boron center can be accurately studied by removing the vacant π -orbitals from the expansion space of MOs. Although this simple orbital deletion procedure (ODP) technique is limited to the analysis of positive hyperconjugation in carbocations and boranes, it has been generalized and extended to the BLW method.

The BLW method combines the MO and VB theories. In this method, the wavefunction for a localized (diabatic) state is defined by limiting the expansion of each MO (called block-localized MO) to a predefined subspace instead of allowing all MOs to be a combination of all AOs, as in MO theory. Block-localized MOs belonging to different subspaces are generally non-orthogonal. The BLWs for diabatic states are optimized self-consistently, and the adiabatic state is a combination of a few (usually two or three) diabatic state wavefunctions.

For example, for propene, the delocalized and localized (BLW) wave functions can be expressed as $\Psi(\text{del}) = \hat{A}(\sigma 1a''^2 2a''^2)$ and $\Psi(\text{loc}) = \hat{A}(\sigma \pi^2_{\text{C=C}} \pi^2_{\text{CH}_3})$, where $\pi_{\text{C=C}}$ and π_{CH_3} are group orbitals expanded in $\text{CH}_2=\text{CH}$ and CH_3 groups, and are non-orthogonal. In contrast, canonical MOs $1a''$ and $2a''$ are delocalized for the whole system and

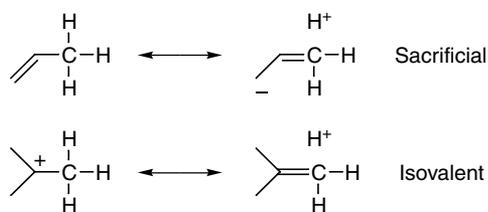


FIGURE 4 | Comparison of contributing resonance structures in sacrificial and isovalent hyperconjugation.

are orthogonal. In this example, the energy difference between these two wave functions, which are independently optimized self-consistently, is taken as the vicinal hyperconjugative interaction between the π double bond and the adjacent methyl group.

TYPES OF HYPERCONJUGATION

Isovalent Versus Sacrificial Hyperconjugation

The characteristic resonance description of hyperconjugation involves the so called ‘double bond/no-bond resonance’ contributing structure. Depending on the relative number of two-electron bonds in the two contributing structures, hyperconjugation is classified as either ‘heterovalent’ or ‘isovalent’ hyperconjugation. This classification dates back to Mulliken⁸³ who referred to heterovalent hyperconjugation in neutral systems as ‘ordinary’ or ‘sacrificial’, and to hyperconjugation in cations as ‘strong’ or ‘isovalent’.

In sacrificial hyperconjugation, the contributing structure contains one 2-electron bond less than the normal Lewis formula. In contrast, contributing structures describing the so-called ‘isovalent’ hyperconjugation between σ -bonds and an unfilled or partially filled π - or p-orbital in carbenium ions, carbanions, and radicals contain the same number of two-electron bonds as the main Lewis formula (Figure 4).

The two resonance patterns are not unique for hyperconjugation—the same distinction can be made for conjugation patterns. For example, resonance in butadiene can be taken as an example of sacrificial conjugation, whereas resonance in allyl systems (cation, anion, and radical) can be considered as an example of isovalent conjugation.

Neutral, Negative, and Positive Hyperconjugation

Another historically common classification of hyperconjugative interactions is based on their separation into neutral, negative, and positive hyperconjugation.

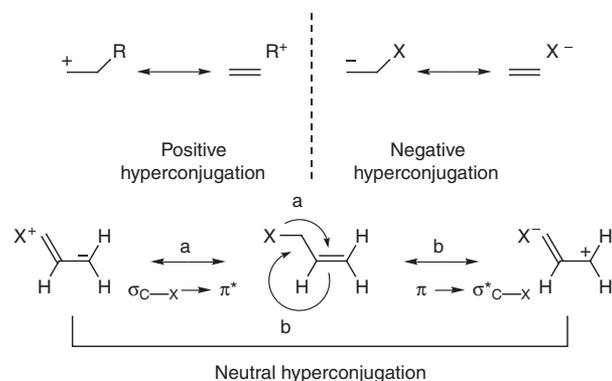


FIGURE 5 | Contributing resonance structures for positive, negative, and neutral hyperconjugation.

The interactions between filled π - or p-orbitals and adjacent antibonding σ^* -orbitals are referred to as negative hyperconjugation. Donation of electron density from filled σ -orbitals into π^* -orbitals or p-type unfilled orbitals is called positive hyperconjugation. Both negative and positive hyperconjugation are two-electron stabilizing interactions that result in building π -character between nominally single-bonded atoms.

Classification of hyperconjugation as positive or negative is useful when either referring to an individual interaction or to an imbalanced situation, when a very strong donor or a strong acceptor orbital is present in the molecule, and when interaction of this unusual orbital with the rest of the molecules dominates over other delocalization effects. This imbalance often occurs when either a lone pair acts as a donor or when an empty p-orbital, or a strongly polarized π^* - or σ^* -orbital, acts as an acceptor.^{84–87} Use of these terms in other situations can be misleading.

In the absence of dominating unidirectional interactions, hyperconjugation is classified as neutral hyperconjugation. This is the most common hyperconjugative pattern that blends together the negative and the positive hyperconjugation. For example, the delocalizing interaction between a π -bond and an adjacent σ_{C-X} bond in Figure 5 is displayed as a pair of donor–acceptor $\pi \rightarrow \sigma^*_{C-X}$ and $\sigma_{C-X} \rightarrow \pi^*$ interactions. In this case, the interaction is bidirectional and the same C–X moiety, where X is a main group element from groups IVa–VIIa, serves as both a σ -donor and a σ -acceptor.

Negative Hyperconjugation

Donation of electron density from filled π -orbitals or lone pairs into σ^* -orbitals (negative hyperconjugation) is important not only in anions, but also in many neutral molecules. In particular, it is implicated in the

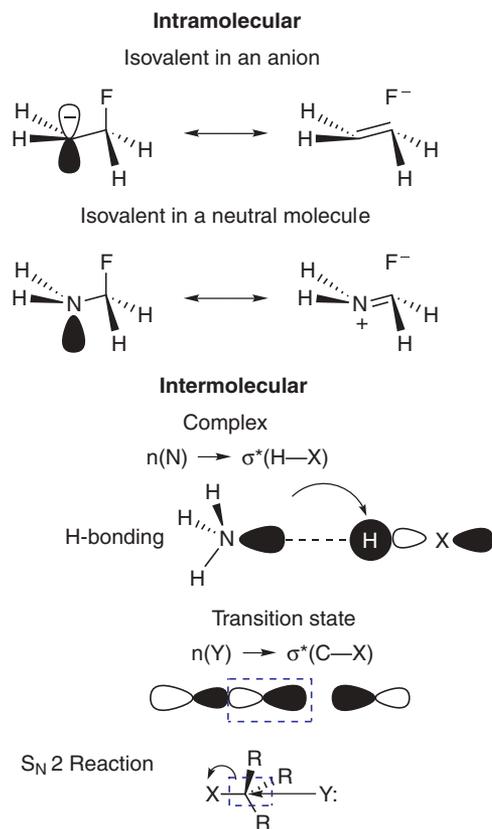


FIGURE 6 | Selected patterns of intra- and intermolecular negative hyperconjugation.

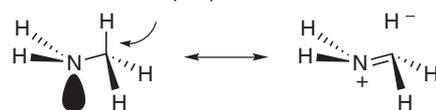
anomeric effect (and its spectroscopic counterparts—the Bohlman⁸⁸ and the Perrin effects,^{89–92} see Figure 7) and as a provider of covalent character and directionality of H-bonding. Negative hyperconjugation that involves nonbonding orbitals is isovalent (Figure 6) and the one that involves π -orbitals is sacrificial (Figure 5).

Positive Hyperconjugation

This conjugation pattern dominates when a very strong p - or π -acceptor, or a very strong σ -donor is present in a molecule. In particular, positive hyperconjugation is very important in carbenium ions and boranes (Figure 8).⁹³

The effect of alkyl substituents on the stabilities of carbenium ions provides the electronic basis of the Markovnikov's rule.⁹⁴ For a carbenium ion, the more alkyl groups that are connected to the cationic center, the more stable the carbocation is.⁹⁵ The stabilizing effect of hyperconjugation on the stability of carbenium ions is illustrated by the gas phase hydride ion affinities for the selected carbocations in Figure 9. In these gas phase data, the stabilizing potential of

Bohlman effect: lower IR-stretching frequency for the antiperiplanar C—H bond



Perrin effect: smaller one-bond NMR coupling constants for the longer C—H bonds

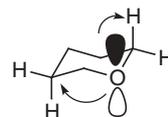


FIGURE 7 | Spectroscopic effects associated with negative hyperconjugation.

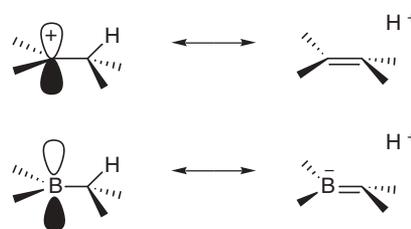


FIGURE 8 | Positive hyperconjugation in a cation and a neutral molecule.

conjugation is expressed to its maximum degree because it is not attenuated by solvation effects. It is clear that the stabilizing effect of hyperconjugation is significant—under these conditions, a methyl group provides ca 70% of stabilization by a double bond in the allyl cation. Although the stabilizing effects of second and third methyl groups are progressively smaller, positive hyperconjugation in secondary and tertiary cations provides much more stabilization to the cationic center than conjugation in the allyl cation and rivals stabilization provided by the lone pairs of oxygen in HOCH_2^+ , i.e., the stabilities increase in the order of methyl cation < primary < allyl < secondary < hydroxycarbenium < tertiary cation (Figure 9).

These trends agree well with the trends in relative stabilities of carbocations from gas phase heterolytic C—Br bond dissociation energies in alkyl bromides: CH_3^+ (0.0 kcal/mol) < CH_3CH_2^+ (36 kcal/mol) < $(\text{CH}_3)_2\text{CH}^+$ (55 kcal/mol) < $(\text{CH}_3)_3\text{C}^+$ (69 kcal/mol).⁹⁵ Hyperconjugation energies from ODP computations are noticeably smaller (CH_3CH_2^+ = 13 kcal/mol, $(\text{CH}_3)_2\text{CH}^+$ = 21 kcal/mol and $(\text{CH}_3)_3\text{C}^+$ = 26 kcal/mol).⁷² This discrepancy can be attributed to the structural relaxation, for example, from pyramidal structure to planar structure.

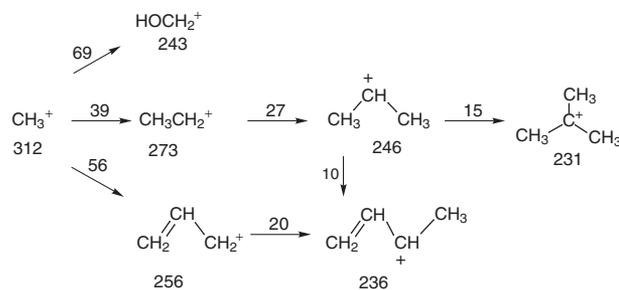


FIGURE 9 | Absolute (data below the structures) and relative (data near the arrows) gas phase hydride ion affinities for selected carbocations. All energies are in kcal/mol.⁹⁶

The stabilizing effect of positive hyperconjugation increases for stronger σ -donors. For example, the stabilizing effect of a silyl substituent in β -silylethyl cation is calculated to be ca 38 kcal/mol in the gas phase.^{97–99} Effects of Ge, Sn, and Hg are also substantial^{100,101}; for example, hyperconjugative activation by a Sn–C bond can accelerate a reaction by a factor of >10 .^{14,97–99,102}

Neutral Hyperconjugation

In this type of hyperconjugation, donor and acceptor interactions are balanced and often there is no dominating effect. As a result, the importance of sacrificial hyperconjugation in neutral hydrocarbons has been controversial. However, recent work suggests that this effect is important, and effects of hyperconjugation were reported even on X-ray geometries of neutral molecules.¹⁰³

Part of the challenge is that structural effects of neutral hyperconjugation are often small and indirect experimental approaches can thus be complicated.¹⁰⁴ For example, Basso and coworkers¹⁰⁵ reported that although calculated structural parameters (bond lengths, valence and dihedral angles) and NBO analysis were in a good agreement with the expected trends of hyperconjugative interactions between a double bond and an allylic substituent (for $M = \text{C}, \text{Si}, \text{Ge}$), neither computed nor experimental NMR C–C coupling constants, $^1J_{\text{C}-\text{C}}$, in these systems correlated with the structural parameters.

When exploring the possibility of using NMR coupling constants as a probe of structural and electronic consequences of hyperconjugation, Lambert and coworkers observed that variations of M in benzylic systems did not produce the monotonous increase in the coupling constant between the benzylic and ipso-carbons, which are doubly-bonded in the contributing no-bond, double-bond structure (Figure 10). This result illustrates that the NMR cou-

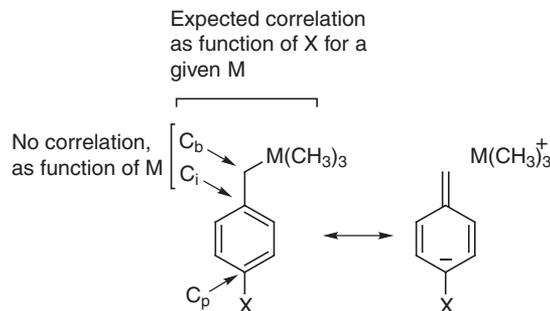


FIGURE 10 | Effects of neutral hyperconjugation on the direct nuclear magnetic resonance coupling constants.

plings depend not only on the bond lengths but also on other factors such as bond polarity or rehybridization.¹⁰⁶ Interestingly, when such factors are kept constant (*via* varying electron demand of a p -substituent X for the same hyperconjugative donor M at the benzylic position), the monotonic decrease in the direct M–C coupling constants has been observed with increasing electron withdrawal for ^{13}C – ^{29}Si and ^{29}C – ^{119}Sn bonds.¹⁰⁷ This change is consistent with the increased importance of hyperconjugation.

Neglect of neutral hyperconjugation can lead to serious fundamental misconceptions. For example, omission of hyperconjugative effects led to the apparent disappearance of conjugation between two triple bonds in butadiyne (see *Neutral Hyperconjugation in Alkenes and Alkynes*). We will further illustrate the importance of this ubiquitous phenomenon in *Examples/Stereoelectronic Effects*.

Extended Patterns of Hyperconjugation

The chemical community is accustomed to the idea that conjugation through π -arrays can provide long-range orbital communication. For example, conjugated arrays are commonly used as bridges for electron/hole transport both in nature's photosynthetic center and in artificial devices for light harvesting and conversion. Although it is less clear how far hyperconjugation extends, a number of extended hyperconjugation patterns have been investigated.¹⁰⁸ Some of these patterns are provided in Figure 11, which follows the lucid classification of Lambert and Ciro.¹⁰⁹

Homohyperconjugation is observed when a saturated center intervenes between donor and acceptor orbitals. When the acceptor is a cationic p-orbital, the phenomenon is called the γ -effect or, sometimes, percaudal interaction. It has been particularly well studied for silicon and tin.^{110–113} When the acceptor is a σ^* -orbital and donor is a lone pair, this effect is referred to as homoanionic effect.¹¹⁴ Both the γ -effect

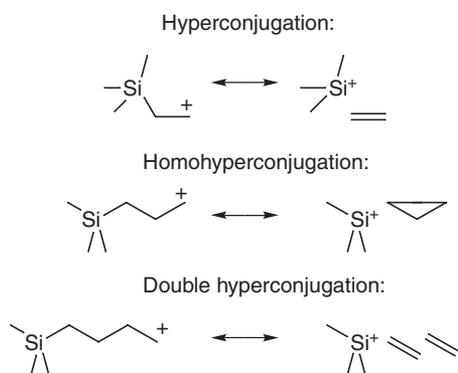


FIGURE 11 | Comparison of normal and extended positive hyperconjugation.

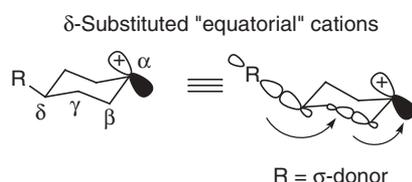


FIGURE 12 | The significant stabilization of a δ -cyclohexyl cation by a series of equatorial substituents via double hyperconjugation.

and the homoanomeric effect are considered to result primarily from direct through-space interactions.

Double hyperconjugation extends the delocalization range even further by placing a σ -bridge between a donor and an acceptor. In the chemistry of cations, this interaction has been called the δ -effect and found experimentally to be significant for silicon and tin.^{115–117} Expansion of these studies to a larger set of cations^{118,119} showed that, double hyperconjugation with a number of equatorial substituents can provide significant stabilization (R = AlH₂, GaH₂, GeH₃, AsH₂, SiH₃, PH₂, BH₂, SeH) or destabilization (R = SH, Br, NH₂, Cl, O, F) to the δ -cyclohexyl cation with the equatorially oriented empty p-orbital (Figure 12, equatorial 'hyperconjomer', *vide infra*). These stabilization effects were used for the development of a new scale for the hyperconjugative donor ability of σ -bonds (see *Anomeric and Homoanomeric Effects* for additional details).

FACTORS CONTROLLING HYPERCONJUGATION

Overlap/Orbital Symmetry

Vicinal orbitals have to be coplanar to ensure the optimal interaction. Regarding the two possible coplanar geometries, the common stereoelectronic feature

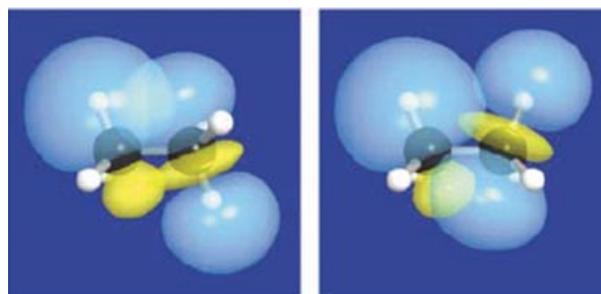
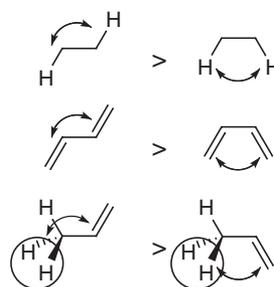


FIGURE 13 | Top: The antiperiplanar stereoelectronic preference for vicinal conjugation and hyperconjugation. Bottom: Key hyperconjugative interactions between σ_{C-H} and σ^*_{C-H} orbitals (Reprinted with permission from Refs 59 to 61).

observed for the interaction of vicinal orbitals is the general preference of antiperiplanar arrangement over synperiplanar geometry. This effect is displayed in the higher stability of the staggered conformation of ethane, *s-trans* conformation of butadiene and eclipsed (an obvious misnomer) conformation of propene (Figure 13, top). The origin of this preference, for the case of ethane, is illustrated in the bottom part of Figure 13, which clearly displays the unfavorable overlap between the σ_{C-H} orbital and a node of the σ^* -orbital for the synperiplanar arrangement in the eclipsed conformation.^{120,121}

Because vicinal hyperconjugation is increased in the antiperiplanar conformation, a number of hyperconjugative stereoelectronic effects are fully displayed in the most favorable geometry, where the best donor and the best acceptor are antiperiplanar to each other (see *Examples/Stereoelectronic effects* for a number of illustrative examples).¹²²

For intermolecular interactions dominated by negative hyperconjugation, the best stereoelectronic arrangement involves a collinear arrangement where the donor orbital interacts with the back lobe of the σ^* -orbital. Such geometries are characteristic for S_N2 reactions and H-bonding, both of which involve electron density transfer from a lone pair to a back lobe of a polarized σ^* -orbital. Because such interactions lead to an increase in the population of an antibonding X–Y orbital, they elongate the

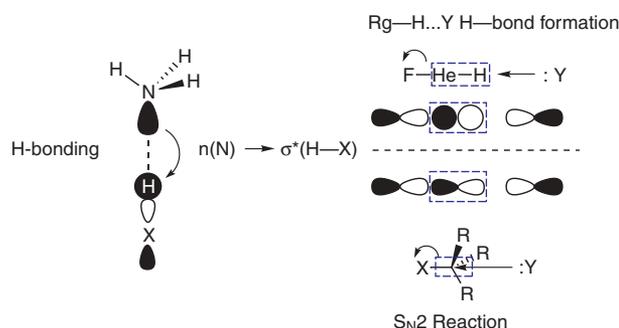


FIGURE 14 | Left: Hyperconjugative stabilization of H-bonded complexes. Right: The analogy of $F \cdots He \cdots H \cdots Y^+$ fragmentation of $FHeH \cdots Y$ complexes with an S_N2 reaction.

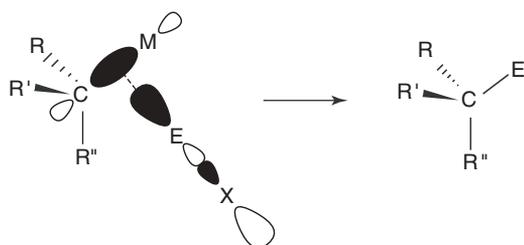


FIGURE 15 | Intermolecular positive hyperconjugation in the transition state for an S_E2 process with retention of configuration. M is an electrofuge, R is an alkyl group, and E is the electrophilic site in the reagent EX.¹²⁶

X–Y bond,^{2,123} leading to the bond cleavage (for the S_N2 reaction), or the well-known red-shift in the IR-stretching frequency widely regarded as the ‘signature of H-bonding’.¹²⁴ The stereoelectronic covalent component of H-bonding is also responsible for the well-defined structural requirements such as the collinear $Y \cdots H-X$ arrangement, which plays a key role in H-bonded supramolecular assemblies. H-bonding and S_N2 -type bond cleavage are merged together in the process of hyperconjugative Rg–H bond elongation in $Rg-H \cdots Y$ complexes, where Rg is a rare gas element (Figure 14).¹²⁵

For intermolecular positive hyperconjugation, the possible interaction geometry is not restricted to the back lobe of the σ -bond. Coordination of an electrophile can occur at the center of the donor bond, leading to a front-side attack in an S_E2 bond cleavage event (Figure 15).

For remote hyperconjugative interactions, the above stereoelectronic requirements can blend into a complex picture. For example, homohyperconjugation has several favorable patterns different in the relative position of the donor and acceptor orbitals in space. Interaction of an equatorial lone pair with the back lobe of an equatorial σ^*_{C-Y} orbital (the W-

effect) is important in azacyclohexanes^{114,127} but not in oxa- and thiacyclohexanes, where an alternative pattern (the Plough effect, Figure 16(b)) plays a more important role. The ‘mirror image’ of the Plough effect, illustrated in Figure 16(c), provides no hyperconjugative stabilization to the molecule (due to the same stereoelectronic reasons that disfavor a front lobe attack in an S_N2 process) but leads to a noticeable elongation of the axial bond. This observation seems to be the first documented hyperconjugative effect without a concomitant stabilization.¹²⁸

Acceptor Ability of Sigma Bonds: The Opposing Roles of Electronegativity and Orbital Energies

A systematic study of the general trends in σ -acceptor properties of C–X bonds in monosubstituted ethanes revealed that 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. Enhancement of acceptor ability of C–X σ -bonds in periods, parallels the increase in electronegativity of X as the result of favorable changes in the σ^* -polarization, which increases both the Fock matrix and overlap matrix elements for the interaction.^{65,129}

On the other hand, augmentation of acceptor ability in these groups is opposite to the changes in electronegativity of X and the C–X bond polarization, following instead the decrease in the energy of σ^*_{C-X} orbitals when one moves from top to the bottom within a group. These trends can be readily understood based on Eq. (1) given in *Natural Bond Orbital (NBO) Analysis*.

The NBO relative order of acceptor ability of σ^*_{C-X} bonds towards an antiperiplanar C–H bond is in the following order (the energies of $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interactions are given in parentheses): X = Br (6.3) > Cl (6.2) > SH(1) (5.4) > F (5.1) > OH(1) (4.7) \approx SH(2) (4.7) \approx SeH (4.7) \approx PH₂(1) (4.6) \approx AsH₂ (4.5) \approx NH₂(1) (4.5) > OH(2) (4.2) > PH₂ (2) (4.0) > NH₂(2) (3.8) \approx GeH₃ (3.8) > SiH₃ (3.6) > CH₃ (3.4) > H (3.2). Two values for several substituents correspond to different conformers.

This simple picture of the acceptor ability of σ -bonds being controlled by electronegativity in periods and by σ^* -orbital energy in groups is changed in monosubstituted ethenes, where the role of electronegativity of the substituent X becomes more important due to increased overlap between σ -orbitals (Figure 17). As a result, the acceptor ability of the σ -bonds in monosubstituted ethenes changes in a more complex fashion. Overall, the acceptor ability of

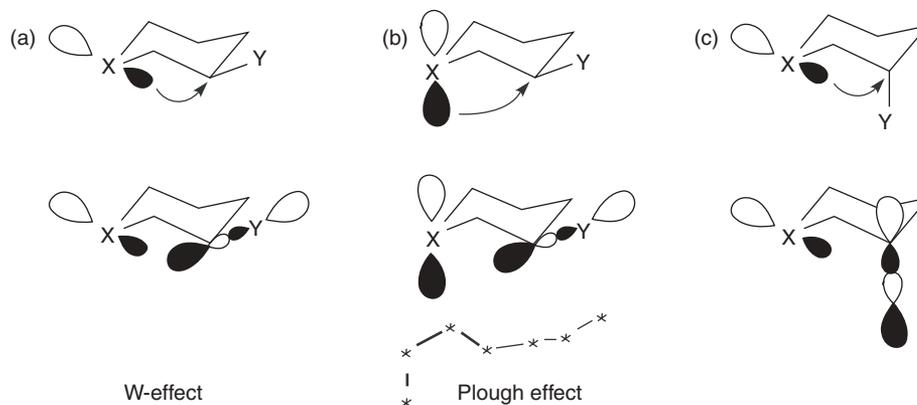


FIGURE 16 | A schematic representation of three possible homoanomeric interactions in six-membered saturated heterocycles: (a) the W-effect, (b) the Plough (the 'Big Dipper') effect, and (c) the 'mirror image' of the Plough effect. Differences in hybridization are neglected.

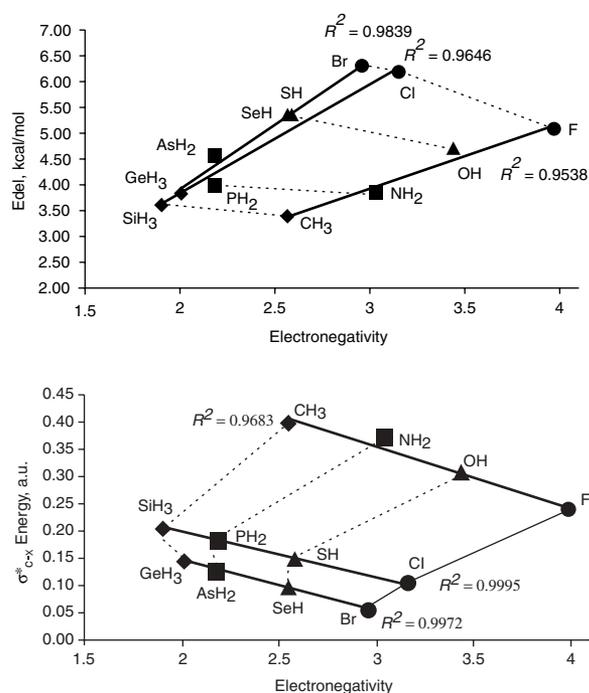


FIGURE 17 | Top: Correlation of energy of vicinal NBO $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interaction, E_{del} with electronegativity of element X in substituted ethanes, CH_3CH_2X . Bottom: Correlation of energy of σ^*_{C-X} orbitals with electronegativity of element X in substituted ethanes, CH_3CH_2X .

σ -bonds can be significantly modified by substitution and is conformer-dependent.

Interestingly, stereoelectronic effects displayed by C–X bonds with X from second and third periods are highly anisotropic. For example, C–chalcogen bonds are excellent σ -acceptors at the carbon end but poor σ -acceptors at the chalcogen end.⁶⁵

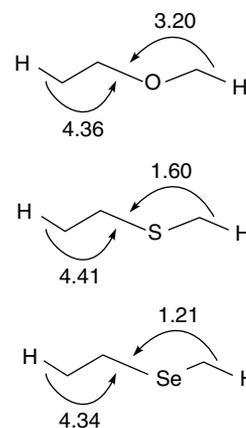


FIGURE 18 | Comparison of acceptor ability (natural bond orbital E_{del} energies in kcal/mol) of C–X bonds in different directions.

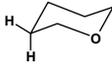
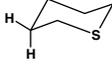
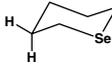
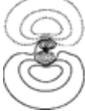
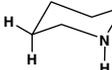
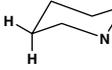
Donor Properties of Lone Pairs

The relatively subtle differences in the hyperconjugative energies given in Figure 18 become more pronounced and chemically significant in hyperconjugative interactions with better donors, such as a lone pair at nitrogen. The NBO data of α -halogen amines indicate that both the high energy of the nonbonding orbital (decreasing the ΔE term) and its higher polarizability (increasing the $F_{i,j}$ term) account for the increased interaction energy.⁶⁵ Selected properties of nonbonding electronic orbitals (lone pairs) of O, S, Se, and N are presented below and summarized in Table 1 and Figure 19.¹¹⁴

Hybridization of Lone Pairs

Differences in hybridization are particularly important for stereoelectronic hyperconjugative interactions due to several reasons. First, hybridization is directly related to molecular geometry, and determines

TABLE 1 | The NBO s-Character, Hybridization and Energy of all Lone Pairs (X = N, O, S, Se) in Selected Saturated Heterocycles at the B3LYP/6–31G** Level, the NBO Plots of the Lone Pairs and s-Character in C–X Bonds. The Axial and Equatorial Lone Pairs are Drawn as Dissected by H_{ax}–C3–X1 or H_{eq}–C3–X1 Planes, Respectively

	s-Character in n(X), % ¹	sp ⁿ (X)	E(X), a.u. ¹	n(X) _{ax} , e	n(X) _{eq} , e	s-Character in C–X, % ²
	0.03 (44.16)	p(sp ^{1.26})	–0.27(–0.54)			20.53 (C); 27.89 (O)
	0.03(69.89)	p (sp ^{0.43})	–0.22(–0.61)			20.54 (C); 15.18 (S)
	0.05 (76.66)	p(sp ^{0.30})	–0.21(–0.67)			18.51 (C); 11.74 (Se)
	17.99	sp ^{4.55}	–0.27	–		23.51 (C); 29.94 (N)
	17.86	sp ^{4.59}	–0.27		–	23.62 (C); 29.65 (N)

¹For X = O, S, Se, the data for the equatorial lone pairs are given in parentheses. Note that NBO energies are different from the canonical MO energies. ²s-Character in hybrid orbitals forming C–X (X = N, O, S, Se) bonds.

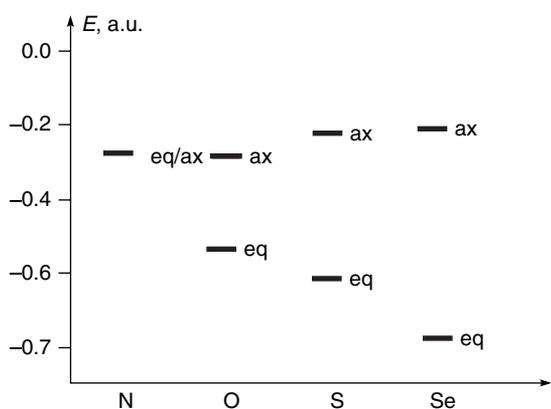


FIGURE 19 | Natural bond orbital energies (in a.u., 1 a.u. = 627.5 kcal/mol) of axial and equatorial lone pairs in oxa-, thia-, seleno-, and azacyclohexane calculated at the B3LYP/6–31G** level.

the valence angles and the direction in which non-bonding orbitals are projected in space for the overlap with acceptor orbitals. Second, hybridization controls the relative size of the two lobes of a lone pair. The front and back lobes are equivalent for purely p-lone pairs, whereas the back lobe decreases in size with decrease in the p-character in hybrid spⁿ lone pairs. Third, hybridization of a donor orbital is related to its absolute energy (Figure 19). An increase in the p-character leads to an increase in orbital en-

ergy that decreases the energy gap between the donor lone pair and an acceptor σ*– or π*–orbital. In general, the donor ability parallels the amount of p-character of a lone pair—lone pairs with 100% p-character are intrinsically better donors than the respective spⁿ hybrids.

Oxygen

In tetrahydropyran, the presence of a higher energy p-orbital (instead of an sp³ hybrid) parallel to the vicinal axial acceptors maximizes the hyperconjugative anomeric n → σ*_{C–Y} interaction. NBO analysis, which determines ‘the best hybrids’ describing a Lewis structure, finds two lone pairs of different hybridizations in tetrahydropyran: a purely p-orbital and an sp^{1.3} hybrid. The deviation from sp hybridization predicted by the idealized model is readily explained by Bent’s rule.^{106,130}

Sulfur and Selenium

In contrast to oxygen, the sulfur atom in thiacyclohexane uses *more* p-character (sp^{5.55}) in its bond with carbon than one would expect from the idealized model. As a result, only a little p-character is left for the equatorial lone pair (sp^{0.4}). This makes this lone pair a relatively poor donor and explains the origin of the drastic differences between the equatorial

lone pairs of sulfur and oxygen in respective saturated heterocycles.

Nitrogen

Nitrogen is more electronegative than carbon and hydrogen and, as expected from Bent's rule, it uses hybrid orbitals with increased s-character for the formation of N-C and N-H bonds (Table 1). This leaves more p-character for the lone pairs compared with what one would expect from the textbook sp^3 hybridization picture. This phenomenon leads to the well-known deviation of valence angles at nitrogen from the classic tetrahedral angle and contributes to the relatively high donor ability of nitrogen lone pairs. In general, an increase in the size of alkyl substituents at nitrogen leads to an increase in the p-character of the nitrogen lone pairs.¹¹⁴

Energies of Lone Pairs

The orbital interaction energy is inversely proportional to the energy gap, ΔE in Eq. (1), which depends on the relative energies of lone pairs. Relative trends in the lone pair energies can be readily understood in terms of their hybridization (percentage of s-character) and the electronegativity of X. An increase in electronegativity and decrease in the p-character lowers the orbital energies of the lone pairs (Figure 16). Although oxygen is more electronegative than nitrogen, the purely p-'axial' lone pair on oxygen has essentially the same energy as the ca sp^5 axial and equatorial nitrogen lone pairs. In this case, effects of hybridization and electronegativity compensate each other. In chalcogens, the energies (and donor ability) of the axial lone pairs increase on going from oxygen to selenium ($O < S < Se$), whereas the energies and donor ability of equatorial lone pairs decrease in the opposite direction ($O > S > Se$). The first trend is explained by the difference in electronegativity and the period number, and the second trend by the increase in the s-character for S and Se relative to that of O. As a result of these two effects, the energy gap between the axial and equatorial lone pairs of chalcogens increases with their atomic number. In every case, the higher energy axial orbitals with 100% p-character are intrinsically better donors than the respective equatorial sp^n hybrids.

Because of the above differences, stereoelectronic effects observed in O- and S-heterocycles cannot be automatically transferred to the N-heterocycles and *vice versa*. The analogy between different chalcogens (O, S, Se) is generally more reliable but the differences in the magnitudes of $n_{ax} \rightarrow \sigma^*_{ax}$ interactions call for caution as well.

Donor Ability of Sigma Bonds

It is well established that such donors as C-Si, C-Ge, and C-Sn bonds are capable of providing significant stabilization to a developing positive charge.¹³¹⁻¹³⁷ However, the relative ability of many common sigma donors, including the most ubiquitous case of C-H versus C-C bonds, is still widely debated. The difference between these two bonds is small in ground-state neutral molecules.¹³⁸ For example, a low temperature X-ray structural study by Spinello and White¹³⁸ found that the differences in the donor abilities of C-C and C-H bonds towards σ_{C-O} acceptors of variable electronic demand are comparable to the experimental uncertainty of measurements. Recent computational studies also found that these differences are small. NBO analysis indicates that C-H bonds are slightly better donors than σ_{C-C} bonds in cyclohexane and related molecules.¹³⁹ A similar conclusion was made by Rablen et al.¹⁴⁰ in a theoretical study on the origin of gauche effect in substituted fluoroethanes. In contrast, EDA computations of Frenking and coworkers¹⁴¹ suggested a slight preference in the opposite direction.

Hyperconjugative effects are expected to be stronger in cations. Baker and Nathan¹⁴² reported that a Me group provides more stabilization to the developing positive charge at the p-benzylic position than Et, i-Pr, and t-Bu groups in the solvolysis of p-alkyl substituted benzyl bromides, and attributed this order of reactivity to the greater donating ability of C-H bonds compared with that of C-C bonds. Although these results are consistent with the trends in³⁴⁻³⁷ carbon NMR chemical shifts of the β -carbon in β -substituted styrenes in solvents of different polarity,¹⁴³ the opposite trend was found in the gas phase pyrolysis of 1-arylethyl acetates, which cast a shadow of doubt on the original interpretation of Nathan-Baker effect.¹⁴⁴

Local steric and electrostatic effects can be minimized and a more balanced description of relative donor ability of σ -bonds can be accomplished if the donor and acceptor sites are not *directly* connected. This approach has been tested computationally using two independent criteria: (1) relative total energies and geometries of two conformers ('hyperconformers') of δ -substituted cyclohexyl cations and (2) NBO analysis of electronic structure and orbital interactions in these molecules.^{118,119}

These effects are estimated by the three isodesmic reactions given in Figure 20. The stabilization energies provided by these isodesmic reactions give different information. Effects of substituents in axial cations, which are described in the top part of Figure 20, include a complicated interplay of many

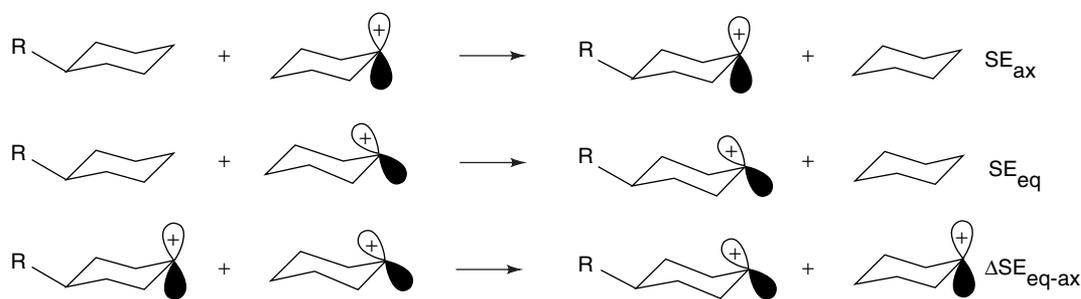


FIGURE 20 | Three isodesmic equations used to calculate substituent stabilization energies [SE_{ax} (top), SE_{eq} (middle), and ΔSE_{eq-ax} (bottom)] in the equatorial and axial cyclohexyl cations.

factors such as hybridization, inductive and field effects, which are still present in these species even when double hyperconjugation is minimized. Interestingly, most of the δ -substituents are destabilizing when compared to the unsubstituted ‘axial’ cation.

In sharp contrast with the situation in ‘axial’ cations, many substituents have a stabilizing effect on the ‘equatorial’ cations (Figure 20, middle). Such effects can be rather large, indicating that δ_{C-X} bonds are capable of efficient interaction with the cationic p-orbital as long as all orbitals participating in the double hyperconjugation interaction relay can overlap efficiently. For the same reason, the destabilizing effects of σ -acceptors such as C–X bonds are also more pronounced in equatorial cations. Thus, the above ‘equatorial’ stabilization energies (SE_{eq}) include stabilization or destabilization provided by σ_{C-X} donors through the double hyperconjugation mechanism. They also include other effects, such as those mentioned in the previous paragraph.

Subtraction of axial SE (SE_{ax}) from SE_{eq} provides the bottom equation of Figure 20, where the contributions of the above nonhyperconjugative (inductive, field, etc.) effects are partially compensated. Although this compensation is not perfect, the ΔSE_{eq-ax} values give an improved estimate of the hyperconjugative stabilization of ‘equatorial’ cations, which has its source predominantly in double hyperconjugative stabilization.

Although the ΔSE_{eq-ax} values from all periods are reasonably well described by a single correlation (Figure 21(a)), suggesting that the ΔSE_{eq-ax} values indeed provide a reasonable estimate of the relative trends in hyperconjugative donor ability of C–R bonds, the δ -substituents cluster into three groups. As shown in Figure 21(a), the first group displays positive ΔSE_{eq-ax} values and consists of cation-destabilizing, strongly electronegative acceptors with Pauling electronegativity of ≥ 3 . The second group includes elements of intermediate electronegativity, which form

C–R bonds with donor abilities close to that of C–H bonds. The final group includes relatively electropositive substituents with negative ΔSE_{eq-ax} values. In this group, the ΔSE_{eq-ax} values are scattered and electronegativity is not a good indicator of donor ability towards the δ -cationic center. The scattering is related to the differences in polarizabilities^{145,146} of C–R bonds in the different periods, as shown in Figure 21(b). The divergence of the curves for different periods is caused by the fact that the more polarizable C–R bonds with heavier elements are more sensitive to the introduction of a positive charge at the remote position even when the electronegativities of the respective elements are close (note H vs B and B vs Ge). The differences in polarizability between the elements of the first and second rows are especially pronounced.

Interestingly, the relative positions of carbon and hydrogen switch depending on the evaluation method. According to SE_{eq} values (‘apparent donor ability’ of substituent R), the CH_3 group is a stronger donor than the H substituent, a trend that is reversed according to ΔSE_{eq-ax} values (‘apparent hyperconjugative donor ability’ of σ_{C-R} bond). In addition, similar switches are observed for a number of other pairs including potentially important combinations of other orbitals of similar donor ability (Cl/O, Br/O, S/O, B/P, C/P, N/Se, etc.).

The difference in the total energies of the axial and equatorial hyperconjugomers (ΔSE_{eq-ax}) gives an estimate of σ -donor ability that follows the order (Al,Ga) \gg Ge > As \geq Si > P > B > Se > H > C > S > Br > N > Cl > O > F (\geq means that difference is less than 0.5 kcal/mol, \gg stands for the difference more than 3 kcal/mol). Although this scale may not isolate hyperconjugation completely from the other components, these SE are chemically meaningful and can be verified experimentally.

The hyperconjugative origin of these substituent effects has been confirmed with NBO dissection,

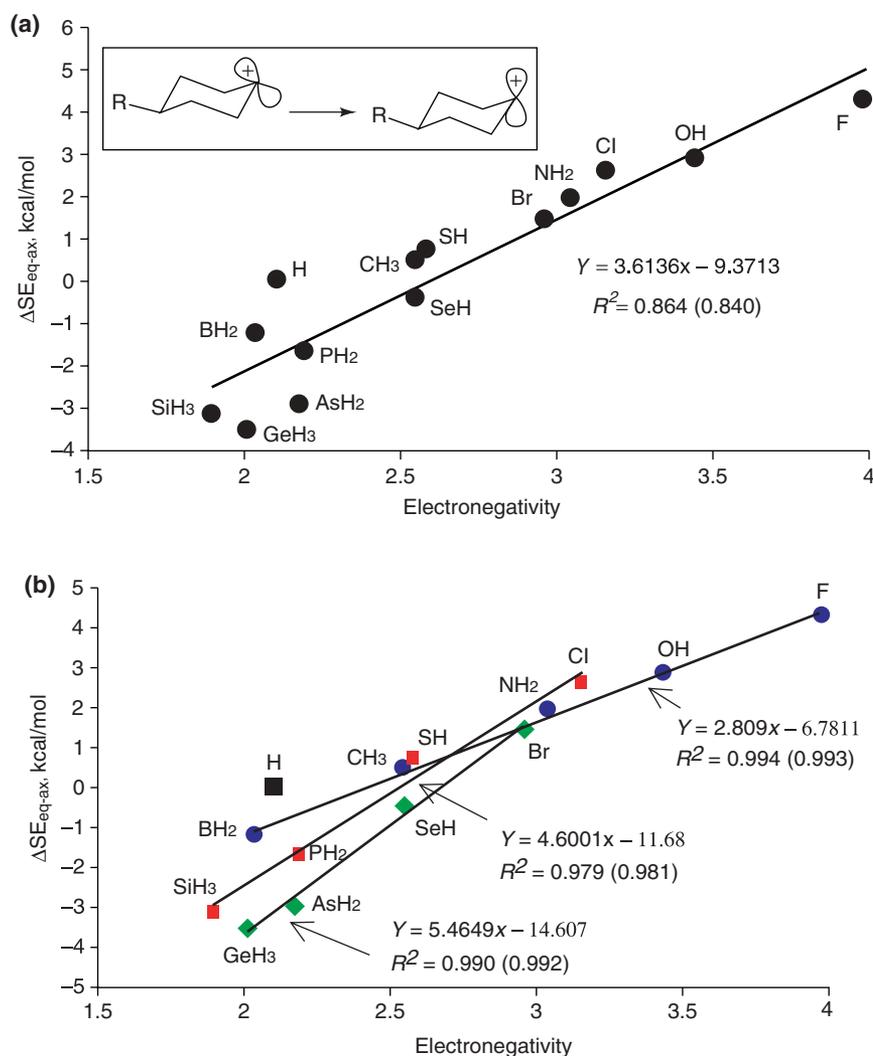


FIGURE 21 | Two correlations between the differences in stabilization energies of δ -XHn substituents in the equatorial and axial cyclohexyl cations (Figure 12) and electronegativity of X. (a) The left plot corresponds to the general correlation. (b) The right plot gives separate correlations for each row. Calculations were performed at the B3LYP/6-31G** (B3LYP/6-311++G**) level (Reprinted with permission from Refs 118 and 119).

which included analysis of the interaction energies and orbital populations. Interestingly, the C–C bond is not a spectator, but a dynamic gating factor capable of fine-tuning double hyperconjugation—shutting it off when a strong acceptor is present at the δ -position or turning it on when a strong donor at this position is available.

The above data illustrates that the somewhat larger intrinsic donor ability of the C–H bonds compared with that of C–C bonds can be overshadowed by cooperative double hyperconjugation with participation of remote substituents. As a result, the *apparent* donor ability of C–C bonds can vary in a wide range and the relative order of donor ability of C–H and C–C bonds can be easily inverted depend-

ing on the molecular connectivity and environment. Analogously, the order of donor ability of other sigma bonds in organic molecules is not set in stone but can be changed by communication with remote substituents *via* the σ -framework.

Decreasing the Energy Gap: Stretched Bonds as Donors and Acceptors in Hyperconjugative Interactions

Stretched bonds are good partners in hyperconjugative interactions (both donors and acceptors) due to the fact that C–X bond weakening decreases the $\sigma_{C-X}/\sigma_{C-X}^*$ energy separation, due to the

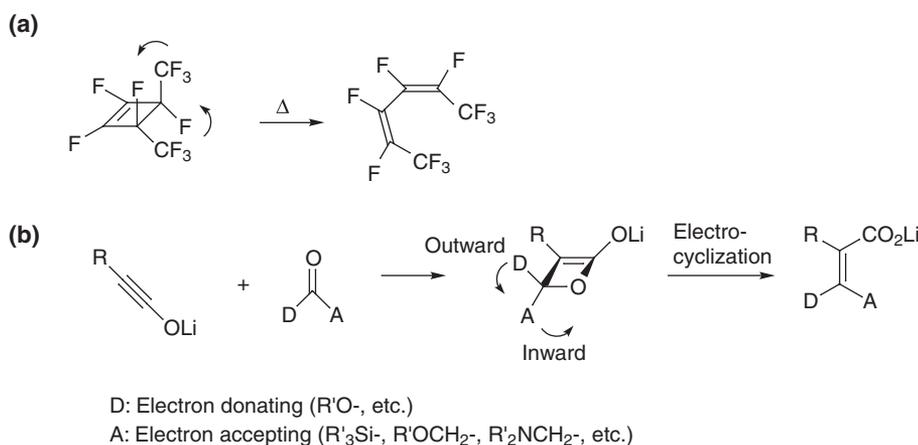


FIGURE 22 | Examples of stereoselective cyclobutene and oxacyclobutene ring openings.

simultaneous destabilization of $\sigma_{\text{C}-\text{X}}$ and stabilization of $\sigma^*_{\text{C}-\text{X}}$ as they are transformed into the non-bonding orbitals.

Torque selectivity

An example of dramatic hyperconjugative effects on reactivity is provided by torque selectivity (the preference for ‘inward’ or ‘outward’ rotation of substituents in electrocyclic ring opening reactions) in thermal cyclobutene ring opening.^{147,148} Although the opening can proceed through two symmetry-allowed conrotatory pathways, Dolbier et al.^{149,150} observed a dramatic kinetic preference for the inward versus outward rotation for different substituents (Figure 22). Another illustrative example in Figure 22 is provided by elegant work of Shindo and coworkers¹⁵¹ who efficiently used hyperconjugation to obtain stereodefined products from oxacyclobutenes. Similarly, Murakami et al.^{152,153} reported that boryl and silyl groups behave as σ -acceptors and prefer to rotate inward in the cyclobutene ring-opening reaction despite the steric congestion. In all examples, electron donors rotate outward whereas the acceptors prefer an inward rotation.

Houk and coworkers provided convincing theoretical rationale for these striking selectivities. The key stereodefining effect is interaction of the σ and σ^* associated with the breaking of $\text{C}-\text{C}$ bonds with donor and acceptor orbitals of the substituents. As the $\text{C}-\text{C}$ bond is stretched, the energy of the σ -orbital is raised and that of σ^* -orbital is lowered and, in the TS, they become the HOMO and the LUMO, respectively (Figure 23).

Antiperiplanar orbital arrangement in the outward rotation maximizes interaction between the donor orbital of the substituent and σ^* -orbital of the

stretched cyclobutene bond (the LUMO of the TS). On the other hand, acceptor substituents with a low-lying vacant orbital prefer an inward conrotation, in which this orbital overlaps directly with the σ^* -orbital of the stretched bond (the HOMO of the TS). Both of these effects correspond to a two-electron interaction and stabilize the TS.

Diastereoselection in Nucleophilic Addition to Carbonyl Compounds and Other π -Systems

A widely discussed model proposed by Cieplak suggests that the key stereoelectronic factor determining the axial approach of nucleophilic attack on the $\text{C}=\text{O}$ group involves electron donation from axial $\text{C}-\text{H}$ bonds to the antibonding orbital associated with the incipient (forming) bond between incoming nucleophile (Nu) and the carbonyl carbon. In this model, the axial approach is favored because the above stabilizing interaction is more efficient than the analogous interaction with $\text{C}-\text{C}$ bonds during the equatorial approach of Nu (Figure 24).¹⁵⁴⁻¹⁵⁹ The larger donor ability of $\text{C}-\text{H}$ bonds compared to that of $\sigma_{\text{C}-\text{C}}$ bonds is the cornerstone of this model.¹⁶⁰ This suggestion stimulated many experimental¹⁶¹⁻¹⁶⁶ and theoretical¹⁶⁷⁻¹⁶⁹ studies.

Accentuation of Homoanomeric Interactions by Stretching of Acceptor Bonds

The relatively small interactions can be amplified dramatically when acceptor bonds are further stretched and polarized, for example, in the process of heterolytic bond cleavage as demonstrated in Figure 25.

Homoconjugative assistance by the lone pair of nitrogen plays a key role in the heterolytic $\text{C}-\text{Cl}$ bond cleavage in β -chloropiperidine.¹¹⁴ As the $\text{C}-\text{Cl}$ bond stretches, the energy of the $n(\text{N}) \rightarrow \sigma^*_{\text{C}-\text{Cl}}$

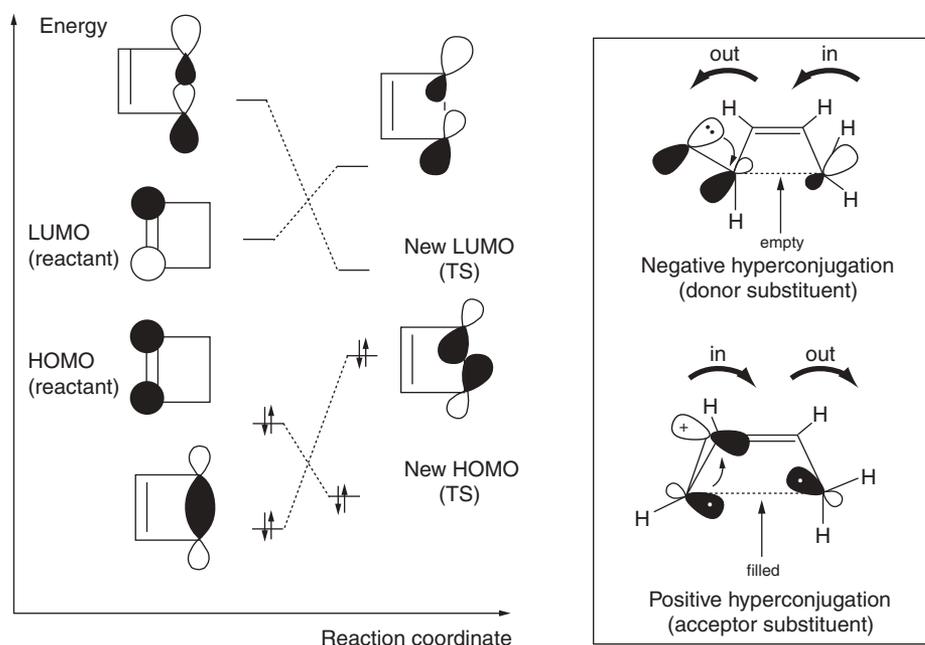


FIGURE 23 | Left: Changes in HOMO and LUMO upon stretching and twisting of the central σ -bond. Right: Dominant hyperconjugative interactions that control outward rotation of a donor substituent and inward rotation of an acceptor substituent. In the first case, the key interaction is negative hyperconjugation between the transition state (TS) HOMO (a stretched and twisted σ -orbital) with a substituent empty p-orbital (same topology is important for an acceptor σ^* - or a π^* -orbital). In the second case, the key interaction is positive hyperconjugation between the TS LUMO (a stretched and twisted σ^* -orbital) with a substituent filled p-orbital (same topology is important for a donor σ - or a π -orbital).

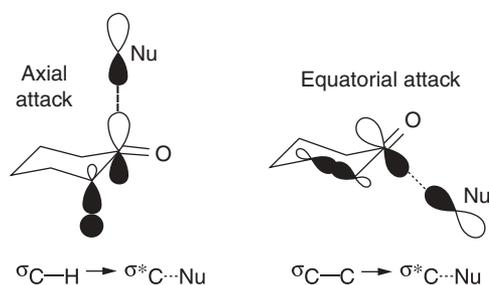


FIGURE 24 | The most important transition state stabilizing hyperconjugative interactions for axial and equatorial nucleophilic addition to cyclohexanone according to the Cieplak's model.

interaction increases significantly even at β -C–N distances, which are well above that for C–N covalent bond formation. Figure 25 also quantifies electron density transfer from the nitrogen lone pair to the acceptor $\sigma^*_{\text{C-Cl}}$ orbital that results in a smooth transformation of this initially weak homohyperconjugative interaction into an intramolecular $\text{S}_{\text{N}}2$ reaction, as the line between hyperconjugation and chemical reaction blurs.

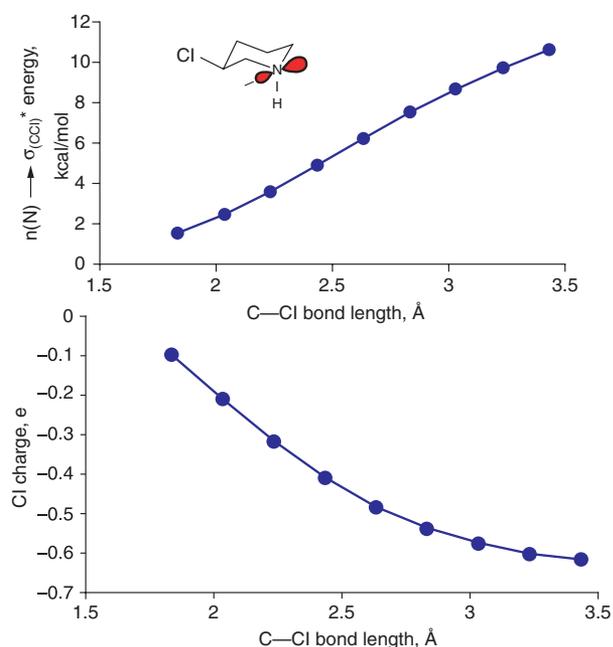


FIGURE 25 | Correlation of C–Cl distance with the natural bond orbital (NBO) energies of $n(\text{N}) \rightarrow \sigma^*_{\text{C-Cl}}$ interaction and the NBO charge at Cl during the process of C–Cl bond stretching in 3-chloropiperidine.

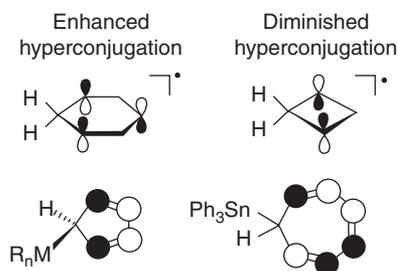


FIGURE 26 | Molecular orbital symmetry effects on hyperconjugation efficiency in cyclic systems.

Cooperativity of Hyperconjugative Interactions

Molecular symmetry can lead to an enhancement (or cancellation) of hyperconjugative hyperfine coupling in the electron paramagnetic resonance spectroscopy of cyclic π -conjugated organic radicals (Figure 26).¹⁷⁰ Davies¹⁷¹ suggested that this observation can be readily extended to hyperconjugation in spin-paired molecules as well. For example, the cyclopentadienylmetal compound in Figure 26 has a symmetrical LUMO and should show symmetry-enhanced hyperconjugation. In contrast, triphenylstannylcycloheptatriene has an antisymmetric LUMO, which renders the positive $\sigma_{C-Sn} \rightarrow \pi^*$ interaction less favorable.

This effect has consequences for the relative isomer stabilities, bond lengths, angles, and one-bond NMR coupling constants. Systems in which the effect plays a significant role include the Wheland intermediates of electrophilic aromatic substitution, the loose complexes formed between metal cations and arenes, and η^1 -cyclopentadienylmetal compounds.¹⁷¹

Even within the same overlap topology, one can change symmetry properties by populating additional MOs. Hyperconjugative patterns in saturated six-membered heterocycles illustrate how cooperativity depends on the number of electrons. In these systems, donation from a lone pair to two σ^*_{C-H} orbitals (a two-electron pattern) is cooperative, whereas donation from two lone pairs to the same σ^*_{C-H} orbital (a four-electron pattern) is anticooperative (Figure 27).¹¹⁴ These effects are fully consistent with the different symmetry of the frontier MOs. Interestingly, when the strength of negative hyperconjugation increases 2.5-fold upon a change from σ^*_{C-H} to σ^*_{C-Cl} , the cooperativity effect increases four times. A further increase in acceptor ability of σ^* orbital transforms the $2\sigma^* + n(X)$ interaction into the classic σ -homoaromatic array.^{172–177}

Hyperconjugation with σ^* bridge orbitals can also provide an efficient coupling pathway (usually

referred to as through bond (TB) coupling) for non-bonding electrons, which can compete with the direct through space interactions. The dominant role of TB interactions in coupling of the two radical centers in p-benzynes and related molecules is illustrated by observed energy lowering of the antisymmetric combination of the two radical centers with the σ^* -orbitals of the bridge.^{178–184} This interaction renders the Bergman cyclization a symmetry allowed process¹⁸⁵ and provides an additional 3–5 kcal/mol of stabilization energy to the p-benzyne-type diradical, which is not available in related monoradicals.^{186–189} Because this stabilizing effect is lost in the first H-abstraction by p-benzyne, it renders this species less reactive and more selective in H-abstraction reactions in comparison to the phenyl radical. Interestingly, coupling between the nonbonding orbitals is dramatically enhanced upon one-electron reduction.¹⁹⁰

EXAMPLES/STEREOELECTRONIC EFFECTS

Because of the prevalence of σ -bonds in chemical structures, hyperconjugation displays itself in numerous effects on structure, conformation, and reactivity. An important feature of hyperconjugative interactions is their stereoelectronic component—such interactions that depend on overlap of orbitals in space. This feature leads to several preferred overlap modes of intramolecular and intermolecular hyperconjugation patterns, which we will illustrate with several examples given below.

Rotational Barriers: Ethane

The forces controlling the barrier to rotation around formally single bonds serve as one of the cornerstones of conformational analysis. Not surprisingly, ethane, the parent system for studies of rotational barriers, has been extensively investigated. The origin of the ~ 3 kcal/mol lower energy of the staggered conformation responsible for the rotational barrier in ethane has usually been attributed to steric repulsion between electrons in the C–H bonds in the eclipsed conformation.¹⁹¹ Alternatively, rotation-induced weakening of the central C–C bond¹⁹² and hyperconjugation^{17,193–195} has been considered to be the reasons for the higher stability of the staggered conformation. Mulliken,¹⁹⁶ as early as 1939, conjectured that hyperconjugation plays an important role in the internal rotation potential of ethane-like molecules.

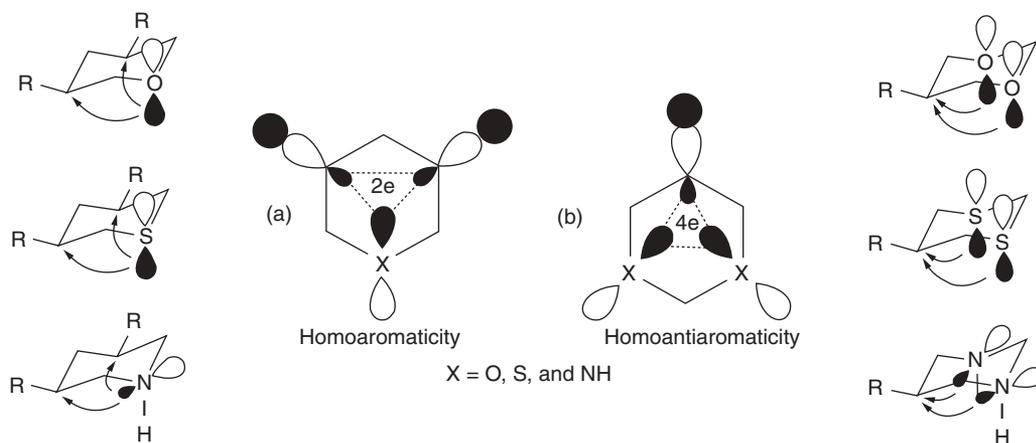


FIGURE 27 | σ -Homoaromaticity (two-electron system a) and antiaromaticity (four-electron system b) in six-membered heterocycles.

Pophristic and Goodman¹²⁰ used NBO analysis to dissect the contributions of the three principal contributors to ethane's structural preferences and separate steric and hyperconjugative interactions. They found that removal of vicinal hyperconjugation interactions yields the eclipsed structure as the preferred conformation, whereas Pauli exchange (steric) and electrostatic (coulombic) repulsions have no influence on the preference for a staggered conformation. The hyperconjugative preference for the staggered conformation is attributed to the antiperiplanar stereoelectronic requirement summarized in Figure 13.

Subsequent studies by Bickelhaupt and Baerends¹⁹⁷ and by Mo et al.¹⁹⁸ resurrected the steric repulsion explanation as the dominant contribution in the overall barrier. Bickelhaupt and Baerends by their EDA-based study found hyperconjugative stabilization in the staggered conformation to be ~ 0.4 kcal/mol. BLW-based analysis by Mo and coworkers suggested that hyperconjugation interaction did favor the staggered conformation but provided only one-third of the total barrier. These discrepancies are based on the conceptual differences between the EDA, BLW, and NBO models discussed in the section *Positive Hyperconjugation*, such as on the nonorthogonality of initial orbitals in the two former procedures and the conceptual differences in the treatment of steric effects.

Neutral Hyperconjugation in Alkenes and Alkynes

Thermochemistry

Not only has neutral hyperconjugation in closed-shell species been controversial, but recently even

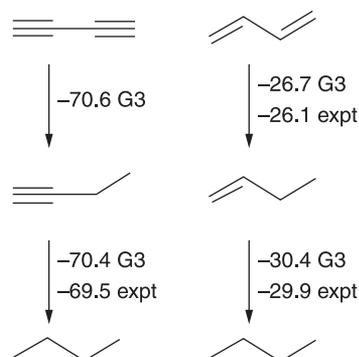


FIGURE 28 | Comparison of the G3(MP2) calculated enthalpies of formation ΔH_f^{298} (G3) and experimental hydrogenation ΔH_{hyd} (expt) in kcal/mol of butenes and butynes. According to these estimates, the conjugation energy of 1,3-butadiene (right) is 3.9 ± 0.1 kcal/mol, but for 1,3-butadiyne (left), it is zero.

the importance of classic π -conjugation came under scrutiny. In a provocative series of papers, Rogers et al.^{199,200} disclosed that 'conjugation stabilization of 1,3-butadiene is zero' when estimated through the classic approach of Kistiakowsky et al.²⁰¹ Kistiakowsky suggested that conjugative stabilization in butadiene can be assessed by stepwise hydrogenation first to 1-butene and then to butane (Figure 28). The first step is 3.8 kcal/mol less exothermic than the second step, which according to Kistiakowsky et al. indicates the strength of the π -conjugation in 1,3-butadiene. Although one would expect 1,3-butadiyne, which has two pairs of conjugating double bonds, to have stronger conjugative stabilization than 1,3-butadiene, the two steps in hydrogenation of 1,3-butadiyne yields are equally exothermic, suggesting that the conjugation in the former compound is zero! Why would conjugation disappear in alkynes?

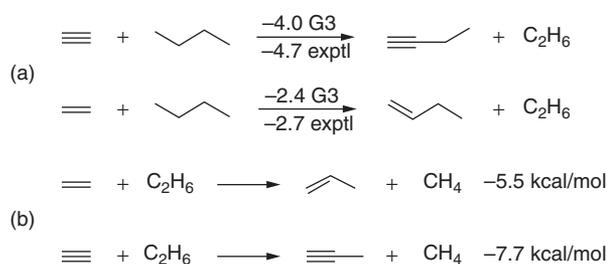


FIGURE 29 | (a) Conventional equations for the evaluation of hyperconjugation.²⁰² (b) Revised bond separation energy values for alkene and alkyne hyperconjugation, corrected for protobranching.⁵¹

Interpretation of the above results clearly underscores the importance of neutral hyperconjugation for the stability of unsaturated compounds. Jarowski et al.²⁰² pointed out that the reference compounds for 1,3-butadiyne and 1,3-butadiene are stabilized significantly by hyperconjugation, which is not present in 1,3-butadiyne and 1,3-butadiene. In order to take hyperconjugative interactions into account, the stabilization of ethylene (in kcal/mol) by an ethyl substituent (2.4 G3; 2.2 G3 (MP2); 2.7 experimental) can be estimated from the difference between the heats of hydrogenation of ethylene and 1-butene. Likewise, the hyperconjugative stabilization of acetylene by an ethyl group [4.9 G3; 4.8 G3 (MP2); 4.7 experimental] is the difference between the heat of hydrogenation of acetylene and 1-butyne. Equivalently, the hyperconjugative stabilization can also be described by isodesmic reactions in Figure 29(a) that produces data consistent with the above evaluation.

Determined by the modified method, the conjugative stabilization of butadiyne and butadiene were both found to be significant. After correction for unequal hyperconjugative stabilization, the conjugation energies were estimated as 9.3 and 8.2 kcal/mol for diynes and dienes, respectively. Pertinent to this discussion is the observation that when evaluated by the conventional method, hyperconjugation in alkynes is twice as large as hyperconjugation in alkenes and that the conjugative stabilization for butadiene and butadiyne in Kistiakowsky's scheme is partially compensated by the hyperconjugative stabilization of 1-butene and 1-butyne. These hyperconjugative interactions are large enough to fully obscure the conjugative stabilization in 1,3-butadiyne! Later, it was suggested that hyperconjugative values from Figure 29(a) are too low because the reference²⁰³ compound in both these equations, propane, is stabilized by protobranching. Equations in Figure 29(b) give new estimates for hyperconjugation in alkenes and alkynes

(based on the assumption that no protobranching corrections are needed for propyne and propene).

Furthermore, Frenking and coworkers¹⁴¹ provided EDA-based evaluation of delocalizing interactions in alkenes and alkynes and reported that hyperconjugation is roughly half as strong as π -conjugation between two multiple bonds. The calculated values for the hyperconjugation in propene and its trimethyl-substituted derivative $\text{H}_2\text{C}=\text{CHCMe}_3$ ($\Delta E_\pi = -9.3$ – 9.5 kcal/mol) suggests that the hyperconjugative stabilization of C–H and C–C bonds with olefinic double bonds is half as strong as that of alkyne triple bonds. As a result, hyperconjugative stabilization of the degenerate π -systems in alkyl substituted alkynes ($\Delta E_\pi = -20.1$ kcal/mol) such as 1-propyne and 4,4-dimethyl-1-butyne is as strong as the conjugative stabilization in 1,3-butadiene (-19.5 kcal/mol).¹⁴¹

Considering these findings, it is not surprising that hyperconjugation is capable of rationalizing the well-known thermodynamic preferences for the formation of more substituted alkenes (Saytzeff rule). BLW estimates by Hiberty and coworkers²⁰⁴ suggest that for both C_4H_8 and C_5H_{10} , hyperconjugation effects stabilize the most substituted product by ~ 6 kcal/mol. This contribution is larger than the actual thermodynamic preference expressed by Saytzeff's rule.

Conformational Equilibrium

Another illustration of the importance of neutral hyperconjugation in propene is provided by its conformational profile. The stable propene conformation is called 'eclipsed' because one methyl C–H bond eclipses the vicinal $\sigma_{\text{C}-\text{C}}$ bond. The 'staggered' conformation, in which one methyl C–H bond eclipses the adjacent vinyl C–H bond, is less stable by ~ 2 kcal/mol.²⁰⁵ These names are misnomers because the 'eclipsed' conformation of propene is stereoelectronically analogous to the staggered conformation of ethane (Figure 13) and *vice versa*.

NBO analyses by Lin et al.²⁰⁶ confirmed that the hyperconjugation interaction is the main reason for the greater stability of the eclipsed structure of propene. The most important hyperconjugation interaction observed between the methyl and vinyl groups is divided into three components: the $\pi_{\text{CH}_3} \rightarrow \pi^*_{\text{C}=\text{C}}$ interaction, the $\pi^*_{\text{CH}_3} \rightarrow \pi_{\text{C}=\text{C}}$ interaction, and the vicinal interaction between the in-plane $\sigma_{\text{C}-\text{H}}$ orbitals of the methyl group and the σ^* -orbital of the antiperiplanar vinyl C–H bond (Figure 30). A similar explanation has been offered for the origin of conformational preferences in carbonyl compounds by Basso and coworkers.²⁰⁷

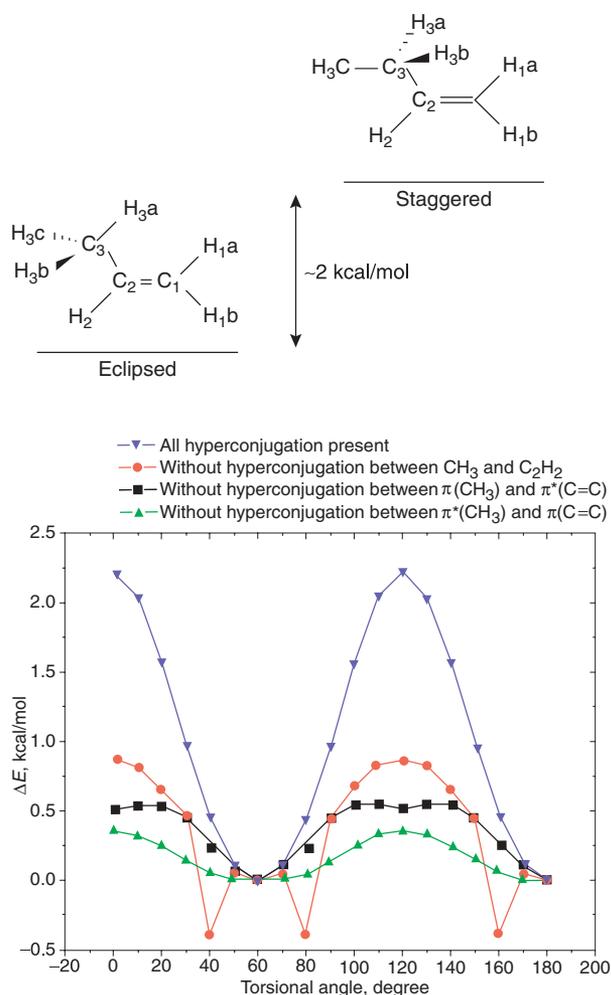


FIGURE 30 | The difference between eclipsed and staggered conformers of propene and natural bond orbital-derived rotational potential energy surface without certain hyperconjugation interactions (reprinted with permission from Ref 206).

Hyperconjugation in Cyclohexane and Cyclohexyl Cation: Hyperconjomers

Because of their well-defined geometries, cyclic systems lend themselves for studies of hyperconjugative interactions. Hyperconjugation has been proposed to explain why the axial C–H bonds are longer and weaker than the equatorial bonds,¹³⁹ as well as the rationale for the lower energy of the equatorial conformer of methyl cyclohexane (Figure 31), its 4-oxa, 4-aza, 4-thia analogues,²⁰⁸ as well as other substituted cyclohexanes^{209,210} and cyclohexenes.^{211,212}

The role of hyperconjugation increases dramatically in cyclohexyl cations where it has a profound effect on structure and stability. An elegant study of Rauk and coworkers^{213,214} reported that the different hyperconjugation stabilization patterns lead to

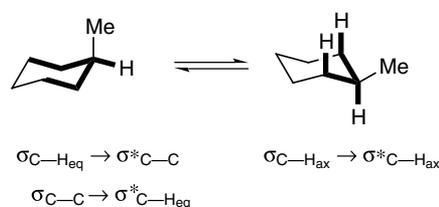


FIGURE 31 | Bonds involved in the main hyperconjugative interactions which influence the conformational equilibrium of methylcyclohexane (Reprinted with permission from Ref 208).

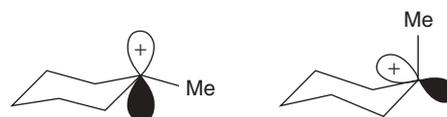


FIGURE 32 | Axial and equatorial 'hyperconjomers' of cyclohexyl cations.

the formation of two chair conformers of 1-Me-1-cyclohexyl cation where the carbocation p-orbital is oriented either 'axially' or 'equatorially.' These conformers, called 'hyperconjomers', have distinctly different modes of hyperconjugative stabilization. The axial cationic orbital in the first hyperconjomers interacts strongly with the adjacent axial C–H bonds, whereas the equatorial vacant p-orbital in the second cation interacts most strongly with the antiperiplanar C–C bonds (Figure 32).

A detailed NBO analysis of the electronic structures of these species is summarized in Figure 33. As suggested earlier by Rauk et al.^{213,214} for 1-Me-cyclohexyl cations, the $\sigma_{C-C} \rightarrow n(Cl)$ and $\sigma_{C-H_{ax}} \rightarrow n(Cl)$ interactions play the dominant roles in stabilizing the equatorial and axial 'hyperconjomers'. Interestingly, the $\sigma_{C-C} \rightarrow n(Cl)$ interaction is larger than the $\sigma_{C-H_{ax}} \rightarrow n(Cl)$ effect in contrast to the $\sigma_{C-H_{ax}} \rightarrow \sigma^*_{C-H_{ax}} > \sigma_{C-H_{eq}} \rightarrow \sigma^*_{C-C}$ order in neutral cyclohexane.¹³⁹ This observation does not indicate inversion of the relative donor ability of C–H/C–C bonds. Instead, its origin is in a nonperfect overlap of the vacant orbital with the 'axial' C2–H bond as a result of planarization at C1. On the other hand, planarization also increases the overlap of the positive center with the 'equatorial' C2–H bond, thus allowing the cation to benefit from the hyperconjugative interaction with two donors at the same time. Although the energy of combined $\sigma_{C-H_{ax}} \rightarrow n(Cl)$ and $\sigma_{C-H_{eq}} \rightarrow n(Cl)$ interactions in the 'axial' conformer is greater than that of $\sigma_{C-C} \rightarrow n(Cl)$ interactions in the 'equatorial' conformer, 31.5 versus 27.2 kcal/mol¹, the balance of hyperconjugative effects is tipped in favor of the 'equatorial' conformer

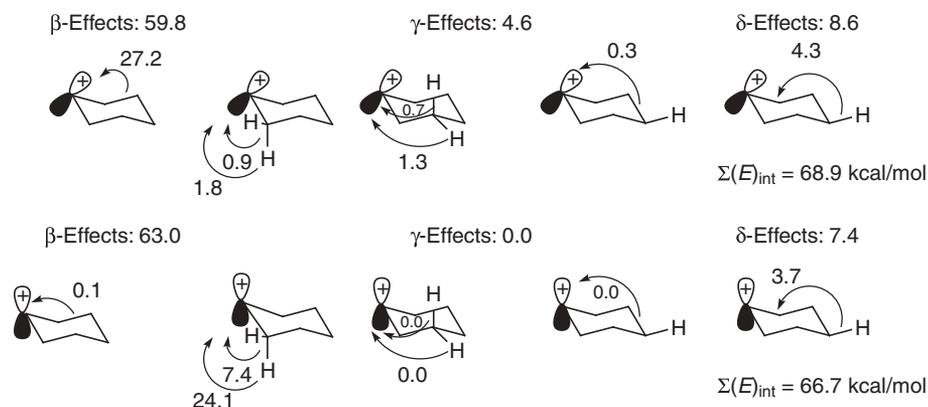


FIGURE 33 | Second-order perturbation natural bond orbital energies in kcal/mol for important hyperconjugative interactions in axial and equatorial cyclohexyl cations (B3LYP/6-31G**).

by subtle effects involving remote donor moieties: γ - $\sigma_{\text{C-H}_{\text{eq}}} \rightarrow n_{\text{C1}}$ homohyperconjugation with through-space participation of $\gamma_{\text{C-H}}$ bonds and an increased double hyperconjugation manifested in the δ - $\sigma_{\text{C-H}_{\text{eq}}} \rightarrow \sigma^*_{\text{C-C}}$ interaction.

These observations underscore the importance of double hyperconjugation in hyperconjugomers which renders these species useful tools for the analysis of the relative donor ability of σ -bonds (*Donor ability of sigma bonds*)

Anomeric and Homoanomeric Effects

The anomeric effect is one of best documented and the well-studied of the hyperconjugative effects.^{8-16,215-217} This effect was originally defined as the preference for an electronegative substituent positioned next to an oxygen atom in a tetrahydropyran ring (or at the anomeric carbon of pyranoses) for occupying an axial rather than an equatorial position.^{8-16,218} It was subsequently recognized that this preference is a consequence of a more general effect, which requires that a lone pair n_{X} at heteroatom X and C-Y bond in a YCH_2X moiety are aligned in an antiperiplanar geometry²¹⁹⁻²²¹ that maximizes the hyperconjugative $n(\text{X}) \rightarrow \sigma^*_{\text{C-Y}}$ interaction (Figure 34). Similar stereoelectronic requirements for the relative positions of donor and acceptor orbitals are also manifested in conformational equilibria of substituted cyclohexanes.²⁰⁹ Although there are several components of the anomeric effect, such as an electrostatic component (e.g., dipole-dipole interactions and steric effects), the above hyperconjugative interaction of the antiperiplanar orbitals plays a particularly important role. This is reflected in structural changes (C-Y bond elongation and C-X bond

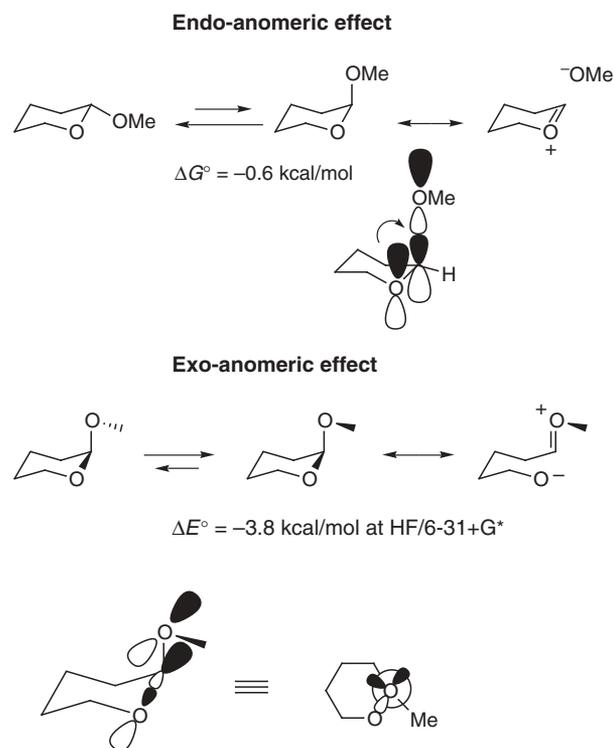


FIGURE 34 | Dominating antiperiplanar negative hyperconjugative interactions involved in endo- and exo-anomeric effects.

shortening), in the distribution of electron density (increased negative charge on Y), and in reactivity (C-Y bond weakening). An analogous interaction with the lone pair of an exocyclic heteroatom Y and $\sigma^*_{\text{C-X}}$ of the ring provides a stereoelectronic basis for the so-called exo-anomeric effect—preference for the synclinal (gauche) arrangement of the Y-C and C-X bonds. The same preference is observed for the acyclic

X–C–Y–C systems where X and Y are heteroatoms with at least one lone pair, commonly oxygen, nitrogen, and fluorine.²²² The latter is sometimes called the gauche effect (*vide infra*) and is important for determining the conformational energy profiles for important classes of organic molecules such as acetals and esters.

The relative roles of the W- and the Plough homoanomeric effects in aza-, oxa-, thio-, and selenaheterocycles were investigated with NMR experiments and NBO analyses (Table 1).^{223–225} These effects play an important role in the relative trends in one-bond $^1J_{\text{CH}}$ coupling constants, needed for the understanding of conformational properties of carbohydrates, azacarbohydrates, and other substrates of biological interest.^{7, 226–232}

Although the homoanomeric effects are considerably weaker than the classic vicinal anomeric $n(\text{X})_{\text{ax}} \rightarrow \alpha\text{-}\sigma^*_{\text{C}-\text{Y}_{\text{ax}}}$ interactions, their importance increases significantly when the acceptor ability of σ^* -orbitals increases as a result of bond stretching and/or polarization. For example, solvolysis of piperidines and pyrrolidines with a leaving group at the β -carbon proceeds through the formation of cyclic aziridinium cations, due to anchimeric assistance from the nitrogen lone pair.^{233–235} The presence of such intermediates leads to retention of configuration and efficient transfer of chirality in their respective ring contraction or expansion reactions.²³⁶ Topologically similar transformations are the key mechanistic steps of Payne and aza-Payne rearrangements.^{237–239}

In addition to the anchimeric assistance in the formation of bridged cationic intermediates, there is clear structural and spectroscopic evidence for homoanomeric interactions in neutral ground state molecules at their energy minimum conformations. For example, the C5–H equatorial bond in 1,3-dioxane is longer than the C5–H axial bond, and the respective direct NMR $^{13}\text{C}-^1\text{H}$ coupling constant is smaller than that for the axial bond ($^1J_{\text{CH}_{\text{eq}}} < ^1J_{\text{CH}_{\text{ax}}}$).^{240–242} This phenomenon (the reverse Perlin effect) contrasts with the ‘normal’ situation, for example, in cyclohexane, where the axial C–H bond is longer and the corresponding $^1J_{\text{CH}}$ constant is smaller (the normal Perlin effect). The key hyperconjugative interaction leading to the reverse Perlin effect in 1,3-dioxane is that of the equatorial C5–H bond with the pseudoaxial lone electron pair on the β -oxygen (the Plough effect) and that the $n_{\text{eq}} \rightarrow \sigma^*_{\text{eq}}$ (the W-effect) was unimportant in 1,3-dioxane, 1,3-dithiane, and 1,3-oxathiane.¹¹⁴ The situation changes in azacyclohexanes, where the W-effect is greater than the Plough effect due to more favorable hybridization of nitrogen lone pairs.¹¹⁴

Hydrogen Bonding

Although hydrogen bonding is a complex phenomenon and many subtle factors may be involved in the formation of X–H \cdots Y hydrogen bonded complexes,^{243–250} $n(\text{Y}) \rightarrow \sigma^*_{\text{X}-\text{H}}$ negative hyperconjugation (which is often called ‘covalent component’ or ‘charge transfer component’, Figure 1) is one of the two largest H-bond stabilizing effects, along with the electrostatic interaction between inherent and induced dipoles.

The importance of hyperconjugative interactions from a lone pair of the H-bond acceptor to the $\sigma^*_{\text{X}-\text{H}}$ orbital of the H-bond donor is well-documented by NBO energetic analysis.² Because such interactions lead to an increase in the population of an antibonding X–H orbital, they elongate the X–H bond. Only when the hyperconjugative component of H-bonding is weak, can the above bond-lengthening effect be compensated by bond repolarization and rehybridization, and the formations of the so-called blue-shifting H-bonds occur (Figure 35).¹⁹⁰

The Gauche Effect

The gauche effect is the preference for the gauche conformation in X–C–C–Y systems (1,2-disubstituted ethanes) in the case of two acceptor substituents X and Y (Figure 36).^{251,252} Although X and Y are usually F or O, the choice of the second substituent Y is quite broad in fluoroethanes, X = F.²⁵³ The gauche effect is useful for control of chemical structure and reactivity.^{254–257} For example, the gauche effect has been utilized to achieve efficient and ‘strain-free’ conformational control in the elusive 5-endo-dig cyclization of carbon-centered radicals.²⁵⁸

The dominating role of antiperiplanar hyperconjugative $\sigma_{\text{C}-\text{H}} \rightarrow \sigma^*_{\text{C}-\text{X}}$ and $\sigma_{\text{C}-\text{H}} \rightarrow \sigma^*_{\text{C}-\text{Y}}$ interactions in this effect has been shown with the NBO analysis.²⁵⁹ For X = Cl, Br, and I, the anti-conformation is more stable than the gauche due to the fact that bonds to heavier halogens are not only good acceptors but good donors as well and the $\sigma_{\text{C}-\text{Y}} \rightarrow \sigma^*_{\text{C}-\text{X}}$ interactions become sufficiently large to compete with the $\sigma_{\text{C}-\text{H}} \rightarrow \sigma^*_{\text{C}-\text{X}}$ interactions. A stereoelectronic preference for the synclinal conformation in acyclic X–C–Y–C systems is often also called the gauche effect but is, in fact, an example of anomeric effect (See *Anomeric and Homoanomeric Effects*) dominated by $n \rightarrow \sigma^*$ interactions (Figure 34).

In a similar way, *cis* isomers of 1,2-difluoroethene and 1,2-dichloroethene are experimentally more stable than the *trans*-isomers (0.9

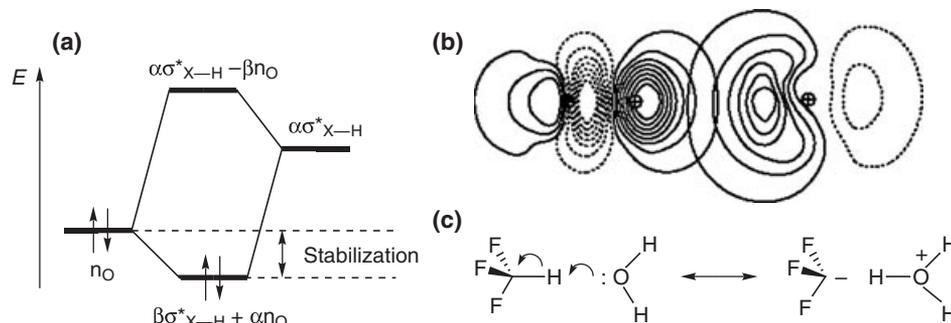


FIGURE 35 | (a) Energy lowering due to hyperconjugative interaction between $n(Y)$ and σ^*_{X-H} orbitals in $X-H \cdots Y$ complex. (b) Natural bond orbital plots illustrating the overlap of the σ^*_{C-H} of fluoromethane and the $n(O)$ orbital of the oxygen atom in water in the fluoromethane/water complex and (c) description of the hyperconjugative $n(O) \rightarrow \sigma^*_{C-H}$ interaction in this complex in terms of resonance theory illustrating effective charge transfer from H-bond acceptor (water) to H-bond donor (fluoromethane).

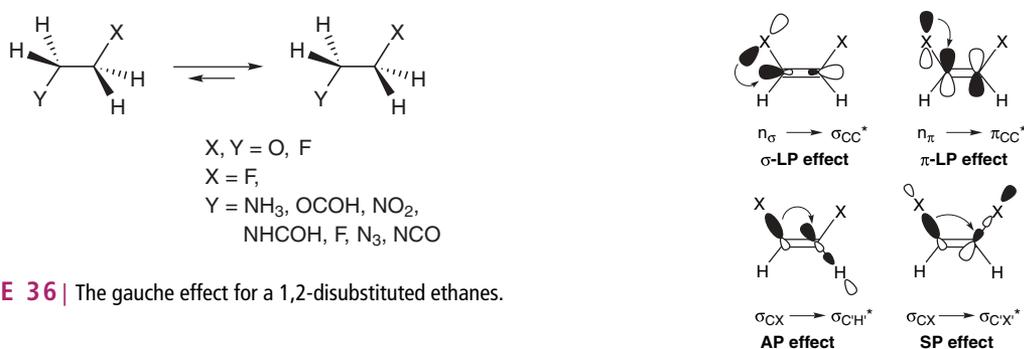


FIGURE 36 | The gauche effect for a 1,2-disubstituted ethanes.

and 0.43 kcal/mol) whereas the two isomers of 1,2-dibromoethene have equal stability, within the experimental error. This extensively analyzed phenomenon is called the ‘*cis*’ effect,^{260–274} and bears similarity to the gauche effect shown in Figure 36.

Most recently, Yamamoto et al.²⁷⁵ have estimated the contributions of electron delocalizations and steric exchange repulsions using NBO theory at MP2/6–311++G(3df,3pd) level, capable of reproducing the experimental energy differences between the geometric isomers. Two delocalization mechanisms, periplanar hyperconjugations (synperiplanar and antiperiplanar effects) and halogen lone pair delocalizations into the C=C bond antibonding orbitals (lone pair delocalization effect, Figure 37, left), were found to be the *cis* stabilizing forces.

Although the common stereoelectronic preference for the anti- arrangement of the best donor and the best acceptor dominated for $X = F$ (Figure 37, right), the difference in the energies of the antiperiplanar interactions decreased for the two isomers of the heavier halogens where the $\sigma_{C-X} \rightarrow \sigma^*_{C-X}$ interactions increase in relative importance due to the greater donor ability of the σ_{C-Cl} and σ_{C-Br} bonds.

Interestingly, although hyperconjugative interactions of σ -orbitals clearly favored the *cis*-

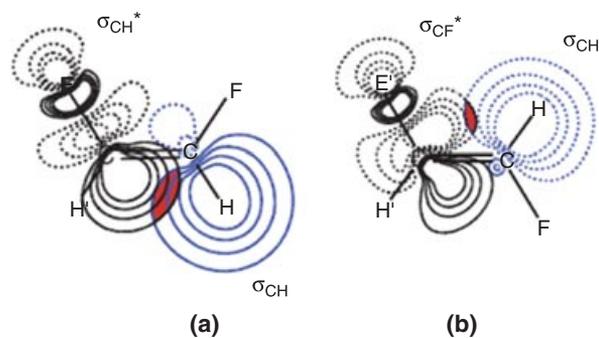


FIGURE 37 | Top: Definitions of the lone pair ($n\sigma$ and $n\pi$) delocalization effect (σ - or π -LP effect), the antiperiplanar hyperconjugation effect (the AP effect) and the synperiplanar hyperconjugation effect (the SP effect) within the natural bond orbital framework for *cis*-1,2-dihaloethenes ($X = F, Cl, \text{ or } Br$). Bottom: Comparison of hyperconjugative interactions involving C–F bonds in (a) *cis*- and (b) *trans*-1,2-difluoroethenes. (B) The interaction is greater for the antiperiplanar interaction in the *cis* isomer (Reprinted with permission from Ref 275).

isomer, the interactions of the lone pairs with the π - and σ -orbitals of the bridge were found to have an even larger effect. The authors explained this observation as a favorable symmetry-enforced

through-space interaction of the lone pairs (analogous to that discussed in *Cooperativity of Hyperconjugative Interactions*).¹⁹⁰

CONCLUSION

It is difficult to describe the rich and complex role of hyperconjugation in chemical structures and reactivity within a short review. We apologize to those whose important contributions we could not discuss in detail

but hope that this summary will contribute to further research in this important area. The ubiquitous nature of hyperconjugation in chemistry is illustrated by the key role it plays in numerous stereoelectronic effects on structure and reactivity. With the arrival of powerful computational techniques which can assist future experimental studies in disentangling the relative importance of hyperconjugation in comparison to other electronic and steric effects, the true role of hyperconjugation will continue to reveal itself in many chemical phenomena.

ACKNOWLEDGEMENTS

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REFERENCES

1. Dewar MJS. *Hyperconjugation*. New York: Ronald Press Co.; 1962.
2. Reed AE, Curtiss LA, Weinhold F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem Rev* 1988, 88:899–926.
3. Mulliken RS. Intensities of electronic transitions in molecular spectra. IV. Cyclic dienes and hyperconjugation. *J Chem Phys* 1939, 7:339–352.
4. Mulliken RS, Rieke CA, Brown WG. Hyperconjugation. *J Am Chem Soc* 1941, 63:41–56.
5. Bohlmann F. Configuration determination of quinolizidine derivatives. *Angew Chem* 1957, 69:641–642.
6. Wolfe S, Kim CK. A theoretical study of conformational deuterium isotope effects and bond dissociation energies of diastereotopic hydrogens. *Can J Chem* 1991, 69:1408–1412.
7. Juaristi E, Cuevas G. Manifestations of stereoelectronic interactions in JC–H one-bond coupling constants. *Acc Chem Res* 2007, 40:961–970.
8. Romers C, Altona C, Buys HR, Havinga E. Geometry and conformational properties of some five- and six-membered heterocyclic compounds containing oxygen or sulfur. *Topics Stereochem* 1969, 4:39–97.
9. Zefirov NS, Schechtman NM. Anomeric effect. *Usp Khim* 1971, 40:593–624.
10. Juaristi E, Cuevas G. Recent studies on the anomeric effect. *Tetrahedron* 1992, 48:5019–5087.
11. Graczyk PP, Mikolajczyk M. Anomeric effect: origin and consequences. *Top Stereochem* 1994, 21:159–349.
12. Kirby AJ. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*. Berlin: Springer-Verlag; 1983.
13. The Anomeric Effect and Associated Stereoelectronic effects. In: Thatcher GRJ, ed. *ACS Symposium Series 539*. Washington, DC: American Chemical Society; 1993.
14. Juaristi E, Guevas G. *The Anomeric Effect*. Boca Raton, FL: CRC Press; 1994.
15. In: Juaristi E, ed. *Conformational Behavior of Six-Membered Rings*. New York: VCH Publishers; 1995.
16. Uehara F, Sato M, Kaneko C, Kurihara H. The effect of a para substituent on the conformational preference of 2,2-diphenyl-1,3-dioxanes: evidence for the anomeric effect from X-ray crystal structure analysis. *J Org Chem* 1999, 64:1436–1441.
17. Reed AE, Weinhold F. Natural bond orbital analysis of internal rotation barriers and related phenomena. *Isr J Chem* 1991, 31:277–285.
18. Goodman L, Pophristic V, Gu H. Flexing analysis of ethane internal rotation energetics. *J Chem Phys* 1999, 110:4268–4275.
19. Goodman L, Pophristic V, Weinhold, F. Origin of methyl internal barriers. *Acc Chem Res* 1999, 32:983–993.
20. Cramer CJ. Hyperconjugation as it effects conformational analysis. *J Mol Struct: Theochem* 1996, 370:135–146.
21. Pophristic V, Goodman L, Guchhait N. Role of lone-pairs in internal rotation barriers. *J Phys Chem A* 1997, 101:4290–4297.

22. Lu KT, Weinhold F, Weishaar JC. Understanding barriers to internal rotation in substituted toluenes and their cations. *J Chem Phys* 1995, 102:6787–6805.
23. Baddeley G. Delocalization into anti antibond orbitals. *Tetrahedron Lett* 1973, 14:1645–1648.
24. Chang JWA, Taira K, Urano S, Sorenstein DG. Stereoelectronic effects on the nucleophilic addition of phosphite to the carbonyl double bond. *Ab initio* molecular orbital calculations on reaction surfaces and the σ -effect. *Tetrahedron* 1987, 43:3863–3874.
25. Um IH, Chung EK, Lee SM. An unusual ground-state stabilization effect and origins of the σ -effect in aminolysis of Y-substituted phenyl X-substituted benzoates. *Can J Chem* 1998, 76:729–737.
26. Deslongchamps P. Stereoelectronic control in the cleavage of tetrahedral intermediates in the hydrolysis of esters and amides. *Tetrahedron* 1975, 31:2463–2490.
27. Doddi G, Ercolani G, Mencarelli P. The problem of regioselectivity in nucleophilic additions to pyridinium and related cations. Role of generalized anomeric effect. *J Org Chem* 1992, 57:4431–4434.
28. Roberts BP, Steel AJ. The substituent effect of a β -carbon–oxygen bond in radical reactions. *Tetrahedron Lett* 1993, 34:5167–5170.
29. Wagner PJ, Scheve BJ. Absence of intramolecular charge-transfer quenching in photoexcited 4-benzoylpiperidines. *J Am Chem Soc* 1977, 99:1858–1863.
30. Lambert JB, Zhao Y, Emblidge RW, Salvador LA, Liu X, et al. The β -effect of silicon and related manifestations of σ conjugation *Acc Chem Res* 1999, 32:183–190.
31. Borden WT. Effects of electron donation into C–F σ^* -orbitals: explanations, predictions and experimental tests. *J Chem Soc Chem Commun* 1998:1919–1925.
32. Maier ME. Synthesis of medium-sized rings by the ring-closing metathesis reaction. *Angew Chem Int Ed Engl* 2000, 39:2073–2077.
33. Beckwith ALJ, Duggan PJ. The quasi-homo-anomeric interaction in substituted tetrahydropyranyl radicals: diastereoselectivity. *Tetrahedron* 1998, 54:6919–6928.
34. Muller N, Mulliken RS. Strong or isovalent hyperconjugation in some alkyl radicals and their positive ions. *J Am Chem Soc* 1958, 80:3489–3497.
35. Raabe G, Gais HJ, Fleischhauer J. *Ab Initio* study of the effect of fluorination upon the structure and configurational stability of σ -sulfonyl carbanions: the role of negative hyperconjugation. *J Am Chem Soc* 1996, 118:4622–4630.
36. Ganguly B, Fuchs B. Stereoelectronic effects in negatively and positively (protonated) charged species. *Ab initio* studies of the anomeric effect in 1,3-dioxane systems. *J Org Chem* 1997, 62:8892–8901.
37. Kirchen RP, Ranganayakulu K, Sorensen TS. 1-Methyl-1-cyclohexyl cations. Equilibria in search of structures. *J Am Chem Soc* 1987, 109:7811–7816.
38. Weinhold F. Nature of H-bonding in clusters, liquids, and enzymes: an *ab initio*, natural bond orbital perspective. *J Mol Struct: Theochem* 1997, 398:181–197.
39. Cieplak AS. Stereochemistry of nucleophilic addition to cyclohexanone. The importance of two-electron stabilizing interactions. *J Am Chem Soc* 1981, 103:4540–4552.
40. Cieplak AS, Tait BD, Johnson CR. Reversal of π -facial diastereoselection upon electronegative substitution of the substrate and the reagent. *J Am Chem Soc* 1989, 111:8447–8462.
41. Cherest M, Felkin H, Prudent N. Torsional strain involving partial bonds. The stereochemistry of the lithium aluminum hydride reduction of some simple open-chain ketones. *Tetrahedron Lett* 1968, 9:2199–2204.
42. Cherest M, Felkin H. Torsional strain involving partial bonds. The steric course of the reaction between allyl magnesium bromide and 4-tert-butylcyclohexanone. *Tetrahedron Lett* 1968, 18:2205–2208.
43. Cherest M. Nature of H-bonding in clusters, liquids, and enzymes: an *ab initio*, natural bond orbital perspective. *Tetrahedron*, 1980, 36:1593–1598.
44. Ahn NT, Eisenstein O. 1,2-Asymmetric induction. *Ab initio* comparison of the Cram, Cornforth, Karabatsos, and Felkin models. *Tetrahedron Lett* 1976, 17:155–158.
45. Ahn NT. Regio- and stereo-selectivities in some nucleophilic reactions *Top Curr Chem* 1980, 88:145–162.
46. Alabugin IV, Manoharan M, Buck M, Clark RJ. Substituted anilines: the tug-of-war between pyramidalization and resonance inside and outside of crystal cavities. *J Mol Struct: Theochem* 2007, 813:21–27.
47. Mulliken RS, Rieke CA, Brown WG. Hyperconjugation. *J Am Chem Soc* 1941, 63:41–56.
48. Karpichev B, Reislser H, Krylov AI, Diri K. Effect of hyperconjugation on ionization energies of hydroxyalkyl radicals. *J Phys Chem A* 2008, 112:9965–9969.
49. Hernández-Soto H, Weinhold F, Francisco JS. Radical hydrogen bonding: origin of stability of radical-molecule complexes. *J Chem Phys* 2007, 127:164102.
50. Wheeler SE, Houk KN, Schleyer PVR, Allen WD. A hierarchy of homodesmotic reactions for thermochemistry. *J Am Chem Soc* 2009, 131:2547–2560.
51. Wodrich MD, Wannere CS, Mo Y, Jarowski PD, Houk KN, Schleyer PVR. The concept of protobranching and its many paradigm shifting

- implications for energy evaluations. *Chem Eur J* 2007, 13:7731–7744.
52. Bickelhaupt FM, Baerends EJ. The case for steric repulsion causing the staggered conformation of ethane. *Angew Chem Int Ed Engl* 2003, 42:4183–4188.
 53. Cappel D, Tullmann S, Krapp A, Frenking G. *Angew Chem Int Ed Engl* 2005, 44:3617–3620.
 54. Fernandez I, Frenking G. Direct estimate of the conjugative and hyperconjugative stabilization in diynes, dienes, and related compounds. *Faraday Discuss* 2007, 135:403–421.
 55. Fernandez I, Frenking G. Direct estimate of the strength of conjugation and hyperconjugation by the energy decomposition analysis method. *Chem Eur J* 2006, 12:3617–3629.
 56. Mo Y, Wu W, Song L, Lin M, Zhang Q, et al. The magnitude of hyperconjugation in ethane: a perspective from *ab initio* valence bond theory. *Angew Chem Int Ed Engl* 2004, 43:1986–1990.
 57. Weinhold F, Carpenter JE. Some remarks on non-orthogonal orbitals in quantum chemistry. *J Mol Struct: Theochem* 1988, 165:189–202.
 58. Corcoran CT, Weinhold F. Antisymmetrization effects in bond-orbital models of internal rotation barriers. *J Chem Phys* 1980, 72:2866–2868.
 59. Weinhold F. Chemistry: a new twist on molecular shape. *Nature* 2001, 411:539–540.
 60. Weinhold F. Rebuttal to the Bickelhaupt–Baerends case for steric repulsion causing the staggered conformation of ethane. *Angew Chem Int Ed Engl* 2003, 42:4188–4194.
 61. Weinhold F, Landis CR. *Valency and Bonding*. London: Cambridge University Press; 2005, Secs. 1.4 and 4.11. Available at: http://www.chem.wisc.edu/~nbo5/tut_neda.htm. (Accessed October 10, 2010).
 62. Gross KC, Seybold PG. Substituent effects on the physical properties and pKa of phenol. *Int J Quantum Chem* 2001, 85:569–579.
 63. Weinhold F, Schleyer PVR, eds. *Encyclopedia of Computational Chemistry*. New York: John Wiley & Sons; 1998, 3, 1792.
 64. Reed AE, Weinhold F. Natural localized molecular-orbitals. *J Chem Phys* 1985, 83:1736–1740.
 65. Alabugin IV, Zeidan TA. Stereoelectronic effects and general trends in hyperconjugative acceptor ability of σ bonds. *J Am Chem Soc* 2002, 124:3175–3185.
 66. Badenhoop JK, Weinhold F. Natural bond orbital analysis of steric interactions. *J Chem Phys* 1997, 107:5406–5422. Badenhoop JK, Weinhold F. Natural steric analysis of internal rotation barriers. *Int J Quantum Chem* 1999, 72:269–280.
 67. Weisskopf VF. Of atoms, mountains, and stars: a study in qualitative physics. *Science* 1975, 187:605–612.
 68. Bickelhaupt FM, Baerends EJ, Evert J. Kohn–Sham density functional theory: predicting and understanding chemistry. *Rev Comput Chem* 2000, 15:1–86.
 69. TeVelde G, Bickelhaupt FM, Baerends EJ, van Gisbergen SJA, Snijders JG, et al. Chemistry with ADF. *J Comput Chem* 2001, 22:931–967.
 70. Ziegler T, Rauk A. On the calculation of bonding energies by the Hartree–Fock Slater method. I. The transition state method. *Theor Chim Acta* 1977, 46:1–10.
 71. Morokuma K. Molecular orbital studies of hydrogen bonds III. C=O \cdots H–O hydrogen bond in H₂CO \cdots H₂O and H₂CO \cdots 2H₂O. *J Chem Phys* 1971, 55:1236–1244.
 72. Mo Y. Intramolecular electron transfer: computational study based on the orbital deletion procedure (ODP). *Curr Org Chem* 2006, 10:779–790.
 73. Mo Y, Gao J. Theoretical analysis of the rotational barrier of ethane. *Acc Chem Res* 2007, 40:113–119.
 74. Mo Y, Wu W, Song L, Lin M, Zhang Q, et al. The magnitude of hyperconjugation in ethane: a perspective from *ab initio* valence bond theory. *Angew Chem Int Ed Engl* 2004, 43:1986–1990.
 75. Mo Y, Peyerimhoff SD. Theoretical analysis of electronic delocalization. *J Chem Phys* 1998, 109:1687–1697.
 76. Mo Y, Zhang Y, Gao J. A simple electrostatic model for trisilylamine: theoretical examinations of the $n \rightarrow \sigma^*$ negative hyperconjugation, $p\pi \rightarrow d\pi$ bonding, and stereoelectronic interaction. *J Am Chem Soc* 1999, 121:5737–5742.
 77. Mo Y, Gao J, Peyerimhoff SD. Energy decomposition analysis of intermolecular interactions using a block-localized wave function approach. *J Chem Phys* 2000, 112:5530–5538.
 78. Mo Y, Subramanian G, Ferguson DM, Gao J. Cation– π interactions: an energy decomposition analysis and its implication in δ -opioid receptor–ligand binding. *J Am Chem Soc* 2002, 124:4832–4837.
 79. Mo Y, Song L, Wu W, Zhang Q. Charge transfer in the electron donor–acceptor complex BH₃NH₃. *J Am Chem Soc* 2004, 126:3974–3982.
 80. Mo Y, Gao J. An *ab initio* molecular orbital–valence bond (MOVb) method for simulating chemical reactions in solution. *J Phys Chem* 2000, 104:3012–3020.
 81. Mo Y, Gao J. *Ab initio* QM/MM simulations with a molecular orbital–valence bond (MOVb) method: application to an S_N2 reaction in water. *J Comput Chem* 2000, 21:1458–1469.
 82. Mo Y. Resonance effect in the allyl cation and anion: a revisit. *J Org Chem* 2004, 69:5563–5567.
 83. Muller N, Mulliken RS. Strong or isovalent hyperconjugation in some alkyl radicals and their positive ions. *J Am Chem Soc* 1958, 80:3489–3497.

84. Exner O, Boehm S. Negative hyperconjugation of some fluorine containing groups. *New J Chem* 2008, 32:1449–1453.
85. Frenking G, Koch W, Schwarz H. Theoretical investigations on fluorine-substituted ethylene dications $C_2H_nF_{4-n}^{2+}$ ($n = 0-4$). *J Comput Chem* 1986, 7:406–416.
86. Saunders WH Jr. Negative ion hyperconjugation in fluorocarbanions and the nature of the borderline between E1cB and E2 mechanisms. An *ab initio* study. *J Org Chem* 1999, 64:861–865.
87. Wiberg KB, Rablen PR. Origin of the stability of carbon tetrafluoride: negative hyperconjugation reexamined. *J Am Chem Soc* 1993, 115:614–625.
88. Bohlmann F. Configuration determination of quinolizidine derivatives. *Angew Chem* 1957, 69:641–642.
89. Perrin CL, Young DB. Stereoelectronic control in addition of nucleophiles to an amidinium ion. *J Am Chem Soc* 2001, 123:4451–4458.
90. Perrin CL, Young DB. Is there stereoelectronic control in hydrolysis of cyclic guanidinium ions? *J Am Chem Soc* 2001, 123:4446–4450.
91. Perrin CL, Fabian MA, Brunckova J, Ohta BK. Absence of reverse anomeric effect in glycosylimidazoles. *J Am Chem Soc* 1999, 121:6911–6918.
92. Perrin CL, Engler RE, Young DB. Bifunctional catalysis and apparent stereoelectronic control in hydrolysis of cyclic imidatonium ions *J Am Chem Soc* 2000, 122:4877–4881.
93. Mo Y, Jiao H, Schleyer PVR. Hyperconjugation effect in substituted methyl boranes: an orbital deletion procedure analysis. *J Org Chem* 2004, 69:3493–3499.
94. Prakash S, Schleyer PVR, eds. *Stable Carbocation Chemistry*. New York: John Wiley & Sons; 1996.
95. Olah GA. 100 years of carbocations and their significance in chemistry. *J Org Chem* 2001, 66:5943–5957.
96. Wieting RD, Staley RH, Beauchamp JL. Relative stabilities of carbonium ions in the gas phase and solution. Comparison of cyclic and acyclic alkylcarbonium ions, acyl cations and cyclic halonium ions. *J Am Chem Soc* 1974, 96:7552–7554.
97. Anslyn EV, Dougherty DA. *Modern Physical Organic Chemistry*. Mill Valley, California: University Science Books; 2006, 88.
98. Wierschke SG, Chandrasekhar J, Jorgensen WL. Stabilization of positive charge by β -silicon. *J Am Chem Soc* 1985, 107:1496–1500.
99. Lambert JB, Wang G, Finzel RB, Teramura DH. Stabilization of positive charge by β -silicon. *J Am Chem Soc* 1987, 109:7838–7845.
100. Lambert JB. The interaction of silicon with positively charged carbon. *Tetrahedron* 1990, 46:2677–2689.
101. Lambert JB, Wang G, Teramura DH. Interaction of the carbon–germanium or carbon–tin bond with positive charge on a β -carbon. *J Org Chem* 1988, 53:5422–5428.
102. Lambert JB, Emblidge RW. Nucleophilic catalysis in deoxymercuration: the beta effect of mercury. *J Phys Org Chem* 1993, 6:555–560.
103. Mayr H, Patz M. Nucleophilic and electrophilic scales as the principles for classification of polar organic and organometallic reactions. *Angew Chem Int Ed Engl* 1994, 33:938–955.
104. Laube T, Ha TK. Detection of hyperconjugative effects in experimentally determined structures of neutral molecules. *J Am Chem Soc* 1988, 110:5511–5517.
105. Lambert JB, Singer RA. Neutral hyperconjugation. *J Am Chem Soc* 1992, 114:10246–10248.
106. Bocca CC, Pontes RM, Basso EA. Implications of hyperconjugative effects on bond lengths of allylic systems. An NMO investigation. *J Mol Struct: Theochem*. 2004, 710:105–110.
107. Alabugin IV, Manoharan M. Rehybridization as a general mechanism for maximizing chemical and supramolecular bonding and a driving force for chemical reactions. *J Comp Chem* 2007, 28:373–390.
108. Lambert JB, Shawl CE, Basso E. Neutral hyperconjugation and one-bond couplings between heavy atoms. *Can J Chem* 2000, 78:1441–1444.
109. Schepers T, Michl J. Optimized ladder C and ladder H models for sigma conjugation: chain segmentation in polysilanes. *J Phys Org Chem* 2002, 15:490–498.
110. Lambert JB, Ciro SB. The interaction of π orbitals with a carbocation over three σ bonds. *J Org Chem* 1996, 61:1940–1945.
111. Shiner V Jr, Ensinger MW, Rutkowske RD. γ -Silicon stabilization of carbonium ions in solvolysis. 2. Solvolysis of 4-(trimethylsilyl)-2-butyl p-bromobenzenesulfonates. *J Am Chem Soc* 1987, 109:804–809.
112. Grob CA, Gruendel M, Sawlewicz P. Polar effects. Part 15. Twin γ -substituent effects in the formation of 1-adamantyl cations. *Helv Chim Acta* 1988, 71:1502–1507.
113. Bentley TW, Kirmse W, Llewellyn G, Soellenboehmer F. Polar effects. Part 15. Twin γ -substituent effects in the formation of 1-adamantyl cations. *J Org Chem* 1990, 55:1536–1540.
114. Davis DD, Black RH. Deoxymetalation reactions. Concerted nature of 1,3-deoxystannylation. *J Organomet Chem* 1974, 82:C30–C34.
115. Alabugin IV, Manoharan M, Zeidan TA. Homoanionic effects in saturated heterocycles. *J Am Chem Soc* 2003, 125:14014–14031.
116. Lambert JB, Salvador LA, So JH. The γ and δ effects of tin. *Organometallics* 1993, 12:697–703.
117. Adcock W, Coope J, Shiner VJ Jr, Trout NA. Evidence for 2-fold hyperconjugation in the solvolysis of

- 5-(trimethylsilyl) and 5-(trimethylstannyl)-2-adamantyl sulfonates. *J Org Chem* 1990, 55:1411–1412.
117. Adcock W, Kristic AR, Duggan PJ, Shiner VJ Jr, Coope J, et al. Through-bond transmission of substituent effects in the bicyclo[2.2.2]octane ring system: solvolysis of 4-deuterio- and 4-metalloidal ($M(CH_3)_3$, $M =$ silicon, germanium and tin)-substituted bicyclo[2.2.2]oct-1-yl p-nitrobenzenesulfonates and methanesulfonates. *J Am Chem Soc* 1990, 112:3140–3145.
118. Alabugin IV, Manoharan M. Effect of double hyperconjugation on the apparent donor ability of σ -bonds: insights from the relative stability of δ -substituted cyclohexyl cations. *J Org Chem* 2004, 69:9011–9024.
119. Fokin AA, Tkachenko BA, Gunchenko PA, Gusev DV, Schreiner PR. Functionalized nanodiamonds. Part I. An experimental assessment of diamantane and computational predictions for higher diamondoids. *Chem Eur J* 2005, 11: 7091–7101.
120. Pophristic V, Goodman L. Hyperconjugation not steric repulsion leads to the staggered structure of ethane. *Nature* 2001, 411:565–568.
121. Schreiner PR. Teaching the right reasons: lessons from the mistaken origin of the rotational barrier in ethane. *Angew Chem Int Ed Engl* 2002, 41:3579–3581.
122. Kirby AJ. *Stereoelectronic Effects*. New York: Oxford University Press, Inc; 2000, 25–27.
123. Alabugin IV, Manoharan M, Peabody S, Weinhold F. The electronic basis of improper hydrogen bonding: a subtle balance of hyperconjugation and rehybridization. *J Am Chem Soc* 2003, 125:5973–5987.
124. Allerhand A, Schleyer PVR. A survey of C–H groups as proton donors in hydrogen bonding. *J Am Chem Soc* 1963, 85:1715–1723.
125. Alabugin IV, Manoharan M, Weinhold F. Blue-shifted and red-shifted hydrogen bonds in hypervalent rare-gas FRg-HY sandwiches. *J Phys Chem A* 2004, 10:4720–4730.
126. Fukuto JM, Jensen FR. Mechanisms of S_E2 reactions: emphasis on organotin compounds. *Acc Chem Res* 1983, 16:177–184.
127. Anderson JE, Cai J, Davies AG. NMR study of stereoelectronic anomeric and homoanomic effects on the axial and equatorial CH bonds in 1,3-diazacyclohexanes and 1,5-diazabicyclo[3.2.1]octanes. *J Chem Soc Perkin Trans 2* 1997, 12:2633–2637.
128. Cuevas G, Martínez-Mayorga K, Fernández-Alonso MDC, Jiménez-Barbero J, Perrin C, et al. The origin of one-bond C–H coupling constants in OCH fragments: not primarily $n_o \rightarrow {}^*CH$ delocalization. *Angew Chem Int Ed Engl* 2005, 44:2360–2364.
129. Apeilog Y, Schleyer PVR, Pople JA. Molecular orbital theory of the electronic structure of molecules. 35. β -Substituent effects on the stabilities of ethyl and vinyl cations. Comparison with isoelectronic methyl boranes. The relative importance of hyperconjugative and inductive effects. *J Am Chem Soc* 1977, 99:5901–5909.
130. Bent HA. An appraisal of valence-bond structures and hybridization in compounds of the first-row elements. *Chem Rev* 1961, 61:275–311.
131. Green AJ, Giordano J, White JM. Gauging the donor ability of the C–Si bond. Results from low-temperature structural studies of gauche and antiperiplanar β -trimethylsilylcyclohexyl esters and ethers by use of the variable oxygen probe. *Aust J Chem* 2000, 53:285–292.
132. White JM, Clark CI. Stereoelectronic effects of Group IVA metal substituents in organic chemistry. *Top Stereochem* 1999, 22:137–200.
133. Lambert JB, Zhao Y, Emblidge RW, Salvador LA, Liu X, et al. The β effect of silicon and related manifestations of σ conjugation. *Acc Chem Res* 1999, 32:183–190.
134. Lambert JB, Wang GT, Teramura DH. Interaction of the carbon–germanium or carbon–tin bond with positive charge on a β carbon. *J Org Chem* 1988, 53:5422–5428.
135. Lambert JB, Wang GT, Finzel RB, Teramura DH. Stabilization of positive charge by β -silicon. *J Am Chem Soc* 1987, 109:7838–7845.
136. Lambert JB. The interaction of silicon with positively charged carbon. *Tetrahedron* 1990, 46:2677–2689.
137. Cook MA, Eaborn C, Walton DRM. Substituent effects of mono-, bis-, and tris(trimethylsilyl)-methyl groups; determination of σ and σ^+ constants. *J Organomet Chem* 1970, 24:293–299.
138. Spiniello M, White JM. 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. *Org Biomol Chem* 2003, 1:3094–3101.
139. Alabugin IV. Stereoelectronic interactions in cyclohexane, 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane: W-effect, $\sigma_{C-X} \leftrightarrow \sigma_{C-H}$ Interactions, anomeric effect—what is really important? *J Org Chem* 2000, 65:3910–3919.
140. Rablen PR, Hoffmann RW, Hrovat DA, Borden WT. Is hyperconjugation responsible for the “gauche effect” in 1-fluoropropane and other 2-substituted-1-fluoroethanes? *J Chem Soc Perkin Trans 2* 1999, 8:1719–1726.
141. Cappel D, Tullmann ST, Krapp A, Frenking G. Direct estimate of the conjugative and hyperconjugative stabilization in diynes, dienes, and related compounds. *Angew Chem Int Ed Engl* 2005, 44:3617–3620.

142. Baker JW, Nathan WS. Mechanism of aromatic side-chain reactions with special reference to the polar effects of substituents. V. The polar effects of alkyl groups. *J Chem Soc* 1935:1844–1847.
143. Cooney BT, Happer DAR. The Baker–Nathan order: hyperconjugation or a solvent effect? *Aus J Chem* 1987, 40:1537–1544.
144. Taylor R, Smith GG, Wetzel, WH. Substituent effects in pyrolysis. V. A ρ - σ^+ correlation in the pyrolysis of 1-arylethyl acetates. *J Am Chem Soc* 1962, 84:4817–4824.
145. Taft RW, Topsom RD. The nature and analysis of substituent electronic effects. *Prog Phys Org Chem* 1987, 16:1–83.
146. Exner O, Böhm S. Baker–Nathan effect, hyperconjugation and polarizability effects in isolated molecules. *J Chem Soc* 1997, 6:1235–1240.
147. Dolbier WR Jr, Koroniak H, Houk KN, Sheu CC. Electronic control of stereoselectivities of electrocyclic reactions of cyclobutenes: a triumph of theory in the prediction of organic reactions. *Acc Chem Res* 1996, 29:471–477.
148. Kirmse W, Rondan NG, Houk KN. Stereoselective substituent effects on conrotatory electrocyclic reactions of cyclobutenes. *J Am Chem Soc* 1984, 106:7989–1991.
149. Dolbier WR Jr, Koroniak H, Burton DJ, Bailey AR, Shaw GS, et al. Remarkable, contra-steric, electrocyclic ring opening of a cyclobutene. *J Am Chem Soc* 1984, 106:1871–1872.
150. Dolbier WR Jr, Koroniak H, Burton DJ, Heinze PL, Baily AR, et al. Kinetic and thermodynamic studies of the thermal electrocyclic interconversions of perfluorinated dienes and cyclobutenes. *J Am Chem Soc* 1987, 109:219–225.
151. Yoshikawa T, Mori S, Shindo M. The effect of alkynyl groups on torquoselectivity. Highly stereoselective olefination of alkynyl ketones with ynolates. *J Am Chem Soc* 2009, 131:2092–2093.
152. Murakami M, Miyamoto Y, Hasegawa M, Usui I, Matsuda T. Torque control by metal–orbital interactions. *Pure Appl Chem* 2006, 78:415–423.
153. Masahiro M. Stabilizing effect of silicon by negative hyperconjugation. *Organometallic News* 2003, 2:46–49.
154. Cieplak AS. Stereochemistry of nucleophilic addition to cyclohexanone. The importance of two-electron stabilizing interactions. *J Am Chem Soc* 1981, 103:4540–4552.
155. Cieplak AS, Tait BD, Johnson CR. Reversal of π -facial diastereoselection upon electronegative substitution of the substrate and the reagent. *J Am Chem Soc* 1989, 111:8447–8462.
156. Cherest M, Felkin H, Prudent N. Torsional strain involving partial bonds. The stereochemistry of the lithium aluminum hydride reduction of some simple open-chain ketones. *Tetrahedron Lett* 1968, 18:2199–2204.
157. Cherest M, Felkin H. Torsional strain involving partial bonds. The steric course of the reaction between allyl magnesium bromide and 4-tert-butylcyclohexanone. *Tetrahedron Lett* 1968, 18:2205–2208.
158. Cherest M. The influence of torsion interactions on addition reactions of cyclohexanones. General interpretation of the steric course of the reaction of hydrides or organomagnesium compounds with cyclohexanones. *Tetrahedron* 1980, 36:1593–1598.
159. Ahn NT, Eisenstein O. 1,2-Asymmetric induction. *Ab initio* comparison of the Cram, Cornforth, Karabatsos, and Felkin models. *Tetrahedron Lett* 1976, 3:155–158.
160. Cieplak AS. Inductive and resonance effects of substituents on π -face selection. *Chem Rev* 1999, 99:1265–1336.
161. Mengel A, Reiser O. Around and beyond Cram's Rule. *Chem Rev* 1999, 99:1191–1223.
162. Dannenberg JJ. Using perturbation and frontier molecular orbital theory to predict diastereofacial selectivity. *Chem Rev* 1999, 99:1225–1241.
163. Gung BW. Structure distortions in heteroatom-substituted cyclohexanones, adamantanones, and adamantanes: origin of diastereofacial selectivity. *Chem Rev* 1999, 99:1377–1386.
164. Kaselj M, Chung WS, Le Noble WJ. Face selection in addition and elimination in sterically unbiased systems. *Chem Rev* 1999, 99:1387–1413.
165. Adcock W, Trout NA. Nature of the electronic factor governing diastereofacial selectivity in some reactions of rigid saturated model substrates. *Chem Rev* 1999, 99:1415–1435.
166. Wipf P, Jung JK. Nucleophilic additions to 4,4-disubstituted 2,5-cyclohexadienones: Can dipole effects control facial selectivity? *Chem Rev* 1999, 99:1469–1480.
167. Tomoda S. The exterior frontier orbital extension model. *Chem Rev* 1999, 99:1243–1263.
168. Mehta G, Chandrasekhar J. Electronic control of facial selection in additions to sterically unbiased ketones and olefins. *J Chem Rev* 1999, 99:1437–1467.
169. Ohwada T. Orbital-controlled stereoselections in sterically unbiased cyclic systems. *Chem Rev* 1999, 99:1337.
170. Whiffen DH. The CH_2 hyperfine coupling in cyclohexadienyl. *Mol Phys* 1963, 6:223–224.
171. Davies AG. The Whiffen effect of symmetry-enhanced and symmetry-forbidden hyperconjugation in spin-paired molecules. *J Chem Soc Perkin Trans 2* 1999, 11:2461–2467.
172. Winstein S. Homoaromatic structures. *J Am Chem Soc* 1959, 81:6524–6525.

173. Holder A. Further comments on the lack of homoaromaticity in triquinacene. *J Comput Chem* 1993, 14:251.
174. Williams RV. Homoaromaticity. *Chem Rev* 2001, 101:1185–1204. Stahl F, Schleyer PVR, Jiao H, Schaefer HF III, Chen KH, et al. Resurrection of neutral tris-homoaromaticity. *J Org Chem* 2002, 67:6599–6611.
175. Jiao H, Nagelkerke R, Kurtz HA, Williams V, Borden WT, et al. Annelated semibullvalenes: a theoretical study of how they “cope” with strain. *J Am Chem Soc* 1997, 119:5921–5929.
176. Freeman PK, Dacres JE. A Study into the possible homoaromatic nature of some related carbene and cationic intermediates with the potential for transannular interaction. *J Org Chem* 2003, 68:1386–1393.
177. Goren AC, Hrovat DA, Seefeldler M, Quast H, Borden WT. The search for bishomoaromatic semibullvalenes and barbaralanes: computational evidence of their identification by UV/Vis and IR spectroscopy and prediction of the existence of a blue bishomoaromatic semibullvalene. *J Am Chem Soc* 2002, 124:3469–3472.
178. Hoffmann R, Imamura A, Hehre WJ. Benzyne, dehydroconjugated molecules, and the interaction of orbitals separated by a number of intervening sigma bonds. *J Am Chem Soc* 1968, 90:1499–1509.
179. Hoffmann R. Interaction of orbitals through-space and through-bonds. *Acc Chem Res* 1971, 4:1–9.
180. Paddon-Row MN. Some aspects of orbital interactions through bonds: physical and chemical consequences. *Acc Chem Res* 1982, 15:245–251.
181. Gleiter R, Paddon-Row MN. Effects of through-bond interaction. *Angew Chem Int Ed Engl* 2003, 13:696–701.
182. Brodskaya EI, Ratovskii GV, Voronkov MG. Orbital interactions through-space and through-sigma bonds. *Usp Khim* 1993, 62:975–990.
183. Paddon-Row MN, Shephard MJ. Through-bond orbital coupling, the parity rule, and the design of ‘superbridges’ which exhibit greatly enhanced electronic coupling: a natural bond orbital analysis. *J Am Chem Soc* 1997, 119:5355–5365.
184. Verhoeven JW. Sigma-assistance; the modulation of intramolecular reactivity by through-bond interaction. *Recl Trav Chim Pays-Bas* 1980, 99:369–379.
185. Alabugin IV, Manoharan M. Reactant destabilization in the Bergman cyclization and rational design of light and pH-activated enediyne. *J Phys Chem A* 2003, 107:3363–3371.
186. Logan CF, Chen P. Ab initio calculation of hydrogen abstraction reactions of phenyl radical and p-benzyne. *J Am Chem Soc* 1996, 118:2113–2114.
187. Schottelius MJ, Chen P. 9,10-Dehydroanthracene: p-benzyne-type biradicals abstract hydrogen unusually slowly. *J Am Chem Soc* 1996, 118:4896–4903.
188. Kraka E, Cremer D. Computer design of anticancer drugs. a new enediyne warhead. *J Am Chem Soc* 2000, 122:8245–8264.
189. Pickard FC IV, Shepherd RL, Gillis AE, Dunn ME, Feldgus S, et al. Ortho effect in the Bergman cyclization: electronic and steric effects in hydrogen abstraction by 1-substituted naphthalene 5,8-diradicals. *J Phys Chem A* 2006, 110:2517–2526.
190. Alabugin IV, Manoharan M. Radical-anionic C1–C5 and C1–C6 cyclizations of enediyne: remarkable substituent effects in cyclorearomatization reactions. *J Am Chem Soc* 2003, 125:4495–4509.
191. Sovers OJ, Kern CW, Pitzer RM, Karplus M. Bond-function analysis of rotational barriers: ethane. *J Chem Phys* 1968, 49:2592–2599. Christiansen PA, Palke WE. A study of the ethane internal rotation barrier. *Chem Phys Lett* 1975, 31:462–466.
192. Bader RFW, Cheeseman JR, Laidig KE, Wiberg KB, Breneman C. Origin of rotation and inversion barriers. *J Am Chem Soc* 1990, 112:6530–6536.
193. Lowe JP. Simple molecular orbital explanation for the barrier to internal rotation in ethane and other molecules. *J Am Chem Soc* 1970, 92:3799–3800.
194. Brunck TK, Weinhold F. Quantum mechanical studies on the origin of barriers to internal rotation about single bonds. *J Am Chem Soc* 1979, 101:1700–1709.
195. Goodman L, Pophristic V, Weinhold F. Origin of methyl internal rotation barriers. *Acc Chem Res* 1999, 32:983–993.
196. Mulliken RS. Intensities of electronic transition in molecular spectra. IV. Cyclic dienes and hyperconjugation. *J Chem Phys* 1939, 7:339–352.
197. Bickelhaupt FM, Baerends EJ. The case for steric repulsion causing the staggered conformation of ethane. *Angew Chem Int Ed Engl* 2003, 42:4183–4188.
198. Mo Y, Wu W, Song L, Lin M, Zhang Q, et al. The magnitude of hyperconjugation in ethane: a perspective from ab initio valence bond theory. *Angew Chem Int Ed Engl* 2004, 43:1986–1990.
199. Rogers DW, Matsunaga N, Zavitsas AA, McLafferty FJ, Liebman JF. The conjugation stabilization of 1,3-butadiene is zero. *Org Lett* 2003, 5:2373–2375.
200. Rogers DW, Matsunaga N, McLafferty FJ, Zavitsas AA, Liebman JF. On the lack of conjugation stabilization in polyynes (polyacetylenes). *J Org Chem* 2004, 69:7143–7147.
201. Kistiakowsky GG, Ruhoff JR, Smith HA, Vaughan WE. Heats of organic reactions. IV. Hydrogenation of some dienes and of benzene. *J Am Chem Soc* 1936, 58:146–153.
202. Jarowski PD, Wodrich MD, Wannere CS, Schleyer PVR, Houk KN. How large is the conjugative stabilization of diynes? *J Am Chem Soc* 2004, 126:15036–15037.
203. Gronert S. The folly of protobranching: turning repulsive interactions into attractive ones and rewriting

- the strain/stabilization energies of organic chemistry. *Chem Eur J* 2009, 15:5372–5382.
204. Benoit B, Vinca P, Hiberty PC. The physical origin of Saytzeff's rule. *Angew Chem Int Ed Engl* 2009, 48:5724–5728.
205. Lide DR Jr, Mann DE. Microwave spectra of molecules exhibiting internal rotation. I. Propylene. *J Chem Phys* 1957, 27:868–873.
206. Lin BL, Xie Z, Liu R, Liu L, Guo QX. Importance of σ -type hyperconjugation to the eclipsed structure of propylene. *J Mol Struct: Theochem* 2003, 633:15–19.
207. Jalbouta AF, Basso EA, Pontesc RM, Dasa D. Hyperconjugative interactions in vinylic systems: the problem of the barrier to methyl rotation in acetone. *J Mol Struct: Theochem* 2004, 677:167–171.
208. Ribeiro DS, Rittner R. The role of hyperconjugation in the conformational analysis of methylcyclohexane and methylheterocyclohexanes. *J Org Chem* 2003, 68:6780–6787.
209. Kleinpeter E, Taddai F, Wachter P. Electronic and steric substituent influences on the conformational equilibria of cyclohexyl esters: the anomeric effect is not anomalous! *Chemistry*. 2003, 9:1360–1368.
210. Kleinpeter E, Rolla N, Koch A, Taddai F. Hyperconjugation and the increasing bulk of OCOCX_3 substituents in *trans*-1,4-disubstituted cyclohexanes destabilize the diequatorial conformer. *J Org Chem* 2006 71:4393–4399.
211. Shishkina SV, Shishkin OV, Desenko SM, Leszczynski J. Conjugation and hyperconjugation in conformational analysis of cyclohexene derivatives containing an exocyclic double bond. *J Phys Chem A* 2008, 112:7080–7089.
212. Anizelli PR, Vilcachagua JD, Cunha NA, Tormena CF. Stereoelectronic interaction and their effects on conformational preference for 2-substituted methylenecyclohexane: an experimental and theoretical investigation. *J Phys Chem A* 2008, 112:8785–8789.
213. Rauk A, Sorensen TS, Maerker C, Carneiro JW, Sieber S, et al. Axial and equatorial 1-methyl-1-cyclohexyl cation isomers both have chair conformations but differ in C–C and C–H hyperconjugation modes. *J Am Chem Soc* 1996, 118:3761–3762.
214. Rauk A, Sorensen TS, Schleyer PVR. Tertiary cyclohexyl cations. Definitive evidence for the existence of isomeric structures (hyperconjomers). *J Chem Soc Perkin Trans 2* 2001, 6:869–874.
215. Romers C, Altona C, Buys HR, Havinga E. Geometry and conformational properties of some five- and six-membered heterocyclic compounds containing oxygen or sulfur. *Topics Stereochem* 1969, 4:39–97.
216. Juaristi E, Cuevas G. Recent studies of the anomeric effect. *Tetrahedron* 1992, 48:5019–5087.
217. Graczyk PP, Mikolajczyk M. Anomeric effect: origin and consequences. *Top Stereochem* 1994, 21:159–349.
218. Perrin CL. The reverse anomeric effect: fact or fiction? *Tetrahedron* 1995, 51:11901–11935.
219. David S, Eisenstein O, Hehre WJ, Salem L, Hoffmann R. Superjacent orbital control. Interpretation of the anomeric effect. *J Am Chem Soc* 1973, 95:3806–3807.
220. Wolfe S. Gauche effect. Stereochemical consequences of adjacent electron pairs and polar bonds. *Acc Chem Res* 1972, 5:102–111.
221. Reed AE, Schleyer PVR. The anomeric effect with central atoms other than carbon. 2. Strong interactions between nonbonded substituents in mono- and polyfluorinated first- and second-row amines, $\text{F}_n\text{AH}_m\text{NH}_2$. *Inorg Chem* 1988, 27:3969–3987.
222. Tvaroska I, Carver JP. *Ab initio* molecular orbital calculation of carbohydrate model compounds. 5. Anomeric, *exo*-anomeric, and reverse anomeric effects in C–, N–, and S-glycosyl compounds. *J Phys Chem* 1996, 100:11305–11313.
223. Reany O, Goldberg I, Abramson S, Golender L, Ganguly, et al. The 1,3,5,7-tetraazadecalins: structure, conformation, and stereoelectronics. Theory vs. experiment. *J Org Chem* 1998, 63:8850–8859.
224. Ritter J, Gleiter R, Irngartinger H, Oeser T. Conformations of azacyclodeca-3,8-diyne and 1,6-diazacyclodeca-3,8-diyne and the generalized anomeric effect: a test for current conformational models for azaheterocycles. *J Am Chem Soc* 1997, 119:10599–10607.
225. Anderson JE, Cai J, Davies AG. NMR study of stereoelectronic anomeric and homoanomeric effects on the axial and equatorial C–H bonds in 1,3-diazacyclohexanes and 1,5-diazabicyclo[3.2.1]octanes. *J Chem Soc Perkin Trans 2* 1997, 12:2633–2637.
226. Church TJ, Carmichael I, Serianni AS. ^{13}C – ^1H and ^{13}C – ^{13}C spin-coupling constants in methyl β -D-ribofuranoside and methyl 2-deoxy- β -D-erythro-pentofuranoside: correlations with molecular structure and conformation. *J Am Chem Soc* 1997, 119:8946–8964.
227. Tvaroska I, Taravel FR. Carbon-proton coupling constants in the conformational analysis of sugar molecules. *Adv Carbohydr Chem* 1995, 51:15–61.
228. Peruchena NM, Contreras RH. Theoretical analysis of interactions affecting $^1\text{J}(\text{CH})$ NMR couplings in an sp^3 hybridized carbon atom. Part 1. The *exo*-anomeric effect in 3-methoxy-1,2,4,5-tetroxane. *J Mol Struct: Theochem* 1995, 338:25–30.
229. Andersson P, Nordstrand K, Sunnerhagen M, Liepinsh E, Turovskis I, et al. Heteronuclear correlation experiments for the determination of one-bond

- coupling constants. *J Biomol NMR* 1998, 11:445–450.
230. Callam CS, Gadikota RR, Lowary TL. Sensitivity of $^1\text{J}_{\text{C}1\text{-H}1}$ magnitudes to anomeric stereochemistry in 2,3-anhydro-O-furanosides. *J Org Chem* 2001, 66:4549–4558.
231. Lewis BE, Schramm VL. Conformational equilibrium isotope effects in glucose by ^{13}C NMR spectroscopy and computational studies. *J Am Chem Soc* 2001, 123:1327–1336.
232. Kamienska-Trela K, Wojcik J. Applications of spin-spin couplings. *Nucl Magn Reson* 2001, 30:132–180.
233. Fuson RC, Zirkle CL. Ring enlargement by rearrangement of the 1,2-aminochloroalkyl group; rearrangement of 1-ethyl-2-(chloromethyl)pyrrolidine to 1-ethyl-3-chloropiperidine. *J Am Chem Soc* 1948, 70:2760–2762.
234. Reitsemma RH. Novel rearrangement of a piperidine ring. *J Am Chem Soc* 1949, 71:2041–2043.
235. Hammer CF, Heller SR, Craig JH. Reactions of β -substituted amines. II. Nucleophilic displacement reactions on 3-chloro-1-ethylpiperidine. *Tetrahedron* 1972, 35:239–253.
236. Sakagami H, Ogasawara K. Diastereocontrolled synthesis of enantiopure 5-allylprolinols. *Synlett* 2001, 1:45–48.
237. Payne GB. Epoxide migrations with α,β -epoxy alcohols. *J Org Chem* 1962, 27:3819–3822.
238. Hanson RM. Epoxide migration (Payne rearrangement) and related reactions. *Org React* 2002, 60:1–156.
239. Ibuka T. The aza-Payne rearrangement: a synthetically valuable equilibration. *Chem Soc Rev* 1998, 27:145–154.
240. Anderson JE, Bloodworth AJ, Cai JQ, Davies AG, Tallant NA. One-bond carbon–hydrogen NMR coupling constants in 1,2,4-trioxanes: a reversed Perlin effect. *J Chem Soc Chem Commun* 1992, 22:1689–1691.
241. Anderson JE, Bloodworth AJ, Cai JQ, Davies AG, Schiesser CH. An NMR and *ab initio* MO study of the effect of β -oxygens in 1,3-dioxanes. *J Chem Soc Perkin Trans 2* 1993, 4:601–602.
242. Cai JQ, Davies AG, Schiesser CH. NMR parameters for 1,3-dioxanes: evidence for a homoanomeric interaction. *J Chem Soc Perkin Trans 2* 1994, 6:1151–1156.
243. Scheiner S. *Hydrogen Bonding*. New York: Oxford University Press; 1997.
244. Jeffrey GA. *An Introduction to Hydrogen Bond*. New York: Oxford University Press; 1997.
245. Desiraju GR, Steiner T. *The Weak Hydrogen Bond*. Oxford: Oxford University Press; 1999.
246. Hobza P, Havlas Z. Blue-shifting hydrogen bonds. *Chem Rev* 2000, 100:4253–4264.
247. Fulton RL, Perhacs P. Sharing of electrons in molecules: characterization of hydrogen bonds. *J Phys Chem* 1998, 102:9001–9020.
248. Guerra CF, Bickelhaupt FM, Snijders JG, Baerends EJ. The nature of the hydrogen bond in DNA base pairs: the role of charge transfer and resonance assistance. *Chem Eur J* 1999, 5:3581–3594.
249. Guerra CF, van der Wijst T, Bickelhaupt FM. Supramolecular switches based on the guanine-cytosine (GC) Watson-Crick pair: effect of neutral and ionic substituents. *Chem Eur J* 2006, 12:3032–3042.
250. Guerra CF, Baerends EJ, Bickelhaupt FM. Orbital interactions and charge redistribution in weak hydrogen bonds: Watson-Crick GC mimic involving C–H proton donors and F proton acceptor groups. *Int J Quantum Chem* 2006, 106:2428–2443.
251. Wolfe S. Gauche effect. Stereochemical consequences of adjacent electron pairs and polar bonds. *Acc Chem Res* 1972, 5:102–111.
252. Goodman L, Gu H, Pophristic V. Gauche effect in 1,2-difluoroethane. Hyperconjugation, bent bonds, steric repulsion. *J Phys Chem A* 2005, 109:1223–1229.
253. Buissonneaud DY, van Mourik T, O'Hagan D. A DFT study on the origin of the fluorine gauche effect in substituted fluoroethanes. *Tetrahedron* 2010, 66:2196–2202.
254. Schuler M, O'hagan D, Slawin AMZ. The vicinal F–C–C–F moiety as a tool for influencing peptide conformation. *Chem Commun (Camb)* 2005, 34:4324–4326.
255. Tavasli M, O'hagan D, Pearson C, Petty MC. The fluorine gauche effect. Langmuir isotherms report the relative conformational stability of (+/–)-erythro- and (+/–)-threo-9,10-difluorostearic acids. *Chem Commun (Camb)* 2002, 11:1226–1227.
256. Briggs CRS, O'hagan D, Rzepa HS, Slawin AMZ. Solid state and theoretical evaluation of β -fluoroethyl esters indicate a fluorine-ester gauche effect. *J Fluorine Chem* 2004, 125:19–25.
257. Hunter L, O'hagan D, Slawin AMZ. Enantioselective synthesis of an all-syn four vicinal fluorine motif. *J Am Chem Soc* 2006, 128:16422–16423.
258. Alabugin IV, Timokhin VI, Abrams JN, Manoharan M, Ghiviriga I, Abrams R. In search of efficient 5-endo-dig cyclization of a carbon-centered radical: 40 years from a prediction to another success for the Baldwin rules. *J Am Chem Soc* 2008, 130:10984–10995.
259. Souza FR, Freitas MP, Rittner R. On the stereo-electronic effects governing the rotational isomerism of 1,2-dihaloethanes. *J Mol Struct: Theochem* 2008, 863:137–140.
260. Pitzer KS, Hollenberg JL. *Cis*- and *trans*-dichloroethylenes. The infrared spectra from

- 130 to 400 cm^{-1} and the thermodynamic properties. *J Am Chem Soc* 1954, 76:1493–1496.
261. Craig NC, Piper LG, Wheeler VL. Thermodynamics of *cis-trans* isomerizations. II. 1-Chloro-2-fluoroethylenes, 1,2-difluorocyclopropanes, and related molecules. *J Phys Chem* 1971, 75:1453–1460.
262. Wiberg WB. Bent bonds in organic compounds. *Acc Chem Res* 1996, 29:229–234.
263. Engkvist O, Karlstrom G, Widmark PO. On the origin of the gauche effect. A quantum chemical study of 1,2-difluoroethane. *Chem Phys Lett* 1997, 265:19–23.
264. Yamamoto T, Tomoda S. On the origin of *cis*-effect in 1,2-difluoroethene. *Chem Lett* 1997, 10:1069–1070.
265. Novak I. Chlorofluoroethenes. Thermochemical stability and *cis*-effect. *J Org Chem* 2000, 65:5057–5058.
266. Kanakaraju K, Senthilkumar K, Kolandaivel P. Origin of the *cis* effect-nonbonded intramolecular interactions: quantum chemical studies on 1,2-dihaloethylene molecules. *J Mol Struct: Theochem* 2002, 589–590:95–102.
267. Yamamoto T, Kaneno D, Tomoda S. The importance of lone pair electron delocalization in the *cis-trans* isomers of 1,2-dibromoethenes. *Chem Lett* 2005, 34:1190–1191.
268. Binkley JS, Pople JA. Relative stability of 1,2-difluoroethylenes. *Chem Phys Lett* 1977, 45:197–200.
269. Cremer D. The role of correlation in calculations on 1,2-difluoroethylenes. The *cis-trans* energy difference. *Chem Phys Lett* 1981, 81:481–485.
270. Gandhi SR, Benzel MA, Dykstra CE, Fukunaga T. Role of electron correlation and polarization functions in the energy difference between *cis*- and *trans*-1,2-difluoroethylene. *J Phys Chem* 1982, 86:3121–3126.
271. Dixon DA, Fukunaga T, Smart BE. Geometries and energies of the fluoroethylenes. *J Am Chem Soc* 1986, 108:1585–1588.
272. Saebø S, Sellers H. Effect of electron correlation on the structures and relative stability of *cis*- and *trans*-1,2-difluoroethylene. *J Phys Chem* 1988, 92:4266–4269.
273. Epiotis ND, Yates RL. Overlap repulsion as an important contributor to aromaticity. *J Am Chem Soc* 1976, 98:461–469.
274. Bernardi F, Bottoni A, Epiotis ND, Guerra M. Quantitative nonempirical estimates of the effects of orbital interactions. Applications to difluoroethylenes. *J Am Chem Soc* 1978, 100:6018–6022.
275. Yamamoto T, Kaneno D, Tomoda S. The origin of *cis* effect in 1,2-dihaloethenes: the quantitative comparison of electron delocalizations and steric exchange repulsions. *Bull Chem Soc Japan* 2008, 81:1415–1422.

FURTHER READING

- Reed AE, Curtiss LA, Weinhold F. Intermolecular interactions from a natural bond orbital, donor–acceptor viewpoint. *Chem Rev* 1988, 88:899–926.
- Juaristi E, Guevas G. *The Anomeric Effect*. Boca Raton, FL: CRC Press; 1994.
- Schreiner PR. Teaching the right reasons: lessons from the mistaken origin of the rotational barrier in ethane. *Angew Chem Int Ed Engl* 2002, 41:3579–3581.
- Kirby AJ. *Stereoelectronic Effects*. New York: Oxford University Press, Inc; 2000, 25–27.
- Weinhold F, Landis CR. *Valency and Bonding*. Cambridge: Cambridge University Press; 2005.
- Dolbier WR Jr, Koroniak H, Houk KN, Sheu CC. Electronic control of stereoselectivities of electrocyclic reactions of cyclobutenes: a triumph of theory in the prediction of organic reactions. *Acc Chem Res* 1996, 29:471–477.
- Anslyn EV, Dougherty DA. *Modern Physical Organic Chemistry*. New York: University Science Books; 2006, 88.
- Fukuto JM, Jensen FR. Mechanisms of $\text{S}_{\text{E}}2$ reactions: emphasis on organotin compounds. *Acc Chem Res* 1983, 16:177–184.
- Lambert JB, Ciro SB. The interaction of π orbitals with a carbocation over three σ bonds. *J Org Chem* 1996, 61:1940–1945.
- Borden WT. Effects of Electron Donation into C–F π^* Orbitals: explanations, predictions, and experimental tests. *Chem Commun* 1998, 1919.
- Hoffman R, Radom L, Pople JA, Schleyer PvR, Hehre W, Salem L. Strong conformational consequences of hyperconjugation. *J Am Chem Soc* 1972, 94:6221–6223.
- Reed AE, Schleyer PvR. Chemical bonding in hypervalent molecules. The dominance of ionic bonding and negative hyperconjugation over d-orbital participation. *J Am Chem Soc* 1990, 112:1434–1445.
- Salzner U, Schleyer PvR. Generalized anomeric effects and hyperconjugation in $\text{CH}_2(\text{OH})_2$, $\text{CH}_2(\text{SH})_2$, $\text{CH}_2(\text{SeH})_2$, $\text{CH}_2(\text{TeH})_2$. *J Am Chem Soc* 1993, 115:10231–10236.