

Stereoelectronic Effects

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A Bridge Between Structure and Reactivity

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Supplementary Material

Instructors can access PowerPoint files of the illustrations presented within this text, for teaching, at:
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1

Introduction

When people thought the earth was flat, they were wrong. When people thought the earth was spherical, they were wrong. But if you think that thinking the earth is spherical is just as wrong as thinking the earth is flat, then your view is wronger than both of them put together. I. Asimov

1.1 Stereoelectronic effects – orbital interactions in control of structure and reactivity

It is easy to believe that the Earth is flat when driving through the Great Plains. Furthermore, the “flat Earth” approximation works quite well in many other aspects of everyday life. Because the small deviation from planarity – only 8 inches per mile – does not make a difference for everyday activities, we can order a cup of coffee or play a game of golf without worrying about the fine details of planetary shapes. However, once one prepares to launch a satellite instead of a golf ball or to navigate “around the globe”, the planet’s curvature becomes crucial. But *is* Earth a globe? A closer look from space finds that Earth is not a sphere but an “oblate spheroid” that bulges at the equator. Another revision! When should refinements stop and why should a chemist care?

The story of the flat Earth, borrowed from Isaac Asimov,¹ reflects the common evolution of scientific models. Sometimes, models are discarded completely (e.g. phlogiston) but, more often, they are refined and taken to the next level of applicability (such as Newton’s theory of gravity paving the way for Einstein’s theory of relativity). How does it apply to organic chemistry? How adequate are the undergraduate organic foundations for the broad understanding of structure and reactivity? Do we really need to go deeper?

The importance of continuous improvement of models is illustrated by the following “diagnostic quiz” given to first-year graduate students at the Florida State University. Take a minute and test yourself.

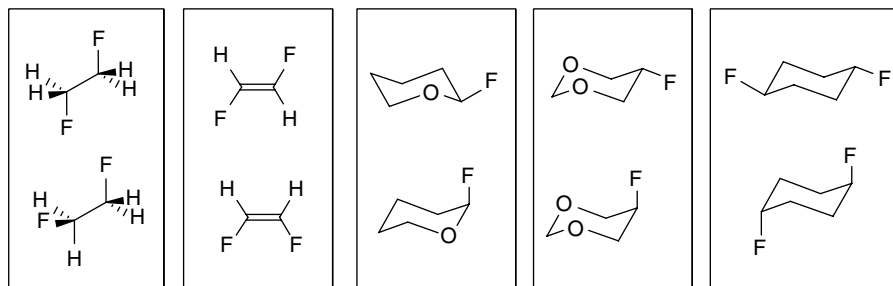


Figure 1.1 Circle the more stable structure in each of the above pairs.

The answers may or may not be surprising, depending on how far the reader is separated from the undergraduate organic class. For each pair in Figure 1.1, the *bottom structure is more stable* than the top structure. In particular, the *gauche* conformation of 1,2-difluoroethane is more stable than the *anti* conformations; *cis*-difluoroethene is more stable than the *trans*-isomer; the equatorial conformers of the two fluoro-substituted oxacyclohexanes are less stable than their axial counterparts; and the *diaxial* 1,4-difluorocyclohexane is ~ 1 kcal/mol *more* stable than the diequatorial conformer. The answer in each case is opposite to expectations based on the steric repulsion – the “flat Earth” models that have served reasonably well as a foundation of undergraduate organic chemistry.

It is not surprising that it is a rare undergraduate student who gives correct answers to all of the above problems. Almost invariably, the correct answers come as a surprise, even to a student with a good mastery of undergraduate organic chemistry. Clearly, a new set of concepts is needed to refine the initial model of organic structure and reactivity. This book aims to introduce these concepts in a way that will provide a logical ascension from a simplified discussion of an undergraduate textbook to a level appropriate for a practicing organic chemist.

Undergraduate organic chemistry lays the foundation of chemical knowledge – a reasonable approximation and a useful and often sufficient way to describe molecules as Lewis structures augmented, as needed, by resonance. However, once one realizes that organic molecules are quantum objects delocalized in space, far from the flat two-dimensional drawings on a sheet of paper or a blackboard, it may not be a complete surprise that this simple concept has its limitations.

The way to get to the next step in understanding molecular structure is to move from the flat Lewis structures on a flat sheet of paper to the 3rd dimension. The elements of stereochemistry are introduced, of course, in undergraduate courses. However, this important step is not enough – when one needs to design, understand, and control new reactions, it is crucial to start thinking about organic molecules as intrinsically delocalized and spatially anisotropic quantum objects. This book focuses on the importance of delocalization – the deviation of real molecules, quantum objects par excellence, from idealized Lewis structures.

The laws of chemical attraction in the world of atoms and molecules are defined by quantum mechanics. Constructive interference of electronic wavefunctions is the quantum essence of chemical bonding that “glues” smaller fragments into larger molecular assemblies. As a result, the chemical world at the molecular level is defined by interactions between atomic and molecular orbitals. Because orbitals and molecules are three-dimensional, such interactions depend on the relative atomic arrangements in space. The modulations of electronic interactions by changes in molecular geometry are generally referred to as *stereoelectronic effects*. In organic chemistry, stereoelectronic effects can be defined as *stabilizing electronic interactions maximized by a particular geometric arrangement which can be traced to a favorable orbital overlap*. Stereoelectronic interactions are omnipresent in chemistry, as only a small subgroup of electronic effects, i.e. the long-range² electrostatic effects, can be considered, with a degree of approximation, as not having a substantial stereoelectronic component.

There is one common misunderstanding that needs to be addressed early: “stereoelectronic” is not the same as “steric + electronic”! By definition, stereoelectronic effects are *always* stabilizing, reflecting increased delocalization at favorable conformations. Repulsive steric interactions also depend on the arrangement of orbitals in space but, historically, are not included under the umbrella of stereoelectronic effects.

Stereoelectronic factors control interactions between different atoms or molecules and interactions between different parts of a single molecule. Although our focus will be on the latter, we will also briefly illustrate the fundamentals of intermolecular interactions, because they broaden the conceptual foundation for subsequent discussion and illustrate the key patterns for orbital overlap without intramolecular constraints being imposed on the geometries.

Understanding the role of orbital interactions can be beneficial from the practical perspective. For example, the symmetry of frontier molecular orbitals can explain why thermal [2+2] cycloaddition fails, whereas the analogous reaction of transition metal alkylidenes, compounds that can be described as having a metal–carbon double bond, proceeds efficiently under mild conditions (Figure 1.2). In this case, *an extra orbital node is the difference between a failed reaction and a Nobel Prize!*

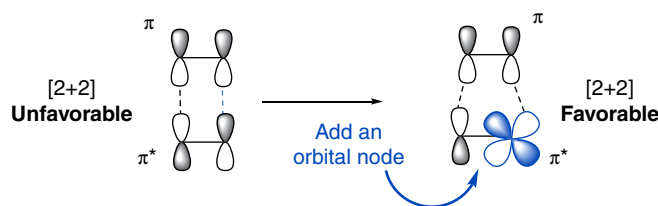


Figure 1.2 The striking effect of orbital symmetry on [2+2] cycloadditions.

1.2 Orbital interactions in theoretical chemistry

The concept of stereoelectronic effects resulted from the cross-pollination of quantum-mechanical ideas (both valence bond, VB and molecular orbital, MO) with the three-dimensional thinking of organic chemists. The involvement of orbitals evolved over the 20th century from the qualitative ideas of Lewis and Pauling through the approximations of Hückel and semi-empirical treatments to the sophisticated accuracy of modern multiconfigurational approaches. However, even the most complex wavefunctions can still be analyzed in terms of individual orbitals using such methods as natural bond orbital (NBO) analysis (introduced in Chapter 4). Such dissection allows one to recover the basic Lewis concepts that seem to be lost in the mathematical jungle and to use them as a foundation for developing the deeper understanding of electronic structure.

In parallel, experimental organic chemistry grew in scope and sophistication. A large body of information was acquired allowing precise measurements of molecular geometries, spectroscopic parameters, and reaction kinetics to provide the necessary basis for the fruitful application of stereoelectronic ideas on a quantitative basis.

The accuracy of computational methods has started to rival experimental measurements, but finding the optimal compromise between computational accuracy and cost is an ever-moving target. Time-resolved experimental techniques allow understanding reactivity on the fly, accessing increasingly exotic and increasingly unstable species with even transition states³ and, more recently, hilltops on potential energy surfaces⁴ succumbing to experimental scrutiny. This is a productive interplay. Experiments are important for benchmarking and testing theory,⁵ whereas theory is useful in guiding and streamlining experiments.

1.3 The birth of stereoelectronic concepts in organic chemistry

Initially, even the simple 3D description of molecules was a controversial idea. In fact, Van't Hoff's 1874 book *La chimie dans l'espace* was ridiculed by such eminent chemists as Adolph Kolbe, the editor of the *Journal für Praktische Chemie*, who stated:

A Dr. H. van't Hoff of the Veterinary School at Utrecht has no liking, apparently, for exact chemical investigation. He has considered it more comfortable to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his "La chimie dans l'espace" how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight.⁶

However, the situation had already changed drastically before the early 1950s when important stereochemical concepts had already permeated the fabric of organic chemistry. In 1954, the term "stereoelectronic" was born in a paper by Hirschmann et al.⁷ who disclosed a remarkable coordinated ring contraction/expansion in rockogenin (Figure 1.3).⁸ The authors stated that "the stereoelectronic requirements are fulfilled only in the case of the natural C₁₂- β -configuration. The significance of this geometrical factor is reflected in the extraordinary ease with which this rearrangement occurs." The unprecedented rearrangement to a new ring system took place instead of the more mundane methyl migration or elimination without rearrangement.

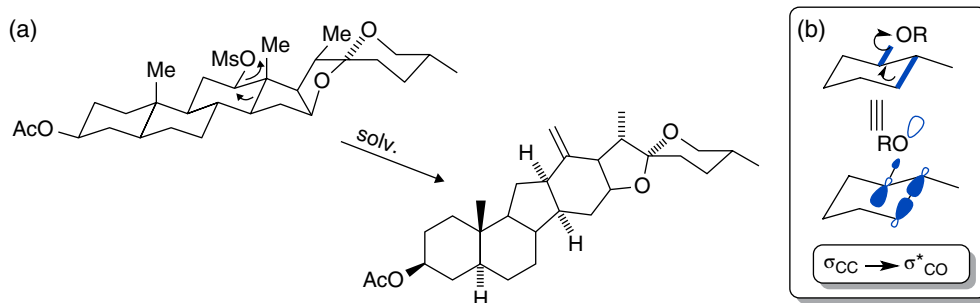


Figure 1.3 (a) Rearrangement of rockogenin as reported by Hirschmann (Source: Hirschmann 1954 (7). Reproduced with permission of American Chemical Society). (b) Orbital interactions involved in the bond reorganization.

Two years later, in 1956, E. J. Corey, a young professor at the University of Illinois used "stereoelectronic" in the title of a paper ("Stereoelectronic Control in Enolization-Ketonization Reactions").⁹ In this paper, he associated the faster loss of axial hydrogen in enolization and the faster gain of axial hydrogens in ketonization with the more favorable orbital overlap of the carbonyl π -system with the axial C-H bonds relative to the equatorial C-H bonds (Figure 1.4).

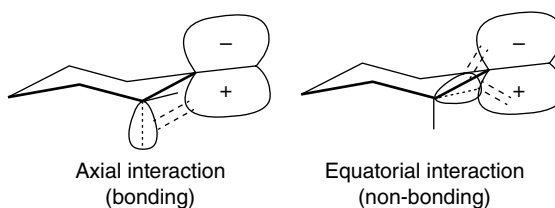


Figure 1.4 Early comparison of the carbonyl π -system overlap with the axial and equatorial C-H bonds. (Source: Corey 1956 (9). Reproduced with permission of American Chemical Society.)

The evolution of stereoelectronic concepts was further catalyzed by steroid synthesis and rapid development of conformational analysis recognized by the 1969 Nobel Prize to Barton and Hassel. However, it was not until 1983, that an organized treatise dedicated to stereoelectronics was published (the important books by Deslongchamps and Kirby).¹⁰

What does the future hold, or “Are we living on an oblate spheroid”? To take the Earth analogy even further, one can illustrate that the basic stereoelectronic concepts are likely to have their own limitations as well. Further refinements of our understanding of chemical structure are unavoidable. For example, stereoelectronic concepts discussed in the following sections are still just an approximation of the exuberant variety of bonding patterns created by the chemical cornucopia known as the periodic table. There are systems so delocalized that starting with a Lewis structure is simply too far off for arriving to a useful description. For such highly delocalized structures, the Lewis approximation is just too crude, and the perturbative approach, which we refer to as resonance, is not able to correct this deficiency. In such cases, it is more productive to describe a molecular system from an MO perspective. Striving to delocalization, transition states and unstable reactive intermediates defy the limitations imposed by the classic two-center two-electron bond: the Lewis structure’s line between atoms. Odd-electron systems are incapable of perfect electron-pairing by their nature. Aromatic and antiaromatic molecules, inorganic clusters, and multicentered bonding in reactive intermediates are examples that further emphasize the primary importance of electronic delocalization.

Quantum tunneling Furthermore, the assumption that nuclear motion is slow enough to be separated from the motion of electrons (the Born–Oppenheimer approximation) and the expectation, that one can always assign distinct connectivity to a molecule, are also only approximations. In the world of quantum phenomena, the whole system of electrons and nuclei can take advantage of Heisenberg’s uncertainty principle and “miraculously” morph into a different molecule with different connectivity even under conditions approaching absolute zero, as long as the barrier separating the two molecular structures is relatively narrow (“quantum tunneling”)¹¹ – Figure 1.5.

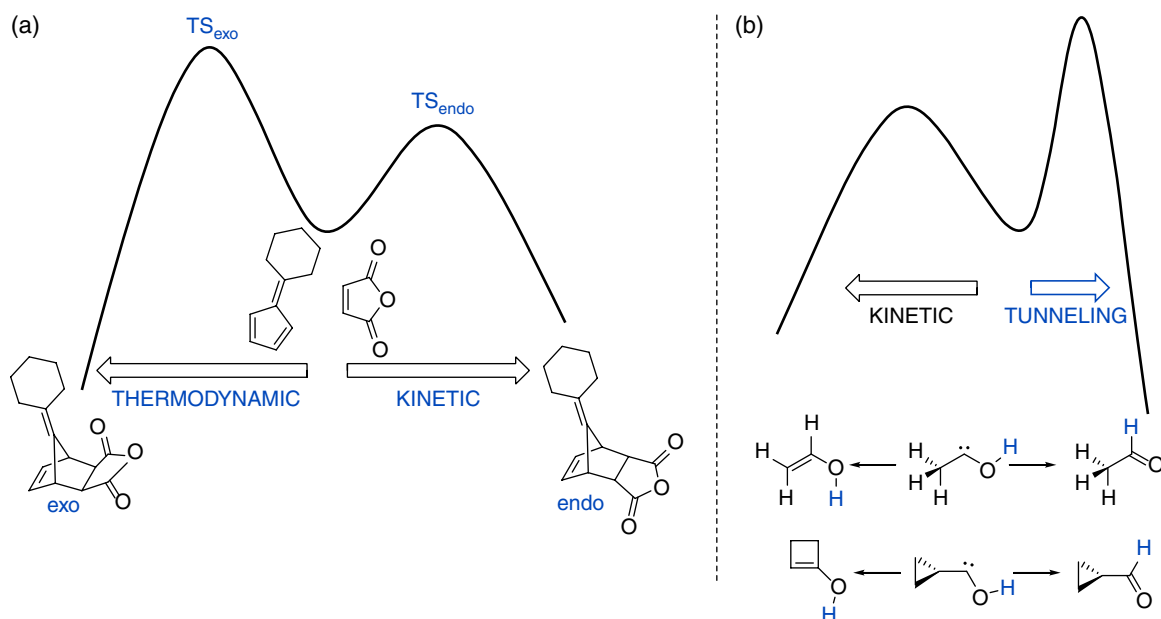
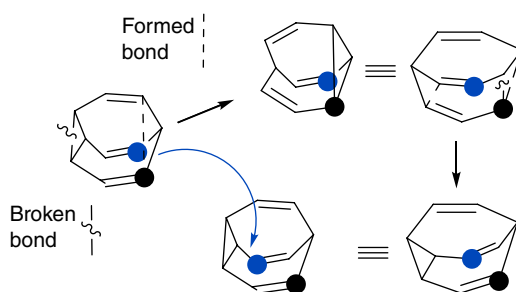


Figure 1.5 Three regimes of reaction control. (a) kinetic vs. thermodynamic control¹² (b) kinetic vs. tunneling control.¹¹

Molecular trajectories Further conceptual limitations of our understanding of chemical reactivity are illustrated by the simple notion that even the exact knowledge of energies and structures of every stationary point at the potential energy surface for a chemical system is not sufficient for accurately predicting the distribution of products for a given set of starting materials. One has to know the shape of the TS region in the 3N–6 dimensional space and the forces that affect a N-atom molecular system that traverses this region on its route from reactants to products.¹³

“Shapeshifting molecules” Not just the position of atoms but also molecular connectivity can be dynamic in the most unusual ways. In so-called fluxional molecules, the whole concept of a single Lewis structure fails at a different level. In these systems, *nuclear* structural reorganization and bond breaking/bond reforming are fast on the chemical timescale.¹⁴ For example, the 10 carbon atoms of bullvalene have identical bonding environment at 140 °C. Both the proton and the carbon NMR spectra show single signals (at 4.2 and 86.4 ppm, respectively), indicating that every carbon atom experiences the identical surroundings and that 10!/3 or 1,209,600 contributing Lewis structures interconvert in this unique “molecule”. There are no permanent C–C bonds in bullvalene, but every atom is equally connected to any other atom! As stated by Doering: “all ten carbon atoms [must] inevitably wander over the surface of a sphere in ever changing relationship to each other”.¹⁵ In the presence of several substituents, each bullvalene molecule becomes a “dynamic library” of compounds¹⁶ – Figure 1.6.

Transposition of atoms via sequential Cope rearrangements



The blue atom moves away from the black atom in the array of seemingly identical structures

Figure 1.6 Part of the extended reaction network connecting multiple isomers of bullvalene via degenerate Cope rearrangements. Although the structure seems to remain unchanged, note that the blue carbon atom moves away from the black atom.

The future of chemistry is full of surprises and, as the boundary with the unknown parts of the chemical universe continues to expand, we need to refine our models as we move deeper into the rich world of fuzzy objects at the subnanoscale.

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2

Direct Effects of Orbital Overlap on Reactivity

Stabilizing orbital interactions come in a variety of patterns. For example, in intramolecular scenarios, they can either involve formation of covalent bonds from two non-bonding orbitals (e.g. two p-orbitals in a π -bond, or a lone pair and an empty p-orbital in oxycarbenium ions, heteroatom-substituted singlet carbenes etc.), or be responsible for a plethora of “second order interactions”. The latter include interactions between π -bonds (conjugation), between non-bonding orbitals and σ -bonds (classic negative or positive hyperconjugation), or between two σ -bonds (σ -conjugation). The intermolecular scenarios can involve supramolecular contacts with $n \rightarrow \sigma^*$ or $n \rightarrow \pi^*$ components (Figure 2.1). The list of such interactions rapidly expands from the familiar hydrogen bonding to halogen, pnictogen, chalcogen and tetrel bonding (vide infra).

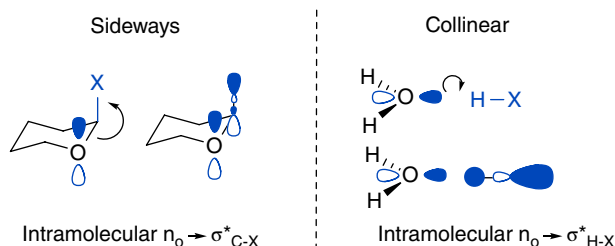


Figure 2.1 Comparison of intramolecular and intermolecular overlap patterns for interaction between lone pairs and antibonding orbitals.

We will start with the simplest case – interaction of two non-bonding orbitals with an overall population of two electrons. This case corresponds to the classic formation of a two-center/two-electron (2c,2e) chemical bond. However, even this familiar situation allows for a number of interesting modifications. For example,

even within a narrow class of bonds, e.g. C-C and C=C bonds, remarkable variations in the apparent bond strength can be found (Figure 2.2).¹

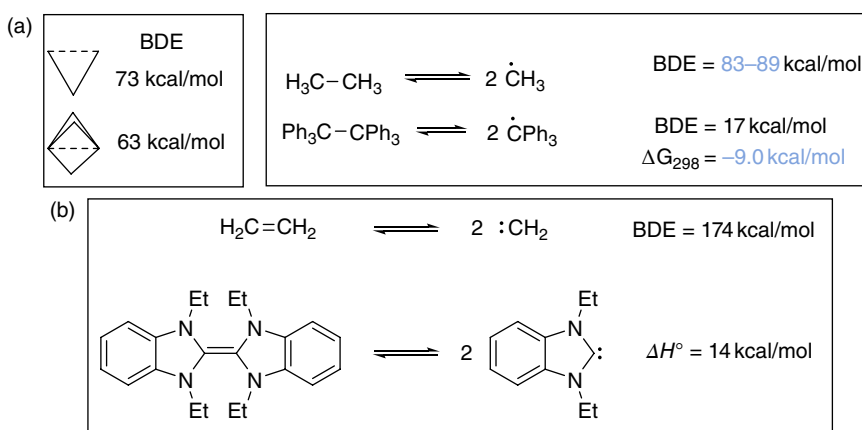


Figure 2.2 Variations in apparent bond strength as evaluated by selected bond dissociation energies (BDEs) and enthalpies. (a) C-C bonds, (b) C=C bonds.

2.1 Bond formation without bond breaking: types of overlap in two-orbital interactions

In the language of molecular orbital theory, the 2c,2e chemical bond is described via the formation of two new orbitals: the low energy filled bonding orbital and the high energy empty antibonding orbital, (Figure 2.3). In such systems, bond formation is not complicated by simultaneous bond breaking. Furthermore, one does need to consider the effect of four-electron repulsion. Nevertheless, this process is still controlled by stereo-electronic effects, and many interesting variations are possible.

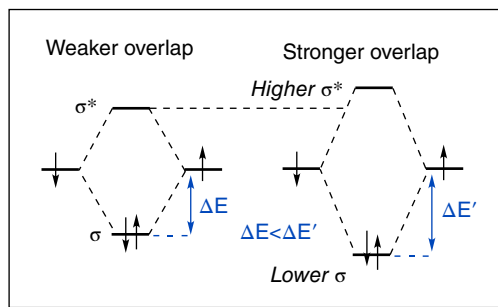


Figure 2.3 Formation of two-center two-electron chemical bonds and role of overlap in bond strength. The stronger overlap also leads to lower energy bonding orbitals and higher energy antibonding orbitals.

Interactions of s-, p-, and d-orbitals are usually classified within the three main types of orbital overlap: σ , π , and δ (Figure 2.4).

For the intermolecular formation of a single bond between two interacting fragments, the direct approach where interacting orbitals overlap along the line connecting the two atomic centers is preferred, leading to the textbook description of σ -bond formation.

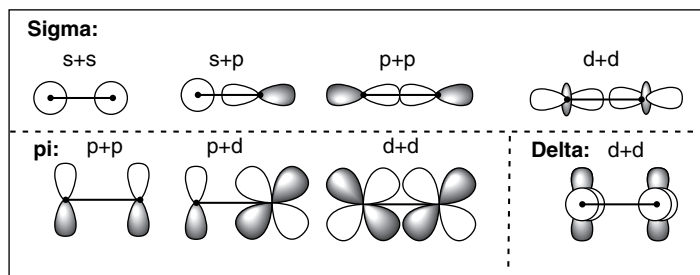


Figure 2.4 Making bonds out of atomic orbitals: σ , π , and δ -overlaps of s -, p -, and d -orbitals.

The second type of overlap, the π -type, is characteristic for molecules that already possess a σ -bond. In this approach, the two orbitals are parallel rather than collinear. Not only does this overlap pattern describe such important functional groups as alkenes, alkynes, aromatics, and carbonyl derivatives, but the π -type overlap often plays a key stereoelectronic role even in molecules *without* a double bond. For example, the π -overlap is important in vicinal hyperconjugative interactions (Figure 2.5), providing a stereoelectronic basis to such phenomena as the anomeric effect, gauche effect, and *cis*-effect (vide infra).

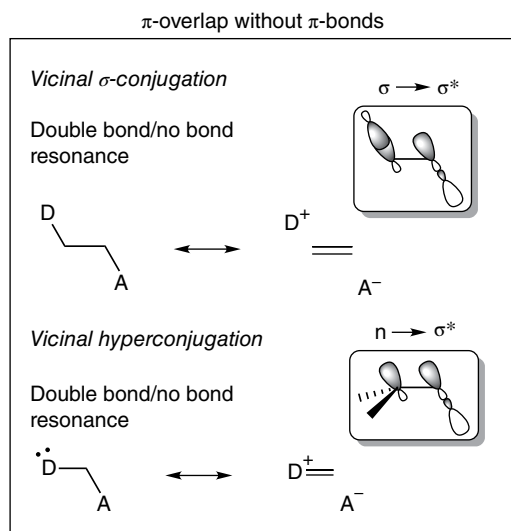


Figure 2.5 Examples of interactions using π -overlap in systems lacking formal double bonds in the main Lewis structure.

Finally, metal–metal interactions may include δ -bonding, where *four* lobes of one atomic orbital overlap with four lobes of the other atomic orbital (Figure 2.4). The δ -bonds have two nodal planes which intersect at the internuclear axis (for the first compound with a δ -bond and for the first example of d-aromaticity, see references 2 and 3, respectively).

The σ, π, δ -overlaps can combine to make compounds with bond orders exceeding those available to organic molecules (e.g. 1 σ , 2 π , and 2 δ orbitals for a quintuple bond order) and, in combination with structural constraints, can lead to very short M–M bonds (Figure 2.6).⁴ The 1.706 Å metal–metal distance observed in a quintuply bonded Cr–Cr bimetallic complex is the same as the longest C–C bond in stable alkanes.⁵

The efficiency of the overlap is generally reflected in the strength of the chemical bond formed by this overlap: $\sigma > \pi > \delta$. As a result, it is common to have σ -bonds without π and δ bonds in a molecule, but

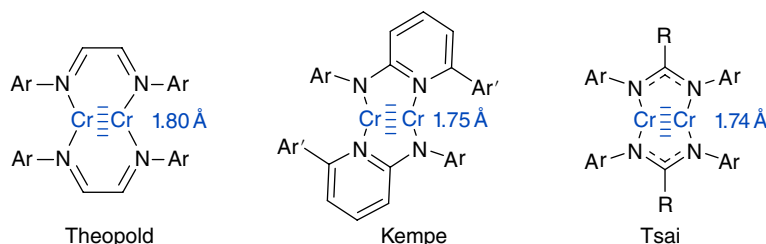


Figure 2.6 Selected molecules with very short metal–metal bonds.

a bonding situation where, for example, a π -bond is formed without a single bond is uncommon; although, curiously, it is not impossible. For example, C₂ can be considered as a molecule held together by two “levitating π -bonds” without a single bond.⁶ Furthermore, four and even five atoms in the Mg_3^- , NaMg_3^- , and Na_2Mg_3 species, respectively, were suggested to be held together by only a single π -bond without involving σ -bonds.⁷

A useful, but relatively rare, alternative description for the systems with both σ - and π -bonds between two atoms is the bent bond model. In this model, the double bond is described as a combination of two equivalent “banana bonds” formed from sp^5 hybrid orbitals (Figure 2.7a). Such orbitals correspond to the linear combinations of the classic sp^2 and p -orbitals of the σ, π -description.⁸ The two descriptions are complementary because the linear combinations of two orbitals correspond to the same overall electron density.⁹ We will show in a later chapter that there are cases when such an unconventional description of alkenes can be helpful in understanding conformational effects. In a few cases, when a double bond is connected to a σ -acceptor group that draws additional p -character from the central atom to satisfy Bent’s rule (the classic correlation between hybridization and electronegativity introduced by H. Bent),¹⁰ there is not enough p -character left for formation of normal π -bond and the banana bond description becomes the *only* choice for making a double bond.¹¹ Furthermore, the dichotomy between σ/π vs. “mixed hybrids” descriptions of a pair of orbitals at a given atom also displays itself in systems with two non-bonding orbitals, e.g. CH₂ (singlet carbene) and H₂O. The two systems have the same set of molecular orbitals (MOs), albeit populated with a different number of electrons. In both cases, two of the MOs can be considered non-bonding. It is curious that whereas the non-bonding MOs (NBMOs) of carbene are generally considered different and assigned as σ (for the occupied MO) and π (for the empty MO), the choice between the two different descriptions for the lone pairs of water is often made in a seemingly sporadic fashion. In a physical chemistry textbook, the lone pairs can be different (σ and π) and look very similar to the non-bonding MOs of carbene. On the other hand, an organic chemistry

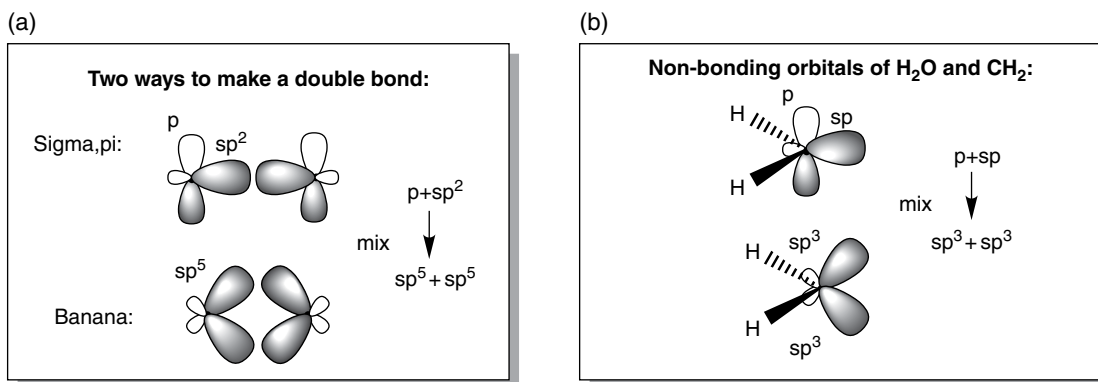


Figure 2.7 Two descriptions of double bonds and two descriptions of lone pairs in water.

paper will often utilize equivalent sp^3 hybridized “rabbit ears” (Figure 2.7b). An excellent discussion of this and other “orbital anachronisms” can be found in a recent educational review of Weinhold and coworkers.¹² We will provide a detailed discussion of lone pairs of oxygen and other heteroatoms in Chapter 5.

Another example of “bent” bonds is provided by the chemical bonding in heavier analogues of carbon, where hybridization is hampered by the cost of electron promotion. The double bonds in distannane may be regarded as two banana donor–acceptor (dative) bonds as opposed to the common description of double bond model of one σ -bond and one π -bond. This description explains why, instead of the “usual” alkene-like geometry, these species are “trans-bent” with a weak $\text{Sn}=\text{Sn}$ double bond.¹³ The heavier triple bond analogues, such as disilyne,¹⁴ also have the “trans-bent” structure. In the latter case, bonding involves two donor–acceptor (dative) banana bonds augmented by one π -bond (Figure 2.8).

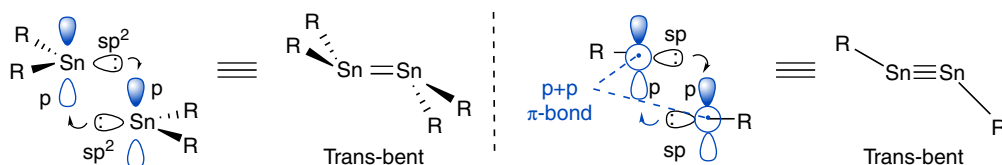


Figure 2.8 Banana double and triple bonds in heavier elements.

2.1.1 Factors controlling σ -bond overlap

Hybridization As we saw above, unusual hybridizations can lead to unusual bonding patterns and geometries. Such effects are not limited to “exotic” species made out of heavier atoms. Carbon also has its surprises.

It is well-known that σ -overlap of two p-orbitals or two s-orbitals does not take full advantage of the available orbital density. In order to maximize σ -overlap, the interacting atoms change their orbital shapes in a non-symmetric way (rehybridize). Because hybridization is associated with changes in orbital overlap, it can be considered as one of the most basic stereoelectronic effects that can impose significant modulations on other stereoelectronic interactions.

Even for a σ -bond between the same pair of atoms, hybridization strongly affects the bond strength as illustrated by the differences in BDEs for $sp(C-H) > sp^2(C-H)$ and $sp^3(C-H)$ (Figure 2.9). Both the greater overlap and the increased polarity contribute to this BDE increase. In bonds with increased s-character, carbon behaves as a more electronegative element. From the sp -hybridized carbon point of view, the homolytic C-H bond cleavage is an oxidation reaction that goes against the natural C-H bond polarization in this system! On the other hand, deprotonation at an sp -hybridized carbon is, of course, more favorable in comparison to the C-H bonds with lower s-characters since it takes advantage of the increased electronegativity of sp -hybridized carbon. Such textbook observations reflect the strong correlation between hybridization and electronegativity.

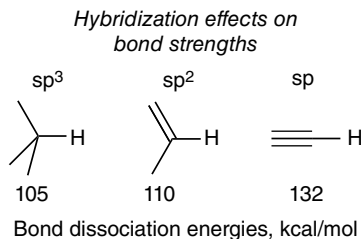


Figure 2.9 Hybridization effects on bond strengths in C-H bonds.

Hybridization is commonly applied to carbon-based chemistry since all σ -bonds formed by carbon atoms are hybridized.¹⁵ However, this concept extends to a variety of other bonds across the periodic table, with electronegativity and orbital size effects leading to dramatic variations in hybridization efficiency for the different bond types.¹⁶ On occasions, other elements can form sigma bonds with little or no help from hybridization (e.g. the orbitals forming the F-F bond in F_2 have >90% of p-character, corresponding to $\sim sp^9$ hybridization). In general, s/p mixing becomes progressively less important as the nuclear charge increases from left to right in the periodic table because the energy of s-electrons decreases faster than the energy of p-electrons (Figure 2.10). In the case of F_2 and similar cases with large s,p energy separation, the gain in overlap does not compensate for the cost of electron promotion (i.e. the involvement of the low energy s-electrons in chemical bonding). When mixing of s and p-orbitals becomes unfavorable, unusual reactivity is often observed.¹⁷

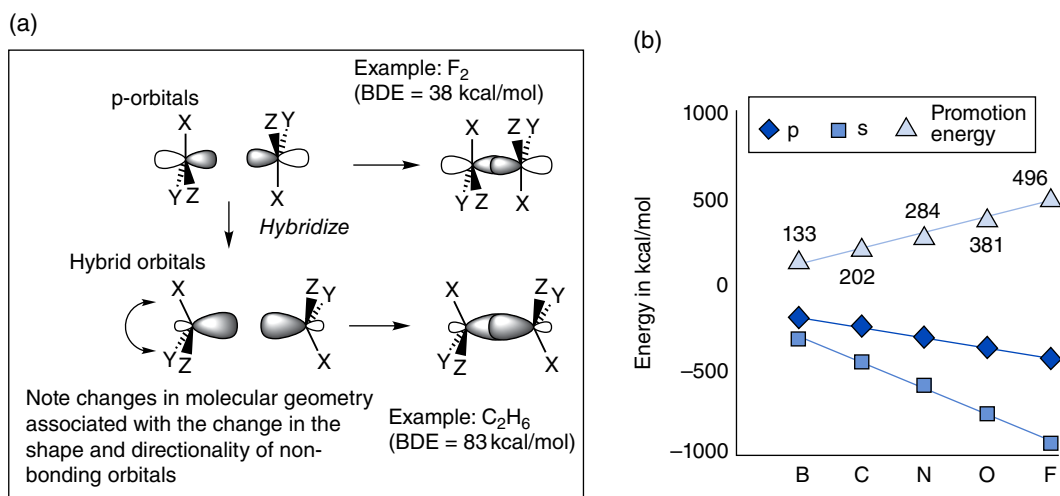


Figure 2.10 Optimization of orbital overlap in bond formation provided by hybridization of atomic orbitals: energy of the p-orbitals (diamonds), s-orbitals (squares) and the promotion energy (triangles) for B, C, N, O, and F. As the promotion energy rises, the importance of hybridization is expected to decrease. Values from ref. 18.

Although hybridization is more often used in VB theory, this concept is introduced naturally in MO theory via mixing of s and p-orbitals. Modern computational techniques (such as NBO analysis discussed in Chapter 4) can find the “optimal” hybridization for localized orbitals constituting a particular wavefunction, providing a convenient approach to quantifying hybridization trends. In addition to polarity, hybridization is related to bond strength and can be probed via isotope effects and spectroscopic methods. Furthermore, it manifests itself in numerous effects on structure and reactivity. An expanded analysis of such effects with the particular emphasis on a very useful correlation between hybridization and electronegativity (Bent’s rule) can be found in the recent literature (ref. 10,11) and will not be repeated here.

Orbital size mismatch Orbital size differences play a role in determining the strength of bonds between different partners.¹⁹ For example, the relatively strong C-H bond, one of the most stable structural units of organic chemistry, starts to weaken considerably as carbon is changed to its heavier cousins (Si, Ge, Sn, Pb in Figure 2.11).²⁰ In particular, the enormous utility of organostannanes (“lovingly” referred to as “the Tyranny of Tin” by radical chemists) for the initiation of radical transformations stems from the weakness of the Sn-H bond originating from the large difference in size between tin and hydrogen (Figure 2.11). This bond can be broken relatively easily with carbon-centered radicals, and the generated tin radicals can attack weaker carbon-halogen bonds, i.e. the C-Br and C-I bonds to form stronger Sn-Br and Sn-I bonds.

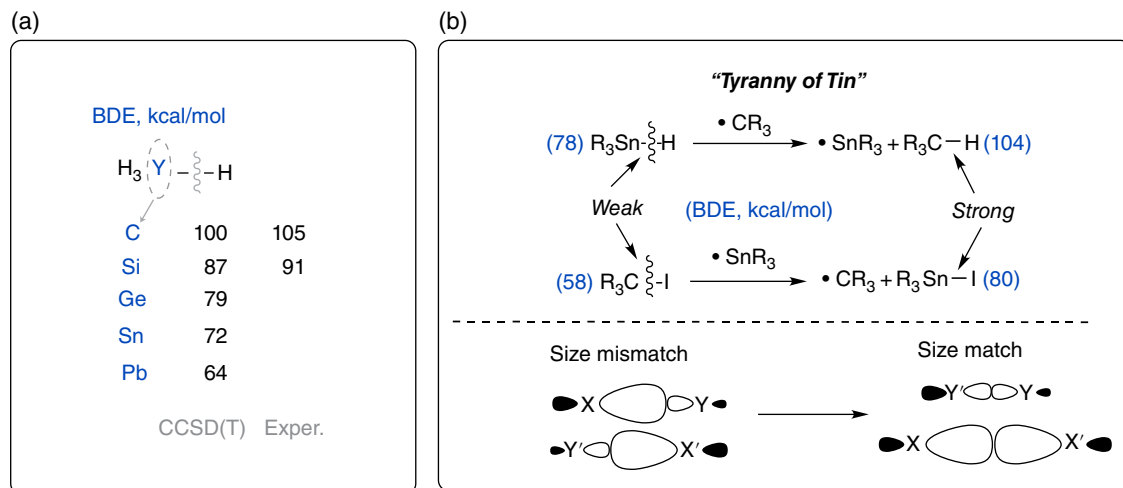


Figure 2.11 (a) Relative orbital size affects bond strength.²¹ (b) Progression from weaker bonds to stronger bonds drives the radical chain process. BDEs for bonds involved in this transformation are shown in parenthesis. *X, X'* are larger atoms, *Y, Y'* are smaller atoms.

Steric effects Geometric restrictions to the σ -overlap inspired the elegant concept of frustrated Lewis pairs (FLPs).²² The FLP concept takes advantage of steric effects to weaken chemical bonds, rendering such systems structurally "unsaturated" and catalytically active. The structural implications of steric "frustration" are shown in Figure 2.12.²³ Interestingly, even though the P...B distance is too long for the formation of a dative covalent bond (Figure 2.12), the combination of multiple C-H...F hydrogen bonds and dispersion interactions leads to an association energy of -11.5 kcal/mol (SCS-MP2). FLPs show enormous potential in activating small unreactive molecules such as H_2 and CO_2 .

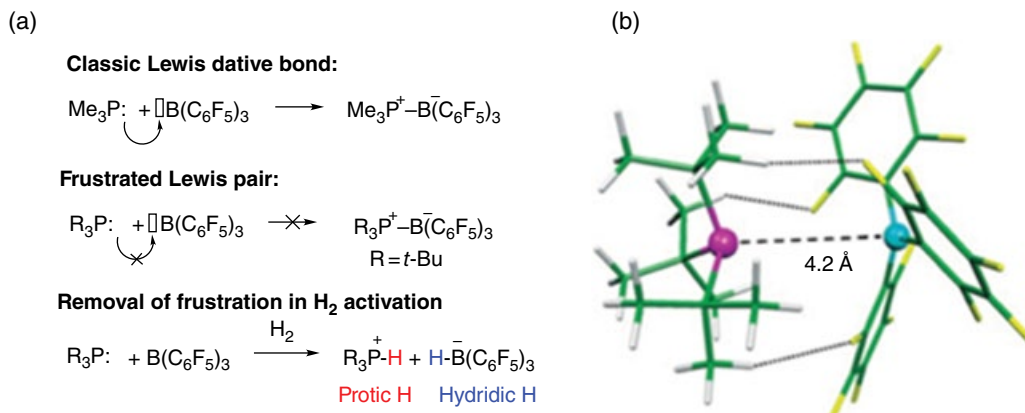


Figure 2.12 (a) Transition from dative bonds to frustrated Lewis pairs (FLPs) upon increase in the size of substituents at the donor and acceptor sites and utility of FLPs in H_2 activation. (b) Decreased overlap as a result of steric congestion in FLPs. The calculated structure of the $[(tBu)_3P] \cdots [B(C_6F_5)_3]$ complex (SCS-MP2 curve). C-H...F type hydrogen bonds (with $d(H-F) < 2.4$ Å) are indicated with dotted lines. The dashed line indicates distance between the "frustrated" atoms (Source: Rokob 2008 (23). Reproduced with permissions of John Wiley and Sons.)

An important insight into the nature of binding energies in sterically crowded molecules (including but not limited to FLPs) is provided by the work of Schreiner and coworkers on the role of dispersion effects. Such non-covalent interactions can significantly increase apparent bond strength in seemingly strained and unstable structures.²⁴ In an apparent paradox, surprisingly strong *and* long C-C bonds were found in a family of sterically congested alkanes (Figure 2.13).

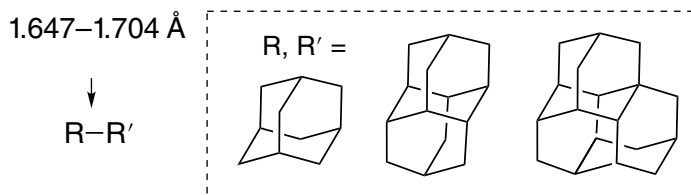


Figure 2.13 Long, yet strong C-C bonds in sterically congested alkanes.

These compounds are stable (up to 300 °C) despite having C-C bonds longer than 1.7 Å. A large part of the apparent bond strength is drawn not from the two atoms in the formal C-C bond but from numerous dispersive interactions. These results suggest that similar interactions can contribute significantly to the bonding energy in FLPs.

Directionality mismatch The importance of directionality in chemical bonding is illustrated by “inverted bonds” such as the central bond of [1.1.1]propellane (Figure 2.14). In such systems, strain and hybridization combine to weaken the bond.²⁵ The bonds are also weakened when the stereoelectronic requirement of collinearity is violated and orbitals forming a single bond are not directed along the shortest distance between atoms (i.e. “banana bonds” in small cycles).^{8,26} Angle strain can be considered a negative stereoelectronic effect originating from suboptimal overlap of orbitals forming a σ -bond.

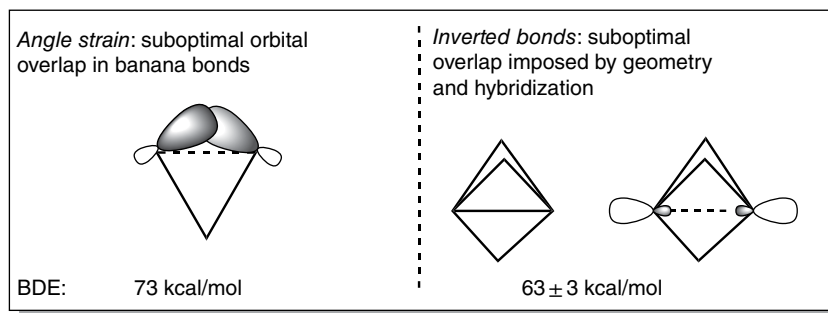


Figure 2.14 Geometrical constraints leading to reduced overlap and weaker bonds in strained systems.

The application of variable orbital overlaps can expand in unexpected directions. For example, it has been creatively utilized by Michl and coworkers in engineering excited state energies for singlet fission (transformation of an excited state singlet into two lower energy triplet states).²⁷ The application of this phenomenon towards the design of solar cells has the promise of significant increase in their maximum theoretical efficiency. The key energetic requirement for singlet fission is that the singlet excitation energy ($S_0 \rightarrow S_1$) should be approximately twice the first triplet excitation energy but lower than the energy of the second triplet state. It was shown that real chromophores satisfying these stringent photophysical conditions can be designed based on understanding of the evolution of biradicaloid energy states within a simple two-electron,

two-orbital model. Two such models for the low energy states of H_2 and ethylene are shown in Figure 2.15. They illustrate how variations in the internuclear separation and in the double-bond twist angle control the relative energies of multiple excited states. This data illustrates that stereoelectronic effects in excited states can provide a new tool for scientists interested in utilizing solar energy for practical applications.

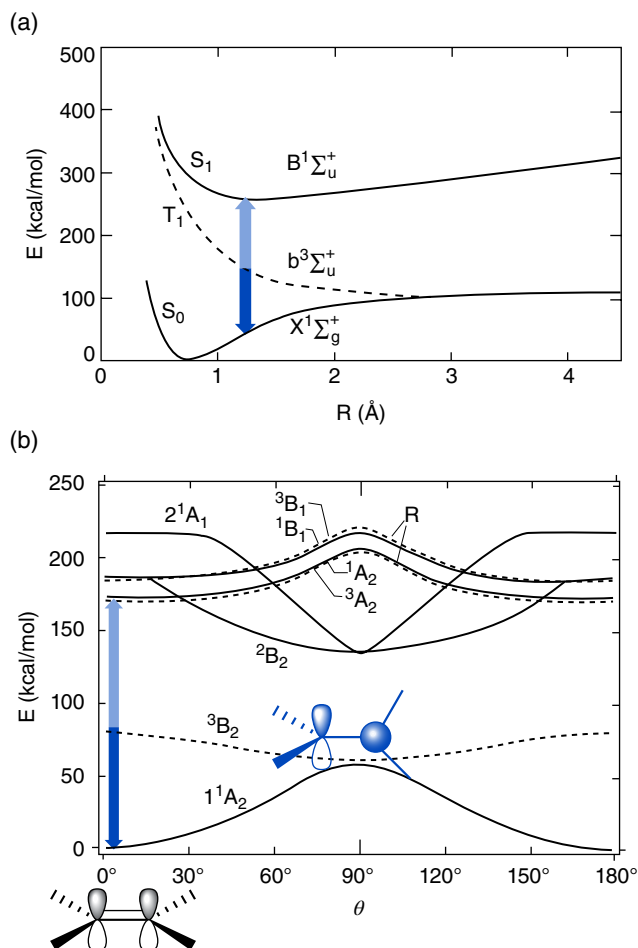


Figure 2.15 Computed potential energy curves of low-energy states of H_2 (a) and ethylene (b), as a function of internuclear separation R and of twist angle θ , respectively. Rydberg states of ethylene are indicated by letter R. (Source: Wen 2015 (27). Reproduced with permission of American Chemical Society.)

Ionic bonds In extreme cases, when electronegativity differences between two atoms (groups) are large, the covalent term becomes unimportant in comparison to the Coulombic attraction between ions of opposite charge formed by electron transfer from the more electropositive atom to the more electronegative partner. In addition to this general textbook scenario, it was suggested recently that ionic terms can play a significant role even in the formation of chemical bonds between two atoms of similar (or even identical) electronegativity. Such bonds, referred to as “charge-shift bonds” were suggested to occur when covalent overlap is inefficient but classic ionic bond is impossible (vide infra).

Charge-shift bonds: Shaik and coworkers introduced the concept of charge-shift bonds for a variety of bonds, from the relatively weak F-F bond in F_2 to very strong C-F and Si-F bonds.²⁸ These bonds were suggested to originate from the superposition of two ionic resonances without significant contribution of covalent resonance where the electron pair is shared *between* the atoms. This idea is illustrated by comparison of the electron localization function (ELF) domains for F_2 and ethane that shows little electron density localization in the bonding region of F_2 .

In the formalism of valence bond (VB) theory, the overall energy of an A-B bond can be represented by the three terms, one covalent and two ionic:

$$\Psi(\text{VB}) = c_1 \phi_{\text{cov}}(A-B) + c_2 \phi_{\text{ion}}(A^+B^-) + c_3 \phi_{\text{ion}}(A^-B^+) \quad (2.1)$$

The first term dominates for a covalent bond and one of the ionic terms plays the largest role for an ionic bond. For example, term two of Eq. (2.1) dominates when B is much more electronegative. In the case of charge-shift bonds, there is no single dominant term. In these systems, the covalent term is often weak whereas *both* of the ionic terms contribute at the same time, so the charge distribution is relatively balanced. If both ionic terms contribute equally, the system can be non-polar (i.e. F_2). Shaik and coworkers suggested that such bonds are ubiquitous and not limited to the exotic inverted bonds of propellanes discussed above. Many classic systems and bond types (i.e. C-F, H-F, Si-O, and others) are dominated by charge-shift bonding.

Some of the above conclusions are provocative: for example, the F-F molecule, commonly defined as having a covalent bond, would not be a bound molecule if covalent VB structure were included alone (Figure 2.16). This is, of course, a counterintuitive suggestion because F-F is a homonuclear bond, where static ionicity

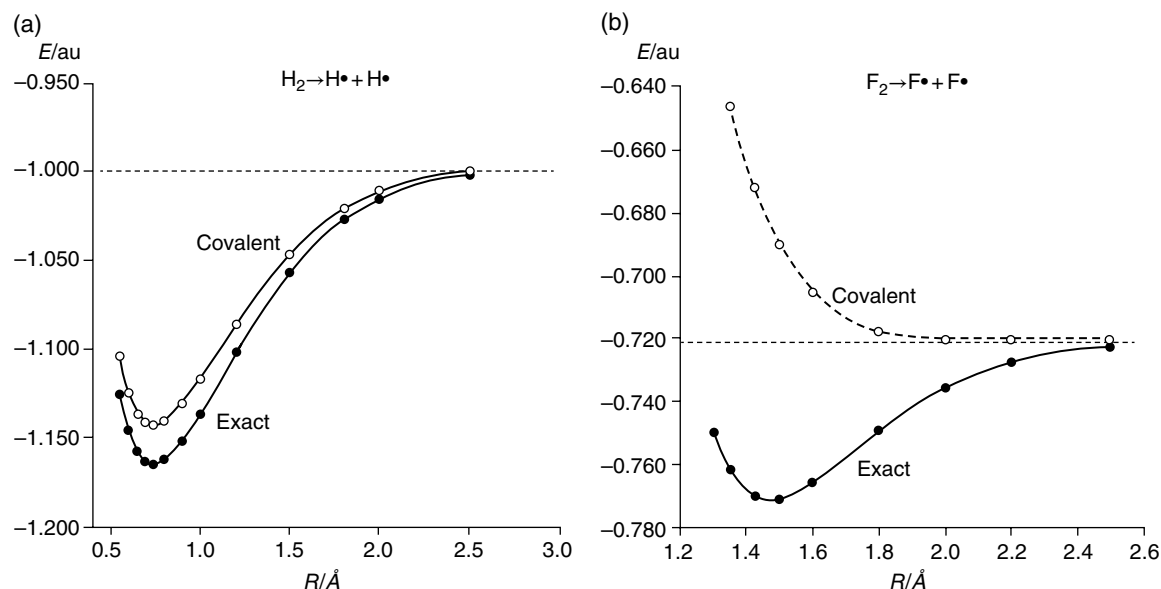


Figure 2.16 Dissociation energy curves for (a) H_2 and (b) F_2 . Open circles: the purely covalent VB structure. Bold lines, filled circles: the optimized covalent + ionic “exact” ground state. (Source: Shaik 2005 (28). Reproduced with permission of John Wiley and Sons.)

should not matter. However, Shaik suggests that F_2 is sustained by the very large charge-shift resonance energy, where the bonding mostly originates from dynamic ionicity (“the ionic-covalent fluctuation of the electron pair density”). This idea is consistent with the abovementioned unusual hybridization in F-F bond ($\sim 90\%$ p-character), that is not optimized for efficient covalent bonding.

Control of π -overlap Although π -overlap allows binding interactions in two regions of space, the combined orbital overlap in a π -bond is weaker than σ -overlap. The weaker overlap accounts for the higher reactivity of alkenes. C-C π -bonds are so commonly used that it is easy to forget that they are highly strained. The bent bond description of alkenes reminds us that a double bond can be considered as the smallest cycle – with much more strain *per carbon* than cyclopropane or cyclobutane.

The energy cost for the formation of a π -bond can be described by the reaction energies in Figure 2.17. Redistribution of chemical bonds in two propane molecules to give $CH_2=CH_2$ and two ethanes increases the overall energy by 28 kcal/mol. The double bond is a truly high energy functionality! Similarly, the “formation” of the triple bond of ethyne from bond metathesis of 2-methylpropane (Figure 2.17, bottom) comes with the energy penalty of >65 kcal/mol. The high energy of alkynes accounts for many interesting features of this functional group.²⁹

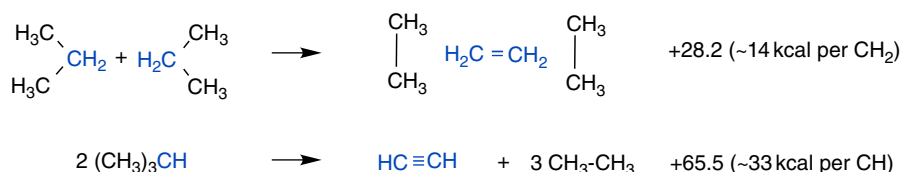


Figure 2.17 Energy cost for formation of π -bonds. Calculated at the MP2/6–311++G(d,p) level of theory.

Another illustration of the strain associated with π -bonds can be provided by thermodynamics of the dimerization of ethylene into cyclobutane (Figure 2.18). This process is enthalpically favored by 18.2 kcal/mol, suggesting that ethylene is a highly strained molecule even when compared to cyclobutane!³⁰ Due to hybridization effects, the difference increases even further for fluorinated alkenes, accounting for their facile $[2+2]$ reactions.³¹

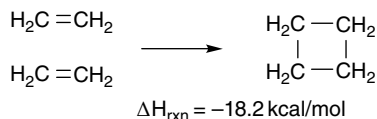


Figure 2.18 The favorable thermodynamics of the dimerization of ethylene to cyclobutane illustrates high strain in alkene π -bonds.

Variations in orbital overlap can make π -bonds stronger or weaker. For example, the shorter C-C distance in alkynes increases π -overlap and renders the π -bonds of alkynes stronger than the π -bonds of alkenes (Figure 2.19).^{32,29}

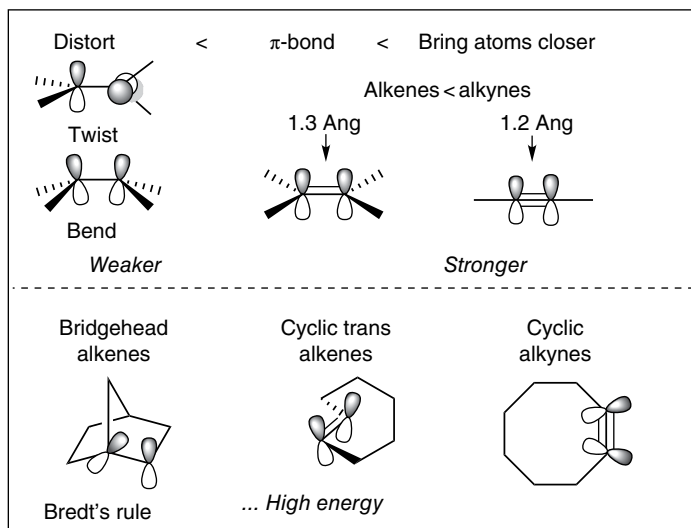


Figure 2.19 π -Overlap between parallel orbitals is responsible for double and triple bond formation. Various changes in geometry and overlap account for stronger or weaker π -bonds.

Two types of structural distortion are commonly associated with weakening of π -overlap: alkene twisting and alkene/alkyne pyramidalization/bending (Figure 2.20).³³ Such geometric perturbations, especially bending, also involve rehybridization. The penalty for such distortions is generally incorporated in the energy needed to reach transition states for chemical reactions of such functionalities.³⁴



Figure 2.20 Selected geometric distortions of π -bonds in alkenes and alkynes.

Distortions are usually introduced by strain or steric effects. For example, *trans*-diphenyl-substituted 2,2'-biadamantylidene is forced to twist due to the steric clash between substituents at the spatially adjacent positions (Figure 2.21).³⁵ According to X-ray analysis, this alkene has a twist angle of 23.2°. The cyclic voltammogram shows a reversible electron oxidation wave, which is 0.2V lower than that in the unsubstituted analogue, indicating that the distortion causes a significant increase in the HOMO energy.

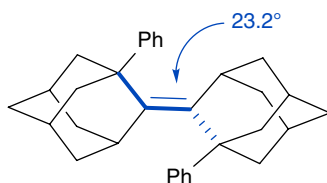


Figure 2.21 Highly distorted 2,2'-biadamantylidene.

Alkenes and alkynes destabilized by such distortions display increased reactivity in reactions that alleviate this penalty for example in different variations of catalyst-free “click” chemistry for biological applications.³⁶ For example, the calculated activation barrier for the cycloaddition of methyl azide to cyclooctyne is half that for cycloaddition to 2-butyne (10.5 vs. 21 kcal – Figure 2.22).³⁷

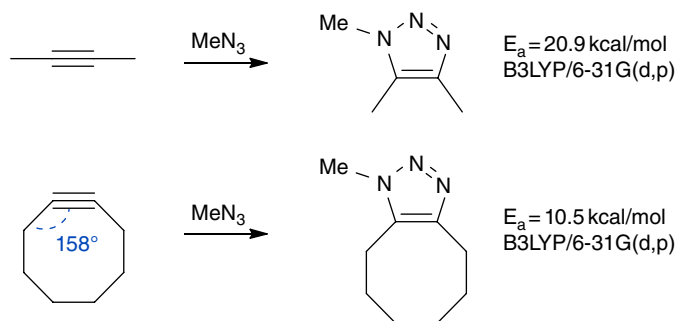


Figure 2.22 The advantage of strained alkyne in cycloadditions with azides.

From the respective heats of hydrogenation, *trans*-cyclooctene is 11 kcal/mol less stable than the *cis*-isomer. With larger rings, the difference in energy decreases, and for cycloundecene, the *trans* isomer is more stable.³⁰ Bridgehead and cyclic alkenes show high reactivity relative to their distortion-free analogues.³⁸ For example, *trans*-cyclooctene undergoes dipolar cycloaddition with picryl azide ~10,000 times faster than *cis*-cyclooctene (Figure 2.23).³⁹ The extremely rapid Diels–Alder cycloaddition between *trans*-cyclooctene and tetrazine has been utilized for the development of fast ligation techniques for biochemical applications.⁴⁰

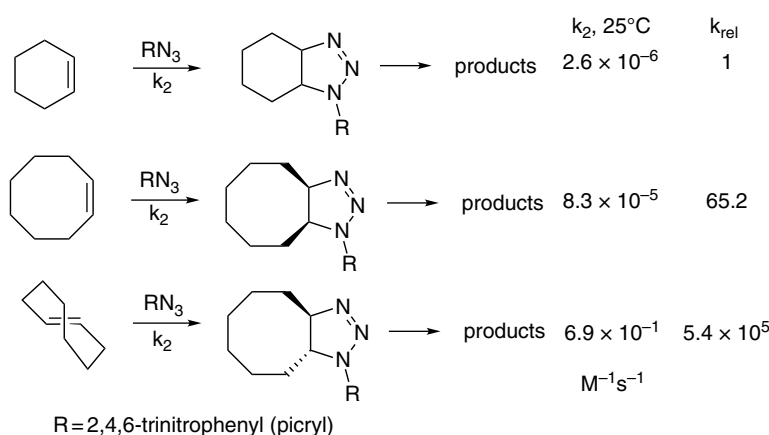


Figure 2.23 Azide cycloadditions with alkenes. Strained systems react extremely rapidly.

The X-ray geometry of *trans*-2-cycloocten-1-yl 3,5-dinitrobenzoate illustrates the combination of structural deformations in this highly reactive (but isolable!) molecule. The *trans*-double bond suffers from ~20° twisting and 22° out-of-plane bending. The C–C=C–C torsion angle is ~138° (Figure 2.24).⁴¹

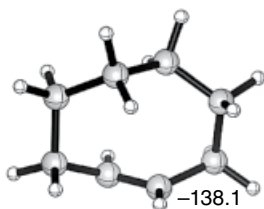


Figure 2.24 Trans-cyclooctene – a highly distorted alkene.

The high energy of twisted alkenes and the associated penalty for their formation provide the foundation for Bredt's rule. The rule is named after J. Bredt, who, on the basis of several unsuccessful experiments described in Figure 2.25, related to the synthesis of bicyclic molecules, suggested that "a carbon double bond cannot occur at the branching positions of a carbon bridge".⁴²

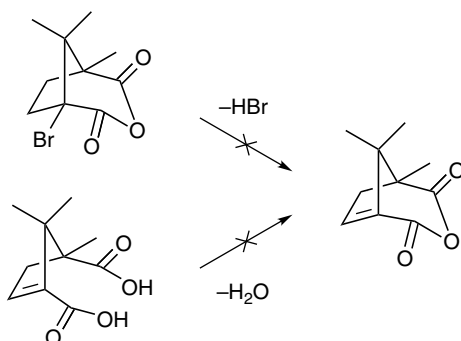


Figure 2.25 Bredt's attempted elimination reactions.

Bridgehead alkenes, often referred to as "anti-Bredt" molecules, are indeed unstable. The problem with these compounds can be understood by inspection of orbital overlap in such systems. The p-orbital at the bridgehead is far from the necessary coplanarity with the other p-orbital. In order to achieve π -bonding, the system must be strongly twisted. In the extreme cases, where the p-orbitals of the "double bond" are close to orthogonality, such molecules can be considered as electronic analogues of excited states of alkenes (Figure 2.26).

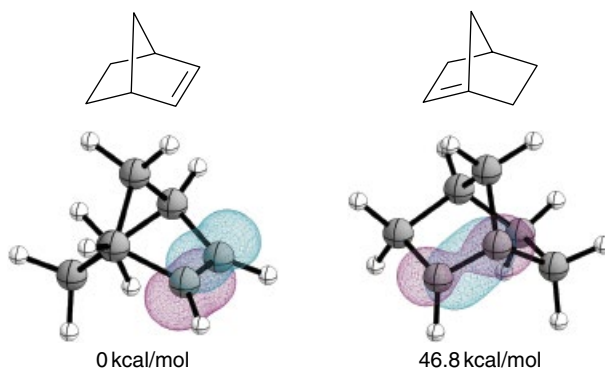


Figure 2.26 Comparison of norbornene and its "anti-Bredt's" isomer. Geometries optimized and energies obtained at the G4 level of theory. NBOs generated at the B3LYP/6-311++G(d,p) level of theory.

Bredt's rule only applies to relatively small cycles. For the larger cycles, π -overlap is possible, and the distortion penalty is significantly alleviated.⁴³ Early attempts to establish a boundary were made in 1948/49 by Prelog in intramolecular aldol condensations. Compounds with a bridgehead double bond were formed smoothly from the homologs with $n > 5$; the one with $n = 5$ was formed in addition to an alternative reaction product, and compounds with $n < 5$ were not obtained.

Bicyclic alkenes with bridgehead double bonds constitute a very interesting group. Compounds with a *trans* double bond in an eight-membered ring can be isolated, but, at the ambient conditions, compounds with the *trans* double bond in a smaller ring are formed only transiently as reactive intermediates (Figure 2.27).

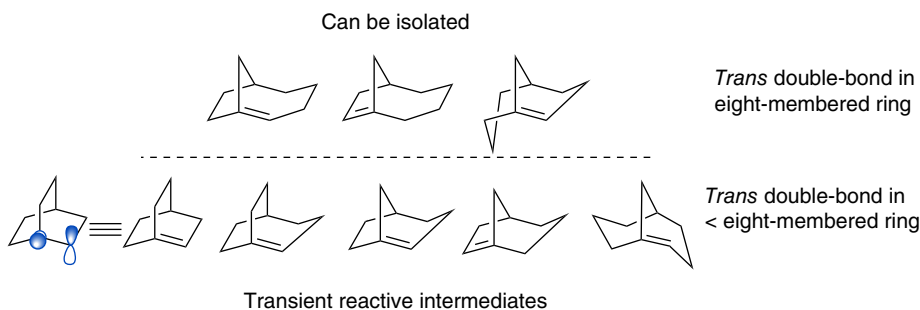


Figure 2.27 Bridgehead alkenes that can be isolated or formed transiently.

Such transient species can be remarkably strained. For example, hydrogen chloride elimination from chloroquadricyclane with *t*-butyllithium or *n*-butyllithium/potassium *tert*-butoxide leads to the formation of didehydroquadricyclane which can be trapped as a Diels–Alder adduct. The olefinic strain energy (i.e. the difference between the heat of hydrogenation of the strained alkene and that of an unstrained reference alkene) for this alkene was evaluated as 71 kcal/mol (Figure 2.28).⁴⁴

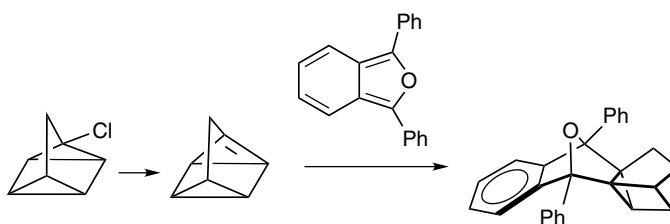


Figure 2.28 Trapping of didehydroquadricyclane as a Diels–Alder adduct.

Understanding the limitations of Bredt's rule is important due to the existence of natural products containing bridgehead double bonds.⁴⁵ An illustrative example is provided by the [5.3.1] core of Taxol, an important anticancer drug (Figure 2.29). In order to evaluate the stability of bicyclic systems of varying size, rules were suggested based on the sum of the numbers of bridge atoms ($x + y + z$) in a bicyclo[$x.y.z$] alk-1-ene, the size of cycles and bridges that contain the double bond, and the strain energies of the *trans*-cycloalkene unit.⁴⁶

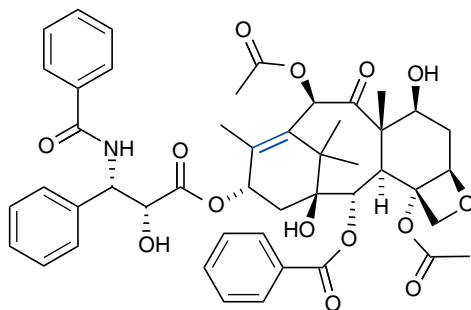


Figure 2.29 Taxol – anticancer natural product with a bridgehead double bond.

Other distortions of alkenes Pyramidalization and bending of double bonds can also be used to enhance reactivity. Norbornene is pyramidalized in the endo direction (out-of-plane angle of 7°).⁴⁷ The seemingly subtle structural differences between cyclohexene and norbornene lead to large differences in cycloaddition reaction rates (Figure 2.30). The structural distortion contributes to the exo-stereoselectivity of cycloaddition to norbornene.⁴⁸

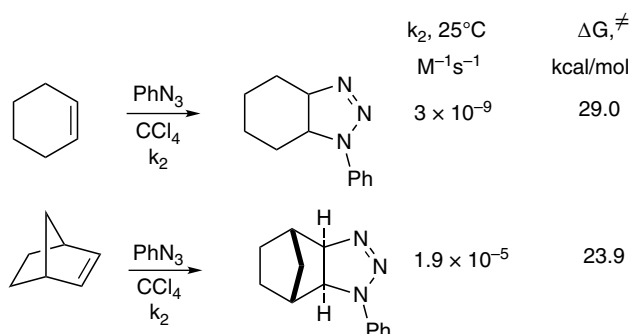


Figure 2.30 Increased reactivity of norbornene, a pyramidalized alkene, in cycloaddition with phenyl azide.

The unusually high cycloaddition reactivity of norbornenes and analogues is used in bioconjugation.⁴⁹ The enhanced electrophilicity of activated oxanorbornadienes was coupled with the “jailbreaking” retro-Diels–Alder fragmentation for the design of protein-modifying prodrugs capable of tunable cleavage after reaction with nucleophiles (Figure 2.31).⁵⁰ Norbornene derivatives are also among the most commonly used alkenes in ring-opening metathesis polymerization (ROMP).

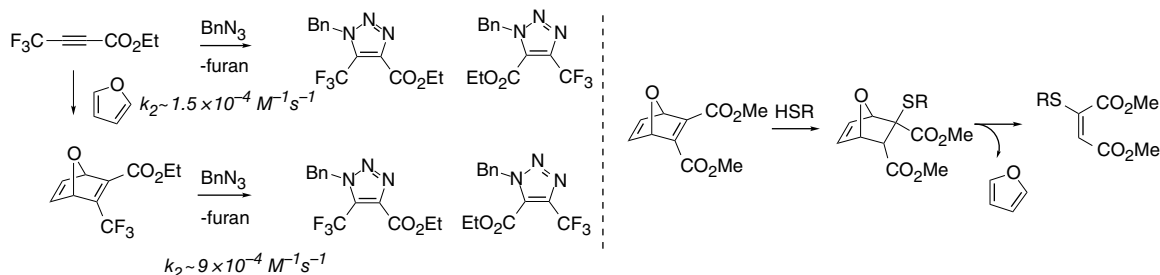


Figure 2.31 Enhanced reactivity of alkenes contained within bicycles.

Other ways to change bond strength – making bonds weaker with delocalization To give a balanced description, mention must be made that direct orbital overlap in a bond is not the only factor controlling bond strength. Because the bond dissociation energy (BDE) – the commonly used way to evaluate bond strength – depends on the relative energies of the bonded species and the two fragments, BDE can be decreased by stabilizing the dissociated fragments. In the case of homolytic cleavage of a single bond, the fragments will be two radicals. A classic example of making a bond weaker by strong delocalization in the two radicals is the case of hexaphenylethane (“Gomberg’s hydrocarbon”).⁵¹ This hydrocarbon has a calculated dissociation energy of only ~10 kcal/mol. Entropic and solvation effects further favor the two radicals, rendering the free energy of dissociation negative and the overall dissociation process exergonic at room temperature.⁵²

However, the situation is not that simple. Paradoxically, hexaarylethanes, the apparently overcrowded molecules, can be *stabilized* by increasing steric bulk. Introduction of 12(!) bulky *tert*-Bu substituents shifted the equilibrium towards the non-dissociated state (ethane) whereas equilibrium in the less sterically crowded parent hexaphenyl ethane favors dissociation (radicals) (Figure 2.32). Dispersion interactions were shown to be the source of these counterintuitive equilibria.⁵¹

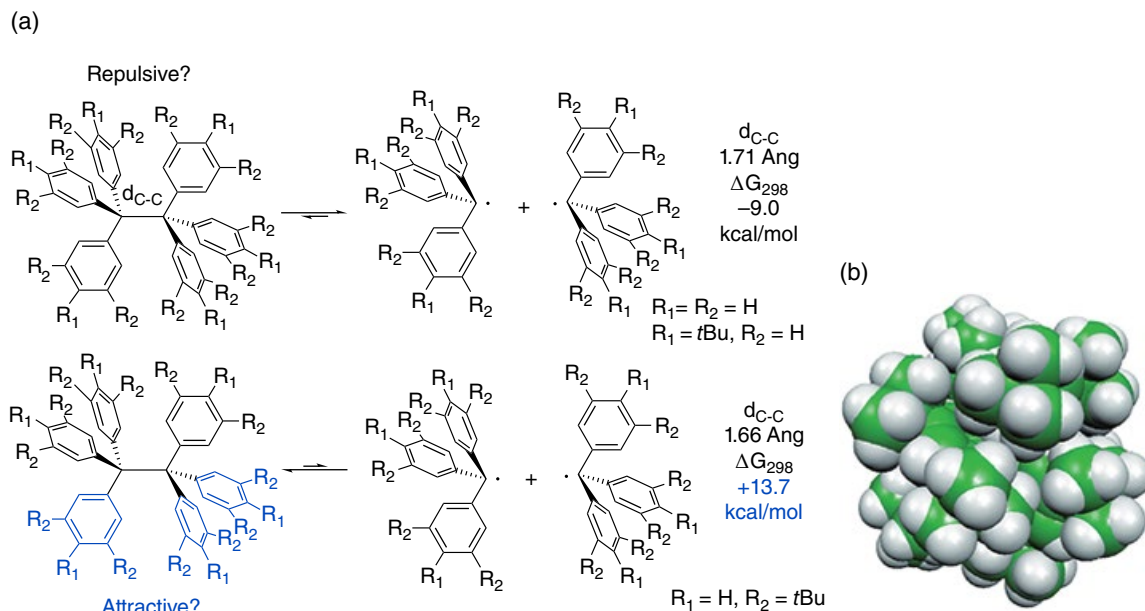


Figure 2.32 (a) Paradoxical hexaaryl ethanes. Calculations at the TPSS/TZV(2d,2p) level of theory with “D3” dispersion corrections find C-C bond scission to be unfavorable in the most sterically crowded case. ΔG_{298} are for the gas phase calculations. Inclusion of solvation provides ~10–12 kcal/mol to the radical products. (b) A space-filling model of the hexaaryl ethane with 12 *t*-Bu groups. (Source: Grimme 2011 (52). Reproduced with permission of John Wiley and Sons.)

In a similar way, resonance stabilization of dissociated species can also be used to make C=C double bonds weaker. Instead of radicals formed from a single bond, dissociation of a double bond produces carbenes. Approaches to carbene stabilization can involve a variety of resonance patterns. For example, the C=C

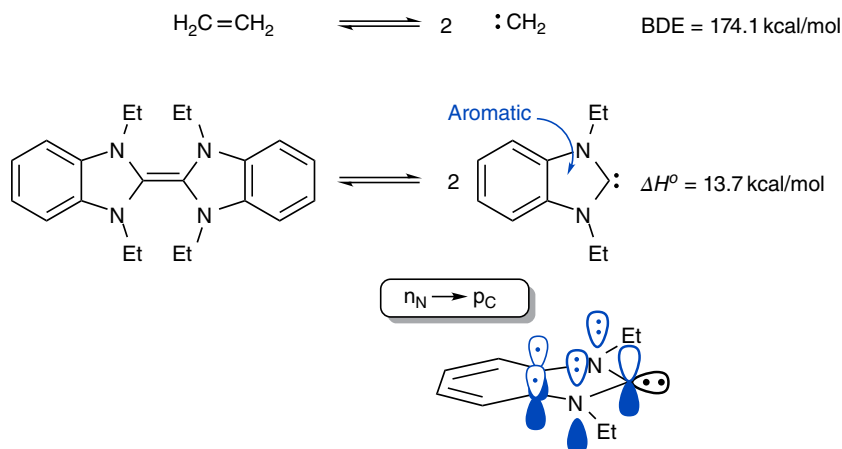


Figure 2.33 Weakening of C=C double bonds by stabilizing the “monomer” carbene species via delocalization in the products.

bond strength in the “tetraamino”-substituted alkene involved in the reversible formation of the carbene in Figure 2.33 is only 13.7 kcal/mol.⁵³ This is a dramatic decrease relative to the bond dissociation energy found in ethylene of 174 kcal/mol!⁵⁴ Stabilization of the resulting carbene is provided by $n_{\text{N}} \rightarrow p_{\text{C}}$ conjugative interactions of the empty p-orbital. Although the ~160 kcal/mol difference between the BDE of C=C bond in ethylene and the diaminocarbene dimer seems to be very large, the stabilization provided by nitrogen lone pairs (~80 kcal/mol per carbene, ~40 kcal/mol per nitrogen) is not extreme. In fact, this stabilization is smaller than that provided to carbocations by an oxygen lone pair (~70 kcal/mol).⁵⁵ Despite the absence of charge (stabilizing interactions are often stronger in charged species, see Chapter 3), the large stabilization provided by the four nitrogens benefits from the lower electronegativity of nitrogen relative to oxygen. In addition, the π -system within the five-membered ring in the diaminocarbene contains six electrons, gaining additional stabilization from $4n+2$ Hückel aromaticity.

2.2 Bond formation coupled with bond breaking

2.2.1 Three-orbital interactions: stereoelectronic reasons for the preferred trajectories of intermolecular attack at a chemical bond

When the target orbital is already part of a bond, the pattern of orbital interactions becomes more complex. Instead of two single atomic (or hybrid) orbitals, one has to consider interaction of the incoming species with both the bonding and the antibonding orbitals associated with a breaking bond. The simplest case for attack of an incoming nucleophile or electrophile at a target bond is a three-orbital interaction (Figure 2.34). The interaction of a filled non-bonding orbital with a σ/σ^* orbital pair corresponds to an $S_{\text{N}}2$ process, whereas the interaction with a π/π^* pair corresponds to a nucleophilic addition. Similar MO diagrams are involved in the formation of 3c,4e-bonds in stable hypervalent species (e.g. XeF_2) and H-bonds.

Figure 2.34a describes the TS for a degenerate $S_{\text{N}}2$ -like reaction $\text{X}-\text{Y} + \text{X}^- \rightarrow \text{X}^- + \text{Y}-\text{X}$. Due to the symmetry, in the TS where the bond breaking and the bond forming occur to the same extent, the MO diagram bears resemblance to the allyl system, the other very common three-center interaction pattern.

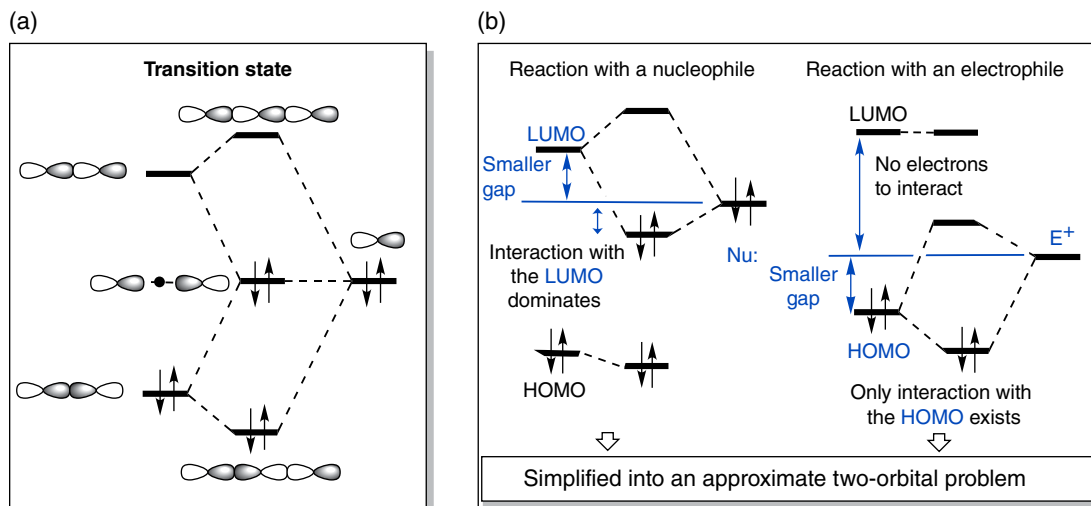


Figure 2.34 (a) Transition state for a degenerate nucleophilic attack ($X-Y + X^- \rightarrow X^- + X-Y$), a symmetric three-orbital interaction. (b) The two simplified situations where orbital interactions can be approximated via a two-orbital model.

Frontier MO (FMO) interactions for nucleophilic, electrophilic, and radical reactions In less symmetric situations, the energy gaps between the non-bonding orbital of the attacking species and one of the two frontier molecular orbitals (FMOs) of the target can differ significantly (Figure 2.34b). Usually, the high energy occupied orbital of a nucleophile is closer in energy to the target LUMO (lowest unoccupied molecular orbital), whereas the low energy empty orbital of an electrophile is closer in energy to the target HOMO (highest occupied molecular orbital). Because the orbital interaction energy is inversely proportional to the energy gap between the interacting orbitals, the situation can be treated within the two-orbital approximation.

Such simplified analysis, based on the dominant two-electron stabilizing interaction between FMOs, is commonly used for understanding stereoelectronic preferences in intermolecular interactions. In particular, the preferred trajectories of nucleophilic additions or substitutions optimize the overlap of incoming nucleophile HOMO with the σ^* and π^* LUMO of the target (vide infra, Figure 2.38). On the other hand, in electrophilic reactions, the favorable $2e^-$ interaction involves the electrophile LUMO and the target HOMO.

Interaction of partially filled orbitals (i.e. singly occupied MOs–SOMOs) plays a significant role in radical chemistry. Depending on the relative energy of the SOMO, either the three-electron interaction with the HOMO or the one-electron interaction with the LUMO may become dominant, leading to polar effects in radical chemistry (Figure 2.35).

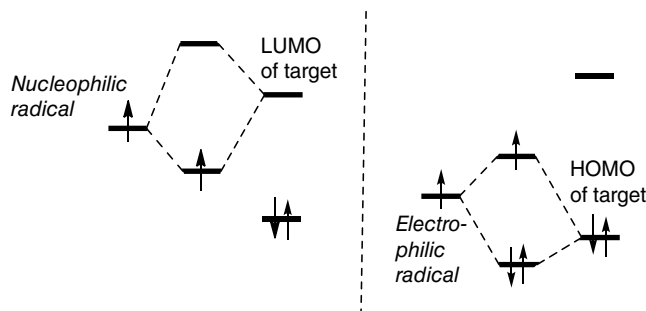


Figure 2.35 Possible frontier MO (FMO) interactions in radical reactions.

Preferred attack trajectories – effect of the target bond For a particular type of attacking species, the stereoelectronic factors involved in bond breaking/formation depend on the FMO symmetry of the target (Figure 2.36). For example, the preferred trajectories for breaking single and double bonds via nucleophilic attack are different: the former is based upon the classic backside approaches of S_N2 reactions, whereas the latter prefers the obtuse (~ 105 – 109°) Bürgi–Dunitz⁵⁶ angle. In both cases, the incoming nucleophile tries to optimize the 2-electron stabilizing interaction with the LUMO and minimize the repulsive 4-electron interaction with the HOMO. These stereoelectronic preferences become more important as the attacking reactive species approaches the target, gaining maximum importance in the vicinity of the transition state. At greater distances, large deviations are common, leading to a “cone of trajectories”.

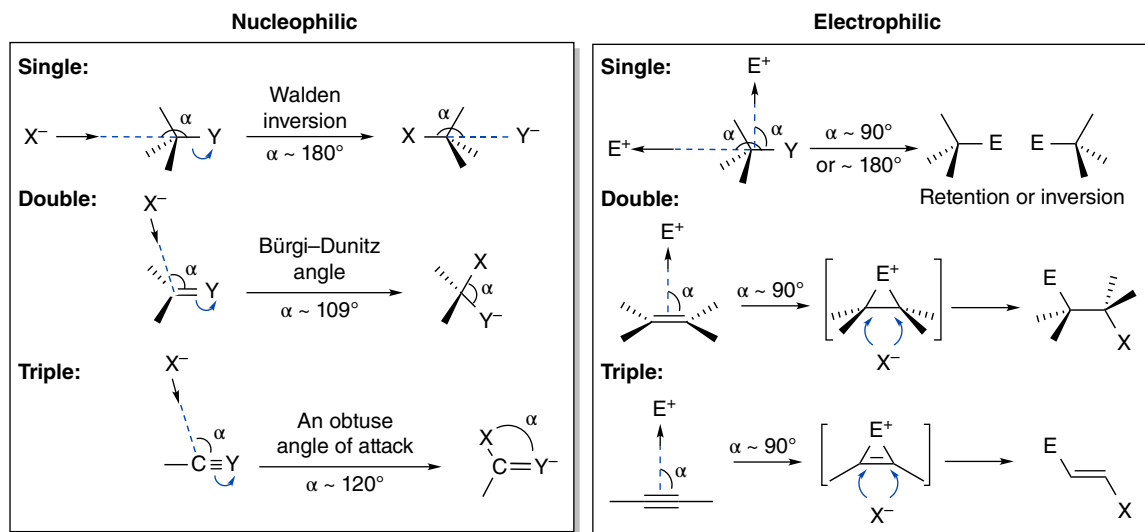


Figure 2.36 Favored trajectories for bond formation at the expense of a single, double, and triple bond in nucleophilic and electrophilic processes. Note that electrophilic processes are not subject to the same stereoelectronic restrictions as their nucleophilic counterparts.

Trajectories of nucleophilic attack at the π -bond are incorporated in the Felkin–Anh model of stereoselection⁵⁷ in nucleophilic addition to carbonyls (Figure 2.37).

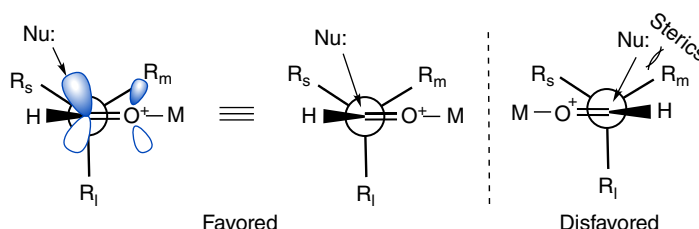


Figure 2.37 Bürgi–Dunitz trajectories used in the Felkin–Anh model of stereoselection.

In a classic 1976 paper, Baldwin used the Bürgi–Dunitz trajectory to define the well-known rules for the design of cyclizations (the Baldwin rules).⁵⁸ However, stereoelectronic factors for a bond formation to alkynes have been controversial. Originally, the rules for alkyne cyclizations were based on the assumption that nucleophiles add to alkynes along an acute trajectory, instead of the obtuse Bürgi–Dunitz angle of attack. Subsequent experimental and computational⁵⁹ analysis suggested that this trajectory is stereoelectronically

unfavorable, as it brings the nucleophile at the node of the target π^* -orbital. More favorable is an obtuse trajectory similar to the Bürgi–Dunitz trajectory for alkenes. This modified trajectory for alkyne attack led to revised rules for alkyne cyclization (*vide infra*).⁶⁰

Attack trajectories for electrophilic reagents are quite different from the above nucleophilic trajectories. For example, electrophiles can attack a single bond with retention of configuration. In another example, cationic 1,2-shifts are ubiquitous in contrast to the topologically analogous, but unfavorable, anionic 1,2-shifts.

The latter proceed via non-concerted pathways.⁶¹ Electrophilic attack at alkenes and alkynes can follow an acute trajectory, which brings electrophiles at the center of the π -bond on route to the formation of 3-center, 2-electron non-classical cations.

The stereoelectronic basis for these trajectories is illustrated below. Trajectories of nucleophilic attack avoid the node in the antibonding orbitals because the unfavorable symmetry of orbital overlap involved in the attack at the node leads to the cancelation of bond-forming 2e-interactions. Attacks of electrophiles have no such restrictions because both σ - and π -orbitals are bonding and, thus, do not have a node between the atoms. The lack of a symmetry restriction in electrophilic reactions opens stereoelectronic routes not available to nucleophiles. For σ -bonds, this is the frontside attack with retention of configuration (Figure 2.38). For π -bonds, this is the acute (or perpendicular) attack leading to the so-called endo-cyclizations (*vide infra*).

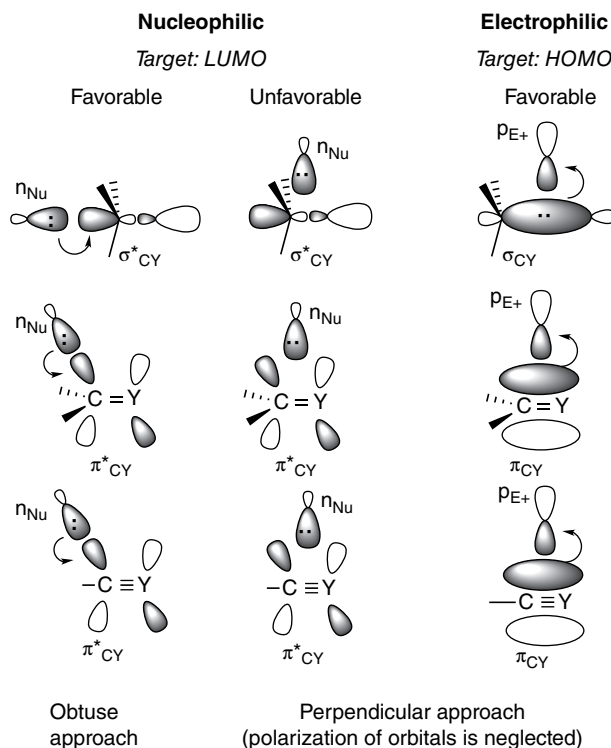


Figure 2.38 Frontier MO symmetries explain the stereoelectronic differences in nucleophilic and electrophilic attacks at the σ - and π -bonds.

LUMO umpolung in reactions of π -systems with nucleophiles It is possible to invert stereoelectronic requirements for nucleophilic processes and render them similar to the stereoelectronics of electrophilic reactions.⁶² Such polarity inversion (“the umpolung”) can be accomplished via coordination of a π -bond to an

external Lewis acid. After such coordination, there is no stereoelectronic penalty for a perpendicular approach of nucleophiles to the π -system of the target (Figure 2.39), in the same way as such penalty is absent for the perpendicular approach of electrophiles to a free alkyne (Figure 2.38, right).

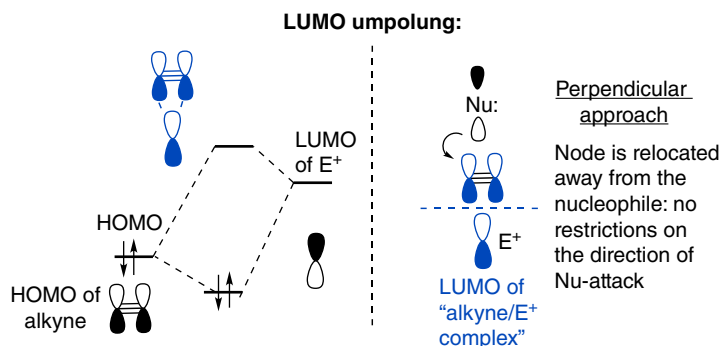


Figure 2.39 Summary of orbital interactions involved in "LUMO umpolung" in alkynes.

2.3 Stereoelectronics of supramolecular interactions

2.3.1 FMO interactions in intermolecular complexes

H-bonding, the prevalent supramolecular force The donor-acceptor FMO interactions are also involved in stabilizing interactions *between* molecules (Figure 2.40). The stereoelectronic features of the $n_Y \rightarrow \sigma^*_{X-H}$ interaction (also referred to as "charge transfer") are responsible for the partial covalency and the key geometric features of H-bonds (e.g. the preferred 180° X-H...Y angle).⁶³

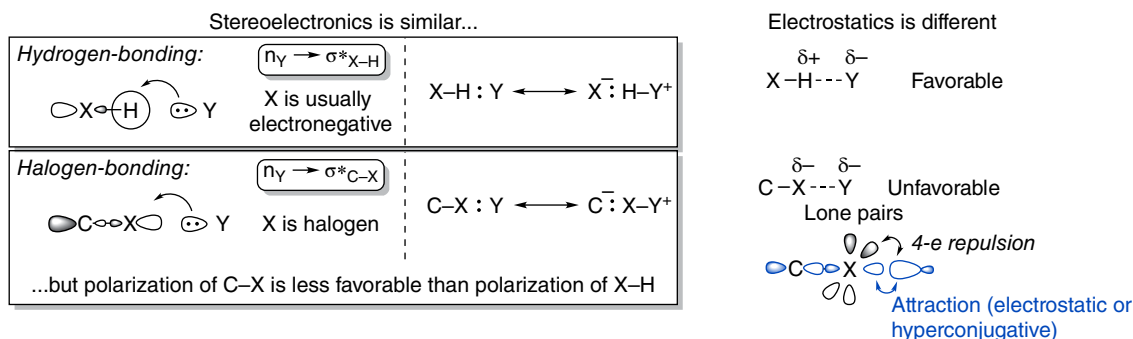


Figure 2.40 Analogous hyperconjugative interactions and contrasting electrostatics involved in hydrogen- and halogen-bonding.

The covalent character in H-bonding spans a continuum from the essentially electrostatic interactions⁶⁴ to the strong covalency in 3-center, 4-electron systems ($F-H \cdots F^-$). The significance of stereoelectronics parallels the increase in covalent characters. Stereoelectronics are especially important in the strong, short low-barrier H-bonds often encountered in enzyme catalysis. On the other hand, the bifurcated and trifurcated bonds, where the importance of individual orbital contacts is diluted, often sacrifice stereoelectronics to reach the maximum Coulombic stabilization.

2.3.2 Expanding the palette of supramolecular interactions: from H-bonding to Li-, halogen, pnictogen, chalcogen and tetrel binding

Every chemical bond is associated with an antibonding orbital, and thus can serve as a hyperconjugative acceptor in intermolecular interactions. This simple idea contributes to the recent explosion in the discoveries of new supramolecular “bonds”. Intermolecular interactions of other σ -acceptors (σ^*_{X-Y} , where neither X nor Y is hydrogen) with lone pairs at a different atom were found to be involved in new types of supramolecular interactions, such as “halogen bonding”, a ubiquitous supramolecular force gaining increasing appreciation.⁶⁵ In addition, tetrel bonds⁶⁶ involve coordination at group IV elements (i.e. carbon, silicon, etc.) whereas pnictogen⁶⁷ and chalcogen⁶⁸ bonds correspond to coordination with atoms from groups V and VI, respectively.

The Li-bond is another conceptually important supramolecular interaction.⁶⁹ For Li-bonds, donation from Lewis base to the n^*_{Li} (empty non-bonding orbital at Li) was reported to be 10 times more important than donation to the σ^*_{C-Li} bond.⁷⁰ This difference accounts for the unusual features of Li-bonds.

The balance of electrostatics and covalency depends on the type of supramolecular interactions. Although the current theoretical description of many such interactions is dominated by electrostatics,⁷¹ the nature of resulting bonds varies greatly. For elements from groups V–VII, the positively charged regions (σ -holes) are detected on atoms with predominantly negative electrostatic potential. In contrast, the group IV atoms do not display the negatively charged regions but possess σ -holes that are more positive than the surroundings.

More recently, $n_Y \rightarrow \sigma^*_{Hal-X}$ interactions were identified as stereoelectronic components in halogen bonding (Figure 2.41).⁷² Although those models emphasize the parallels between hydrogen and halogen bonding, significant differences between the two interactions exist due to the presence of lone pairs on the halogen (and thus, large regions of repulsive interactions), as well as differences in charge, size, and polarizability. H-bonding is unique because hydrogen, unlike other atoms, does not have lone pairs or additional substituents that can participate in repulsive 4-electron interactions with Y. Halogen bonding is less forgiving – the trajectory is limited to the approach that orients the lone pairs towards the “ σ -hole”, strictly along the Z-Hal axis. Furthermore, the relative importance of the electrostatic component increases in comparison with H-bonding.

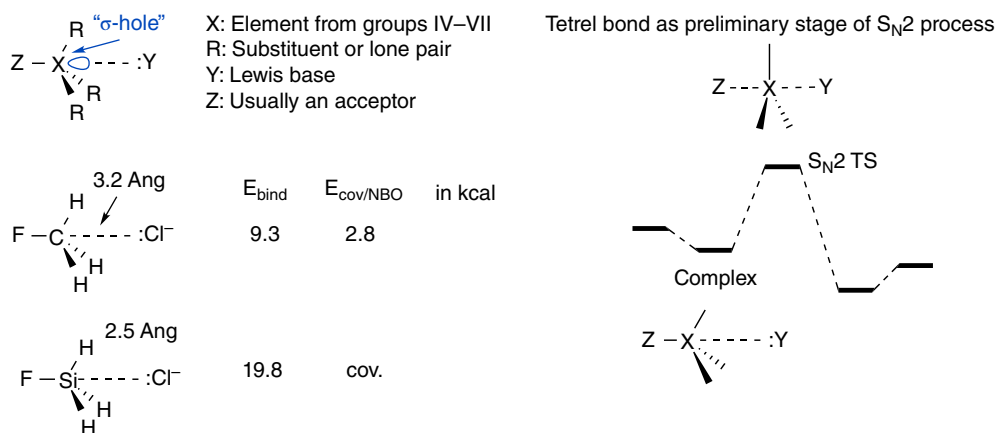


Figure 2.41 Selected supramolecular interactions with stereoelectronic components (E_{bind} is the overall binding energy, E_{cov} corresponds to the covalent component to the binding energy based on the NBO energies of $n_Y \rightarrow \sigma^*_{X-Z}$ interactions).

Directionality of H-bonding Due to the high donor ability of non-bonding orbitals, most H-bonds involve a suitable lone pair as an electron donor (often alternatively, and confusingly, referred to as “H-bond acceptor”) in $n_Y \rightarrow \sigma^*_{X-H}$ hyperconjugative interactions. Such interactions involve two stereoelectronic components. First, the symmetry of the electron acceptor (σ^*_{X-H}) defines the 180° X-H...Y angle of attack (note the stereoelectronic analogy between H-bonding and the S_N2 transition state). Such stereoelectronic factors and ensuing directionality at the “H-bond donor” site weaken as the strengths of H-bonds decrease for less polarized H-bond donors (= weaker σ^* acceptors). Figure 2.42 illustrates how the decreases in directionality parallels the polarity of the X-H group: O-H > C(sp)-H > C(sp²)-H > C(sp³)-H.

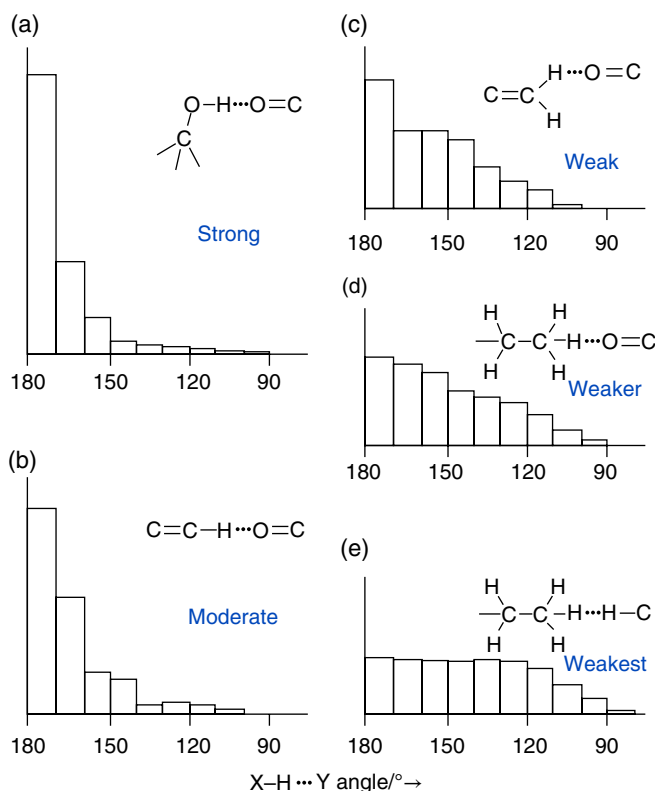


Figure 2.42 The directionality of H-bonding is directly dependent on the strength (and covalency) of the interaction. (Source: Steiner 2002 (73a). Reproduced with permission of John Wiley and Sons.)

The second preferred directional dependence (H...Y-Z angle, i.e. angle at the “H-bond acceptor” site :Y-Z) provides information on the orientation of lone pairs of Y. This dependence is straightforward for simple H-bond acceptors with a single lone pair (i.e. CH₃CN or NH₃) but can be complicated by the presence of additional lone pairs as at the oxygen atoms of ketones and water (Figure 2.43).⁷⁴

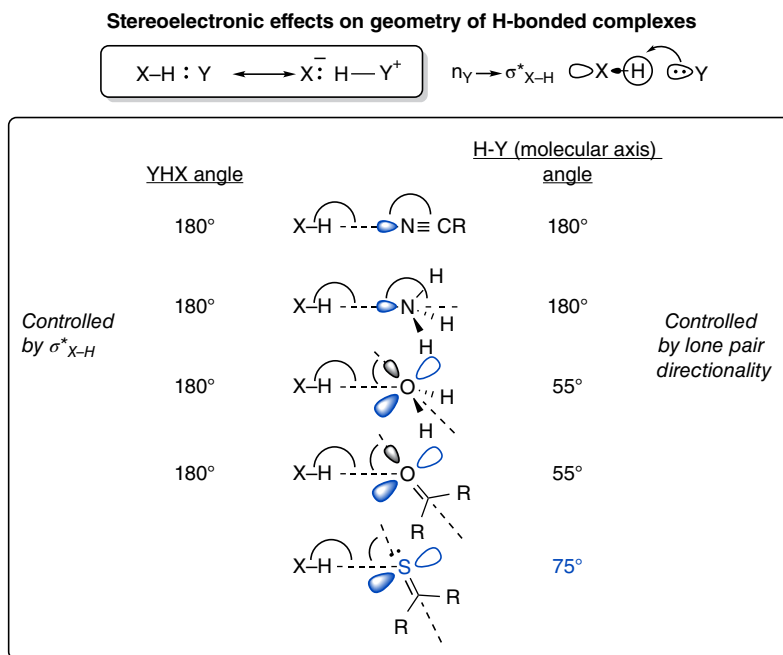


Figure 2.43 H-bonding results from a balance of favorable electrostatics and orbital interactions. The stereoelectronic aspect is reflected in the preferred geometries when a large covalent aspect is present. Lone pairs that play a primary role in directionality are shown in blue, lone pairs that play a secondary role (i.e. for O-compounds) are in black. The second lone pair at S is not shown because it plays only a minor role (see Chapter 5 and ref. 75 for a more detailed discussion).

For example, the geometry of the water dimer clearly reflects the interaction of the O-H bond of one water molecule with *both* p and sp lone pairs of the second water molecule. Such bonding situations account for the popularity of the description of oxygen lone pairs as two hybrid “rabbit ears” (sp^3 in the idealized description). Such a description is justifiable in this situation because two sp^3 orbitals correspond to the linear combinations of the p and sp lone pairs (see Chapter 5 for a more detailed description). In fact, the NBO description of water finds that the oxygen atom that serves as donor of electrons rehybridizes its lone pairs in agreement with the rabbit-ear model. The calculated NBOs are shown in Figure 2.44 along with the predicted geometry of water at a very high level of theory (CCSD(T)-F12b/CBS limit).⁷⁶

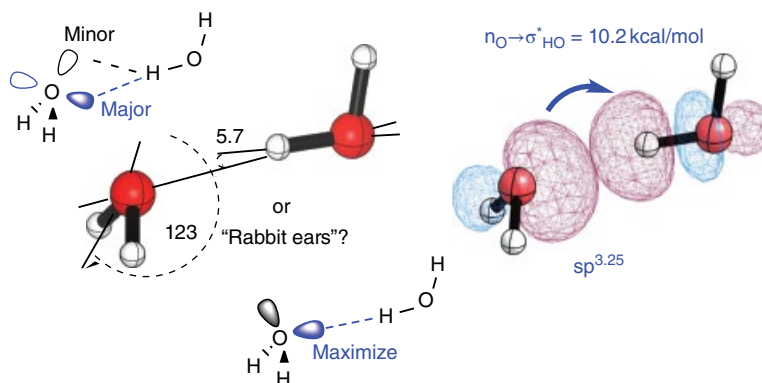


Figure 2.44 Calculated geometry and selected NBO interactions of the water dimer.

On the other hand, the sp^n lone pairs on S-containing compounds have much more s-character ($n \sim 0.4$),⁷⁴ and thus have both energy and directionality that are unfavorable for H-bond formation. As the result, $H \cdots S=C$ angles in H-bonds to thiocarbonyls are much closer to 90° ($\sim 75^\circ$). A more extensive discussion of hybridization effects on directionality of these and other orbital interactions is given in Chapter 5.

In more complex molecules, the intrinsic H-bonding geometries can be further masked by electrostatic and steric effects. For example, an interesting directionality pattern is observed in H-bonds to metal-bonded halogen atoms ($X-H \cdots Cl-M$) in crystals. These H-bonds are mostly perpendicular to the $M-Cl$ bond (angular range $80-140^\circ$).⁷⁷ This preference can be rationalized by the favored coordination at the more basic p-type lone pair at the halogen (Figure 2.45).

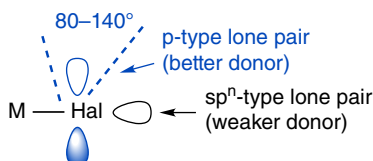


Figure 2.45 Directionality in H-bonds to metal-bonded halogen atoms ($X-H \cdots Cl-M$).

The presence of multiple lone pairs increases the probability of multiple H-bonding contacts. Such weaker contacts can be less directional, especially when they have to satisfy more than two partners. In many situations, the covalent component of H-bonding favors a classic H-bond (single donor/single acceptor) but electrostatic components, not equally sensitive to directionality, readily accommodate the presence of multiple interactions (bifurcated or even trifurcated H-bonds).

Unusual stereoelectronic preferences for H-bonding in enzymes A remarkable change in the preferred mode of H-bonding to carbonyls is observed in enzymes containing oxyanion holes.⁷⁸ Instead of the usual 0° dihedral angle, dihedral angles between the H-bond donors and the carbonyl oxygen cluster near 90° (Figure 2.46).

This illustrates the unusual stereoelectronic preference of enzyme active sites for coordination of H-bond donors at the carbonyl π -bond instead of the oxygen lone pair. An interesting hypothesis suggests that although this arrangement does not provide strong reactant stabilization, it is built into the catalytic site to provide significant stabilization to the TS. In the process of nucleophilic attack, a stronger H-bond acceptor (the oxyanion lone pair) will develop from the π -bond to benefit fully from the presence of an appropriately positioned H-bond donor.^{77,79} This design of the catalytic site avoids unproductive reactant stabilization and concentrates the stereoelectronic power of H-bonding on providing maximum stabilization to the TS.

A related consequence of coordination of H-bond donors at the carbonyl π -system was reported by Anslyn and coworkers⁸⁰ who found that the stereochemistry of hydrogen bonding controls the acidity of carbonyl α -C-H bonds. Significant stabilization is achieved via electrophile coordination at the π -bond as opposed to traditional coordination with a lone pair. The authors suggested that there is a greater change in bond strength during deprotonation when the hydrogen bonds are oriented at the π -system. In accord with this proposal, many enzymes preferentially activate their substrates through an electrophilic coordination directed towards the π -bond of the carbonyl. Such a supramolecular approach to the stereoelectronic control of deprotonations can be potentially expanded to other situations, such as to coordination of π -systems with acceptor metals (Figure 2.47).

Direct stereoelectronic assistance in the above systems can be supplemented by lowering of the π^* -orbitals, which is suggested to be significant even when Lewis acid coordination occurs orthogonally to the deprotonated C-H bond. For example, the acidity of the carbonyl α -hydrogens is increased by up to 24 pK_a units upon the coordination of Lewis acids at the carbonyl oxygen⁸¹ and more than 26 pK_a units effect on the acidity of propargylic hydrogens was reported for the alkyne-Au(I) complexes where the orbitals mediating the Lewis acid “pull” and the base “push” were constrained to orthogonality.⁸²

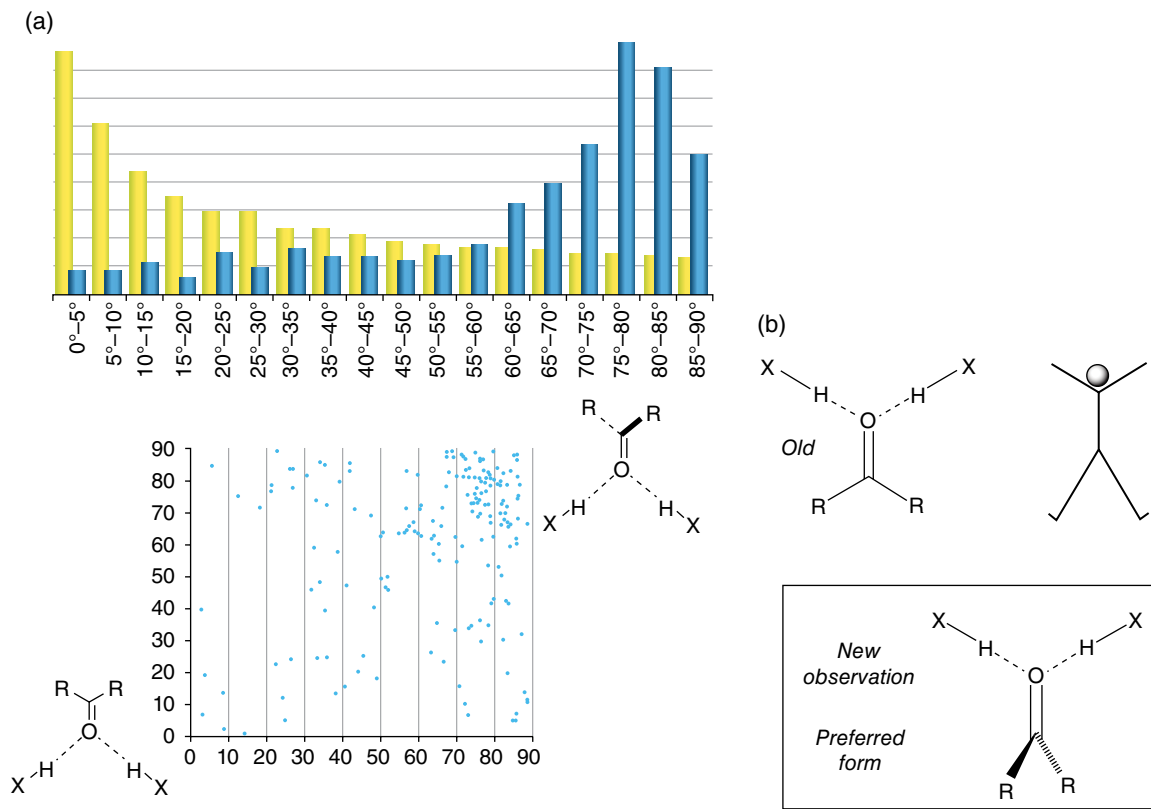


Figure 2.46 (a) top: distribution of H-bond dihedral angles in molecules in the CSD (light) and in enzymes (dark); bottom: scatter plot of the dihedral angles in enzymes. The $R-C=O\cdots HX$ dihedral angle prefers values around 90° rather than 0° . (b): Differences between H-bonding to carbonyl outside (old) and inside (new) of enzymes. (Source: Simón 2012 (78). Reproduced with permission of Royal Society of Chemistry.)

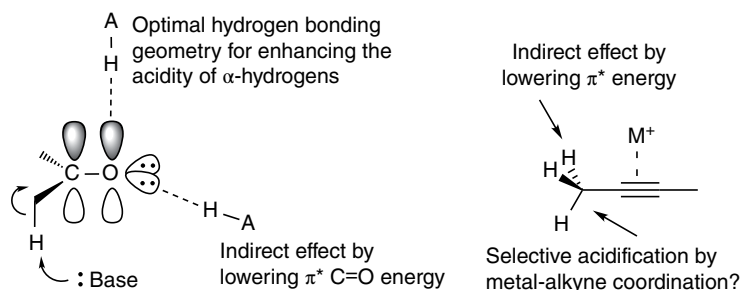


Figure 2.47 Stereoelectronic aspects of α -C-H bond acidification via H-bonding to the carbonyl and Lewis acid coordination at an alkyne.

Supramolecular interactions with π -systems π -bonds are weaker donors than lone pairs, but their interaction with strong electrophiles can lead to the formation of interesting supramolecular complexes.⁸³ The umpolung of the above interaction, anion- π^* interactions with acceptor π -systems can be applied to the

development of interesting systems.⁸⁴ For example, coordination of anions with extended chromophores based on naphthalene diimides (NDI) led to the development of a new family of sensors for such anions by Saha and coworkers (Figure 2.48).⁸⁵ DFT analysis of the interaction of this acceptor with fluoride anion predicts that fluoride is preferentially located on top of an imide ring carrying two electron withdrawing C=O groups. The calculated energy of the NDI/F⁻ interaction in the gas phase is ca. 45 kcal/mol, which is stronger than F–H···F⁻ hydrogen bond in HF₂⁻ (ca. 40 kcal/mol) but weaker than a covalent C–F bond (ca. 110 kcal/mol). The closest distance from fluoride to NDI (1.64 Å) involves the carbonyl carbon in the imide ring. The O=C···F angle is 111.9°, close to the Bürgi–Dunitz angle. NBO calculations show that there is ~0.27 electron transferred from the lone pair of fluoride to the π^* -orbital of NDI.

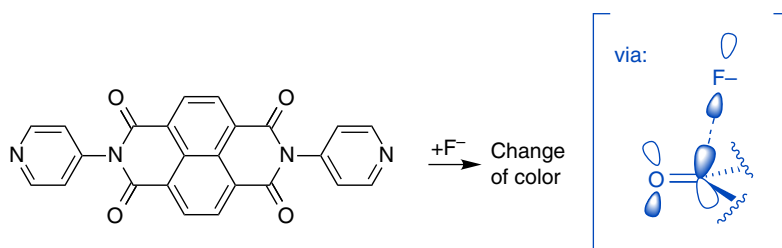


Figure 2.48 Intermolecular lone pair/ π^* coordination in supramolecular chemistry can be used in sensor design.

A weaker, intramolecular version of the $n \rightarrow \pi^*$ interaction between a lone pair and a carbonyl group has been implicated in structural changes associated with pyramidalization of carbonyl groups in peptides. Raines and coworkers used crystallographic analysis to demonstrate that such interactions can induce chirality in an otherwise planar, prochiral carbonyl group (Figure 2.49).⁸⁶

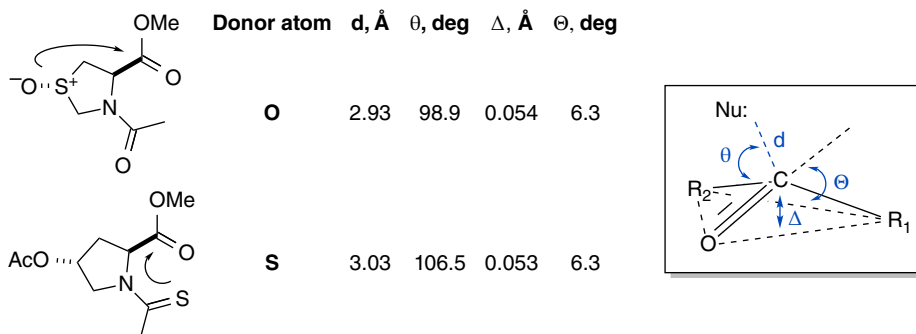


Figure 2.49 Intramolecular lone pair/ π^* interactions are associated with pyramidalization of carbonyls.

Transition from non-covalent interactions to new types of covalent bonding Very strong supramolecular interactions straddle the boundary between non-covalency and covalency in the same way as H-bonding does, spanning the continuum from weak, mostly electrostatic interactions, to strong bonds with significant covalent character and extensive orbital interactions. In Figure 2.50 we show several systems, in each of which the nature of bonding is based on the same orbital interaction pattern (3c,4e-bonds) that bears resemblance to the MOs of allyl. It is remarkable that the same type of bonding links supramolecular complexes to hypervalent compounds and transition states.

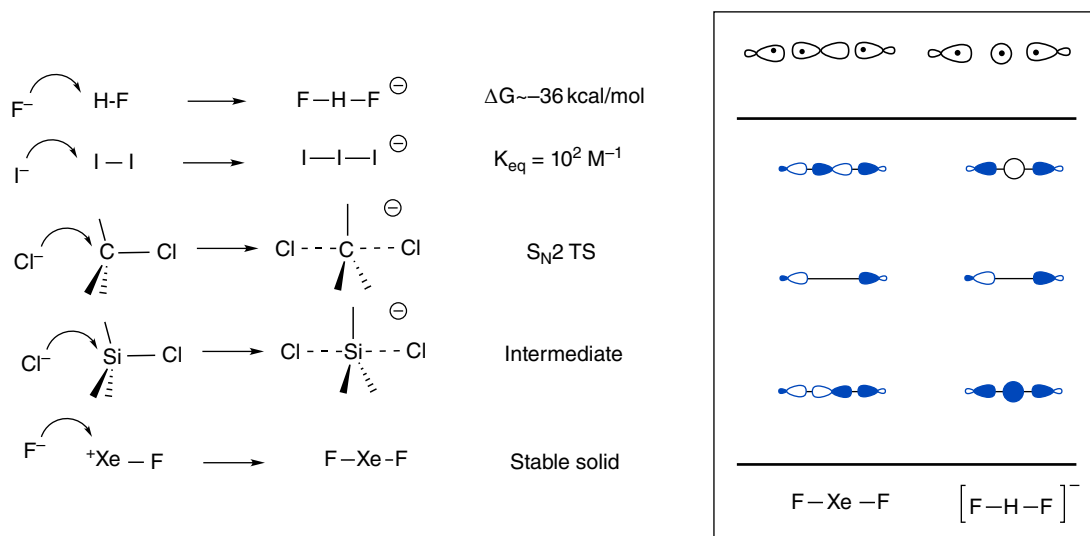


Figure 2.50 3c,4e-bonds link supramolecular complexes to hypervalent compounds and transition states.

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3

Beyond Orbital Overlap: Additional Factors Important for Orbital Interactions. Classifying Delocalizing Interactions

In this section, we will analyze several features that are generally important for intramolecular electron delocalization: conjugation and hyperconjugation. In the following discussion, we will refer to all delocalization patterns as “conjugation.”¹ The diversity of such effects is illustrated by the more general classification of delocalizing interactions given in Figure 3.1.

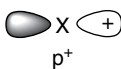
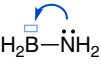
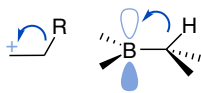
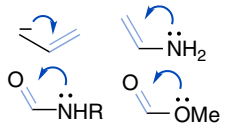
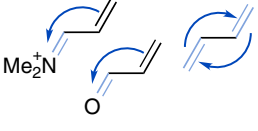
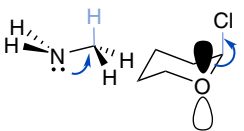
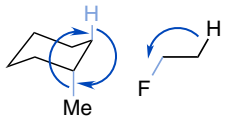
	non-bonding X:	π -bond =Y	σ -bond -Z	Donors
 p^+				
=Y π^*				
-Z σ^*				
Acceptors				

Figure 3.1 The variety of delocalizing interactions.

The nine patterns correspond to different types of participating orbitals: non-bonding, σ -, and π -. In each case, however, the interaction was mediated by two electrons from the donor orbitals. This is just an example. The development of modern chemistry continuously expands bonding concepts to new chemical systems, including systems with a different number of electrons. Considering their increased importance in redox, catalytic, and radical processes, we will discuss a few representative examples of unusual “odd-electron” chemical bonds in the following section.

3.1 Electronic count: two-electron, one-electron and three-electron bonds

Two-electron two-orbital interactions are the most favorable. Once the number of electrons is changed, the benefits of orbital overlap change as well. A simple way to weaken a bond and to diminish the respective stereoelectronic consequences of the direct orbital overlap is to inject either an electron or a hole (i.e. take out an electron, Figure 3.2).

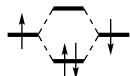
	BDE, kcal/mol	Bond order	Bond type	
$\text{H}_2 \longrightarrow \text{H}^\bullet + \text{H}^\bullet$	101	1	2c,2e	
$\text{H}_2^+ \longrightarrow \text{H}^\bullet + \text{H}^+$	64	1/2	2c,1e	
$\text{H}_2^- \longrightarrow \text{H}^\bullet + \text{H}^-$	52	1/2	2c,3e	

Figure 3.2 Electron counts, bond orders and UMP2=full/6-311++G(d,p) bond dissociation energies (BDEs) for various two-center bonds.

For the symmetric dihydrogen systems, the effects are relatively simple and correlate well with the bond orders – the bond dissociation energy (BDE) in vacuum for a 1e bond in the radical cation is ~60% of the bond dissociation energy for the 2e bond of the neutral H_2 molecule. Interestingly, BDE for the radical-anion is slightly smaller (~50% of that in H_2).

The power of 2c,2e-bonding is further illustrated by He_2^{2+} , a metastable species with a fascinating “volcanic”² combination of kinetic stability and thermodynamic instability (Figure 3.3). The He...He dimer is a weak van der Waals complex with an energy of 8×10^{-6} kJ/mol and a He-He “bond” length of ca. 6.2 Å. In contrast, the corresponding dication He_2^{2+} has a large (33.2 kcal/mol) barrier to dissociation despite the 200 kcal/mol exothermicity originating from the strong Coulombic repulsion of the two positive charges.³ Interestingly, the very short He-He distance of 0.704 Å is shorter than both the H-H bond of the hydrogen molecule and “the world’s shortest bond” of the H-T molecule, the heavier isotope of H_2 .⁴

The oxidative approach to the formation of chemical bonds by removal of electrons can be extended to relatively complex organic molecules in solution. For example, neutral 1,6-diazabicyclo[4.4.4]-tetradecane (with the N-N distance of 2.806 Å) is transformed upon removal of two electrons into a N^+-N^+ dication,

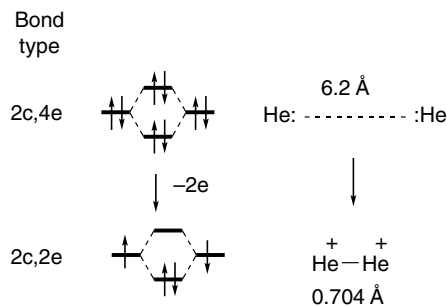
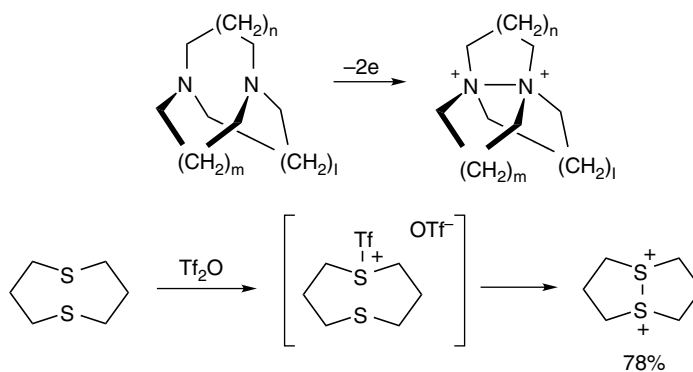


Figure 3.3 Making bonds by removing electrons: contrasting He...He distances as function of number of electrons.

where the distance between the positively charged nitrogen atoms is reduced to 1.532 Å (Figure 3.4).^{4,5} Formation of the N-N bond is particularly noteworthy – not only does it overcome Coulombic repulsion and bring the formally positively charged nitrogen atoms closer than their uncharged forerunners but it corresponds to the strained “intra bridgehead” bond type. A similar transition from the non-bonding interactions between two lone pairs into a 2c,2e bond between two cationic S-centers is observed in 1,5-dithiacyclooctanes.⁴



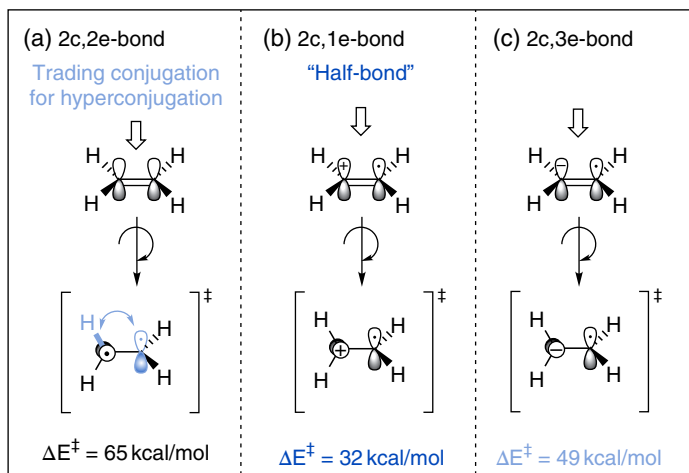


Figure 3.5 Energy costs for the 90 degree twist in (a) ethylene (experimental), (b) ethylene radical cation (MP2/6–31G**), and (c) ethylene radical anion (B3LYP/6–311++G(3df,3pd)).⁸

On the other hand, conversion of ethylene into the radical cation changes the 2c,2e π -bond into a 2-center, 1-electron (2c,1e) “half-bond.” As a result, the energy cost for the rotation is decreased to $\sim 32 \text{ kcal/mol}$, approximately half of the original value in the neutral system. The 2-center, 3-electron (2c,3e) bond in the radical anion is also weakened in comparison to the “normal” 2c,2e bond, as the extra electron now populates an antibonding MO. The barrier for rotation in ethylene radical-anion is significantly lowered relative to that in the parent ethylene (from 65 to 49 kcal/mol , Figure 3.5).⁸ This example illustrates that the importance of stereoelectronic constraints may change dramatically in odd-electron “half-reduced” or “half-oxidized” species. The differences in the rotation barriers between the 1e- and 3e-systems are likely to originate from rehybridization and hyperconjugation effects in the twisted species.

The relatively high stabilization provided by 2c,3e-bonds can explain why the triplet state of molecular oxygen is a favorable electronic alternative to the singlet O_2 . Students are often confused by the seeming contradiction between the following two experimental data: a) the *paramagnetic* properties of O_2 suggest the presence of unpaired electrons, but b) the O–O bond length in O_2 ($1.21 \text{ \AA}$) is close to the expected value for a double bond (a typical O–O single bond is ca. $1.48 \text{ \AA}$). However, these “contradicting” observations are reconciled once the double bond of O_2 is made from a σ -bond and two three-electron π *half*-bonds (Figure 3.6). This description reconciles the overall bond order of two *and* with the presence of two radical centers.

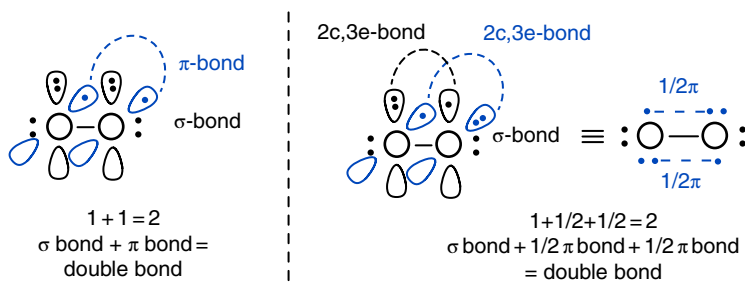


Figure 3.6 Two ways for making a “double” bond.

Three-electron bonds are far from being just chemical curiosities – they are encountered in many persistent radicals (e.g. 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (=TEMPO), nitric oxide (NO), ketyl). Their formation (sometimes transient) can lead to significant consequences for reactivity. For example, strong 2c,3e bonds provide additional stabilization to the conjugate base of α -hydroxy radicals, explaining the much higher OH acidity in these compounds in comparison to the acidity of normal alcohols (Figure 3.7).⁹

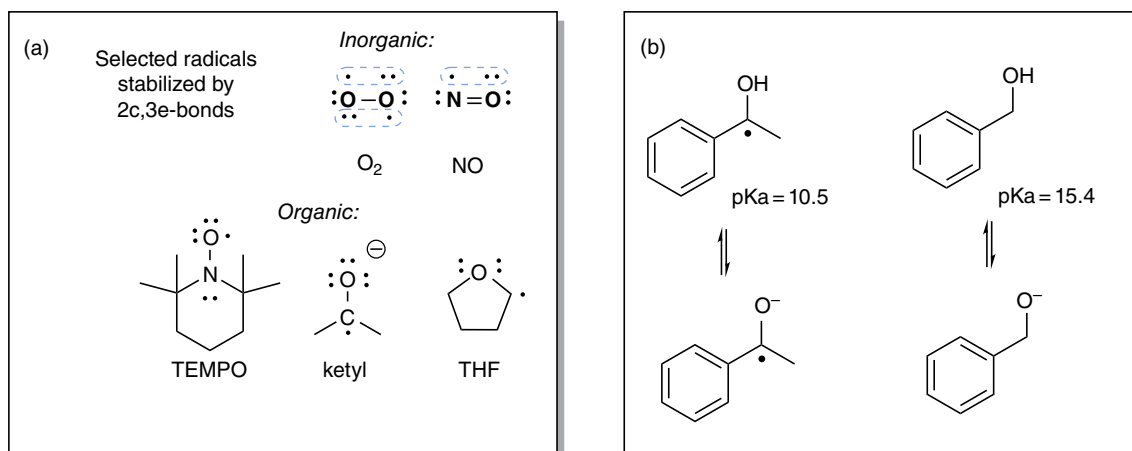


Figure 3.7 (a) Selected examples of radicals stabilized by 2c, 3e bonds. (b) 3e bonding can be used to stabilize anions as well.

Stabilization provided by 2c-3e bonds has also been used in the design of radical fragmentations. Although the C-C bond is generally hard to break, the introduction of an O or an N atom next to the incipient radical center facilitates the C-C bond cleavage greatly (Figure 3.8).¹⁰

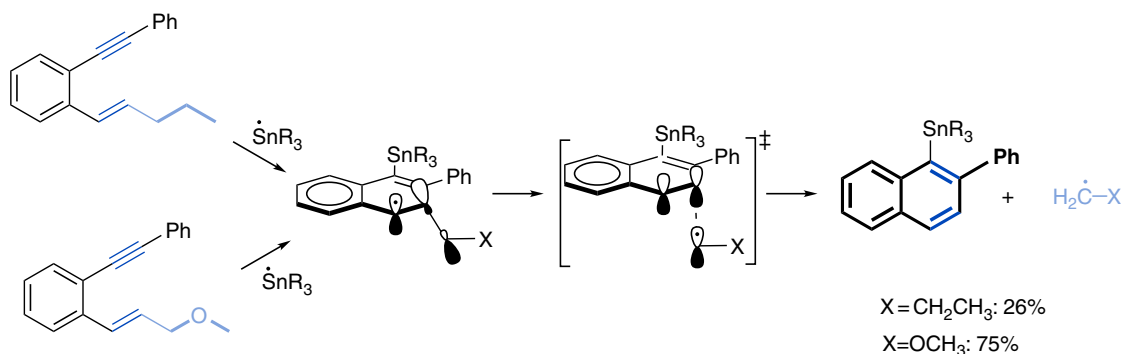


Figure 3.8 Formation of 2c-3e bonds can be used to facilitate C-C bond cleavage.

Of course, no π -bond can be formed *without* electrons in the π -orbitals and, as expected, the planar conformation of ethylene dication has a relatively long 1.587 Å bond. In a sharp contrast to the neutral ethylene, the ethylene dication is stabilized by 28 kcal/mol in the “perpendicular” geometry, formed upon 90° rotation around the C-C bond. In the more stable twisted geometry, the C-C bond is relatively short (1.398 Å,

MP2/6-31G*), due to the strong $\sigma_{\text{C-H}} \rightarrow \text{p}^+$ hyperconjugative interaction of the two cationic centers with vicinal C-H bonds.¹¹ For the same reasons, the planar conformation of $\text{BH}_2\text{-CH}_2^+$ is ~ 25 kcal/mol less stable than the perpendicular conformation (Figure 3.9).¹²

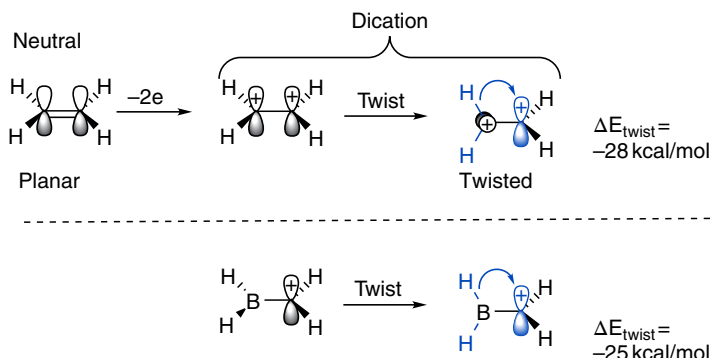


Figure 3.9 “Zero-electron bonds” provide no stabilization, as illustrated by the twisted geometry preference for systems without π -electrons at the two adjacent sp^2 -hybridized atoms.

The number of electrons changes stability in a more complex way in three-center systems, i.e. the allyl and related species. In this case, delocalization of charge is much more important than delocalization of spin. For example, rotation around the C-C bond becomes much more difficult in the allyl cation (~ 38 kcal/mol) compared to the allyl radical (~ 13 (calculated), 15.7 (experimental) kcal/mol).¹³ Allylic anions have a lower rotation barrier relative to the cation (~ 23 vs. ~ 38 kcal/mol).^{14a} In the case of anions, additional stabilization to the twisted form (~ 8 – 14 kcal/mol) is provided by rehybridization, which partially offsets the lower efficiency of hyperconjugation in the twisted anion than in the twisted cation. The calculated barriers for the allyl system depend strongly on the methods employed, but the trend of cation > anion > radical remains. The same trend is observed for the rotation barriers in the benzyl radical and cation (Figure 3.10).¹⁵

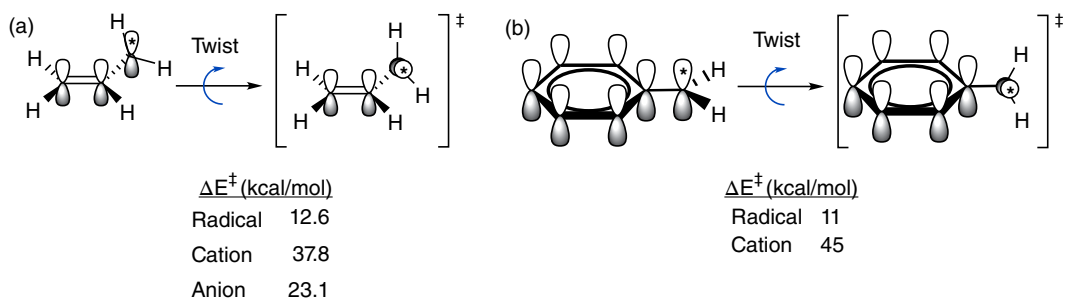


Figure 3.10 Energy costs for the 90° rotation in the (a) allyl radical, cation, and anion; (b) the benzyl radical and cation.

The rotational barrier in allyl radicals also illustrates the effect of the number of orbitals in the conjugated array on the conjugation. Removing one p-orbital from conjugation via the 90° twist in allyl radical imposes the energy penalty of only ~ 15 kcal/mol – considerably less costly than the penalty for the analogous rotation in ethylene (~ 65 kcal/mol).

3.2 Isovalent vs. sacrificial conjugation

Another common approach for the comparison of different delocalization patterns involves the concept of sacrificial and isovalent conjugation. The characteristic resonance description of conjugation includes a combination of several contributing structures, i.e. “double bond/no-bond resonance” for hyperconjugation or Kekulé structures for aromaticity. Depending on the relative number of two-electron bonds in the two contributing structures, conjugation is classified as either “heterovalent” (commonly referred to as “sacrificial”), or “isovalent” (Figure 3.11). Analogous considerations apply to hyperconjugation. For example, Mulliken¹⁶ distinguished between heterovalent hyperconjugation in neutral systems and “strong” or “isovalent” hyperconjugation in cations.

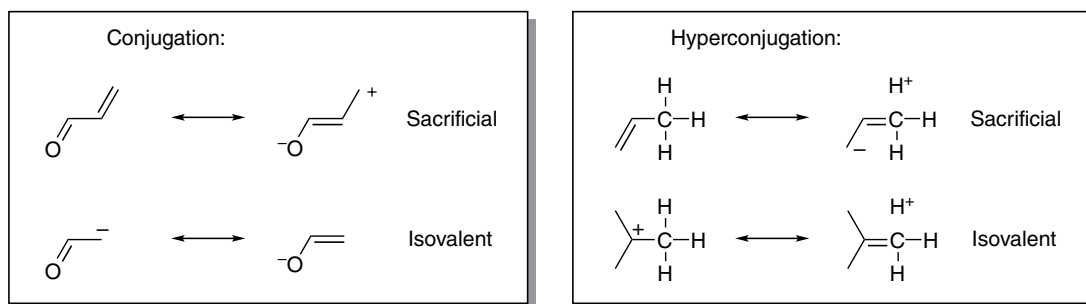


Figure 3.11 Comparison of contributing resonance structures in sacrificial and isovalent conjugation and hyperconjugation.

In sacrificial conjugation, the contributing resonance structure contains one fewer two-electron bond than the normal Lewis formula. In contrast, contributing structures describing the so-called “isovalent” conjugation contain the same number of two-electron bonds as the main Lewis formula. Such patterns are common for the stabilization of carbenium ions, carbanions and radicals (Figure 3.11). 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.

The differences between isovalent and sacrificial resonance are illustrated by the relative magnitudes of rotational barriers in 1,3-butadiene and its radical-cation. Twisting around the central bond of 1,3-butadiene is even less costly than it is in the allyl radical – the 5.9 kcal/mol experimental barrier for the *s-cis/s-trans* transformation is in an agreement with the 5.7 kcal/mol G2 energy¹⁷ difference between the more stable *s-trans* conformation and the twisted transition state (TS).¹⁸ Although these values cannot be taken as precise values for conjugative stabilization, due to the “switching on” of hyperconjugative interactions that emerge in the twisted conformations, it is clear that conjugation between two π -bonds is weaker than interactions between a π -bond and a radical.

In contrast, the rotation barrier increases to ~29 kcal/mol when an electron is removed from 1,3-butadiene to form the respective radical cation (Figure 3.12). This significant increase in the energy cost is consistent with the much stronger isovalent resonance stabilization in the one-electron oxidized species.¹⁹

The predictive utility of isovalent conjugation breaks down for the cyclic conjugation. For example, resonance in both cyclobutadiene and benzene is clearly isovalent, but it leads to aromatic stabilization only for the case of benzene.

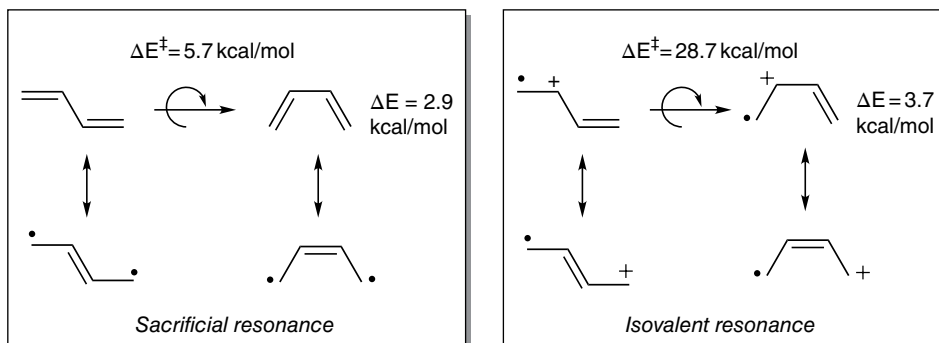


Figure 3.12 Contrasting energy costs for the rotation around the central C-C bond in 1,3-butadiene and 1,3-butadienyl radical cation illustrates the differences between sacrificial and isovalent conjugation.

3.3 Neutral, negative, and positive hyperconjugation

Another historically common classification that is used particularly often for hyperconjugative interactions is based on their separation into neutral, negative, and positive hyperconjugation (Figure 3.13). The interactions between filled π - or n-orbitals and adjacent antibonding σ^* -orbitals are called negative hyperconjugation. Donation of electron density from filled σ -orbitals into π^* -orbitals or p-type cationic centers is referred to as positive hyperconjugation. Both negative and positive hyperconjugation are two-electron stabilizing interactions which result in building π -bonding character between the nominally singly bonded atoms. Analogous classification can be designed for conjugative interactions between π -bonds and p-orbitals but is used less often.

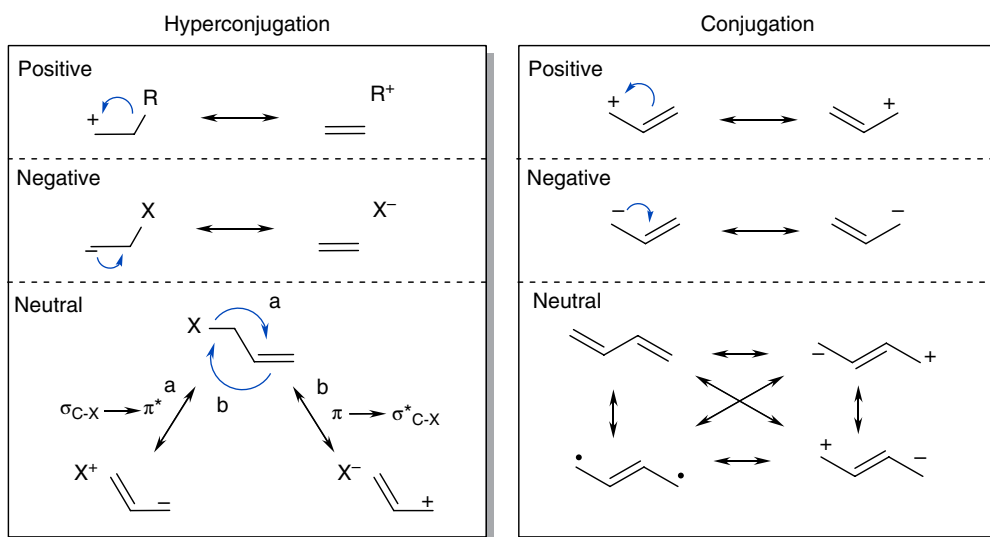


Figure 3.13 Contributing resonance structures for positive, negative, and neutral hyperconjugation and conjugation.

Negative conjugation and hyperconjugation are important not only in anions, but also in many neutral molecules with significant donation of electron density into π^* - and σ^* -orbitals. In particular, negative hyperconjugation is implicated in the anomeric effect (and its spectroscopic counterparts – the Bohlmann²⁰ and the Perlman effects²¹) and as a provider of covalent character and directionality of H-bonding (Figure 3.14). Negative hyperconjugation with non-bonding orbitals is isoivalent, whereas negative hyperconjugation with π -donors is sacrificial.

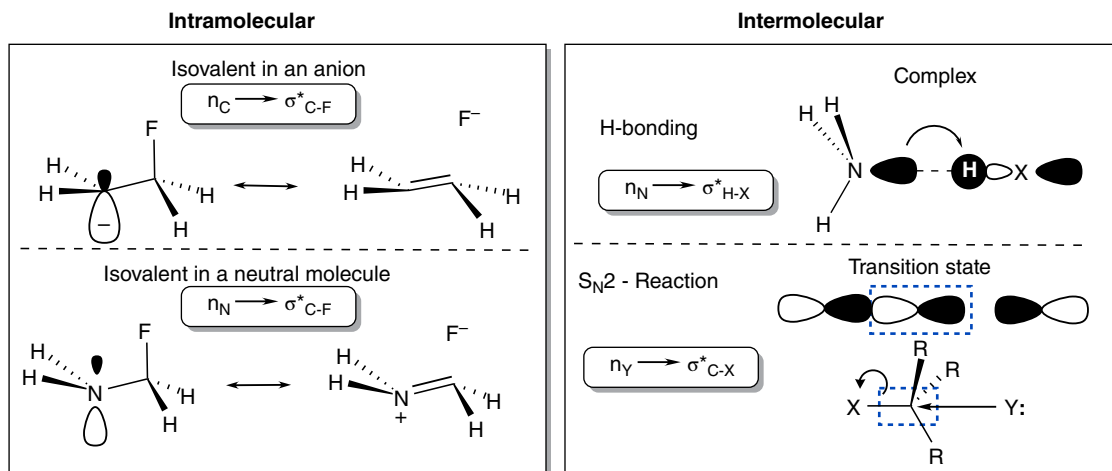


Figure 3.14 Selected patterns of intra- and intermolecular negative hyperconjugation.

Positive conjugation dominates when a very strong p- or π -acceptor is present in a molecule. In particular, this pattern is very important in carbenium ions and boranes (Figure 3.15).²²

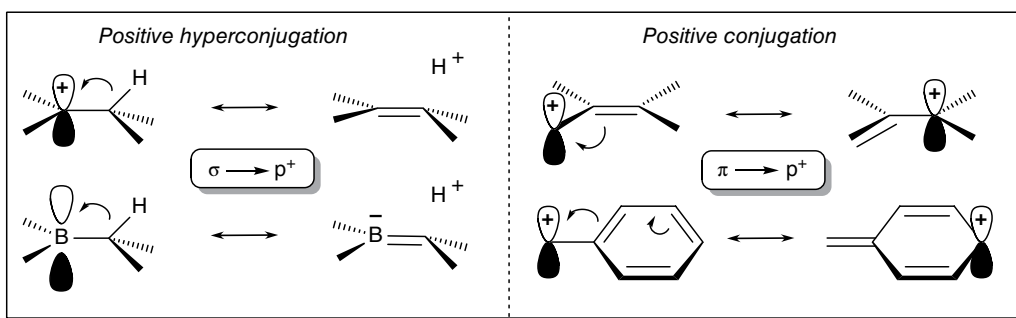


Figure 3.15 Positive hyperconjugation and conjugation in a cation and a neutral molecule.

The effect of alkyl substituents on the stabilities of carbenium ions²³ provides the electronic basis of the textbook Markovnikov's rule.²⁴ 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 stronger than a C-H donor of the ethyl cation in the gas phase (see Section 6.3).²⁵ The effects of Ge, Sn, and Hg are also substantial.²⁶ For example, hyperconjugative activation by a Sn-C bond^{26,27} can accelerate a reaction by a factor of $>10^{14}$.

Classification of hyperconjugation and conjugation as positive or negative is useful when either referring to an individual interaction or to an imbalanced situation, as is the case of an interaction with a very strong donor or acceptor orbital with the rest of the molecule dominating over other delocalization effects. This imbalance often occurs when either a lone pair acts as a donor or when an empty p-orbital acts as an acceptor.²⁸ Use of these terms in other situations can be uninformative or even misleading.

In the absence of dominating unidirectional interactions, hyperconjugation can be classified as neutral hyperconjugation. This is the most common conjugative pattern that blends together the negative and positive hyperconjugation. For example, the delocalizing interaction between a π -bond and an adjacent $\sigma_{\text{C-X}}$ bond in Figure 3.13 is displayed as a pair of donor-acceptor $\pi \rightarrow \sigma_{\text{CX}}^*$ and $\sigma_{\text{C-X}} \rightarrow \pi^*$ interactions. In this case, the interaction is bidirectional, and the same C-X moiety serves as both a σ -donor and a σ -acceptor. Similar classification can be used for interactions between p/ π -type orbitals.

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 initially controversial. However, now the effects of hyperconjugation on X-ray geometries of neutral molecules are well-documented.^{29,30}

Neglect of neutral hyperconjugation can lead to fundamental misconceptions. For example, omission of hyperconjugative effects led to the apparent “disappearance of conjugation” between two triple bonds in butadiyne.³¹ We will further illustrate the importance of this ubiquitous phenomenon in Chapter 6.

To calibrate ourselves, it is instructive to compare the relative magnitudes for the three types of hyperconjugation using the same group (Me) as a reference point. The importance of positive hyperconjugative is the greatest (~ 14 kcal/mol) in agreement with the electron deficient nature of methyl borane. This molecule is isoelectronic to ethyl cation. It cannot satisfy the octet rule, and hence relies heavily on the non-Lewis contributions as a supplementary source of stability. Negative hyperconjugation between the aligned C-H and the lone pair of nitrogen is smaller. However, this effect is still significant (~ 9 kcal/mol) because it provides a way to involve the non-bonding orbital into chemical bonding. The neutral C-H/C-H delocalization between the $\sigma_{\text{C-H}}$ bonds and the associated σ^* orbitals is the weakest from the three types. Even though it is manifested as a pair of symmetry-related interactions, their NBO total energy is only ~ 6 kcal/mol (Figure 3.16).

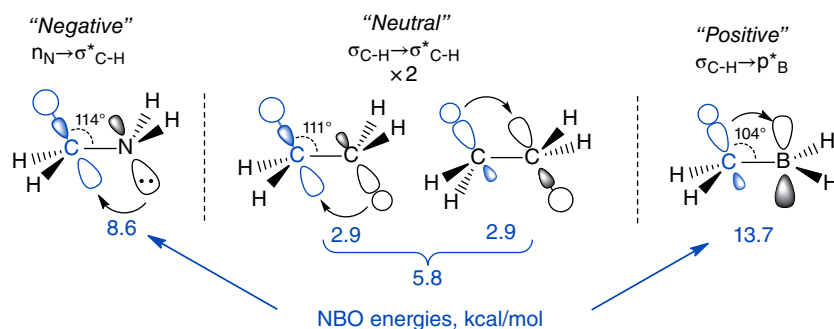


Figure 3.16 NBO comparison of hyperconjugative stabilization of negative hyperconjugation in methyl amine, neutral hyperconjugation in ethane, and positive hyperconjugation in methyl borane at the M06-2X/6-311++G(d,p) level of theory. For the details of NBO calculations, see Chapter 4.

In summary, this chapter has provided three possible ways to classify delocalizing interactions: 1) by the type of orbitals, 2) by the number of electrons, 3) by directionality (or lack of thereof) of the overall electron density transfer. We will come back to the first of these classifications and discuss its quantitative aspects in much more detail in Chapter 5, after giving a brief outline of practical approaches to the quantitative analysis of delocalization in Chapter 4.

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4

Computational and Theoretical Approaches for Studies of Stereoelectronic Effects

The most interesting features of stereoelectronic effects lie in their sometimes subtle, but often decisive, role in the structure and reactivity of molecules. Consequently, stereoelectronics manifest themselves in a variety of kinetic and conformational preferences.¹ We will outline these preferences separately. This section includes a general description of theoretical approaches to detecting, quantifying, and understanding stereoelectronic effects.

4.1 Quantifying orbital interactions

Conformational energies Relative energies of conformations formed via rotation around a single bond are particularly important for identifying and evaluating stereoelectronic effects that can be “switched off and on” depending on orbital overlap. As a result, conformational analysis continues to play an important role in the development of theoretical organic chemistry. However, such 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. Furthermore, switching one effect off frequently activates a different effect. We will discuss such complex interplay in Chapter 6.

Isodesmic equations In order to “isolate” a desired electronic effect, chemists often design hypothetical reactions of different degrees of sophistication (e.g. isogyric, isodesmic, homodesmotic, etc., as described in detail in ref. 2). The advantage of these equations is that, in many cases, the thermochemical data can either be obtained experimentally or calculated with a high degree of accuracy. The challenge lies in isolating the key electronic effect without introducing additional structural and electronic perturbations. An “ideal”

reaction for the analysis of a delocalizing electronic effect would involve no changes in hybridization and the bond types. In addition, it should also have negligible changes in steric and electrostatic factors. Meeting all of these requirements is often a challenge.

Figure 4.1 illustrates the complications in choosing a suitable equation for evaluating the hyperconjugative donor abilities of σ -bonds towards a cationic center. In order to minimize the local steric and electrostatic effects and achieve a more balanced description of relative donor ability of σ -bonds, a system can be chosen where the donor and acceptor sites are not *directly* connected, and interact instead via a hyperconjugative *relay* (i.e. double hyperconjugation, see Chapter 9 for additional discussion). The three equations presented in Figure 4.1 are based on relative total energies of two conformers (“hyperconjomers”, see Chapter 6 for further discussion) of δ -substituted cyclohexyl cations with distinctly different delocalization patterns. These equations evaluate interaction between the donor orbitals and the cationic center transmitted via “double hyperconjugation” (discussed in more detail in Chapter 8).³

The stabilization energies provided by the three isodesmic reactions provide different information. Effects of substituents in axial cations, which are described in Figure 4.1a, include a complicated interplay of many factors such as hybridization, inductive, and field effects, which are still present in these species even when double hyperconjugation (interaction of donor and acceptor through the sigma bridge) is minimized.

Substituent effects on the “equatorial” cations (Figure 4.1b) reflect the double hyperconjugation interaction of $\sigma_{\text{C-R}}$ bonds with the cation p-orbital via the relay C-C bridge. Both the destabilizing effects of sigma acceptors and the stabilizing effect of sigma donors are also more pronounced in equatorial cations. Thus, the above “equatorial” stabilization energies (SE_{eq}) include stabilization or destabilization provided by $\sigma_{\text{C-R}}$ donors through the double hyperconjugation mechanism. However, they still include other effects mentioned in the previous paragraph.

Subtraction of stabilization energies for the axial (SE_{ax}) cations from such energies for the equatorial cations (SE_{eq}) provides the bottom equation of Figure 4.1, where the contributions of the non-hyperconjugative (inductive, field etc.) effects are partially compensated. The $\Delta SE_{\text{eq-ax}}$ values give an improved estimate of the hyperconjugative stabilization of “equatorial” cations which has its source predominantly in double hyperconjugative stabilization. These values will be used in Chapter 5 for the discussion of the relative donor ability of σ -bonds.

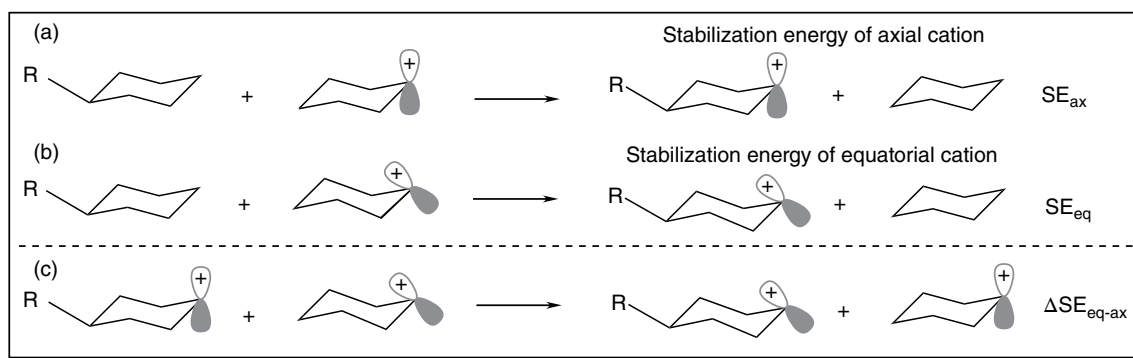


Figure 4.1 Three isodesmic equations used to calculate substituent stabilization energies (SE_{ax} (a), SE_{eq} (b), $\Delta SE_{\text{eq-ax}}$ (c)) in the equatorial and axial cyclohexyl cations.

The above discussion illustrates the challenges in isolating the stereoelectronic effect under analysis in its pure form from isodesmic equations. Are there any alternatives?

4.2 Localized orbitals from delocalized wavefunctions

The previous sections provided several indirect schemes for analyzing orbital interactions. Quantifying such electronic effects via a direct computational approach is seemingly straightforward. Conceptually, all one needs to do is calculate the energy penalty when this interaction is removed from the delocalized wavefunction. The difference in energy between the non-interacting, localized state (sometimes called diabatic state) and the full state (sometimes called adiabatic) can be taken then as the interaction energy. The main challenge lies in defining the appropriate 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),⁴ and the block-localized wavefunction method (BLW).⁵

All of these methods share a conceptual similarity in comparing the full wavefunction with a hypothetical localized construct. The key difference between these methods lies in the starting basis set of orbitals used to describe delocalization. Whereas NBO utilizes *orthogonal* orbitals to describe the localized reference, the other two methods start with *non-orthogonal* orbitals.⁶ This difference leads to significant variations in the estimated magnitude of delocalizing interactions and increases the role of steric effects in the methods based on non-orthogonal orbitals.

It is important to mention that the non-orthogonal initial orbitals cannot be the eigenfunctions of any physical (Hermitian) Hamiltonian that can serve as the reference “unperturbed system.” Although the overlap contamination effects do not change energies evaluated on the basis of the *overall* molecular wavefunctions (whether orbitals of a determinantal wavefunction are orthogonal or not has no effect on 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 non-orthogonal orbitals.⁷

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

Furthermore, Figure 4.2a illustrates the origin of “four-electron destabilization” between two non-orthogonal filled orbitals that is often taken as the physical origin of the steric destabilization. According to Weinhold et al., such destabilization is a mathematical artifact of non-orthogonality 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 4.2b). When at least one unoccupied orbital is added to the system, the overall interaction becomes stabilizing (Figure 4.2c).⁸

After this general preface, let’s describe the three popular approaches in more detail.

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 (NAOs), hybrid orbitals (NHOs), and bond orbital (NBOs). Each of these localized basis sets is complete, orthonormal, and describes the wavefunction with the minimal amount of filled orbitals in the most rapidly convergent fashion. Filled NBOs describe the hypothetical, strictly localized Lewis structure. NPA charge assignments based on NBO analysis correlate well with empirical charge measures.⁹

The interactions between filled and antibonding orbitals represent the deviation from the localized Lewis structure and can be used as a measure of delocalization. Since the occupancies of filled NBOs are highly condensed, the delocalizing interactions can be treated by a standard second order perturbation approach

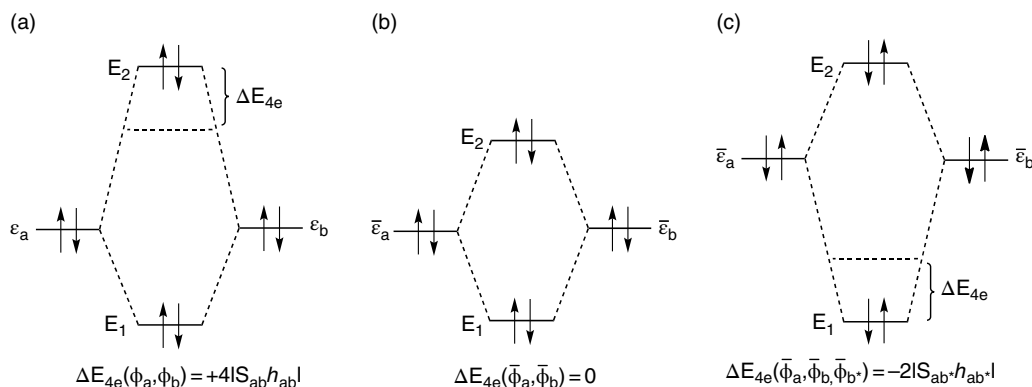


Figure 4.2 (a) Four-electron destabilizing interaction expressed in terms of non-orthogonal “unperturbed” orbitals (for which there is no imaginable Hermitian perturbation theory). (b) Four-electron non-stabilizing interaction expressed in terms of orthogonalized unperturbed orbitals (for which there exists a valid Hermitian). (c) Four-electron stabilizing interaction for a proper three-term description of orbital energies in terms of Löwdin-orthogonalized basis orbitals. (Source: Weinhold 2003 (8b). Reproduced with permission of John Wiley and Sons.)

(Eq. 4.1) 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)^{10,11} where $\langle \sigma/F/\sigma^* \rangle$, or F_{ij} is the Fock matrix element between the orbitals (NBOs) i and j , ε_σ and ε_{σ^*} are the energies of the σ and σ^* NBOs, and n_σ is the population of the donor σ -orbital.¹² Usually, there is a good linear correlation between the deletion (E_{del}) and perturbation ($E(2)$) energies.¹³ Deviation from such correlation often reflects cooperativity between the individual delocalizing interactions.

$$E(2) = -n_\sigma \frac{\langle \sigma/F/\sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{i,j}^2}{\Delta E} \quad (4.1)$$

Natural steric analysis¹⁴ in the NBO procedure is based on the model of Weiskopf, where orbital orthogonalization leads to the “kinetic energy pressure” which opposes interpenetration of matter.¹⁵ 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.

The NBO procedure is not the only localization technique for transforming delocalized MOs into the intuitive Lewis structure description. Foster and Boys,¹⁶ Edmiston and Ruedenberg,¹⁷ and Pipek and Mezey¹⁸ reported alternative localization procedures that provide additional bridges between MO and VB theories. From the organic chemist’s point of view, these approaches are conceptually similar to NBO and, for the sake of brevity, will not be discussed here.

The set of localized bonding Lewis systems can be extended to 3c-2e bonds, and even to electron pairs, localized over bigger fragments via adaptive natural density partitioning (AdNDP).¹⁹ When lone pairs are truly delocalized over all of the available atoms in a cyclic system, it can be taken as a sign of aromaticity.

An example of NBO analysis of intramolecular delocalization: hierarchy of orbital interactions in the most stable conformation of glycine. The conformational preferences of glycine, the simplest of natural

α -aminoacids, are important for understanding the structure and properties of these basic building blocks of life. It was suggested that the interplay between hyperconjugation and steric hindrance drives the rotational isomerism of glycine, and the most stable conformer combines considerable hyperconjugation stabilization with the absence of large steric effects.²⁰ Here, we will use delocalizing effects in the most stable conformation of this flexible molecule to illustrate the diversity of information that can be obtained from NBO analysis (Figure 4.3).

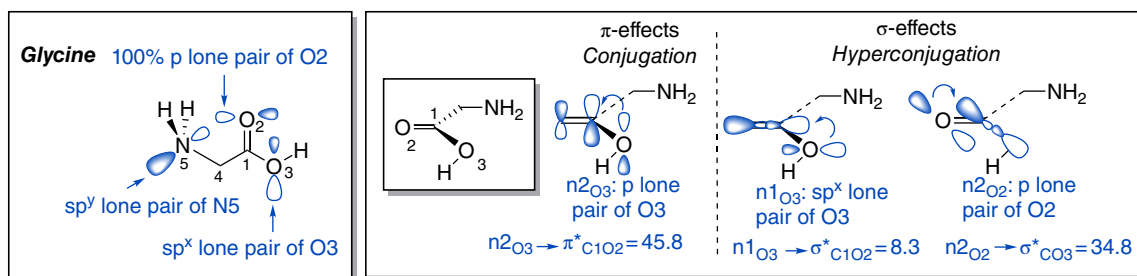


Figure 4.3 Selected lone pairs in the lowest energy conformation of glycine. NBO energies in kcal/mol for interactions between selected orbitals illustrate σ - and π -interactions between lone pairs of O3 and the carbonyl moiety.

So, what are the delocalizing effects in glycine and what conclusions can one make from the NBO data? First, NBO finds (and quantitatively evaluates) all three types of delocalization: conjugation, hyperconjugation, and σ -conjugation. Conveniently for the illustrative purposes, glycine has all three major orbital types: a variety of σ -bonds (C-C, C-H, C-O, C-N, N-H), a π -bond (C=O), and lone pairs of different energies and hybridizations (sp^y lone pair of nitrogen and an sp^x hybrid and a pure p-lone pair at each of the two oxygens). Second, the comparison of these delocalizations offers interesting insights into the interplay between different factors that control stability and reactivity.

Comparison of lone pairs as donors (Figure 4.3): The magnitude of $n2_{O3} \rightarrow \pi^*_{C1O2}$ and $n1_{O3} \rightarrow \sigma^*_{C1O2}$ interactions is drastically different (45.8 vs. 8.3 kcal/mol). Does it really mean that π^* is a >5-fold stronger acceptor than σ^* (i.e. that the conjugation is so much stronger than hyperconjugation)? Not at all!

Note that the donor abilities of the two lone pairs are quite different. The hybrid “in-plane” lone pair in the $n1_{O3} \rightarrow \sigma^*_{C1O2}$ hyperconjugative interaction is intrinsically a much weaker donor than the “out-of-plane” p-lone pair that participates in the $n2_{O3} \rightarrow \pi^*_{C1O2}$ conjugation with the carbonyl π -system. Once the stronger lone pair is used, hyperconjugative effects grew noticeably stronger as illustrated by much larger donation from p-lone pair of O2 to the σ^*_{C1O3} (34.8 kcal/mol). A slight difference in substitution at oxygen play some role, but it is clear that the greater donor ability of p-lone at O2 in comparison to the sp^n lone pair at O3 is the greatest factor.

It is also interesting to note that the hybrid lone pair at N is a weaker donor than the 100% p-lone pair at the carbonyl oxygen (9.2 vs. 18.7 kcal) towards the same σ -acceptor (the C1-C4 bond). This difference illustrates how hybridization effects can override differences in electronegativity (Figure 4.4).²¹

Conjugation vs. hyperconjugation (Figure 4.3): A better comparison of these two delocalization effects is given by the relative magnitudes of $n2_{O3} \rightarrow \pi^*_{C1O2}$ and $n2_{O2} \rightarrow \sigma^*_{C1O3}$ interactions (45.8 vs. 34.8 kcal/mol) where the donor lone pairs have the same hybridization. Conjugation is a stronger effect but the difference is not dramatic (conjugation is only 30% stronger – far from the >500% differences in the $n2_{O3} \rightarrow \pi^*_{C1O2}$ and $n1_{O3} \rightarrow \sigma^*_{C1O2}$ interactions discussed in the previous paragraph!).

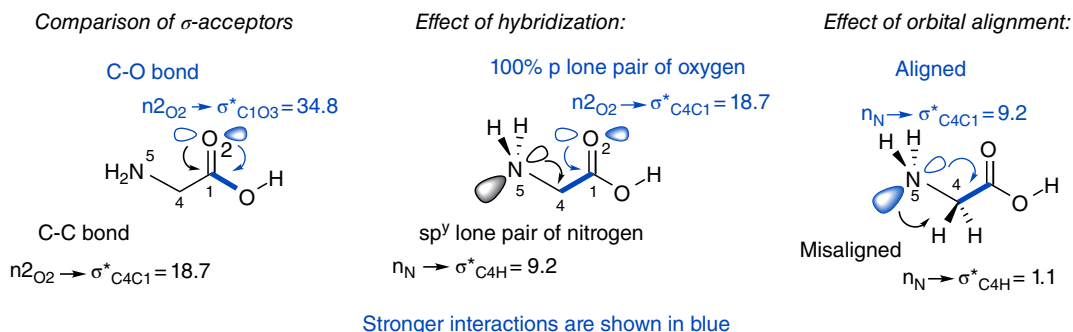


Figure 4.4 NBO energies in kcal/mol for interactions between selected orbitals in glycine illustrate general trends in hyperconjugative effects.

Comparison of σ -acceptors (Figure 4.4): The high energy p-lone pair at O2 serves as a very strong donor even towards a moderate acceptor, such as a C-C bond ($n_{2O_2} \rightarrow \sigma^*_{C1C4} = 18.7$ kcal/mol). This effect is ~ 2 -fold weaker than the 34.8 kcal/mol $n_{1O_3} \rightarrow \sigma^*_{C1O_2}$ interaction but still significant. This example shows how hyperconjugative effects of the same kind (negative hyperconjugation and conjugation) can cover the wide range of values as a function of factors that we describe in this book.

Effect of orbital alignment (Figure 4.4): The large difference in the interaction energies between nitrogen lone pairs and two vicinal acceptors of similar strength ($n_N \rightarrow \sigma^*_{C4C1}$ and $n_N \rightarrow \sigma^*_{C4H}$ – 9.2 vs. 1.1 kcal/mol, respectively) originates from the much better alignment of the lone pair with the antiperiplanar C-C bond than with the synclinal C-H bond.

Energy decomposition analysis (EDA)²² This analysis starts with “a zeroth order” wavefunction from the overlapping orbitals of the isolated molecular fragments. 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 molecular orbitals 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 which 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) method²³ The electron delocalization to the cationic carbon and neutral boron center can be estimated by removing the vacant p-orbitals from the expansion space of molecular orbitals. 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 block localized wavefunction (BLW) method.^{5,24,25}

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. Block-localized MOs belonging to different subspaces are generally non-orthogonal. A conceptual advantage of this method is that 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) wavefunctions can be expressed as $\Psi(\text{del}) = \hat{A}(\sigma 1a'' 2a'')$ and $\Psi(\text{loc}) = \hat{A}(\sigma \pi^2_{\text{C}=\text{C}} \pi^2_{\text{CH}_3})$, where $\pi_{\text{C}=\text{C}}$ 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 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.

Other approaches to the wavefunction analysis The electronic structure and chemical bonding of molecular systems can also be described via electron sharing indexes (ESI)²⁶ and a variety of approaches that quantify the extent of electronic sharing between two atoms using the concept of bond order (bond index).²⁷

Alternatively, a variety of approaches to the analysis of chemical bonding avoids the notion of “chemical bonds” altogether and replaces them with the analysis of charge density, such as the topological properties of the Laplacian of the electron density (quantum theory of atoms in molecules, QTAIM),²⁸ or electron localization function (ELF) that defines “localization attractors” of bonding, non-bonding, and core type.²⁹

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5

General Stereoelectronic Trends – Donors, Acceptors, and Chameleons

5.1 Three types of delocalization: conjugation, hyperconjugation, and σ -conjugation

In Chapter 2, we discussed the primary bond-forming interactions. In this chapter, we will concentrate on “second order” interactions – deviations from the main Lewis structure that are needed to describe real molecules. All of these phenomena correspond to delocalization – expanding the potential energy box further and allowing “parts” of the molecules (e.g. different functional groups or group orbitals) to interact.

As discussed briefly in Chapter 3, intramolecular delocalizing interactions are commonly divided into three general types: 1) conjugation,¹ 2) hyperconjugation,^{2,3} and 3) σ -conjugation based on the type of orbitals involved in the interactions. The word “conjugation” is sometimes used to describe all types of delocalization but, more specifically, it refers to interactions either between π -bonds or between π -bonds and p-orbitals. IUPAC defines interaction between σ - and π -orbitals as hyperconjugation, and delocalization of a free electron pair (n) into an antibonding σ -orbital (σ^*) as “n- σ^* delocalization” or “negative hyperconjugation”. Interaction of σ -orbitals is sometimes referred to as sigma conjugation.

Mulliken^{2b} emphasized that “differences in conjugating power” among saturated and unsaturated groups are “quantitative rather than qualitative”. He suggested using 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 -interactions. It is clear now that stabilization provided by hyperconjugation with strong σ -donors rivals the conventional conjugation. Underestimation of hyperconjugative stabilization can lead to conclusions that challenge common sense, such as the provocative suggestion⁴ that conjugative stabilization of 1,3-dynes is zero, despite the expectations that it should be at least twice larger than the energy of conjugation between two π -bonds in 1,3-butadiene. This seeming paradox is readily resolved once effective hyperconjugation in alkynes is taken into consideration (see Chapter 6).

The separation between conjugation and hyperconjugation is based on an arbitrary treatment of σ - and π -orbitals on a different basis. Because the separation is artificial, the lines between the three effects are often blurred. For example, the term conjugation is also extended to the analogous interaction involving a double bond and a non-bonding p-orbital. This extension opens the possibility of crossing the line between hyperconjugation and conjugation because lone pairs are often hybridized and possess significant s-character.⁵ Analogously, in the process of an allylic sigma C-Cl bond stretching and breaking in allyl chloride, hyperconjugation with the sigma-bond is smoothly transformed into conjugation with the non-bonding orbital (the cationic or radical center). This transition between hyperconjugation and conjugation proceeds without a well-defined border (Figure 5.1).

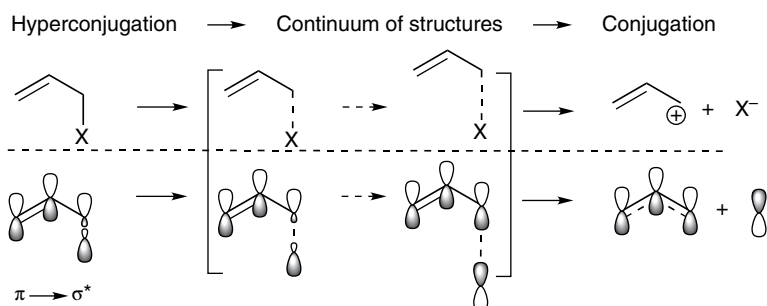


Figure 5.1 Transition from hyperconjugation to conjugation.

5.2 Geminal and vicinal interactions

Geminal interactions correspond to interactions of orbitals at the same atom (Figure 5.2). Although such interactions are ubiquitous and provide important contribution to the overall molecular stability,^{6,7} they are not readily “switchable” by conformational changes. We will not discuss these effects in detail in this book.

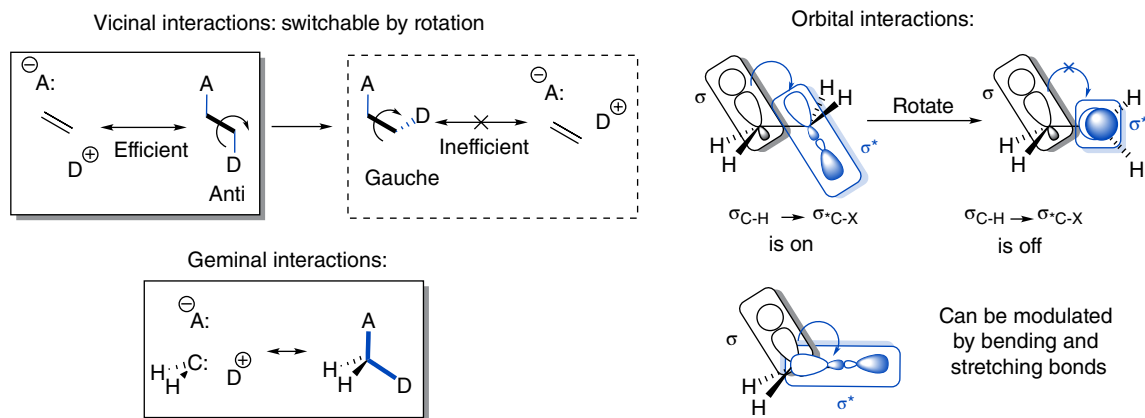


Figure 5.2 Vicinal and geminal interactions.

On the other hand, vicinal interactions are also very common because they correspond to the interactions of orbitals at two directly connected atoms. The stereoelectronic aspects of such interactions are immediately obvious when stability and reactivity change as a function of relative arrangement of the interacting bonds in space (i.e. via rotation around the bridging bond). Vicinal interactions are responsible for the majority of stereoelectronic effects discussed in this book.

5.3 Stereoelectronic main rule: antiperiplanarity

The effects of directionality and symmetry are intertwined in stereoelectronic effects. A particularly simple, yet surprisingly powerful generalization – often referred to as the “main stereoelectronic rule” – is the pronounced preference for antiperiplanarity of the vicinal donor and acceptor orbitals (Figure 5.3). The rule can be expressed in the following way: “There is a stereoelectronic preference for conformations in which the best donor lone pair or bond is antiperiplanar to the best acceptor bond.”⁸

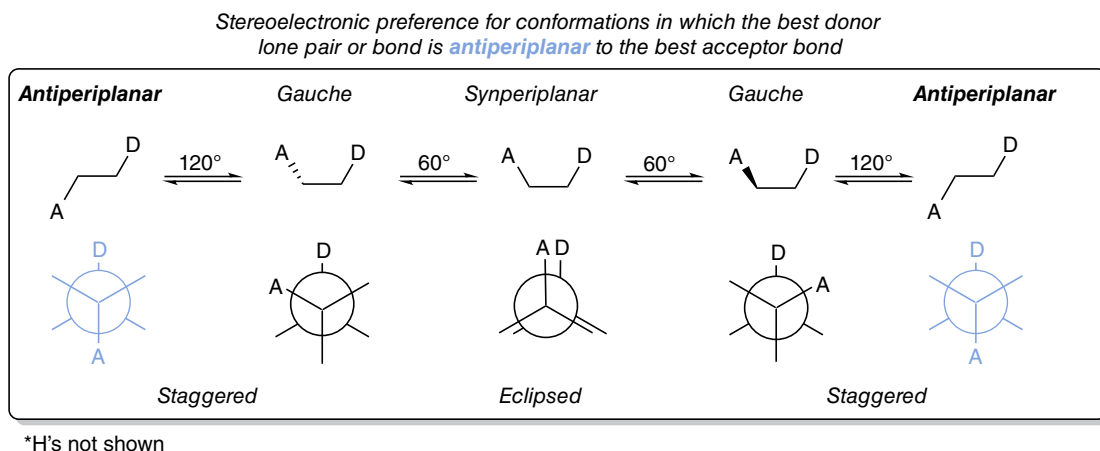


Figure 5.3 Newman projections showing the possible conformations in a donor/acceptor substituted ethane molecule. The “main stereoelectronic rule” favors the antiperiplanar conformation.

The general preference of the antiperiplanar arrangement over syn-periplanar geometry is displayed in the higher stability of the staggered conformation of ethane, *s-trans* conformation of butadiene, eclipsed (an obvious misnomer, as we will show later!) conformation of propene (Figure 5.4(a)), and the majority of stereoelectronic effects in the following chapters. The origin of this preference is illustrated for the case of ethane in Figure 5.4, which clearly displays the unfavorable overlap between the $\sigma_{\text{C-H}}$ -orbital and a node of the σ^* -orbital for the syn-periplanar arrangement in the eclipsed conformation.^{9,10}

Since 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 Chapters 6 and 7 for a number of illustrative examples).⁸ Of course, the antiperiplanar preference may be modified by the effects of sterics and electrostatics. In addition, as we have discussed earlier, the “main rule” is only applicable to intramolecular vicinal interactions. Intermolecular preferences are different.

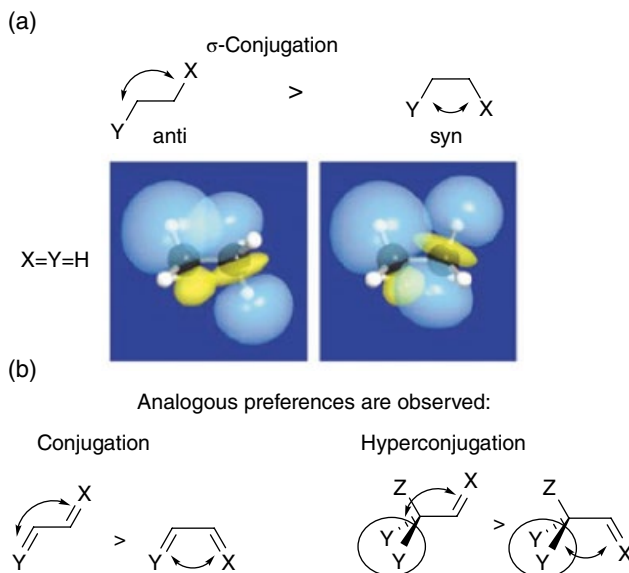


Figure 5.4 (a) Key hyperconjugative interactions between σ_{C-H} - and σ_{C-H}^* -orbitals. (Source: Weinhold 2003 (11). Reproduced with permission of John Wiley and Sons.) (b) The antiperiplanar stereoelectronic preference for vicinal conjugation and hyperconjugation.

In the following sections, we discuss intrinsic properties of common donor and acceptor orbitals that can provide additional modulations of stereoelectronic interactions. We will start with a general outline of polarity trends.

5.3.1 Effects of bond polarity

The simple MO model for 2c,2e-bonds readily describes the formation of polar bonds. For a non-symmetric A-B bond, the distribution of molecular density is also non-symmetric. In particular, the bonding orbital has greater contribution from the more electronegative element B (Figure 5.5), whereas the antibonding orbital is polarized in the opposite direction with a greater orbital coefficient at the less electronegative element A.

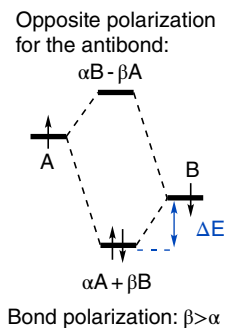


Figure 5.5 Formation of a polar two-center two-electron chemical bond between different atoms A and B leads to non-symmetric distribution of electron density and adds ionic component to bonding.

Polarization of antibonding orbitals explains the regiochemistry of *intermolecular* nucleophilic reactions, such as the generally observed attack at carbon atom in C-X bond of alkyl halides and C=O bonds of carbonyls (Figure 5.6).

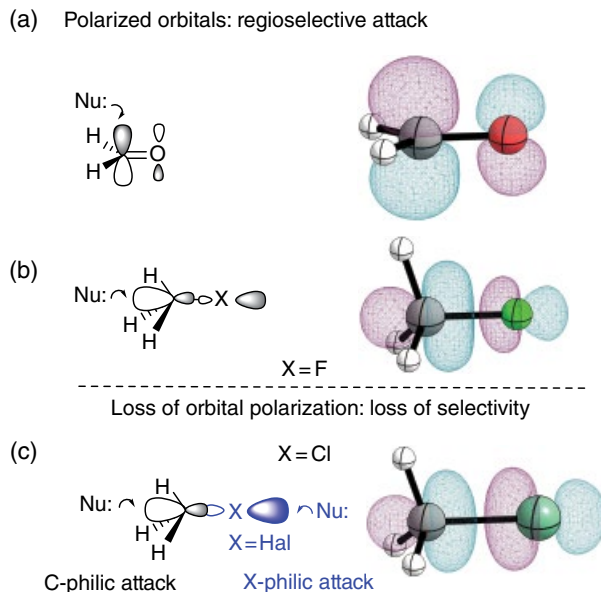


Figure 5.6 Polarization of $\pi^*C=O$ (a) and σ^*C-F (b) orbitals illustrates orbital contributions to the common regiochemistry of nucleophilic reactions at carbon in alkyl halides and carbonyls. Bonds to larger elements do not reflect polarization in the same way (i.e. the C-Cl bond in example c) and X-philic attacks become possible. Note that the common ChemDraw representations cannot always accurately describe the shape of antibonding orbitals.

The dominant role of electronegativity in bond polarization is readily illustrated by the correlation of NBO polarization with Pauling electronegativity. The correlation is not surprising because the Pauling electronegativity scale was defined using polarity effects on bond strengths but it still is not trivial because NBO polarity is based on electron density (not energy). Thus, correlation in Figure 5.7 provides one more justification for the Pauling's electronegativity scale.¹²

Decreased C-X bond polarization opens the alternative direction of nucleophilic attack (the X-philic reactions),¹³ especially when normal attack at the carbon is disfavored by steric shielding and when the departed carbanion has increased stability. For CH_3X systems in the gas phase, ion-molecule complexes $CH_3 \cdots X \cdots X^-$, corresponding to pre-reaction complexes in direct collinear halophilic attack, were found for $X=Br$ and I but not for $X=F$ and Cl .¹⁴ The calculated halophilic complexation energies (ΔH_{comp}) are considerably smaller (1.7 and 4.6 kcal/mol for $X=Br$ and I , respectively) than the corresponding pre-reaction complexes for S_N2 attack at carbon, i.e. at the carbon end of the C-X bond (9.8 and 8.6 kcal/mol for $X=Br$ and I , respectively). Nucleophilic substitution reactions at the halogen atom in CH_3X ($X=F-I$) (halophilic reactions) are highly endothermic due to the low stability of the methyl anion. On the other hand, transition state geometries for aryl bromide/alkyl lithium exchange were shown to be consistent with a halophilic S_N2 attack at the Br end of the C-Br bond.¹⁵

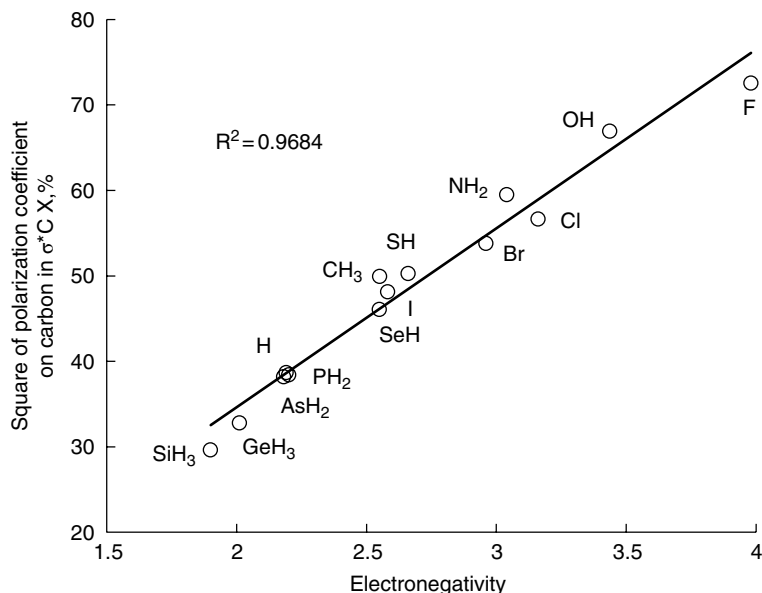


Figure 5.7 Correlation of polarization of σ_{C-X}^* orbitals with Pauling electronegativity of element X in substituted ethanes, CH_3CH_2X . (Source: Alabugin 2002 (12). Reproduced with permission of American Chemical Society.)

Large nucleophiles (such as phosphorus) often prefer the equally large (and sterically accessible) end of the C-X bond for X=Cl or Br. For example, attack of PPh_3 at the halogen atoms of CCl_4 and CBr_4 initiates, respectively, the Appel¹⁶ and the Corey–Fuchs reaction.¹⁷

Halophilic reactions are also possible for other bond types. For example, they are quite common for N-Cl bonds since electronegativity of N and Cl is not drastically different but Cl is less sterically encumbered. As the result, either nitrogen or halogen can be transferred to the nucleophile in a $R_2NH\text{-Cl}/Nu$ reaction.

The halophilic attack often presents a problem in chemistry of S(VI) halides. In particular, it limits utility of sulfonyl chlorides as sulfur electrophiles.¹⁸ Increased polarity of the S-Hal bond in sulfur(VI) fluorides (e.g. $R\text{-SO}_2\text{-F}$ and SO_2F_2) significantly increases their robustness in reactions with nucleophiles, accounting for the status of sulfonyl fluorides as “privileged warheads in chemical biology” with the growing list of applications for affinity labeling and drug discovery (Figure 5.8).¹⁹

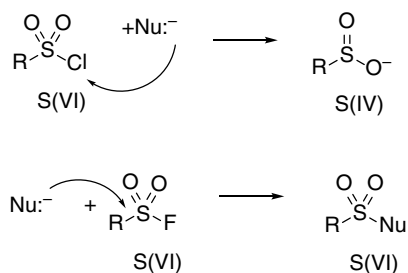


Figure 5.8 Switch from a halophilic attack to an S-philic attack in sulfonyl halides with S-X bonds of increased polarity.

5.3.2 Polarity-induced acceptor anisotropy

Another corollary from the 2c,2e model is that stronger overlap lowers the energy of bonding orbitals and raises the energy of antibonding orbitals. Consequently, such stronger bonds are generally weaker donors and weaker acceptors in the further “second” order delocalizing interactions (i.e. hyperconjugation). This corollary explains, for example, why C-Cl bonds can be better hyperconjugative acceptors than C-F bonds (vide infra).¹²

Polarization of 2c,2e A-B bonds also means that such a bond will be a stronger acceptor at the “A” end in intramolecular interactions if A is more electronegative. This trend accounts for anisotropy of stereoelectronic effects. For example, it explains why C-O bonds are stronger acceptors than O-C bonds (Figure 5.9).²⁰

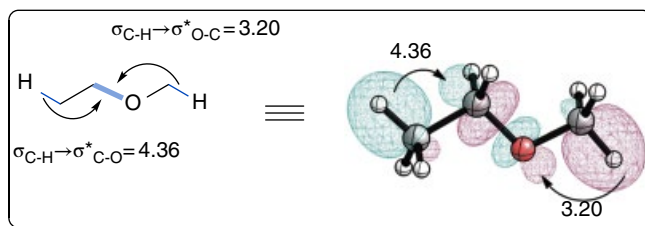


Figure 5.9 Polarization of σ^*_{C-O} explains why C-O bond is a much stronger acceptor at the carbon end (hyperconjugative $\sigma_{C-H} \rightarrow \sigma^*_{C-O}$ interactions are stronger than $\sigma_{C-H} \rightarrow \sigma^*_{O-C}$ interactions).

5.4 Scales of donor and acceptor ability of orbitals: polarization, hybridization, and orbital energy effects

5.4.1 Donors

π , p , and σ The stabilizing effect of conjugation and hyperconjugation on the stability of carbenium ions can be used for the comparison of donor ability for the different types of orbitals. In the gas phase, the effects are maximized since the stabilizing potential of conjugation is not attenuated by solvation effects. As expected, the relative order of donor ability is $n > \pi > \sigma$. Figure 5.10 also illustrates the quantitative differences between the three types of donor orbitals. The $n_O \rightarrow p+$ interaction provides $> \sim 70$ kcal/mol of conjugative stabilization in the hydroxycarbenium ion $^+CH_2OH$, more than sufficient for overriding inductive destabilization by the electronegative oxygen atom. A double bond in the allyl cation is also an excellent donor, as it offers ~ 60 kcal/mol of stabilization relative to the methyl cation.

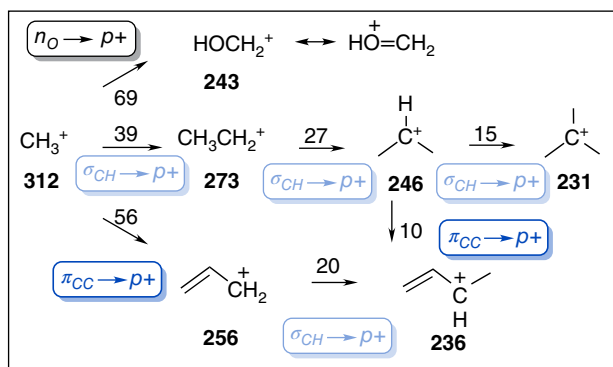


Figure 5.10 Absolute (data below the structures) and relative (data near the arrows) gas phase hydride ion affinities for selected carbocations. All energies are in kcal/mol and taken from ref. 21.

The stabilizing effect of hyperconjugation is smaller (~ 40 kcal/mol) but still significant: a methyl group in ethyl cation provides ca. 70% of stabilization of the allylic double bond. Although the stabilizing effect of additional alkyl substituents gets progressively smaller, the combined effect of hyperconjugative stabilization by several alkyl groups in secondary and tertiary cations provides much more stabilization to the cationic center than conjugation with a single π -donor in the allyl cation and rivals stabilization provided by the lone pairs of oxygen in HOCH_2^+ . As a result, stabilities increase in the order of methyl cation < primary < allyl (parent) < secondary < hydroxycarbenium < tertiary cation (Figure 5.10).

These trends agree well with the trends in relative stabilization 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).²² However, one should add a note of caution: these effects are partially masked in the latter case because the C-Br is a good acceptor, and thus the stability of the starting alkyl bromides in the presence of donor substituents increases as well. Surprisingly, hyperconjugation energies from ODP (orbital deletion procedure) 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).²³ This discrepancy is consistent with the generally smaller estimates of delocalization stabilization by this method in comparison to other methods discussed earlier (e.g. NBO). In this case, the effects of the structural relaxation, such as from pyramidal structure to planar structure, can contribute to the difference as well.

Donor properties of lone pairs Due to the high energy and polarizability of lone pairs, they are the best donors in orbital interactions. As a result, their stereoelectronic properties often play a key role in inter- and intramolecular donor–acceptor interactions.

The order of donor ability of lone pairs towards an adjacent carbocationic center can be obtained from the trends in hydride affinities (Figure 5.11). For heteroatoms from the second period, this trend clearly follows changes in electronegativity ($\text{N} > \text{O} > \text{F}$). The effects of resonance stabilization are very large. If the methyl cation is used as a reference point, even fluorine has a significant stabilizing effect at the adjacent cationic center. This effect is consistent with the fact (carefully omitted from the undergraduate organic textbooks!) that fluorine behaves as an *activating* para substituent in electrophilic aromatic substitution as long as the rate of reactions at the para-position of PhF is compared with that at a single position of benzene.²⁴ The effect of F is ~ 17 kcal/mol smaller, however, than the hyperconjugative stabilization provided by an additional Me group (hydride affinity of the ethyl cation is 273 kcal/mol – 39 kcal/mol smaller than for the methyl cation). For O- and N-substituted carbocations, the conjugative stabilization is larger than the hyperconjugative stabilization by an alkyl group or conjugative stabilization by a double bond (hydride affinity of allyl cation is 256 kcal/mol). For such large stabilization effects, the alternative resonance structures that correspond to oxonium and iminium ions are fully justified.

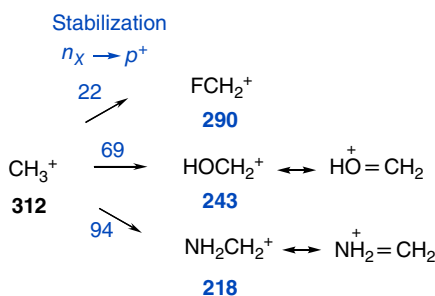


Figure 5.11 Gas phase hydride ion affinities for carbocations with α -heteroatoms. All energies are in kcal/mol and taken from ref. 25.

The apparent donor trends within a periodic table group follow more complicated patterns, where the overall stabilization depends on the interplay between the p-donor ability of lone pairs and the cost of planarization needed for the optimal orbital overlap. The first factor is stabilizing, and the second is destabilizing but both generally increase when going down the periodic table. The methyl stabilization energies evaluated from the following equation by Kapp et al.²⁶ are illustrative (Figure 5.12).

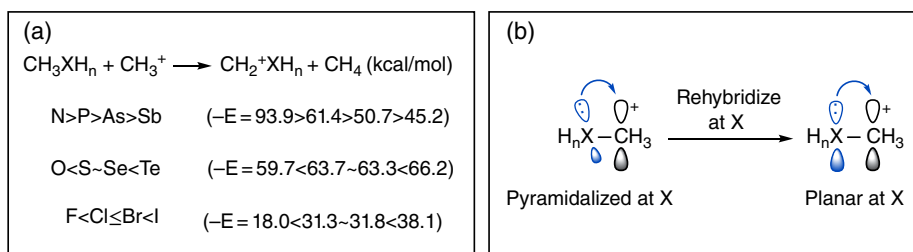


Figure 5.12 (a) Gas phase hydride ion affinities for carbocations with α -heteroatoms. All energies are in kcal/mol and taken from ref. 26. (b) Cost of rehybridization at a heteroatom X is included (as a penalty) in stabilization provided to a carbocation by the lone pair of X. The different trend for compounds of Group V originates from the higher cost of planarization for the heavier elements (N<P<As<Sb – 4.2<35.5<45.1<48.4 (kcal/mol), respectively). This cost originates from the greater amount of p-character that is allocated to the C-X bonds as the orbital size of X increases.²⁷

Donor abilities of lone pairs are less important in neutral systems than in cations. However, they still can play a significant role. For example, difluorocarbene is a relatively stabilized species and less reactive than many other carbenes.²⁸ Carbenes with two nitrogen substituents can be quite stable.

Table 5.1 and Figure 5.13 summarize selected properties of O, S, Se, and N lone pairs in saturated six-membered heterocycles. The donor properties are controlled by energies and further modified by hybridization effects.

Table 5.1 The NBO s-character, hybridization, and energy of all lone pairs (X=N, O, S) 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. If two lone pairs are present at an atom, data for equatorial lone pair are given in parenthesis.

	s-character in n(X), % ^a	sp ⁿ (X)	E(X), a.u. ^a	n(X) _{ax} , e	n(X) _{eq} , e
	0.03 (44.16)	sp ^{1.26}	–0.27 (–0.54)		
	0.03 (69.89)	p (sp ^{0.43})	–0.22 (–0.61)		
	17.99	sp ^{4.55}	–0.27	—	
	17.86	sp ^{4.59}	–0.27		—

^a For X=O, S, the data for the equatorial lone pairs are given in parentheses.

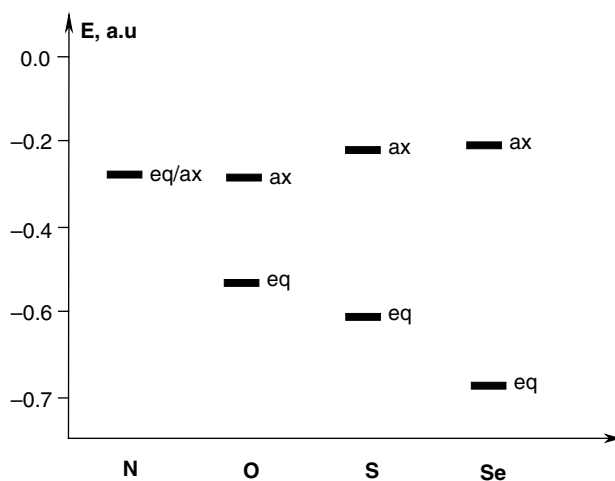


Figure 5.13 NBO energies (in a.u., 1 a.u.=627.5 kcal/mol) of axial and equatorial lone pairs in oxa-, thia-, seleno-, and azacyclohexane, calculated at the B3LYP/6-31G** level.³⁰

The “unusual” non-integer hybridizations for these lone pairs should not be surprising: any combination of hybridization parameters is possible as long as the total s% and p% add to 100 and 300%, respectively (i.e. one s-orbital and three p-orbitals). Such flexible and variable rehybridization in individual orbitals is needed to provide the most stable bonding situation for complex electronic distribution of a non-symmetric molecule.²⁹

Energies and hybridizations 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 lower the orbital energies of the lone pairs (Figure 5.13).

Sometimes these two factors change in the opposite directions.³⁰ For example, the p-type lone pair on oxygen has essentially the same energy as the ca. sp^5 hybridized lone pair on nitrogen (Figure 5.13). In this case, effects of hybridization and electronegativity compensate each other. When two lone pairs are present at an atom, the energies (and donor ability) of one of the lone pairs (e.g. the axial lone pair of the respective heterocyclohexane) increase when going from oxygen to selenium, ($O < S < Se$), whereas the energies (and donor ability) of the other lone pair (“the equatorial lone pairs”) fall in the opposite direction ($O > S > Se$). The first trend is explained by the difference in electronegativity and the orbital size whereas the second trend stems from 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. An increase in the s-character lowers orbital energy, which increases the energy gap between the donor lone pair and an acceptor orbital. In general, the donor ability parallels the amount of p-character of a lone pair, and lone pairs with 100% p-character are intrinsically better donors than the respective sp^n hybrids.

Due to the above differences, stereoelectronic effects in O- and S-heterocycles cannot be automatically transferred to the N-heterocycles and vice versa. Differences in hybridization were shown to be important for stereoelectronic hyperconjugative interactions.^{27,30} Not only is hybridization of a donor orbital related to its absolute energy, but hybridization determines the direction in which non-bonding orbitals are projected in space. Consequently, directionality of sp^n hybrids can change considerably as a function of substitution. Furthermore, 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 sp^n lone pairs (Table 5.1). Both shape and directionality of sp^n hybrids can change to a large extent as a function of substitution.

When differences in hybridization are removed, the relative trends in the donor ability of lone pairs correlate well with the electronegativity of heteroatoms. In a textbook example, reactivity of carboxylic acid derivatives increases in the following order: amide < ester < acyl fluoride due to decrease in $n_X \rightarrow \pi_{CO}$ interaction ($X = N > O > F$). Lower importance of negative conjugation leads to increased positive charge and electrophilicity of the carbonyl carbon (see Chapter 6 for further discussion).

The specific differences in the properties of lone pairs that have an effect on stereoelectronic interactions are discussed in additional detail below.

Oxygen In atoms that bear two or more lone pairs, there are various ways in which these lone pairs can be hybridized. Oxygen, for instance, has often been described as directing orbitals of sp^3 hybridization towards both substituents and each of lone pairs, rendering the lone pairs equivalent (“the rabbit ears” model). The alternative model uses one purely p-orbital for the first lone pair and allocates the rest of the s-character to the remaining sp^n ($\sim sp^1$) hybrid.³¹ Differences between the two models lead to different descriptions of stereoelectronic effects but it is important to point out that the overall density at oxygen does not change in the two descriptions because the two sets of orbitals are linear combinations of each other (Figure 5.14).

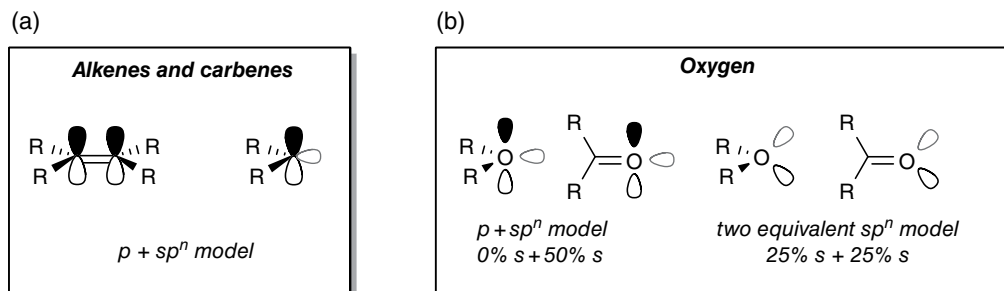


Figure 5.14 (a) Comparison of s,p -orbital description in carbon compounds and water. (b) Two mathematically equivalent descriptions of oxygen lone pairs. The idealized hybridization values are shown for simplicity.

For example, the higher energy p-orbital (instead of an sp^3 hybrid) parallel to the vicinal axial acceptor maximizes the hyperconjugative anomeric $n \rightarrow \sigma_{C-Y}^*$ interaction in tetrahydropyrans (see Chapter 6). NBO analysis which determines “the best hybrids” describing a Lewis structure finds two lone pairs of different hybridization in tetrahydropyran: a purely p-orbital and an $sp^{1.3}$ hybrid.³² The deviation from sp hybridization predicted by the idealized model is readily explained by Bent’s rule,^{33,34} where atoms direct orbitals of different hybridization towards neighboring atoms based on electronegativity and size. When the dominant delocalization is intermolecular, the preferred hybridization can change. For example, NBO finds two $\sim sp^3$ hybrids for the two lone pairs of the H_2O molecule that serves as H-bond acceptor in the water dimer.

Sulfur 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 small amount of 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.³⁰ This trend develops even further for selenium.

Implications O- and S-containing compounds are ubiquitous in organic and supramolecular chemistry and we will see multiple examples of their involvement in stereoelectronic interactions where the fundamental and structural features described above come into play. For example, the differences between energies and hybridizations of oxygen and sulfur lone pairs readily explain the large differences in directionality of H-bonds formed by carbonyl and thiocarbonyl compounds (Figure 5.15). For sulfur, the hybridized lone pair has so much s-character that it is hardly available for H-bonding.

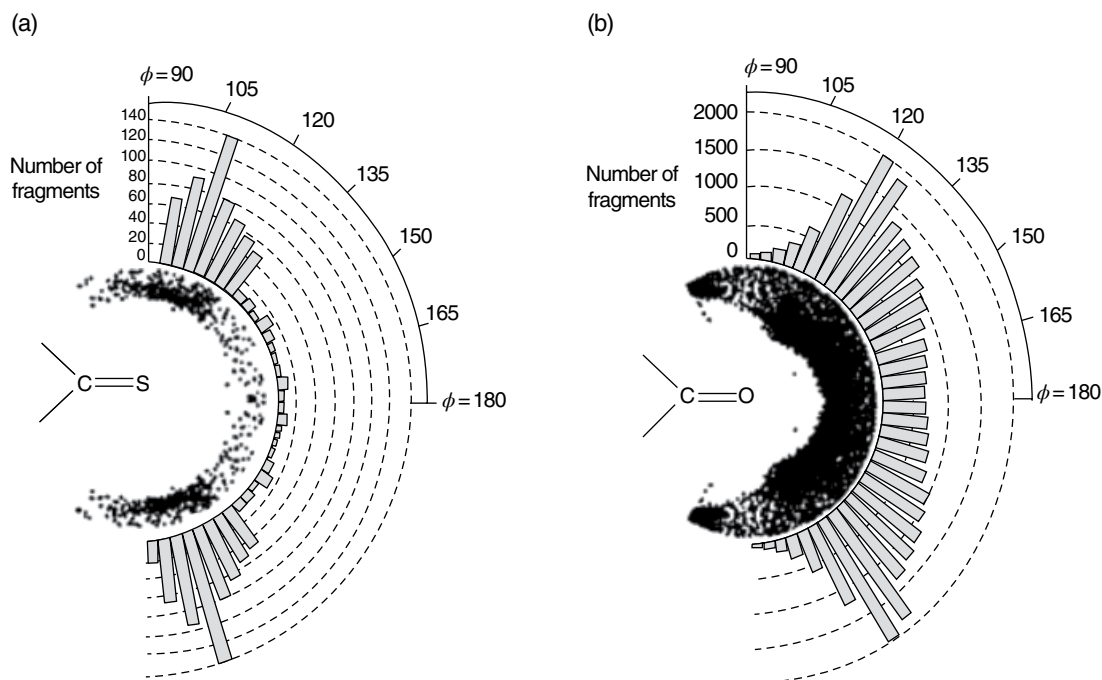


Figure 5.15 Acceptor directionality of $C=S$ (a) and $C=O$ (b) groups in $N/O-H \cdots O/S=C$ hydrogen bonds. Note that the directionality is much closer to the perpendicular approach (coordination with the p -type lone pair) for $C=S$. (Source: Allen 1997 (35). Reproduced with permission of International Union of Crystallography.)

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 to 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. Furthermore, planarization imposed by larger alkyl substituents at nitrogen can increase p-character of the nitrogen lone pairs, enhancing their donor ability (Figure 5.16).³⁰ Alternatively, one can also use structural effects to decrease p-character and donor ability of a nitrogen lone pair. For example, the lone pair of aziridines has significantly more s-character due to reallocation of p-character to the p-rich ($\sim sp^5$) banana N-C bonds in the strained cycle (Figure 5.16).

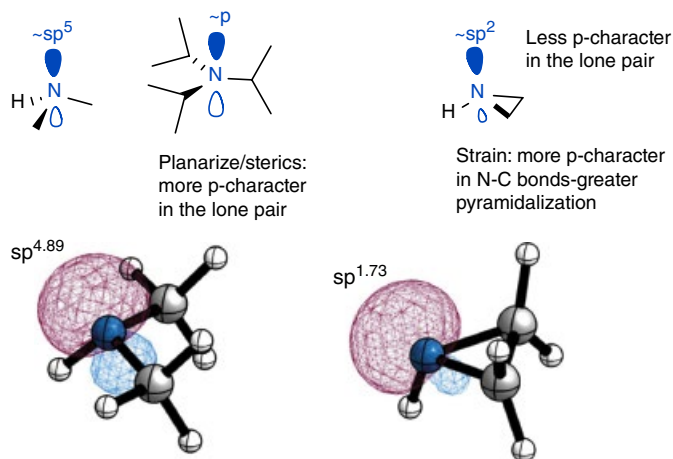


Figure 5.16 Structural perturbations that modify hybridization and donor ability of nitrogen lone pair.

As a consequence of unusual hybridization and decreased donor ability, the nitrogen atom in aziridines possesses a combination of unusual properties (Figure 5.17). For example, the pK_a of aziridinium ion is lower than the pK_a of dimethyl ammonium ion (8.0 vs. 10.7) whereas rotational barrier around the N-C(O) bond in amides derived from aziridine is much lower than such barriers for “normal amides” (4 kcal/mol vs. 16 kcal/mol for dimethylacetamide).

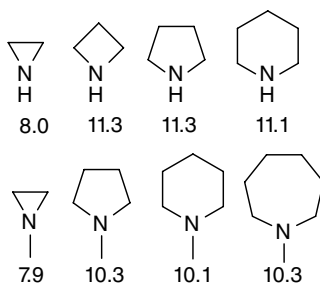


Figure 5.17 Effects of ring size on the basicity of nitrogen lone pairs (numbers below the structures correspond to the pK_a s of the conjugate acids).³⁶

Although the basicity of parent azetidine is similar to that of pyrrolidine and piperidine, attachment of an extra π -conjugating substituent imposes the requirement of additional p-character reallocation from the strained C-N bonds of the four-membered ring to the lone pair. This adjustment is more difficult than rehybridization in simple anilines and related compounds where nitrogen is not incorporated in the small cycle. The tug-of-war between hybridization and resonance decreases donor ability of the nitrogen lone pair. This decrease can be utilized in practical designs. For example, it leads to dramatic increase in fluorescence quantum yield for the family of amino-containing chromophores where the excited state is deactivated by intramolecular electron transfer (Figure 5.18).³⁷ The replacement of N,N-dialkyl groups with azetidines was efficient for a variety of classic fluorophores with absorbance maxima from the UV to the far red.

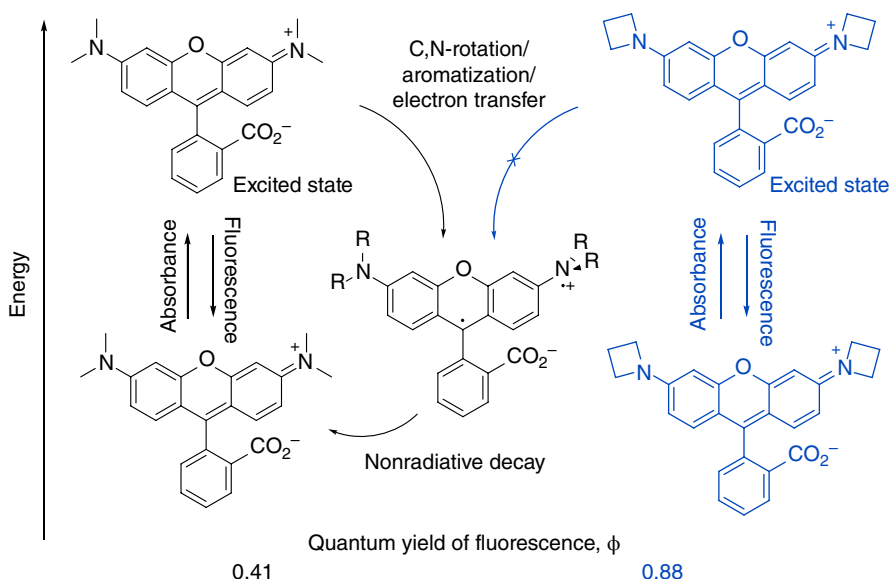


Figure 5.18 Strain-mediated electronic changes lead to the design of improved fluorophores for biological applications.

Livant and coworkers designed a family of tri-alkyl amines that are virtually planar at nitrogen by combining steric congestion with electronic effects.³⁸ The nitrogen atom of the hexahydroxy derivative deviates only $\sim 0.08 \text{ \AA}$ out of the plane defined by the three attached carbons. The corresponding out-of-plane displacement is $0.282 \text{ \AA}$ for triisopropylamine and ca. $0.4 \text{ \AA}$ for uncongested tri-alkylamines (Figure 5.19).

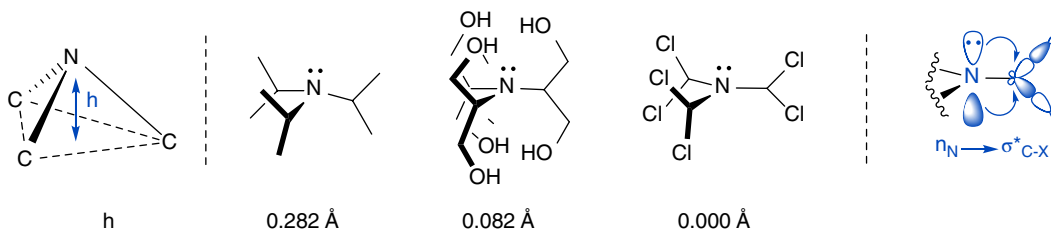


Figure 5.19 Planarization of tri-alkyl amines imposed by electronic interactions.

The rehybridization is imposed by an electronic effect that involves σ^* acceptors that form a group orbital of π -symmetry (Figure 5.19, right). The stabilizing donor-acceptor interaction is maximized in the planar amine geometry. Support for this stereoelectronic model is provided by the correlation of increased planarity at nitrogen with contraction of the N-C bond. Due to the above-mentioned hyperconjugative stabilization, the conjugate acid of the hexaol-amine is very strong: $\text{pK}_a = 3.08$ (much lower than the 10.7 pK_a of Et_3NH^+) and, again, comparable to slightly deactivated anilines.

The hyperconjugative planarization described above is conceptually similar to rehybridization imposed by resonance in amines with π -conjugating acceptors, e.g. anilines with acceptor groups. For the parent aniline, the $n\text{-}\pi^*$ benzylic conjugation is insufficient for completely overriding the intrinsic preference for amine pyramidalization and enforcing sp^2 hybridization at the nitrogen. The balance between hybridization and conjugation can be shifted by making resonance stronger. In particular, electron acceptors at the para-position decrease the difference in the relative stabilities of the pyramidal and planar conformations (Figure 5.20).⁵ As the donor-acceptor conjugative interaction between the lone pair of the amino nitrogen and the aromatic system increases when para acceptor substituents are introduced, the amino group planarizes to enhance the stabilizing resonance. In contrast, electron donors increase pyramidalization at nitrogen (Table 5.2).

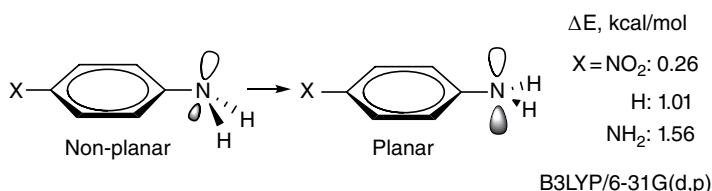
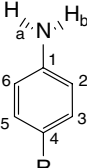


Figure 5.20 Two conformations of anilines and substituent effects on the cost of planarization at nitrogen.

Table 5.2 The C-N distances ($\text{\AA}$), CCNH dihedral angle (degrees), and % of s-character in the lone pair of nitrogen in pyramidal and planar forms illustrate the roles of hybridization and resonance in pyramidalization of the NH_2 group in para-substituted anilines at the B3LYP/6-31G** level.

	r (C-N)	ϕ_1	s-char (LP) _N
R = NO_2	1.378	19.6	7.1
R = H	1.398	25.8	11.9
R = NH_2	1.409	29.2	14.6

$$\phi = [(C_6 - C_1 - N - H_a) + (C_2 - C_1 - N - H_b)]/2$$

Furthermore, these hybridization effects correlate well with the donor ability and basicity of substituted anilines as illustrated in Figure 5.21.⁵ Remarkably, relatively small changes in s-character are associated with basicity changes in the order of several pK_a units.

The reverse correlation is also valid: when planarity is imposed by sterics or structural constraints without negative hyperconjugation or conjugation, such a geometric feature leads to increased p-character in the lone

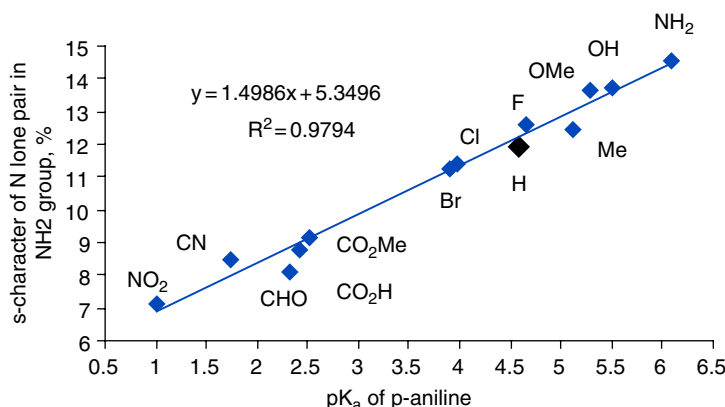


Figure 5.21 Correlations of *s*-character in the NH_2 lone pair with pK_a of para-substituted anilines. Adapted from ref. 5.

pair with the concomitant increase in the nitrogen donor ability. This correlation of structural and electronic properties is very useful for the design of amines for organocatalysis. For example, embedding of the nitrogen atom of *p*-dialkyl pyridine in a five-membered ring forces the amine out of its native pyramidal geometry, an effect that is similar to the flattening effect imposed by isopropyl groups at the nitrogen. Conformational lock of the dialkylamino moiety could further increase the catalytic activity.³⁹ The bicyclic constraints in azajulolidine combine structural restraints with additional donating effect of the alkyl substituents, providing very active acylation catalysts (Figure 5.22).⁴⁰

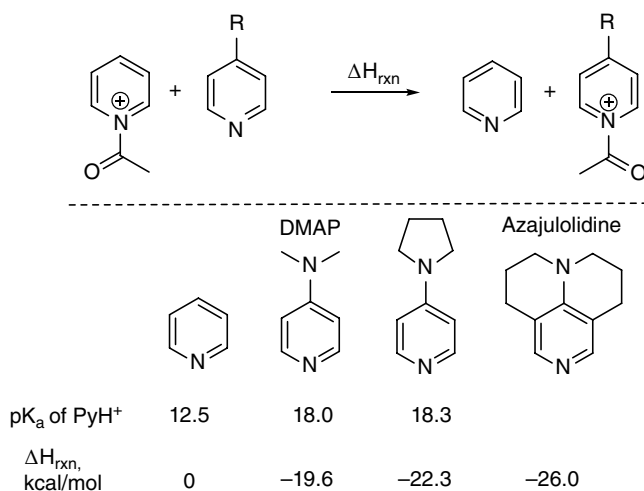


Figure 5.22 Structural modification controls basicity and nucleophilicity of pyridine-derived acylation catalysts.

Sigma donors It is well-established that such donors as C-Si, C-Ge, and C-Sn bonds are capable of providing significant stabilization to positive charge.^{41,42} The donor ability of C-Si bond and C-Sn bonds approaches that of lone pairs. For example, Lambert and coworkers reported 10^{12} rate enhancements upon

trimethylsilyl substitution in the elimination proceeding through a stabilized carbocation (Figure 5.23).^{41c} The hyperconjugative interaction with the antiperiplanar TMS group was suggested to be responsible for $\sim 10^{10}$ acceleration, with the rest (10^2) originating from inductive interactions. The diminished reactivity of the other conformer is associated with the less favorable (gauche) arrangement of the departing group relative to the C-Si donor.

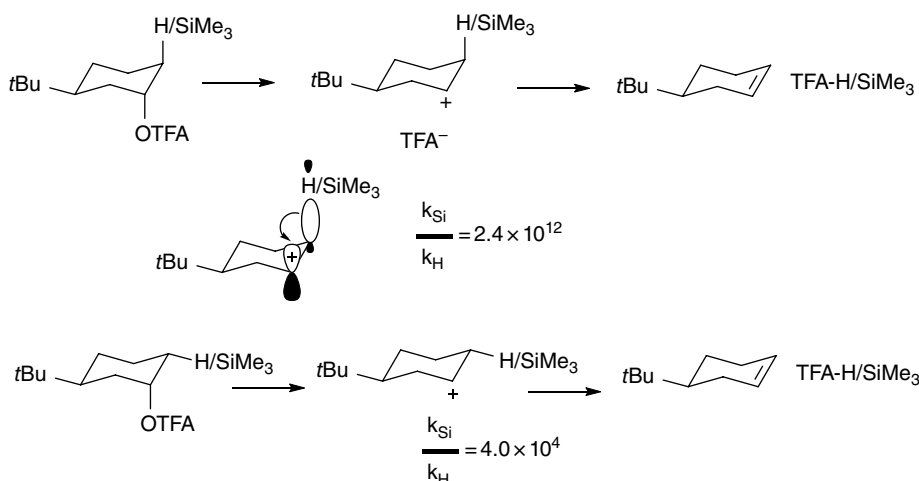


Figure 5.23 Conformational effects on the rate of cationic eliminations reflect stereoelectronics of the developing cation stabilization by C-Si σ -donors.

Stannyl and germynl substituents provide even greater stabilization to positive charge at the β position. For example, the diaxial trimethylgermyl trifluoroacetate and the trimethylstannyl acetate react 10^{14} and $\gg 10^{14}$ times faster than the corresponding metal free analogs.^{42a} The C-M (M=Si, Ge, Sn) bonds are particularly effective at stabilizing positive charge for two reasons: a) the high energy C-M (M=Si, Ge, Sn) σ -orbitals have a small energy gap with the vacant carbenium ion orbital, b) the polarization of C-M bonds towards the carbon results in effective overlap with the adjacent p orbital (Figure 5.24).

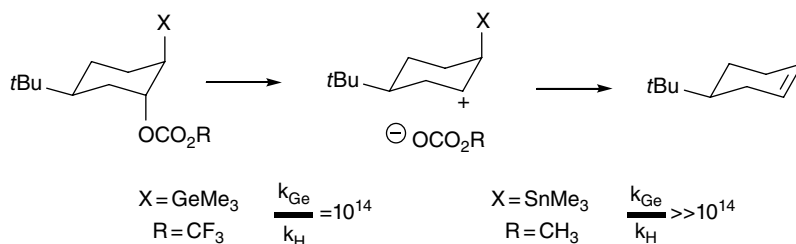
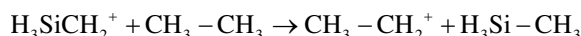


Figure 5.24 β -effect of stannyl and germynl substituents.

The 10^{10} beta effect of mercury is larger than that of silicon and comparable to that of germanium. Interestingly, hyperconjugative assistance with mercury increases with the nucleophilicity of the solvent, suggesting that coordination of solvent with mercury in the transition state increases polarizability and nucleophilicity of

the mercury group.⁴³ Structural effects of hyperconjugation with such strong donors were investigated and reviewed in detail by White and coworkers.⁴⁴

α - and β -Si effects on cation stability are dramatically different: in comparison to the methyl group, α -SiH₃ group is a cation destabilizing substituent! This observation was briefly controversial in the past when relatively low levels of theory available at that time led to the prediction of the H₃SiCH₂⁺ cation was slightly more stable than ethyl cation based on the following equation:



More recently, higher level MP4/6-31G* computations reversed these earlier predictions and demonstrated that the Me-group provides ~17 kcal/mol *more* stabilization to a carbenium ion than the H₃Si moiety. This data is fully consistent with the recent experimental study by Laub and Mayr⁴⁵ who found that H₂C=C(CH₃) (SiMe₃) reacts with Ar₂CH⁺ electrophiles one order of magnitude faster than propene. This finding indicates that α -silyl-stabilization of the intermediate carbenium ion is significantly weaker than α -methyl stabilization because H₂C=C(CH₃)₂ is 10³ times more reactive than propene.

The reasons for dramatically different effects of α - and β -silyl groups lie in the geometric features associated with the overlap of empty p-orbital at the cationic center with the σ -donor orbitals at the β -carbon (or the $\pi(\text{XH}_3)$ group orbital, to be more precise). The C-Si distance is much longer than C-C distance. Because β -C-Si bond overlaps with the cationic p-orbital better, it is a better donor than β -Si-C (or Si-H) bond (Figure 5.25). In fact, much stabilization of the α -silyl group is likely to come not from hyperconjugation but from direct donation through the polarization of Si-C bond to the cationic center.

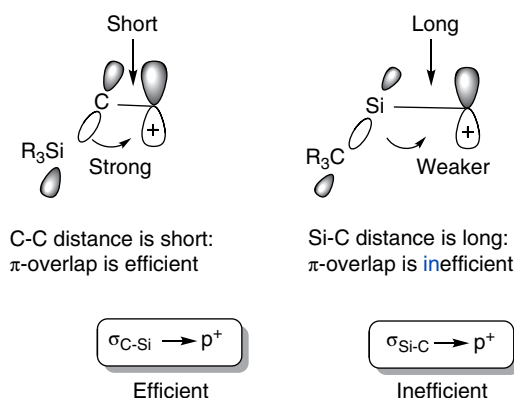


Figure 5.25 Overlap effects explain dramatic difference between α - and β -silyl effects on cation stability.

The relative ability of many common sigma donors, including the most ubiquitous case of C-H vs. C-C bonds, is still debated. Nathan and Baker reported that, in the solvolysis of *p*-alkyl substituted benzyl bromides, an Me group provides more stabilization to the developing positive charge at the *p*-benzylic position than Et, *i*-Pr, and *t*-Bu groups⁴⁶ and attributed this order of reactivity to the greater donating ability of C-H bonds compared to that of C-C bonds. Although these results are consistent with the trends in ¹³C NMR chemical shifts of the β -carbon in β -substituted styrenes in solvents of different polarity,⁴⁷ the opposite trend in the gas phase pyrolysis of 1-arylethyl acetates casts a shadow of doubt on the original interpretation of the Nathan–Baker effect.⁴⁸

The difference between these two bonds is small in ground state neutral molecules. For example, a low temperature X-ray structural study found that the differences in the donor abilities of C-C and C-H bonds

towards $\sigma_{\text{C-O}}$ acceptors of variable electronic demand are comparable to the experimental uncertainty of measurements.⁴⁹ Recent computational studies also found that these differences are small. Natural bond orbital (NBO) analysis indicates that C-H bonds are slightly better donors than sigma C-C bonds in cyclohexane and related molecules.⁵⁰ A similar conclusion was made by Rablen et al. in a theoretical study on the origin of gauche effect in substituted fluoroethanes.⁵¹ In contrast, EDA computations of Frenking and coworkers suggested a slight preference in the opposite direction.⁵²

A balanced description of relative donor ability of σ -bonds can be accomplished if the donor and acceptor sites are not *directly* connected, e.g. by comparing the relative total energies and geometries of two conformers (“hyperconjomers”) of δ -substituted cyclohexyl cations. In these systems, interaction between the $\sigma_{\text{C-R}}$ -bond and the empty p-orbital is transmitted via the double hyperconjugation mechanism (see Chapter 8). Such description partially cancels the non-hyperconjugative contributions such as the inductive and field effects (Figure 5.26).⁵³

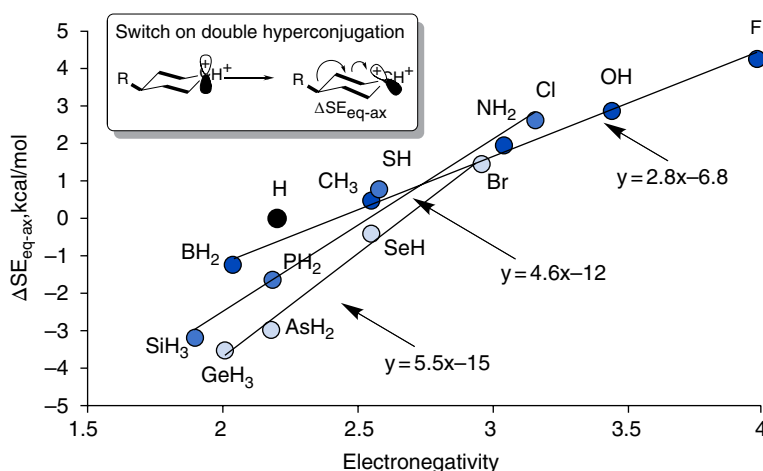


Figure 5.26 Correlations between the differences in stabilization energies of δ - XH_n substituents in the equatorial and axial cyclohexyl cations and electronegativity of the X with separate correlations for each row. Calculations were performed at the B3LYP/6-31G** level. (Source: Alabugin 2004 (53). Reproduced with permission of American Chemical Society.)

Although the $\Delta\text{SE}_{\text{eq-ax}}$ values (defined in the insert in Figure 5.26) from all periods are reasonably well described by a single correlation, the data for the relatively electropositive substituents with negative $\Delta\text{SE}_{\text{eq-ax}}$ values is scattered. For this group, electronegativity alone is not a good indicator of donor ability of C-R bonds in the different periods towards the δ -cationic center (Figure 5.26).⁵⁴ 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 different rows are significant, as illustrated by the two-fold increase in the correlation slopes in Figure 5.26 (2.8 vs. 5.5).

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 CH₃ group is a stronger donor than the H substituent, a trend which is reversed according to $\Delta\text{SE}_{\text{eq-ax}}$ values (“apparent hyperconjugative donor ability” of $\sigma_{\text{C-R}}$ -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 hyperconjomers (ΔSE_{eq-ax}) gives an estimate of sigma donor ability that follows the order of (Al,Ga) $\gg$ Ge > As $\geq$ Si > P > B > Se > H > C > S > Br > N > Cl > O > F (> means “greater”, $\geq$ means that the difference is less than 0.5 kcal/mol, $\gg$ stands for the difference of more than 3 kcal/mol).

Furthermore, the NBO dissection, which includes analysis of the interaction energies and orbital populations, reveals that the C-C bond is not a spectator, but an electronic gate capable of fine-tuning remote electronic communication, i.e. shutting it off when a strong acceptor is introduced or turning it on when a strong donor is available.⁵³

This data illustrates that the somewhat larger intrinsic donor ability of the C-H bonds compared to that of C-C bonds can be overshadowed by cooperative double hyperconjugation with participation of remote substituents. As the 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 depending 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.

5.4.2 Acceptors

σ -bonds: the opposing roles of electronegativity and orbital energies The relative order of acceptor ability of σ^*_{C-X} -bonds towards an antiperiplanar C-H bond determined by NBO analysis⁵⁵ is as follows (the energies of $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interactions are given in parentheses, in kcal/mol): 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) (Figure 5.27). Two $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ energies are given for several substituents corresponding to different conformers (SH, OH, PH₂, NH₂).

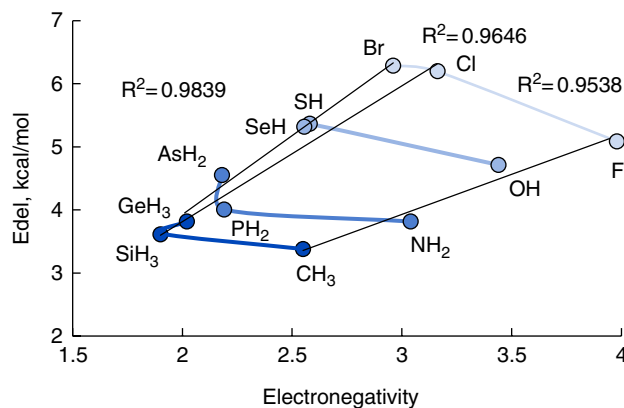


Figure 5.27 Correlation of energy of $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interaction, E_{del} with electronegativity of element X in substituted ethanes, CH_3CH_2X . (Source: Alabugin 2002. Reproduced with permission of American Chemical Society.)

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 (Figure 5.28).^{55,56}

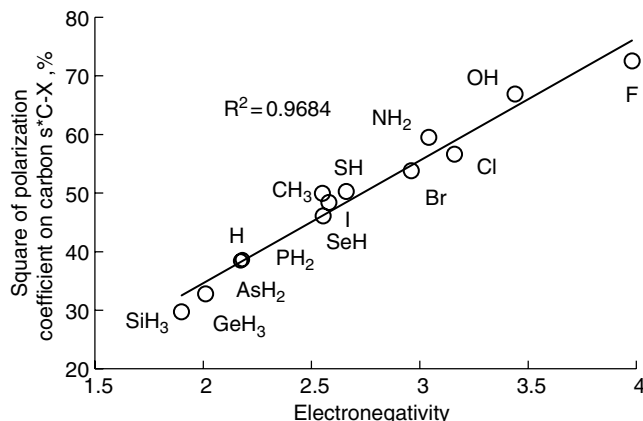


Figure 5.28 Correlation of polarization of σ^*_{C-X} -orbitals with electronegativity of element X in substituted ethanes, CH_3CH_2X . (Source: Alabugin 2002. Reproduced with permission of American Chemical Society.)

On the other hand, augmentation of acceptor ability in groups is opposite to the changes in electronegativity of X and in the C-X bond polarization, following instead the decrease in the energy of σ^*_{C-X} -orbitals when one moves from top to bottom within a group. Even when the polarity of C-X bonds decreases, the C-X bond can still function as a good acceptor as long as the σ^*_{C-X} has low energy (Figure 5.29).

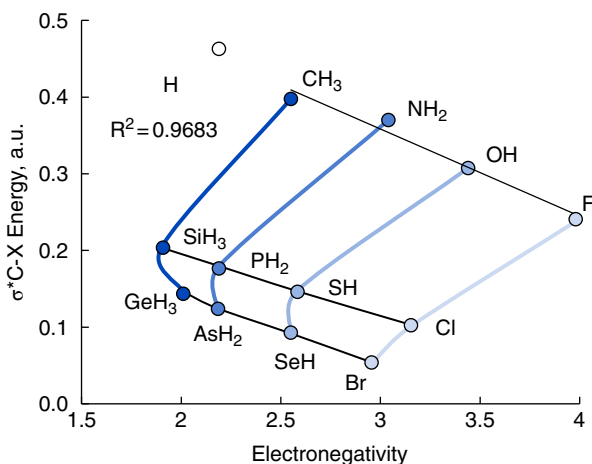


Figure 5.29 Correlation of energy of σ^*_{C-X} orbitals with electronegativity of element X in substituted ethanes, CH_3CH_2X . (Source: Alabugin 2002. Reproduced with permission of American Chemical Society.)

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 (see Chapter 7). As a result, the acceptor ability of the σ -bonds in monosubstituted ethenes changes in a more complex fashion. Overall the acceptor ability of σ -bonds can be significantly modified by substitution and is conformer-dependent (Figure 5.30).

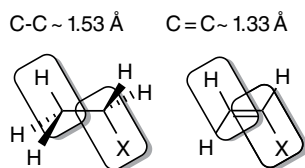


Figure 5.30 Vicinal $\sigma_{C-H} \rightarrow \sigma_{C-X}^*$ interactions in ethanes and ethenes. The boxes around C-H and C-X bonds illustrate the difference in the overlap (the difference is exaggerated for illustrative purposes). (Source: Alabugin 2002. Reproduced with permission of American Chemical Society.)

Interestingly, stereoelectronic effects displayed by C-X bonds with X from second and third periods are highly anisotropic (Figure 5.31). For example, C-chalcogen bonds are excellent σ -acceptors at the carbon end but poor σ -acceptors at the chalcogen end.²⁰ The latter differences result from the longer lengths of the C-S bond that connects the interacting vicinal orbitals.

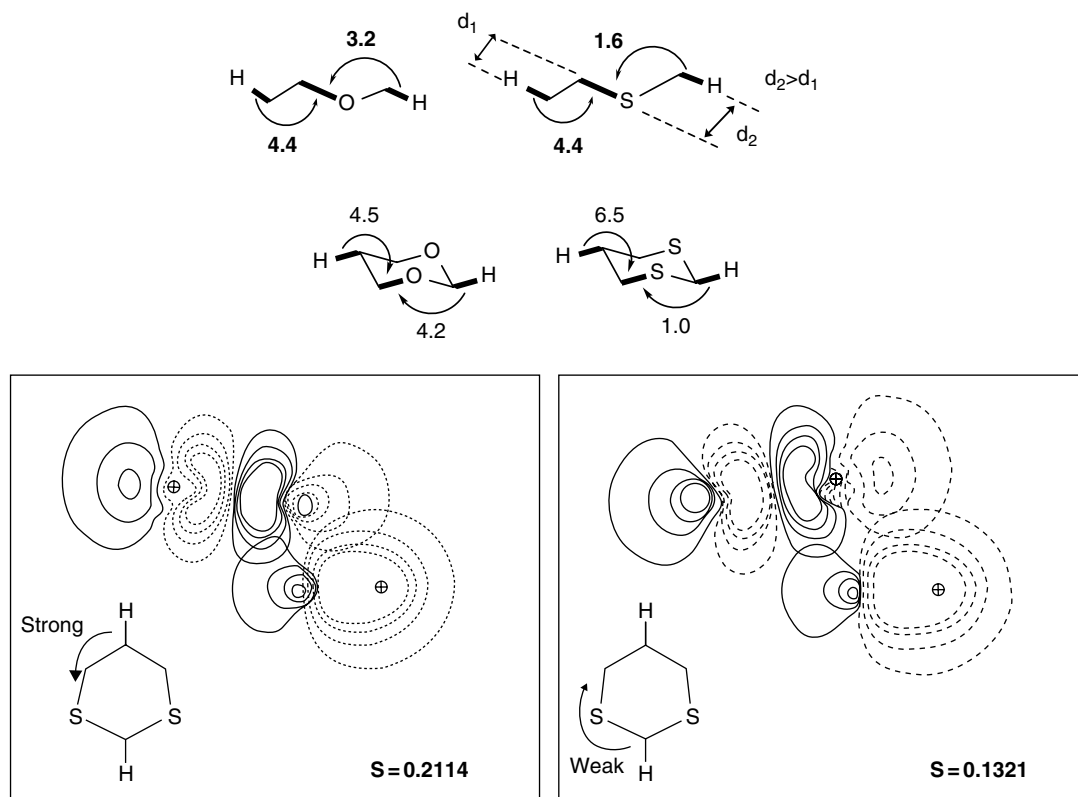


Figure 5.31 Comparison of acceptor ability of C-X bonds in different directions using NBO σ/σ^* interaction energies in kcal/mol. (Source: Alabugin 2000 (20). Reproduced with permission of American Chemical Society.)

These effects can be further accentuated by additional deviations from collinearity in cyclic structures. For example, the C₄-S in 1,3-dithianes are directed *away* from the C2-H donors but *towards* C5-H donors due to ring distortion imposed by the the greater lengths of the C-S bond in this system (Figure 5.31, bottom).⁵⁰

Orbital energy effects also apply to the reactivity of π^* -acceptors. For example, reactivity of symmetric non-polarized $X=X$ systems towards electron-rich systems increases in the order of $C=C$ (alkenes) $< N=N$ (diazo compounds) $< O=O$ (singlet oxygen). The effects of electronegativity in lowering the energy are quite large, explaining why, even without polarity contribution and fully satisfying the octet rule, singlet oxygen is a very reactive chemical species.

5.4.3 Stereoelectronic chameleons: donors masquerading as acceptors

Chameleonic behavior of functional groups is not uncommon in chemistry. In fact, chemical reactions routinely convert donors into acceptors. A smaller subset of such chemical reactions is reversible. For example, the lone pair of electrons responsible for the donor properties of amines becomes unavailable as it is transformed into a N-H bond as the result of protonation under acidic conditions. Such chameleonic behavior of the amine group can find useful applications. For example, it can be used in the pH controlled cleavage of DNA using light-activated processes. At neutral pH, a nitrogen lone pair can quench the DNA cleaver's excited state, while at lower pHs (those of cancer cells) quenching is no longer possible (Figure 5.32).⁵⁷

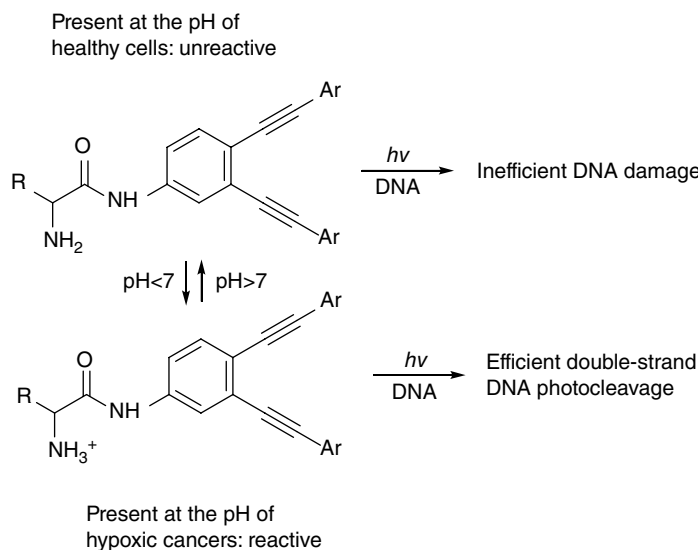


Figure 5.32 pH-gated DNA-cleaving ability of enediyne-aminoacid hybrids.

Orbitals of different types have different donor/acceptor character (σ/σ^* profiles). Whereas lone pairs (non-bonding orbitals) don't have an associated antibonding orbital and, thus, can only display the electron donor properties, any covalent C-X bond can be both a donor (via σ_{C-X}) and acceptor (via σ^*_{C-X}) in two-electron hyperconjugative interactions. As we discussed earlier, this is in fact a *typical* pattern for neutral hyperconjugation. Often one of these interactions is disproportionally high and we treat such an unbalanced group as either a "donor" or an "acceptor". However, one should keep in mind that such a balance can shift depending on electronic demand, and that weaker stereoelectronic preferences can be masked by other factors.

The focus of the following section will be on stereoelectronic "conversion" of donors into acceptors caused by a conformational change.

Transforming donor to acceptor via rotation An interesting possibility exists for the situations when both donor and acceptor orbitals are present at the *same* atom but are projected to different directions. For such atoms, rotation around bonds connecting such an atom with the rest of the molecule can turn the donor and acceptor effects on and off. In some cases, this rotation can invert the overall electronic nature of the substituent, converting an effective donor into an apparent acceptor and vice versa.

Methoxy groups as stereoelectronic chameleons Rotation of the *p*-OMe substituent has profound stereo-electronic consequences for the regioselectivity of reductive cyclization of enediynes (Figure 5.33).⁵⁸ Reactions proceed via a TS with a strong accumulation of negative charge at the internal carbon of one of the breaking triple bonds. The acceptor at the para-position can provide stabilization to this TS and control regioselectivity of the ring closure.

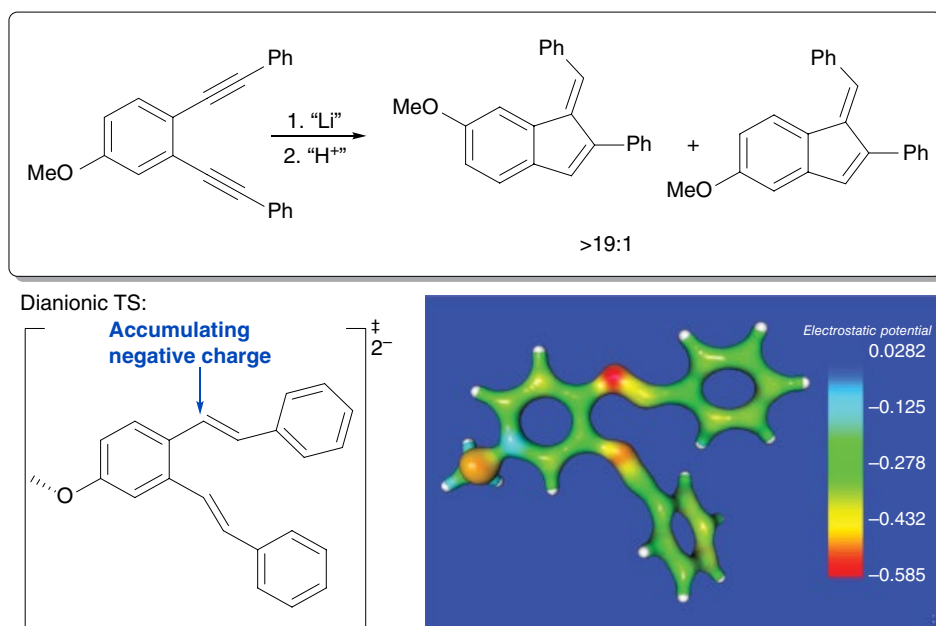


Figure 5.33 Stereoelectronic umpolung accounts for the observed regioselectivity of anionic C_1 - C_5 cyclizations of methoxy-substituted enediynes where the σ^*_{O-C} -orbital serves as a hyperconjugative acceptor and stabilizes negative charge accumulating in the TS.

The conformational change “inverts” the electronic character of the OMe group converting it from a *p*-donor to a hyperconjugative σ -acceptor. Figure 5.34 illustrates the generality of such conformational preferences and the associated electronic effects in benzylic cation, radical, and anion.

Another example of an OR group as a stereoelectronic chameleon is provided by change in the preferred conformation in trifluoromethoxybenzene. Unlike anisole, it favors conformation where the O- CF_3 bond is perpendicular to the phenyl plane (Figure 5.35).⁵⁹

This conformational change is due to the change in the dominating stereoelectronic effect. Presence of the three fluorine atoms in CF_3 has two complementary stereoelectronic effects: 1) it decreases the donor ability of the oxygen lone pair, 2) it increases the acceptor ability of the $\sigma^*(O-C)$ orbital, so the latter can benefit much more from the interaction with the aromatic π -system. The change in the preferred conformation is likely to play a role in pharmacological properties of molecules that incorporate the OCF_3 group.

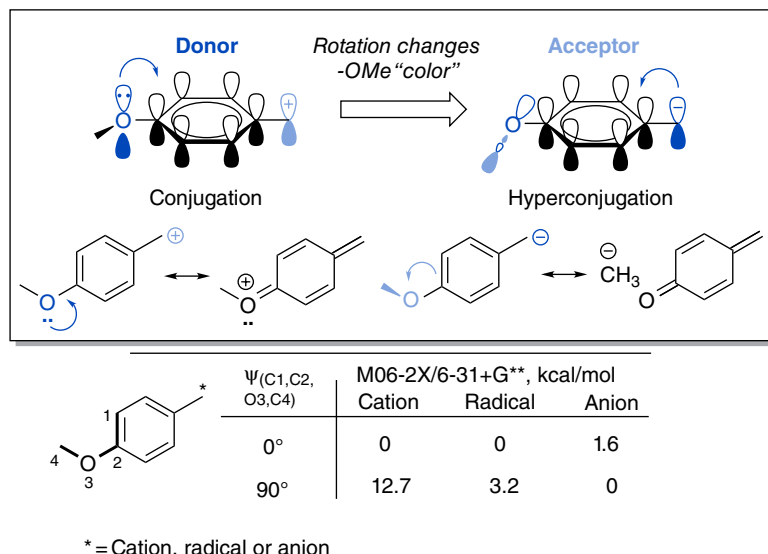


Figure 5.34 “Stereoelectronic chameleon”: the two faces of the OMe group. Methoxy serves as a donor in cationic and radical reactions, but behaves as an acceptor towards anionic species.

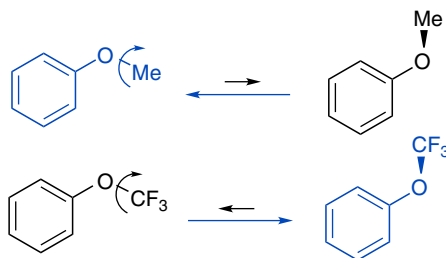


Figure 5.35 Differences in the conformational preferences of anisole and trifluoromethoxybenzene.

Amides as stereoelectronic chameleons The higher stability of amides in the family of carboxylic acid derivatives stems from the large magnitude of amide resonance ($n_{\text{N}} \rightarrow \pi_{\text{C=O}}^*$ interaction). In this system, nitrogen behaves as an electron donor that stabilizes and deactivates the carbonyl moiety towards nucleophilic attack. Several interesting reports illustrate how the electronic effect of nitrogen at the carbonyl group can be reversed. For example, torsion in highly strained lactams “deactivates” the amide resonance and leads to dramatic increase in the rate of solvolysis.⁶⁰ Interestingly, such torsion has also been implicated in catalysis by polypeptide lyase, so it is possible that nature has been taking advantage of stereoelectronic chameleons for a long time.⁶¹

An interesting variation of this theme is observed in sterically hindered amides where the ground-state structures still correspond to “normal” amides but exceptional reactivity is observed, suggesting the presence of hidden electronic effects that facilitate reaching the transition states.⁶² As the nitrogen center becomes more crowded, the barriers to N-C(O) rotation decrease because steric decompression can partially compensate for the loss of $n \rightarrow \pi^*$ resonance. Because the $\pi_{\text{C=O}}$ is aligned with a sigma acceptor ($\sigma_{\text{N-C}}^*$) instead of a lone pair, the carbonyl π -system is capable of better stabilization of the partial negative charge at the α -carbon (accumulated in the TS according to the Hammett linear free-energy analysis). “Steric decompression” and charge neutralization lead to the elimination of amine and formation of the highly reactive ketene intermediate, shifting the reaction from the common formation of tetrahedral intermediate towards an alternative mechanism.

The umpolung of dominant stereoelectronic interactions between amine and carbonyl imposed by the sterically demanding substituents leads to experimental observations that differ dramatically from the usual trends observed in acyl substitutions. Usually, thioesters can serve as acylating agents for amines, but the reaction proceeds in the opposite direction for the unusual amides from Figure 5.36. In these systems, PhSH readily displaces the amine in a nearly quantitative, room-temperature, non-catalyzed reaction (Figure 5.37). The authors compare reactivity of such amides with the reactivity of acyl chlorides.

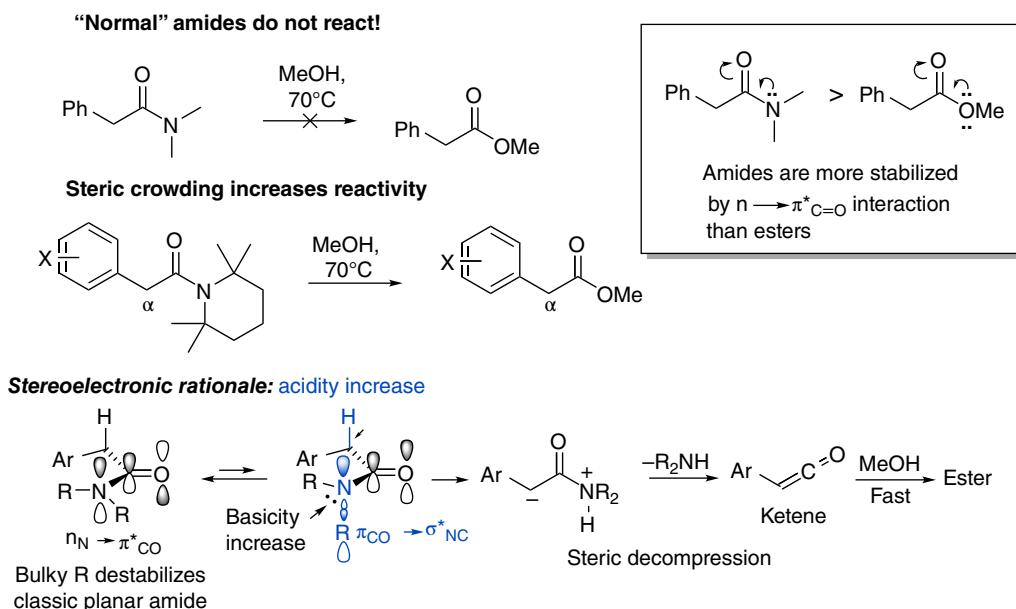
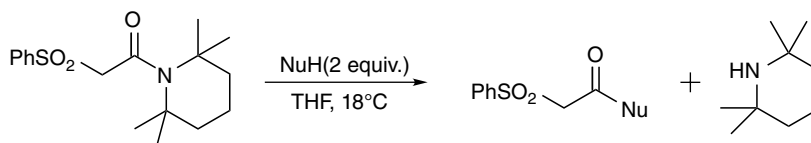


Figure 5.36 Effect of steric decomposition in crowded amides on the mechanism of their reactions with nucleophiles.



NuH	Conversion, %	t, h	Yield, %
H ₂ O	>99%	24	94
MeOH	>99%	6	95
PhSH	>99%	2	97
t-BuNH ₂	>99%	4	97

Figure 5.37 Sterically crowded amides are highly reactive.

Singlet carbenes – chameleonic reactivity in cycloadditions A very interesting functional group with two orthogonal orbitals of drastically different electronic properties is the carbene moiety. Singlet carbenes are perfect chameleons with mutually orthogonal non-bonding orbitals of drastically different properties: the in-plane orbital is populated with two electrons whereas the out-of-plane orbital is empty. This electronic duality means that carbenes, like Dr Jekyll and

Mr Hyde, can change their nature, and play as either electrophiles or nucleophiles, depending on the reaction partners and stereochemistry of interactions. Recently, Moss and coworkers illustrated convincingly how systematic change of substituents at the carbene center can modulate carbene electrophilicity and nucleophilicity.⁶³

This discussion will highlight the ability of carbenes to behave as either a nucleophile or an electrophile, depending on their orientation relative to the target. When both of these properties are important (i.e. the target has both donor and acceptor properties), carbenes find the best compromise between the two possible FMO interactions, as illustrated by the non-direct approach of carbenes to alkenes (Figure 5.38).

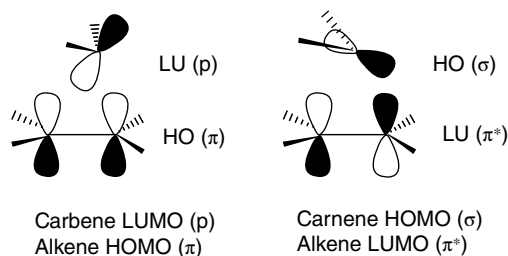


Figure 5.38 The two FMO interactions for the carbene/alkene cycloadditions.

An example of such a transformation is provided by a complicated molecular dance along the internal reaction coordinate (IRC) path in cyclopropanation of alkenes with singlet carbenes. As a four-electron process, this reaction is forbidden according to the Woodward–Hoffmann rules unless it has an antarafacial component. However, such cyclopropanations are known to occur under rather mild conditions. Quasiclassical trajectory calculations using quantum mechanical energies revealed that the initial approach of carbene to the target directs the empty orbital of carbene towards the π -system.⁶⁴ Only when formation of the first bond is sufficiently advanced, the second bond starts to form in an asynchronous process that is accompanied by rotation of the CCl_2 moiety relative to its target (Figure 5.39).

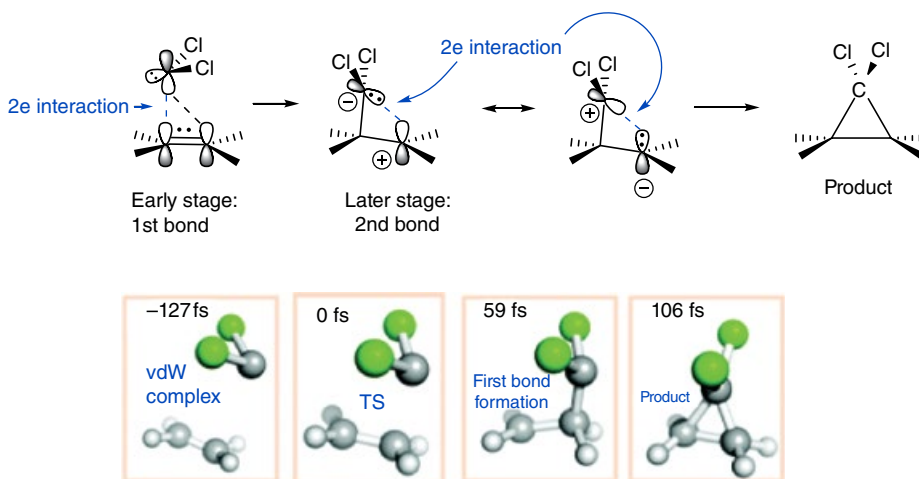


Figure 5.39 Changes in relative orientation at the different stages of approach of dichlorocarbene to an alkene. (Source: Xu 2011 (64). Reproduced with permission of American Chemical Society.)

These stereoelectronic peculiarities of carbenes make seemingly simple reactions intriguingly complex (Figure 5.40). Kraka and Cremer suggested that cyclopropanations belong to the diverse family of reactions with hidden intermediates and hidden transition states.⁶⁵

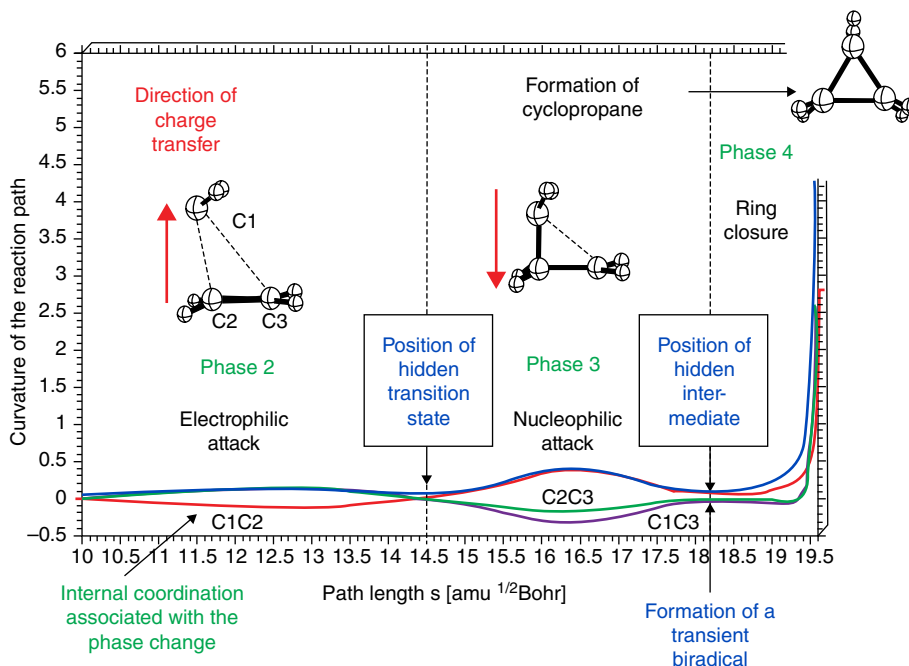


Figure 5.40 Hidden intermediates and transition states in carbene cycloaddition to alkenes. (Source: Kraka 2010 (65) reproduced with permission of American Chemical Society.)

The presence of two orthogonal orbital arrays is very useful for stabilization of unusual reactive species derived from both the main group elements and transition metals (Figure 5.41).⁶⁶

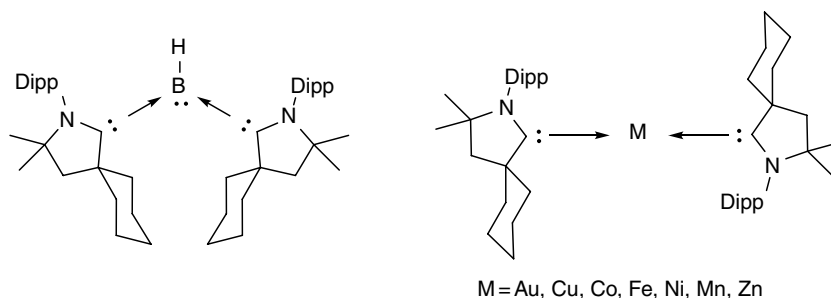


Figure 5.41 Unusual coordinatively unsaturated species stabilized by carbene ligands. Dative bonds are shown with arrows. Dipp = 2,6- $i\text{Pr}_2\text{C}_6\text{H}_3$.

Chameleonic features of carbenes can be further amplified by complexation with transition metals (Figure 5.42). In complexes with low valent/low oxidation state late transition metals (Fischer carbenes), carbenes display electrophilic properties, and often behave similarly to a carbonyl compound. Such carbenes also often have p-donor substituents, such as $-\text{OR}$ or $-\text{NR}_2$, on the carbene carbon and π -acceptor ligands at the metal. In contrast, carbene complexes with high valent/high oxidation state early transition metals (Schrock carbenes) are nucleophilic.⁶⁷ The ability of metal in the Schrock carbenes is further enhanced by donor ligands.

Alkynes also have chameleonic potential that stems from the presence of orthogonal π -systems but this potential is yet to be explored in full detail.⁶⁸

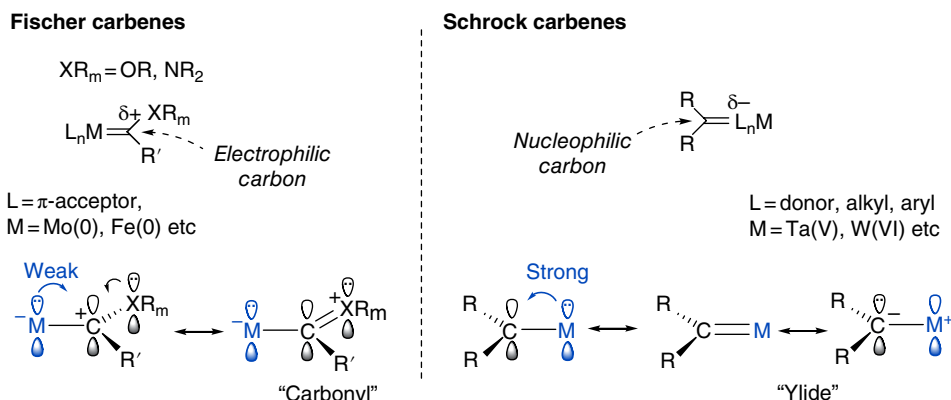


Figure 5.42 Chameleonic nature of carbene moiety can be amplified by metal coordination.

Supramolecular stereoelectronic chameleons Chemical chameleons often come from “orthogonal” functional groups, i.e. functionalities with two sets of orbitals constrained to orthogonality. The carbonyl family is one such chameleon. Carbonyl is a π -acceptor but its oxygen’s lone pair is a sigma donor. Reactions of carbonyls with electrophiles and nucleophiles proceed via different trajectories – nucleophilic attack from above the molecular plane and electrophilic attack within the molecular plane. It is less well appreciated that such common groups as ethers, sulfides, amines, phosphines, and even halides can also be considered stereoelectronic chameleons as well. The chameleonic nature of these groups manifests itself in supramolecular interactions, such as pnictogen, chalcogen, and halogen bonding. For examples, the regions of high electron density correspond to the location of lone pairs that can serve as targets for electrophiles or H-bonding partners. On the other hand, the region of lower electron density at the extension of $\sigma^*_{\text{Y-X}}$ -bond can function as an electron acceptor site capable of coordination with nucleophiles or halogen bond forming partners (Figure 5.43).

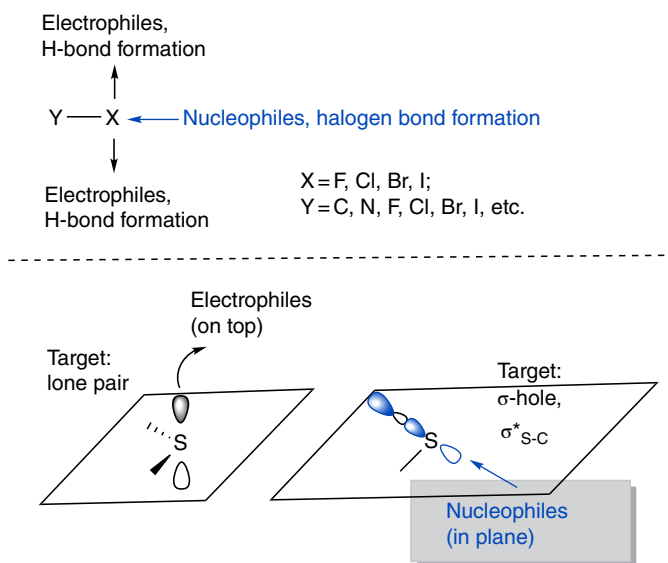


Figure 5.43 Many common functional groups can switch between donor and acceptor behavior in chemical and supramolecular processes depending on the trajectory of attack.

5.5 Cooperativity of stereoelectronic effects and antiperiplanar lone pair hypothesis (ALPH) theory – several donors working together

An interesting combination of potentially synergistic stereoelectronic effects is observed in systems where more than one donor can interact with a single acceptor or when multiple acceptors compete for the same donor. A well-studied and much discussed set of systems involves orthoesters and other structures related to tetrahedral intermediates of nucleophilic reactions of carbonyls. For such systems, Deslongchamps introduced the “antiperiplanar lone pair” (ALP) model which explained observed reactivity trends via cooperativity (or lack of thereof) between anomeric $n_{\text{O}} \rightarrow \sigma_{\text{C-X}}^*$ interactions.⁶⁹ Because this model is discussed in much detail and critically evaluated in the literature,^{70,71} we will limit ourselves to only a relatively short discussion of this interesting question using a simplified model (*vide infra*). We will use a cyclic system to decrease the number of conformational degrees of freedom and we will only concentrate on the best donor (p-type lone pair) on oxygen instead of considering the two “rabbit ears” hybrid lone pairs in the original model.

This model is illustrated below using the chair geometry of tetrahydropyran. In short, heterolysis of an anomeric C-X bond (or another reaction where this bond is cleaved with the development of a positive charge at the anomeric carbon) in this system was suggested to be accelerated in the presence of an endocyclic substituent with a lone pair. In the ideal situation, the endo-anomeric effect and the exo-anomeric effect can work together to weaken the axial C-X bond. Double assistance for breaking the endocyclic C-O bond is only possible if there are two exocyclic substituents with the right conformation to place their lone pairs antiperiplanar to the endocyclic C-O bond (Figure 5.44).

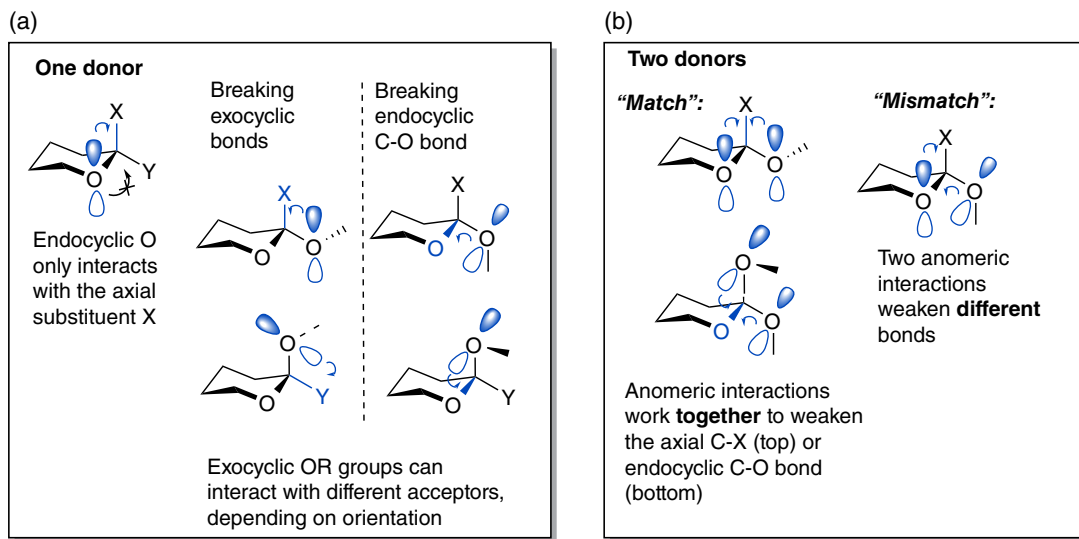


Figure 5.44 (a) lone pair of endocyclic oxygen can only efficiently assist the departure of axial group, whereas the exocyclic oxygen lone pair(s) can be oriented antiperiplanar to either axial or equatorial substituents. Only the “stereoelectronically active” lone pairs are shown. (b) Cooperative or mismatched effects of two donors depend on the conformations of exocyclic substituents.

This model was used to explain a number of intriguing experimental observations such as the preference for the acyclic products to the formation of lactones in hydrolysis of cyclic hemi-orthoesters (involved, for example in ozonolysis of acetals⁷²). In this reaction, the equatorial C-O bond needs to be broken for the

formation of lactone. No double anomeric assistance to this reaction is possible from the low energy (chair) conformation. Although the axial bond is broken easily with double assistance from endocyclic and equatorial oxygens, this step is “invisible” because it simply changes one axial OR into another. For the cleavage of the endocyclic C-O bond, the two exocyclic oxygens should adopt conformations where they cooperatively weaken the endocyclic bond (exo-anomeric effect). In the absence of cyclic or steric constraints, this is readily possible and explains the observed experimental observations (Figure 5.45).

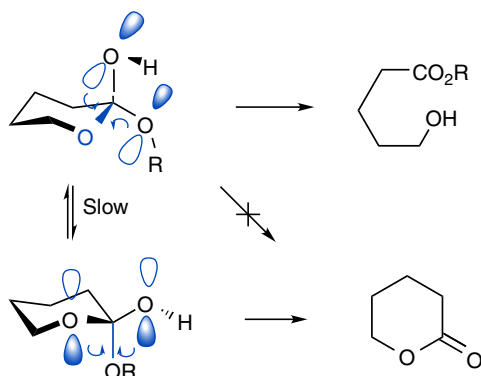


Figure 5.45 Stereoelectronic control in hydrolysis of cyclic hemi-orthoesters. Only *p*-type lone pairs antiperiplanar to a leaving group are shown.

This system, however, is much more complex than the simple description in Figure 5.45 suggests. The proper analysis of such systems has to involve the Curtin–Hammett analysis of interconversion of reactive and unreactive conformers and the evolution of stereoelectronic effects along the interconnected reaction pathways.⁷³ The critical examination of APL theory by Perrin also suggested that the role of conformational equilibria of reactive species, the involvement of syn-periplanar lone pairs, and the different stability of products should be included in the analysis.⁷⁰ We will continue our discussion of cooperativity and anti-cooperativity between stereoelectronic effects in Chapter 11.

5.6 Summary

This chapter outlined several fundamental factors that control the magnitude and importance of stereoelectronic effects. In the following chapters, we will discuss what the consequences of donor–acceptor orbital interactions are. We will focus on the two questions of general importance for organic chemists: stability and reactivity. In the very next chapter, we will provide examples of conformational effects controlled by vicinal stereoelectronic interactions. We will illustrate that such effects often provide the key electronic stabilization that is responsible for the preferred conformational profiles and explains the shapes of many key organic functional groups.

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6

Stereoelectronic Effects with Donor and Acceptor Separated by a Single Bond Bridge: The Broad Spectrum of Orbital Contributions to Conformational Analysis

This chapter outlines the variety of common stereoelectronic effects where donor and acceptor orbitals are separated by a single bond. With a few exceptions, the sigma bridge will not be directly considered as a contributor to the hyperconjugative interactions. It will be treated as simply a means for keeping the interacting vicinal orbitals in the parallel sidewise arrangement.

The unifying feature of such orbital interactions is that they can be switched on or off via rotation around the single bond (Figure 6.1a). Because molecules tend to adopt geometries where stabilizing interactions are maximized, the influence of such interactions on stability can be directly probed experimentally via conformational analysis.

Before discussion of stereoelectronic effects on conformations, we will need a way to describe conformations. We will follow the accepted convention of Klyne and Prelog described below.¹ This convention specifies one proximal and one distal group, designated here as A and B, and separates the conformational space defined by the A-X-Y-B dihedral into eight well-defined regions as shown in Figure 6.2.

Evaluating stereoelectronics from conformational profiles is a simplification because, in reality, one stereoelectronic effect is generally “traded off” against another. For example, the $n_N \rightarrow \pi^*_{C=O}$ conjugation in the planar amide conformation is converted into $n_N \rightarrow \sigma^*_{C=O}$ hyperconjugation in the twisted amide (Figure 6.1b). Although such alternative arrangements are usually less stabilizing than the original effects (otherwise the most stable geometry would be different!), they can still considerably alleviate the energy cost for a conformational change.²

Most stereoelectronic effects involve interactions of orbitals at least one of which corresponds to a σ -bond. Consequently, they are classified under the umbrella of hyperconjugative interactions. However, also included are n - π , p - π , and π - π conjugative effects that display similar stereoelectronic features.

Often, the most stable geometry corresponds to antiperiplanar arrangement of donor and acceptor. As discussed earlier, the coplanarity corresponds to the π -overlap of orbitals and is preferred for the same

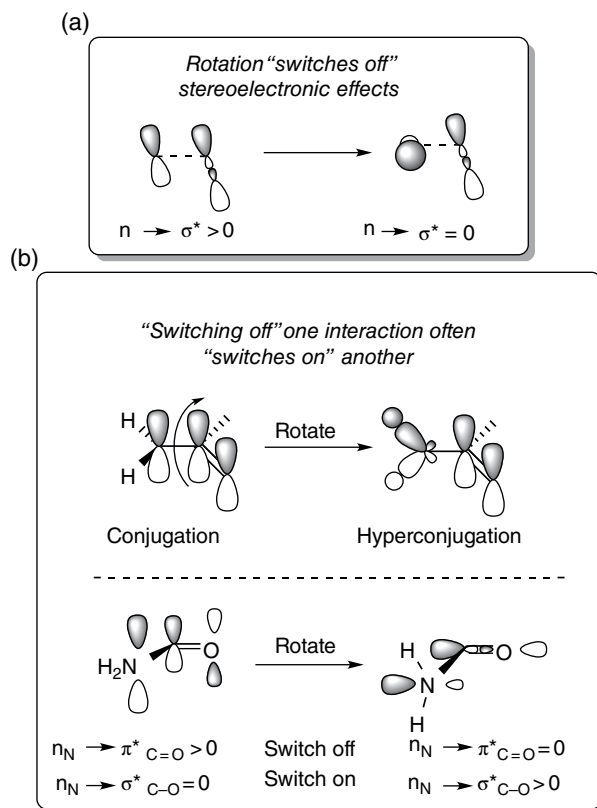


Figure 6.1 (a) Switching off a stereoelectronic effect by rotation. (b) The caveat – one interaction is converted into another (i.e. amide $n_N \rightarrow \pi^*_{C=O}$ resonance into negative hyperconjugation, $n_N \rightarrow \sigma^*_{C=O}$ or allylic resonance into neutral $\sigma_{C-H}/\pi_{C=C}$ hyperconjugation) as interactions are "switched off" and "on".

Describing conformations

Torsion angle τ	Designation	Abbreviation
$0^\circ \pm 30^\circ$	$\pm$ <i>synperiplanar</i>	$\pm$ <i>sp</i>
$+30^\circ$ to $+90^\circ$	$+$ <i>synclinal</i>	$+$ <i>sc</i>
$+90^\circ$ to $+150^\circ$	$+$ <i>anticlinal</i>	$+$ <i>ac</i>
$+150^\circ$ to $+180^\circ$	$+$ <i>antiperiplanar</i>	$+$ <i>ap</i>
-30° to -90°	$-$ <i>synclinal</i>	$-$ <i>sc</i>
-90° to -150°	$-$ <i>anticlinal</i>	$-$ <i>ac</i>
-150° to -180°	$-$ <i>antiperiplanar</i>	$-$ <i>ap</i>

Figure 6.2 Convention for description of conformations suggested by Klyne and Prelog. (Source: Testa 2013 (1). Reproduced with permission of John Wiley and Sons.)

reason that it renders planar alkenes more stable than twisted alkenes. The higher stability of antiperiplanar geometry vs. syn- arises from symmetry considerations described in the previous sections.

Disruption of conjugative interactions can have dramatic consequences. A textbook example for the interruption of electronic communication imposed by spatial orthogonality is provided by steric inhibition of resonance (Figure 6.3). For example, once the acceptor nitro group is rotated so that its π -system is orthogonal to the aromatic π -system in nitrobenzene, the accelerating effect of the acceptor on nucleophilic aromatic substitution is greatly diminished.³ Steric inhibition of resonance also applies to electrophilic aromatic substitution reactions: whereas *N,N*-dimethylaniline readily reacts with benzene diazonium cation, *N,N*,2,6-tetramethylaniline is unreactive.

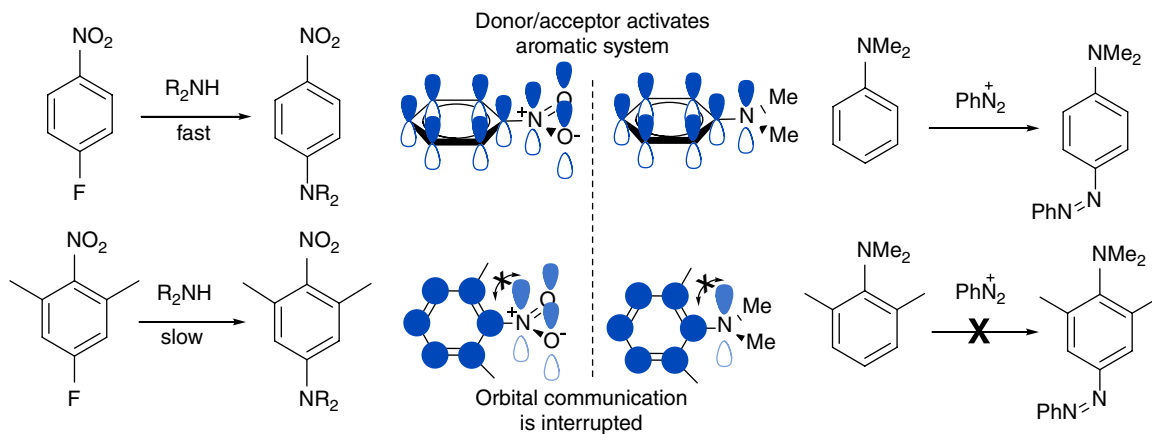


Figure 6.3 Steric inhibition of resonance: interruption of electronic communication imposed by spatial orthogonality.

In the first part of this chapter, we will focus on energies and conformational preferences. This is not the full story. Even though the rotational barriers in the initially discussed functional groups are generally small, the interactions, which have a minor effect on the conformational landscape in the ground state, can manifest themselves to a much larger extent in the TS and have a large effect on reactivity. Representative examples of such reactivity changes will be provided, but we will postpone the broader discussion of such effects until Chapter 10.

6.1 σ/σ -Interactions

Orbital interactions are complex and depend on the combination of stabilizing delocalizations, sterics, and electrostatics. Again, in the spirit of the definition of stereoelectronic effects in the introduction, we will concentrate on stabilizing effects, such as hyperconjugation and conjugation.

6.1.1 Rotational barrier in ethane

The forces controlling the barrier of rotation around formally single bonds serve as one of the foundations of conformational analysis. Not surprisingly, ethane, the parent system for studies of rotational barriers, has been extensively investigated and its conformational profile is well-known (Figure 6.4). Historically, the origin of the ~ 3 kcal/mol lower energy of the staggered conformation responsible for the rotational barrier in ethane has often been attributed to steric repulsion between electrons in the C-H bonds in the eclipsed conformation.⁴ Alternatively, rotation-induced weakening of the central C-C bond⁵ and hyperconjugation^{6,7} have been

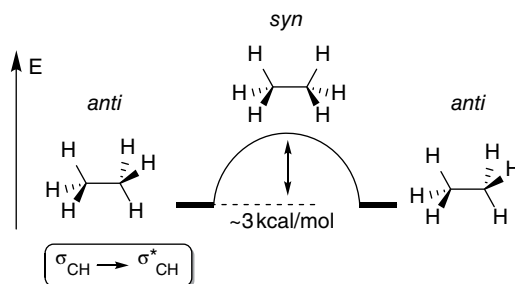


Figure 6.4 Rotational barrier and staggered and eclipsed conformation of ethane.

considered to be the reasons for the higher stability of the staggered conformation. Mulliken himself, as early as 1939, conjectured that hyperconjugation plays an important role in the internal rotation potential of ethane-like molecules.⁸

NBO analysis has been used to dissect the contributions of the three principal contributors to ethane's structural preferences and separate steric and hyperconjugative interactions.⁹ It was 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 decisive 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 6.5.

This analysis provides a description of rotational barriers that is very different from the steric picture. Weinhold described it in the following way:

When bonding electrons delocalize, they can lead to alternative bonding patterns (resonance structures). For example, the electron delocalization associated with the $\sigma_{\text{CH}}-\sigma_{\text{CH}}^*$ interaction corresponds to a partial double bond resonance structure, as represented in chemical notation below. Twisting about a double carbon-carbon bond is difficult, so rotation is inhibited.^{9b}

This description is fully consistent with the π -type character that is apparent in several ethane MOs, i.e. in its two HOMOs.

Subsequent studies^{11,12} restarted the controversy by bringing back the steric repulsion explanation as the dominant contribution to the rotation barrier. An energy decomposition analysis (EDA) study found additional hyperconjugative stabilization in the staggered conformation to be only about 0.4 kcal/mol. A block-localized wavefunction (BLW) analysis suggests that the hyperconjugation interaction does favor the staggered conformation but provides only ~0.8 kcal/mol, one-third of the total barrier. These discrepancies are based on the conceptual differences between the EDA, BLW, and NBO approaches discussed in Section 4.3, such as the non-orthogonality of localized orbitals in the first two procedures and non-identical approaches to the treatment of steric effects.

Notwithstanding these differences, it is important to remember that neither the 0.4 nor the 3 kcal/mol values correspond to the energy of hyperconjugation in the ethane. Instead, these values merely represent the *difference* between the hyperconjugative energies of the two forms, *each* of which is strongly stabilized by hyperconjugation. The absolute values of hyperconjugative stabilization in staggered and eclipsed ethane are much larger. For example, even the BLW analysis, which generally gives lower hyperconjugative energies than NBO, estimates the total energy of geminal and vicinal hyperconjugative interactions in staggered ethane as 11.6 kcal/mol (larger than the 10.2 kcal BLW estimate of the energy for the conjugative interaction between the two π -bonds in the *s-trans* 1,3-butadiene).²

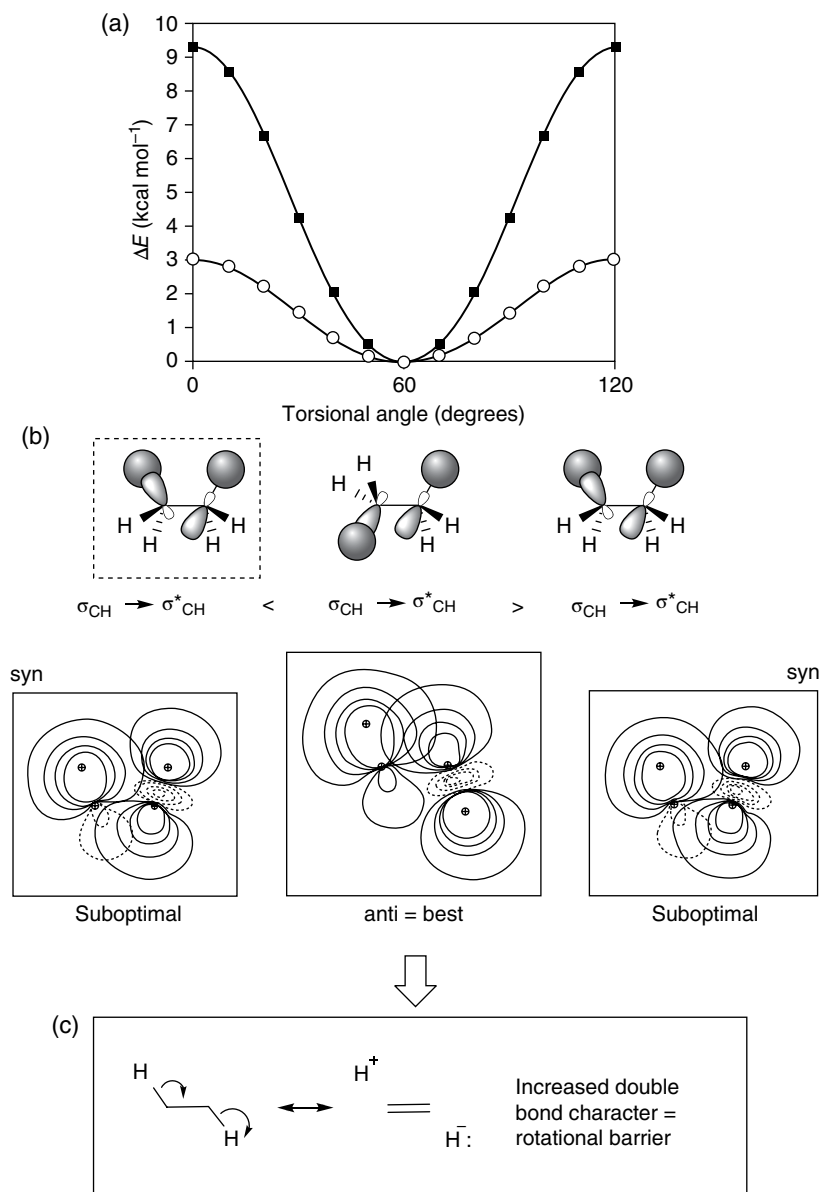


Figure 6.5 (a) Torsional angle dependencies of the energy of real ethane (solid line) and a hypothetical ethane with exchange repulsion absent (dashed line). (Source: Pophristic 2001 (9a). Reproduced with permission of Nature Publishing Group.) (b) Comparison of $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ overlaps in the staggered and eclipsed geometries.¹⁰ (c) Increased double bond character in the staggered geometry.

CH_3CH_3 vs. BH_3NH_3 – isoelectronic cousins with dramatically different hyperconjugation patterns The importance of hyperconjugation in rotational barriers is illustrated by the comparison of ethane and ammonia borane. The two molecules are isoelectronic (CH_3CH_3 vs. BH_3NH_3) and only differ in the position of one internuclear proton. However, the different charge distribution leads to hybridization patterns

that drastically weaken hyperconjugation and decrease the rotational barrier of BH_3NH_3 (2.0 kcal/mol¹³) in comparison to ethane. Since the B-N bond is strongly polarized towards nitrogen, boron uses hybrids with lower s-character than carbon in C_2H_6 , whereas nitrogen uses hybrids with higher s-character than carbon in C_2H_6 .¹⁴

Rehybridization in BH_3NH_3 imposes changes in orbital alignment, orbital shape, and bond length which move the interacting σ/σ^* pair from the favorable π -type overlap. NBO analysis illustrates that the suboptimal orbital overlap weakens the stabilizing hyperconjugative interaction.¹⁴ Similar results were found with the use of an energy decomposition approach – stabilization via the $\sigma_{\text{B-H}} \rightarrow \sigma_{\text{N-H}}^*$ donation is only 50% of that in ethane (~5 vs. ~10 kcal/mol, Figure 6.6).¹⁵ Because hyperconjugation between vicinal orbitals leads to the partial C=C bond character and bond shortening, the decreased importance of this interaction is likely to cause significant elongation of the polar B-N bond of ammonia borane (1.66 Å at B3LYP/6-311++G(d,p) level) relative to the non-polar C-C bond in ethane (1.53 Å).

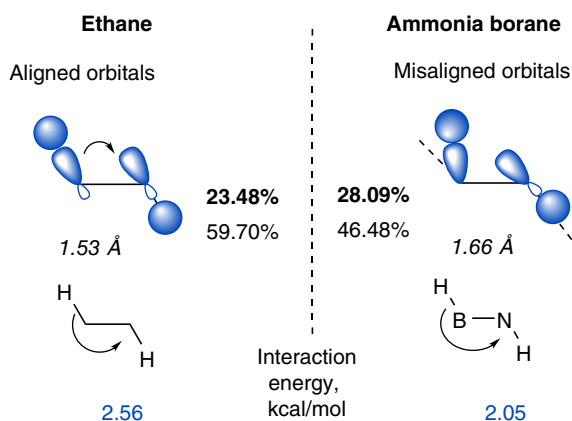


Figure 6.6 Comparison of vicinal hyperconjugation in the staggered conformations of ethane and ammonia borane according to NBO analysis at B3LYP/6-311++G(d,p) level. The $\sigma_{\text{N-H}} \rightarrow \sigma_{\text{B-H}}^*$ interactions are even smaller (<0.5 kcal/mol). The s-character (larger font, bold) and the polarization (smaller font) of C-H and B-H bonds are indicated.

Conformational analysis of alkanes Comparison of the conformational profile of ethane with the conformational profiles of the higher alkanes provides further insights into the competition between sterics and delocalization in these basic structural units of organic chemistry. Interestingly, many conformational effects are transferrable, allowing accurate estimation of energy profiles for rotation around the single C-C bonds in these molecules (Figure 6.7). For example, from the barrier for rotation around the C-C bond in ethane, one can estimate the “penalty” for each eclipsing C-H/C-H interaction as 0.9–1.0 kcal. The slight increase in the rotational barrier in propane (3.4 kcal) provides the energy cost for an additional eclipsing C-H/C-C element (1.3–1.4 kcal). Transferability of such interactions allows one to calculate the rotational barrier about the C1-C2 bond in isobutane (3.8 kcal/mol).

Note that the energy increase is relatively minor. Based on the steep increase in the energy of repulsive interactions (illustrated, for example, by the $1/r^{12}$ repulsive part of Lennard-Jones potential), one would expect that, if C-H/C-Me interaction were dominated by sterics, such penalty would be greater.

Much of butane’s conformational profile can be constructed from the eclipsing energies of ethane and propane. For example, the energy difference between conformations **A** and **B** of butane (Figure 6.8) are $1.0 + 1.4 + 1.4 = 3.8$ kcal, in good agreement with the 3.6 kcal value reported by Allinger.¹⁶

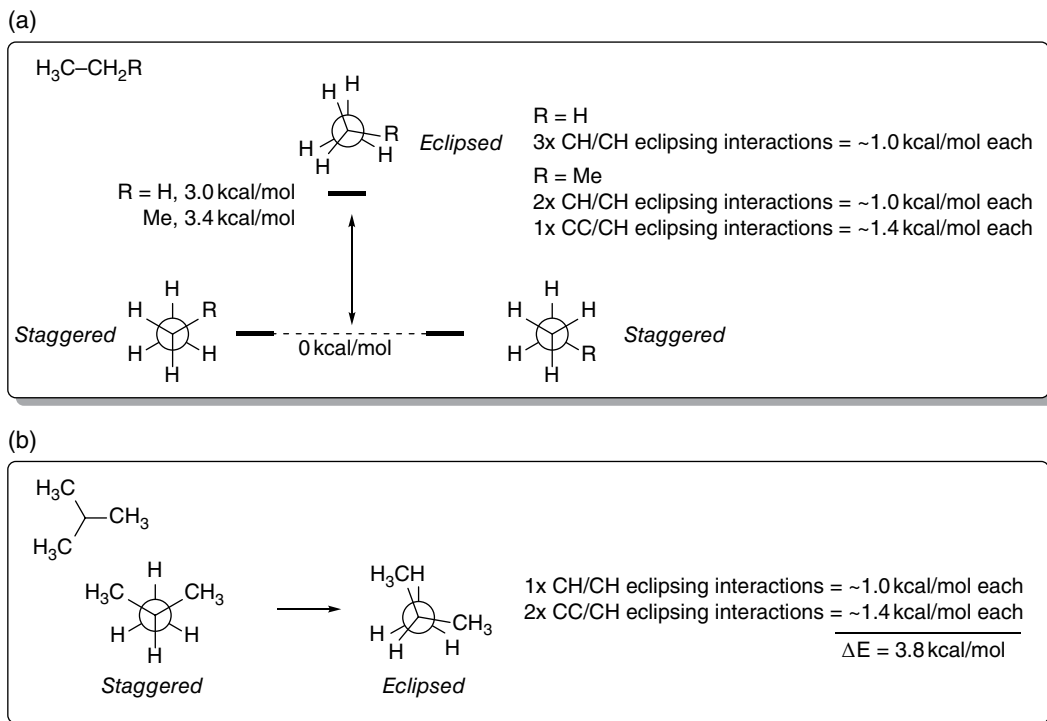


Figure 6.7 (a) Known rotational barriers allow dissection into the magnitude of the energy cost for each eclipsing interaction. (b) This information can be used to reliably predict rotational barriers.

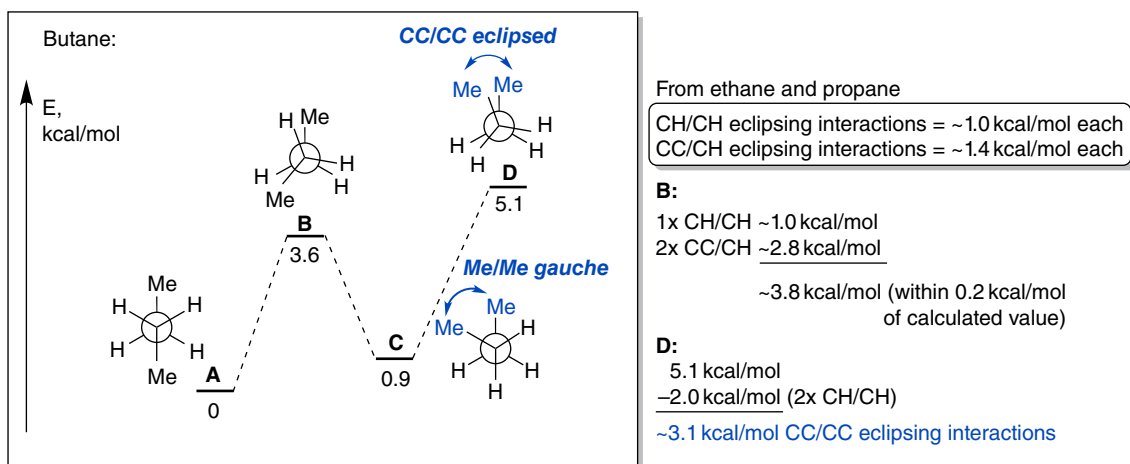


Figure 6.8 Rotational profile of butane gives insights into Me/Me gauche interactions and C-C/C-C eclipsing interactions. (Calculated energy profile from ref. 16.)

In the case of eclipsed conformation **D**, ~3.1 kcal/mol of energy is unaccounted for after subtraction of the two C-H/C-H eclipsing interactions from the overall 5.1 kcal barrier. This difference can be assigned to the remaining new interaction, the C-C/C-C eclipsing interaction. The BLW analysis of Mo and coworkers¹⁷ suggested that steric and hyperconjugative interactions contribute approximately 75% and 25% to the rotational barriers, respectively. According to this theoretical model, hyperconjugative interactions play a secondary role. Instead, the conventional steric repulsion dominates the BLW energy curve and barriers in butane.

The difference between the two staggered butane conformations **A** and **C** is often attributed to the steric interactions between the two Me groups in the gauche conformation **C**. This gauche interaction is relatively small (0.9 kcal) but manifests itself in a variety of systems, some of which we will discuss later. Its magnitude is similar to that of the “eclipsing H/H interactions” but much smaller than the eclipsing Me-Me interaction (3.1 kcal, Figure 6.9), which is most likely dominated by steric factors.

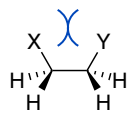
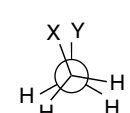
		X	Y	$\Delta E_{\text{interaction}}$, kcal/mol
		H	H	~0.9–1.0
		H	Me	~1.3–1.4
		Me	Me	~3.1

Figure 6.9 Relative magnitudes of destabilizing eclipsing interactions.

Reliance on steric effects as the dominant structural force in alkanes cannot provide a satisfactory explanation of the question why branched alkanes are lower in energy than their linear isomers – see Figure 6.10 (note that accurate calculations of such energies pose a challenge to theory).¹⁸

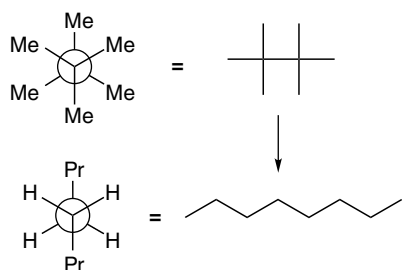
		Method	ΔE , kcal/mol
		MP2	4.6
		Experiment	1.9+/-0.5

Figure 6.10 Greater stability of branched alkanes in comparison to their linear isomers.

When small effects are involved, energy dissections are particularly difficult and are often open to alternative interpretations. However, Cormanich and Freitas calculated the conformational profile of butane without hyperconjugative effects and found a decrease in the energy difference between the anti and gauche conformations of butane. This analysis suggests that the 0.9 kcal/mol anti/gauche difference has a hyperconjugative component.¹⁹ The key difference between the anti and gauche geometries is that they correspond to the two different patterns of neutral hyperconjugation: $\sigma_{\text{CC}} \rightarrow \sigma_{\text{CC}}^* + \sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ (in the anti conformation, interactions involve either C-C or C-H bonds) vs. $\sigma_{\text{CC}} \rightarrow \sigma_{\text{CH}}^* / \sigma_{\text{CH}} \rightarrow \sigma_{\text{CC}}^* + \sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ (in the gauche-conformation, interactions occur also between C-C and C-H bonds). NBO analysis of the key antiperiplanar interactions that change upon transition from **A** to **C** confirms that hyperconjugation is 0.4 kcal stronger for conformer **A**, mostly due to lower energy of interactions where the σ_{CC} orbitals serve as donors (Figure 6.11). In a similar way, the BLW total electron delocalization energy in the gauche form is 0.25 kcal smaller than it is in the anti form.¹⁷

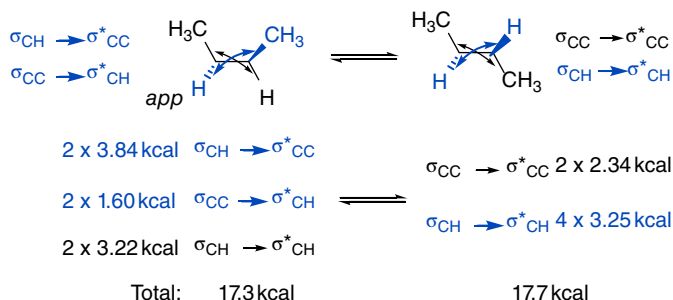


Figure 6.11 Effect of hyperconjugation on the conformational profile of butane. One of the pairs of interacting orbitals is color coded to provide visual assistance.

While various computational methods disagree on the magnitude of the relative roles of sterics and hyperconjugation, the 0.9 kcal/mol penalty for the gauche conformations is a useful conformational observation that can be transferred to larger systems. For example, such interactions in chair cyclohexane moieties illustrate why adamantane and related diamondoid compounds are not completely free of strain.

Furthermore, the $2 \times 0.9 = 1.8$ kcal/mol difference between the axial and equatorial conformations of methylcyclohexane (“the A-value for the Me-group”) can be traced back to the two gauche interactions in the axial conformer (see the following section).

In pentane, the most important new interaction is the 1,3-Me-Me (“double gauche”, “syn-pentane strain”) interaction (estimated as +3.7 kcal, Figure 6.12). Together with the two gauche interactions, it accounts for the 5.1 kcal energy increase for the two gauche conformations relative to the most stable all anti geometry.

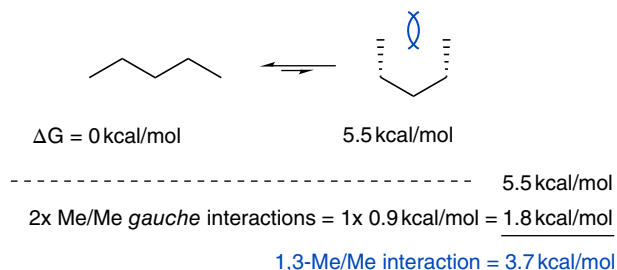


Figure 6.12 Conformational analysis of pentane reveals a destabilizing 1,3-Me/Me interaction (“the syn-pentane strain”).

6.1.2 Axial/equatorial equilibrium in methylcyclohexane

As a result of their well-defined geometries, cyclic systems lend themselves to studies of hyperconjugative interactions. Here, some rotations around single bonds may be impossible, but other geometric changes can still be in play and lead to stereoelectronic consequences. Of particular importance are the differences in the free energies of axial and equatorial substituents in monosubstituted cyclohexane rings (“the A-values”). These values are commonly used in undergraduate organic chemistry courses to compare the steric size of different substituents. The axial conformer is considered to be destabilized by two repulsive 1,3-diaxial interactions (Figure 6.13). The latter can be simply considered as a combination of two gauche interactions between the substituent and the C-C bonds of the cycle. For R=Me, these interactions are analogous to the gauche interactions in butane discussed in the previous section with the total energy penalty of $2 \times 0.9 = 1.8$ kcal/mol (A-value of the Me group).

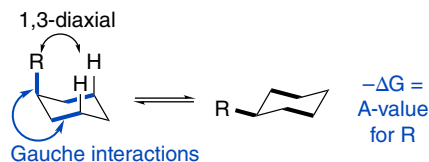


Figure 6.13 Traditional explanations of equatorial preference of alkyl-substituted cyclohexanes based on the 1,3-diaxial repulsive interactions or the presence of gauche interactions.

Methylcyclohexane is the cornerstone of the conformational analysis of cyclohexane derivatives. The conformational dynamics of this molecule can be observed directly by low-temperature ^{13}C NMR.²⁰ Although the textbook explanation of the lower stability of the axial conformer is based on the steric repulsion between the methyl group and a syn-axial hydrogen (“the 1,3-diaxial interactions”), the experimental enthalpies for Me, Et and *i*-Pr slightly *decrease* with the increased size of the alkyl group (Figure 6.14). Furthermore, the structural features of optimized alkyl cyclohexane structures by Wiberg et al. suggest that axial substituents affect only local geometry, and 1,3-diaxial interactions between a methyl, ethyl, or isopropyl group and a synaxial hydrogen have no apparent structural importance.²¹

1,3-diaxial repulsion?

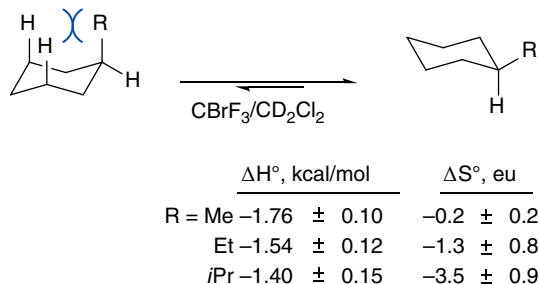


Figure 6.14 Decreasing $\Delta\Delta H^\circ_{\text{eq-ax}}$ with increased steric bulk in alkyl cyclohexanes.

It has been shown that the axial C-H bonds are longer and weaker than the equatorial bonds in cyclohexane because hyperconjugative $\sigma_{\text{CHax}} \rightarrow \sigma_{\text{CHax}}^*$ interactions are stronger than the analogous interactions that include the equatorial C-H bonds and C-C bonds of the ring (Figure 6.15).²² Subsequently, the analogous subtle differences in the donor and acceptor ability of the C-H and C-C bonds were used as the rationale for the lower energy of the equatorial conformer of methyl cyclohexane²³ and extended later to its 4-oxa, 4-aza, 4-thia analogues, and other substituted cyclohexanes²⁴ and cyclohexenes.²⁵

Also interesting is the following combination of two conformational effects. The Ph group in phenylcyclohexane has a larger A-value (2.9) than the Me group in methylcyclohexane (1.8). However, in an apparent paradox, the Ph group is forced into the axial position in 1-methyl-1-phenylcyclohexane (Figure 6.16).²⁶ These observations further illustrate that simple steric models based on effective volume of substituents cannot explain the full diversity of conformational profiles of substituted cyclohexanes.

In another illustrative example, Juaristi and coworkers had shown that, at lower temperatures, the conformer with the larger benzyl substituent at the axial position is favored, and the equatorial preference for this group at ambient temperature is due to the entropy term (Figure 6.17).²⁷ Paradoxically (for the steric model), enthalpy favors the conformation where the larger benzyl substituent is axial.

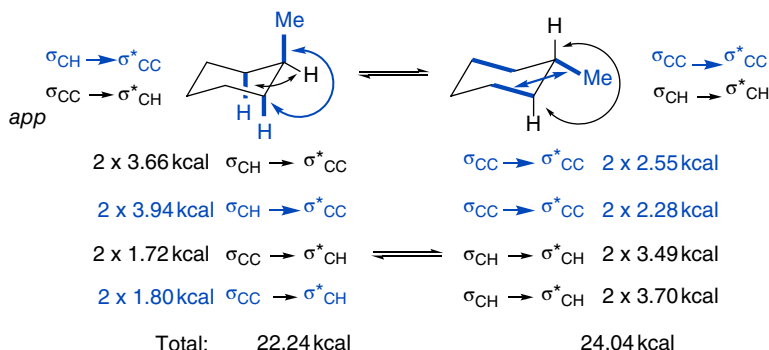


Figure 6.15 NBO analysis of hyperconjugative interactions of the main hyperconjugative interactions that influence the conformational equilibrium of methylcyclohexane.²³

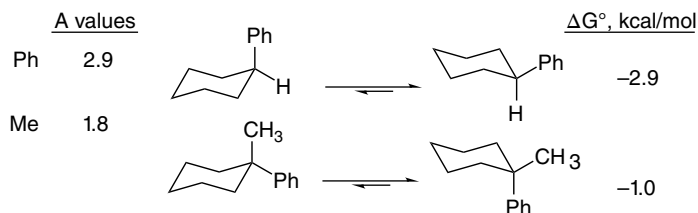


Figure 6.16 The larger A value for phenylcyclohexane than for methylcyclohexane does not translate into the equatorial preference for the phenyl group in 1-methyl-1-phenylcyclohexane. Calculated at the QCISD/6-311G(2df,p) level of theory.²⁶

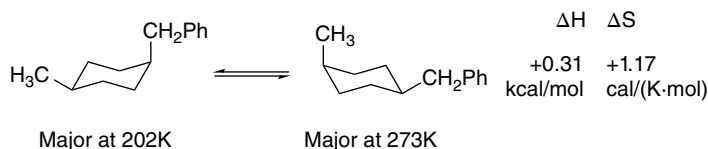


Figure 6.17 Equatorial preference for the larger substituent may be determined by entropy.

Heteroatoms: lone pairs and polar bonds The stereoelectronic component of conformational effects in the previous section was largely based on the relatively subtle differences between the donor and acceptor abilities of C-H and C-C bonds. Heteroatoms introduce a new array of stereoelectronic effects associated with the presence of polar bonds and lone pairs. These effects can be significantly stronger than the above C-H and C-C interactions, especially when lone pairs (good donors) and σ^*_{CX} (good acceptors) can directly interact with each other.

Such effects manifest themselves at the most fundamental levels. For example, strong $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ interactions explain the seemingly anomalous trends in the C-F BDEs of alkyl fluorides ($\text{Me-F} < \text{Et-F} < \text{i-Pr-F} < \text{t-Bu-F}$, Figure 6.18). The greater C-F bond strength in t-butyl fluoride is at odds with the expectations based on the relative stability of alkyl radicals and the BDE trends for the analogous C-H bonds.²⁸ Because $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugative stabilization of alkyl fluorides is greater than the analogous interactions of radical the center with the C-H bonds of alkyl substituents, additional substitution stabilizes alkyl fluorides more than alkyl radicals, thus increasing the BDEs. These observations can be expanded to differentiate

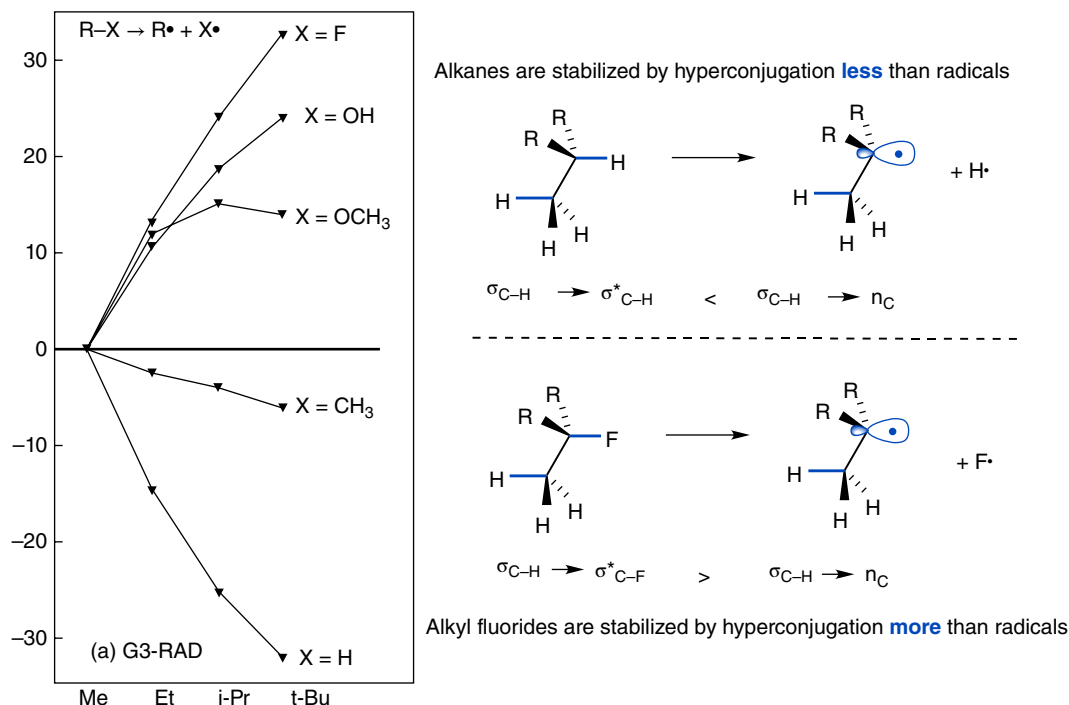


Figure 6.18 Contrasting effects of alkyl substitution on BDEs for C-H, C-C, C-O, and C-F bonds. (Source: Izgorodina 2005 (28). Reproduced with permissions of American Chemical Society.) The BDEs increase in the more substituted alkyl fluorides, alcohols, and ethers but decrease in respective alkanes.

σ -donors from σ -acceptors. For example, albeit alkyl groups decrease BDEs for non-polar C-C bonds, they increase BDEs for polar C-O bonds.

Another way to evaluate the stabilizing effect of C-H/C-F hyperconjugation is based on the following isodesmic equations (Figure 6.19).²⁹ Addition of each vicinal methyl group next to a C-F bond leads to ~3–6 kcal/mol stabilization. As expected, each additional donor has a slightly weaker effect, and transfer of fluorine to a double bond is also stabilizing as a result of the C-H/C-F and $n_F \rightarrow \pi_{C=C}^*$ interactions.

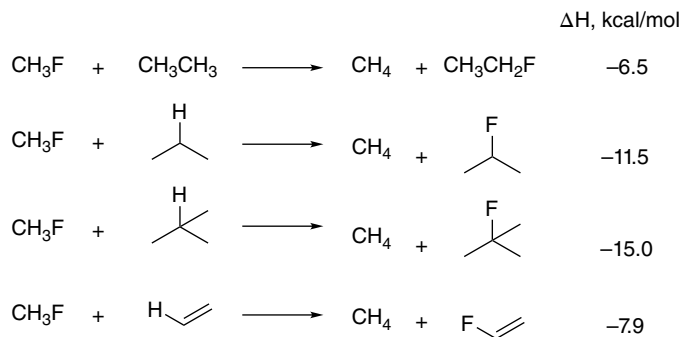


Figure 6.19 Stabilizing consequences of fluorine introduction to hydrocarbons.

The introduction of heteroatoms provides new conceptual tools for testing the relative importance of delocalization. The presence of lone pairs strongly impacts the interplay between sterics and hyperconjugation. For example, the ~ 1 kcal cost of CH/CH eclipsing interactions obtained from the ~ 3 kcal rotational barrier in ethane agrees well with the rotational barriers in methylamine and methanol (1.9 and 1.1 kcal, respectively, Figure 6.20), corresponding to the decreased number of eclipsed CH/XH interactions (two and one, respectively, in the eclipsed conformations). However, when one of the methyl hydrogens in MeOH is replaced by fluorine, the rotational barrier increases to 3.7 kcal/mol, even though the value of CH/CF eclipsing contacts in 1,1,1-trifluoroethane is only 1 kcal (not very different from CH/CH in ethane).³⁰

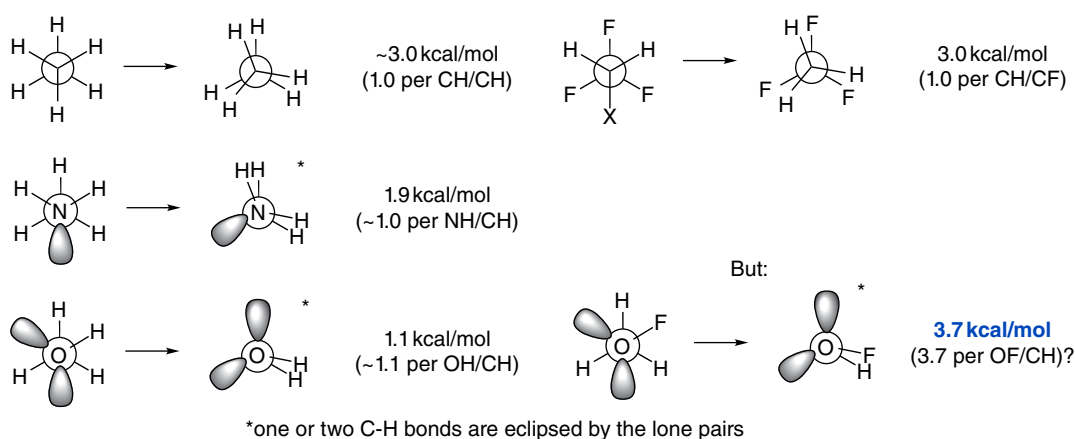


Figure 6.20 Breakdown of the simple model that assigns specific energy values to eclipsing contacts.

Houk and Wu attributed this apparent paradox to hyperconjugative effects similar to those involved in the gauche effect discussed in the following section. They suggested that the rotational barrier around the C–O bond in methyl hypofluorite (MeOF, 3.7 kcal/mol) or methyl hypochlorite (MeOCl, 3.5 kcal/mol) increases relative to the corresponding rotational barrier in methanol (1.1 kcal/mol) due to two factors: a) increased importance of $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{O-X}}^*$ hyperconjugation for X = F, Cl in comparison to X = H, b) the interaction between $\pi_{\text{O-X}}$ -orbital derived from the lone pairs of O and X with π -type CH_3 group orbitals derived from the $\sigma_{\text{C-H}}^*$. The latter stereoelectronic contribution, analogous to hyperconjugation in propene described in the following section, involves π -orbitals made of the lone pairs of the two heteroatoms, O and X, and the coplanar C–H bonds. The stereoelectronic effects are supported by the geometric differences between the two conformers (Figure 6.21).³⁰

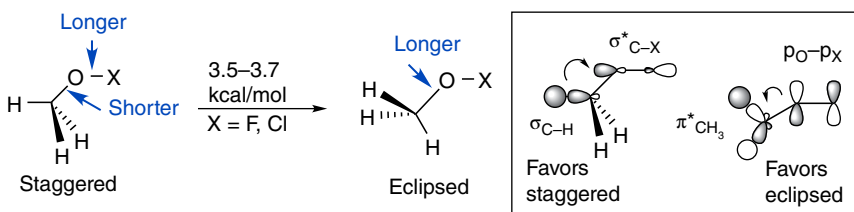


Figure 6.21 Orbital interactions and geometric parameters for staggered and eclipsed conformations of heteroatom derivatives of methanol.

6.1.3 The gauche effect

Another effect that contradicts expectations based solely on steric arguments is the gauche effect, i.e. the preference for the gauche conformation in X-C-C-Y systems (1,2-disubstituted ethanes) with two acceptor substituents X and Y.³¹ 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 the anomeric effect (see Section 6.6.4) dominated by $n \rightarrow \sigma^*$ interactions (Figure 6.22). The gauche effect in disubstituted ethanes should also be distinguished from the gauche interaction in butane described in the previous sections (Figure 6.22).

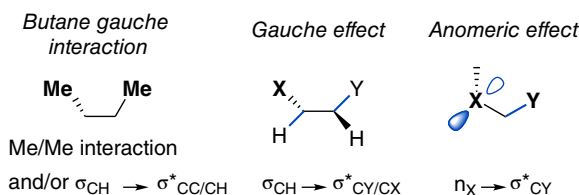


Figure 6.22 Three conformational effects that are sometimes referred to as “gauche effect” in the literature. This section concentrates on the middle system.

Although X and Y are usually fluorine or oxygen, the choice of the second substituent Y is quite broad in fluoroethanes of general formula $\text{FCH}_2\text{CH}_2\text{Y}$, where $\text{Y} = \text{F}, \text{NO}_2, \text{OCOH}, \text{NHCOH}, \text{N}_3, \text{NCO}$.³² The gauche effect has been studied both experimentally^{33,34} and computationally (Figure 6.23).^{31,32,35} The dominating role of the antiperiplanar hyperconjugative $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-X}}$ and $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-Y}}$ interactions in the gauche effect in 1,2-difluoroethane has been shown using NBO analysis.³⁵ EDA-based estimates suggest that both delocalization and electrostatic interactions contribute to stabilizing the gauche conformer.³⁶ The magnitude of this preference is very sensitive to solvent effects, due to the large difference in polarity of the two conformers. Electrostatics is an important contributor to the conformational effect because the gauche conformers generally

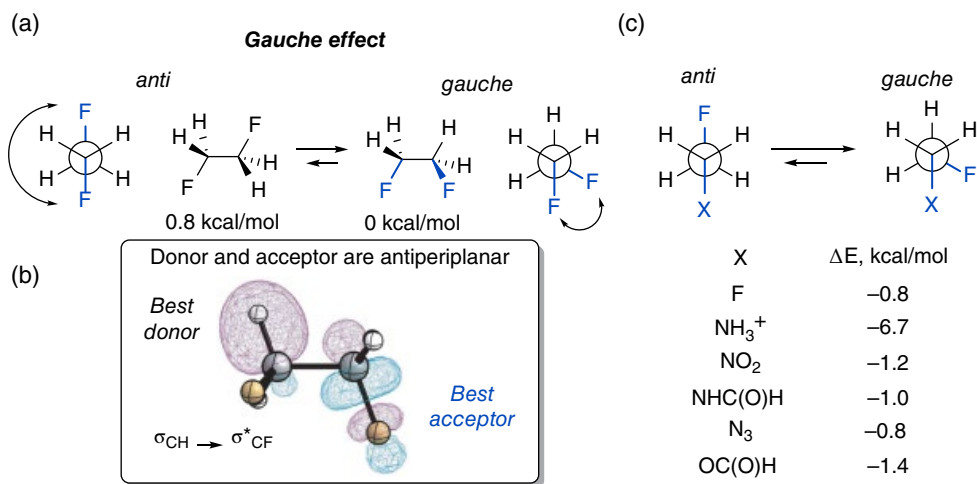


Figure 6.23 (a) The gauche effect for 1,2-difluoroethane. (b) Anti and cis overlaps of $\sigma_{\text{C-H}}$ and $\sigma^*_{\text{C-F}}$ bonds, show the greater overlap in the anti geometry. (c) Expanded list of substituents that prefer gauche conformation relative to a β -C-F bond (gas phase energies at B3LYP/6-311+G(d,p) level).

have a significantly larger dipole moment and are more stabilized in polar solvents. Electrostatic contributions are considered to be the dominant cause of the gauche effect in the charged β -ammonium system (vide infra).

The importance of $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$ interactions is reflected in the C-C bond shortening and the concomitant C-C BDE increase upon progressive fluorination of one of the ethane carbons (Table 6.1).³⁷

Table 6.1 Carbon-carbon bond lengths and strengths in fluoroethanes.

Compound	C-C distance, Å	BDE(C-C), kcal/mol
$\text{CH}_3\text{-CH}_3$	1.532	90.4
$\text{CH}_3\text{-CH}_2\text{F}$	1.502	91.2
$\text{CH}_3\text{-CHF}_2$	1.498	95.6
$\text{CH}_3\text{-CF}_3$	1.494	101.2

Another illustrative example of the gauche effect is provided by trans-1,2 difluorocyclohexane (Figure 6.24a). In this case, stereoelectronic stabilization for the gauche conformation is smaller than in 1,2-difluoroethane since it comes from the $\sigma_{\text{C-C}} \rightarrow \sigma_{\text{C-F}}^*$ interactions that are less effective than $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$ interactions in 1,2-difluoroethane. As the result, the system is very sensitive to substituent effects and switches preferred conformation from an axial/axial (anti) to the equatorial/equatorial (gauche) conformer only in polar solvents³⁸ where electrostatic/dipole factors that favor axial conformer are diminished allowing the gauche (eq/eq) conformer to dominate.

Similarly, the axial preference for axial fluorine atoms in 3-fluoropiperidinium and 3-fluoro-N,N-dimethylpiperidinium has a strong, likely dominating, electrostatic component (Figure 6.24b). Snyder, Lankin, and

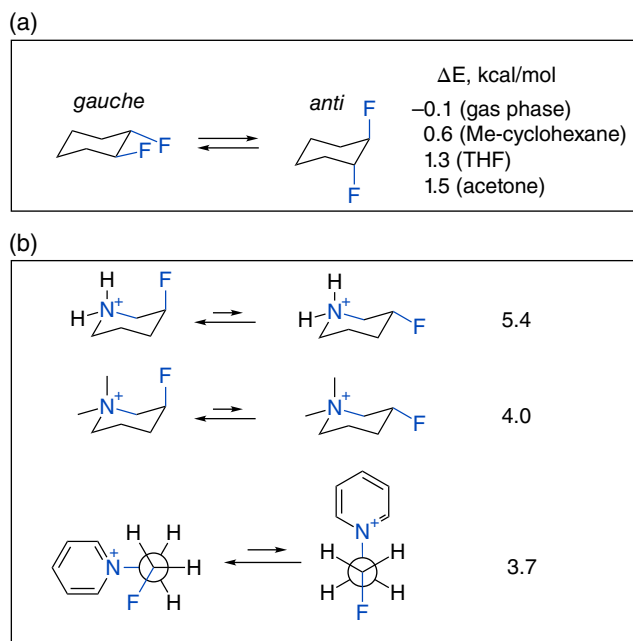


Figure 6.24 (a) Solvent effects on the gauche/anti equilibrium in 1,2-difluorocyclohexane. (b) The strong gauche preference in fluoro compounds with positively charged β -substituents.

coworkers established that a ~4.0–5.4 kcal/mol preference between the gas-phase anti and gauche conformations persists in these systems.³⁹ The strong gauche preference remains when the possibility of intramolecular H-bonding is eliminated in β -fluoro- and β -hydroxy-N-ethylpyridinium cations.⁴⁰

For $X = \text{Cl, Br, I}$, the anti conformations are more stable. The gauche preference weakens in these systems because bonds to heavier halogens are not only good acceptors but also relatively good donors (better than C-F bonds). As a consequence, the $\sigma_{\text{C-Y}} \rightarrow \sigma_{\text{C-X}}^*$ interactions become sufficiently large to compete with the $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-X}}^*$ interactions (Figure 6.25). Furthermore, additional stabilization for the anti conformations is provided by homoanomeric $n_{\text{Cl}} \rightarrow \sigma_{\text{C-F}}^*$ interactions (vide infra). Hyperconjugative interactions in 1,1,1-trihaloethanes (CH_3CX_3 , $X = \text{F, Cl, and Br}$) were evaluated using the BLW method.⁴¹ The overall hyperconjugative interactions in 1,1,1-trihaloethanes is dominated by $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CX}}^*$ with minor contribution from $\sigma_{\text{CX}} \rightarrow \sigma_{\text{CH}}^*$. The BLW estimate will range from 9.6 to 7.3 kcal/mol in the staggered structures and decreases in the order $\text{Br} > \text{Cl} > \text{F}$. Out of 81 conformers considered for 3-fluoro-1,2-diX-propane, the major four conformers, accounting for more than 70% of the conformational space in the gas phase and in solution, were found to exhibit gauche relationships among the three substituents in a computational study of Freitas and coworkers.⁴²

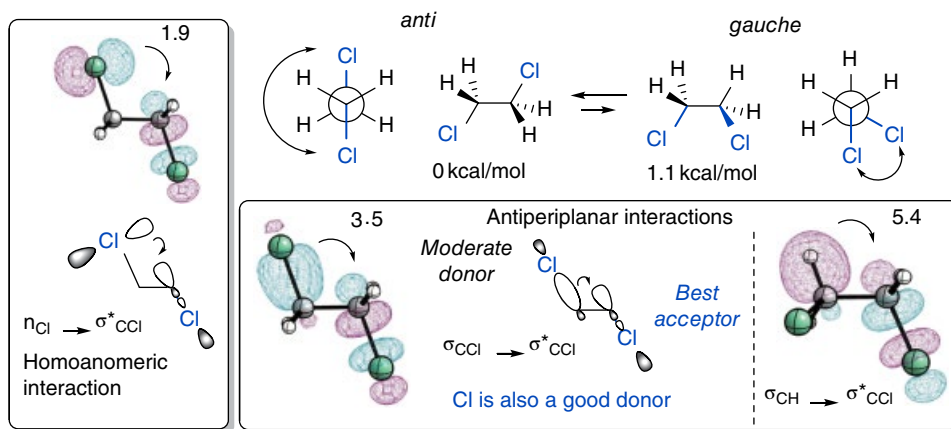


Figure 6.25 Gauche effect disappears in heavier halogens, as donor ability of C-Hal bonds increases. Additional assistance is provided by homoanomeric $n_{\text{Cl}} \rightarrow \sigma_{\text{C-F}}^*$ interactions. Geometries are optimized at G4 level, NBO analysis at B3LYP/6-311++G(d,p) level.

On the other hand, the conformations of 2,3-difluorobutane are controlled by a complex interplay of several effects, which are of similar magnitude but often of opposite sign. In the threo-form, only the AG(T) conformation (the conformation names are defined in Figure 6.26) combines the two favorable features: methyl substituents are antiperiplanar, and the fluorine atoms are gauche. In contrast, destabilizing methyl gauche interactions in the two GG(E) rotamers in the erythro form are expected to be offset by a fluorine gauche arrangement. However, DFT (M06-2X) analysis found unexpected deviations in conformational energies and populations. It was suggested that vicinal C-F bonds in butane do not ensure the dominance of the linear conformation.⁴³ Although these results cannot be readily rationalized by chemical intuition based on hyperconjugative interactions, through-space attractive interactions between C-H and C-F bonds at the gauche groups can contribute to the observed differences. In good agreement with the calculated solvents effects, such interactions are known to be weaker in polar solvents.⁴⁴ One should note that the conformational profile of 2,3-difluorobutane may not be directly transferrable to the larger systems where longer hydrocarbon chains should impose larger steric effects and may restore the expected conformational preferences.

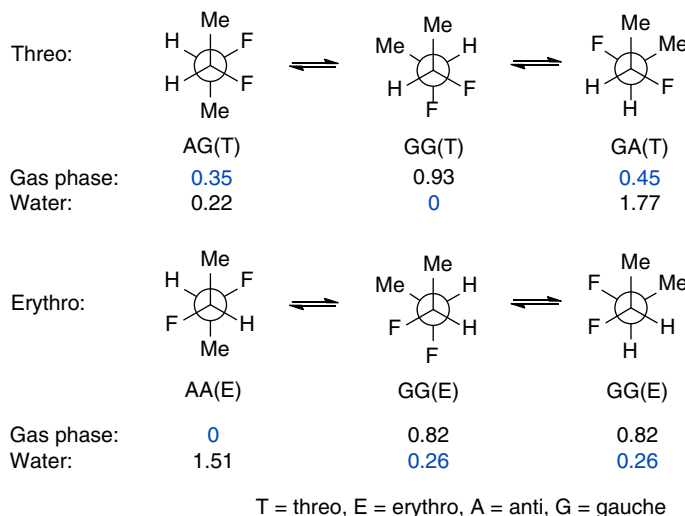


Figure 6.26 Geometries and relative energies of conformers of threo- and erythro-2,3-difluorobutane in vacuo and in water. The lower energy conformer(s) for each of the diastereomers is shown in blue.

6.2 σ/π -Interactions

Both carbonyl compounds and alkenes are well-known to be stabilized by hyperconjugative interactions with adjacent C-H bonds. In particular, the greater thermodynamic stability of more substituted alkenes, illustrated in Figure 6.27, serves as the basis of Zaitsev's rule (often re-transliterated with German spelling as "Saytzeff's" rule) in eliminations. The formation of more substituted alkenes is more favored because of their hyperconjugative stabilization.

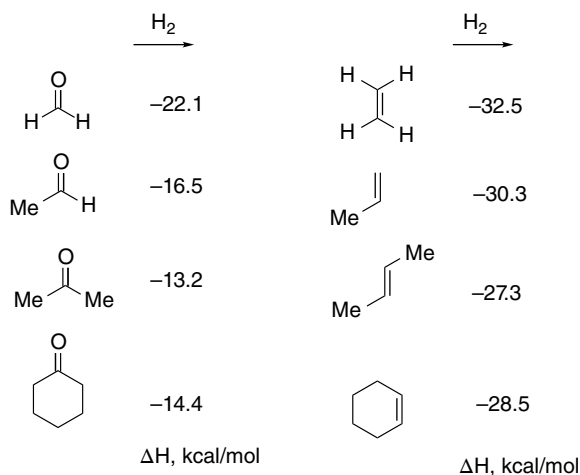


Figure 6.27 Experimental heats of hydrogenation for selected carbonyl compounds and alkenes.⁴⁵

BLW estimates by Hiberty and coworkers suggest that for both C_4H_8 and C_5H_{10} alkenes, hyperconjugation effects stabilize the most substituted product by about 6 kcal/mol.⁴⁶ NBO analysis of such interactions will be discussed below along with the discussion of the role of hyperconjugative effects in conformational behavior of alkenes.

6.2.1 “Eclipsed” and “staggered” conformations of alkenes – stereoelectronic misnomers

The importance of neutral hyperconjugation in propene is illustrated by its conformational profile. The stable propene conformation is called “eclipsed” because one methyl C-H bond eclipses the vicinal σ_{C-C} bond. The “staggered” conformation, in which one methyl C-H bond eclipses the adjacent vinyl C-H bond, is less stable by about 2 kcal/mol (Figure 6.29).⁴⁷ These names are misnomers because the “eclipsed” conformation of propene is stereoelectronically analogous to the staggered conformation of ethane and vice versa. A better name for the higher energy conformation is “bisected” (Figure 6.28).⁴⁸

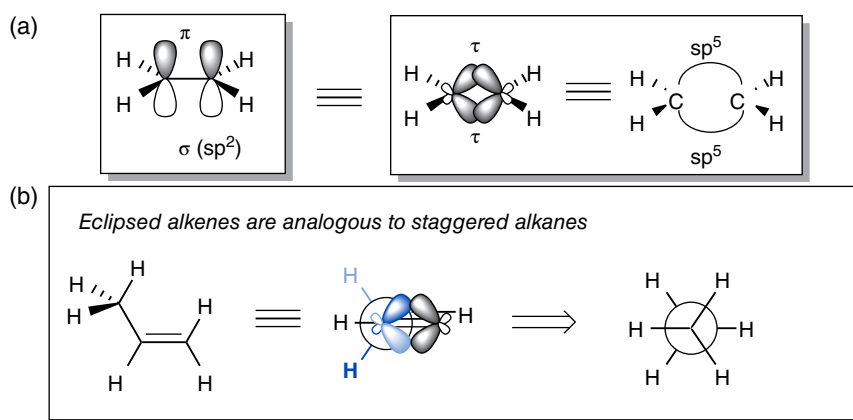


Figure 6.28 (a) Mathematically equivalent description of alkene double bonds as a σ/π double bond or two τ -bonds. (b) Antiperiplanar C-H/C-C bonds in the eclipsed (misnomer) alkene and analogous staggered conformation of alkanes.

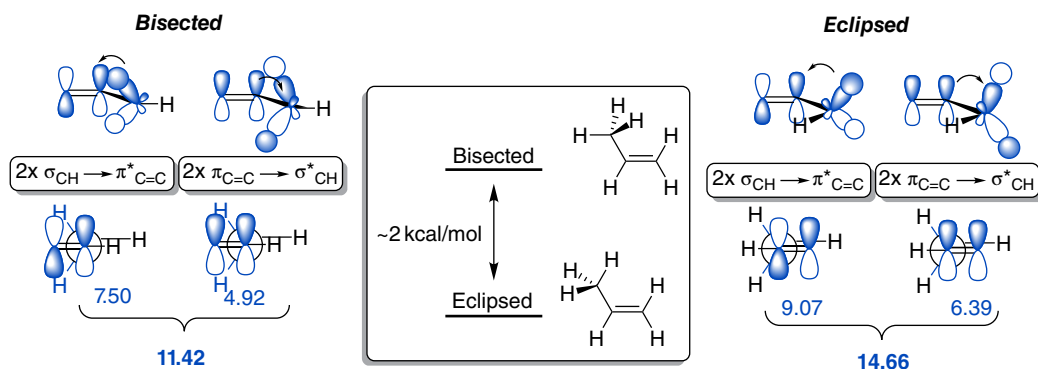


Figure 6.29 The energy difference between eclipsed and bisected conformers of propene. The sp^2/p description of double bonds is shown.

We will see that the preference for eclipsed conformation is generally observed not only in alkenes but also carbonyl compounds. This preference is easily understood with the help of a less common description of the double bond.⁴⁸ Similar to the case of two sets of lone pairs (in oxygen, sulfur, and selenium) where one can either take on identical sp^3 hybridization or place one lone pair in a p-orbital and the other in a hybridized orbital, there are two alternative descriptions of bonding in unsaturated systems. The more generally accepted Hückel description of a σ/π -framework⁴⁹ and the Pauling description of two bent τ -bonds are depicted in Figure 6.28. In the eclipsed conformation of propene, two C-H bonds are antiperiplanar to the bent τ -bonds, accounting for the stability relative to the staggered conformation.

According to NBO analysis, hyperconjugative interactions are the main reason for the greater stability of the eclipsed structure of propene (Figure 6.29).⁵⁰ The most important hyperconjugative interactions observed between the methyl and vinyl groups are divided into three components: the $\sigma_{\text{CH}} \rightarrow \pi_{\text{C}=\text{C}}^*$ interaction, the $\pi_{\text{C}=\text{C}} \rightarrow \sigma_{\text{CH}}^*$ interaction, and the vicinal interaction between the in-plane $\sigma_{\text{C-H}}$ orbitals of the methyl group and the σ^* -orbital of the antiperiplanar vinyl C-H bond.

Even the two spatially close Me groups of *cis*-2-butene prefer doubly eclipsed conformation despite the relatively close H...H contact (Figure 6.30).⁵¹

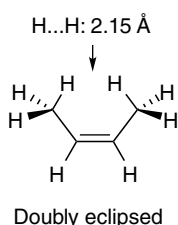


Figure 6.30 The doubly eclipsed conformation is preferred in *cis*-2-butene despite the close H...H contact.

The relative importance of different eclipsed conformations in substituted propenes can be controlled stereoelectronically by variations in the donor and acceptor properties of allylic C-X bonds and the alkene (Figure 6.31). For example, the difference between the two conformations of allyl fluoride is small (the ~ 0.2 – 0.8 kcal/mol gas phase preference for the conformation with the C-F eclipsed bond). This is an apparent violation of the main stereoelectronic rule (the best acceptor, $\sigma_{\text{C-F}}^*$ is orthogonal to the best donor $\pi_{\text{C}=\text{C}}$ in this conformation). Attractive H...F interaction⁴⁴ is a possible reason for this seeming anomaly. If an electron acceptor (nitro group) is introduced trans to the CH_2F moiety, the preference for keeping C-F bond orthogonal to the π -system increases (from 0.7 kcal for $\text{Y}=\text{H}$ to 2.0 kcal for $\text{Y}=\text{NO}_2$ at B3P86/6–311G(3d,2p) level). If a donor is introduced ($\text{Y}=\text{OH}$), the conformational preference is reversed – the C-F bond in the more stable conformer aligns with the π -system (-1.5 kcal).⁵²

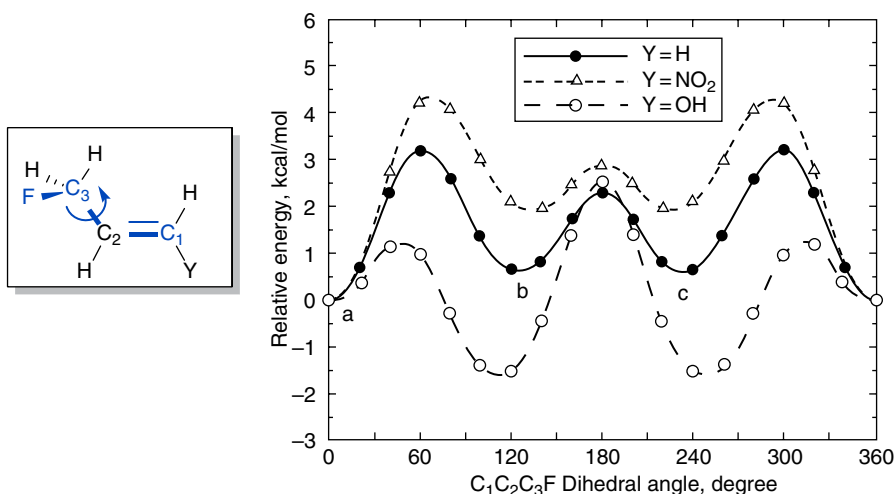


Figure 6.31 The relative importance of different eclipsed conformations in substituted allyl fluorides. (Source: Qiu 2011 (52). Reproduced with permission of John Wiley and sons.)

The authors analyzed the complexity of stereoelectronic effects in this system using NBO analysis of all vicinal interactions involved in electronic communication between the vinyl moiety and the substituted allyl group. The total hyperconjugative energies closely follow the overall conformational profiles.

In alkyl substituted systems,⁵³ such as 1-butene, and 4,4-dimethyl-1-pentene, where several eclipsed conformations are also possible, the preference develops for the hydrogen to eclipse the alkene σ_{C-C} bond to avoid unfavorable through-space interaction known as 1,3-allylic strain ($A^{1,3}$, Figure 6.32).⁵⁴ 1,3-Allylic interaction between a hydrogen atom and a vicinal methyl group does not impose a large penalty – both eclipsed conformers are present in nearly 1:1 ratio.⁵⁵ Steric bulk has to be simultaneously increased at the *terminal* end of the double bond as well. For example, when two jousting substituents (e.g. the two Me groups) are introduced, the $A^{1,3}$ effect becomes sufficiently large to control fully the conformational landscape. This requirement is satisfied in 4-methyl-2-pentene where the hydrogen eclipsed conformation becomes favored over the methyl eclipsed conformation (by >4 kcal/mol).⁵³

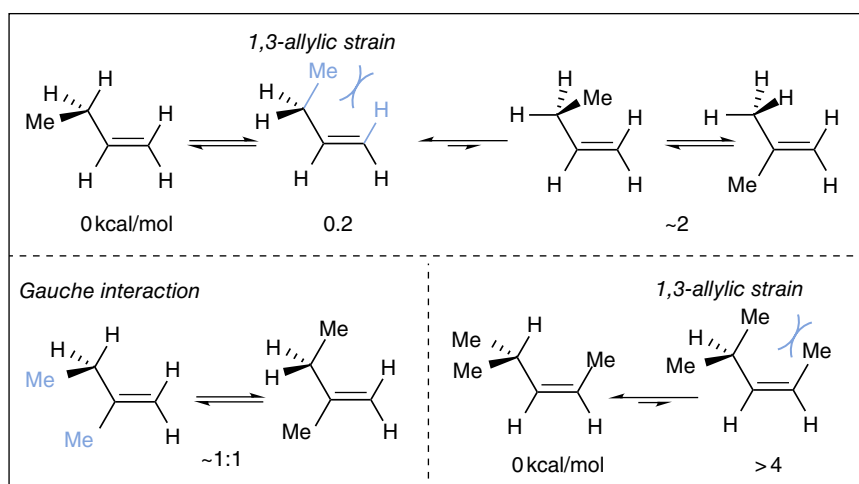


Figure 6.32 Balance between stereoelectronics and sterics in substituted-alkenes.

Conformational constraints imposed by 1,3-allylic ($A^{1,3}$) strain can provide practical advantages. For example, substituents at an asymmetric allylic carbon can adopt a well-defined conformation that creates conformationally locked chiral space capable of remarkable transfer of chirality. Consequently, high stereoselectivity can be attained in many reactions (Figure 6.33), including pericyclic reactions, cyclizations, cycloadditions, etc. in properly substituted allyl, carbonyl, and benzylic systems.⁵³

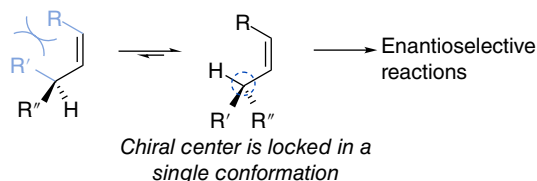


Figure 6.33 1,3-Allylic strain, in combination with stereoelectronic preferences, can be used for the design of stereoselective reactions of allylic systems.

The interplay between hyperconjugation and conjugation plays an important role in structures of neutral nonplanar polyenes.⁵⁶ Hyperconjugation also contributes to the greater stability of internal alkenes versus their terminal isomers (Figure 6.34).⁵⁷ It also partially masks the stabilizing effect of conjugation if it is evaluated by the Kistiakowsky approach (vide infra).

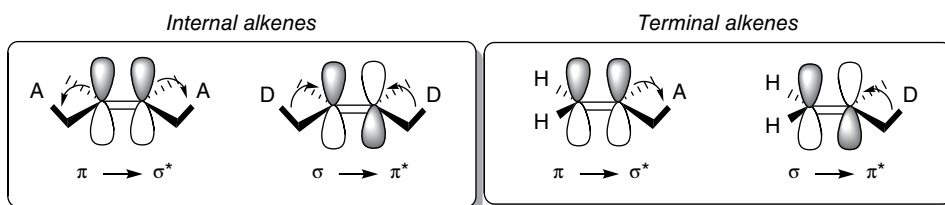


Figure 6.34 Additional hyperconjugative interactions account for the greater stability of internal alkenes relative to terminal alkenes.

The “benzylic anomeric effect” was suggested to explain the preferred perpendicular orientation of benzylic C-X bonds with respect to the plane of the benzene ring ($X = \text{S}(\text{O})\text{Me}$, SO_2Me , SH , SMe , Cl) in ArCH_2X compounds.⁵⁸ Except for $X = \text{F}$, these compounds have a low energy conformation in which the C-X bond is aligned with the benzene π -system (Figure 6.35). The magnitude of this effect is a function of X : $\text{S}(\text{O})\text{Me}$, $\text{SO}_2\text{Me} > \text{Cl} > \text{SH}$, $\text{SMe} > \text{F}$. The unusual conformation of $X = \text{F}$ stems from an electrostatic attraction between the heteroatom and a syn-periplanar ortho-hydrogen. For $X = \text{Cl}$, $\pi \rightarrow \sigma^*_{\text{C-Cl}}$ interaction was suggested to play a dominant role. For $X = \text{SH}$, the interaction between C-X bond and the aromatic π -system is not unidirectional and both $\sigma_{\text{C-S}} \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*_{\text{C-S}}$ interactions were implicated as the possible sources for the observed conformational preference.

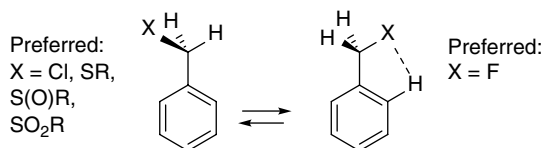
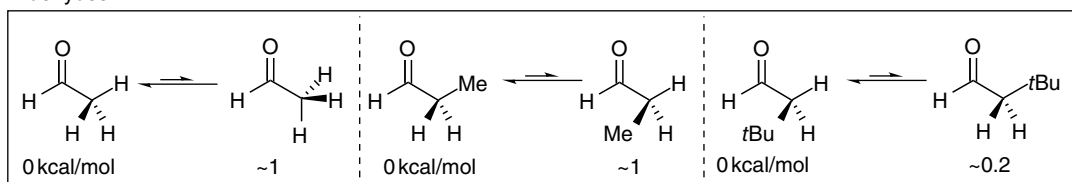


Figure 6.35 The interplay of hyperconjugative and electrostatic interactions determines orientation of benzylic C-X bonds relative to the adjacent aromatic system.

6.2.2 Carbonyls

Conformation preferences in carbonyl compounds were suggested to share their stereoelectronic origin with the earlier discussed hyperconjugation in alkenes.⁵⁹ The interaction is less balanced and more unidirectional: the $\sigma_{\text{CH}} \rightarrow \pi^*_{\text{C=O}}$ interactions become more important in carbonyls, as the $\pi^*_{\text{C=O}}$ acts as a better acceptor due to polarization and the higher electronegativity of oxygen. It has been found that the eclipsed conformation is favored over the bisected in straight chain aldehydes and ketones.⁶⁰ Contrary to the expectations based on steric reasoning, linear alkyl groups prefer to eclipse the carbonyl. The conformational preference can be traced back to the slightly higher donor ability of σ_{CH} bonds over that of σ_{CC} bonds in the $\sigma \rightarrow \pi^*$ interactions. The doubly methyl-eclipsed conformation is the most stable rotamer of 3-pentanone. For the larger alkyl groups (i.e. *t*-butyl), the preference is for the hydrogen group to eclipse the carbonyl (Figure 6.36).

Aldehydes



Ketones

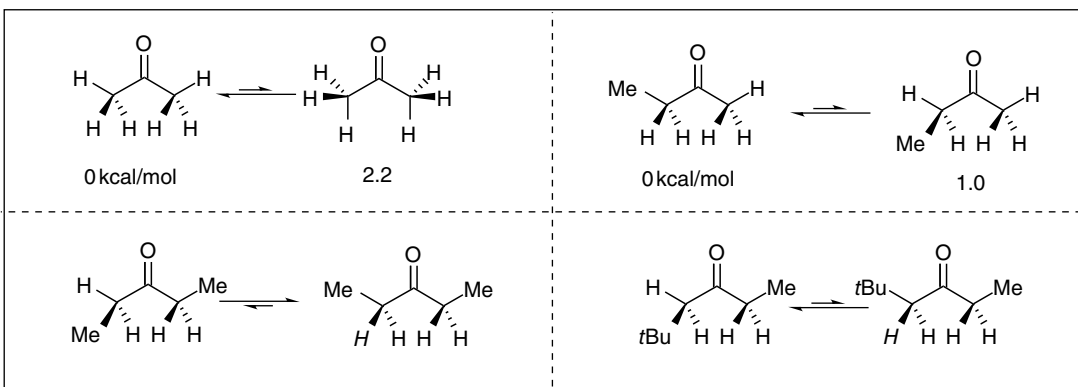


Figure 6.36 Stereoelectronic preference for the eclipsed conformation in carbonyl compounds is analogous to the preference in alkenes.

Below, we illustrate the application of NBO analysis for dissection of hyperconjugative interactions in this important class of organic molecules. Interactions of C-H bonds with $\pi_{\text{C=O}}$ increase when C-H bonds are anti to carbonyl (i.e. in the eclipsed conformation). The respective combined NBO energies for the donation to and from the carbonyl increase from 13.2 vs. 14.9 kcal/mol. One can stop here as we did in the analysis of alkene conformations, because this answer does capture the most important change in the magnitude of delocalization. However, it is instructive to take a moment and examine the vicinal effects in greater detail, approaching closer to the full complexity of this system and getting a deeper insight into the interplay between multiple delocalizing interactions of a different nature (Figure 6.37).⁶¹

The “2nd level” of interactions that are different in the two conformation includes the vicinal interactions between anti- and syn-periplanar σ -bonds. Changes in the individual interactions are quite large. For example, the 0.9 kcal/mol interaction of the in-plane C-H bond with the $\sigma^*\text{C-O}$ orbital increases to 4.8 kcal due to the change from syn- to antiperiplanar arrangement between these orbitals. However, the energy of $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-H}}$ interactions between the two vicinal in-plane C-H bonds changes in the opposite direction and compensates for the difference in C-H/C-O interactions.

The 3rd level of interactions involves the imperfectly aligned *syn*- and *anticlinal* vicinal σ -bonds. Here, the effect of $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-H}}$ interactions favors the bisected conformation where these orbitals are anticlinal. However, this effect is smaller and cannot overcome the π -effects that impose a greater bias towards the eclipsed conformation.

Finally, the strongest hyperconjugative effect in this system, the $n_{\text{O}} \rightarrow \sigma^*$ delocalization, remains a bystander that imposes no apparent influence on this conformational tug-of-war. The $n_{\text{O}} \rightarrow \sigma^*$ interactions are very large (23–26 kcal/mol) but they change only slightly upon the conformational change. They are important for determining the overall stability of carbonyl compounds but impose hardly any effect on the conformational equilibrium.

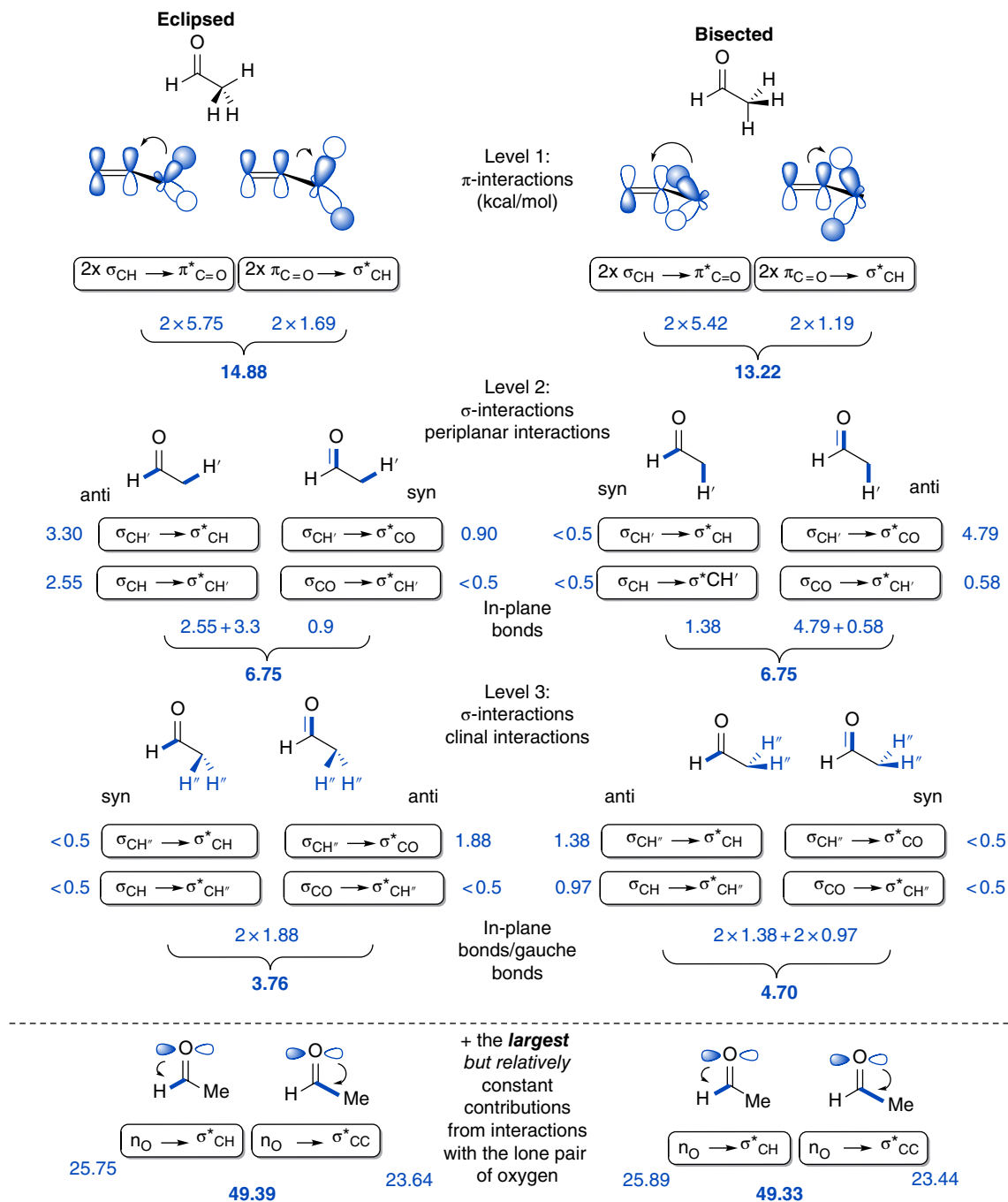


Figure 6.37 NBO analysis of stereoelectronic interactions involved in the conformational profile of ethanal. The combined energies should be treated as approximate because interaction with energies below the default NBO threshold of 0.5 kcal/mol were not used in determining the overall balance.

There are several take-home messages from this analysis. First, there are several layers of conjugative interactions even in a relatively simply system. A subset of these interactions can play a determining role but the other factors may attenuate the overall outcome. The qualitative analysis based on the quantum-mechanical dissection of the high-quality wavefunctions (such as NBO analysis) can help to untangle this complexity. Furthermore, the balance between different “levels” of interactions can change upon physical or chemical changes in the environment.

Effects that are invisible and “unimportant” for conformational equilibria can play key roles in reactivity. For example, the large $n_{\text{O}} \rightarrow \sigma^*_{\text{C-H}}$ interaction in aldehydes evolves, upon the C-H bond scission, into a 2c,3e-bond in acyl radical. The latter effect manifests itself as the source of dramatic weakening of the aldehyde C-H bond dissociation energy (~ 88 kcal/mol) – much smaller than the BDE for C-H bond in ethene (~ 111 kcal/mol).⁶² The difference is especially striking since both carbon atoms are sp^2 hybridized and expected to have relatively strong C-H bonds. However, the C(O)-H bond in aldehydes is even weaker than a typical C-H bond in *alkanes*. This structural feature and resulting ease of acyl radical formation has important consequences for the stability and reactivity of aldehydes under radical conditions (Figure 6.38).

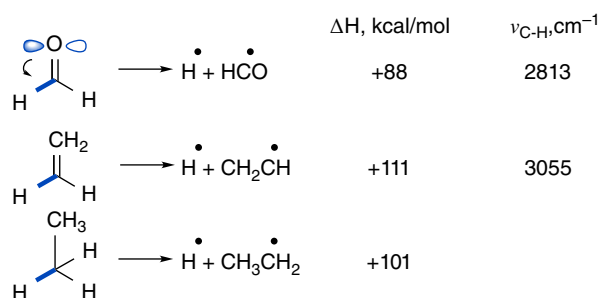


Figure 6.38 The large $n_{\text{O}} \rightarrow \sigma^*_{\text{C-H}}$ interactions manifest themselves as decreased C-H bond BDE and red-shifted C-H stretching frequencies in aldehydes. For additional spectroscopic consequences of these interactions, see Chapter 12.

Similar conformational preferences are expected to apply to iminium ions, one of the key intermediates in many organocatalytic cascades. When such iminium ions undergo deprotonation, the reactive conformation is the one where the breaking C-H bond is aligned with the iminium π -system. In the presence of additional stereocenters that make the two sides of the π -system diastereotopic, the proton abstraction occurs from the sterically more accessible face opposite to the catalyst sidechain. As a result, the opposite enantiomers of chiral aldehydes are transformed into opposite enamine stereoisomer (E- or Z-, Figure 6.39). This stereochemical relationship is maintained in the reverse process which involves protonation on the less hindered face of the enamine. Eventual equilibration of the E and Z enamines is possible but relatively slow.⁶³

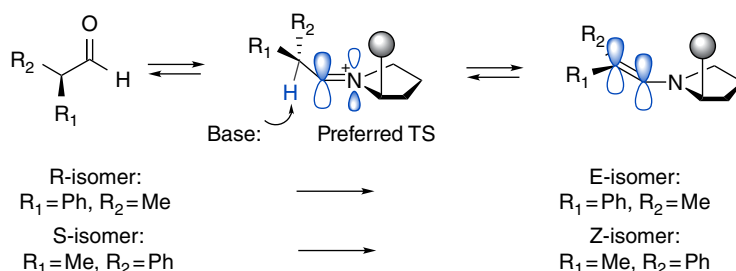


Figure 6.39 Stereoelectronic effects in deprotonation of iminium salts.

6.2.3 Strained bonds

BLW estimates of electronic delocalization from strained substituents to a carbocation suggest that hyperconjugation in these systems can be much larger than typical conjugation effects (Figure 6.40).⁶⁴

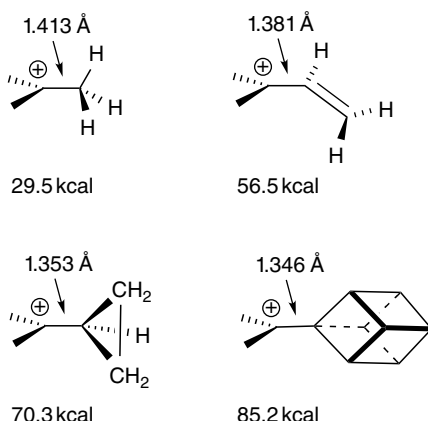


Figure 6.40 B3LYP geometries and block localized wavefunction (BLW) estimates of delocalization energies in substituted carbocations. For details of BLW method, see Chapter 4.

When directly attached to a cyclopropane ring, carbonyl compounds prefer either the *s-cis* or *s-trans* conformation, depending on the substituent, X (Figure 6.41).⁶⁵ In both conformers, the C-O σ -bond is perpendicular to the plane of the cyclopropane ring in order to allow for (hyper)conjugative interactions of the strained banana bonds with the carbonyl π -system. Note that this preference is opposite to that in 2-methylpropanal where the more stable conformation has the C-H bond aligned with the carbonyl π -system and one of the C-C bonds is orthogonal to it. This change in preferred conformation suggests increased donor ability of the strained banana C-C bonds.⁶⁶ Experimental data for the simple case, cyclopropanecarboxaldehyde, favor *s-trans*, and range from 0.3 to 0.9 kcal/mol.^{64f} Conformational profiles of the cyclopropylcarboxylic acid and acid chloride as well as the conformations of bis-cyclopropyl and cyclopropylmethyl ketones show a very slight preference for the *s-cis* geometry, which has been attributed to sterics.

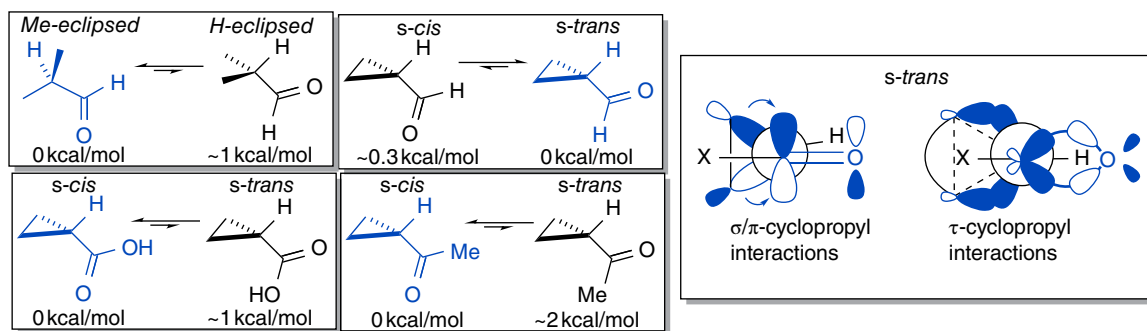


Figure 6.41 Conformational preference for cyclopropylcarbonyls to orient the C-O σ -bond perpendicular to the plane of the cyclopropane ring.

6.3 p/σ-Interactions

6.3.1 Primary, secondary, tertiary carbocation stabilization

Positive hyperconjugation from neighboring C-H bonds stabilizes carbocations, as can be seen by the following decreasing order of hydride affinities: methyl > primary > secondary > tertiary carbocations (Figure 6.42).⁶⁷ Rehybridization effects as a result of Bent's rule stabilize the positive charge as well, since the positive charge is directed into a pure p-orbital also making the stronger sp^2 - sp^3 C-C bonds with neighboring atoms. In primary carbocations, there is only one anti-/syn-periplanar C-H bond available to interact in positive hyperconjugation. As a result, in vinyl and ethyl cations, a non-classical 3-center, 2-electron species forms to delocalize the positive charge (3c, 2e bond can be taken as the result of evolution of the $\sigma_{C-H} \rightarrow p^+$ interaction reference to figure 6.42).⁶⁸

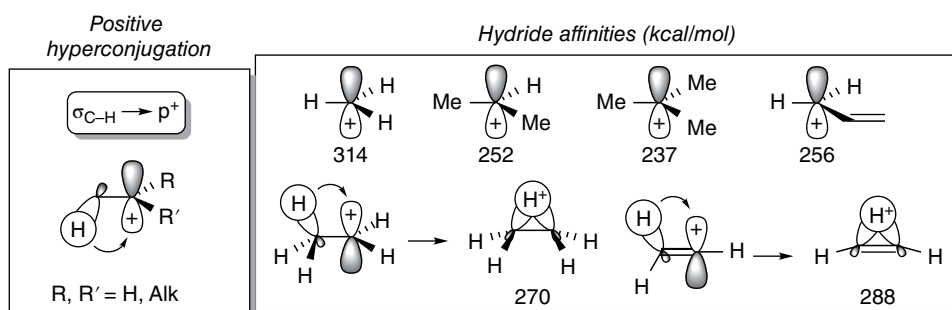


Figure 6.42 Stabilization and hydride affinities in primary, secondary, and tertiary carbocations. Evolution of hyperconjugation to non-classic 3c,2e bonds is also illustrated.

The increased importance of hyperconjugation in cations affects rotational barriers, albeit not in a straightforward way. Computations at HF levels with symmetry restraints suggested that the barrier for ethyl cation itself is, in fact, quite small. The rotational barrier in the ethyl radical is also very small.⁶⁹ Although initially unexpected, this observation can be explained by different symmetry of orbital interactions involved in negative and positive hyperconjugation. With p-orbitals, the notions of syn- and antiperiplanarity disappear (Figure 6.43) and the equivalence of all periplanar conformations results in a 6-fold symmetry of the rotational profile.

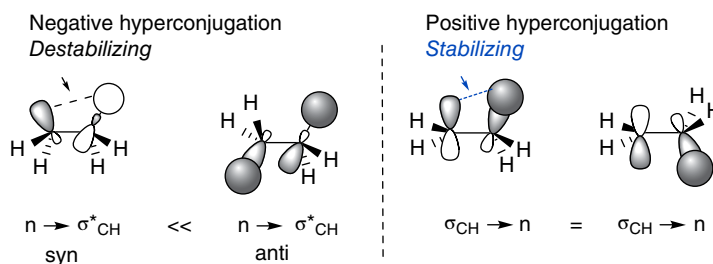


Figure 6.43 Comparison of conformational effects on the efficiency of negative and positive hyperconjugation.

Rotational barriers in the substituted cations have been the subject of a number of classic studies at the relatively low (by modern standards) levels of theory. Although these studies have not been tested with the more accurate recent methods, many of the fundamental insights are still very interesting. The 1972 work of

Hoffmann et al. outlined the general rules for conformational preferences in β -substituted cations $\text{XCH}_2\text{CH}_2^+$ and anions $\text{XCH}_2\text{CH}_2^-$. This work suggested that there may be large barriers to internal rotation due to hyperconjugation in the presence of strong σ -acceptors and donors.⁷⁰ In cations, if X is more electronegative than H, the polar C-X bond at its C end is a better σ -acceptor than C-H, and “perpendicular” conformation B is preferred. If X is less electronegative than H, the C-X bond is a better σ -donor than C-H and “eclipsed” conformation A is more stable (Figure 6.44). For anions, the rules are reversed.⁷¹

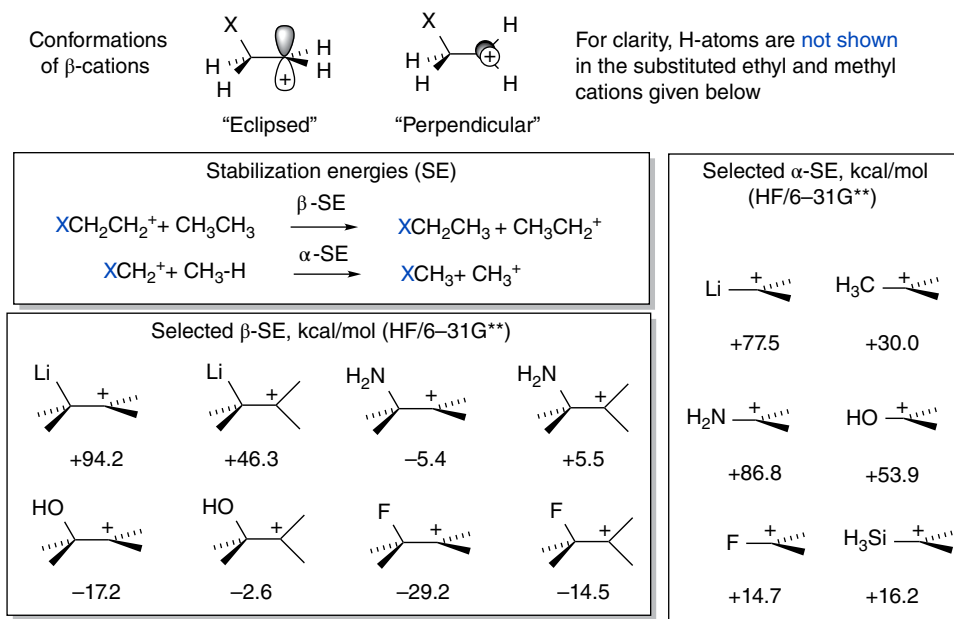


Figure 6.44 Stereoelectronic aspects of substituent stabilization in β -substituted ethyl cations and selected α -substituent effects in methyl cations.

Substituent effects on stability of a carbocation can be estimated from the following isodesmic reactions (Figure 6.43, performed at HF/6-31G** level).⁷² Again, stabilization energies have a clearly manifested stereoelectronic component as illustrated by differences in stabilization energies imposed by substituents in the eclipsed and perpendicular conformations.

The stereoelectronic considerations readily explain the chameleonic behavior of substituents that can switch from being a donor to being an acceptor depending on their position and orientation relative to the cationic center. For example, α -F substituent stabilizes the cationic center by ~ 15 kcal/mol whereas β -F in the eclipsed geometry exerts a destabilizing effect of 29.2 kcal/mol. In the first case, fluorine lone pair is aligned with the vicinal cationic p-orbital and behaves as a p-donor. In the second case, the empty p-orbital at the cationic center is aligned with the vicinal C-F bond, and fluorine behaves as a σ -acceptor.

Another example that illustrates the value of stereoelectronic thinking is the straightforward rationalization of the differences in α -stabilizing effects of NH_2 and Li substituents on cation stability. The relative stabilizing power of these two substituents (NH_2 (87 kcal/mol) $>$ Li (78 kcal/mol)) is opposite to the expectation based on the much greater electronegativity of nitrogen but is fully consistent with the stabilization provided by the lone pair at nitrogen (something that Li lacks) to the cationic center via direct orbital overlap with the cationic p-orbital.

6.3.2 Hyperconjomers of cyclohexyl cations

Hyperconjugation has a profound effect on structure and stability of cyclohexyl cations. An elegant study⁷³ combined theoretical results with experimental data to confirm that different hyperconjugative stabilization patterns lead to the formation of two equilibrating conformers of the 1-methyl-1-cyclohexyl cation where the carbocation p-orbital is oriented either pseudoaxially or pseudoequatorially.

These conformers, called hyperconjomers, are distorted from the ideal chair conformation to have distinctly different modes of hyperconjugative stabilization. The cationic orbital in the “equatorial” hyperconjomer interacts strongly with the antiperiplanar C-C bonds, whereas the vacant p-orbital in the “axial” cation interacts most strongly with the adjacent axial C-H bonds (Figure 6.45). A detailed NBO analysis of the electronic structures of these species confirmed the importance of hyperconjugative interactions for the existence and relative stabilities of the two conformers.⁷⁴

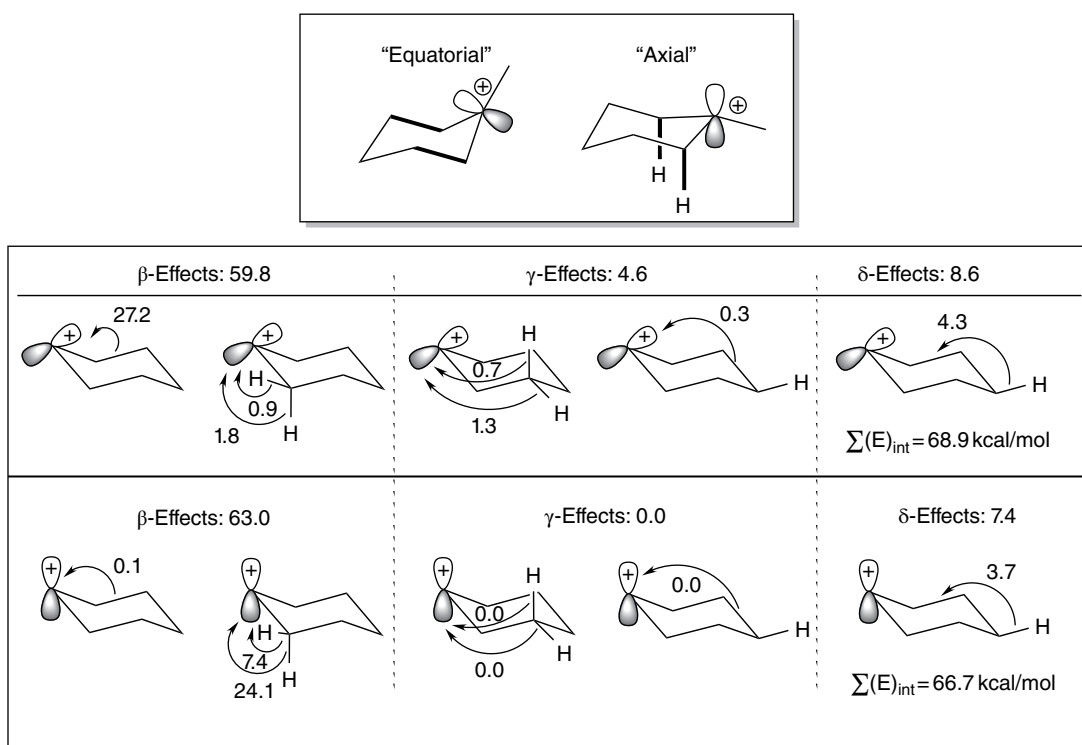


Figure 6.45 Stabilizing hyperconjugative effects in the axial and equatorial “hyperconjomers” of cyclohexyl cations.

6.3.3 β-Silicon effect and related β-effects

Carbocations positioned β to a silyl group benefit from large stabilizing interactions (Figure 6.46). Unless strongly stabilizing substituents are present that can stabilize the cation at the α-position,⁷⁵ the silyl group acts as a dominating directing group in electrophilic addition to vinyl and allyl silanes.⁷⁶ The cation formation in these systems is guided by $\sigma_{\text{C-Si}} \rightarrow \text{p}^+$ positive hyperconjugation, known as the β-silicon effect.⁷⁷ The stabilization provided by the C-Si bond relative to C-H and C-C can be predicted using the isodesmic equation shown

in Figure 6.46.⁷⁸ In the allyl case, hyperconjugation in the TS is smoothly transferred into the Me_3Si cation loss with a shift of the double bond. This effect provides considerable stabilization to the TS for electrophilic addition. In contrast, the donor C-Si bond in electrophilic addition is orthogonal to the developing positive charge at the early reaction changes and cannot provide stereoelectronic assistance in the TS.

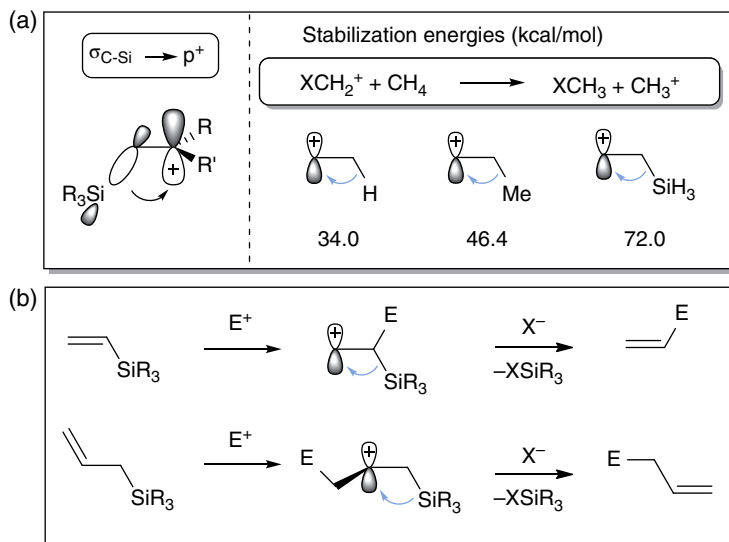


Figure 6.46 (a) Positive hyperconjugative stabilization of carbocations in the β -silicon effect and relative stabilization energies provided by C-H, C-C, and C-Si donors. (b) Selectivity observed in vinyl- and allylsilane electrophilic substitutions.

The β -silicon effect has been used to assist in the generation of otherwise unstable cations, such as the phenyl cation.⁷⁹ Because singlet phenyl cations have a localized cation orthogonal to the aromatic system, formation of the respective triplet species,⁸⁰ with diradical character, becomes favorable in some cases. The singly occupied orbital of the triplet aryl cation allows the charge to be delocalized within the ring,⁸¹ providing stability and selectivity in further reactions. While π -donors stabilize the triplet, silyl groups *ortho* to the cation (radical) selectively stabilizes the singlet via vicinal hyperconjugation (Figure 6.47).⁷⁹

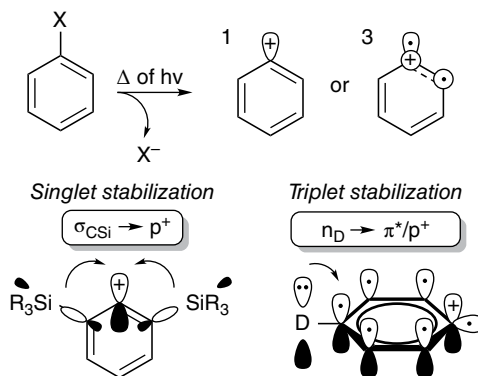


Figure 6.47 Alternative modes of stabilization in singlet and triplet aryl cations.

The β -C-Sn bond provides significant stabilization to cationic centers as well, providing a possible tool for the control and design of chemical transformations. For example, the evolution of $\sigma_{\text{C-Sn}} \rightarrow \text{p}^+$ interaction in *o*-Sn substituted aryl cations leads to elimination of Me_3Sn cation and formation of *o*-benzyne (Figure 6.48).⁸²

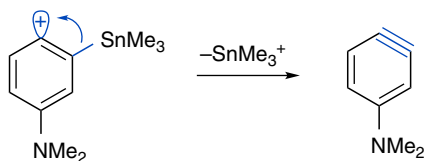


Figure 6.48 Evolution of positive hyperconjugation leads to elimination of Me_3Sn cation and formation of *o*-benzyne from *ortho*-Sn-substituted aryl cations.

Bonds to other metals can also behave as strong sigma donors. For example, formation of dicobalt octacarbonyl-stabilized propargylic cations serves as a key step in the Nicholas reaction, a useful process for the preparation of functionalized alkynes (Figure 6.49).⁸³

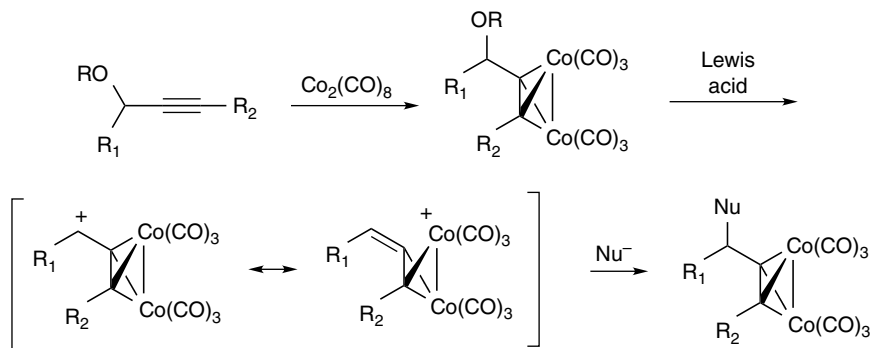


Figure 6.49 The Nicholas reaction benefits from strong hyperconjugative assistance to cation formation.

6.4 n/σ -Interactions

Similar to ethane, the barriers in methylamine and methanol appear to be dominated by hyperconjugative stabilization of the anti conformation. The barrier decreases ($2.9 \rightarrow 2.0 \rightarrow 1.1$ kcal/mol) in proportion to the number of antiperiplanar C-H/C-H interactions. This is counterintuitive because $n \rightarrow \sigma_{\text{C-H}}^*$ interactions are expected to be greater than the $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-H}}^*$ interaction.

Furthermore, the role of hyperconjugation is expected to increase even more in anionic species. However, the difference between staggered and eclipsed conformation is only slightly higher in ethyl anion (2.3 kcal at the CCSD(T)/6-311+G(d,p)//B3LYP/6-311++G(3df,2p) level of theory) than in methyl amine and much lower than in ethane.⁸⁴

Goodman and Sauers analyzed the reasons for this apparent paradox by applying NBO dissection to ethyl anion. They found that when vicinal hyperconjugative interactions are switched off, the staggered conformational preference is lost; i.e. the eclipsed conformer is ~ 1.6 kcal/mol more stable than the staggered structure. This result suggests that hyperconjugation does play an important role in determining the conformational preference in this anionic system. Furthermore, the well-pronounced structural evidence (e.g. the lengthening of C-H bond antiperiplanar to the lone pair) also suggests the strong role of hyperconjugation.

A more detailed analysis of individual contributions provided deeper insights in the observed lowering of the rotational barrier. While the single most important vicinal hyperconjugative interaction involves lone pair and antiperiplanar $\sigma_{\text{C-H}}^*$ orbital, this interaction is only a single effect that coexists with multiple $\sigma_{\text{C-H}}/\sigma_{\text{C-H}}^*$ vicinal interactions. The combination of multiple interactions can overwhelm the single effect. A few of such effects are shown in Figure 6.50.

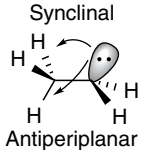
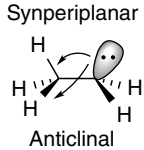
		
Ethyl anion	12.4	5.8
	1.0×2	3.3×2
Sum:	14.4	12.4
	Staggered	Eclipsed
Methyl amine	8.2	4.8
	1.0×2	2.1×2
Sum:	10.2	9.0

Figure 6.50 The two conformers of ethyl anion equilibrium and methyl amine and NBO interactions of lone pair with the vicinal C-H bonds (in kcal/mol). In both cases, the overall energy between staggered and eclipsed conformers is ~ 2 kcal/mol.

Furthermore, in order to adjust for the presence of negative charge, the staggered conformer undergoes significant structural distortion, with the increase in the C-C-H angle (to an almost “sp²” value of 118°) being especially significant. This geometric change reflects the rehybridization imposed by the redistribution of electron density. The antiperiplanar C-H bond is significantly weakened and lengthened (1.128 Å). The importance of negative hyperconjugation has been further analyzed with NBO in a number of alkyl and cycloalkyl carbanions.⁸⁵

A few systematic investigations of rotational profiles for carbanions with stronger vicinal σ -acceptors were carried out. Although the quantitative estimates may be approximate because of the relatively low levels of theory and a number of structural constraints used in these studies, the overall trends indicate clearly that hyperconjugative effects play a key role in the structure and conformational flexibility of substituted carbanions. For example, Apeloig et al.⁸⁶ analyzed β -substituted ethyl anions of the general formula ZXCH₂CYY' (Figure 6.51) using HF/STO-3G optimization with single point calculations with the 4-31+G and 6-31G' basis sets. All the carbanions are more stable in the perpendicular conformation where the carbanionic lone pairs and the C-X bonds are aligned. The barriers to rotation around the C-C bonds correlated very well with the $\sigma_{\text{C-X(Z)}}^*$ acceptor ability. Electron-withdrawing α -substituents stabilize the anionic center, decrease the importance of hyperconjugation, and significantly reduce the rotational barriers.

Conclusive evidence that negative hyperconjugation significantly accelerates reactions that lead to the formation of carbanions was provided by King et al.,⁸⁷ who reported that the rate of α -sulfonyl carbanion formation from a set of 19 β -substituted sulfones shows strong dependence on the H-C _{α} -C _{β} -X torsion angle (Figure 6.52). For β -alkoxy sulfones (X=OR), donation of the partial negative charge of the incipient carbanion into the $\sigma_{\text{C-O}}^*$ orbital can accelerate deprotonation by 3–4 orders of magnitude. Both syn- and antiperiplanar C-O bonds had large accelerating effects. Other substituents (X=RS, R₂N, and R₃N⁺) also showed significant effects. Corrections for steric assistance, inductive, and field effects were made as well.

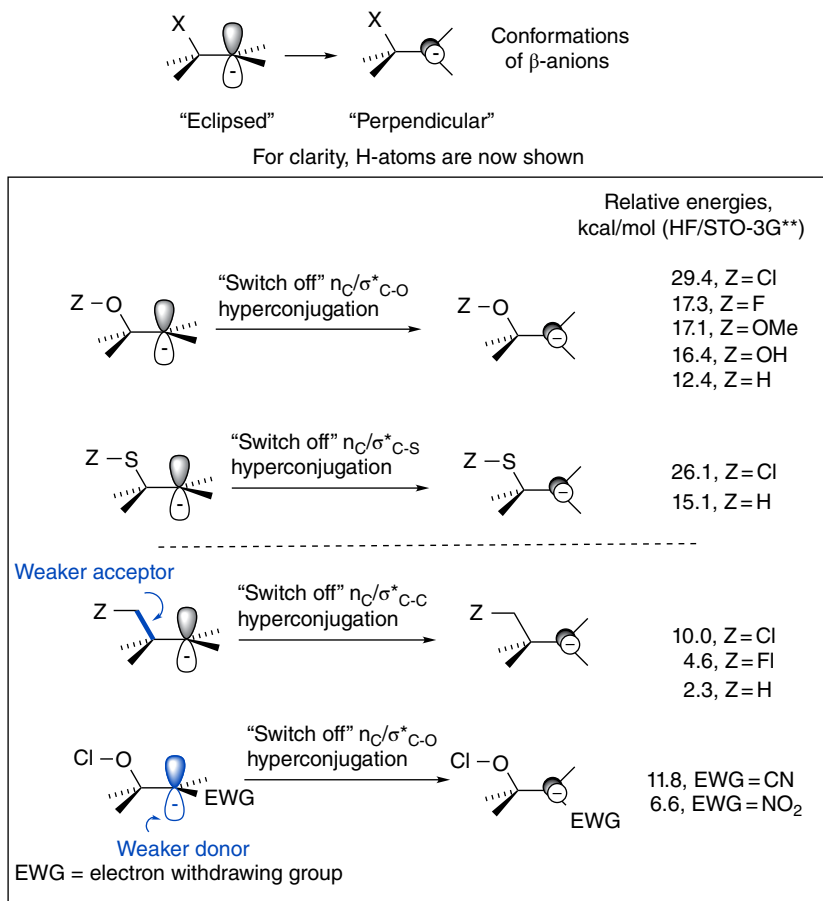


Figure 6.51 Stereoelectronic aspects of substituent stabilization in β -substituted carbanions. “Eclipsed” and “perpendicular” correspond to the relative arrangement of anionic orbital and acceptor C-X bond. The carbanionic center was kept planar in these computations.

Substrate	OCCH dihedral	Model	$k_{\text{exch}}/k_{\text{exch}}(\text{model})$
	78 (64)		5
	6 (26)		11,500
	148 (145)		32,400

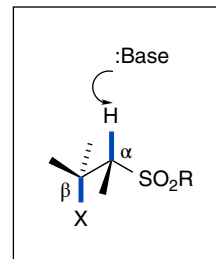


Figure 6.52 Stereoelectronic factors in stabilization of incipient carbanionic centers in constrained β -substituted sulfones. OCCH dihedrals are from X-ray data; values in parenthesis were calculated at PCM4 level.

One important caveat in the application of negative hyperconjugation involves the differences between free carbanions and compounds with carbon metal bonds. These two types of strong donors have important differences. In particular, charge localization due to the presence of a metal counter-ion (or formation of partially covalent C-M bond) can result in decreased/interrupted delocalization.

6.4.1 Anomeric effects

This section will discuss systems where strong donors (lone pairs) coexist with vicinal strong acceptors (bonds to electronegative elements). The key interaction of this type is the anomeric effect (AE), which is one of the most intensively studied,^{88,89,90} but still controversial, stereoelectronic effects. Originally, the anomeric effect was 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 position that is relatively unfavorable in cyclohexanes.

Some of the classic examples where the anomeric effect was first recognized are, in fact, quite complicated. The true importance of the anomeric effect is often masked in these cases because other steric or stereoelectronic interactions are present at the same time. Again, it is the full picture and the balance of multiple effects that matter in molecules with multiple polar C-X bonds (Figure 6.53b).

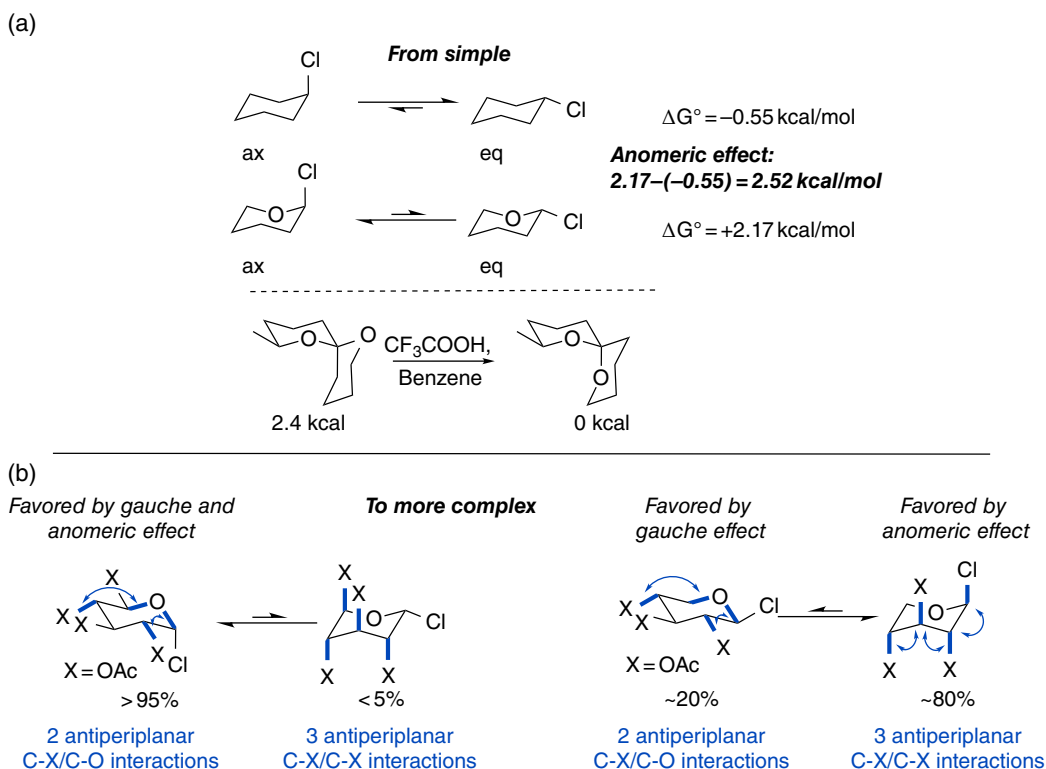


Figure 6.53 (a) Axial preference for acceptor groups at the anomeric positions.⁹¹ (b) Combination of gauche and anomeric effects in control of sugar conformations.⁹² The gauche effect (preference for conformations with fewer anti CX/CY interactions between vicinal bonds with acceptor elements X and Y) may be either synergistic or competitive with the anomeric effect.

As the acceptor ability of C-X bond at the anomeric position increases, the preferences for the axial position of the X group grows stronger (Figure 6.54).⁹¹

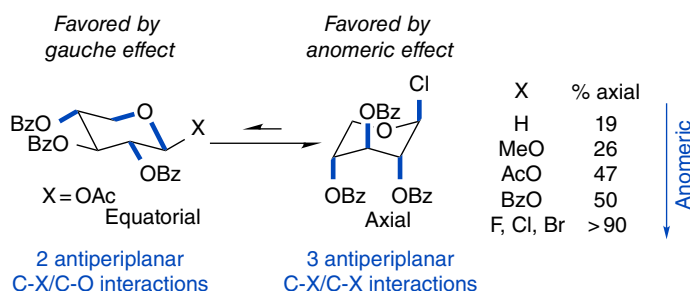


Figure 6.54 Competition between gauche and anomeric effects shifted by acceptor ability of the anomeric group X.

The interplay between the classic covalent bonding and strong anomeric interactions can lead to molecules with “frustrated” structures balancing at the edge between the two descriptions (Figure 6.55). For example, ionic, salt-like reactivity features were reported for N-(chloromethyl)piperidine.⁹³ The chlorine “atom” in this crystalline compound is quantitatively precipitated by AgNO_3 and can be exchanged to a perchlorate anion. Dynamic nuclear magnetic resonance studies suggest that the fluorine atom at the anomeric position of 2-fluoro-4,4,5,5-tetramethyl-1,3-dioxole switches rapidly from one face of the ring to the opposite one. The rate of this process is 30,000 times faster in nitroethane than in tetrahydrofuran. The pronounced solvent polarity effect on the exchange rate supports the intermediacy of a dioxacarbenium/fluoride ion pair.⁹⁴

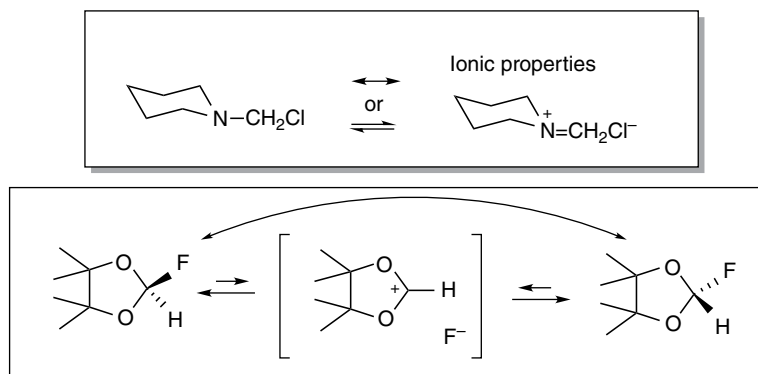


Figure 6.55 Strong anomeric interactions unveil hidden ionicity of organic molecules.

A simple and convenient way to evaluate anomeric stabilization is to compare energy associated with the change from axial to equatorial position in oxacyclohexane and cyclohexane (Table 6.2).⁹¹ It has been suggested that this approach underestimates the anomeric effect because C-O bonds are shorter and axial substituents in oxacyclohexane suffer from greater 1,3-diaxial repulsions with the axial hydrogens. Franck suggested the following equation to correct for this difference: $\Delta\Delta G(\text{AE}) = \Delta G(\text{heterocycle}) - 1.53 \cdot \Delta G^\circ(\text{steric}(\text{cyclohexane})) - 0.08$.⁹⁵

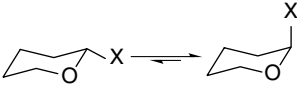
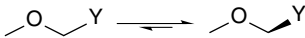
Cyclic constraints provide a convenient platform for observing anomeric effects due to relatively rigid and well-defined conformations. Subsequently, the anomeric effect has been shown to be a manifestation of much a more general phenomenon (the generalized anomeric effect) controlling conformations of systems where two

Table 6.2 Differences for the energy cost of moving substituent from the axial to equatorial substituents in cyclohexanes and oxacyclohexanes can be used to evaluate anomeric stabilization.⁸⁹

X	ΔG (oxacyclohexane)	ΔG (cyclohexane)	Anomeric effect ($\Delta\Delta G$), kcal/mol
Cl	1.8	-0.6	2.4
Br	1.8	-0.5	2.3
OCH ₃	0.9	-0.8	1.7
OCH ₂ CH ₃	0.8	-0.8	1.6
SCH ₃	0.5	-1.0	1.5
OH	-0.1	-0.9	0.8
NHCH ₃	-0.9	-1.3	0.4
CO ₂ CH ₃	-1.4	-1.3	-0.1

heteroatoms X and Y are separated by a one-atom bridge (e.g. X-CH₂-Y). When both X and Y are electronegative atoms with lone pair(s), the preferred conformation in the X-CH₂-Y moiety is gauche rather than anti (or axial rather than equatorial if two atoms of the X-CH₂-Y moiety are part of a ring, Table 6.3). Such preferences are manifested more strongly in the gas phase and often become less pronounced (or even reversed) in polar solvents.

Table 6.3 Conformational preferences in anomeric cyclic and acyclic systems in the gas phase (M06-2X/6-311G++(d,p) data in kcal/mol)⁹⁶

					
X	ΔE	ΔG	Y	ΔE	ΔG
Cl	-3.9	-3.5	Cl	-4.8	-4.5
F	-3.0	-2.7	F	-4.4	-3.6
OMe	-3.9	-3.6	OMe	-3.8	-2.7
OH	-1.1	-0.7	OH	-0.4	-0.3
NH ₂	-1.0	-0.8	NH ₂	-2.8	-2.5

According to NBO analysis, the key component of anomeric effect is the negative hyperconjugative interaction between the lone pair of X and the low-lying $\sigma^*_{\text{C-Y}}$ orbital. When both X and Y have at least one lone pair, a more balanced description also involves $n_Y \rightarrow \sigma^*_{\text{C-X}}$ donation in the opposite direction. For the 2-alkoxy-substituted tetrahydropyrans, the overall conformational profile originates from the combination of $n \rightarrow \sigma^*_{\text{C-O}}$ hyperconjugative interactions, responsible for both the endo- and exo-anomeric effects (Figure 6.56).

In addition to the hyperconjugative model, alternative explanations have been proposed to rationalize the anomeric effect. In particular, the electrostatic model⁹⁷ is based on favorable local dipole-dipole interactions and a smaller net dipole in the axial conformation relative to the equatorial conformation (Figure 6.57). BLW, NBO, and EDA analyses give slightly different weights to the importance of electrostatic and conjugative effects. For example, a computational study by Y. Mo based on the block-localized wavefunction (BLW) method (see Chapter 4) suggested that hyperconjugative delocalization is a much smaller factor in the anomeric effect than sterics (electrostatic interactions + Pauli repulsion).⁹⁸ A more recent NBO study by Freitas suggested that there

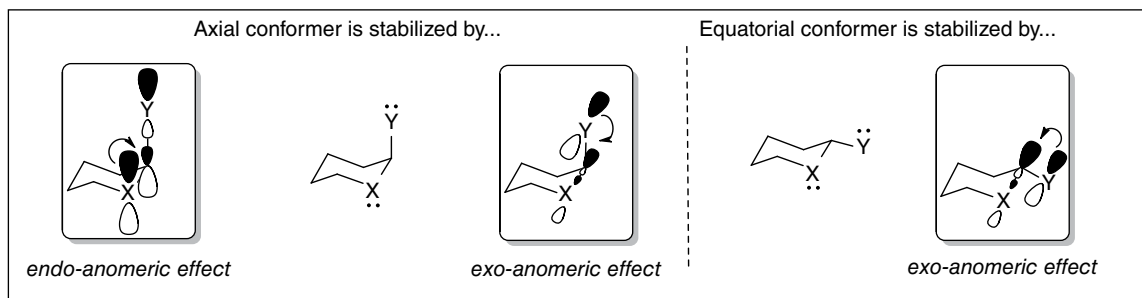


Figure 6.56 Antiperiplanar negative hyperconjugative interaction in the endo- and exo-anomeric effects.

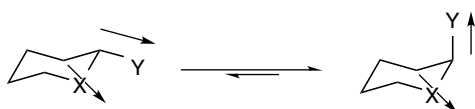


Figure 6.57 Electrostatic explanation for the axial preference of electronegative substituents in the anomeric effect. C-Y and C-X bond dipoles point to the same direction in the equatorial conformer, destabilizing the molecule.

are examples where each model plays the major role.⁹⁹ Yet another recent study utilizing EDA suggests that the anomeric effect is dominated by exchange energies, and electrostatics have minor contribution.¹⁰⁰

The electrostatic model is consistent with the stabilizing effects of polar solvents that often favor the equatorial isomer in anomeric systems (Figure 6.58).¹⁰¹

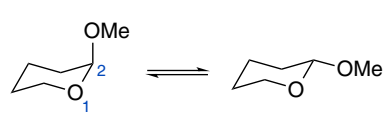
	Solvent:		
	% axial	ϵ	
	83	2.2	CCl ₄
	82	2.3	Benzene
	71	4.7	CHCl ₃
	72	20.7	Acetone
	69	32.6	Methanol
	68	37.5	Acetonitrile
	52	78.5	Water

Figure 6.58 Solvent effects on conformational equilibrium in 2-methoxytetrahydropyran.

An advantage of the hyperconjugative model is that it readily explains the structural changes associated with the anomeric effect. In particular, preference for axial position is accompanied by a characteristic combination of structural changes that can be attributed to the increased contribution of $n_{\text{O}} \rightarrow \sigma^*_{\text{C-X}}$ interactions.⁸⁷ Shortening the O-C2 distance in the axial conformer is consistent with the increased O-C2 double bond character, whereas C-X bond elongation reflects the transfer of additional electron density to the antibonding $\sigma^*_{\text{C-X}}$ orbital. The axial and equatorial C-Cl bond length in *cis*-2,3-dichloro-1,4-dioxane are different (Figure 6.59). The axial C-Cl bond (at C3) is considerably longer than the equatorial C-Cl bond (at C2). The corresponding changes in the C-O bond length occur in the opposite direction. In a similar manner, shortening of the endocyclic bond C2-O and concomitant lengthening of the exocyclic bond C2-F are observed in the axial conformer of tri-OBz-2-fluorotetrahydropyran.¹⁰² The axial and equatorial C-F bonds in 3,4,5,6-tetraOAc-2-desoxyglucopyranose are distinctly non-identical.¹⁰³

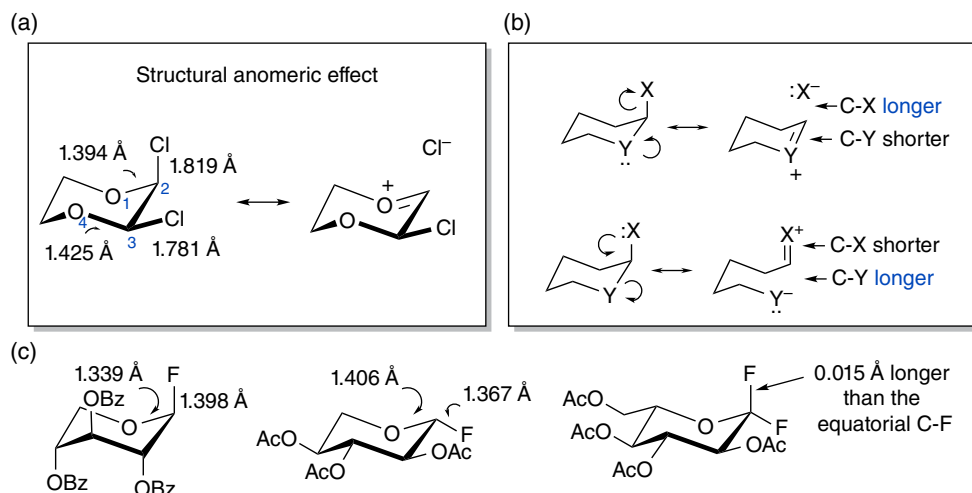


Figure 6.59 Structural consequences of anomeric effect. (a) Selected bond lengths in *cis*-2,3-dichloro-2,4-dioxane. (b) The opposing effects of endo- and exo-anomeric effects on geometries. (c) Selected structural consequences of anomeric effect in OCF moiety.

In equilibrium isotope effects, deuterium generally prefers the stronger bonds. Anet and Kopelevich have found that the deuterium in 5,5-dimethyl-1,3-dioxane-2- d_1 prefers the equatorial position by about 50 cal/mol (this preference in cyclohexane is only 6 cal/mol).¹⁰⁴ The weakening effect of the endocyclic anomeric effect at the exocyclic C-X bonds is fully consistent with the hyperconjugative model (Figure 6.60).

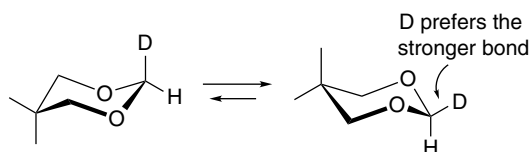


Figure 6.60 Deuterium isotope effect at the anomeric position.

The hyperconjugative component of the exocyclic anomeric effect makes the endocyclic C-Y distance shorter but the exocyclic anomeric effect has the opposite effect. Because the exocyclic anomeric effect is present in both axial and equatorial conformers, its effect on the *relative* geometries of the two conformers often remains invisible.

However, the exo-anomeric effect can depend on the geometric arrangement of orbitals at the exocyclic group as a function of rotation around the exocyclic C-O bond (Figure 6.61).

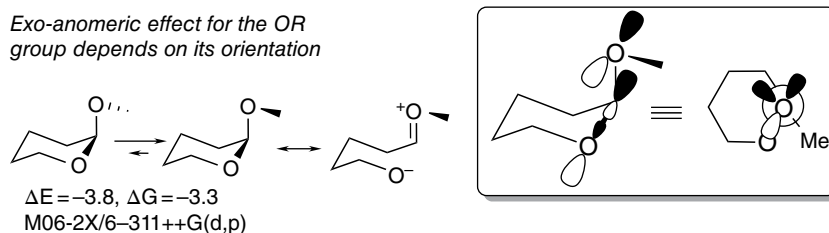


Figure 6.61 Rotation around the exocyclic C-O bond “switches on” the exo-anomeric effect.

Generalized anomeric effect The stereoelectronic requirement that a lone pair n_X at a heteroatom X and C-Y bond in a YCH_2X moiety are aligned in an antiperiplanar geometry^{31,105} for maximizing the hyperconjugative $n_X \rightarrow \sigma^*_{C-Y}$ interaction also leads to interesting conformational preferences in acyclic systems (Figure 6.62).

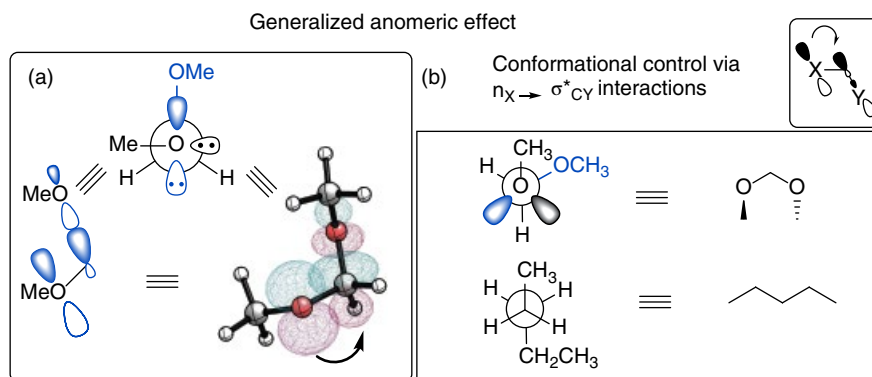


Figure 6.62 (a) Stereoelectronic basis for the anomeric effect illustrated in dimethoxymethane. (b) Contrasting shapes of pentane and dimethoxymethane ("2,3-dioxapentane"). Both p/sp and sp^3/sp^3 representations of oxygen lone pairs are shown (in the panels a and b, respectively). NBO analysis finds that the p/sp model for the oxygen lone pairs is preferred.

These preferences are also reflected in structural changes (C-Y bond elongation and C-X bond shortening), in the distribution of electron density (increased negative charge on Y) and in reactivity (C-Y bond weakening).

This effect is manifested broadly and encountered frequently. For example, the anomeric effect contributes to the inertness of CF_2 moieties incorporated in many pharmaceuticals. It also operates in many common systems such as hydrogen peroxide, dialkoxy methanes, freons, and hydrazine. The C-F BDEs of CF_nH_{3-n} molecules increases for $n > 1$ (Figure 6.63a).¹⁰⁶ Interestingly, the analogous effects in CCl_nH_{3-n} molecules are much smaller.

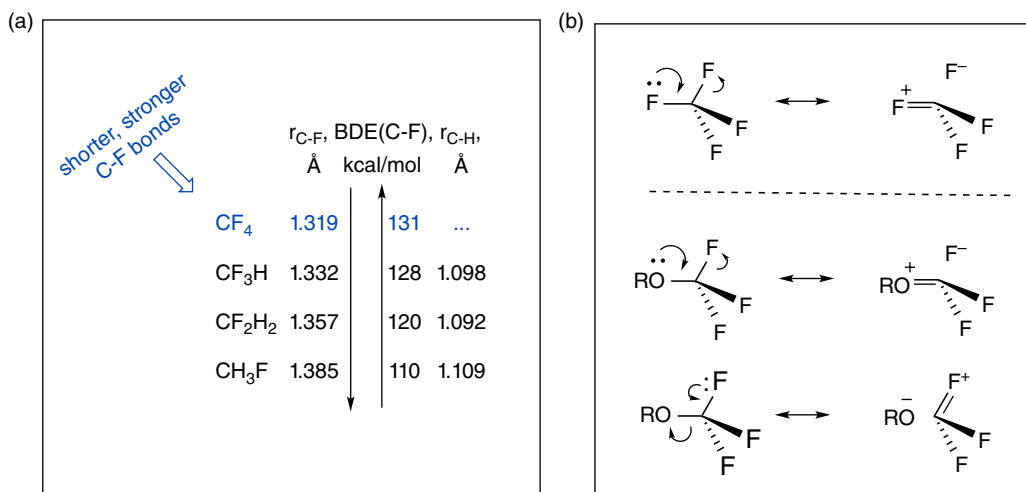


Figure 6.63 (a) Effects of anomeric interactions in CF_nH_{3-n} molecules on geometry and C-F/C-H bond strength. Data are from ref. 105c. (b) Anomeric interactions in CF_4 and CF_3OR molecules.

The anomeric effect plays an important role in stabilization of fluorinated ethers, sulfides, and amines, a surprisingly well-represented family of heteroatom-rich compounds. The OCF_3 functionality is unusually stable due to multiple anomeric effects (Figure 6.63b) and finds numerous applications.¹⁰⁷ Schlosser and coworkers, for example, estimated that ~30,000 OCF_3 -containing structures were described in >7000 literature references before 2005.¹⁰⁸ These compounds find applications that range from electro-optical displays to plant growth regulators to neurologic drugs. Perfluoropolyethers are used as high-boiling inert fluids for demanding environments. The latter have the longest liquid range known, from -100 to 350°C .¹⁰⁹

The ~ 2.5 – 2.7 kcal/mol preference for the gauche conformation of hydrazine and tetramethyl hydrazine originates from a stabilizing effect of the two antiperiplanar $n(\text{N}) \rightarrow \sigma^*(\text{N-H})$ interactions (Figure 6.64).¹¹⁰ In the anti conformations of hydrazine, the calculated $r_{\text{N-N}}$ distance is longer ($1.489 \text{ \AA}$) than in the gauche conformation ($1.448 \text{ \AA}$). The similar energy profile and geometry trends in tetramethyl hydrazine suggest that the larger steric bulk of methyl groups in comparison to hydrogen has little effect on either the gauche/anti geometry or stability.

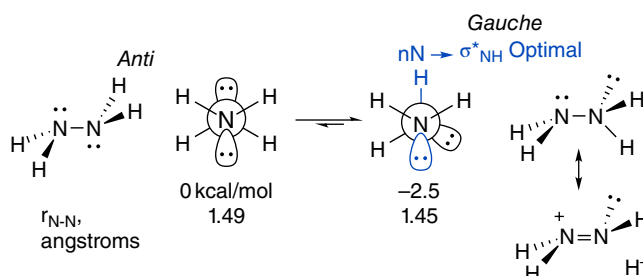


Figure 6.64 Anomeric effects in hydrazine resulting from two $n_{\text{N}} \rightarrow \sigma^*_{\text{NH}}$ interactions.

When applying stereoelectronic reasoning to conformational equilibria, it is important to analyze the full inventory of competing effects. For example, the anti conformer of tetrafluorohydrazine is 0.4 kcal/mol more stable than the gauche conformer. This change in the conformational preference has been attributed to another stereoelectronic effect ($n_{\text{F}} \rightarrow \sigma^*_{\text{N-F}}$).¹¹¹ In the gauche conformer, the stabilizing interactions involve two $n_{\text{N}} \rightarrow \sigma^*_{\text{N-F}}$ and two $\sigma_{\text{N-F}} \rightarrow \sigma^*_{\text{N-F}}$ interactions. In the anti conformer, there are no $n_{\text{N}} \rightarrow \sigma^*_{\text{N-F}}$ interactions but *four* $n_{\text{F}} \rightarrow \sigma^*_{\text{N-F}}$ interactions are present instead (Figure 6.65). The competitiveness of “homoanomeric” donation (vide infra) from the F lone pairs relative to the classic anomeric donation from the N lone pairs is further increased by the larger s-character (and the poor donor ability) of the N lone pairs as a consequence of Bent’s rule.

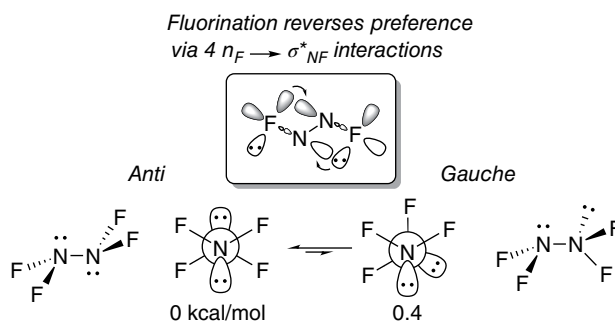


Figure 6.65 Reversal of conformational preference in hydrazine upon fluorination. Lone pairs of fluorine can participate in homoanomeric $n_{\text{F}} \rightarrow \sigma^*_{\text{N-F}}$ stabilizing interactions.

The non-planar geometry of hydrogen peroxide has also been attributed to $n_{\text{O}} \rightarrow \sigma^*_{\text{O-H}}$ interactions. However, the gauche preference in peroxides is weaker than it is in acetals. In dimethyl peroxide, the close energies of anti and gauche conformations suggest that steric effects successfully compete with stereoelectronics. The importance of anomeric effect in peroxides is greatly diminished in alkyl peroxides due to the anisotropic properties of $n_{\text{O}} \rightarrow \sigma^*_{\text{X-Y}}$ interactions (Figure 6.66). As discussed in Chapter 5, the magnitude of hyperconjugative effects depends on directionality – C-O bonds are better acceptors than O-C bonds, reflecting polarization of σ^*_{CO} orbital towards carbon.¹¹²

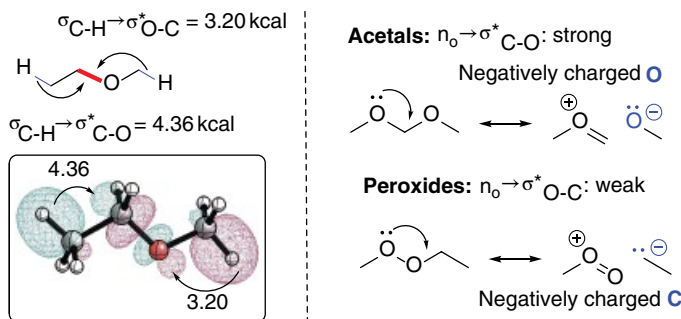


Figure 6.66 Comparison of anomeric effects in acetals and peroxides.

An interesting development of this trend is illustrated by the structure of larger H_2O_3 and related compounds with the longer $-\text{O}_n-$ chains. For example, the O-O bond of H_2O_3 , 1.428 Å, is shorter than that of H_2O_2 , 1.464 Å.¹¹³ The apparent strengthening of O-O bond in H_2O_3 and its non-planar geometry agree well with the importance of anomeric interactions and the greater acceptor ability of O-O bonds in comparison with O-H bonds (Figure 6.67). This observation may provide an explanation as to why H_2O_3 is far more stable than was previously expected and has interesting implications for the formation of longer oxygen chains.¹¹⁴

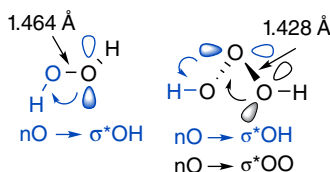


Figure 6.67 Selected stereoelectronic interactions and bond lengths in H_2O_2 and H_2O_3 .

A “comeback” of the anomeric effect in peroxides was identified recently as the source of unusual stability of bis- and tris-peroxides. The anomalous stability of these molecules contradicts the conventional wisdom – such bis-peroxides can even melt without decomposition at temperatures exceeding 100 °C. This surprising behavior is associated with the stereoelectronic stabilizing effect that two peroxide groups can exert on each other. This stabilization originates from strong anomeric $n_{\text{O}} \rightarrow \sigma^*_{\text{CO}}$ interactions that are absent in mono-peroxides but appear when the additional peroxide moiety is introduced and separated by a +one-atom bridge (Figure 6.68).⁹⁵

Other examples of structures with multiple heteroatoms that are stabilized by networks of anomeric effects are known (Figure 6.69). Cooperativity between such interactions in two- and three-dimensional cyclic arrays is likely to depend on the symmetry of the interacting orbitals.

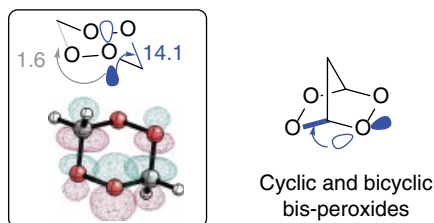


Figure 6.68 NBO plots and energies for $n_{O_2} \rightarrow \sigma^*_{O_1-C_6}$ and $n_{O_2} \rightarrow \sigma^*_{C_3-O_4}$ interactions in 1,2,4,5-tetraoxacyclohexane.

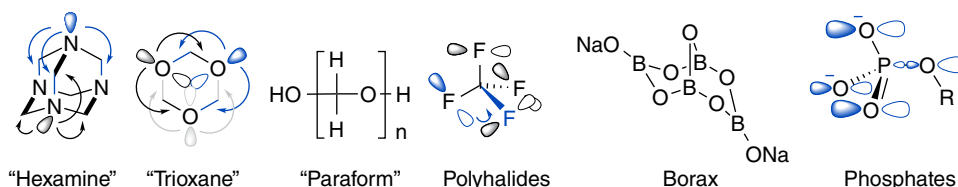


Figure 6.69 Selected molecules with multiple anomeric interactions. For clarity, only a subset of the fluorine lone pairs and only one $n_f \rightarrow \sigma^*_{C-F}$ interaction are shown for CF_4 .

Non-oxygen heterocycles – nitrogen and sulfur as donors in anomeric systems The preference for acceptor groups to prefer the axial position extends to cycles with other heteroatoms within the ring. It was found that even a group as bulky as *tert*-butyl can occupy up to 85% axial position due to stereoelectronic factors in 1,3,5-tri-alkylhexahydro-1,3,5-triazines (Figure 6.70).¹¹⁵ The steric effect of bulky substituent leads to planarization and rehybridization on nitrogen, increasing the amount of p-character in the lone pair and making it a better donor. The preference begins to disappear in 1,3-diazacyclohexanes with less bulky *N*-substituents,¹¹⁶ where the less favorable hybridization of nitrogen lone pairs renders them weaker donors (see Chapter 5).

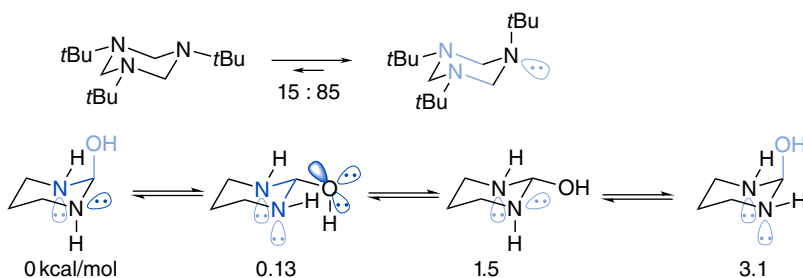


Figure 6.70 Extension of anomeric effect to *N*-containing heterocyclohexanes.

Similar preferences for the axial position have also been observed in 1,3-dithianes, where a variety of C2-substituents prefer the axial position.¹¹⁷ Comparison of these conformational preferences with the analogous cyclohexyl systems suggests the presence of anomeric stabilization of ~ 2 kcal/mol for systems (Figure 6.71). The axial preference is diminished in the more polar solvents, indicating the importance of

dipole–dipole interactions in these systems in addition to orbital interactions. Juaristi et al.¹¹⁸ have shown that in 2-carbomethoxy-1,3-dithiane at low temperatures the axial conformation is preferred in polar solvents. In changing from methylene chloride to acetone to methanol, the ΔG for the equilibrium increases from 0.83 to 0.92 to 1.13 kcal/mol, respectively.

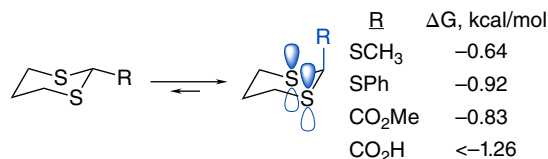


Figure 6.71 Conformational equilibrium of 2-substituted-1,3-dithianes in CD_2Cl_2 at low temperature.

Anomeric effect involvement was suggested for rather unusual systems. For example, a significant deshielding of the syn-axial H(4,6) protons in 2-diphenylphosphinoyl-1,3-dithiane by the phosphoryl group suggested the predominantly axial orientation of this substituent.¹¹⁹ In order to quantify this conformational effect, conformationally rigid equatorial and axial derivatives were equilibrated under basic conditions (Figure 6.72). The experimentally determined product ratio corresponded to $\Delta G_0 = +1.0$ kcal/mol, favoring the axial conformer.¹²⁰ Recent investigation suggested that the anomeric effect for 2-diphenylphosphinoyl group in 1,3-dithiane in chloroform is worth $2.71 - (-2.74) = 5.45$ kcal/mol (the A value for this substituent is 2.74 kcal/mol).¹²¹ NBO analysis supports the existence of dominant $n_X \rightarrow \sigma^*_{C-Y}$ stabilizing interactions in the axial conformers.

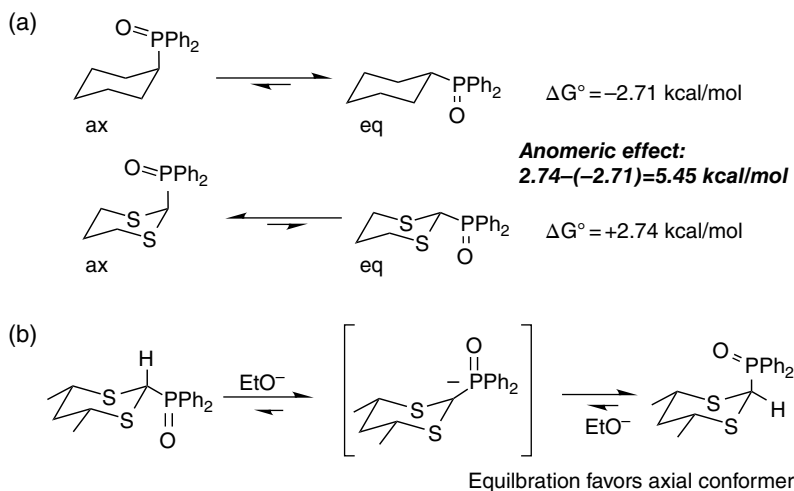


Figure 6.72 (a) Predominance of the axial conformation in the conformational equilibrium of 2-diphenylphosphinoyl-1,3-dithiane. (b) Chemical equilibration of dimethyl analogues of axial and equatorial 2-diphenylphosphinoyl-1,3-dithiane.

This stereoelectronic axial preference for the methoxy group in six-membered phosphate esters is so strong that the trans isomer of 5-tert-butyl-2-methoxy-1,3,2-dioxaphosphorinane adopts the diaxial conformation in the solid state (Figure 6.73).¹²²

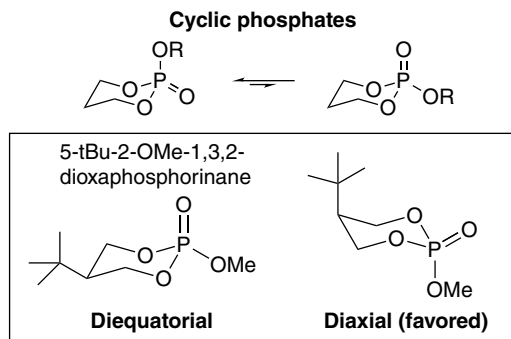


Figure 6.73 Conformational preferences in six-membered cyclic phosphate esters.

Syn-anomeric effect In order to achieve a better understanding of the conformational dependence of stereoelectronic effects in anomeric systems, Dunitz and coworkers asked whether a syn-oriented lone pair could provide “a similar, if perhaps weaker, effect on structure and reactivity relative to an anti-oriented lone pair” and play a role when the antiperiplanar orientation is inaccessible. Indeed, it was found that the “syn anomeric effect” is weaker but is still a strongly stabilizing effect in α -fluoroamines. Furthermore, it has similar structural features: an elongated C-F bond and a shortened C-N bond.¹²³ Taking into account the presence of two eclipsed CH/NH contacts and approximating their energies as ~ 1 kcal/mol (similar to the cost of CH/CH eclipsing in ethane), one can approximate the $n_N \rightarrow \sigma_{C-F}^*$ stabilization for the anti- and syn geometries as 8 vs. 5 kcal/mol, respectively (Figure 6.74).

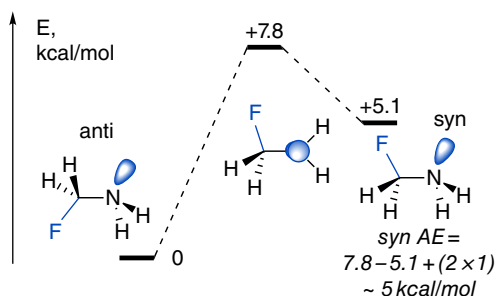


Figure 6.74 Comparison of anti- and syn-anomeric effects for fluoromethyl amine.

The anomeric effect is especially important in the chemistry of sugars and carbohydrates (more details in Chapter 10).¹²⁴ It facilitates a variety of reactions where a leaving group is positioned next to a lone pair containing heteroatom. For example, the acid catalyzed hydrolysis of the alcohol protecting group, methoxymethyl ether, is aided by C-O bond weakening due to the anomeric effect. The anomeric effect also assists in other reactions of acetals such as the Petasis–Ferrier rearrangement when the leaving group is a tethered enol ether (Figure 6.75).

Anomeric effects without carbon atoms Anomeric effects are also present in non-carbon systems. For example, the anomeric effect in an O-B-Cl moiety was used to synthesize enantiomerically pure chloroborane¹²⁵ and obtain the first X-ray structure of a chiral borane species (Figure 6.76a). Anomeric interactions through boron in a BF_2 moiety also contribute to the stability of the popular family of BODIPY dyes (Figure 6.76b).

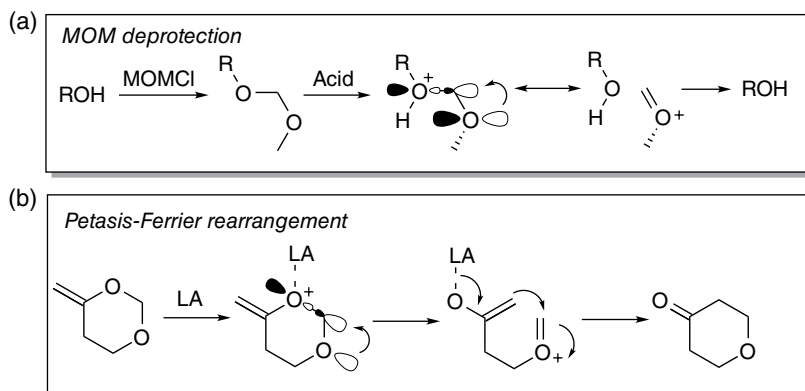


Figure 6.75 Examples of anomeric assistance to reactivity. (a) MOM deprotection; (b) Petasis-Ferrier rearrangement.

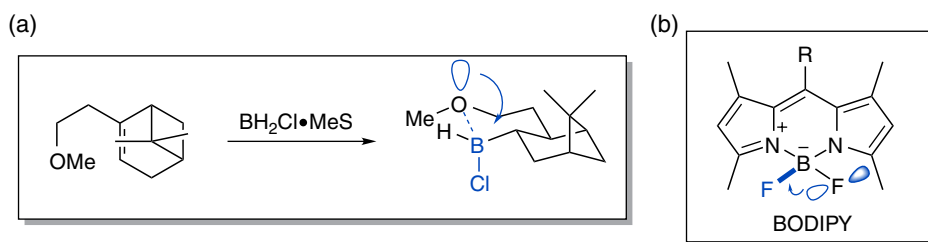


Figure 6.76 (a) Synthesis of enantiomerically pure chloroborane compound utilizing the anomeric effect in a $n_{\text{O}} \rightarrow \sigma^*_{\text{B-Cl}}$ interaction. (b) $n_{\text{F}} \rightarrow \sigma^*_{\text{B-F}}$ interaction in BODIPY dyes.

The hyperconjugative $n_{\text{S}} \rightarrow \sigma^*_{\text{S-O}}$ interaction was suggested to be responsible for the preferred axial orientation of the S=O group in the 1,2-dithiane S-oxide in Figure 6.77.¹²⁶

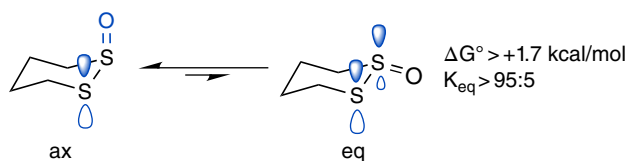


Figure 6.77 Anomeric effect in S-S-O system.

Homoanomeric effects Several interactions that involve a lone pair of atom X with the acceptor $\sigma^*_{\text{C-Y}}$ orbital in a X-CH-CHY- moiety have been suggested in the literature.^{127,128} Such “skipped” versions of the anomeric effect (i.e. the homoanomeric effects) include the W-effect in azacyclohexanes and the Plough effect in oxa- and thiacyclohexanes (Figure 6.78). Such through-space effects are conceptually different from the classic anomeric interactions and will be discussed in more detail in Chapter 9.

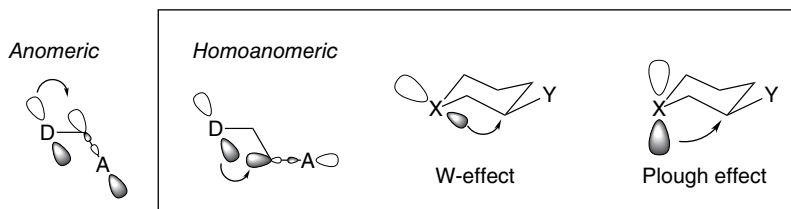


Figure 6.78 Two common homoanomeric interactions in six-membered saturated heterocycles: the W-effect and the Plough (“Big Dipper”) effect.

The vinylogous anomeric effect The anomeric effect can be extended through double bonds in what has been called the vinylogous anomeric effect (VAE). This effect, originally described by Ferrier and Sankey as the allylic effect,¹²⁹ stabilizes pseudoaxial orientation of the acyloxy group at C-3 in a glycal. Note that VAE can compete successfully with the gauche effect as illustrated in Figure 6.79 but is overridden when the gauche effect is assisted by additional axial alkyl substituents. This orbital interaction leads to C3–O bond lengthening and enhanced reactivity. It can be explained in terms of the stabilizing hyperconjugative interaction between the lone pair of endocyclic oxygen and the C3–O antibonding orbital, mediated by the relay alkene (the higher energy combination of lone pair and $\pi_{C=C}$ is shown in Figure 6.79).

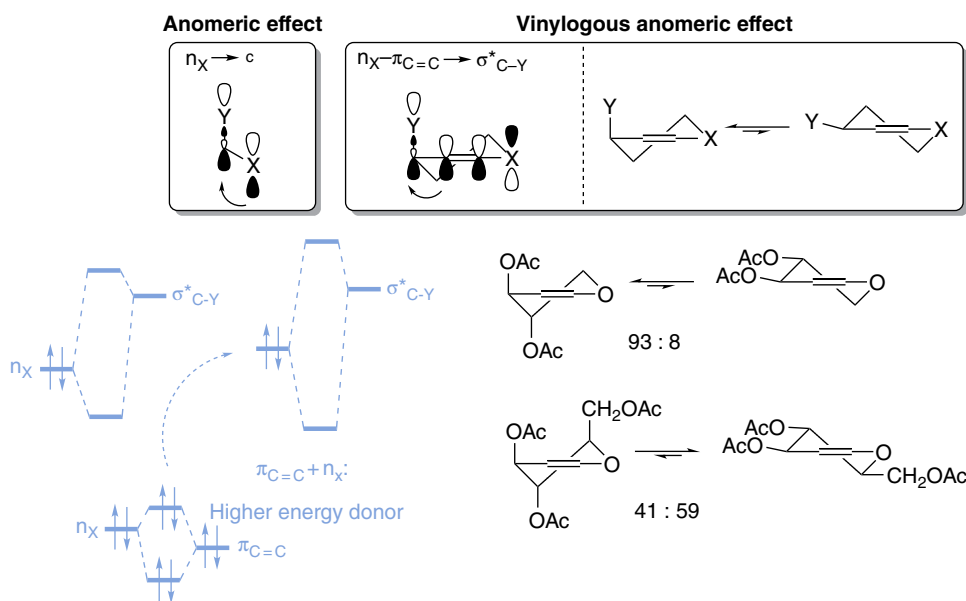


Figure 6.79 Vinylogous anomeric effect, caused by $(n-\pi) \rightarrow \sigma^*$ interactions, stabilizes axial conformers in glycals.

Katritzky and coworkers utilized X-ray crystallography to analyze the structure consequences of VAE in systems with *two* endocyclic double bonds and an exocyclic benzotriazole substituent (Figure 6.80). The two non-equivalent exocyclic bonds of the sp^3 – hybridized carbon atom occupy pseudoaxial (flagpole) and pseudoequatorial (bowsprit) positions. Importantly, the benzotriazole residue generally assumes the pseudoaxial position.¹³⁰ The exocyclic C–N bond is 0.02–0.03 Å longer than the C–N bond of the model compound without oxygen.

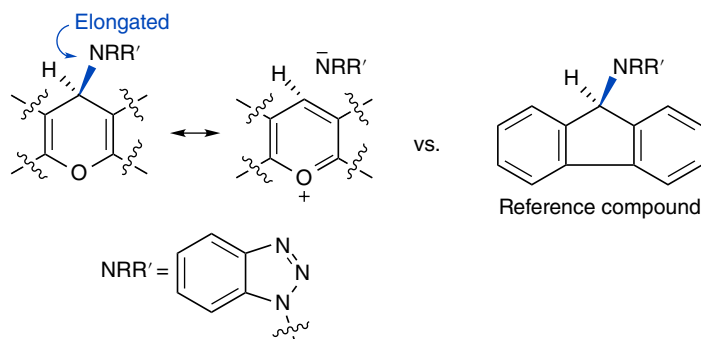


Figure 6.80 Structural consequences of the vinylogous anomeric effect.

VAE was also suggested to operate when the π -system is *exocyclic*, both in alkenes¹³¹ and ketoximes.^{132,133} In the case of ketoximes, the gauche effect is likely to serve as an additional source of destabilization for the pseudoequatorial conformer (Figure 6.81). We will discuss selected implications of VAE for chemical reactivity in Chapter 11.

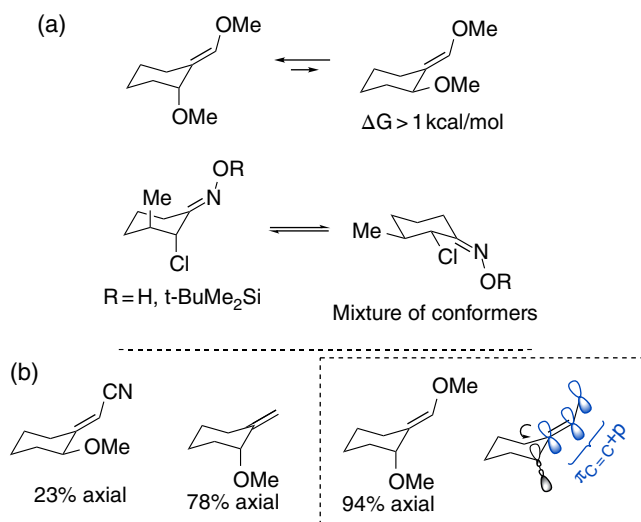


Figure 6.81 (a) VAE with the exocyclic π -systems. (b) electronic effects on the magnitude of VAE.

6.4.2 Reverse anomeric effect

As already mentioned, positively charged substituents can change their preference back to the equatorial position, in what is known as the reverse anomeric effect.¹³⁴ This was first observed for pyranosyl pyridinium ions, where vicinal ^1H NMR coupling constants indicated that the positively charged pyridine ring preferred the equatorial position.¹³⁵ The effective size of the pyridine ring is further increased by solvation of the positively charged substituent, when prohibitive steric repulsion associated with placing the bulky aromatic ring axial forces the pyridinium group into the equatorial positions.¹³⁴

Perrin and coworkers analyzed the reverse anomeric effect using the $\text{NH}_2/\text{NH}_3^+$ pair of substituents with the well-known steric size. The known A-values of NH_2 and NH_3^+ in cyclohexane (1.6 and 1.9 kcal/mol in D_2O , respectively) provide a measure of the steric effect. In contrast to previous studies of the reverse anomeric effect, which involved ring inversion, this choice of experimental system involved equilibration via simple anomerization of the amino group from equatorial to axial. If a reverse anomeric effect were operative, then N-protonation would increase the proportion of the equatorial anomers by more than predicted from the difference in A values. The ratios of amines in the axial and equatorial positions of glucopyranosylamines were determined in both acidic and non-acidic solvents (Figure 6.82).¹³⁶ The ratios were similar in the neutral and protonated species with a larger difference in aqueous media as a result of increased steric bulk of the highly solvated ammonium group. Based on these results, it was concluded that there is no reverse anomeric effect in cationic nitrogen species.¹³⁴ In fact, the slightly negative ΔA values (-0.018 to -0.368) in α - and β -N-(glucosyl)imidazoles are exactly opposite to what is expected from the reverse anomeric effect and are, instead, consistent with the slight *increase* of the normal anomeric effect.¹³⁷

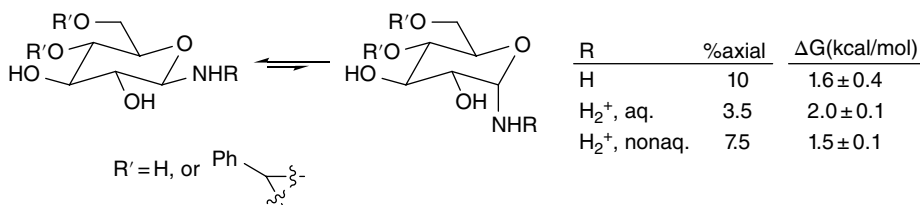


Figure 6.82 Study of the reverse anomeric effect in glucopyranosylammonium ions using the average percent of axial conformer present to determine the axial/equatorial free energy difference.

6.4.3 “Anomeric effects without lone pairs”: beyond the $n \rightarrow \sigma^*$ interactions

The definition of the anomeric effect is sometimes expanded to systems where the general shift in the conformational equilibrium is observed towards the axial conformer, even when such systems lack lone pairs in the ring.

Interesting conformational effects have been long known in disubstituted cyclohexanes (Figure 6.83).¹³⁸ For example, NMR studies found the diaxial conformer to be preferred for both the dichloro and dibromo 1,4-dihalocyclohexanes in the gas phase and in nonpolar solvents. Interestingly, the diequatorial 1,4-dichlorocyclohexane conformer is more stable in polar solvents. Considering the lack of dipole moment in both conformers of this symmetric molecule and the same quadrupole moments obtained from ab initio calculations, the origin of the polar solvent effect is intriguing.

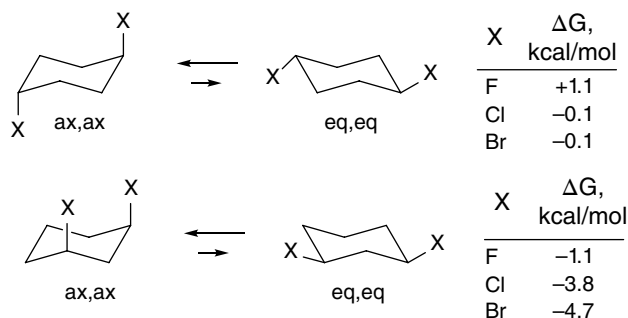


Figure 6.83 Conformational preferences in 1,3- and 1,4-dihalocyclohexanes.

The diaxial preference is further strengthened in 1,4-difluorocyclohexane whereas the ee-isomer is more stable in the respective 1,3-dihalocyclohexanes. This difference suggests that the unusual conformational preference of 1,4-isomer is likely to be stereoelectronic (note the unfavorable double hyperconjugation pattern where two $\sigma^*\text{CF}$ acceptors compete for the same donor – more details in Chapter 9). The conformational preferences in 1,2-difluorocyclohexane can be understood as an extension of the conformational preferences of 1,2-difluoroethane (the gauche effect).

The important role of hyperconjugation in substituted cyclohexanes and the consequences of hyperconjugative interactions of substituents with C-H and ring C-C bonds in the conformational equilibria have been thoroughly analyzed in a series of papers by Kleinpeter and Taddei (Figure 6.84).^{24,139}

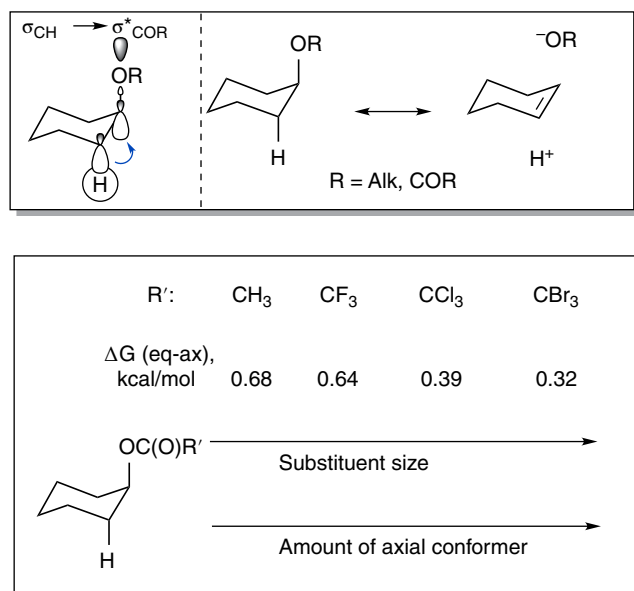


Figure 6.84 Hyperconjugative interactions responsible for stabilization of axial conformers in cyclohexyl ethers and esters.

An interesting switch in favor of diaxial conformer in 1,4-trans-disubstituted esters with the more acceptor CCl_3 and CBr_3 substituents was suggested to originate from the competition between $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-O}}$ (for axial) and $\sigma_{\text{C-C}} \rightarrow \sigma^*_{\text{C-O}}$ (for equatorial) interactions (Figure 6.85).^{24b} The diequatorial conformer is disfavored due to the “anticooperative” interactions of the two σ^*_{CO} acceptors with the same σ -bridge orbitals. This is an interesting manifestation of double hyperconjugation (see Chapter 9 for additional discussion of this remote stereoelectronic effect).

The electronic nature of the latter effect is illustrated by the continuous increase in the energetic preference for the diaxial conformer as the σ -acceptor ability of substituents in the ester group increases ($\text{CH}_3 < \text{CH}_2\text{Cl} < \text{CHCl}_2 < \text{CCl}_3$, Figure 6.85). The stereoelectronic stabilization in the 1,4-disubstituted cyclohexanes was suggested to be 0.3–0.5 kcal/mol higher than in their monosubstituted analogs. The effects of the increased steric demand on the diaxial/diequatorial differences was suggested to originate from the effect of bulky substituents on the orientation of the oxygen lone pairs relative to the ring bonds.

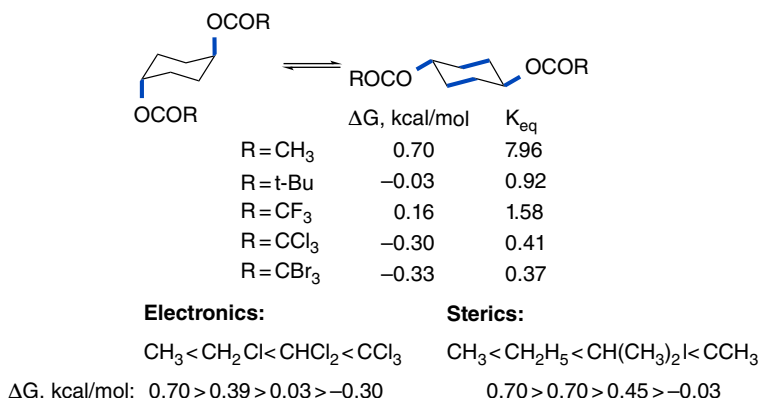


Figure 6.85 Steric and electronic effects in cyclohexyl diesters.

O'Hagan and coworkers recently described an interesting "facially polarized" all-cis 1,2,3,4,5,6-hexafluorocyclohexane.¹⁴⁰ NBO analysis of this molecule revealed strong interactions between fluorine lone pairs and σ^* orbitals associated with the geminal C-C and C-H bonds. Subsequently, Juaristi and Notario expanded the theoretical analysis to fluorinated trioxanes and trithianes and confirmed that fluorine lone pairs are good donors in a variety of $n_F \rightarrow \sigma^*_{C-Y}$ hyperconjugative interactions, where Y = H, C, O, S.¹⁴¹

Umpolung of anomeric effect A further extension of the anomeric effect has been used for C-Y donors and π -acceptors, where cyclohexanones, thiocyclohexanones, and methylenecyclohexanes benefit from $\sigma_{C-Y} \rightarrow \pi^*_{C-X}$ and $\pi_{C-X} \rightarrow \sigma^*_{C-Y}$ interactions.

For methylene cyclohexanes and C-X σ -acceptors (Figure 6.86), the dominant interaction pattern ($\pi_{C=C} \rightarrow \sigma^*_{C-X}$) is reminiscent of the anomeric effect. Experimental NMR conformational measurements and detailed dissection of NBO interactions in these systems has been provided by Tormena and coworkers.¹⁴² The 1,3 allylic strain can serve as an additional destabilizing effect that disfavors equatorial conformers for substituted alkenes.

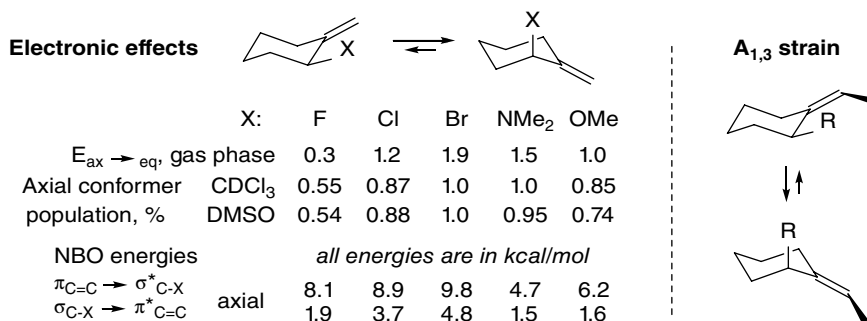


Figure 6.86 Electronic and steric effects in 2-substituted methylene cyclohexanes.

When the π -system is an acceptor (e.g. C=O or C=S) and substituent at the second position can be a donor, the dominant interactions change. Such systems are controlled by the positive hyperconjugation – donation from σ_{C-Y} to the $\pi^*_{C=X}$ orbitals. This change in polarity is opposite to negative hyperconjugation in the classic

anomeric systems discussed in the previous section. This situation can be classified as repolarization (“umpolung”) of the hyperconjugative pattern.

Selected hyperconjugative interactions for the pseudoaxial C(2,6)–H bonds adjacent to the exocyclic C=X group are summarized in Figure 6.87.¹⁴³

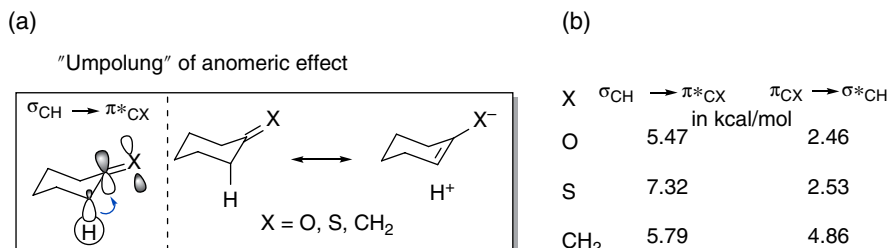


Figure 6.87 (a) “Umpolung of the anomeric effect” – positive hyperconjugation in cyclohexanones, thiocyclohexanones. Similar but more balanced interactions occur in methylenecyclohexanes. (b) NBO energies for donation from C–H bonds to exocyclic π -systems.¹⁴³

The values of $\sigma_{\text{C-H}} \rightarrow \pi^*_{\text{C-X}}$ are significantly larger for X = S than they are for X = O and CH₂. In the latter case, the interaction is more balanced, and the electron transfer in the opposite direction, via $\pi_{\text{C-X}} \rightarrow \sigma^*_{\text{C-H}}$ interaction, is only slightly smaller. The greater value of $\sigma_{\text{C-H}} \rightarrow \pi^*_{\text{C-X}}$ donation to thiacycarbonyl than in the analogous carbonyl compounds originates from the lower energy of the $\pi^*_{\text{C-S}}$ orbitals. Detailed NBO analysis for these structures is available in the literature.¹⁴³

In 1953, Corey reported that conformational equilibrium in α -chloro and bromo-substituted cyclohexanones strongly favors (>97%, ~2.3 kcal/mol) the axial conformer.¹⁴⁴ IR-analysis of the carbonyl stretching frequencies indicated that this conformational effect is accompanied by a red-shift in the carbonyl absorption, indicative of the C=O bond weakening due to the $\sigma_{\text{C-X}} \rightarrow \pi^*_{\text{C=O}}$ interaction.

The axial preference is general for 2-halocyclohexanones in the gas phase.¹⁴⁵ This preference increases in the same order F < Cl < Br < I ($\Delta E_{\text{eq-ax}} = 0.45, 1.05, 1.50,$ and 1.90 kcal/mol, respectively) as the energy of $\sigma_{\text{C-X}} \rightarrow \pi^*_{\text{C-X}}$ donation. However, hyperconjugation is unlikely to be the only important factor in this system. When X is more electronegative than carbon, the equatorial form is destabilized by repulsive dipole-dipole interactions. In polar solvents, such interactions are alleviated and, except for the iodo-derivative, the equatorial conformer becomes predominant.

In fact, the axial conformer of 2-fluorocyclohexanone is only preferred in the gas phase. This preference disappears even in non-polar solvents (Figure 6.88). The axial preference is more robust for the other halides. The axial conformer is the major conformer in all solvents for the iodo compound.¹⁴⁵

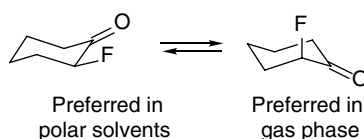


Figure 6.88 Conformational behavior of 2-fluorocyclohexanone.

Interestingly, this conformational preference is retained in 4-X-cyclohexanones (X = Cl, Br, I, OMe). Since direct hyperconjugation is transformed into a weaker C–C bridge-mediated double hyperconjugation, the effect is not strong. Depending on the solvent, the axial conformer of 4-OMe derivative is favored by only

0.01–0.5 kcal/mol.¹⁴⁶ Similar small preferences were reported for 4-halocyclohexanones (0.1–0.4 kcal/mol). In esters of 4-hydroxycyclohexanone, increased polarity of the ester group led to increased population of the axial conformer – $\text{Me} < \text{CH}_2\text{Cl} < \text{CHCl}_2 < \text{CCl}_3$.¹⁴⁷ Base-catalyzed equilibration of 3-ethyl-2-halocyclohexanones gives increasing amounts of cis-isomer with the axial position of X for the heavier halogens: $\text{Cl} < \text{Br} < \text{I}$.¹⁴⁸ Hydrazones, imines, and corresponding salts derived from 4-substituted cyclohexanones display similar properties.¹⁴⁹

These conformational preferences can be used for the control of reaction stereoselectivity. For example, whereas the reduction of 4-Me-cyclohexanone mostly gives the trans product, reduction of the 4-Cl-cyclohexanone leads to the preferential formation of the cis product.¹⁵⁰ Assuming the common axial preference for the nucleophilic attack at the carbonyl, the differences in reaction selectivity should reflect the different axial/equatorial populations of the two carbonyl reactants. Similar conformational preferences were suggested for the nucleophilic attack at oxonium ions (Figure 6.89).¹⁵¹

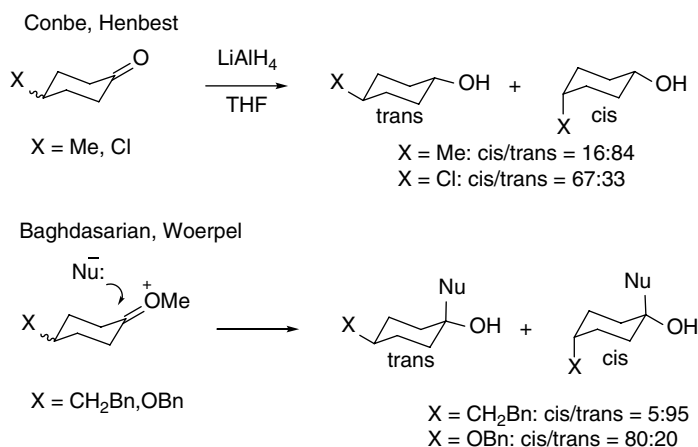


Figure 6.89 Conformational preferences translate into stereoselectivity in cyclohexanone and respective onium ions.

6.5 n/π -Interactions

6.5.1 Esters and related carboxylic acid derivatives

Several layers of stereoelectronic effects contribute to stability, conformational profiles and reactivity of carboxylic acid derivatives. We will illustrate the interplay between these effects using esters as an example.

The first level corresponds to the interactions with the strongest acceptor (the carbonyl group) with the best donor, i.e. the p-type lone pair of oxygen (Figure 6.90). This interaction plays a key role in moderating reactivity of esters towards nucleophiles. Esters are more reactive than amides but less reactive than acyl halides due to the differences in the strength of $n_{\text{X}} \rightarrow \pi^*_{\text{C=O}}$ interactions. Additional stabilizing $n_{\text{X}} \rightarrow \pi^*_{\text{C=O}}$ interactions can be introduced by the second heteroatom substituent in carbonates, carbamates, and ureas. Such double donation notably decreases the carbonyl electrophilicity in such compounds, increases stability, and introduces new reactivity patterns. For example, dimethyl carbonate can react as an alkylating agent in an $\text{S}_{\text{N}}2$ process instead of undergoing the usual addition/elimination reaction at the carbonyl.¹⁵²

The second level is composed of the hyperconjugative interaction of alkyl groups with the carbonyl. Even though this is formally a neutral hyperconjugation pattern, it is dominated by $\sigma_{\text{C-H}}/\sigma_{\text{C-R}} \rightarrow \pi^*_{\text{C=O}}$ donation. The latter effects are particularly significant for the stronger σ -donors. In such cases, the consequences of this conjugation can be utilized in the molecular design, as illustrated by the unusual properties of cyclopropyl esters (vide infra).

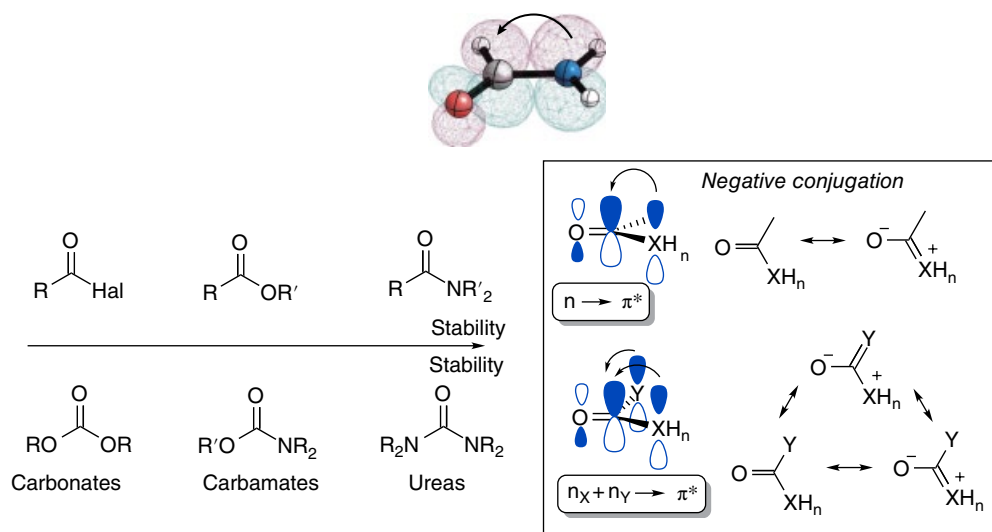


Figure 6.90 Negative conjugation in heterosubstituted carbonyl compounds, such as esters and amides, results in $C=X$ partial double bond character and decreased electrophilicity of the carbonyl carbon.

Because bent C-C bonds of cyclopropanes are good hyperconjugative donors, this group provides significant stabilization to the carbonyls via $\sigma_{C-C} \rightarrow \pi_{C=O}^*$ donation (Figure 6.91). Because this donation is lost in the tetrahedral intermediate of the acid- and base-promoted hydrolysis, this stabilization effect corresponds to selective reactant stabilization and accounts for the decreased reactivity of such esters. “Replacement energies” from the isodesmic equations below suggest that cyclopropyl provides ~ 2.4 kcal more stabilization than a methyl. Based on this hyperconjugative effect, the cyclopropyl esters have been suggested as potential prodrugs with enhanced hydrolytic stability.¹⁵³

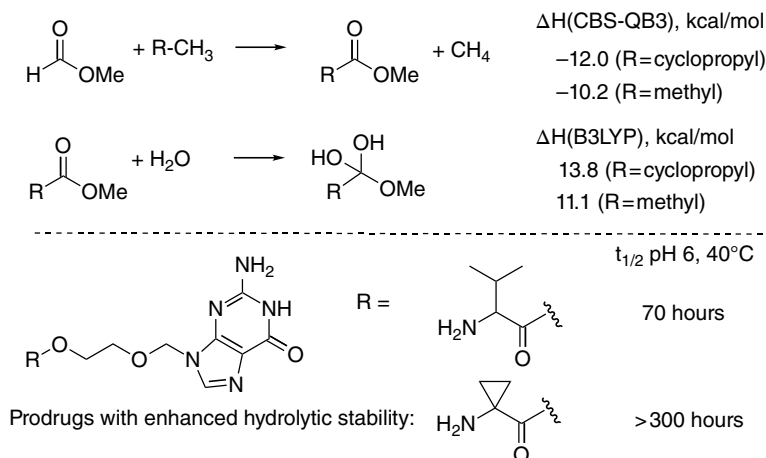


Figure 6.91 Control of the stability and reactivity of esters via $\sigma_{C-C} \rightarrow \pi_{C=O}^*$ interactions with strained cyclopropyl C-C bonds.

Umpolung of the above interactions operates in those molecular systems where $n \rightarrow \sigma_{\text{C-C}}^*$ delocalization is dominant. For example, cyclopropylamine is slower to couple with a carboxylic acid than isopropylamine. Similar reactivity pattern is observed for N-alkylation. In fact, the reactivity of cyclopropylamine in these reactions is comparable to aniline, suggesting the increased importance of $n \rightarrow \sigma_{\text{C-C}}^*$ hyperconjugation for the strained bonds of cyclopropane.

E,Z-conformation of esters and related compounds Esters and carboxylic acids often prefer to orient substituents towards the carbonyl, despite the steric consequences (Figure 6.92). The *Z*-isomer is preferred by ~ 5 kcal/mol in the gas phase for methyl formate. The difference is even larger (~ 8 kcal/mol) for methyl acetate.¹⁵⁴

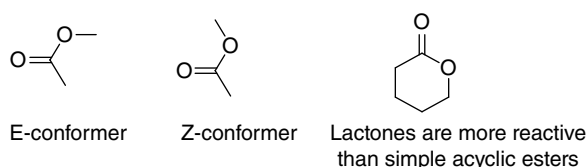


Figure 6.92 Two conformations of esters: which one is more stable?

Even for bulky *t*-Bu groups, there is a 9:1 preference for the *Z*-conformation (Figure 6.93).¹⁵⁵ When the disfavored *E*-conformation is forced by the cyclic framework (i.e. in lactones), decreased stability and greater reactivity are observed. Similar trends are observed for carboxylic acids. For example, microwave spectroscopic data suggests that the *E*-rotamer of formic acid is 3.9 kcal/mol higher in energy than the *Z*-rotamer, and the two structures are separated by a barrier of 13.8 kcal/mol.¹⁵⁶

The preference for the *syn*-isomer can be described via the combination of primary and secondary stereoelectronic effects in the σ/π -model, or via two antiperiplanar lone pair interactions using the τ -model.⁴⁸ Using the more familiar σ/π -model, the *syn*-conformation benefits from hyperconjugative $n \rightarrow \sigma_{\text{CO}}^*$ stabilization analogous to the anomeric effect, in which in-plane lone pairs can donate into the σ_{CO}^* orbital of the carbonyl moiety (Figure 6.93). This is a “second-level” interaction that is weaker than the dominant “first-order” $n \rightarrow \pi_{\text{C=O}}^*$ interaction between the p-type lone pair of oxygen and the carbonyl π -system. However, since the “first order” interaction does not change upon the rotation, it is the “second order” effect that is responsible for the difference in stability.

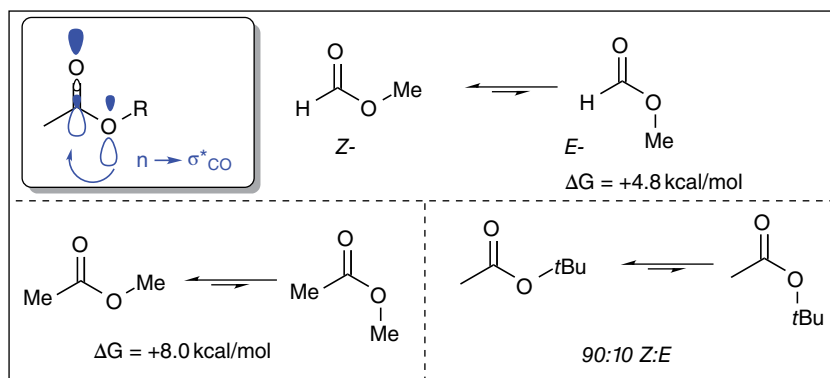


Figure 6.93 Negative hyperconjugation (the anomeric effect) is responsible for the *Z*-preference in esters.

This strong conformational preference may come as a surprise but it is general and valuable in molecular design. Indeed, a recent comprehensive review of conformations of drug-like molecules makes the following comment regarding such preferred geometries: “The $\text{O}=\text{C}-\text{O}-\text{C}$ torsion angle of acyclic esters, for example, is highly constrained, almost never deviating from 0° by more than 10° , yet it is commonly counted as a ‘rotatable bond’”.¹⁵⁷

When the s-trans geometry is enforced in an ester by cyclic constraints, i.e. in the formation of lactones, the absence of this stabilizing effect leads to increased reactivity. For example, lactones are more electrophilic and susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters because the anomeric $n_{\text{O}} \rightarrow \sigma^*_{\text{C-O}}$ donation decreases the carbonyl acceptor ability in acyclic esters but is absent for lactones.

The energy difference between the E- and Z-esters is significantly reduced upon their deprotonation with the formation of respective enolates.¹⁵⁸ For example, the calculated deprotonation energy from the E-conformer of methyl acetate was smaller by 4.7 kcal/mol than that of the Z-conformer.¹⁵⁹ A number of factors can contribute to this difference but, at least partially, this effect can be explained by the reduced acceptor ability of the C-O bond of the enolate where the oxygen atom has significant negative charge and by the subsequent decrease in the energy of the $n_{\text{O}} \rightarrow \sigma^*_{\text{C-O}}$ stabilization (Figure 6.94).

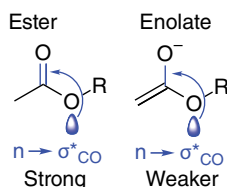


Figure 6.94 Comparison of $n_{\text{O}} \rightarrow \sigma^*_{\text{C-O}}$ stabilization in esters and their enolates.

As the result of this difference, lactones enolize much more readily than acyclic esters ($\text{pK}_{\text{a}} \sim 25$ vs. $\text{pK}_{\text{a}} \sim 30$). This rule also applies to similar dicarbonyl compounds (Figure 6.95).¹⁶⁰

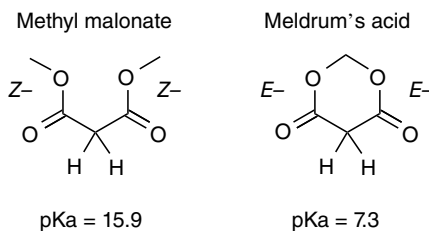


Figure 6.95 The difference in the C-H acidity of E- and Z-esters: the Meldrum's acid ($\text{pK}_{\text{a}} 7.3$, in DMSO at 25°C) is significantly more acidic than its open-chain analogue, dimethyl malonate ($\text{pK}_{\text{a}} 15.9$, in DMSO at 25°C).

The strong Z-conformational preference of esters can be eroded by attaching a stronger $\sigma\text{-C-X}$ acceptor to the carbonyl. Such substituents can provide the E-conformer with $n_{\text{O}} \rightarrow \sigma^*_{\text{C-X}}$ interaction of comparable strength. The experimental IR data supports the presence of a cis-trans conformer in the liquid phase, with an enthalpy difference of 2.6 ± 0.5 kcal/mol between the more stable cis-cis form and the cis-trans conformer.¹⁶¹ The high-level (CCSD(T) and RCCSD(T)-F12) computations find the differences between conformers is ~ 3.1 kcal/mol in the gas phase (Figure 6.96).¹⁶² NBO analysis of the key interactions involved in conformational equilibrium of dimethyl carbonate finds that if the vicinal interactions are deleted, this conformational preference is inverted.¹⁶³ Conformational discussion in carbamates in the literature generally concentrates on rotation around the C-N bond, indicating that rotamer population for the C-O bond is shifted largely to one conformer (likely to be the cis-isomer).¹⁶⁴

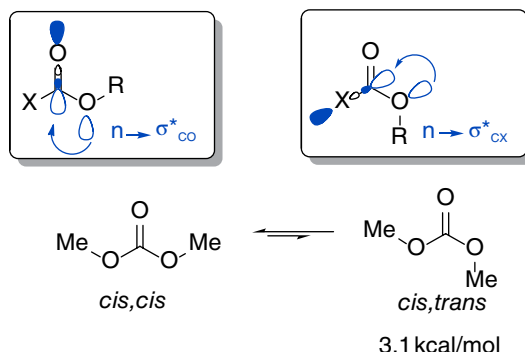


Figure 6.96 Colliding anomeric effects in carbonates.

The syn, syn form of dimethyl thiocarbonate is the major conformation in the gas phase but IR studies in solutions indicate that contribution of the syn, anti- form is considerable and increases further with the increasing solvent polarity. This data is consistent with the lower contribution from the $n_s \rightarrow \sigma_{C=S}^*$ interaction in comparison with the analogous effect in carbonates. This difference can be traced back to the differences in the donor abilities of S and O lone pairs discussed in Chapter 5.

Since $n_X \rightarrow \sigma_{C=O}^*$ interactions involved in E,Z-isomerism of esters and the related carboxylic acid derivatives require the presence of a second lone pair at X, they do not manifest themselves in the ground state geometry of amides where only one lone pair is present on X and it is confined to coplanarity with the π^* of the carbonyl. However, such stereoelectronic effects manifest themselves in transition states for rotation around the C-N bond in amides where $n_N \rightarrow \sigma_{C=O}^*$ interactions accentuate the facilitating role of nitrogen pyramidalization on this process. The pyramidalization TS1 that corresponds to anti arrangement of the nitrogen lone pair and the $\sigma_{C=O}^*$ was found to be ~ 4 kcal/mol lower in energy than the alternative TS2 where the lone pair and the $\sigma_{C=O}^*$ orbital are syn to each other (Figure 6.97). The two transition states have very different polarity and are stabilized by solvent effects to a very different extent.¹⁶⁵ However, when R=OMe in the respective carbamate, the difference between the two transition states is only 0.6 kcal/mol at the same level of theory. This observation is consistent with the greater hyperconjugative stabilization originating from the $n_N \rightarrow \sigma_{C-R}^*$ interaction for R=OMe. The differences in the balance of two hyperconjugative effects in amides and carbamates is involved in the dramatically different solvent effects for the rotation around the C-N bond in these families of carbonyl compounds.¹⁶⁶ It is also possible that $n_O \rightarrow \pi^*$ donation in the twisted carbamate assists in compensating for the loss of $n_N \rightarrow p^*$ donation in the twisted geometry.

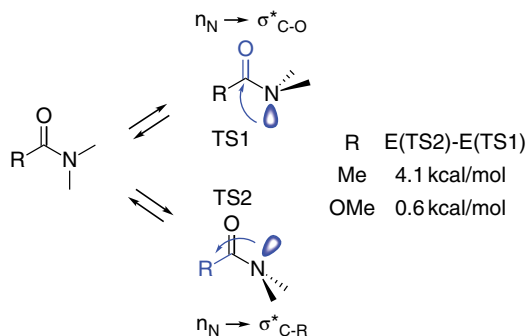


Figure 6.97 Stereoelectronic effects associated with pyramidalization in the twisted transition states for rotation around the C-N in amides and carbamates.

Amides Amides, one of the most important functional groups in chemistry and biology, derive their thermodynamic stability and structural rigidity – the two features that are paramount for the numerous applications of amides as building blocks in biomolecules, synthetic polymers, and pharmaceuticals – from the $n_{\text{N}} \rightarrow \pi^*_{\text{C=O}}$ interaction. The stabilizing conjugation of lone pairs with the carbonyl π^* -orbital is stronger in amides than it is in esters.¹⁶⁷ As the amide bond is omnipresent in peptides, this interaction plays a key role in the conformational rigidity and reactivity of this important class of biomolecules.

The nature of amide resonance has been critically reanalyzed recently and the classic picture has been refined. Wiberg compared three resonance structures and suggested that the latter two are of major importance for the rotational barrier (Figure 6.98).¹⁶⁸ This analysis emphasizes that orbital overlap is between nitrogen and carbon, and that the generally used resonance structure II overestimates charge transfer to oxygen because the $\pi^*_{\text{C=O}}$ orbital is strongly polarized towards carbon (i.e. it has low orbital coefficient on the oxygen). However, this refinement addresses the limitations of resonance structures in describing the electronic consequences of $n_{\text{N}} \rightarrow \pi^*_{\text{C=O}}$ orbital interaction. There is no doubt of the importance of this interaction itself. It remains well-established and generally accepted.

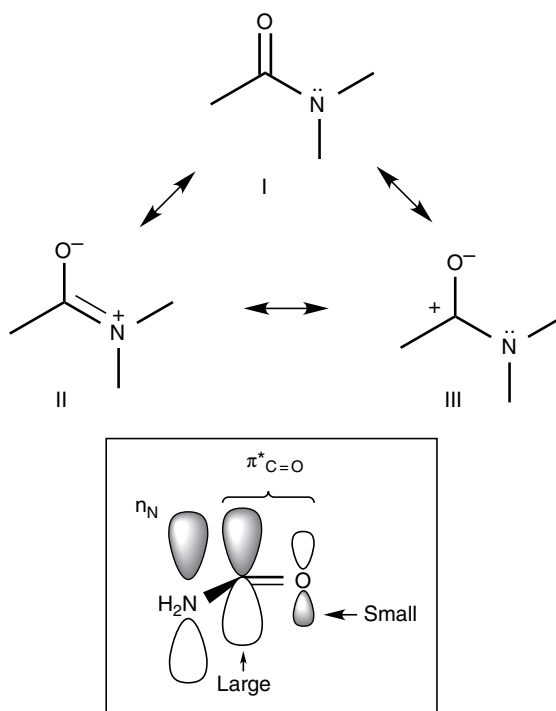


Figure 6.98 Refined description of amide resonance.

The effect of delocalization and its interplay with rehybridization in amides can be evaluated from rotational barriers in Figure 6.99. The flat conjugated geometry is the most stable. Pyramidalization of nitrogen slightly increases the energy (~ 5 kcal/mol for corner (b) in Figure 6.99) because it sacrifices the favorable overlap between the lone pair and the carbonyl. Note, however, that small deviations from planarity have relatively low penalty. On the other side, twisting imposes a much greater energetic penalty. The fully twisted form with sp^2 hybridized nitrogen is almost 25 kcal/mol higher in energy (corner (c) in the figure). Part of this energy cost can be offset by pyramidalization/rehybridization (~ 8 kcal/mol decrease to the overall energy of ~ 16 kcal/mol, corner (d)).

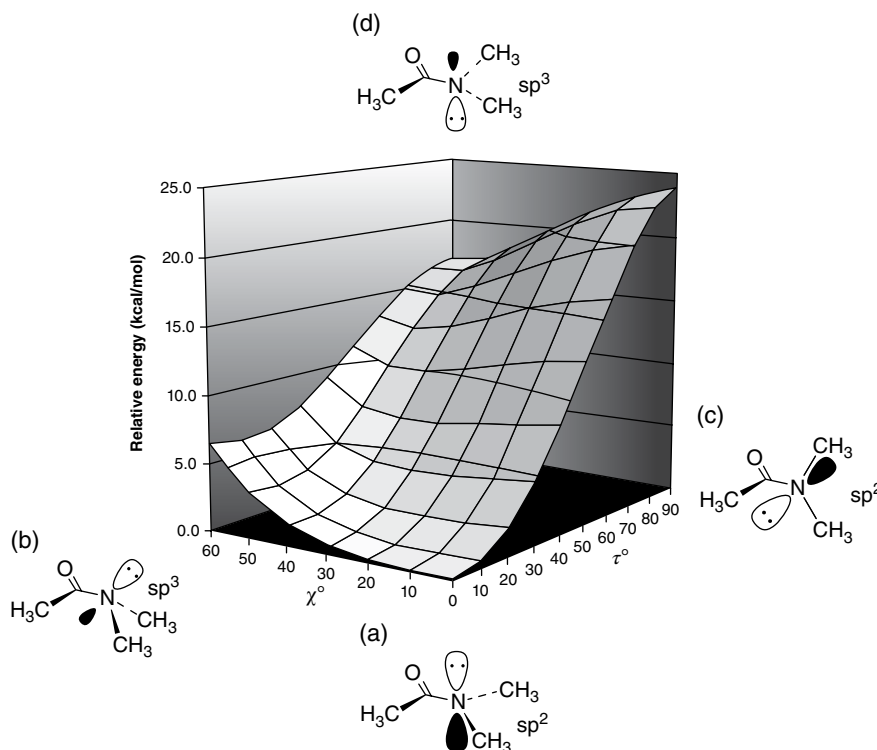


Figure 6.99 B3LYP/6-31G(d) energy surface for the deformation of *N,N*-dimethylacetamide. (Source: Glover 2012 (169). Reproduced with permissions of American Chemical Society.) χ and τ are the pyramidalization and twist parameters in degrees. Structures correspond to: (a) the planar lowest energy conformer; (b) an untwisted form with sp^3 hybridized nitrogen; (c) a fully twisted form with sp^2 hybridized nitrogen; and (d) a fully twisted form with sp^3 hybridized nitrogen. In the last case, rehybridization to the “natural” state of trivalent nitrogen alleviates the loss of conjugation.

The C-N rotational barrier in thioformamide is larger than in formamide. Although the C=S bond is not strongly polarized and the C=S carbon is considerably less electron deficient than the amide C=O carbon, the $\pi^*_{\text{C=S}}$ energy in thioamides is much lower than the $\pi^*_{\text{C=O}}$ in amides (see Chapter 5 for a more detailed discussion of acceptor ability of orbitals). Due to the lower donor/acceptor energy gap, the $n_{\text{N}} \rightarrow \pi^*_{\text{C=S}}$ resonance is significant for thioamides, even in the absence of π -bond polarization.¹⁷⁰ The increased resonance and increased acidity of thiourea protons finds applications in the design of organocatalysts (Figure 6.100).¹⁷¹

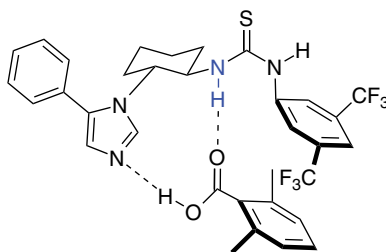


Figure 6.100 Use of the NH bond acidity in a cooperative catalytic system based on a thiourea.¹⁷²

A number of structural and electronic factors can interfere with the amide resonance (Figure 6.101). The reasons for the resonance loss can be structural (enforced twisting due to steric hindrance or due to cyclic restraints that lock the nitrogen lone pair out of alignment with the carbonyl) or electronic (pyramidalization at nitrogen due to rehybridization imposed by strain or electronegativity, i.e. Bent's rule).¹⁶⁹

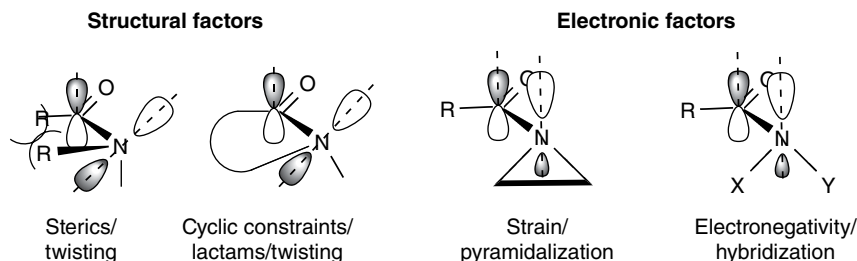


Figure 6.101 Structural and electronic constraints that can interfere with amide resonance.

In order to quantify the deviations from the “ideal” resonance situations, the indexes of “amidicity” have been suggested that compare normal amides, e.g. acetamide, with amides with compromised resonance patterns.¹⁶⁹

Figure 6.102 presents several isodesmic equations and the amidicity indexes for the representative amines. Note that the estimates are sensitive to levels of theory, and the energies can be refined further by corrections for strain, sterics, and other additional factors. For further details on such corrections, see ref. 168. The carbonyl substitution/nitrogen atom replacement (COSNAR) method estimates amide resonance as stabilization gained by translocating a carbonyl and an amine into the same skeleton to give an amide.¹⁷³ The transamidation (TA) method compares amides with N,N-dimethylacetamide. The maximum possible loss of resonance is estimated from the destabilization of the fully twisted 1-aza-2-adamantanone (~18.2 kcal/mol at the B3LYP/6-31G(d) level).¹⁶⁹ The percentage of amidicity relative to N,N-dimethylacetamide is then derived from the following equation: $100 \times (18.17 - \Delta E_{\text{TA}}) / 18.17 (\%)$.

Carbonyl substitution/nitrogen atom replacement (COSNAR) method						
Transamidation (TA) method						
Reference amides 						
Amidicity:	0%	100%	67%	110%	58%	47%
ΔE_{COSNAR}	0	-18.5	-11.4	-20.0	-7.1	-8.6
ΔE_{TA}	+18.2	—	+6.0	-4.0	+7.6	+13.9

Figure 6.102 Amidicity and estimates of amide resonance in representative amides.

The data is generally in agreement with the expectations based on the sterics and structural distortions with the possible exception for the β -lactam where the calculations suggest *higher* amidicity for N,N-dimethylacetamide. Glover and coworkers report that β -lactams are essentially planar, and amide resonance in related monocyclic lactams is also efficient.¹⁶⁹

Electronic factors As already discussed, the stabilizing effect of amide resonance is partially mitigated by the hybridization penalty associated with planarization of the nitrogen atom. When rehybridization is difficult, such planarization can require additional energy. N,N-dialkoxyamides, also referred to as “anomeric amides”, illustrate the importance of hybridization effects on the amide properties.¹⁷⁴ One could, perhaps naively, expect that the nitrogen atom in such molecules would be planar to provide the best possible communication path between the carbonyl and the donor lone pairs of oxygens. However, hybridization factors readily explain why nitrogen is pyramidalized. The electronegative oxygen atoms require the central nitrogen atom to allocate more p-character to the N-O bonds in order to satisfy Bent’s rule.¹⁷⁵ Due to this reallocation, there is not enough p-character left to have a 100% p-lone pair at nitrogen. Introduction of an s-character into the lone pair leads to pyramidalization and a partial loss of resonance. X-ray structures of anomeric N,N-dialkoxyamides confirm that they are highly pyramidalized at nitrogen and have long N-CO bonds, a consequence of drastically reduced amidicity. The solid state structures also display chirality at the nitrogen. N-chloro, N-methoxy 4-nitrobenzamide¹⁷⁶ and N-chloro-N-methoxyurea¹⁷⁷ also show the relatively high degrees of pyramidalization.

Another way to use oxygen substitution to decrease the importance of amide resonance is to allow the lone pair of oxygen to compete directly with the lone pair of nitrogen for donation to the carbonyl acceptor. Such competition between $n_O \rightarrow \pi^*_{C=O}$ and $n_N \rightarrow \pi^*_{C=O}$ defines unusual stereoelectronic features of carbamates where the barriers to rotation around the C-N bond are usually 3–4 kcal/mol (about 15–20%) lower than those in the corresponding amides.¹⁶⁶

Geometric factors Unfavorable geometry can prevent $n_N \rightarrow \pi^*_{C=O}$ conjugation when a bridgehead nitrogen is directly bound to a carbonyl (Figure 6.103), as such orbital interaction would build double bond character, a violation of Bredt’s rule.¹⁷⁸ In the presence of structural modifications that disrupt this resonance, chemical properties and stability of amides drastically change.¹⁷⁹ When the nitrogen lone pair is forced out of alignment with the carbonyl π -system in the twisted form, the usual electronic properties of amides, i.e. the decreased basicity at the nitrogen, are not observed.

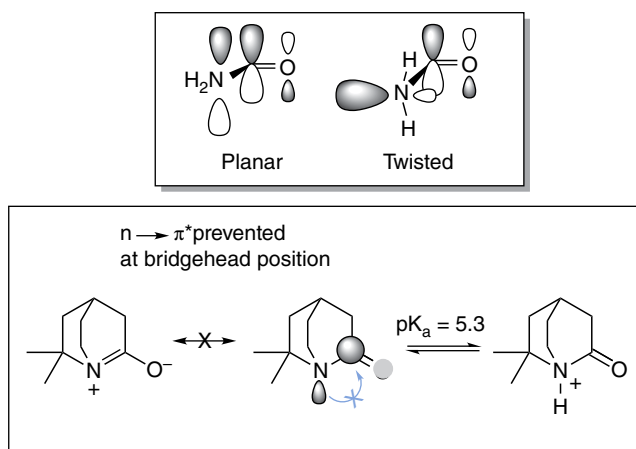


Figure 6.103 Top: Planar and twisted amide bonds. Bottom: “Anti-Bredt’s” amides – nitrogen atoms at the bridgehead of bicyclic compounds cannot participate in negative conjugation characteristic of amides.

Chemical properties of twisted amides are drastically different from the properties of usual amines. For example, protonation on oxygen rather than on nitrogen is favored by 10–15 kcal/mol for unstrained amides and lactams but protonation on nitrogen is favored by ca. 20 kcal/mol for strained bridgehead bicyclic lactams (“2-quinuclidone”¹⁸⁰ and 1-azaadamantan-2-one¹⁸¹).¹⁸² We will discuss chemical peculiarities of such “anti-Bredt” amides along with their interesting history further in Chapter 10.

σ-effects in amides In N-substituted amides, the $\sigma_{\text{N-H}} \rightarrow \sigma_{\text{C=O}}^*$ hyperconjugation may contribute to the observed preference for the s-cis conformer over the s-trans conformer. In amides, the relative importance of steric interactions for the two R groups eclipsing each other and dipole effects is larger than it is in esters. In esters, the difference between the E- and Z-conformers is significantly larger due to the presence of the stronger $n_{\text{O}} \rightarrow \sigma_{\text{C=O}}^*$ interaction. Still, the s-cis conformational difference in amides is likely to play a role in defining the fundamental shapes of protein chains (Figure 6.104).

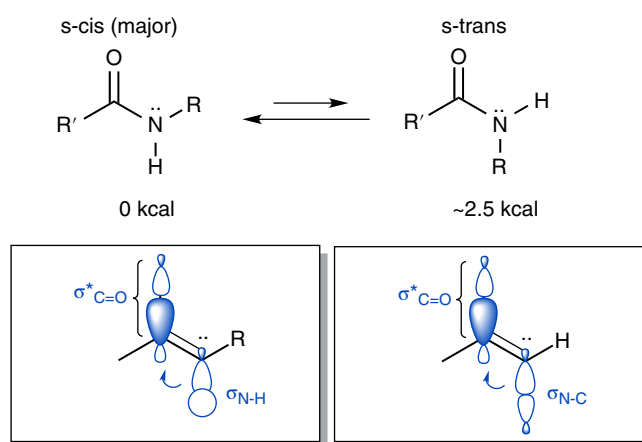


Figure 6.104 *s-cis and s-trans conformers of N-substituted amides.*

In N-monosubstituted carbamates, the anti N-C rotamer is usually favored by 1.0–1.5 kcal/mol. Because the difference is small, it can be overridden by other factors. For example, the syn-conformer can be selectively stabilized by H-bonding with carboxylic acids (Figure 6.105).¹⁸³

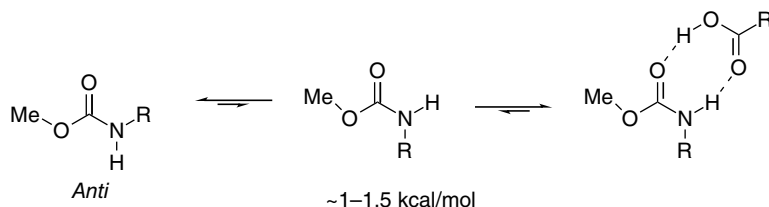


Figure 6.105 *Conformations of N-monosubstituted carbamates.*

The conformational footprint of the amide group can be extended even further as illustrated by the observations of preferred conformational “spaces” for the C-NH-C(O) moieties. For amides at the secondary carbons, there is a preference for α -C-H eclipsing the carbonyl (Figure 6.106). The more substituted amides, where three substituents at the same carbon try to avoid the syn arrangement, have three accessible rotamers.¹⁸⁴

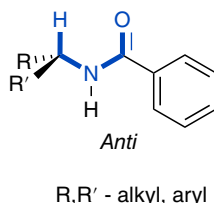


Figure 6.106 Amides at the secondary carbons display a conformational preference for α -C-H bond eclipsing the carbonyl.

6.5.2 Vinyl ethers and enamines

Latent negative hyperconjugation When a heteroatom with a lone pair is connected to a C=C bond, the ground state interaction is still unidirectional ($n \rightarrow \pi^*$) but it is less pronounced than it is in carbonyls. However, the importance of this interaction can increase dramatically in transition states for electrophilic attack at such double bonds, providing stabilization to the developing positive charges. As a result, enamines and vinyl ethers are highly reactive towards electrophiles. Furthermore, these reactions also proceed regioselectively, with the formation of carbocations that are strongly stabilized by $n \rightarrow p_+$ interactions (Figure 6.107).

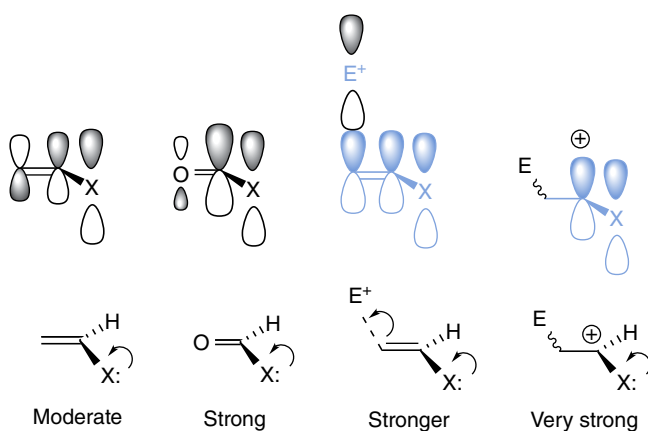


Figure 6.107 Evolution of $n \rightarrow \pi^*/p_+$ interactions in vinyl compounds.

Many new chemical transformations in the burgeoning field of organocatalysis are based on reliable C-C bond formation where enamines serve as reactive and regioselective nucleophilic reagents in reactions with carbon electrophiles. Addition of HBr proceeds via the formation of α -cation stabilized by resonance. When the lone pair is constrained and the overlap with the cation is less efficient, the regioselectivity of addition changes and the cationic center is formed further away from nitrogen (Figure 6.108).¹⁸⁵

The stabilizing effects of $n \rightarrow \pi^*$ interactions in vinyl compounds can be probed via isodesmic equations, such as the group separation reactions of the vinyl derivatives with ethane analyzed in detail by Wiberg and Rablen (Figure 6.109).¹⁸⁶ As always, such energies should be taken as an estimate because they are not free from sigma effects (i.e. rehybridization) and from the imbalances in hyperconjugation (the strong hyperconjugative stabilization of alkyl acetylenes will be analyzed in more detail later in this

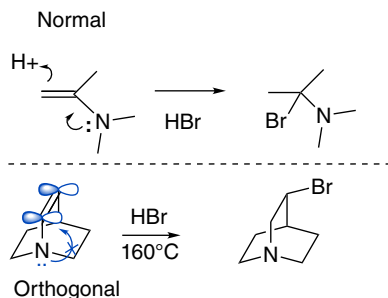


Figure 6.108 Switch from the selective β -attack in normal enamines to an α -attack in the “orthogonal” enamine in reaction with HBr.

	X	ΔE , kcal/mol	Method
$\text{O}=\text{CH}_2 + \text{H}_3\text{C}-\text{CH}_3 \longrightarrow \text{O}=\text{CH}_3 + \text{H}_3\text{C}-\text{X}$	NH_2	+19.6	exp
	OH	+23.4	
	F	+17.9	
$\text{CH}_2=\text{CH}_2 + \text{H}_3\text{C}-\text{CH}_3 \longrightarrow \text{CH}_2=\text{CH}_3 + \text{H}_3\text{C}-\text{X}$	NH_2	+6.3	G2
	OH	+6.4	
	F	+2.4	
$\text{C}\equiv\text{CH} + \text{H}_3\text{C}-\text{CH}_3 \longrightarrow \text{C}\equiv\text{CH}_3 + \text{H}_3\text{C}-\text{X}$	NH_2	-0.2	G2
	OH	-6.2	
	F	-17.4	

Figure 6.109 Comparison of apparent stabilization energies associated with $n \rightarrow \pi^*$ interactions in carbonyl, vinyl, and alkynyl heteroatomic derivatives.

chapter). For example, alkynes with σ -bonds to electronegative elements are destabilized by unfavorable hybridization (a consequence of Bent’s rule¹⁷⁶) to the extent where this effect completely masks the stabilizing effect of $n \rightarrow \pi^*$ interactions.

Rotation around the $\text{C}(\text{sp}^2)\text{-N}$ bond of enamines is slower (4–6 kcal/mol barrier) than the corresponding process in saturated amines. On the other hand, *cis-trans*-isomerization of the $\text{C}=\text{C}$ bond is faster than it is in alkenes without a heteroatom.¹⁸⁷ Both of these effects illustrate the importance of $n_{\text{N}} \rightarrow \pi^*$ resonance for this functional group.

The stabilizing role of the lone pair/ π -bond interaction is illustrated by the position of equilibrium between allyl amines and enamines that generally favors the enamine by ~4 kcal/mol. In 1-azabicyclo[3.2.2]non-3-ene, the “orthogonal enamine” prepared by Doering and coworkers, this difference disappears (Figure 6.110a). In the equilibration of the orthogonal enamine with 1-azabicyclo[3.2.2]non-2-ene, the respective allyl amine, no free energy difference was found between the two molecules.¹⁸⁸

The $n \rightarrow \pi^*$ interaction can be switched off if two strongly acceptor antiperiplanar $\sigma_{\text{C-O}}^*$ orbitals are available for the lone pair of nitrogen (Figure 6.110b). It was also suggested that the alkene π -system orients itself perpendicular to the lone pair to decrease steric repulsion.¹⁸⁹ This enamine is so unreactive that it cannot be isomerized into the *trans* double bond isomer without fission of the heterocyclic ring.¹⁹⁰

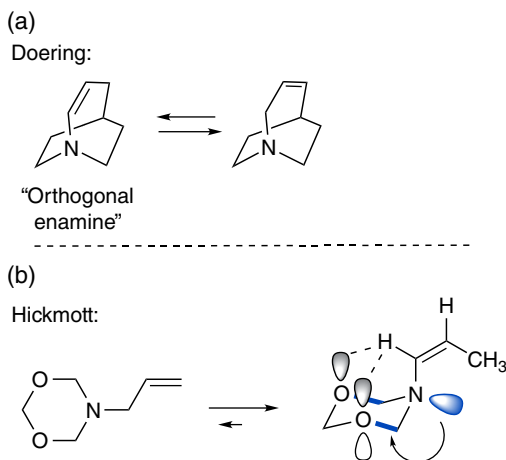


Figure 6.110 Structural and electronic approaches towards deactivation of $n_N \rightarrow \pi^*$ resonance in enamines.

The intrinsic preference of nitrogen to adopt pyramidal geometry introduces a new stereoelectronic effect that is associated with rehybridization at nitrogen and possible deviations from the flat geometry. In fact, a variety of pyramidalization values has been found by X-ray crystallographic analysis (Figure 6.111). Many subtle features of enamine reactivity correlate with this geometric features because it reflects hybridization and donor properties of the nitrogen lone pair.

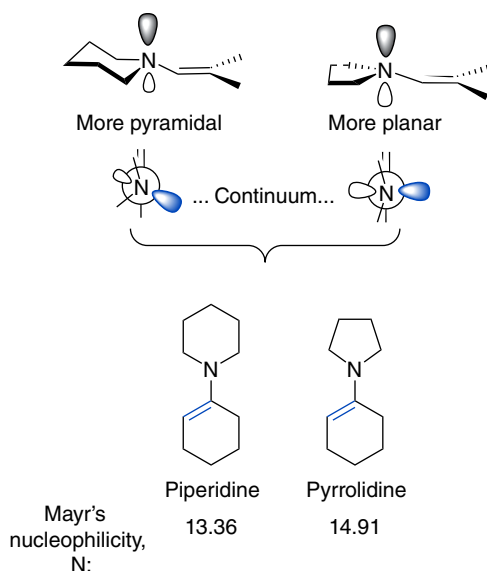


Figure 6.111 Hybridization/geometry effects on nucleophilicity of enamines.

For example, pyrrolidine enamines are more nucleophilic than piperidine and morpholine-based enamines. This difference in reactivity of cyclic amines originates from variations in pyramidalization at nitrogen. The nitrogen atom in a five-membered cycle is much more flat than the nitrogen atom in a six-membered cycle.

Planarization in the pyrrolidine enamines increases p-character in the lone pair and renders nitrogen a stronger donor. Enamines derived from imidazolidinones are 10^3 – 10^5 times less reactive than those based on the proline-derived Hayashi–Jørgensen catalyst.¹⁹¹

The electronic effect explains why the acyl-substituted pyrrolidine enamine shown in Figure 6.112 exists mainly in the conjugated form whereas piperidine enamines usually prefer the less crowded non-conjugated form. Such systems illustrate the competition between delocalization and sterics (Figure 6.112).

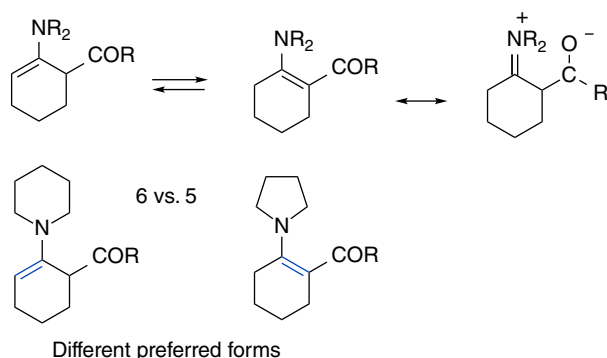


Figure 6.112 The competition between delocalization and sterics in acyl-substituted pyrrolidine and piperidine enamines.

Combined effects of several donor heteroatoms at a double bond increase nucleophilicity of the alkene moiety even further. Such compounds were formed as intermediates in a variety of interesting synthetic transformations (Figure 6.113).¹⁹² Some of them have been isolated and characterized.¹⁹³

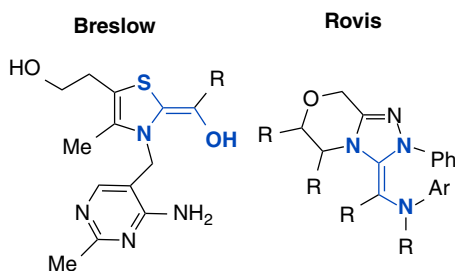


Figure 6.113 Nucleophilic alkenes implicated as intermediates of interesting synthetic transformations.

Similar effects were used for the design of highly reactive donor dienes for the Diels–Alder reactions.¹⁹⁴ Not only are such the dienes highly electron-rich and very reactive but they also interact with acceptor dienophiles in a highly regioselective fashion (Figure 6.114).

The applications of such electronic effects extend to radical chemistry. For example, reactions of electrophilic oxygen-centered radicals display excellent chemoselectivity for cyclization onto the electron-rich silyl enol ether when competing with terminal alkene cyclization, 1,5-hydrogen abstraction, and β -fragmentation pathways (Figure 6.115).¹⁹⁵

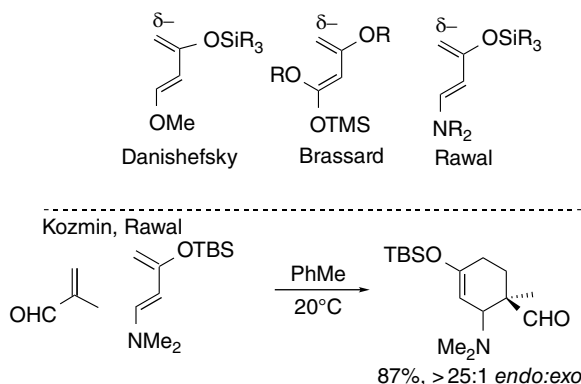


Figure 6.114 Combining multiple *p*-donors for increasing the Diels–Alder reactivity of dienes.

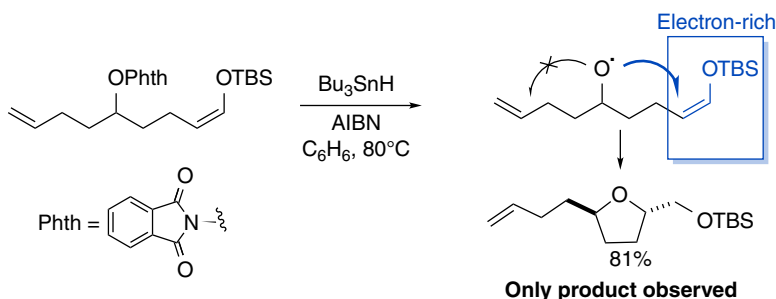


Figure 6.115 Competition between *O*-centered radical cyclization onto a silyl enol ether vs. a terminal alkene.

The 1,1-diaminoethylenes are very polar. When the two nitrogen atoms are included in a imidazolyl ring, the stabilization of positive is so efficient that the olefinic carbon can serve as an anionic center of an ylide (Figure 6.116).¹⁹⁶

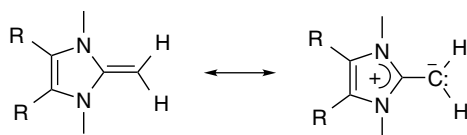
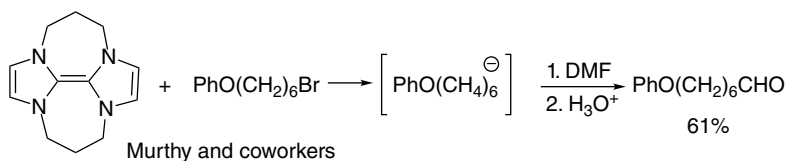


Figure 6.116 Superpolarization of cyclic 1,1-diaminoethylenes.

With four heteroatoms, the combined effect of multiple $n \rightarrow \pi^*$ interactions allows one to utilize such compounds as one- and two-electron reducing agents in remarkable metal-free reactions such as transformation of alkyl bromide to anionic nucleophiles in Figure 6.117. When multiple heteroatoms are creatively combined with additional electronic effects, remarkably reactive compounds can be designed. Such compounds can be considered as organic analogues of metals and have unique reactivity profile such as ability to selectively reduce benzenes to their radical anions “while leaving the well-recognized electrophiles like malonates and cyanoacetates untouched”.¹⁹⁷ Murthy and coworkers creatively utilized the amplifying effect of aromaticity for expanding the list of such organic superdonors. The increased donor ability of the latest generation compounds stems from the formation of aromatic systems as a result of electron removal.



Selected organic donors with their first reductive potentials relative to SCE

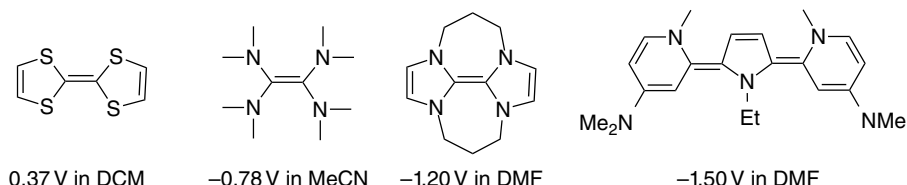


Figure 6.117 Cooperative effects of multiple heteroatoms and reductive rearomatization greatly increase donor ability.

Rotation around C-X bonds in heteroatom-substituted alkenes The preferred orientations of substituent X in the $R_2C=CR'-X$ systems relative to the vinyl moiety are also interesting. Whereas the flat conformation is preferred for $X=O, S$ to allow the perfect alignment of the p-type lone pairs at X with the π -system, the varying degrees of pyramidalization can be observed for $X=N$ as already discussed. When the second lone pair is present ($X=O, S$), rotation around the O-R and S-R bonds is controlled by stereoelectronics in a well-defined manner that arranges this lone pair antiperiplanar to the σ_{C-O}^* orbital. As with aldehydes, esters etc., this situation again illustrates the interplay of different effects that manifest themselves in different observed properties: π -effects ($n \rightarrow \pi^*$) are important for reactivity whereas sigma effects ($n \rightarrow \sigma^*$) define shape of the molecules.

The stereoelectronic explanation for the conformational preferences observed in these systems involves the $n_X \rightarrow \sigma_{CC}^*$ hyperconjugative interaction which is maximized in the antiperiplanar arrangement of the hybrid lone pair on Y and the σ_{CC}^* bond.¹⁹⁸ Methyl vinyl ether prefers the s-cis conformation. The s-trans conformer is about 2 kcal/mol higher in energy.¹⁹⁹ Furthermore, the seemingly more sterically encumbered s-cis form is also the most stable conformation in ethenol, ethenethiol, and methyl vinyl sulfide. This effect resembles the Z-preference of esters but does not have a simple stereoelectronic rationale because the in-plane hyperconjugative $n \rightarrow \sigma_{app}^*$ interactions (σ -effects in Figure 6.118) are similar in magnitude due to similar acceptor ability of

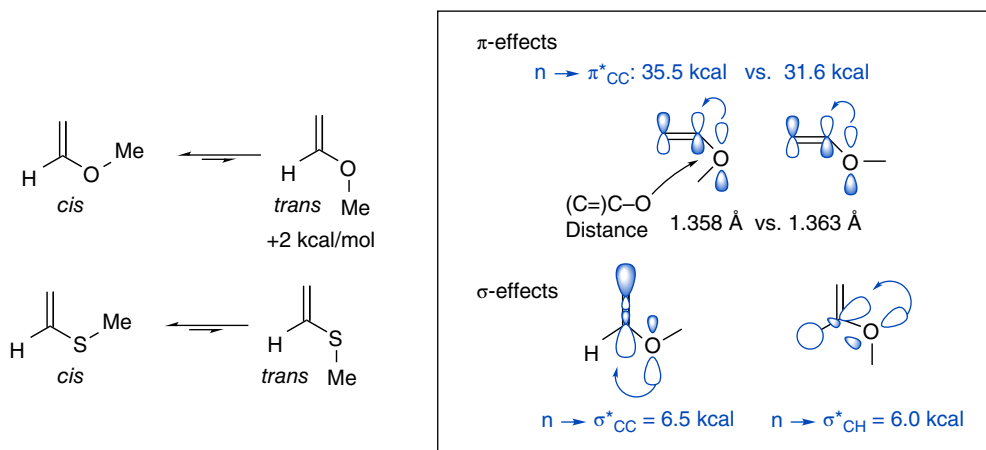


Figure 6.118 Cis conformation is preferred in vinyl ethers and sulfides. NBO delocalization energies and C-O bond lengths at the B3LYP/6-31+G(d,p) level.

the C-H and the C-C σ^* orbitals. A larger stabilizing contribution in favor of the more stable conformer surprisingly comes from the p-effects ($n \rightarrow \pi^*$ donation) that is not expected to change strongly in the two conformations.²⁰⁰ According to NBO analysis, the latter increase comes from more efficient n/π^* orbital overlap that is consistent with the shorter O-C distance in the cis-conformer. An interesting corollary of this explanation is that the π -bond in the cis-conformer should be more electron-rich and behave as a stronger nucleophile.

This conformational profile can be modified by introduction of additional σ -acceptors.²⁰² For example, although the main conformer of 1,1-dimethoxyethene also has both methoxy groups syn-periplanar to the C=C bond, there is a significant population (38%) of a conformer where one methoxy group is oriented syn-periplanar and the other one anticlinal. In the latter conformer, the lone pair of the latter OMe group enjoys anomeric interaction with the σ^* C-O bond of the first substituent (Figure 6.119).

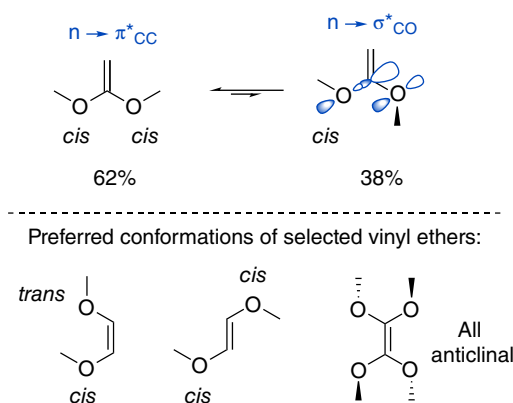


Figure 6.119 Colliding stereoelectronic interactions: $n\text{-}\pi^*$ conjugation and anomeric effect.²⁰²

The preferred geometry changes for fluorinated alkenyl ethers which adopt an anticlinal conformation where the O-C bond is aligned with the π -system (Figure 6.120).²⁰¹ This change has two stereoelectronic components. First, this geometry aligns the oxygen p-type lone with the vicinal $\sigma^*_{\text{C-F}}$ orbital, maximizing the $n \rightarrow \sigma^*_{\text{C-F}}$ interaction. Second, the multiple lone pairs of fluorines make the alkene π -system quite electron rich and induce chameleonic behavior of the OMe-group in the $\pi_{\text{C=C}} \rightarrow \sigma^*_{\text{OC}}$ interaction, where the methoxy moiety behaves as a σ -acceptor relative to the $\pi_{\text{C=C}}$ bond. A similar conformational preference has been observed for the fluorinated thioethers²⁰² and 2,3,5,6-tetrafluoroanisole.²⁰³

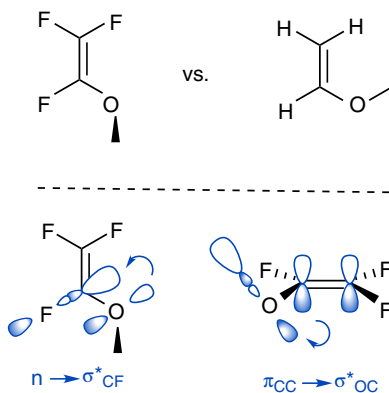


Figure 6.120 Change in the electronic structure of alkene activates chameleonic behavior of the OMe group (see Chapter 5 for additional discussion of stereoelectronic chameleons).

Similar effects apply to aromatic ethers and related compounds. Chein and Corey discovered an interesting stereoelectronic preference for heteroaromatic ethers to orient the OR group in a way that minimizes lone pair repulsion of the exocyclic substituent σ -lone pair and the lone pair of nitrogen²⁰⁴ but maximizes the anomeric interactions between OR lone pairs and endocyclic C-X bond. The antiperiplanar interactions of this type are likely to contribute as well, more so in the six-membered cycles where the interacting orbitals can easily adopt the ideal parallel geometry (Figure 6.121).

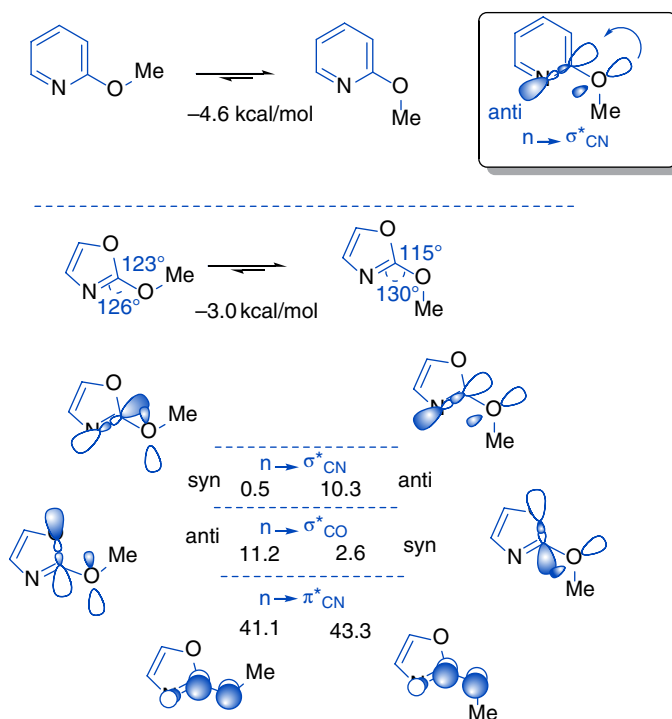


Figure 6.121 Conformational preferences in selected heteroaromatic ethers and NBO energies for the key interactions (kcal/mol, B3LYP/6-31+G(d,p)).

The favorable arrangement is harder to reach in the five-membered heterocycles where the stereoelectronic preferences change in the more subtle way. NBO analysis of these effects (Figure 6.121) illustrates that both anti- and syn-periplanar interactions between endocyclic σ^* acceptors and the in-plane lone pair of OMe group are important, in addition to the interactions between p-type lone pair and the aromatic system. This interesting system deserves more detailed theoretical analysis because such geometric preferences were utilized in drug design as an effective way to control the shape of ligands based on the heteroaromatic ethers.²⁰⁵ Interestingly, analogous interactions with the lone pairs of endocyclic oxygen and sulfur atoms in five-membered heterocycles impose no apparent bias on the conformational profiles. Such differences between nitrogen and chalcogens may seem surprising but can be traced back to differences in lone pairs hybridization described in Chapter 5.

In enamines, only one lone pair can interact with the vinyl moiety and, generally, this pair is engaged in the interaction with the π -system. This means that E/Z-isomerism in these systems does not involve negative hyperconjugation but rather relies on a more subtle balance of electronic (neutral hyperconjugation, electrostatics) and steric effects.

When two bulky groups are attached at the nitrogen atom (i.e. in *Z*-substituted enamines), steric hindrance imposed by these groups is unavoidable and can strongly disfavor the coplanar conformation. In such systems, the nitrogen lone pair can assume a misaligned (even orthogonal) orientation, with the partial loss of the $n_{\text{N}} \rightarrow \pi^*_{\text{C}=\text{C}}$ interaction or, in the extreme case of (*Z*)-1-(dimethylamino)-propene, with the replacement of the above interaction with $n_{\text{N}} \rightarrow \sigma^*_{\text{C-H}}$ hyperconjugation (Figure 6.122).²⁰⁶

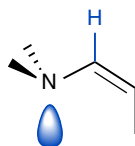


Figure 6.122 The coplanar conformation is disfavored when two groups are attached at the nitrogen atom.

From shape to stereoselectivity The difference between syn and anti conformations of proline-derived enamine of acetaldehyde is only 0.1 kcal/mol (B3LYP-PCM/6-311++G(3df,2p)//B3LYP-PCM/6-31G(d,p) level, Figure 6.123).²⁰⁷ Not only are the two conformers essentially isoenergetic but the barrier for their interconversion (9.5 kcal/mol) is much lower than it is in amides. Hence, the lower energy of $n \rightarrow \pi^*$ resonance in enamines means that both conformers readily interconvert at the ambient conditions and both can participate in reactions with electrophiles.

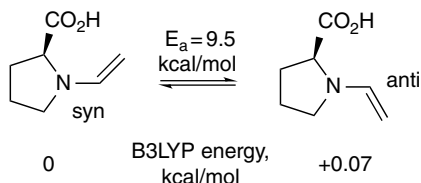


Figure 6.123 The syn-conformations of proline-derived enamine of acetaldehyde is only ~0.1 kcal/mol more stable than the anti conformations.

Another consequence of pyramidalization of enamines is that it creates a chiral environment when the nitrogen has three different substituents. However, the barrier for planarization is small, even smaller than in regular amines, so the presence of additional substituents and increased pyramidalization is needed to define the chiral space in a reliable robust manner.²⁰⁸

Pyramidalization was explored as a direct stereoelectronic source of stereoselectivity in enamine reactions. Seebach and coworkers suggested that the remarkable stereoselectivity of pyrrolidino-enamines derived from proline in reactions with electrophiles originates from stereoelectronic assistance from the lone pair of pyramidalized enamine N-atoms (Figure 6.124).²⁰⁹

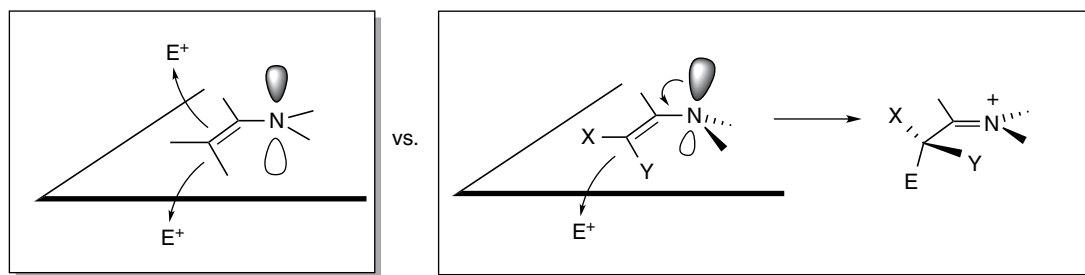


Figure 6.124 Suggested role of stereoelectronic assistance from the lone pair of pyramidalized enamine N-atoms to stereoselectivity of its reactions with electrophiles.

Seebach also pointed out that, unlike enamines carrying an unsubstituted pyrrolidine where the enamine group is essentially planar, enamines derived from proline derivatives are distinctly pyramidalized, similar to enamines derived from six-membered-ring ketones. In the few available X-ray geometries, the substituent at C2 of the pyrrolidine ring assumed the pseudoaxial orientation with regard to the pyrrolidine ring plane that corresponded to the *trans* position relative to the larger lobe of the enamine N-atom lone pair. The following stereoelectronic model was suggested for the TS that involves reactive conformation that features enamines pseudodiaxial anti-arrangement of the large substituent and the lone pair of nitrogen in the “cis-disubstituted” pyrrolidine ring along with s-trans geometry at the enamine moiety. Together these structural components lead to the “lone-pair-assisted” stereoselective electrophile attack from the *Re*-direction.

It was also suggested how the model should be modified to explain results with enamines that carry an unusually large substituent and for enamines that carry a substituent at C2 (i.e. carboxylate) that is capable of through-space assistance (with possible lactonization) during the electrophilic attack (Figure 6.125).

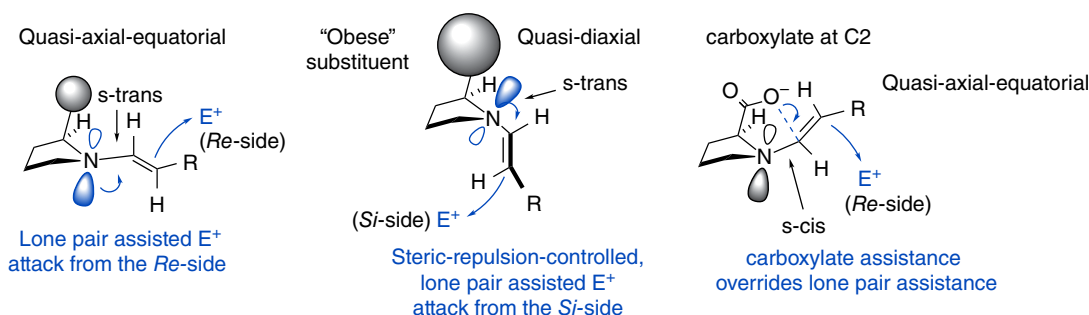


Figure 6.125 Role of substituents in selectivity of reactions of proline-derived enamines.

Anions Many other examples exist for the importance of stereoelectronics in $n\text{-}\pi^*$ interactions. Even under conditions of very large electronic demand such as formation of carbanions, the directly connected π -system can only assist when it aligns properly with the forming carbanionic orbital.²¹⁰ For example, deprotonation at the bridged positions is remarkably difficult (this is, of course, one more manifestation of Bredt’s rule, Figure 6.126).

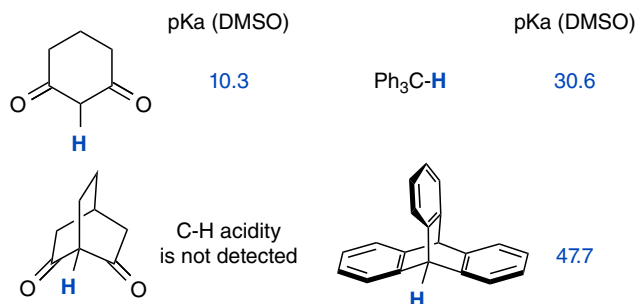


Figure 6.126 Decreased C-H acidity at the bridgehead positions reflects the inefficiency of resonance in the conjugate carbanionic bases.

6.6 π/π -Interactions

Rotation around the σ -bond The conjugation in extended π -systems is also geometry-dependent. In 1,3-butadiene, the *s-trans* conformation is calculated (G2) to be 2.9 kcal/mol more stable than the gauche (skewed *s-cis*) conformation due to increased π/π^* overlap (Figure 6.127).²¹¹ The barrier for rotation is 5.7 kcal/mol relative to the *s-trans* conformation (in good agreement with experimental values of 2.8 and 5.9 kcal/mol). A similar trend holds in methyl-substituted α,β -unsaturated ketones, where the preference for the *s-trans* conformation is dependent on the size of the substituent (Figure 6.127c).²¹²

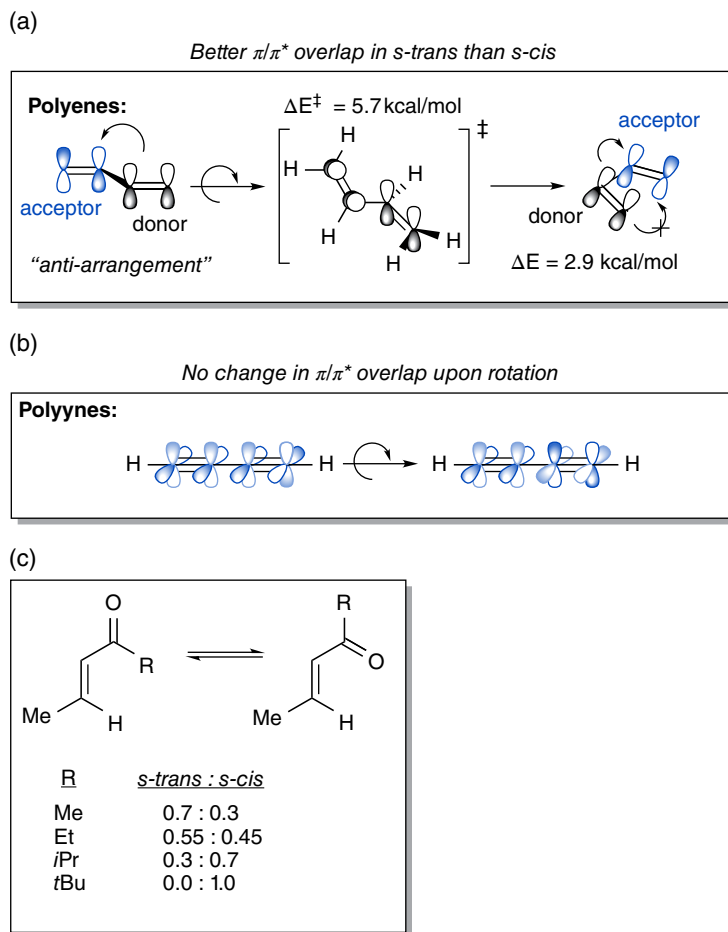


Figure 6.127 (a) Relative energies and barrier for rotation of the *s-trans* and skewed conformations of 1,3-butadiene. (b) Relative abundance of each isomer in α,β -unsaturated ketones. (c) Energy of polyynes is insensitive to rotation due to the presence of two orthogonal π -systems in the alkyne moieties.

Conjugated alkyne systems present a unique situation where the cost of rotation about the σ -bond disappears as a result of a second π -system and unique cylindrical symmetry of the alkyne moiety. Conjugative stabilization is not a directly measurable characteristic and it has been suggested that conjugative stabilization in diynes is zero. We will discuss this paradoxical suggestion in the following section.

6.6.1 Hyperconjugation in alkynes and its relation to the “absence” of conjugation between two triple bonds in 1,3-diyne

From the conformational point of view, rotation around the C-C bonds in alkynes is invisible due to the cylindrical symmetry of alkyne π -cloud. In bis-alkynes, the situation is analogous. However, the question of conjugation between two alkynes or between alkyne functionality and propargylic substituents has been the subject of a great deal of attention and recent debates that we will discuss in this section.

In a provocative series of papers, Rogers et al.²¹³ disclosed that “conjugation stabilization of 1,3-butadiyne is zero” when estimated through the classic approach of Kistiakowsky et al.²¹⁴ who assessed conjugative stabilization in butadiene from the 3.8 kcal/mol differences in the enthalpies in hydrogenation of the first and second double bonds of 1,3-butadiene (Figure 6.128). 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?

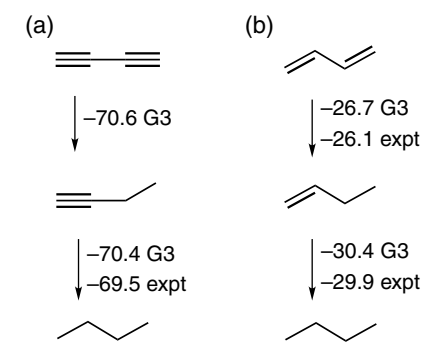


Figure 6.128 Comparison of the G3(MP2) calculated enthalpies of formation ΔH_f^{298} (italic) and hydrogenation ΔH_{hyd} (expt in kcal/mol) of butenes and butynes. According to these estimates, the conjugation energy of 1,3-butadiene (b) is ~ 3.8 kcal/mol, but for 1,3-butadiyne (a), it is close to zero (0.2 kcal/mol).

The proper interpretation of the above results clearly underscores the importance of neutral hyperconjugation for the stability of unsaturated compounds. Jarowski et al.²¹⁵ resolved the seeming paradox by pointing out that the reference compounds for 1,3-butadiyne and 1,3-butadiene are stabilized significantly by C-H/ π neutral hyperconjugation, which is absent in 1,3-butadiyne and 1,3-butadiene (Figure 6.129).

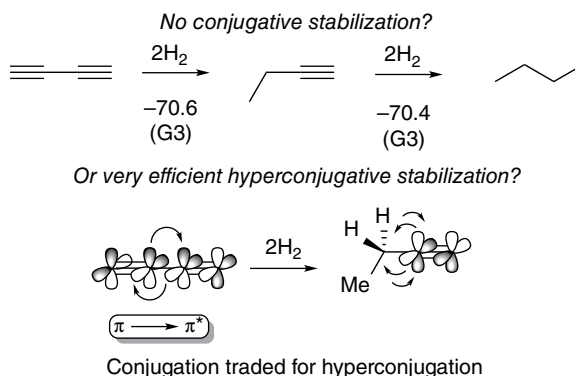


Figure 6.129 Stereoelectronic origins of “disappearing” conjugative stabilization in butadiynes.

The effect of hyperconjugative interactions can be evaluated from the difference between the heats of hydrogenation of ethylene and 1-butene that provides an estimate for stabilization of ethylene (in kcal/mol) by an ethyl substituent (2.4 G3; 2.2 G3- (MP2); 2.7 experimental). Likewise, the hyperconjugative stabilization of acetylene by an ethyl group (4.9 G3; 4.8 G3(MP2); 4.7 expt) 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 6.130 that produces data consistent with the above evaluation:

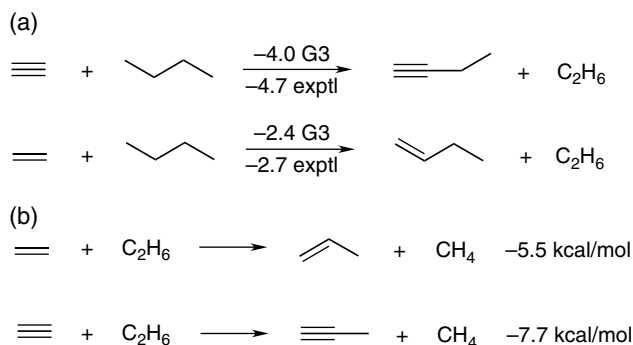


Figure 6.130 (a) Conventional equations for the evaluation of hyperconjugation. (b) Bond separation energy (BSE) values for alkene and alkyne hyperconjugation, corrected for protobranching. (Source: Wu 2012. Reproduced with permissions of American Chemical Society.)

Hyperconjugative stabilization of 1-butene and 1-butyne compensates conjugative stabilization for both butadiene (partially) and butadiyne (completely). Interestingly, hyperconjugation in alkynes is twice as large as hyperconjugation in alkenes. This difference is large enough to fully obscure the conjugative stabilization in 1,3-butadiyne!

Furthermore, an EDA-based study by Frenking and coworkers suggested that hyperconjugation is roughly half as strong as π -conjugation between two multiple bonds and that the hyperconjugative stabilization of C-H and C-C bonds with double bonds is half as strong as such stabilization by the triple bonds.²¹⁷ As the result, hyperconjugative stabilization of the two π -systems in alkyl substituted alkynes (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).

The multiple literature sources discussed above suggest that hyperconjugative interactions are even more energetically important in alkynes. Although their role in conformational equilibrium of propargylic species is “invisible” due to the cylindrical symmetry of the alkyne moiety, only involvement of the $\sigma_{\text{C-H}} \rightarrow \pi^*$ and $\pi \rightarrow \sigma_{\text{C-H}}^*$ interactions allows one to resolve the paradox of disappearing conjugative stabilization in 1,3-diynes.

Summary Although this chapter has outlined a wide variety of stereoelectronic interactions across the broad spectrum of functional groups, these effects can be summarized within several well-defined classes of interactions (σ/σ^* , $\sigma/\pi^*/\pi/\sigma^*$, n/σ^* , n/π^* and π/π^*). Most of these interactions are relatively weak and can be switched off or on by rotation. However, the combination of the best donor (lone pair) and the best acceptor (a π^* -orbitals) can lead to situations where rotation is significantly inhibited at room temperature. Stereoelectronic effects of a different nature can coexist and lead to multiple layers of consequences for structure and reactivity.

However, for each of these patterns, there is a unifying stereochemical preference. It can be summarized in the following short definition which is sometimes referred to as the “main stereoelectronic rule”²¹⁸: “The most interacting pair of orbitals (the best donor and the best acceptor) prefer an antiperiplanar geometry”. We have summarized the key manifestations of this rule for the six important classes of organic compounds in Figure 6.131.

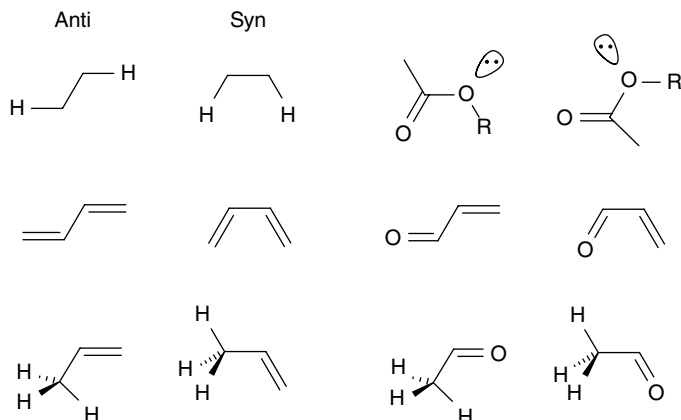


Figure 6.131 The “main stereoelectronic rule” is a common foundation for conformational preferences in a variety of organic functionalities.

The rule is not without exceptions, especially when several effects work in opposite directions. Furthermore, the underlying stereoelectronic bias can be masked or overruled by steric and electrostatic effects but it remains an important component in the overall picture. When (or if) the stereoelectronic component is amplified by bond stretching or breaking in the process of chemical reaction, the previously invisible stereoelectronic effect may come to the fore and define selectivity or reactivity in a chemical system. The richness and diversity of stereoelectronic interactions makes such situations not uncommon, leaving many opportunities for surprising and educational discoveries in the future.

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7

Stereoelectronic Effects with Donor and Acceptor Separated by a Vinyl Bridge

In the previous chapter, we concentrated on conformational changes enabled by rotation around a single bond and presented just a few selected examples of reactivity. For substituents at a double bond, the conformational changes are less important (with the exception of imines and similar compounds). Because the conformational equilibrium is usually frozen by the double bond rigidity, the stereoelectronic effects are more often observed as effects on *reactivity* and relative stability.

There are *quantitative* differences between the stereoelectronic communication of donors and acceptors through a single and a double bond as well. In comparison to delocalizing effects discussed in the previous chapter, the interactions between sigma donors and sigma acceptors separated by a double bond become stronger, due to the shorter C-C bond length (Figure 7.1).¹ The shorter bridge provides better orbital overlap because donor and acceptor orbitals are brought closer. The relative importance of the F_{ij} term (see Chapter 4) increases – the acceptor abilities are more strongly controlled by electronegativity and polarization of the acceptor σ -orbital.

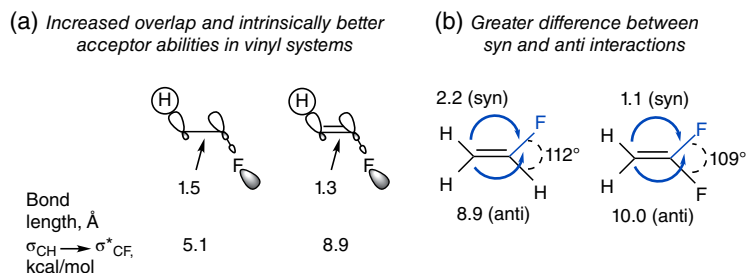


Figure 7.1 (a) Shorter C-C bond provides greater overlap and stronger hyperconjugative interactions, amplifying the effect of acceptor electronegativity. NBO interaction energies calculated at the B3LYP/6-31G(d,p) level of theory from ref. 1. (b) Stronger interactions lead to the greater difference between syn and antiperiplanar interactions (NBO/M06-2X/6-31G(d,p) data).

Although the geometrical constraints imposed by the double bond rigidity facilitate the observation of stereoelectronic effects associated with antiperiplanarity of the interacting orbitals, there is a possible caveat: the stereoelectronic interactions of σ -orbitals in vinyl systems have to coexist with the π -effects.² The π -bonds open an additional conduit for stereoelectronic communication between the vicinal substituents (Figure 7.2). When types of effects are in conflict, their competition can complicate the overall picture. This situation is common when substituents have different σ - and π -effects (e.g. the σ -acceptor, p-donor character of halogens). This difference is illustrated by the importance of interactions through the π -bond of the bridge on the relative magnitude of *cis*-effect (vide infra).

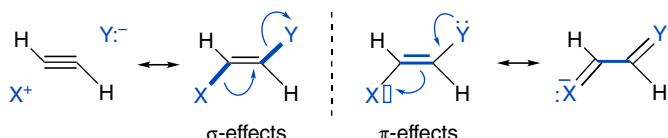


Figure 7.2 Comparison of σ - and π -pathways for the interaction of two vicinal substituents at a double bond.

We will organize our discussion based on the type of orbitals involved in delocalization: σ/σ , σ/π (both neutral hyperconjugation patterns), n/σ^* (negative hyperconjugation), and σ/π^* (positive hyperconjugation) interactions. As we mentioned earlier, we will mostly concentrate on effects on reactivity and stability that are often displayed clearly and unambiguously in these geometrically well-defined systems. The coverage will not be exhaustive since detailed understanding of selected areas is compensated by scarcity of information in other areas.

7.1 σ/σ^* interactions

Two types of effects can be suggested: a) different stability of isomeric *cis*- and *trans*-substituted alkenes and b) different reactivity of two identical groups positioned *cis* and *trans* to a σ -acceptor or a σ -donor group (Figure 7.3). The first phenomenon is the basis of the well-known *cis*-effect discussed in the next section. The second phenomenon is surprisingly scarcely documented and will not be discussed in this book.

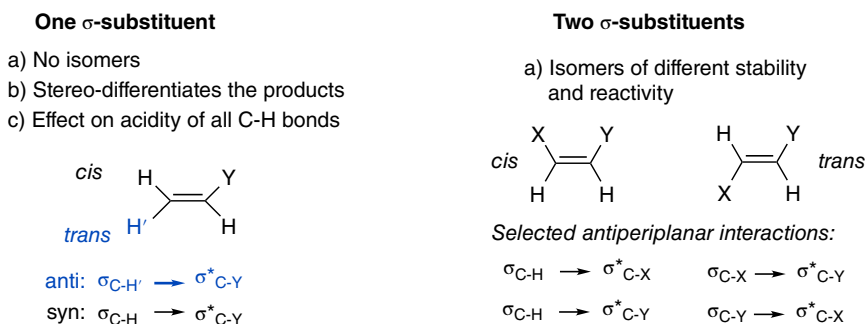


Figure 7.3 Selected systems discussed in this chapter.

7.1.1 *Cis*-effect: the case of two σ -acceptors

The 1,1-difluoroethene is the most stable of the three difluoroethene isomers (>9 kcal/mol) due to the presence of strong “anomeric” $nF \rightarrow \sigma^*C-F$ interactions (Figure 7.4). Comparison of the two 1,2-substituted difluoroethenes reveals a new stereoelectronic effect – the *cis*-isomer is more stable (1.1 kcal/mol at the highly accurate CCSD(T)/

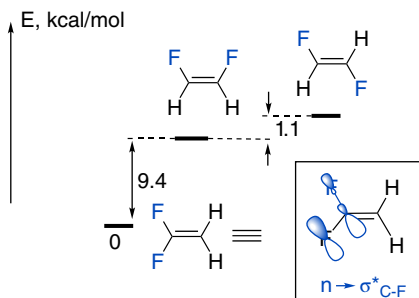


Figure 7.4 Relative energies of the three difluoroethenes.

aug-cc-pV6Z level of theory).³ This extensively analyzed phenomenon is called the “*cis*-effect” and is analogous to the *gauche*-effect in 1,2-haloethanes.⁴

The *cis*-conformational preference erodes for the heavier halogens. For example, the *cis*-isomer of 1,2-dichloroethene is also more stable than the *trans*-isomer but the difference is smaller (only 0.4 kcal/mol). Furthermore, the experimentally determined difference in stability of the two isomers of 1,2-dibromoethene is negligible.

The contributions of electron delocalizations and steric exchange repulsions in 1,2-difluoroethane have been evaluated using NBO analysis.⁵ The common stereoelectronic preference for the anti-arrangement of the best donor and the best acceptor dominated for $X=F$ (Figure 7.5). The difference in the energies of the antiperiplanar interactions decreases for the heavier halogens as the $\sigma_{C-X} \rightarrow \sigma_{C-X}^*$ interactions in the *trans*-geometry become more stabilizing due to the greater donor ability of the σ_{C-Cl} and σ_{C-Br} bonds. Furthermore, the hyperconjugative interactions of σ -orbitals coexist with the interactions of the halogen lone pairs with the π - and σ -orbitals of the bridge which were also found to favor the *cis*-isomers ($\pi \rightarrow LP$ effects in Figure 7.5).

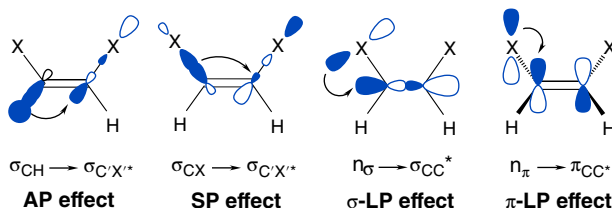


Figure 7.5 The antiperiplanar hyperconjugation effect (the AP effect), the syn-periplanar hyperconjugation effect (the SP effect), and the lone pair delocalization effects (σ - or π -LP effect) coexist in 1,2-dihaloethenes (X =halogen).

7.2 σ/π interactions: allenes vs. alkenes

7.2.1 Neutral systems

The increased importance of stereoelectronic effects in systems where geometry enforces orbital overlap synergetic is illustrated by the high reactivity of allenes. For example, 1,2-propadiene has >20 kcal/mol lower C-H bond dissociation energy than ethene, even though C-H bonds in the two compounds have the same $\sim sp^2$ hybridization. This difference illustrates the greater effect of the vicinal $C=C$ π -orbitals on radical stability in comparison with that of C-H σ -orbitals (Figure 7.6). In alkene, the breaking C-H bond and the formed radical are coplanar to a C-H bond whereas in allenes they are coplanar to a π -C=C orbital.

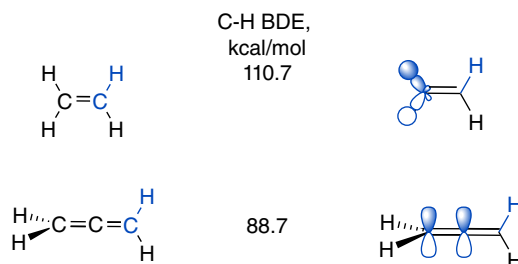


Figure 7.6 Dramatic differences in the C-H bond BDEs in allene and ethylene provide a comparison for the relative stabilizing power of conjugation and hyperconjugation.

7.2.2 Anions

The effects are even larger for carbanions: the gas phase proton affinity of ethylene anion (409 kcal/mol) is ~28 kcal/mol greater than the proton affinity of 1,2-propadienyl anion (381 kcal/mol). The unique stereoelectronics of the allene system where the vicinal donor and the π -system are rigidly aligned is particularly beneficial for anion stabilization, as illustrated by the comparison with 1,3-butadiene where the C2-anion can be also stabilized by $n \rightarrow \pi^*$ conjugation (Figure 7.7). Formation of the latter anion is more difficult, as illustrated by the ~19 kcal/mol higher proton affinity for the 1,3-dienyl anion (400 kcal/mol). From the stereoelectronic perspective, this difference originates from the necessity of rotation that is needed to gain the $n \rightarrow \pi^*$ stabilization in the flexible system that leads to the simultaneous sacrifice of the diene $\pi \rightarrow \pi^*$ stabilization. The difference in anion stability is further amplified by the greater electronegativity of the central sp-hybridized carbon in allene.

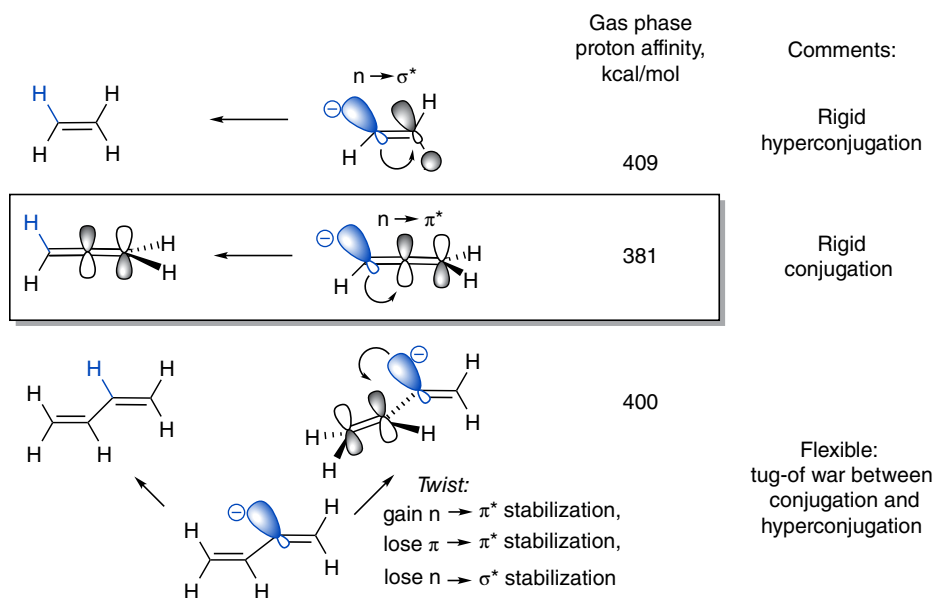


Figure 7.7 The stereoelectronics of the allene system where the C-H bond is rigidly aligned with the vicinal π -system dramatically increases C-H bond acidity.⁶

The relative importance of hyperconjugation and conjugation is also reflected in the inversion barriers for vinyl anions and allenes. Whereas the barrier for vinyl anion is ~ 27 kcal/mol,⁷ the barrier for allenyl anion has been estimated (albeit at a lower level of theory) as only ~ 4 kcal/mol (Figure 7.8).⁸ As a consequence, allenyl anions are significantly less stable configurationally than simple vinyl anions. Furthermore, there are interesting structural distortions in the anions, i.e. the deviation from linearity in the allenyl moiety, that are consistent with amplification of interactions in the antiperiplanar geometry.

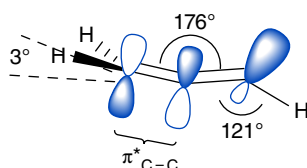


Figure 7.8 Allenyl anions distort from linearity.

7.2.3 Positive conjugation and hyperconjugation in vinyl systems

The manifestations of positive hyperconjugation in these systems are ubiquitous. Even in allenes, the functionality that generally displays a balanced mixture of $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ interactions in the ground state, positive hyperconjugation can grow dramatically in importance in the course of reaction with electron deficient species. Furthermore, the $\sigma \rightarrow \pi^*$ delocalization gains significance as the acceptor ability of the π^* orbital increases (i.e. heterocumulenes) and if an empty p-orbital serves as a “unidirectional” acceptor (vinyl cations, vinylidenes) (Figure 7.9). The role of this delocalization pattern is also significant in the transition states of cationic fragmentations and migrations to electron deficient centers.

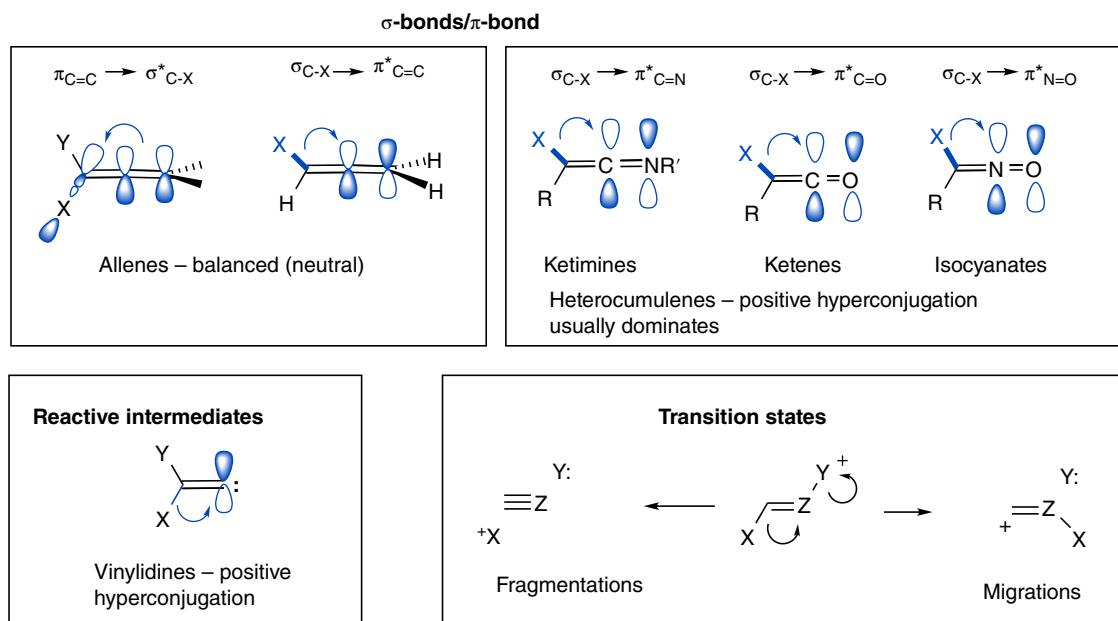


Figure 7.9 Positive hyperconjugation: cation/ π^* -acceptor interacting with a σ -donor.

An important structural feature that distinguishes allenes from alkenes and ketenes is that the donor and acceptor orbitals in the cumulenenic systems are closer in space and constrained to the perfect coplanar conformation. We will see illustrative consequences of these features in the subsequent sections.

7.2.4 $\sigma \rightarrow \pi^*$ delocalization in allenes: allenyl silanes in reactions with electrophiles

Substantial effects associated with positive hyperconjugation lead to interesting and useful reactivity features. For example, the C-Si bond in allenyl silanes is aligned perfectly (and rigidly) with the vicinal π -system (Figure 7.10), suggesting that electrophiles should attack the π -system efficiently and stereoselectively (anti). In this process, the $\sigma_{\text{C-Si}} \rightarrow \pi^*$ interaction continuously grows in strength until it approaches the electronic situation in β -Si-substituted cation, and then finally collapses into a translocated π -bond and a silyl cation (the latter is generally trapped by reaction with a nucleophile).

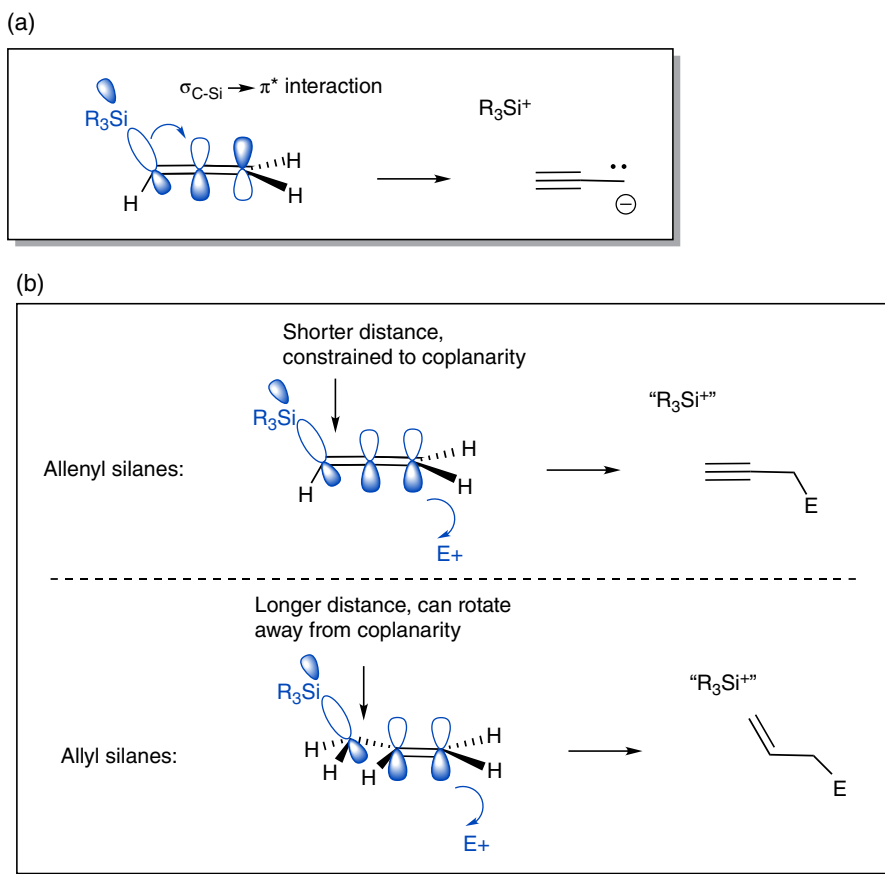


Figure 7.10 (a) Resonance description of the $\sigma_{\text{C-Si}} \rightarrow \pi^*$ interaction in allenyl silanes. (b) Comparison of allenyl and allyl silanes.

The overall $S_{\text{E}}2'$ process is analogous to the $S_{\text{E}}2'$ reactions of allylsilanes but the allenyl systems have the advantage of additional rigidity. As a result, the $S_{\text{E}}2'$ reaction of allenylsilanes often display particularly high anti-stereospecificity.⁹ For example, the chiral allenylsilane gave the alkyne product with the same high level of enantiomeric purity as the starting material (Figure 7.11).

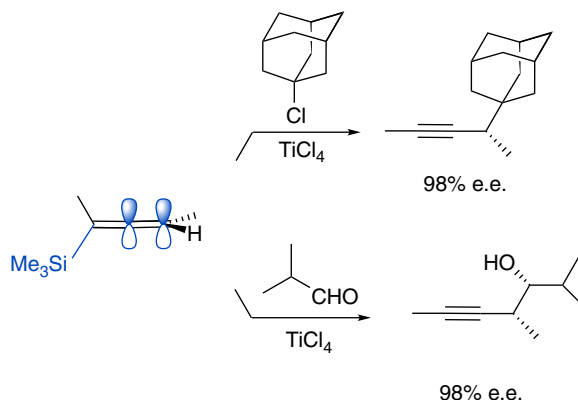


Figure 7.11 Examples of high anti-stereospecificity in S_E2' reaction of allenylsilanes.

$\sigma \rightarrow \pi^*$ delocalization in heteroanalogues of allenes Hyperconjugative interactions in carbonyl analogues of allenes are generally dominated by the acceptor properties of the carbonyl π^* -orbital. Comparison of substituent effects illustrates that ketenes are destabilized by σ -acceptors but stabilized by donors in comparison with both alkenes and allenes, whereas allenes are stabilized relative to ketenes by σ -acceptors (energies are in kcal/mol at HF/6-31G* level of theory).¹⁰ Fluoroketene ($\text{CHF}=\text{C}=\text{O}$) is the least stabilized of the mono-substituted ketenes in Figure 7.12 in comparison to the respective alkenes and allenes.¹¹

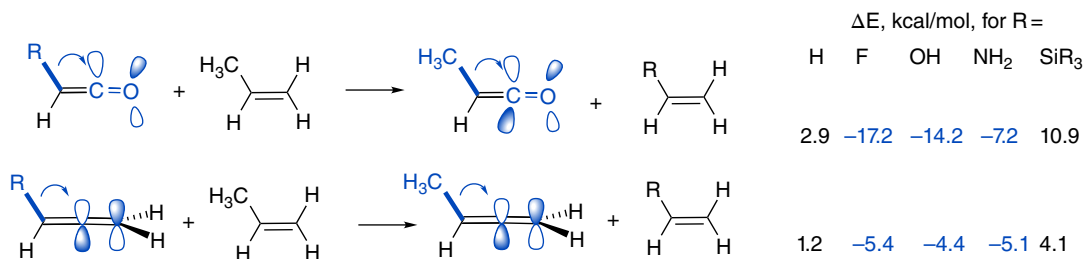


Figure 7.12 Effects of $\sigma \rightarrow \pi^*$ delocalization on stability of ketenes and allenes.

The unusual electronic properties are accompanied by unusual structural features. Kinks in the cumulenonic moieties are observed in both fluoroketene and fluoroallene, such that the $\text{C}=\text{O}$ and $\text{C}=\text{C}$ are bent away from the fluorine (Figure 7.13). This stereoelectronically expected deviation leads to a slightly better overlap of the π -acceptor with the $\text{C}-\text{H}$ bond (a better donor). The σ -donor substituted ketenes show bending in the opposite direction. The Li, BeH, and BH_2 substituted ketenes display large MC_2H_2 and $\text{C}_2\text{C}_1\text{O}$ angles of 124.1, 123.2, and 126.3; and 184.8, 182.1, and 181.3 degrees, respectively, where the oxygen is bent toward the metal. These effects are likely to have an electrostatic component as well.

The instability of fluoroketene is associated with high reactivity. An increase in reactivity can be useful. In particular, it was suggested to play a role in an important enzyme-catalyzed process. Fluoroacetyl-CoA thioesterase (FIK) enzyme, present in the organofluorine-producing microbe *Streptomyces catleya*, has an

Distortions improve orbital overlap

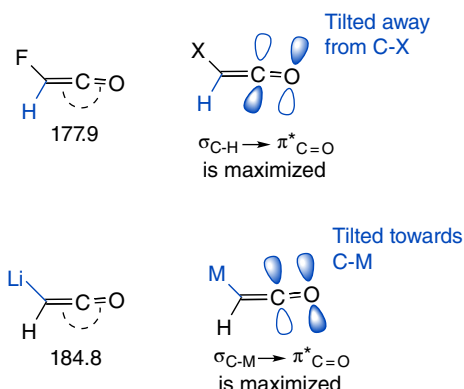


Figure 7.13 Structural consequences of $\sigma \rightarrow \pi^*$ delocalization in ketenes and allenes.

extremely difficult task of selectively reacting with the fluoroacetate derivatives in the presence of significant excess of their hydrogen analogue, acetyl-CoA (Figure 7.14). Remarkably, the rate of hydrolysis is increased by this enzyme by a factor of 10^4 relative to the hydrogen analogue.¹² Instead of relying solely on the relatively subtle differences between hydrogen and fluorine for binding in the active site, the enzyme takes advantage of the alternative hydrolysis mechanism opened by increased acidity of α -C-H bonds in the fluoro-substituted substrate. Kinetic evidence supports deprotonation followed by the formation of the highly reactive ketene intermediate.

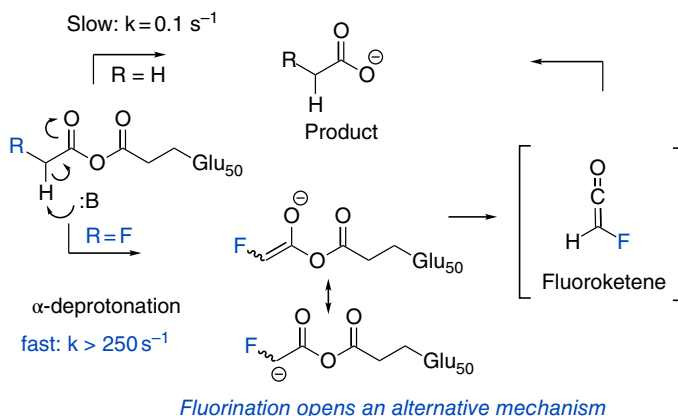


Figure 7.14 Transient formation of fluoroketene was suggested in selective hydrolysis of fluoroacetates by fluoroacetyl-CoA thioesterase.

The even more unstable difluoroketene species was generated (Figure 7.15) in an Ar matrix at 7 K by photolysis of ionized perfluoromethylvinyl ether, $\text{CF}_2=\text{C}(\text{F})\text{OCF}_3$.¹³ The barrier for dissociation of difluoroketene into CF_2 and CO is ~ 10 kcal/mol. The process is exothermic by ~ 6 kcal/mol.

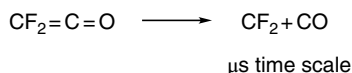


Figure 7.15 Dissociation of difluoroketene into CF_2 and CO .

Understanding of stereoelectronic features of the allene moiety led to the synthesis (Figure 7.16) of extremely bent acyclic allenes that can be characterized as “carbodicarbenes”¹⁴ and their heteroatomic analogues (“carbones”¹⁵). This approach is more efficient in inducing allene bending than the previously utilized application of sterics.¹⁶ The key feature of the electronic design is creation of the two σ -bonds at carbon via the dative mechanism that does not use carbon electrons, leaving carbon in an electronic configuration that approaches having two lone pairs of electrons. Such bent allenes are promising metal ligands since they are even stronger σ -donors than stable singlet carbenes, which have only one lone pair of electrons (along with a partially filled p-orbital).

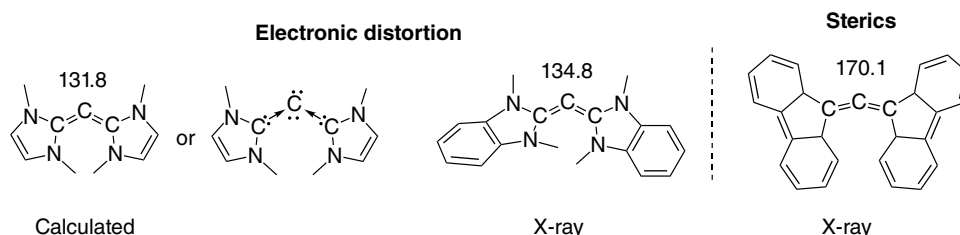


Figure 7.16 Extreme bending of acyclic allenes by electronic effects.

Search for alkylidenecarbenes An empty p-orbital is an even better acceptor than a carbonyl π^* . Consequently, terminal fluorines (Figure 7.17) lead to even more extreme destabilization in vinylidenes (vinyl carbenes) than they do in fluoroketenes. Sander and coworkers referred to fluorovinylidenes as superelectrophilic carbenes, pointing out that these extremely reactive species are markedly different in their reactivity from the stable nucleophilic singlet carbene analogues.¹⁷ This observation contrasts sharply with the parent CF_2 -carbene where F can be considered a stabilizing group due to the interaction of empty carbon orbitals with lone pairs of fluorines. Fluorine in these two situations can be considered a stereoelectronic chameleon (n-donor in carbenes and σ -acceptor in vinylidenes).

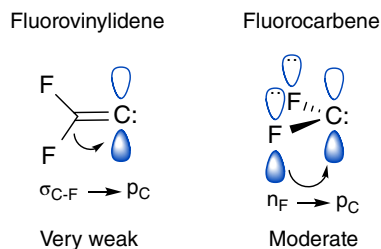


Figure 7.17 Chameleonic nature of fluorine leads to dramatic differences in the electronic structure of difluoro vinylidene and difluoro carbene.

7.3 Vinyl halides and their carbanions (transition from $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-Hal}}$ to $n_{\text{C}} \rightarrow \sigma^*_{\text{C-Hal}}$ interactions)

Due to the greater electronegativity of vinyl carbons, their C-H bonds are more acidic than the analogous C-H bonds at sp^3 carbon. Furthermore, vinyl anions can be produced (Figure 7.18) in reaction of alkynes with anionic nucleophiles and other synthetic routes (e.g. metallation). Since they are readily available and relatively stable, vinyl anions constitute an important class of reactive intermediates. When considering organometallic compounds as carbanion “equivalents”, it is important to keep in mind that there is a difference between these compounds. The presence of a counter-ion in ionic organometallics and the partial covalent character for the systems with C-M bond with more electronegative metals impose significant stabilizing effects, localize the negative charge, and decrease the magnitude of delocalizing interactions.

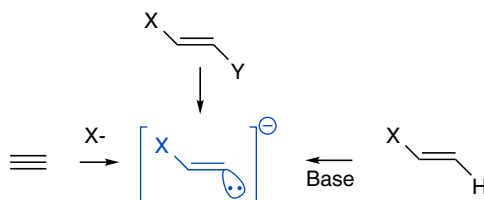


Figure 7.18 Common approaches to vinyl anions.

Because the lone pair at anionic carbon of vinyl anion is oriented (Figure 7.19) perpendicular to the π -system, it can only be stabilized electronically by σ -effects, such as $n \rightarrow \sigma^*_{\text{C-X}}$ hyperconjugation. When X is a good leaving group, such stabilization is also manifested in the TS for alkynogenic elimination, leading to kinetic instability of such species.

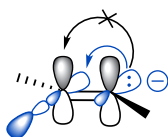
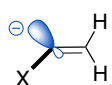


Figure 7.19 Vinyl anions are constrained to orthogonality with their π -system and do not benefit from conjugation. However, they can be stabilized by hyperconjugation (shown in blue).

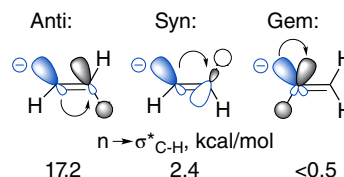
Stereoelectronic features of vinyl anions are associated with their bent geometries and usual configurational stabilities in solution. Theory predicts a sizable inversion barrier for the parent vinyl anion (28.7 kcal/mol at the MP2/6-31+G(d)//HF/6-31+G(d) level). The two conformers of 1-propenyl anion can be formed stereospecifically in the gas phase (via desilylation of E- and Z-1-trimethylsilylpropene) and show different reactivity patterns.¹⁸

Based on stereoelectronic arguments, one can expect basicity of vicinal C-H bonds in vinyl halides to be different (Figure 7.20) due to their different position (syn and anti) relative to a strong σ -acceptor. The absolute magnitudes of delocalizing effects are large but the *differences* between them are not. For example, the gas phase proton affinities of the cis- and trans- β -fluoro-substituted vinyl anion differ by only 1.5 kcal/mol.¹⁹ Interestingly, the stabilizing effect of α -halogen substituents is ~ 2 kcal/mol larger than the effect of analogous β -substituents.

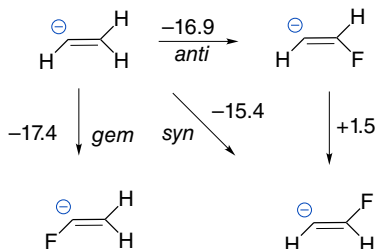
Rehybridization effects play important role:

	X:	F	Cl	Br
	proton affinity:	402	392	388
	p-character in C-X, %:	85	90	92
	s-character in anion, %:	50	54	57

NBO interactions in vinyl anion:



Stereoelectronic effects are smaller but significant:



Differences in proton affinities, in kcal/mol
(gas phase, MP2/cc-pVQZ)

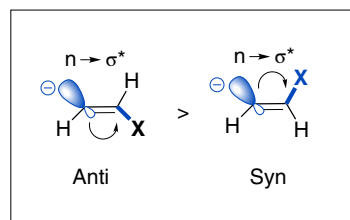


Figure 7.20 The interplay between hybridization and stereoelectronics in substituent effects on the stability of α - and β -halogen-substituted vinyl anions. Lower proton affinity indicates higher anion stability.

In addition to geminal hyperconjugation, rehybridization plays an important role in the α -stabilization. As expected from the modified Bent's rule,²⁰ the p-character at carbon in the C-X bond and the s-character in the anionic orbital increase for the heavier halogens: $\text{F} < \text{Cl} < \text{Br}$. Significant rehybridization in carbanions is further illustrated by the 10–15° CCX bond angle decrease observed when a proton is removed from this end of the molecule.

Selected vicinal NBO interactions for the two stereoisomers of the 2-fluoro vinyl anion are shown in Figure 7.21. Note that these interactions are much stronger than their analogues for the parent vinyl anion describe above. The overall difference in the NBO interactions is much larger than the overall difference in total energies (2.2 kcal/mol at the B3LYP/6-31++G(d,p) level), indicating that other factors compensate for the stereoelectronic imbalance. The interesting feature of these interactions is that they illustrate the advantage

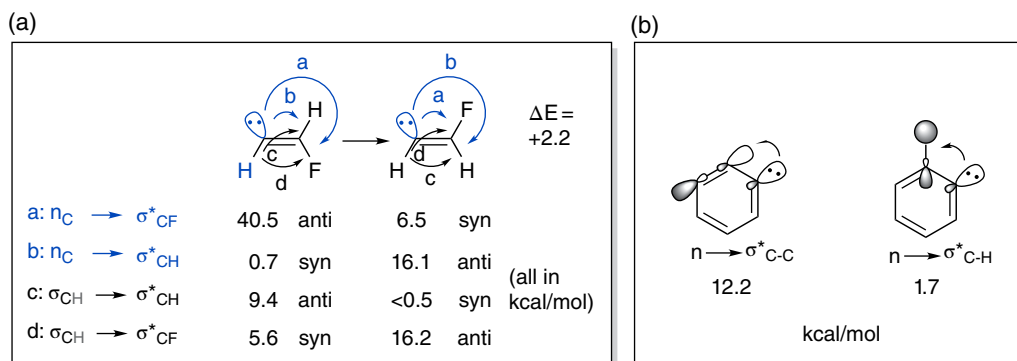


Figure 7.21 NBO energies quantifying selected stereoelectronic interactions in β -fluoro vinyl anion (a) and phenyl anion (b).²¹

of antiperiplanarity: when the best donor and acceptor are antiperiplanar, the interaction is maximized ($n_{\text{C}} \rightarrow \sigma_{\text{C-F}}^* = 40.5 \text{ kcal/mol}$). However, when the best donor (carbanionic orbital) is syn-periplanar to the C-F bond, the interaction energy drops down to 6.5 kcal/mol, much smaller than the 16.2 kcal/mol antiperiplanar interaction of the σ_{CF}^* acceptor with a much weaker C-H donor.

Aryl anions are the other very common sp^2 -anion. Again, the anionic center is perpendicular to the aromatic π -system, so in the absence of conjugation, it is the hyperconjugative effects that provide the main source of conjugative stabilization (Figure 7.22) to the negative center. The trends in stability and reactivity of aryl anions provide useful insights into the role of negative hyperconjugation in anions. Even though these cyclic systems are incapable of E/Z-isomerization, they have the advantage of being readily available in different substitution patterns.

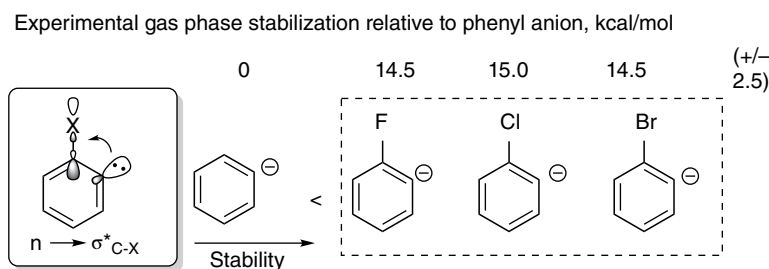


Figure 7.22 Effect of negative hyperconjugation on the stability of aryl anions.

All ortho-halogen substituted aryl anions are ~15 kcal/mol stabilized relative to the phenyl anion. Interestingly, the effects of fluorine, chlorine, and bromine are identical within experimental error, and the stabilizing effect decreases but does not disappear in the meta- and para halogen-substituted aryl anions. As a consequence, even the C-H acidities at remote positions are still higher than the C-H acidity of benzene. The remote effects cannot be explained by inductive and field effects. For example, the effect of a p-Br group (8.9 kcal) is greater than the effect of an m-F group (6.5 kcal). We will discuss the involvement of remote hyperconjugative effects (homo-hyperconjugation and double hyperconjugation) in the *meta* and *para* systems in Chapter 9.

The antiperiplanar arrangement of the carbanionic orbital and the σ -acceptors in aromatic systems can be achieved by introducing endocyclic heteroatoms. The known hydride affinities for N-containing aromatics generally reflect the stabilizing effect of endocyclic $\sigma^* \text{C-N}$ orbitals (Figure 7.23).²² However, the situation is far from simple and cannot be readily explained by the combination of electrostatic and hyperconjugative interactions alone. A computational dissection of the complex interplay of multiple orbital interactions in these systems has not been undertaken so far but it is likely that the observed non-additivity of such effects reflects cooperativity and anticooperativity of stereoelectronic interactions.

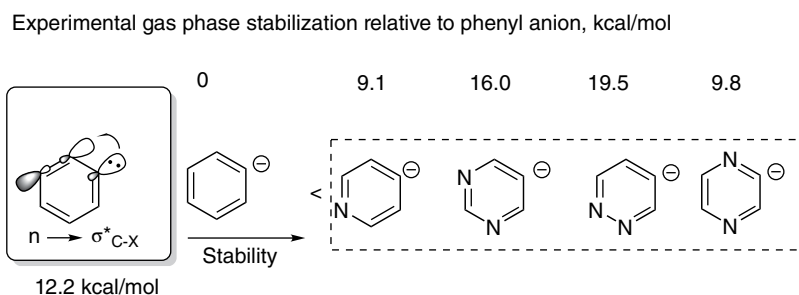


Figure 7.23 Effect of negative hyperconjugation on the stability of N-substituted hetaryl anions.

Sometimes, the analysis of electronic effects has to be expanded beyond stereoelectronic concepts. For example, the greater acidity of C-H bonds in five-membered rings originates from hybridization effects (more important here than hyperconjugation). This underlying reason was not recognized until the recent insightful analysis of Mo and coworkers who have shown that change in the valence $C=C(H)-N$ angle leads to significant rehybridization.²³ This effect can override the relatively subtle stereoelectronic preferences. For example, it explains why the five-membered Me-substituted aromatics undergo deprotonation (Figure 7.24) at a ring C-H bond whereas its six-membered analogue undergoes deprotonation at the benzylic position instead. The smaller valence angle leads to reallocation of additional p-character to the endocyclic hybrids, leaving more s-character for the carbon hybrid that forms the C-H bond. Increased s-character leads to increased C-H acidity, explaining the “anomalous” deprotonation of one of the ring C-H bonds.

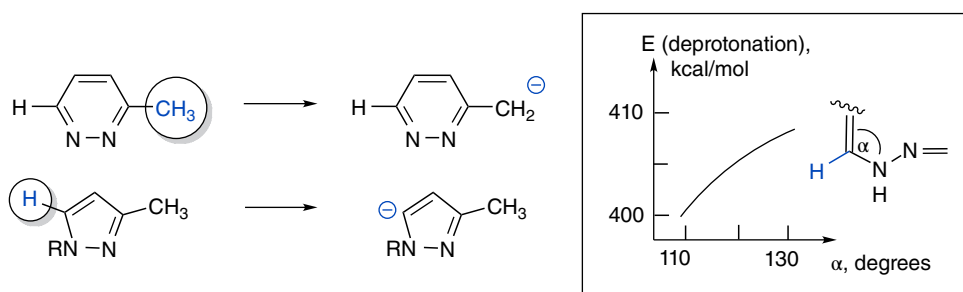


Figure 7.24 Hybridization effects can invert the relative stability of benzylic and aryl anions.

7.3.1 Heteroatom-containing systems

The key stereoelectronic features often associated with the introduction of heteroatoms stem from the presence of polar bonds and lone pairs (Figure 7.25). Such combinations can lead to strong stereoelectronic interactions. Most often, such interactions are discussed in the context of stability and reactivity of nitrogen-containing compounds. Geometric anisotropy that is required for the stereoelectronic control manifests itself in bent compounds with three different substituents at a “sp²-hybridized” atom. Analogously to the situation in vinyl carbanions, stronger acceptors generally prefer anti position relative to the lone pair.

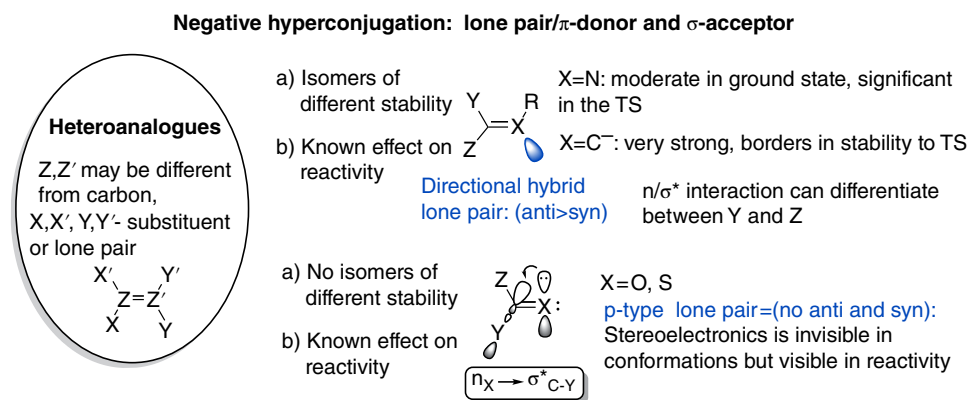


Figure 7.25 Stereoelectronic features associated with the introduction of heteroatoms.

Similar effects are also present in $C=X$ moieties where X is a chalcogen (i.e. carbonyl and thiocarbonyl moieties for $X=O, S$) but, in these systems, such interactions do not have the stereodifferentiating consequences because of the symmetry of the p-lone pair of X . Such interactions will be discussed here only briefly. We will focus the next part on nitrogen-containing compounds.

7.4 Diazenes and the isomerization of azo compounds

Stereoelectronic interactions increase in magnitude and importance when one of the σ -bonds at a vinyl position is changed to a lone pair. An illustrative set of examples (Figure 7.26) is provided by the relative stability of diazenes where the balance is shifted by changes in the σ -acceptor ability of $N-X$ bonds.

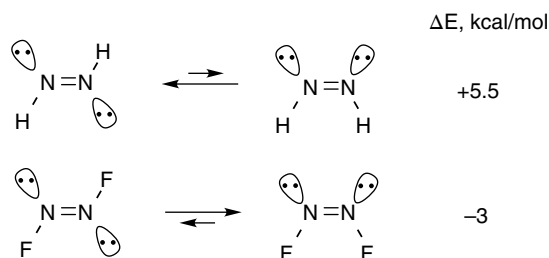


Figure 7.26 The relative stability of diazene isomers changes upon fluorine introduction.

The *cis*-isomer of diazene is also expected (Figure 7.27) to be favored²⁴ due to antiperiplanar $n \rightarrow \sigma_{NH}^*$ interactions. However, recent gas phase calculations predict the *trans*-isomer to be preferred by ~ 5.5 kcal/mol for the parent system, indicating that unfavorable dipole–dipole interactions in the more polar *cis*-isomer outweigh the stereoelectronic factors.²⁵ However, the amount of *cis*-conformer at equilibrium is sufficiently large to allow diazene to participate in metal-free *syn* hydrogenation reactions of alkenes and alkynes²⁶ where concerted transfer of the two hydrogen atoms to a π -system via a cyclic transition state hinges on the thermodynamic and kinetic availability of the less stable *cis*-isomer.

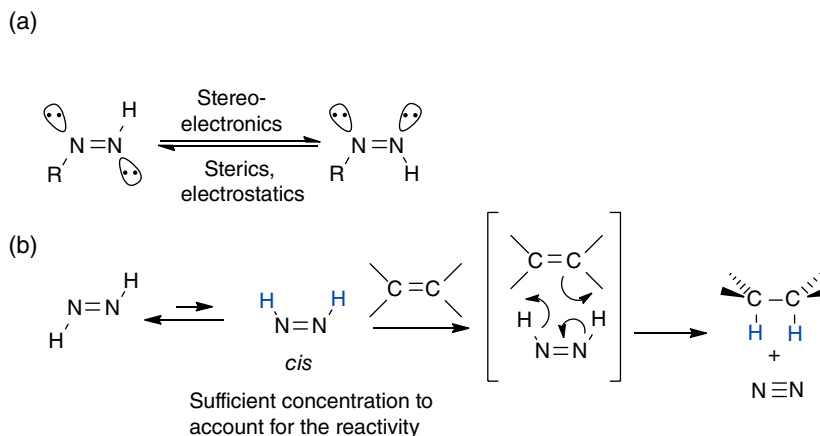


Figure 7.27 (a) Stereoelectronics are outweighed by sterics and electrostatics in the ground state conformation of diazene. (b) *cis*-hydrogenations occur via a concerted cyclic transition state from the less stable *cis*-diazene.

In the above example, the N-H moiety is an insufficiently strong hyperconjugative acceptor due to the unfavorable polarization of the $\sigma_{\text{N-H}}^*$ orbital. As expected from the differences in electronegativity, the larger orbital coefficient is at hydrogen. Presence of a more electronegative atom X enhances the acceptor ability of $\sigma_{\text{N-X}}^*$ orbitals and amplifies stereoelectronic preferences to the extent where they become the controlling factor in the conformational equilibrium that shifts towards sterically disfavored conformations. For example, *cis*-difluorodiazene is ~ 3 kcal more stable than the *trans*-isomer.⁵ The difference in stability is even more pronounced in dichloro- and dibromodiazenes (the calculated B3LYP differences are ~ 3 , 7, and 8 kcal, for F, Cl, and Br, respectively).²⁷ NBO analysis illustrates the stereoelectronic preferences responsible for these conformational features. Since the lone pairs of nitrogen are stronger donors than C-H bonds in the previous section, the $n_{\text{N}} \rightarrow \sigma_{\text{NX}}^*$ interactions are stronger than $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CX}}^*$ interactions responsible for the alkene *cis*-effect. The out-of-plane contributions favor the *cis*-effect as well. The greater *cis*-preference for the heavier halogens is consistent with the greater acceptor ability of the corresponding $\sigma_{\text{N-X}}^*$ orbitals.

Not only do the antiperiplanar interactions define the conformational profile in these compounds but they play an important role in their reactivity as well (Figure 7.28). *cis*-Difluorodiazene is highly reactive²⁸ and the *cis*-isomers of dichloro- and dibromodiazenes are extremely unstable. This reactivity is also a consequence of stereoelectronic interactions because $n_{\text{N}} \rightarrow \sigma_{\text{NX}}^*$ interactions weaken the N-X bonds and stabilize the transition state for the loss of nitrogen. This is an example from the large number of reactions where stereoelectronic effects that are present in the reactants become stronger in the transition state. This evolution of delocalizing interactions is the key to selective transition state stabilization, leading to more thermodynamically stable compounds that, “paradoxically” also display higher reactivity (see Chapter 9 for a more detailed discussion).

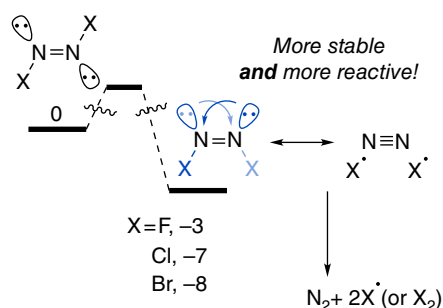


Figure 7.28 Stereoelectronics associated with acceptor substitution antiperiplanar to nitrogen lone pairs in diazenes lead to more conformationally stable, yet more reactive *cis*-isomers. Energies in kcal/mol.

In substituted diazenes,²⁹ or azo compounds, the existence of two relatively stable *cis* and *trans*-isomers is of great experimental³⁰ and theoretical³¹ interest. The photochemical conversion between these species has found many applications, including molecular switches,³² memory storage,³³ and for conformational control in the regulation of biological processes.³⁴

The presence of the two phenyl groups in azobenzene creates a relatively large preference for the *trans*-isomer (14.7 kcal/mol calculated,^{28a} 11.7–13.4 kcal/mol experimentally^{29a,b}), primarily due to steric destabilization of the *cis*-azobenzene, which allows for thermal *cis-trans*-isomerization (with calculated and experimental barriers of 33^{28a} and 27 kcal/mol,^{29c} respectively).

Non-symmetric substitution further illustrates how electronics can reverse the relative stability of *cis/trans*-isomers (Figure 7.29).^{30,27a} As expected, strong sigma acceptors stabilize the *cis*-isomer. Furthermore, they also provide additional stabilization to the linear TS for the inversion at the β -nitrogen, where the lone pair changes its hybridization to the high energy 100% p-orbital, maximizing hyperconjugative interactions with the vicinal sigma acceptor.

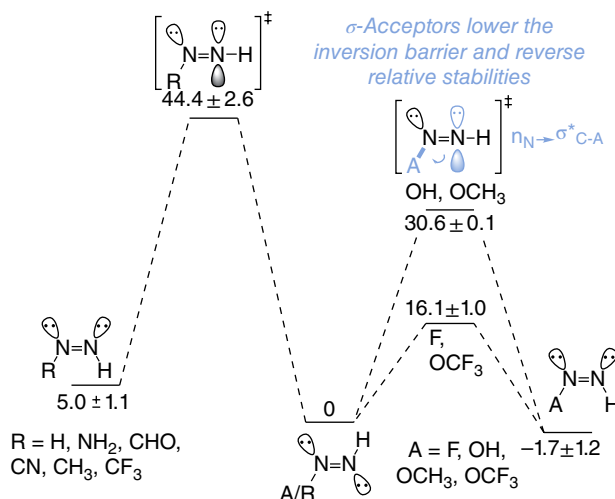


Figure 7.29 Electronic effects on the inversion barrier and relative energies of monosubstituted azo compounds, calculated at the B3LYP/6-311++G(d,p) level of theory. Energies in kcal/mol.

$n \rightarrow \pi^*$ interactions Again, this pattern is observed in cumulenenic systems. In this section, we will discuss the frustrated competition between stereoelectronic effects and hybridization in isothiocyanate.

Despite their unusual structural and electronic features, isothiocyanates are not uncommon and are certainly important. In fact, members of this family were suggested to be responsible for some of the health benefits found for phytochemicals – from reduced hyperglycemia to a lower risk of chemical carcinogenesis. Furthermore, the reactivity of isothiocyanates towards thiols at the mild conditions finds biological applications for protein modification (Figure 7.30).³⁵ Remarkably, the isothionate carbon is practically invisible (“silent”) in ^{13}C NMR. Computational analysis suggested that the isothiocyanate moiety can access a large region of the potential energy surface with the CNC angle in the 120–180° region. The flat potential energy surface and high flexibility of the isothiocyanate group stem from the stereoelectronic frustration originating from a tug-of-war between hybridization and resonance in this system (Figure 7.30).³⁶ Nitrogen in a C-N=C triad naturally prefers a bent geometry where it can allocate some of the s-character to its lone pair in order to satisfy the Bent’s rule. However, a stereoelectronically preferred choice is to have nitrogen linear so the lone pair can be delocalized to the strongly acceptor $\pi^*\text{C}=\text{S}$ orbital. This situation leads to selective stabilization of the transition state for CNC bending and increased conformational mobility that results in broadening and weakening of the respective carbon NMR signal.

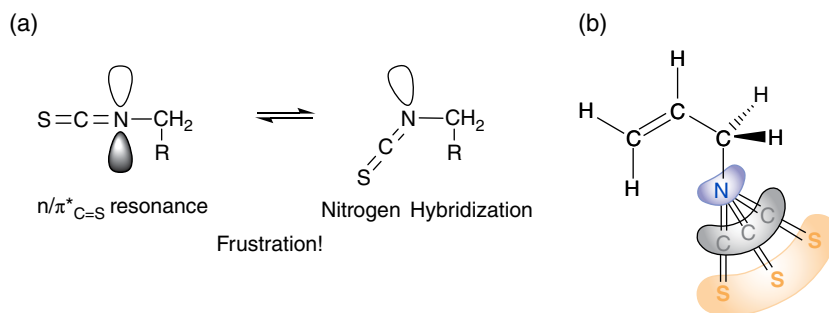


Figure 7.30 (a) The tug of war between resonance and hybridization in isothiocyanates can result in frustration. (b) Increased conformational mobility leads to broadening and weakening of the isothiocyanates carbon NMR signal. (Source: Glaser 2015 (36). Reproduced with permission of American Chemical Society.)

7.5 Antiperiplanarity in coordinated bond-breaking and bond-forming processes: eliminations, fragmentations and additions

The breaking bonds can be either a very strong donor or a strong acceptor depending on their polarization. The $\sigma \rightarrow \sigma^*$ effects outlined in the previous section can be considerably amplified in the transition states and evolve into concerted bond breaking/bond forming processes where departure of an acceptor group is coordinated with the attachment of the donor group at the adjacent carbon and the overall structural rearrangement that illustrates the connection between the “no-bond resonance” description of hyperconjugation with eliminations.

When a C-C bond is broken instead of the combination of C-H/C-Y bonds, such reactions are commonly referred to as fragmentations rather than eliminations. However, such processes are stereoelectronically very similar (Figure 7.31). An interesting feature of C-C fragmentations is that they are directly connected to the so-called carbenoid rearrangements (e.g. when the fragmenting carbon-centered reactive intermediate is unstable and reacts with a different position at the remaining part of the reactant before departing). Again, the key stereoelectronic effects apply and can be used as powerful tools for the control of reactivity.

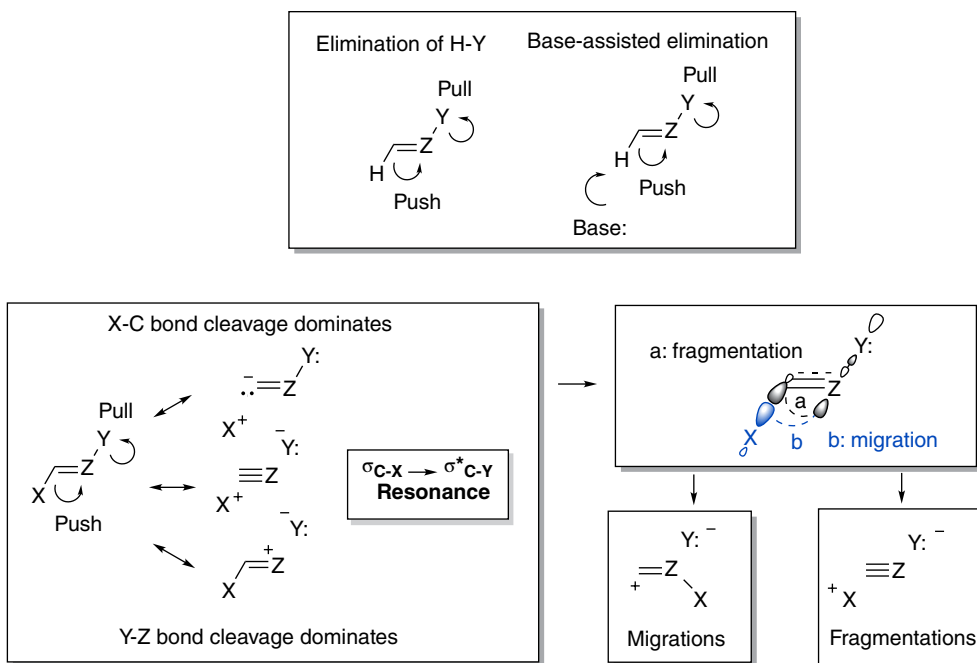


Figure 7.31 Stereoelectronic connections between eliminations, fragmentations, and migrations.

If X is connected with the back lobe of σ^*_{Z-Y} orbital, it leads to a migration of X to the adjacent atom Z. If X is eliminated, this process leads to a fragmentation. The two reactions share common mechanistic and stereoelectronic features. We will discuss these features below, starting with the eliminations.

Eliminations While the antiperiplanar orbital arrangement of the leaving group relative to the developing negative charge in E2 eliminations of alkyl halides can be achieved via rotation around the single bond, such

rotation is impossible in the base-catalyzed formation of alkynes from alkenyl halides. The rigid geometries in the starting vinyl halides simplify understanding the stereoelectronic effects on reactivity. It has long been observed that *trans*-elimination occurs much faster than *cis*-elimination.³⁷ For example, the formation of acetylene dicarboxylic acid proceeds about 50 times faster from chlorofumaric acid than from chloromaleic acid.^{37b} Furthermore, *cis*-dichloroethylene forms chloroacetylene about 20 times faster than *trans*-dichloroethylene.^{37c} In some cases, the *trans*-isomer begins to exhibit alternative reactivity, undergoing addition, rather than elimination (Figure 7.32).³⁸

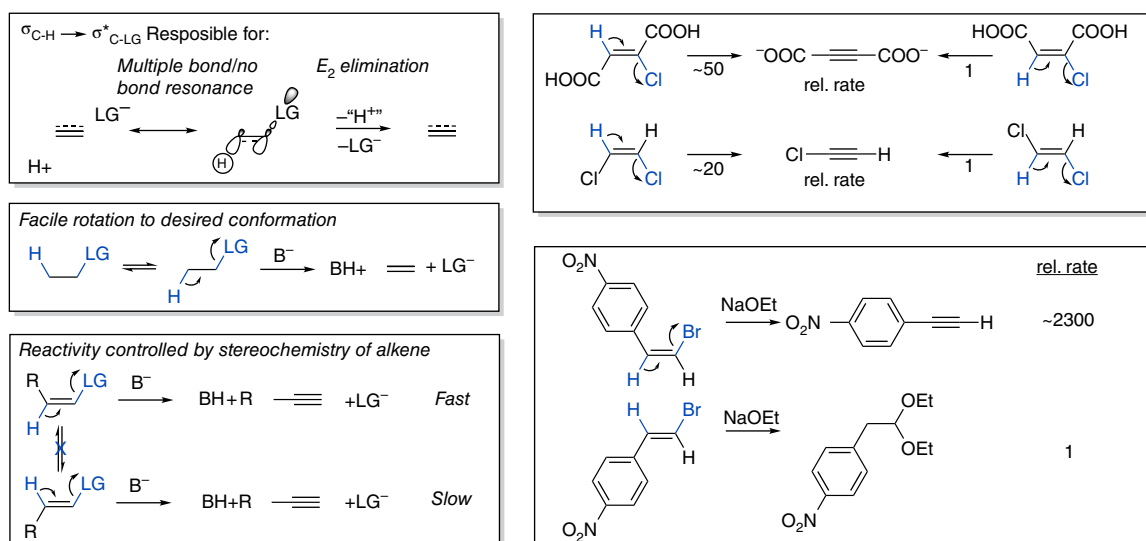


Figure 7.32 Stereoelectronic features of *E2* elimination reactions from alkyl and vinyl substrates.

According to the principle of microscopic reversibility, addition of alkoxides to alkynes also favors stereochemistry where the developing anion is antiperiplanar to the strongly acceptor $\sigma^*\text{C-O}$ orbital (Figure 7.33). Consequently, it has been shown that the base catalyzed addition of methanol to phenyl acetylene gives solely the *Z*-isomer, in ~95% yield.^{36b}

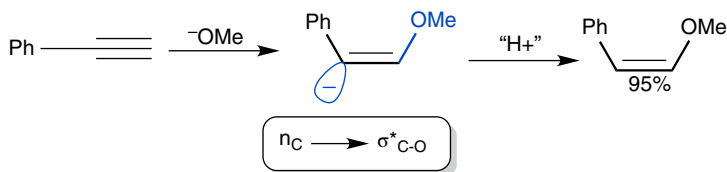


Figure 7.33 Addition of alkoxides to alkynes favors stereochemistry where the developing anion is antiperiplanar to the strongly acceptor $\sigma^*\text{C-O}$ orbital.

Triple bond formation at nitrogen and oxygen The stereoelectronic control of reactivity at multiple bonds is not limited to all carbon species. Due to the presence of a stereoelectronically defined lone pair, sp^2 -hybridized nitrogen compounds provide a number of illustrative examples of stereochemically directed reactivity (Figure 7.34).

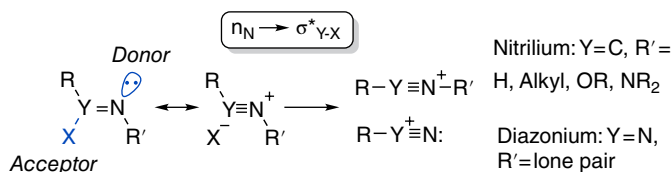


Figure 7.34 Antiperiplanar negative hyperconjugation in nitrogen compounds separated by a vinyl bridge.

For example, elimination of halogens from imines to give nitrilium ions is strongly facilitated by an antiperiplanar $n \rightarrow \sigma^*_{LG}$ interaction (Figure 7.35). The *Z*-isomer of α -chloro oximes undergoes elimination ~450 times faster than the *E*-isomer.³⁹

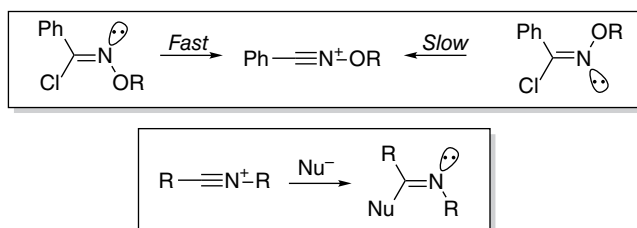


Figure 7.35 Stereoelectronic effects on reactivity of *N*-containing multiple bonds are analogous to those seen in alkenes and alkynes.

For the reverse reaction, addition to nitrilium ions (i.e. benzonitrile oxide), the incoming nucleophiles prefer the *trans*-approach relative to the developing lone pair (Figure 7.36).⁴⁰ This can be useful in subsequent transformations. For example, a method for the synthesis of peptides takes advantage of the faster reactivity of carboxylates relative to amines in the addition to nitrilium ions.⁴¹ The stereoelectronic control of the carboxylate addition gives the *Z*-isomer, stable to O-*N* acyl migration but reactive to external nucleophiles, i.e. amines. After addition of the carboxylate, the (*Z*)-acylisoamide reacts with the amine to give the amide product.

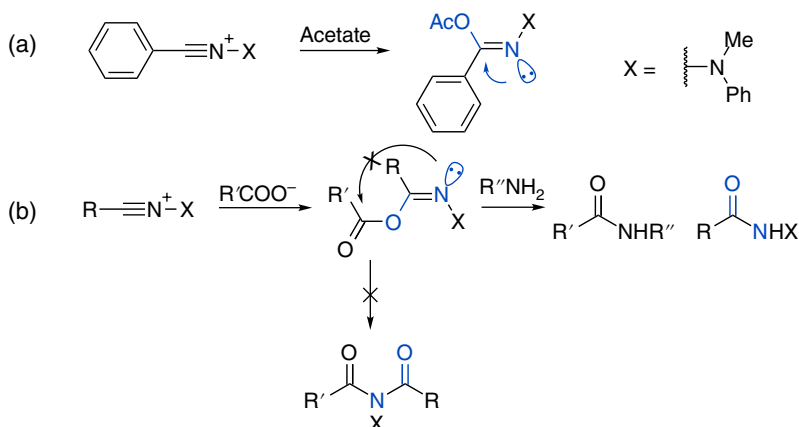


Figure 7.36 (a) Stereoelectronically controlled *trans*-addition to nitrilium ions. (b) Application for the synthesis of peptides.

Analogous stereoelectronic preferences are in play for transformations of azo compounds to the corresponding diazonium salts. Analogous to alkenes and imines, the *Z*-methoxyphenyldiazene undergoes elimination ~four orders of magnitude faster than the *E*-isomer (Figure 7.37).⁴²

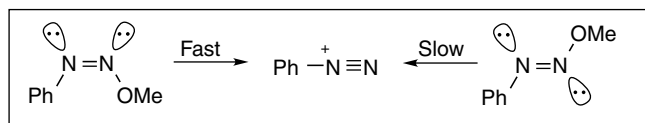


Figure 7.37 Elimination from azo compounds to give diazonium ions is accelerated by $n \rightarrow \sigma^*_{\text{N-O}}$ interactions.

Although the dominant reactivity pattern for carbonyl compounds in reactions with nucleophiles is the direct nucleophilic attack at the carbonyl π^* , eliminations promoted by assistance from the lone pair of oxygen are also possible in those rare cases when X is a strong acceptor with a low energy σ^* (Figure 7.38).⁴³ There is no stereoelectronic bias in this system: the lone pair of oxygen is positioned well to overlap well with both carbonyl substituents and subsequent reactivity is determined by the leaving ability of X vs. R.

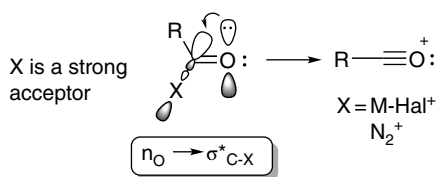


Figure 7.38 Negative hyperconjugation in carbonyls facilitates formation of acylium ions.

Rearrangements and fragmentations The stereoelectronic preference for antiperiplanarity is responsible for the stereoselectivity of the Beckmann rearrangement of oximes (Figure 7.39).⁴⁴ This classic process has significant industrial importance as a route to caprolactam. Although the simplest version shown below does not fully reflect the mechanistic complexity associated with this process (role of solvent molecules, H-bonding etc.), it captures the key stereoelectronic feature: the favored antiperiplanar orbital arrangement of the migrating and leaving group accounts for the concerted character of this reaction and for the high selectivity. The stereochemical analysis is simplified in these systems because the two stereoisomeric oxime reactants have a relatively large barrier for interconversion (vide infra) and can be subjected to the experimental conditions without the danger of being equilibrated. The formed nitrilium can then be subsequently hydrated to give the corresponding amide.

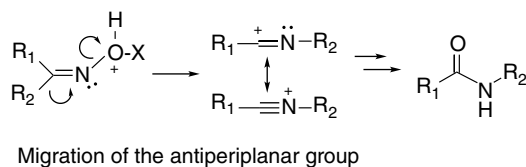


Figure 7.39 Stereoelectronic migration of the group antiperiplanar to the leaving group in the Beckmann rearrangement.

When the anti position to the hydroxyl group of the oxime is occupied by an atom capable of formation of a highly stabilized cation, a nitrile-forming fragmentation can occur instead of the rearrangement. The competition between the two Beckmann processes depends on the relative stabilization of the cationic intermediates that can be formed in the key step. The rearrangement is inherently favorable because it always provides a carbocation that is strongly stabilized by the α -nitrogen lone pair (i.e. the nitrilium cation). In order for the fragmentation to be competitive, sufficient stabilization should be provided to the carbocation left behind after the C-C bond rupture (Figure 7.40). Tertiary cations were reported to be sufficiently stabilizing to promote the fragmentation.⁴⁵ Some of the most interesting and historically important examples (such as morphine degradation by Schöpf, the pioneering work of Grob, and Stork's synthesis of byssochlamic acid)⁴⁶ included stabilization by the lone pairs of heteroatoms.

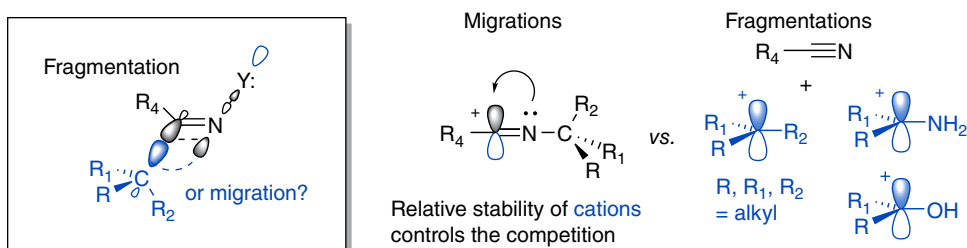


Figure 7.40 The competition of Beckmann rearrangement and fragmentation.

The change of nitrogen to negatively charged carbon transforms the Beckmann rearrangements of oximes to carbenoid rearrangements of α -halovinyl carbanions (Figure 7.41). Despite the introduction of negative charge, the stereoelectronic features of these processes are similar. For example, the Fritsch–Buttenberg–Wiechell rearrangement of 2,2-diaryl-1-haloalkenes⁴⁷ displays an analogous stereoelectronic preference for the migration of the group antiperiplanar to the departing halide.⁴⁸

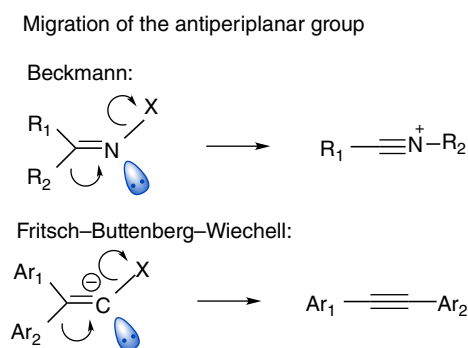


Figure 7.41 The Beckmann and Fritsch–Buttenberg–Wiechell rearrangements share a common stereoelectronic preference for the migration of the group antiperiplanar to the departing halide.

The latter rearrangements are referred to as carbenoid rearrangements because the carbon halogen bond is weakened in the anion, giving a carbene-like character to the intermediate and to the respective migration TS (Figure 7.42).⁴⁹ Electronic effects of vinyl-bridged systems are still in play, however, as electron-donating migrating groups migrate faster than electron-withdrawing groups.⁵⁰

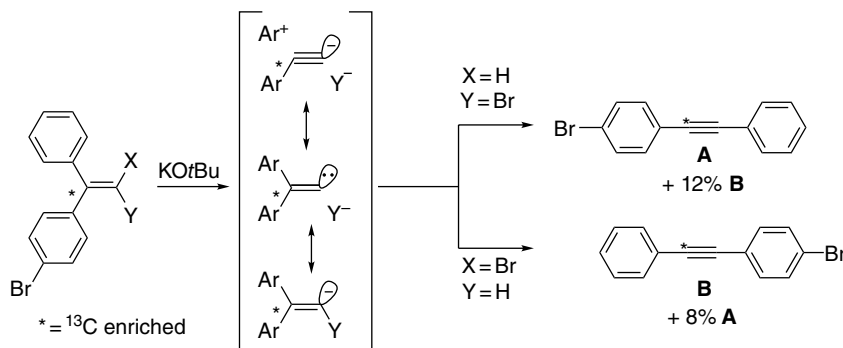


Figure 7.42 Stereoelectronic migration of group antiperiplanar to the C-Hal bond in carbenoid migrations.

In order to account for the high stereoselectivity, the departure of the leaving group has to occur simultaneously with the migration. If the departure of X precedes the migration and a true carbene is formed, the anti/syn stereoselectivity would reflect the intrinsic migratory aptitudes of substituents instead of the stereoelectronic preferences (Figure 7.43).⁵¹

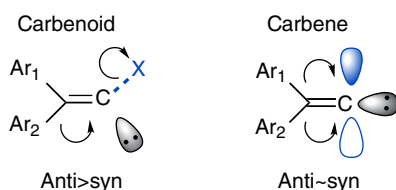


Figure 7.43 Comparison of stereoelectronic control in carbenoids and carbenes.

Aryls⁴⁷ and alkynes⁵² are excellent migrating groups, likely due to the additional π -assistance that these groups can provide in the TS (Figure 7.44). Alkenyls, cyclopropyls, and hydrogens also migrate well. According to the Hammond–Leffler postulate, migration in the less reactive substrates should proceed via a later carbene-like TS where the departure of the X-group is more pronounced. In agreement with this notion, migrations of alkyl and allyl groups display lower stereospecificity.⁵³ Furthermore, the observed migratory aptitudes also depend on the stationary substituents. For example, phenyl “refuses” to migrate in the presence of electron-withdrawing substituents such as halogen, $i\text{PrO}$, N_3 , and Me_2N ,⁴⁷ because the respective alkyne products are destabilized by hybridization effects.²⁰

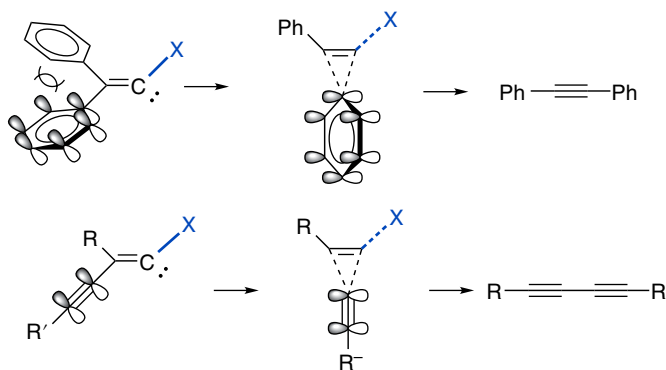


Figure 7.44 Stereo- and regioselectivity of alkynogenic migrations.

The stereoelectronic preferences are clearly illustrated by the comparison of stereoselectivity of the 5-exo-dig cyclizations of carbon^{54,55,56} or oxygen nucleophiles (Figure 7.45).⁵⁷ The carbanionic cyclizations proceed as stereoselective additions due to the preference for concerted, intramolecular *syn*-Li transfer to the developing carbanionic center. In contrast, the 5-exo-dig cyclization of an O-nucleophile is *anti*-stereoselective because of hyperconjugative stabilization of the anion with a strong hyperconjugative acceptor, the developing σ^*_{CO} orbital.⁵⁶ It has been shown that propargylic substituents that are able to coordinate to lithium can switch the selectivity of carbon nucleophile addition from *syn* to *anti*. However, this reactivity does not result from hyperconjugative stabilization of the developing vinyl anion.⁵⁸

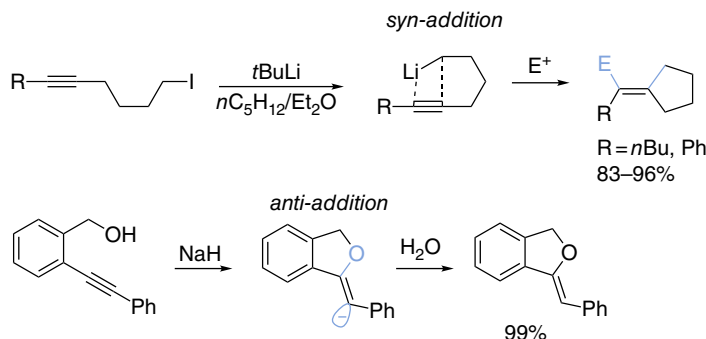


Figure 7.45 The stereoselectivity of addition is controlled by the acceptor ability of the C-Nu bond.

Exo-cyclizations of N-centered nucleophiles show analogous stereoelectronic preferences. For example, the anionic 5-exo-dig cyclization of hydrazides⁵⁹ gives exclusively the *Z*-isomer, corresponding to *anti*-arrangement of the nitrogen nucleophile relative to the developing anion, even though the anion intermediate of the *E*-isomer was calculated to be more stable due to hydrogen bonding (Figure 7.46). The *Z*-selectivity stems from the hyperconjugative stabilization of the developing anion in the TS, while the H-bonding stabilization of the *E*-anion does not fully manifest itself until after the cyclization. These stereoelectronic preferences are fully consistent with the orbital interaction energies between the developing vinyl anion and antiperiplanar sigma-acceptors provided by NBO analysis.

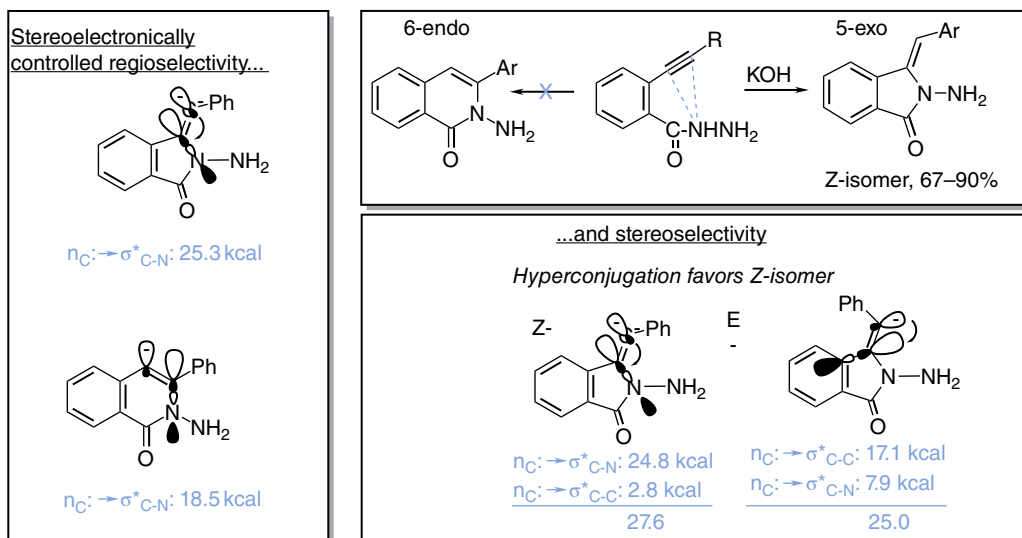


Figure 7.46 Stereoelectronic control of hydrazide cyclizations. NBO interaction energies obtained at the B3LYP/6-31 + G(d,p)^{58b} and B3LYP/6-31G(d,p)^{58c} levels of theory.

Furthermore, the antiperiplanar stereoelectronic interactions play an important role in determining the regioselectivity (5-exo vs. 6-endo) of cyclization.^{58e} The comparison of $n \rightarrow \sigma_{\text{CN}}^*$ interaction energies between the 5-exo and 6-endo products shows the importance of overlap and relative energies of interacting orbitals. Unlike the 6-endo product, the 5-exo anion is not constrained at an endocyclic position. Consequently, the carbanionic center can open the angle ($114^\circ \rightarrow 129^\circ$) in order for the non-bonding orbital to gain more p-character ($sp^{2.1} \rightarrow sp^{3.3}$) and delocalize more efficiently into the terminal phenyl ring and the vicinal σ_{CN}^* orbital (Figure 7.47).

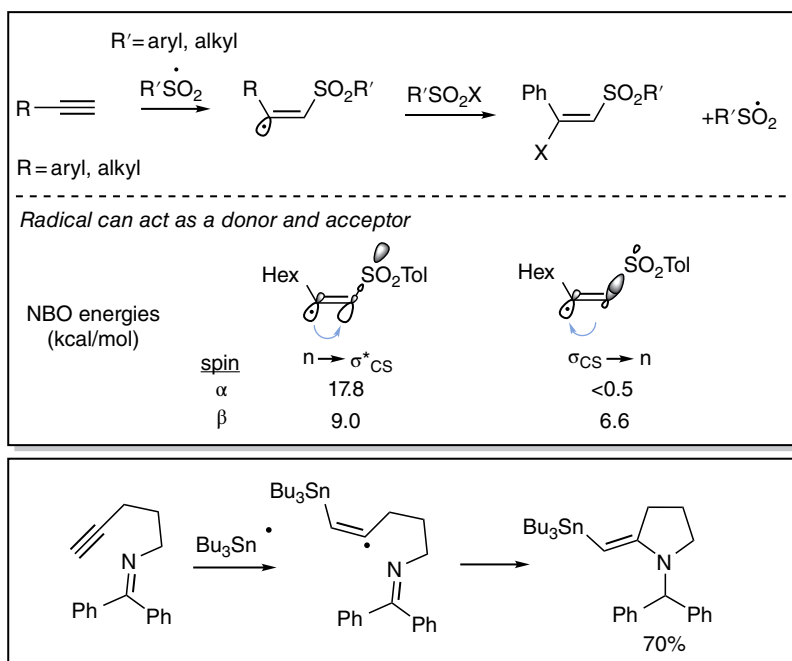


Figure 7.47 Regio- and stereoselectivity observed for sulfonyl radical additions to alkynes. NBO energies calculated at the B3LYP/6-31G(d,p) level of theory, from ref. 59a. The α -spin corresponds to the larger electron subset in the radicals (NBO analysis analyzes the Lewis structures for the α - and β -spins separately).

The stereoelectronic effects of alkyne additions are not limited to anions, as radicals react similarly. The sulfonyl radical adds regio- and stereoselectively to the terminal carbon,⁶⁰ giving the *E*-bromo vinylsulfone. NBO analysis shows that the radical center can act as both a donor and acceptor in interactions with the anti-periplanar C-S bond. In the radical intermediate formed by addition of tosyl radical to 1-hexyne, the donor character dominates. The energy of the $n \rightarrow \sigma_{\text{CS}}^*$ was larger than the $\sigma_{\text{CS}} \rightarrow n^*$ (~ 27 vs. 7 kcal/mol, for the sum of α and β -spins, Figure 7.47).^{59a}

Stereoselectivity of radical addition is not limited to sulfonyl radicals. The *trans*-addition has also been observed for tin,⁶¹ bromine,⁶² chlorine,⁶³ and silyl⁶⁴ radicals. Varying degrees of selectivity has been observed for addition of carbon-centered radicals, depending on the substituents size and effect on the inversion barrier.⁶⁵ Because the importance of negative hyperconjugation decreases for radicals in comparison to the anions, the barriers for inversion decrease in parallel. As a result, the selectivity can erode under conditions when trapping of the radical is slower than the equilibration, e.g. in the thiol-yne click reaction, which often provide a mixture of *E* and *Z*-vinyl sulfides.⁶⁶

7.6 Syn-periplanarity: the second best choice

In those cases where the developing anion cannot attain antiperiplanarity to a good acceptor, lesser but still significant stabilization can be provided by the syn-periplanar arrangement.

Anionic endo-cyclizations The assistance of the appropriately positioned acceptors is particularly useful in the formation of the stereoelectronically disfavored *endo* products. For example, the 5-*endo*-dig cyclization is observed when a carbonyl is introduced at the propargylic carbon (Figure 7.48).⁶⁷ The similarity to a Michael addition is deceiving because the carbanionic orbital in the cyclic product is constrained perpendicularly to the π -bond of the carbonyl moiety. Analogously, N-⁶⁸ and O-anions⁶⁹ show 5-*endo* selectivity in Ph-substituted alkynes with two F-groups at the propargylic bridge carbon. This observation suggests that the stabilizing effect of hyperconjugation on the incipient anionic center is greater than the analogous effect of π -conjugation in the 4-*exo*-TS, despite the exocyclic fluorine atom being “blocked” from achieving the antiperiplanar position. Alkyl substituted alkynes with a propargyl OH group undergoes selective 5-*endo*-dig closure in 94%.⁷⁰

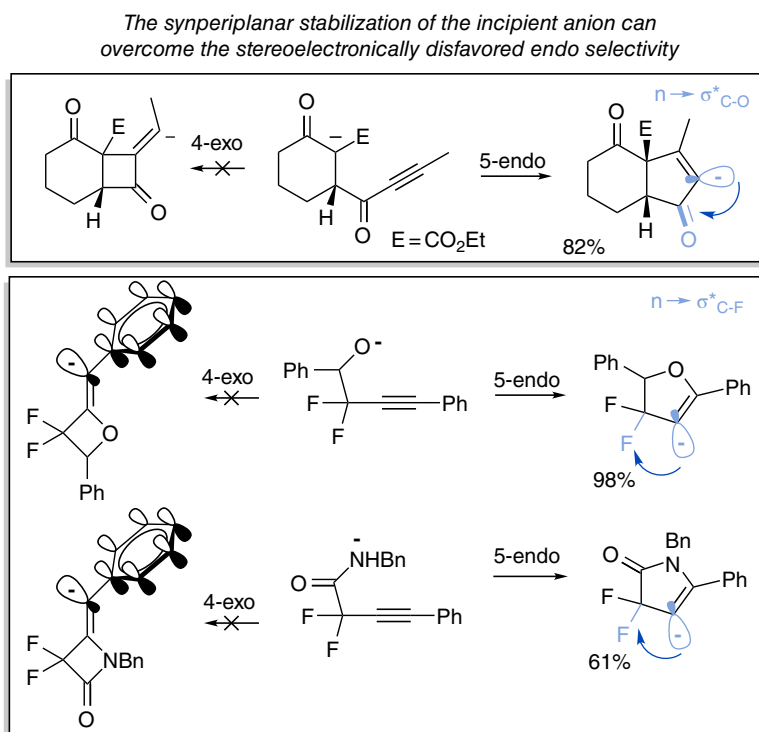


Figure 7.48 Stereoelectronic interactions with hyperconjugative acceptors assist in directing anionic cyclizations to the *endo*-paths. The antiperiplanar interactions between carbanion and the $\sigma^*\text{C-Nu}$ bond, that exist for both the *exo*- and the *endo*- products are not considered as a factor in determining the relative stability of the two cyclization products.

In summary, this chapter has discussed stereoelectronic effects on reactivity and stability which benefit from the rigid preorganization and closer spatial orbital proximity imposed by the presence of a double bond between the donor and acceptor orbitals.

The following chapters will provide further examples of reactivity controlled by stereoelectronics. Our goal in the next chapter is to evaluate the evolution of stabilizing orbital interactions throughout a reaction path and show how it can be used for accelerating or slowing down chemical reactions.

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8

Remote Stereoelectronic Effects

Conjugation through continuously connected extended π -arrays is well-known to provide long-range electronic communication. A number of extended hyperconjugation patterns have been shown to be effective as well.¹ Some of these patterns summarized lucidly by Lambert and Ciro² are illustrated in Figure 8.1. Long-range delocalization can follow a variety of patterns that combine conjugation and hyperconjugation and are mediated by through-bond (TB) and through space (TS) interactions.

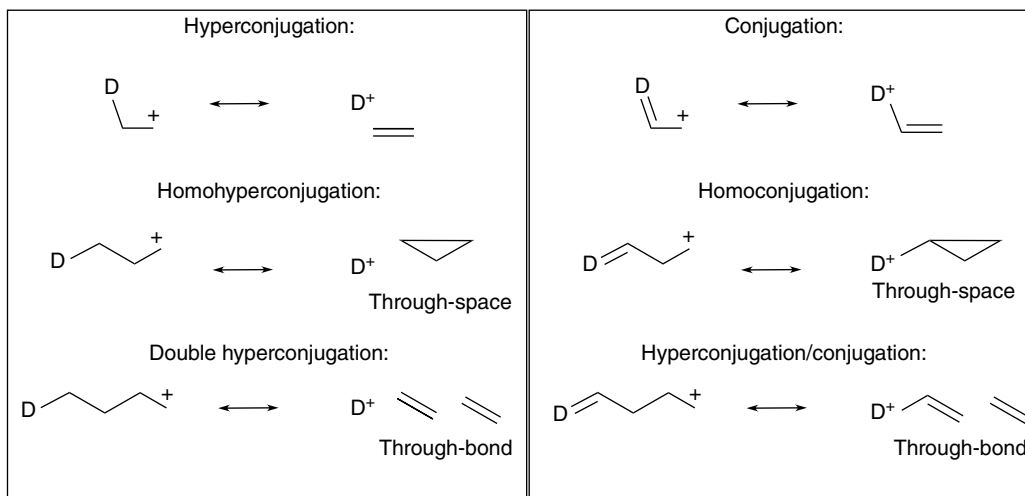


Figure 8.1 Comparison of normal and extended positive hyperconjugation and hyperconjugation types.

One of the challenges in understanding stabilizing consequences of remote orbital interactions is to differentiate them from inductive and field effects. This is often a difficult task that can lead to controversies unless one can rule out inductive contributions and evaluate field effects by analyzing conformational dependence of stabilities and reactivities.

8.1 Extended through space interactions: homoconjugation and homohyperconjugation

Homoconjugation and homohyperconjugation are observed when a saturated center intervenes between donor and acceptor orbitals. Homoconjugation is ubiquitous because π -bonds or lone pairs can serve as excellent donors. Interactions of donor and acceptor orbitals, that are not directly connected, serve as the electronic basis of such interesting phenomena as anchimeric assistance, neighboring group participation, and transannular interactions. As the interactions grow stronger, they can transform into chemical bond formation in a cyclization reaction. Due to the immensity of the topic and the broad variations in geometries that allow such interactions, we will limit our discussion of such effects to several fundamentally important basic patterns.

Strong cation stabilization can also be accomplished via homohyperconjugation with a sufficiently strong donor σ -orbital (Figure 8.2). This phenomenon is called the γ -effect or, sometimes, percaudal interaction. It has been particularly well-studied for silicon and tin.³ When the acceptor is a σ^* -orbital and the donor is a lone pair, this effect is referred to as homoanomeric effect.⁴ Both the γ -effect and the homoanomeric effect result primarily from direct through-space interactions. As the bridge between donor and acceptor gets longer, through-space hyperconjugative interactions merge with the supramolecular delocalizing interactions such as hydrogen, halogen, chalcogen, pnictogen, and tetrel bonding (Chapter 2).

8.1.1 Homoconjugation

Homoconjugation occurs when conjugation is interrupted by a saturated center, e.g. CH_2 (Figure 8.2).⁵ Because this interaction is mostly mediated via through-space overlap, it can be readily extended to other systems. If the orbitals of the intervening saturated center(s) are not involved in the conjugation, a variety of longer-range interaction can still be considered analogous to homoconjugation. Lone pairs (as illustrated by the textbook formation of bromonium and sulfonium ions) and π -bonds participate readily in such interactions.

The potential for cation stabilization provided by delocalization through space is significant. For example, a properly positioned alkene provides dramatic acceleration (10^{11}) of ionization of anti C-X bonds with perfect stereospecificity of substitution.⁶

An interesting feature of homoconjugation is that it is provided “on demand” and reaches maximum magnitude only when additional stabilization of the cationic center is needed desperately. The accelerating effect can be greatly diminished by the introduction of an alternative cation stabilizing group. For example, the *p*-anisyl group at C7 (Figure 8.3) provides sufficient stabilization of the carbonium ion center and the difference in reactivity between the two classes of compounds almost disappears (levels to a factor of 3). The stereospecificity of substitution disappears as well.⁷ The $\sim 10^{10}$ leveling effect of the *p*-anisyl group decreases to $\sim 10^9$ and 10^6 for Ph and *p*-CF₃-Ph substituents.⁸

The ability of the cyclopropyl ring to stabilize the developing positive charge in this system via homohyperconjugation is even higher, leading to the staggering 10^{14} acceleration relative to the respective 7-X-substituted norbornane and 10^3 acceleration even relative to the already highly activated 7-X-substituted norbornene (Figure 8.4).⁹

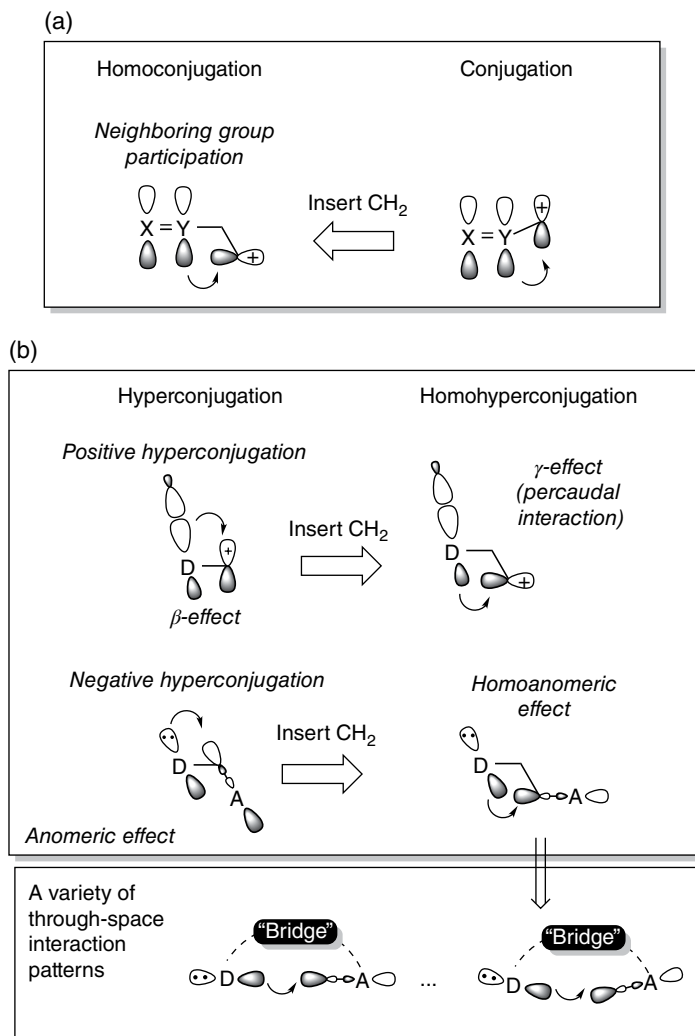


Figure 8.2 Homoconjugation (a) and homohyperconjugation (b) result from the insertion of a saturated center between donor and acceptor orbitals. When the acceptor is an empty p -orbital, homohyperconjugation is referred to as the γ -effect. Insertion of a saturated bridge between a lone pair and σ -acceptor (anomeric effect) gives the homoanomeric effect.

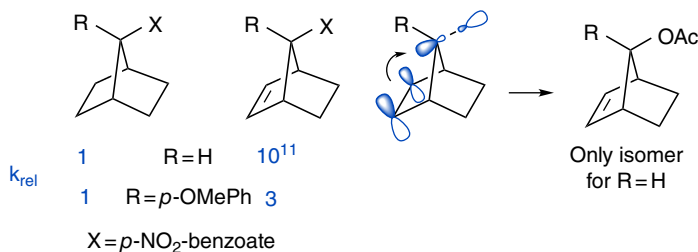


Figure 8.3 Solvolysis assisted by homoconjugation.

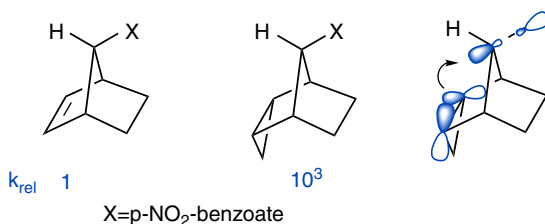


Figure 8.4 Comparison of homoconjugative and homohyperconjugative effects.

Considering the above, it is not surprising that “remote” effects with the participation of lone pairs can be larger than the classic vicinal hyperconjugation. For example, the non-negligible penalty (~ 3 kcal/mol) for moving a moderate σ -acceptor azide group to the axial position in a galactosyl oxocarbenium ion is fully compensated by the much larger effects of through-space interactions with the lone pairs of axial acetate substituents (Figure 8.5).¹⁰

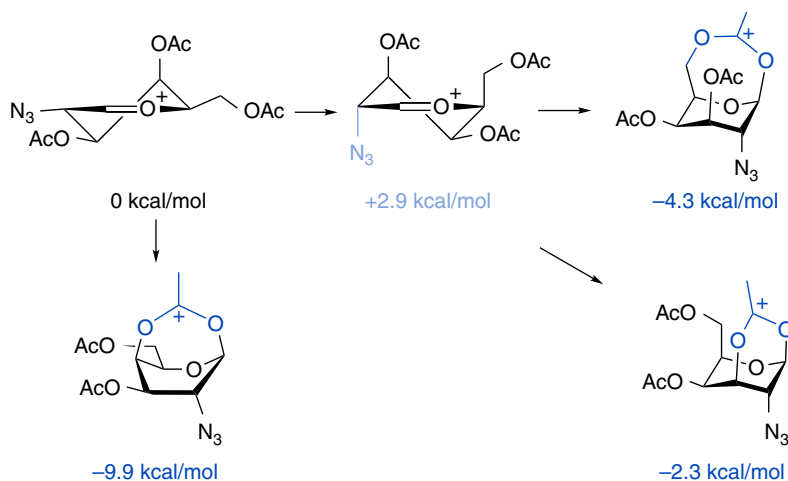


Figure 8.5 Relative stabilization of substituted oxocarbenium ions by neighbor-group participation from remote ester groups (energies are given relative to the first structure).

Symmetry-enforced cyclic conjugation that involves homoconjugative interactions can lead to the formation of homoaromatic systems. Homoaromaticity is well-established in charged systems and can involve either a planar or a three-dimensional array of atoms (Figure 8.6).¹¹ For example, a cyclobutenyl cation is twisted and close to a cyclopropenyl cation in the nature of overlap. Three methylene bridges are present in the homoaromatic “tris-homo-cyclopropenium ion”. The three-dimensional manifestation of this effect was suggested for a dication organized in a tetrahedral geometry within the adamantyl system. This concept can be readily extended to other reactive intermediates and to transition states.

8.1.2 Homoanomeric effects

In our discussion of homohyperconjugation, we will limit ourselves to one well-defined class of interactions – the homoanomeric effects, the family of phenomena where the role of stereoelectronic factors in through-space interactions is well-understood.

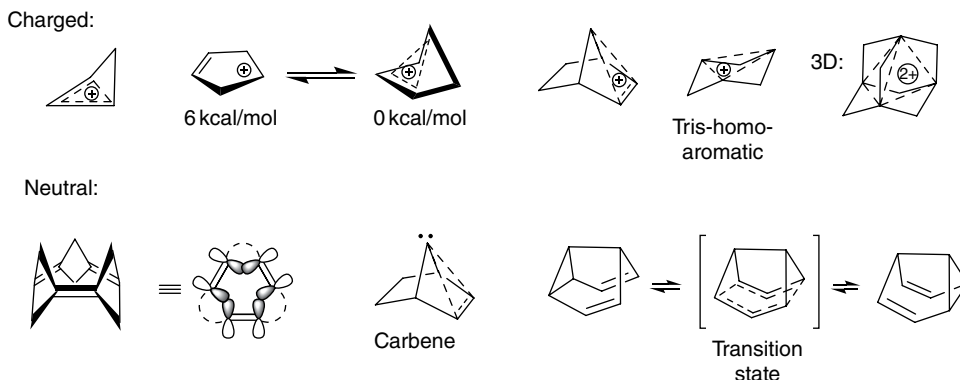


Figure 8.6 Selected examples of homoaromaticity in cations and neutral molecules.

Homohyperconjugation patterns can differ significantly in the relative position of the donor and acceptor orbitals in space. The interaction between an equatorial lone pair with the back lobe of an equatorial $\sigma^*_{\text{C-Y}}$ orbital (the W-effect) is important in azacyclohexanes^{4,12} but not in oxa- and thiacyclohexanes, where an alternative pattern (the Plough effect, Figure 8.7b) plays a more important role. The “mirror image” of the Plough effect, illustrated in Figure 8.7c, provides no hyperconjugative stabilization to the molecule (due to the same stereoelectronic reasons that disfavor a front lobe attack in an $\text{S}_{\text{N}}2$ process) but leads to a noticeable elongation of the axial bond (*vide infra*). This observation is the first documented hyperconjugative effect without a concomitant stabilization.¹³

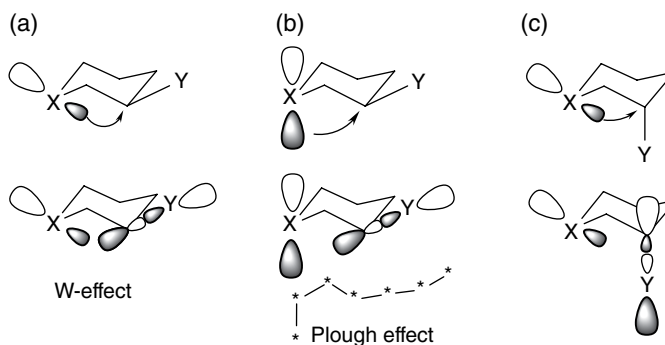


Figure 8.7 A schematic representation of three possible homoanomeric interactions in six-membered saturated heterocycles: (a) the W-effect, (b) the Plough (the “Big Dipper”) effect, and (c) the “mirror image” of the Plough effect. Differences in hybridization are neglected.

There is clear structural and spectroscopic evidence for homoanomeric interactions in neutral ground state molecules at their energy minimum conformations.^{12,14} These effects play an important role in the relative trends in one-bond $^1\text{J}_{\text{CH}}$ coupling constants needed for the understanding of conformational properties of carbohydrates, azacarbohydrates, and other substrates of biological interest.^{15,16} For example, the C(5)-H equatorial bond in 1,3-dioxane is longer than the C(5)-H axial bond and the respective direct NMR ^{13}C - ^1H coupling constant is smaller than that for the axial bond ($^1\text{J}_{\text{CHeq}} < ^1\text{J}_{\text{CHax}}$).¹⁷

This phenomenon (the reverse Perlin effect) contrasts with the “normal” situation, e.g. 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 C(5)-H bond with the pseudoaxial p-type lone electron pair on the β -oxygen (the Plough effect), while the $n_{\text{eq}} \rightarrow \sigma_{\text{eq}}^*$ (the W-effect) is unimportant in 1,3-dioxane, 1,3-dithiane, and 1,3-oxathiane (Figure 8.8).⁴ The equatorial lone pair on oxygen is a poor donor due to increased s-character ($\sim \text{sp}$). In contrast, the lone pair of nitrogen has a sufficient amount of p-character ($\sim \text{sp}^5$), so the situation changes in azacyclohexanes, where the W-effect is greater than the Plough effect.⁴

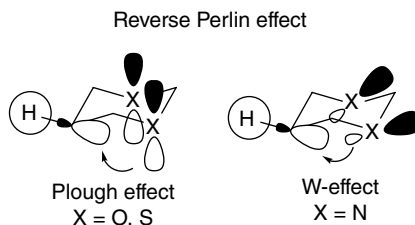


Figure 8.8 Reverse Perlin effect (equatorial C-H bond elongation) stems from the Plough effect in 1,3-dioxane, 1,3-dithiane and 1,3-oxathiane but the W-effect is greater in azacyclohexanes.

The complexity of structural consequences of remote interactions can be illustrated by the analysis of β -CH₂ bond lengths in the 16 parent saturated O,N,S-substituted heterocycles. For the equatorial β -CH bonds, the C-H bond lengths correlated with the combined magnitudes of all hyperconjugative $\sigma(\text{C-X}) \rightarrow \sigma^*(\text{C-H})_{\text{eq}}$ and $\sigma(\text{C-H})_{\text{eq}} \rightarrow \sigma^*(\text{C-X})$ interactions elongating the respective C-H bonds (including all vicinal interactions (direct hyperconjugation) as well as all homoanomeric interactions, Figure 8.9a). A closer scrutiny reveals that the results cluster in three different groups according to the following criteria: a) the combined number of β -CH₂ groups and β -equatorial nitrogen lone pairs is equal to two, b) at least one CH₂ group or equatorial nitrogen lone pair is at the β -position, c) neither β -CH₂ groups nor β -nitrogen equatorial lone pairs are present in the molecule.

The range of delocalization energies for the axial β -C-H bonds are ~ 10 times smaller relative to the respective equatorial C-H bonds (0.6 vs. ~ 6 kcal/mol). Not surprisingly, there is no correlation between the combined energy of hyperconjugative interactions and the axial β -C-H bonds. However, significant differences in the bond lengths *are* observed and, furthermore, they cluster into the same three groups (Figure 8.10b).

Instead of interaction energies and/or of $\sigma^*(\text{C-H})$ population the observed axial β -C-H bond lengths correlate well with the NBO charge at the respective hydrogen atom. This observation indicates that the elongation of the axial C-H bonds and the intramolecular redistribution of electron density, which decreases the positive charge at the hydrogen at the β -position, are related. However, where do these changes come from?

The repolarization of the axial C-H bonds is also a consequence of a hyperconjugative orbital interaction, i.e. the mirror of the Plough effect shown in Figure 8.7c. It shows that even in the absence of stabilization, hyperconjugative interactions can change electronic distribution and geometries. The origin of hyperconjugative interactions that does not lead to stabilization but can be imposed by structural constraints, as illustrated in Figure 8.11. Note the analogy between such effects and the known differences between the backside (favorable) and frontside (unfavorable) trajectories for an S_N2 attack. It will also be related to the difference between endo-tet and exo-tet cyclizations to be discussed in Chapter 12.

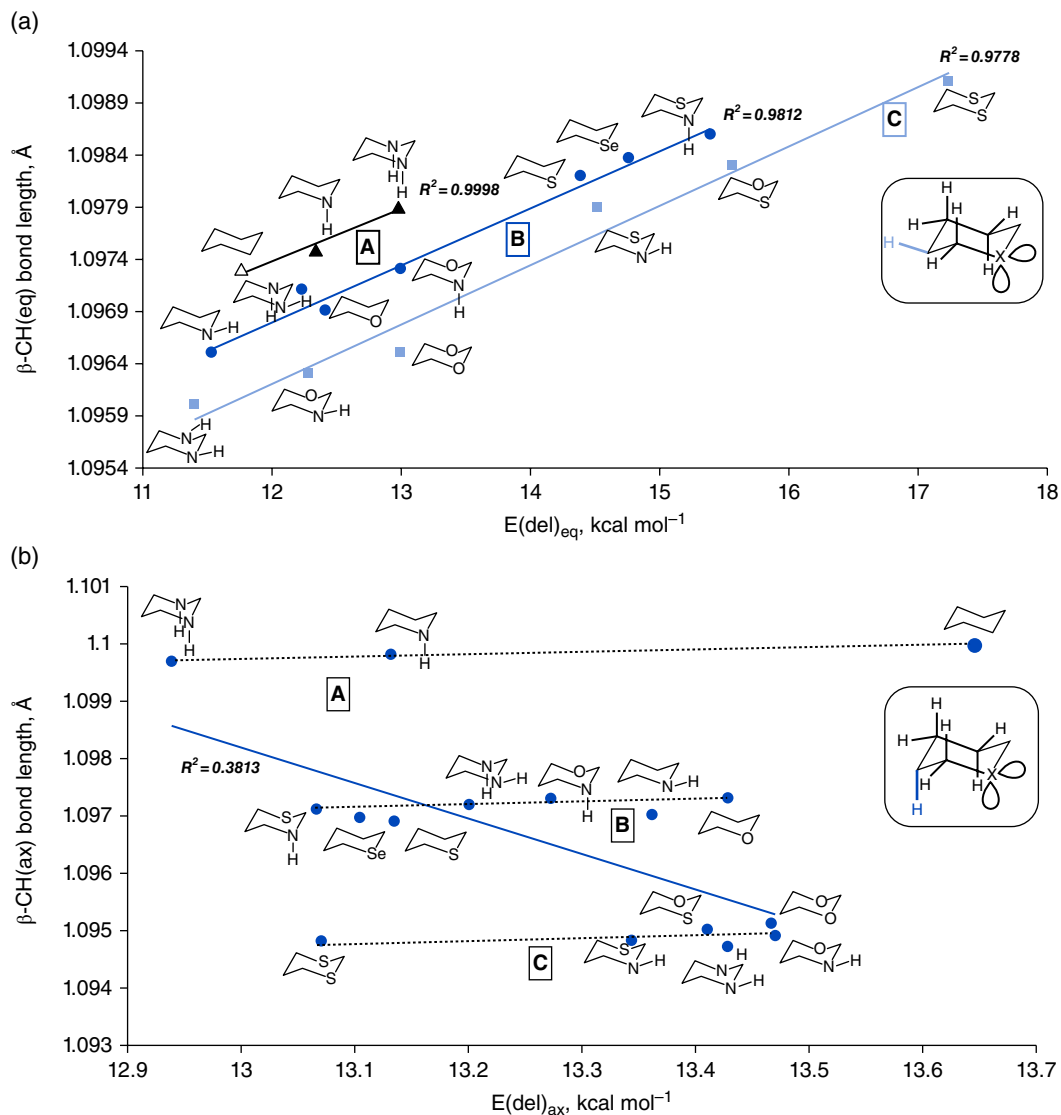


Figure 8.9 The contrasting correlations between NBO deletion energies for all hyperconjugative interactions (both vicinal and homoanomeric) involving axial (a) and equatorial (b) β -CH bonds with the respective C-H bond lengths at the B3LYP/6-31G** level. $E(\text{del})_{\text{ax}}$ and $E(\text{del})_{\text{eq}}$ are defined as the sum of all homoanomeric and vicinal $\sigma \rightarrow \sigma^*$ interactions involving the respective C-H bonds: $E(\text{del})_{\text{eq}} = \Sigma[n(X) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{eq}}] + \sigma(\text{C-C}) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{eq}} + \sigma(\text{C-H}) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{eq}} + \sigma(\text{C-H})_{\text{eq}} \rightarrow \sigma^*(\text{C-C}) + \sigma(\text{C-H})_{\text{eq}} \rightarrow \sigma^*(\text{C-H})$; $E(\text{del})_{\text{ax}} = \Sigma[n(X) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{ax}}] + \sigma(\text{C-C}) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{ax}} + \sigma(\text{C-H}) \rightarrow \beta\text{-}\sigma(\text{C-H})_{\text{ax}} + \sigma(\text{C-H})_{\text{ax}} \rightarrow \sigma^*(\text{C-C}) + \sigma(\text{C-H})_{\text{ax}} \rightarrow \sigma^*(\text{C-H})$. (Source: Alabugin 2003 (4). Reproduced with permission of American Chemical Society.)

Although there is no stabilizing hyperconjugative $n(\text{N})_{\text{eq}} \rightarrow \sigma^*(\text{CH})_{\text{ax}}$ interaction associated with this electron density transfer (Figure 8.11) due to the unfavorable topology for this interaction where the donor orbital points to the node of the acceptor orbital, the repulsive four-electron (exchange) interaction between the occupied $n(\text{N})_{\text{eq}}$ and σ_{ax} orbitals may be significant and may contribute to the change in polarization of the axial C-H bonds.

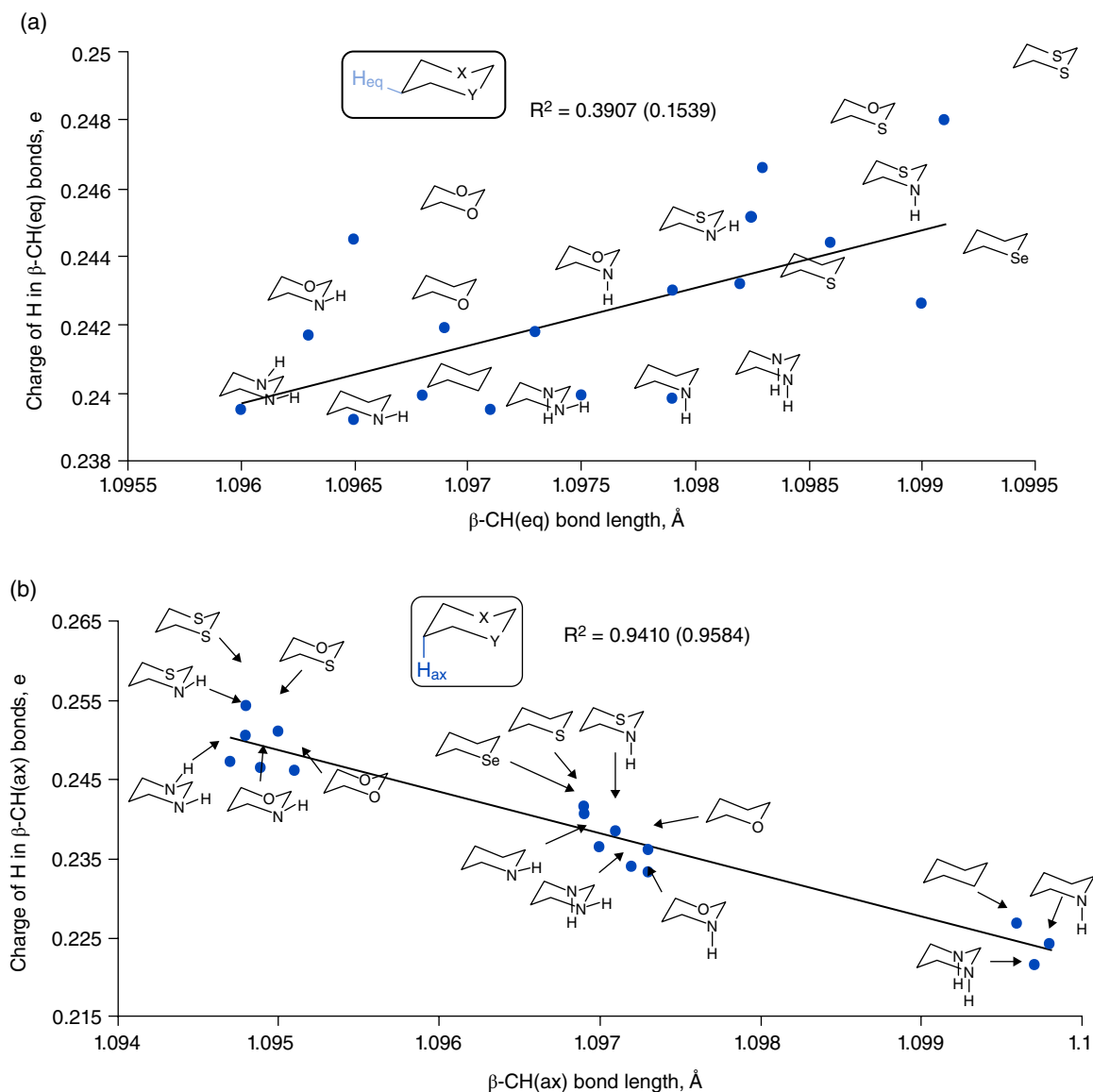


Figure 8.10 The contrasting correlations between NBO charges at equatorial (a) and axial (II) hydrogen atoms in β -CH₂ groups with the respective C-H bond lengths at the B3LYP/6-31G** (B3LYP/6-311++G**) level. (Source: Alabugin 2003 (4). Reproduced with permission of American Chemical Society.)

Although the homoanomeric effects are considerably weaker than the classic vicinal anomeric $n(X)_{ax} \rightarrow \sigma^*_{C-Y_{ax}}$ interactions, their importance increases significantly when the acceptor ability of σ^* -orbitals increases as a result of bond stretching and/or polarization. In the extreme, homoanomeric interactions lead to the formation of three-membered cycles – bromonium, oxonium, aziridinium, etc. From the reactivity standpoint, homoanomeric effects can be considered as the starting point of 3-exo-tet cyclizations (Chapter 12). 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.¹⁸ The

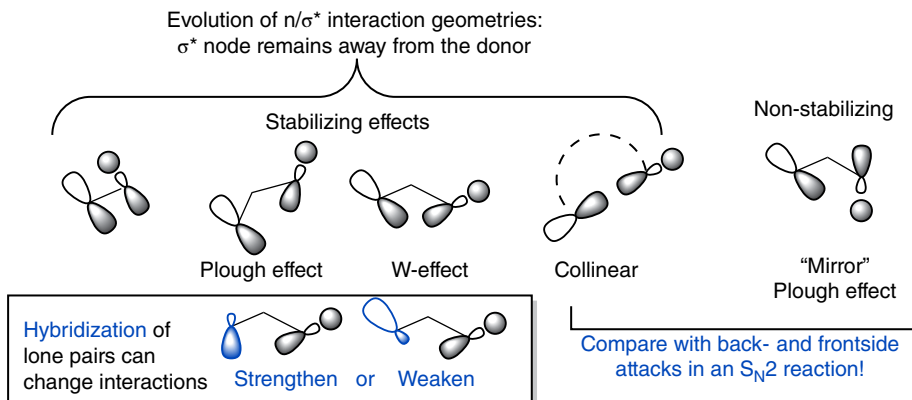


Figure 8.11 Geometric progression that connects stabilizing to non-stabilizing hyperconjugative interactions. The bottom part of the list also shows how hybridization of the lone pair can change the efficiency of through-space interactions.

presence of such intermediates leads to retention of configuration and efficient transfer of chirality in their respective ring contraction or expansion reactions.¹⁹ Topologically similar transformations are the key mechanistic steps of Payne and aza-Payne rearrangements (Figure 8.12).²⁰

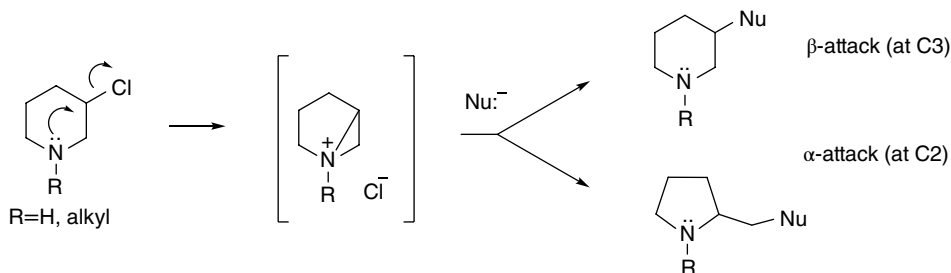


Figure 8.12 Aza-Payne rearrangement in solvolysis of β -substituted cyclic amines.

Another way to increase the importance of such interactions is to increase the donor ability of the lone pair. Such effects are likely to contribute to significant stabilization of meta- X -substituted aryl anions ($X=F, Cl, Br$). Interestingly, Cl and Br impose a larger effect than F in meta and para positions, suggesting that this stabilization does not result from the inductive effect but rather represents an orbital phenomenon (Figure 8.13; for the reasons of increased acceptor ability of bonds to heavier halogens, see Chapter 5).

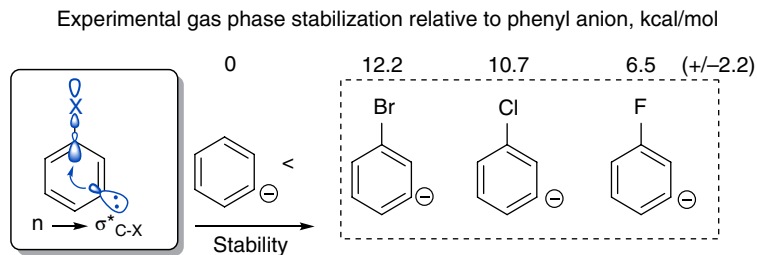


Figure 8.13 Effect of negative homohyperconjugation on the stability of aryl anions.

8.1.3 Cross-hyperconjugation

Although our discussion of homoconjugation focused mainly on communication of π -systems through space, a more recent report of cross-hyperconjugation,²¹ or communication of geminal π -substituents through an sp^3 center (at a Group 14 element, ER_2), focuses on electron delocalization in both σ - and π -bonds (Figure 8.14).²² Symmetry-adapted combinations of the two E-R σ or σ^* -orbitals give orbitals of π -symmetry (pseudo- π and pseudo- π^*). Cross-hyperconjugation results from the delocalization of π -electrons into the pseudo- π^* and vice versa, acting effectively as a cross-conjugated system.

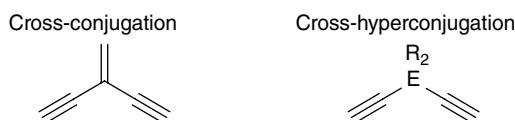


Figure 8.14 Cross-conjugated systems connected with a π -system and cross-hyperconjugated systems connected with a pseudo- π system.

8.2 Double hyperconjugation and through-bond interactions

Competition between through-space and through bond interactions In principle, addition of an extra atom does not always make a dramatic difference in the nature of interaction between orbitals. If the dominant interaction path involves a direct through-space contact of spatially close orbitals, this situation is analogous to homoconjugation and homohyperconjugation. However, when through-space interaction is relatively inefficient, then a conceptually different coupling mechanism comes into play. This mechanism is based on the interaction of the two orbitals mediated by the one-bond bridge between them (through-bond orbital interaction). Figure 8.15 illustrates the latter scenario using two non-bonding orbitals at carbons (i.e. two radicals). The symmetric combination of these orbitals has the right symmetry to interact with the lower energy σ -orbital whereas the symmetry of antisymmetric combination is suitable for interaction with the higher energy σ^* -orbital of the bridge. The latter interaction creates the new HOMO for this 1,4-diradical system.

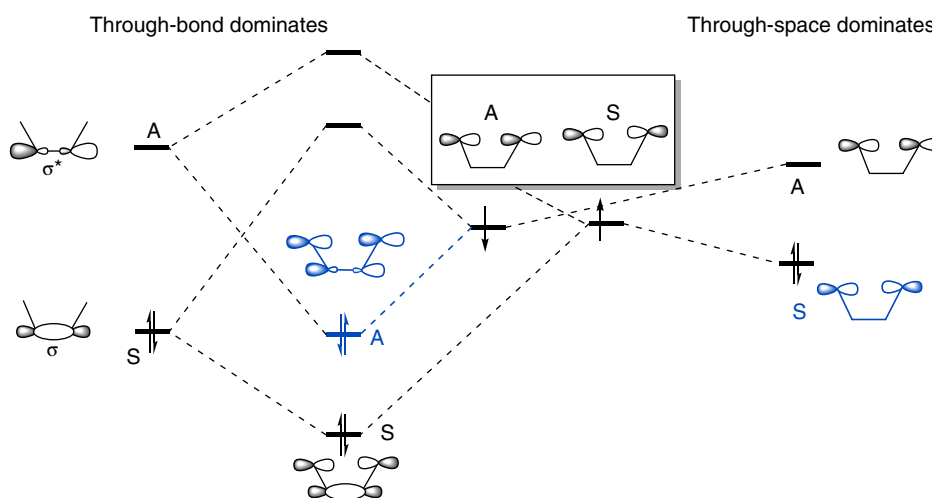


Figure 8.15 The two possible scenarios for the interaction of two radical centers connected via a one-bond bridge.

The through-bond interaction between two orbitals, one of which is a σ -donor or a σ^* -acceptor, corresponds to double conjugation in the Lambert's classification (Figure 8.1). It extends the delocalization range even further by placing a σ -bridge between a donor and an acceptor. In the chemistry of cations, this interaction, the δ -effect, has been found experimentally to be significant for silicon and tin (Figure 8.16).²³ Expansion of these studies to a larger set of cations²⁴ found that double hyperconjugation with a number of equatorial substituents can provide significant stabilization ($R = \text{AlH}_2$, GaH_2 , GeH_3 , AsH_2 , SiH_3 , PH_2 , BH_2 , SeH) or destabilization ($R = \text{SH}$, Br , NH_2 , Cl , O , F) to the δ -cyclohexyl cation with the equatorially oriented empty p-orbital (equatorial "hyperconjugomer" vide infra). These stabilization effects were used for the development of a new scale hyperconjugative donor ability of σ -bonds (as described in Chapter 5).

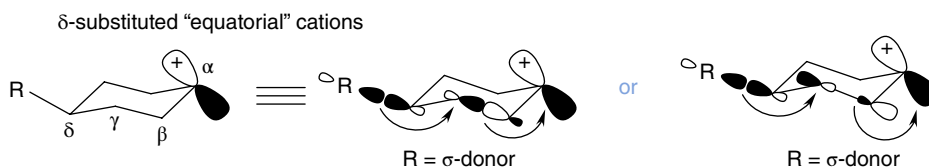


Figure 8.16 The significant stabilization of a δ -cyclohexyl cation by a series of equatorial substituents results from double hyperconjugation.

The stabilizing effect of negative double hyperconjugation is illustrated by increased stability of para halosubstituted aryl cations. The greater stabilization observed for the heavier halogens, $\text{F} < \text{Cl} < \text{Br}$ ($2.1 < 7.3 < 8.9 \text{ kcal/mol}$), suggests strongly that inductive and field effects are of secondary importance and the main contribution to this stabilization comes from the donor–acceptor interaction between carbanion and $\sigma^*_{\text{C-X}}$ orbital mediated by the C–C bridge (Figure 8.17, see Chapter 5 for the general discussion of acceptor ability of σ -bonds).

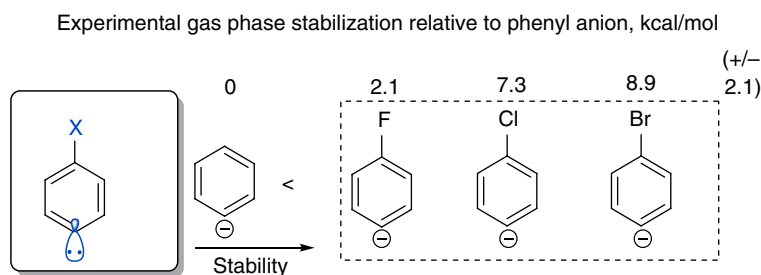


Figure 8.17 Effect of negative double hyperconjugation on the stability of aryl anions.

Negative double hyperconjugation can also be significant as illustrated by the large effect of C4 fluorine substitution on the basicity of piperidines. A thorough discussion of related stereoelectronic effects on basicity with the focus on drug discovery has been provided by Diederich, Kansy, and Müller.²⁵ Such effects are useful not only for the control of protonation state of this biologically important class of compounds but they can also increase metabolic stability of amines against oxidation and dealkylation by cytochrome P450 enzymes. Although the effect has inductive and electrostatic components, the importance of stereoelectronic contribution is supported by the much smaller pK_a decrement for the axial fluorine introduction. Whereas an equatorial C–F bond decreases the pK_a by 1.7 units, the introduction of an additional axial fluorine has only a 0.9 pK_a unit effect on basicity (Figure 8.18).

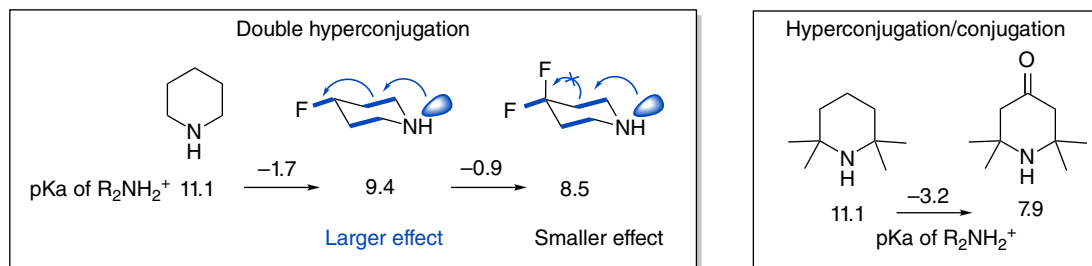


Figure 8.18 Effects of double hyperconjugation on basicity of 4-substituted piperidines.

It is interesting to compare the effect of remote σ -acceptors with the effect of a carbonyl group at the 4th position of piperidine moiety ("hyperconjugation/conjugation" in Lambert's classification, Figure 8.1). The 3.2 kcal/mol decrease in basicity caused by the presence of a $\pi^*\text{C}=\text{O}$ moiety exceeds slightly the combined electronic effect of the two C-F bonds (2.6 kcal/mol). The large electronic effect of through-bond interaction between a carbonyl and a nitrogen lone pair have found a lot of interesting applications in crystal and materials design reported by Castellano and coworkers.²⁶

Hyperconjugation of the two radical centers in *p*-benzyne through the bridging single bonds (the "through-bond" interaction, i.e. hyperconjugation/conjugation in the Lambert's classification),²⁷ renders the Bergman cyclization a symmetry allowed process (Figure 8.19).²⁸ If through-space interaction between the two radical

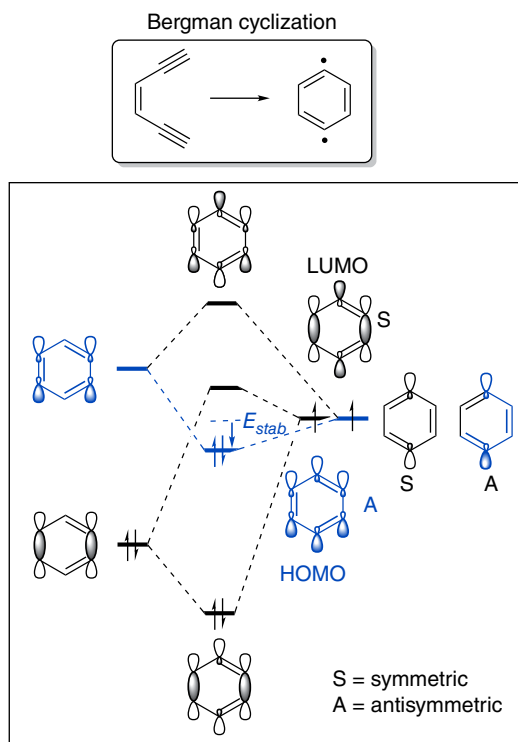


Figure 8.19 The through-bond interaction couples two radical centers in *p*-benzyne via a cooperative effect of two double hyperconjugation orbital arrays. E_{stab} corresponds to stabilization energy originating from this orbital interaction effect.

centers were a dominate force, the HOMO of *p*-benzyne would have a different symmetry. Furthermore, the bonding interaction of the antisymmetric combination of radical centers through the σ^* -bridges has important consequences for the reactivity of *p*-benzyne diradicals. Radical reactions (i.e. H-abstraction) have to pay a penalty for uncoupling the electrons, which is equal to the energy of through bond (TB) interaction (estimated as $\sim 2\text{--}5\text{ kcal/mol}$).²⁹

Because through-bond interactions populate the σ^* -bridge between communicating orbitals, an increase in the magnitude of this interaction can lead to fragmentations of the bridge bonds. During this process, the evolution of through-bond coupling of radical centers³⁰ in the reactant leads to the formation of two π -bonds in the product. Double hyperconjugation can also lead to fragmentations when a good leaving group acts as the acceptor in a through-bond $n \rightarrow \sigma^*$ interaction (Figure 8.20).

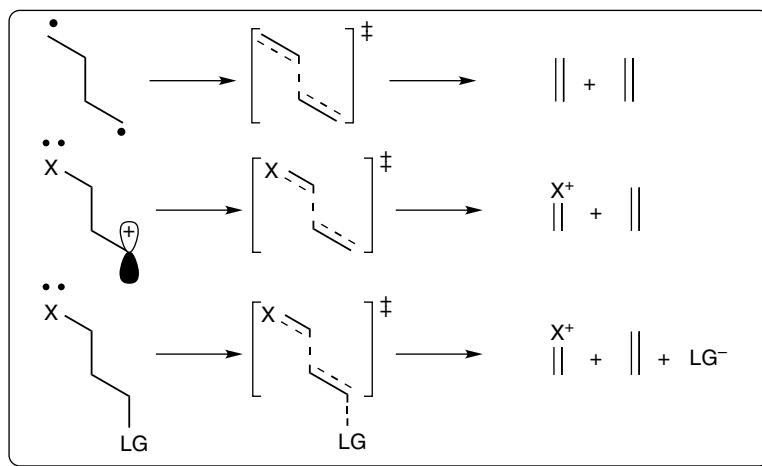


Figure 8.20 Through-bond coupling of 1,4-diradicals, and donor/acceptor pairs leads to efficient fragmentation.

There have been multiple recent reviews on fragmentations,³¹ so we will focus on a small selection of examples that exemplify the stereoelectronics associated with this mode of reactivity.

When the acceptor orbital is associated with a good leaving group, double hyperconjugation can lead to fragmentations that may have a variety of patterns corresponding to the Grob,³² Eschenmoser-Tanabe,³³ and related reactions. As the donor and acceptor communicate through a bridging C-C bond (Figure 8.20), the C-C bridge is weakened due to donation from a lone pair into the σ^* of the C-C bridge in addition to donation from the σ_{C-C} to the σ^* of the leaving group (Figure 8.21).

The stereoelectronic nature of concerted fragmentation reactions is exemplified by the selective fragmentations to give *trans*-decenones.³⁴ Only when the proper orbital alignment is achieved can the concerted fragmentation reaction proceed (Figure 8.21, right).

Another illustration of the stereoelectronic undercurrents is provided by the divergent reactivity of the two diastereomeric azabicycles in Figure 8.22. Whereas the top reactant has the appropriately aligned donor (nitrogen lone pair) and the acceptor (C-Cl) orbitals to allow clean scission of the bridging C-C bond via Grob fragmentation, the isomer with the axial C-Cl bond undergoes E2 elimination with the assistance of an external base.

Even more extended fragmentation cascades have been reported. For example, Grob reported formation of acyclic nitriles from the Beckmann fragmentation of bicyclic Ts-oximes (Figure 8.23).³⁵ Electron flow that led to the scission of two C-C and one N-O bond started from the two strong donors (the appropriately oriented lone pairs of the two oxygen atoms in the tetrahedral intermediate).

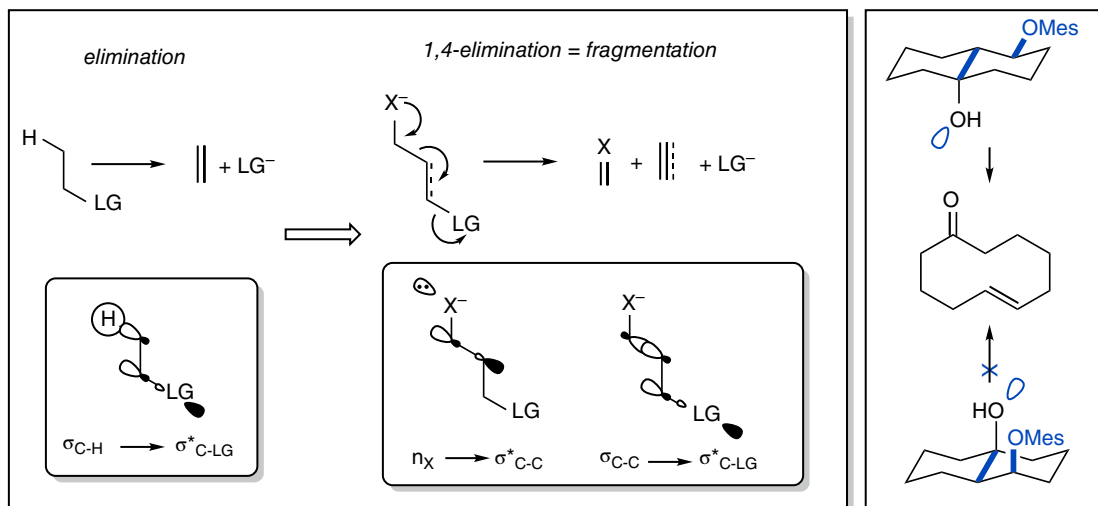


Figure 8.21 Through-bond communication of donor and acceptor orbitals in fragmentation reactions.

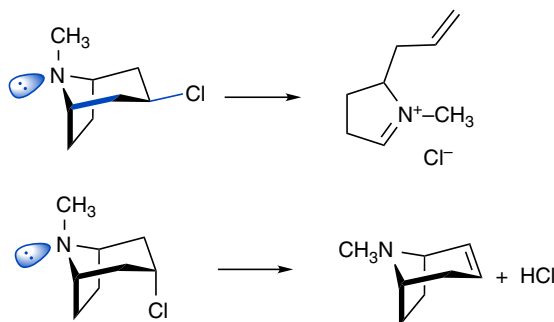


Figure 8.22 Divergent reactivity of the two diastereomeric azabicycles reflects stereoelectronic requirements to fragmentations.

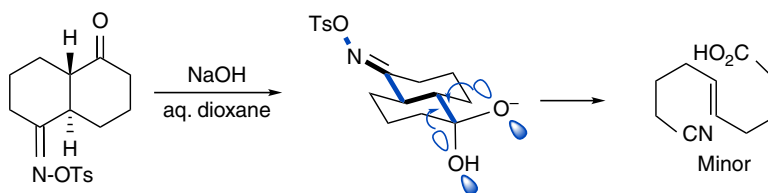


Figure 8.23 Formation of acyclic nitriles from bicyclic Ts-oximes.

Olefinic fragmentations producing alkynes adopt a relatively rigid conformation with desired orbital overlap, as discussed above for elimination reactions of alkenes (see Chapter 7). The Eschenmoser–Tanabe fragmentation³³ is made possible by the communication of a lone pair and a leaving group via three sigma bonds, properly aligned with the help of a C–C and an N–N double bond (Figure 8.24a). A recently developed

methodology utilizes vinylogous acyl triflates for similar “alkynogenic reactions” (Figure 8.24b).³⁶ Such methodology was expanded to the facile synthesis of “high value” alkynes^{37,38} including cycloalkynes for strain-promoted azide-alkyne cycloadditions.³⁹

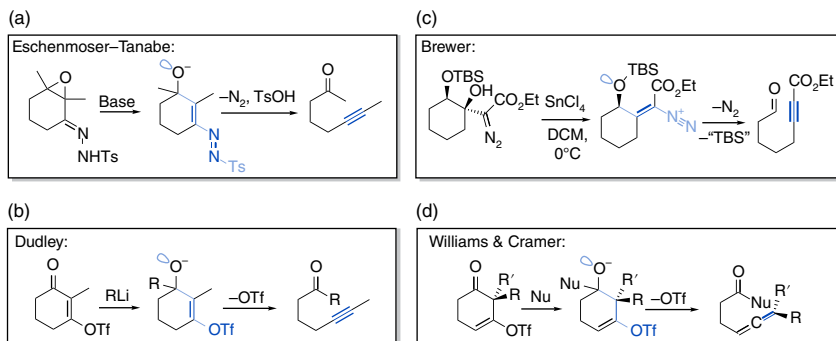


Figure 8.24 Alkynogenic fragmentations are promoted by the orbital overlap imposed by the rigid double bond.

Fragmentations can also occur with alternative placement of the double bond (Figure 8.24c,d). In the case of γ -silyloxy- β -hydroxy- α -diazocarbonyls, a Lewis acid-promoted β -hydroxy elimination (only successful when proper orbital overlap is achieved) affords an exocyclic vinyl diazonium that fragments to give the alkynyl aldehyde.⁴⁰ Allenes can also be generated via analogous fragmentation of vinyl triflates¹³ with a different placement of the initial double bond.⁴¹

8.3 Combined through-bond and through-space interactions

In an interesting parallel to the interrupted Cope rearrangement discussed above (i.e. the Bergman cyclization), through-bond interactions are important in aborted [2,3]-sigmatropic shifts, i.e. anionic 5-endo cyclizations. In this class of pericyclic reactions, the structure that corresponds to the pericyclic transition state is stabilized to the extent where its energy drops *below* that for the reactant and the product of the sigmatropic shift.⁴² In these systems, simultaneous through-bond and through-space interactions of the anion lone pair, alkyne LUMO, and propargylic σ^* (Figure 8.25) create a 6-electron σ -aromatic system in the transition state.

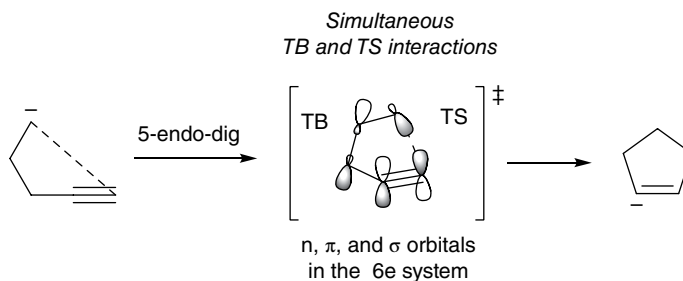


Figure 8.25 Cooperative through bond and through space interactions responsible for σ -aromaticity in the 5-endo-dig cyclization transition state.

8.4 Symmetry and cooperativity effects in cyclic structures

8.4.1 Hyperaromaticity

Orbital symmetries can act to either enhance or diminish hyperconjugative interactions, as illustrated by the negative hyperconjugation of substituted cyclopentadienes. Aromaticity involving a σ/σ^* bridge is termed hyperaromaticity (Figure 8.26). The benzenium ion was proposed to benefit from aromatic stabilization by Mulliken in 1953. The extent of this stabilization was later thought to be overestimated⁴³ and lacking experimental support. More recent computations on benzenium, phenonium,⁴⁴ and substituted cyclopentadienes⁴⁵ have brought hyperaromaticity back into the spotlight.

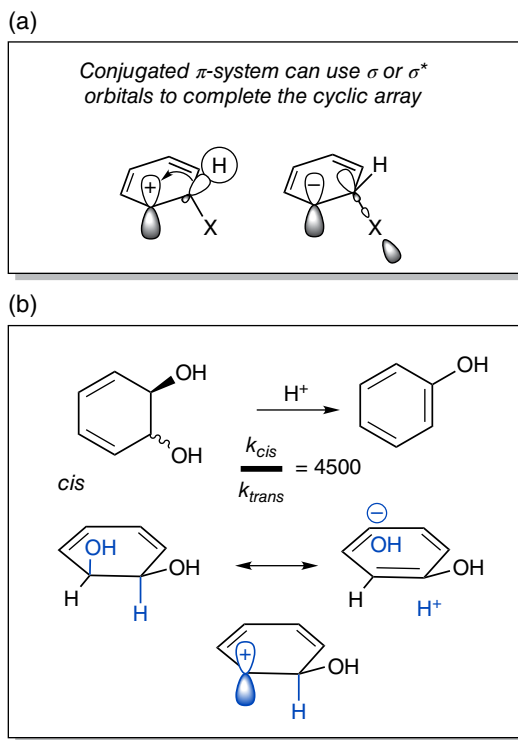


Figure 8.26 (a) Hyperconjugative interactions responsible for hyperaromaticity. (b) Relative rates of the two isomers of the acid catalyzed transformation of the cyclohexadiene diol to phenol.

Both the acid- and base-catalyzed dehydration of *cis*-benzene-1,2-dihydrodiol occur through intermediates taking advantage of hyperaromaticity. In the acid-catalyzed reaction, the benzenium intermediate is produced, which can benefit from hyperaromaticity by interaction with the $\sigma_{\text{C-H}}$ and the diene π -system (Figure 8.26).⁴⁶ The *cis* conformation reacts 4500 times faster than the *trans*, where the hydroxy groups are *gauche* to each other and antiperiplanar to $\sigma_{\text{C-H}}$ -donors (see Section 6.1). The base-catalyzed reaction provides a similar situation, but instead the cyclohexadienide anion is a stronger donor in the interaction with an antiperiplanar $\sigma^*_{\text{C-O}}$ acceptor.⁴⁷ Recent computational work has suggested that this can be a general concept for rings of varying sizes and, depending on substitution, leading to either hyperconjugative aromatic or hyperconjugative antiaromatic systems.⁴⁸

An interesting effect which facilitates [1, 5]-shifts in cyclopentadiene is a larger contribution of the charge-separated aromatic pentadienyl anion resonance structure, as illustrated in Figure 8.27. The increased contribution of this structure is reflected in the more negative NICS(1) values and in the significant increase in the positive charge at the migrating hydrogen for the transition state in the case of cyclopentadiene. In contrast, the positive charge at the migrating hydrogen in the pentadiene and cyclohexadiene cases has barely changed (Figure 8.27).⁴⁹

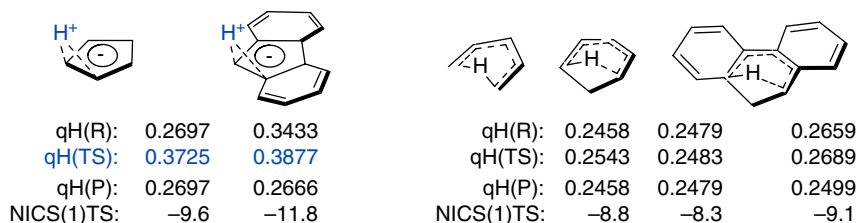


Figure 8.27 Aromatic cyclopentadienyl anion contribution in the TSs of 1,5-H shifts, natural (NBO) charges at the migrating hydrogen atoms, and NICS(1) computations at the center of the five-membered rings made from the reacting carbons.

The spectroscopic manifestation of symmetry effects in cyclic hyperconjugation was reported in electron spin resonance (ESR) spectra.⁵⁰ Symmetric LUMOs show cooperative effects to hyperconjugative interactions, while interactions with antisymmetric LUMOs are cancelled by symmetry (Figure 8.28). Such effects can be extended to spin-paired molecules, Wheland intermediates of electrophilic aromatic substitution, metal cation/arene complexes, and η^1 -cyclopentadienylmetal compounds.⁵¹

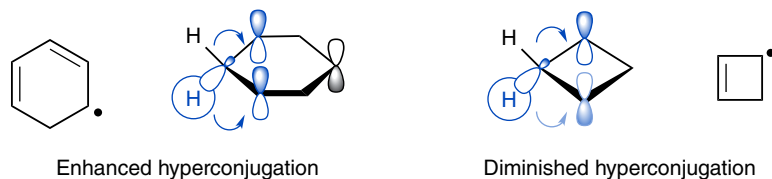


Figure 8.28 The Whiffen effect describes MO symmetry effects on hyperconjugation. Symmetry of the cyclic system favors interaction of a C-H bond with the LUMO of pentadienyl but not with the LUMO of allyl.

8.4.2 σ -Aromaticity

Orbital symmetry also plays a role in the σ -aromaticity in six-membered heterocycles (Figure 8.29).⁴ Hyperconjugative $n \rightarrow \sigma^*$ donation from a single lone pair to two acceptors yields a cooperative 2-electron interaction, where strong acceptors transform the hyperconjugative interaction into a classic σ -homoaromatic system.⁵² When two lone pairs are present to donate into a single σ^* -acceptor orbital, an anticooperative 4-electron (antiaromatic) interaction results.

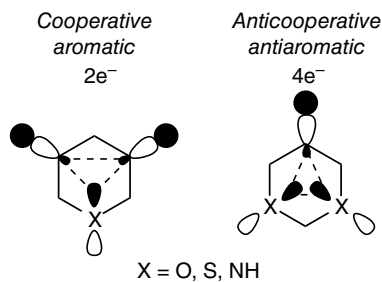


Figure 8.29 In-plane aromaticity and antiaromaticity as a result of $n \rightarrow \sigma^*$ donation in six-membered heterocycles.

8.4.3 Double aromaticity

When σ -aromaticity occurs in the presence of an orthogonal aromatic π -system, interesting reactivity can result. Double aromaticity (the combination of σ - and π -aromaticity) transforms the Cope rearrangement of 1,5-dienes into the Bergman cyclization of enediynes,⁵³ stabilizing the transition state (a transient saddle point) to the *p*-benzyne intermediate, a species with a sufficiently long lifetime to allow trapping.^{28,29,54} The σ -aromatic part of the doubly aromatic system can also be formed via through-space interactions, as shown by the C_6H_3 cation (Figure 8.30).⁵⁵

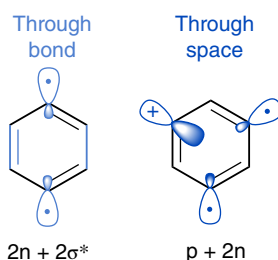


Figure 8.30 Double aromaticity in *p*-benzyne (through-bond) and the C_6H_3 cation (through-space).

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9

Transition State Stabilization with Stereoelectronic Effects: Stereoelectronic Control of Reaction Bottlenecks

Stereoelectronic effects can come into play at different stages of a reaction and modify the corresponding potential energy surface in a variety of ways. The interplay of reactant, transition state (TS), and/or product stabilization can have a multitude of consequences, both negative and positive, for the reaction rates.

A more detailed discussion of the scenarios for the evolution of stereoelectronic effects in chemical reactions will be given in Chapter 10. It is important to keep in mind that transition state stabilization is the most direct way to decrease activation barriers. Like catalysts that have to “express their love for substrates” in the TS, the stereoelectronic effects also have to reach maximum magnitude *at the TS* in order to have an accelerating effect on the reaction. Like catalyst affinity to the ground state, stereoelectronic stabilization of reactants is not kinetically productive.

The importance of TS stabilization is engraved in physical organic chemistry. It also permeates biochemistry as one of the pillars of enzyme catalysis. In order to fully understand the role of this phenomenon, let's apply the Curtin–Hammett principle to the classic case of two rapidly interconverting conformers of different stability and reactivity through the prism of stereoelectronic effects.

Molecular stability results from the tug-of-war of multiple interactions including a variety of electronic, steric, electrostatic factors. In a given molecule, a significant stereoelectronic interaction can be overridden by the combination of several effects that, taken together, can change the more stable structure into the one where the stereoelectronic effect of interest is absent (or considerably weakened). However, even a disappearing stereoelectronic interaction can still be consequential for reactivity and make an impact both on the observed reaction rate and on the nature of reaction products.

The preferential stabilization of a particular TS does not need to mirror the relative energies of ground state conformers. According to the Curtin–Hammett principle, the relative transition state energies determine the nature and the ratio of products, as long as reactive conformers can quickly equilibrate. In other words, even if A is the more stable conformer in the ground state, TS_B may still be the more stable transition state. If TS_B is the

rate- and product-determining TS, stereoelectronic stabilization of A may be, in fact, counterproductive. When such stabilization is lost upon the conversion of A to B and then to TS_B , it will slow down the reaction (Figure 9.1a).

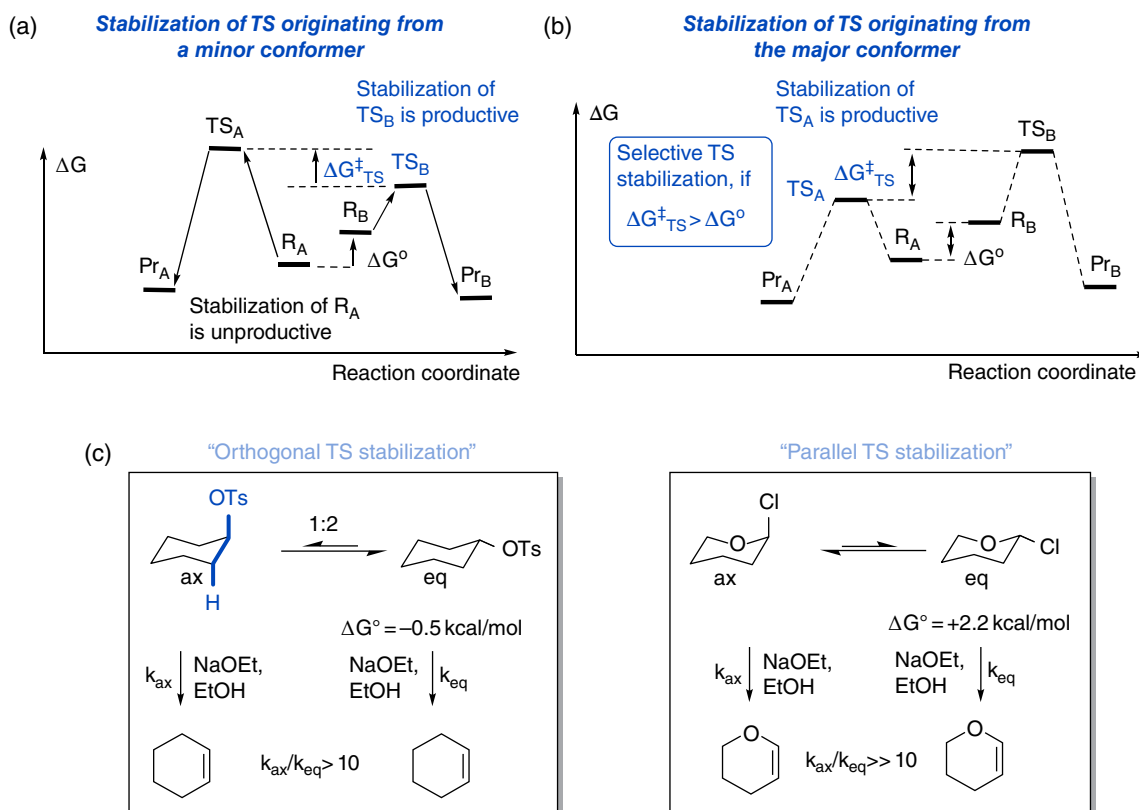


Figure 9.1 TS stabilization can overcome unfavorable ground state properties ("orthogonal stereoelectronic catalysis" – (a)) or amplify a ground state stereoelectronic effect ("parallel stereoelectronic catalysis" – (b)).

A classic example¹ in Figure 9.1c illustrates that reactions can proceed almost exclusively through the minor conformer, sterically or electronically disfavored in the ground state, as long as stereoelectronic TS stabilization is amplified to the extent that it can overcome the ground state bias. Although the axial conformer of the OTs-substituted cyclohexane is ~ 0.5 kcal/mol higher in energy than the equatorial conformer, the E2 elimination from the axial conformer proceeds much faster due to the favorable antiperiplanar arrangement between the C-H and C-OTs bonds in the elimination transition state.

Of course, the major conformer can give the product as well. Dehydrohalogenation of 2-chlorotetrahydropyran illustrates the situation when the stereoelectronic effect already present in the most stable conformer of the reactant is amplified in the TS (selective TS stabilization). Note that, in an E1 scenario, such assistance is unidirectional – since it is amplified upon the transition from reactant to the oxacarbenium product, it assists the *formation* of the cation but does not facilitate its subsequent trapping through the reverse reaction. However, the latter step is usually not rate-limiting. This is an illustration of another common caveat. Stabilization of TS originating from the major conformer by a stereoelectronic effect is only productive when it is greater than the stabilization of reactant by the same effect. If the product is stabilized by the same effect to a greater extent than the TS, then the reverse reaction will be slower.

The difference in timing plays an important role in the effect of hyperconjugative stabilization. A recent experimental study by Laub and Mayr elegantly demonstrated this principle by comparing rates of reactions of electrophiles with vinyl and allyl silanes.² Although the analogously stabilized β -silyl substituted carbenium ions are formed in both cases, the hyperconjugative β -silyl stabilization is already effective in the transition state only in the case of allyl silanes. In vinyl silanes, the C-Si remains orthogonal to the σ -bond and the developing cationic center at the early stages of reactions with electrophiles (Figure 9.2).

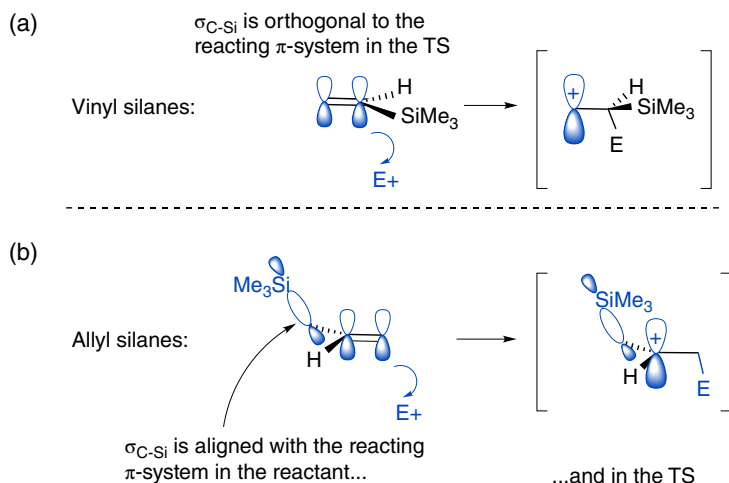


Figure 9.2 Differences of the stereoelectronic effects in reactions of electrophiles with vinylsilanes (a) and allylsilanes (b).

The differences in nucleophilicity of alkenes with different placements of Si-groups were significant. The allylic TMS group increased reactivity ~ 1000 fold in comparison to a hydrogen or an Me group. The β -vinyl TMS group accelerated electrophilic attack 10-fold in comparison to hydrogen but decreased the rate 100-fold in comparison to Me. Even more dramatically, at the α -vinyl position, the TMS substitution slowed reaction relative to both H and Me (Figure 9.3).

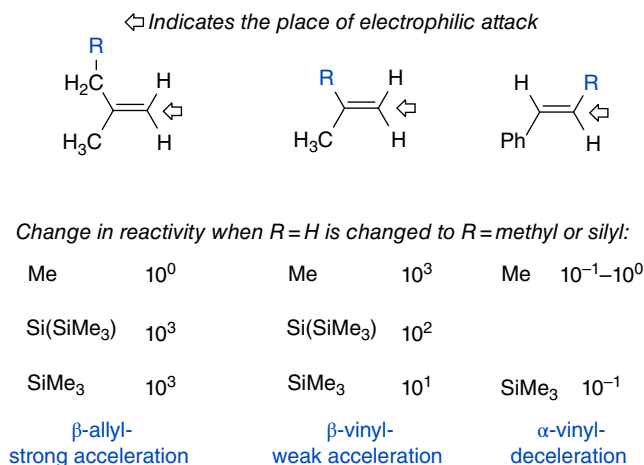


Figure 9.3 Approximate changes of nucleophilicity due to replacement of the substituent R by different groups. (Source: Frenking 1991 (23). Reproduced with permission of WileyVCH Verlag GmbH & Co. KGaA.)

The importance of proper orbital alignment is illustrated by the selectivity of an allyl stannane cyclization in Figure 9.4.³ As always, two cyclization modes are possible a priori: endo and exo. In this system, the endo-cyclization product would be stabilized by resonance with the lone pair of oxygen (formation of an oxacarbenium ion) whereas the exo-product can take advantage of the β -Sn effect. Although the lone pair of oxygen is a powerful donor, achieving proper alignment with the endocyclic donor group is difficult, and the reaction proceeds via the exo-route where the latent positive hyperconjugation in the TS evolves into the elimination of Sn-cation (Figure 9.4). Similar examples of tug-of-war between conjugative and hyperconjugative stabilization can be found in the literature, e.g. for the competition between Sakurai-type 6-exo/7-endo-cyclizations where only the exo-product is formed.⁴

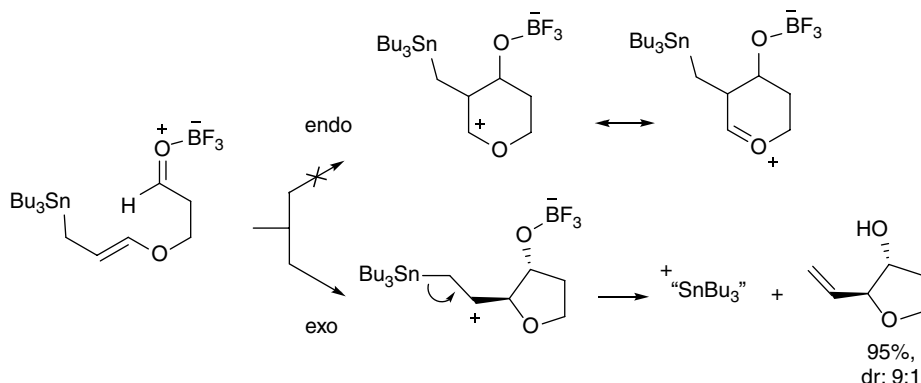


Figure 9.4 Competition between anomeric and β -Sn effects in stabilization of developing cationic center in the endo- and exo- allyl stannane cyclizations.

Unique electronic features of transition states In this chapter, we will concentrate on the unique electronic properties of transition states. These properties lead to both the advantages and the complications at the same time. On one hand, stretched bonds and distorted geometries create opportunities for amplification of stereoelectronic effects. On the other hand, the same factors also create conceptual challenges for the quantification and understanding of such effects.

Stretched bonds are good partners in hyperconjugative interactions (both donors and acceptors) due to the fact that bond weakening decreases the σ/σ^* or π/π^* energy separation, via simultaneous (albeit sometimes asynchronous) destabilization of bonding orbitals and stabilization of antibonding orbitals (Figure 9.5).⁵ As a consequence, the importance of stereoelectronic interactions often increases significantly in the high energy transition state geometries.

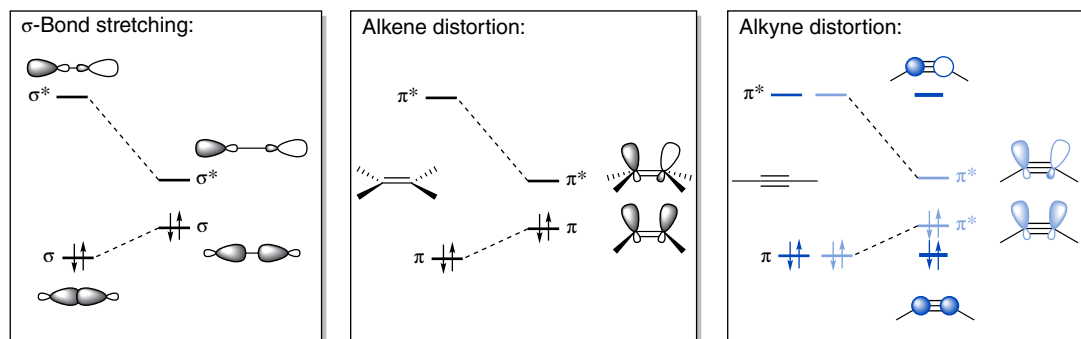


Figure 9.5 Changes in HOMO and LUMO energies, associated with bond breaking in transition states, often lead to amplified stereoelectronic interactions.

Computational analysis of stereoelectronic involvement in TS stabilization is complicated by the intrinsically delocalized nature of transition states. The stretched and/or deformed bonds of the TS (or the forming “incipient” bonds) are sufficiently different from the normal 2c,2e bonds with the very large σ/σ^* or π/π^* separation. This difference complicates comparisons based on the usual logic and intuition derived from the stable ground state structures. For NBO analysis, the choice of a reference point in estimating delocalization can be contentious. Furthermore, the interactions are so strong that the mathematics of second order perturbation estimation is suitable for only *very* crude approximations.

Direct structural analysis of transition states is difficult due to their short lifetimes. Only relatively recently, ultrafast spectroscopy has started to provide direct insights into the nature of transition states, albeit mostly for rather simple reactions.⁶ However, indirect information regarding stereoelectronic factors in the transition state can be glimpsed from a variety of experimental techniques including effects of substituents, solvents, isotopic perturbations, and structural constraints. Introduction of substituents often leads to well-defined stereochemical outcomes. The enhancement of either rate or selectivity can provide insights into reaction mechanisms and transition state structures.

Different patterns of hyperconjugation (and conjugation) have their own peculiarities: neutral hyperconjugation is often more controversial than positive and negative hyperconjugation. In this section, we concentrate on concerted reactions as they are the most difficult type of chemical transformations for the implementation of stereoelectronic control. Because these processes usually avoid the formation of charges, the dominant delocalization pattern is neutral, sometimes without a single dominant effect. Furthermore, one has no other choice but to directly analyze the TS in such systems, because concerted reactions avoid the formation of unstable intermediates.

9.1 Torquoselectivity

A particularly striking example of dramatic hyperconjugative effects on reactivity is provided by torquoselectivity (the preference for ‘inward’ or ‘outward’ rotation of substituents in electrocyclic ring opening reactions) in thermal cyclobutene ring opening.⁷ Electrocyclic ring openings follow either a conrotatory or disrotatory pathway, depending on the symmetry of molecular orbitals. For the 4e electrocyclic opening, this process proceeds via the conrotatory path with both substituents rotating the same direction, clockwise or counterclockwise (Figure 9.6).

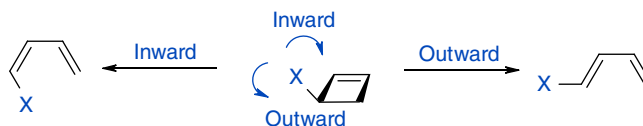


Figure 9.6 Torquoselectivity: the choice between the two rotation modes in electrocyclic ring openings.

Remarkable effects of substituents were reported on the clockwise/counterclockwise competition in the conrotatory pathway.⁸ Without exceptions, electron donors rotated outwards whereas the acceptors preferred an inward rotation (Figure 9.7). This selectivity is particularly impressive since an often perfect electronic control can be achieved in these systems in the absence of charged intermediates, i.e. under the conditions of seemingly weak electron demand.

The generality of this observation has been further confirmed in a variety of electrocyclic ring openings in Figure 9.7. For example, hyperconjugation was also used to obtain stereodefined products from oxacyclobutenes.⁹ Torquoselective ring openings occur despite the steric congestion. The relatively large boryl and silyl groups (π - and σ -acceptors, respectively) rotate inwards,¹⁰ and methoxy donors rotate outwards, forcing the *tert*-butyl group to rotate inwards.¹¹

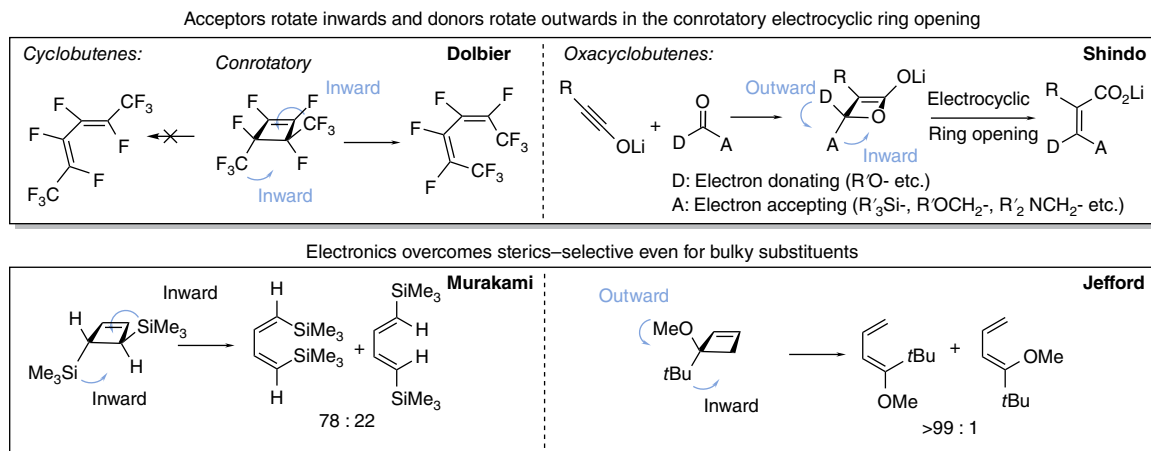


Figure 9.7 Examples of torquoselectivity in cyclobutenes, oxacyclobutenes and sterically crowded cyclobutene ring-openings.

These striking selectivities are rationalized by orbital interactions between the reacting centers and the substituents. Houk and coworkers illustrated that the key stereodefining effect is interaction of the σ and σ^* associated with the breaking C-C (or C-O) bonds with donor and acceptor orbitals of the substituents (Figure 9.8). As the C-C bond is stretched, the energy of the σ -orbital is raised and the σ^* -orbital is lowered. In the TS, they become the HOMO and LUMO, respectively (instead of the π and π^* of the reactant).

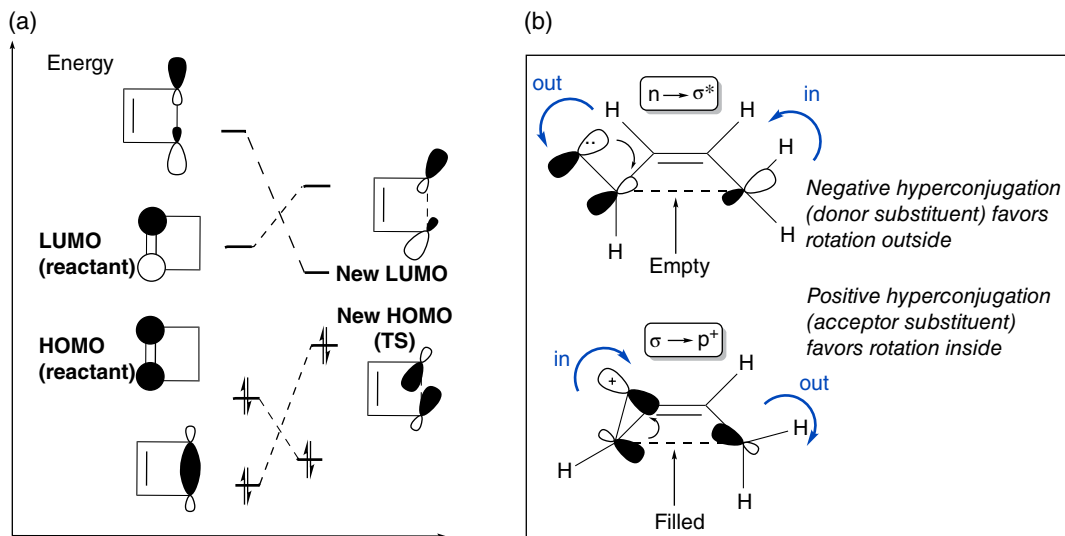


Figure 9.8 (a) Changes in HOMO and LUMO upon stretching and twisting of the central σ -bond. (b) Dominant hyperconjugative interactions which control outward rotation of a donor substituent and inward rotation of an acceptor substituent. In the first case, the key interaction is negative hyperconjugation between the transition state 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 transition state LUMO (a stretched and twisted σ^* -orbital) with a substituent filled p -orbital (the same topology is important for a donor σ - or a π -orbital).

The antiperiplanar orbital arrangement in the outward rotation maximizes the interaction between the donor orbital of the substituent and σ^* -orbital of the stretched cyclobutene bond (the LUMO of the transition state). As a result, the outward rotation is preferred by the donor substituents. On the other hand, acceptor substituents with a low-lying vacant orbital prefer an inward conrotation, where this orbital overlaps directly with the σ -orbital of the stretched bond (the HOMO of the transition state). Both of these effects correspond to a two-electron interaction and stabilize the transition state.

Electronic control is even easier when charges develop in the TS For example, ionization of cyclopropyl halides and tosylates is accompanied by electrocyclic ring opening leading to the formation of allylic cations. In these concerted reactions, the C-C bond breaking occurs simultaneously with (and assists) ionization via C-OTs scission. As a result, the substituent anti to the leaving group should rotate outwards in order to allow electronic assistance by the breaking C-C bond to the C-O heterolytic bond cleavage. Such reactions show dramatically different reactivity depending on the interplay between this intrinsic electronic requirement and steric and structural constraints of the reactants. For example, the all-cis isomer of 1-OTs-2,3-dimethylcyclopropane opens up $\sim 10^4$ times slower than the isomer where the OTs group is positioned trans to the two methyl groups. In the first case, the electronic requirement leads to a steric clash between the two methyl groups that are forced to rotate inside, towards each other (Figure 9.9).¹²

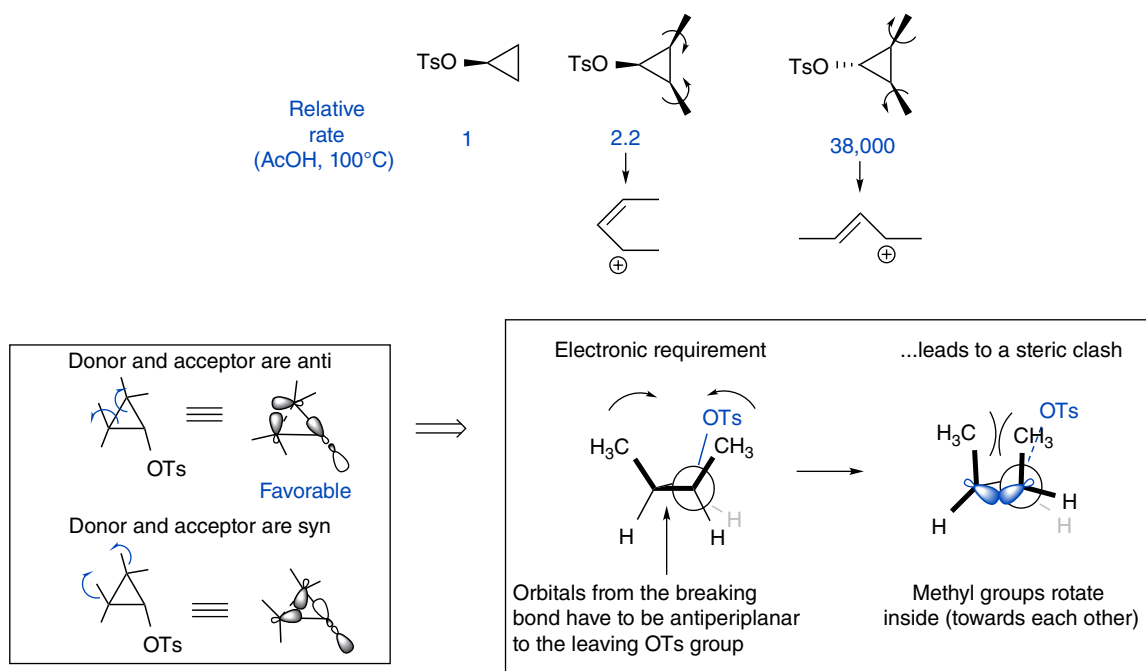


Figure 9.9 Torquoselectivity in cyclopropyl opening/ionization cascade.

In bicyclic systems, such steric requirements can be even more prohibitive. When the two alkyl groups are joined in a ring, the order of reactivity is reversed. For example, whereas the endo isomer of 6-chlorobicyclo[3.1.0]hexane undergoes the ring opening readily, the other one is unreactive. In the latter case, the electronically favorable mode of ring opening places the two hydrogen atoms from the C-H groups inside of the forming cycle.¹³ The analogous trend in reactivity is observed for endo and exo chlorides derived from [4.1.0]bicycloheptanes (Figure 9.10).¹⁴

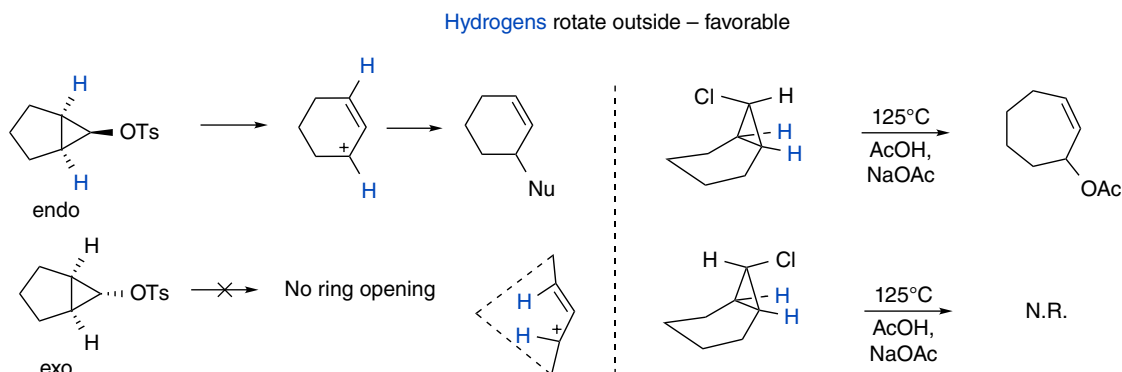


Figure 9.10 Torquoselectivity in cyclopropyl opening/ionization in bicyclic systems.

9.2 Diastereoselection in nucleophilic addition to carbonyl compounds and other π -systems

Another often discussed set of electronic effects in the transition state involves interaction of a stretched or forming (incipient) bond with the adjacent donors and acceptors. This interaction has been discussed particularly frequently in relation to the selectivity of nucleophilic additions to carbonyl compounds. Cram first proposed arguments based on steric effects,¹⁵ which were expanded upon by Felkin¹⁶ and Anh.¹⁷ The Felkin–Anh model suggests that the best acceptor group is positioned antiperiplanar to the incoming nucleophile in order to maximize $\sigma_{\text{incipient}} \rightarrow \sigma^*/\pi^*_{\text{acceptor}}$ interactions (Figure 9.11). For stronger acceptors, the Felkin–Anh model continues to expand its utility. For example, it was shown to control diastereoselectivity in acyl substitution reactions.¹⁸

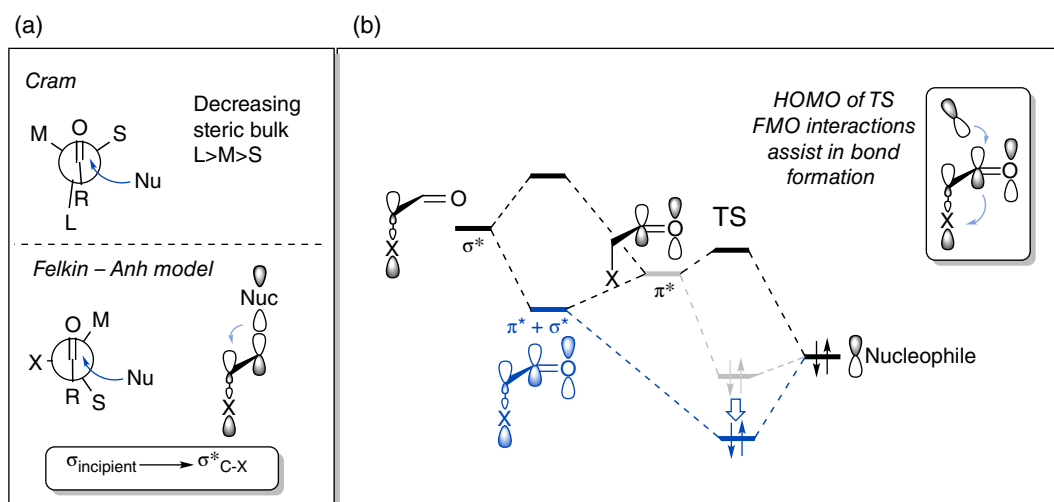


Figure 9.11 (a) Cram's Rule for selectivity in carbonyl additions with the modifications made by Felkin and Anh. (b) Felkin–Anh FMO perturbations in the TS providing stabilization and selectivity. Initial mixing of $\sigma^*_{\text{C-X}}$ and $\pi^*_{\text{C=O}}$ creates a lower energy antibonding LUMO that serves as a stronger acceptor towards the nucleophile lone pair in the bond forming interaction (shown in blue) than interaction with the $\pi^*_{\text{C=O}}$ alone (shown in gray).

The acceptor can provide stabilization in two ways. First, a stronger hyperconjugative interaction can assist in distorting the carbonyl group to the tetrahedral oxyanion geometry. Second, the frontier molecular orbital (FMO) interactions provide assistance to the C-Nu bond formation. Stabilization of distorted π -bonds will be discussed in depth in the following section. Here, we will focus on the FMO interactions in the TS (Figure 9.11b). In the transition state, the nucleophile's lone pair interacts with the carbonyl π^* -orbital via a favorable 2-electron interaction. When an acceptor orbital is properly aligned with the forming C(O)...Nu bond, electron density can be delocalized, increasing the strength of the new bond-forming interaction.

The opposite electronic preferences served as a basis for the alternative model proposed by Cieplak (Figure 9.12).¹⁹ In this model, the key stereoelectronic factor determining the axial approach of nucleophilic attack on the C=O group in cyclohexanones involves electron donation from axial C-H bonds to the antibonding orbital associated with the incipient (forming) bond between an incoming nucleophile (Nu) and the carbonyl carbon. The counterintuitive feature of this model is the suggestion that the carbonyl group becomes a better *acceptor* in the TS, despite gaining electron density from the incoming nucleophile. In this model, the axial approach is favored because such stabilizing interactions are more efficient than the analogous interactions with C-C-bonds during the equatorial approach of Nu (Figure 9.12), due to the larger donor ability of C-H bonds compared to that of sigma C-C bonds.²⁰ This suggestion stimulated many experimental²¹ and theoretical²² studies.

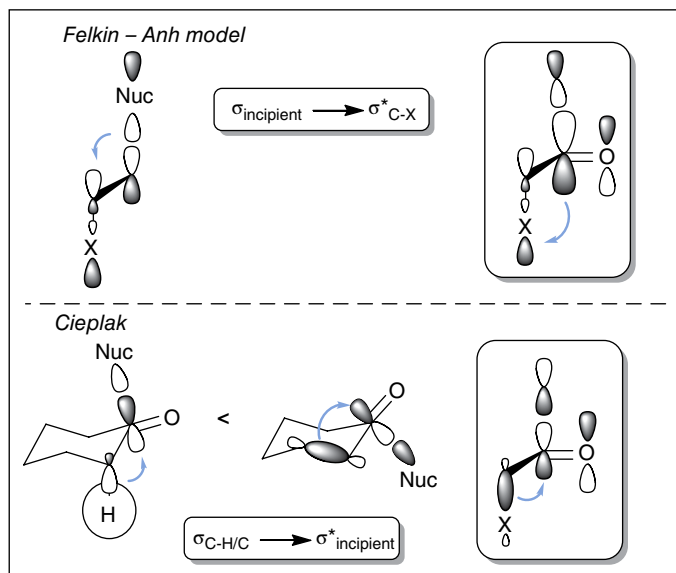


Figure 9.12 Comparison of the dominant transition state stabilizing hyperconjugative interactions for axial and equatorial nucleophilic addition to cyclohexanone according to the Cieplak's model compared to the Felkin-Anh model.

Although forming (and breaking) bonds can indeed be strong acceptors, one has to bear in mind that donation to such bonds would be only kinetically important if it is greater than the delocalizing interactions with the carbonyl π^* orbital in the reactant (a very strong acceptor). Furthermore, the more realistic models

should involve the interplay between the hyperconjugation effects included in the Felkin–Anh and Cieplak models. Such combined analysis is generally more appropriate for neutral hyperconjugation where delocalization is a “two-way street”. NBO analysis of such interactions suggests that the antiperiplanar hyperconjugation with the vicinal C–H and C–C bonds is of minor importance for the TS in the reaction of cyclohexanone with LiAlH_4 .^{20a} Furthermore, the elongation of these bonds, which can be taken as a structural consequence of such hyperconjugation, decreases upon transition from the earlier stages of the reaction to the rather late TS where the formation of the new C–H bond is quite pronounced. The data indicate that the differences between hyperconjugative abilities of C–C and C–H bonds are too small to account for the observed reaction differences.

The observed selectivity has been attributed to the non-symmetric shape of the cyclohexanone π^* -orbital (the LUMO in Figure 9.13).²³ The latter orbital distortion itself may be due to the hyperconjugative $\sigma \rightarrow \pi^*$ interaction in the ground state.²⁴ However, the application of ground state arguments cannot provide the complete picture and the proper analysis should involve the evolution of such electronic or structural effects *en route* to the TS.

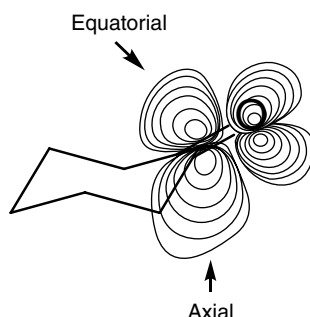


Figure 9.13 Distortion in the π^* -orbital of cyclohexanone.

9.3 Electrophilic addition to enamines

The activation of carbonyl compounds via enamine intermediates is an important part of organocatalysis. List and coworkers analyzed crystal structures of several proline enaminones and compared them with density functional theory-calculated structures of the ground and transition states.²⁵

Among the many interesting observations, we will only discuss how the extent of electron density removal from the π -bond affects the $n_{\text{N}} \rightarrow \pi^*_{\text{C}=\text{C}}$ negative hyperconjugation. The observed changes in N–C distances suggest that the extent of this resonance strongly increases in the transition state for carbonyl addition to enamines. One can see that donation from nitrogen (monitored via C...N bond contraction caused by the increased double bond character) in the TS is intermediate between the ground state enamine reactant and the vinylogous amide with a strong acceptor CF_3CO substituent. Note also that the presence of the H-bonding COOH group can further assist in the flow of electron density from the nitrogen to electrophile by providing stabilization to the developing negative charge at the electrophile (potentially culminating in a proton transfer, Figure 9.14).

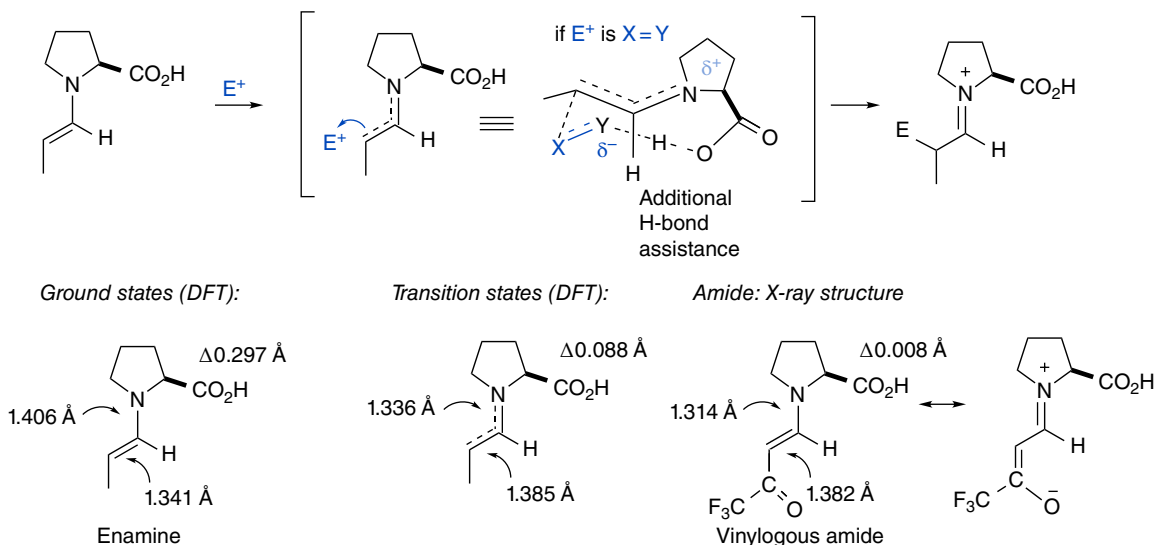


Figure 9.14 Comparison of structural effects of the increased $n_N \rightarrow \pi_{C=C}^*$ negative hyperconjugation in the TS of electrophilic addition to enamines with structures of reactants and the respective vinylogous amides.

9.4 Hyperconjugative assistance to alkyne bending and alkyne cycloadditions

Interaction of substituents with distorted π -bonds allows for TS stabilization in a manner that is similar to the analogous interactions with stretched σ -bonds in the torquoselective transformations and with the pyramidalized carbonyls in the Felkin–Anh model. The decrease in the HOMO/LUMO gap originates from lowering the π^* energy and raising the π energy via alkyne bending. These orbital energy perturbations provide an opportunity to take advantage of transition state stabilization in reactions that involve alkyne π -bonds.

Both intra- and intermolecular reactions can use stereoelectronics to compensate for distortion and bond breaking. For intermolecular reactions, additional stabilization can be achieved via interactions of donors and acceptors from the different molecules.

We will illustrate the interplay between intra- and intermolecular effects in thermal (non-catalyzed) alkyne-azide cycloadditions. In this case, both intra- and intermolecular effects work in synergy and originate from the presence of the same acceptor group at the propargylic carbon. In this example, a single structural design element imbues more than one beneficial effect. The intramolecular effect involves stabilization of alkyne distortion and π -bond breaking, whereas the intermolecular effect involves “assistance to bond formation” (vide infra).

Initial indications that these effects are possible came from the >50-fold acceleration of the azide-alkyne cycloaddition of α,α -difluorocyclooctyne (DIFO) in comparison to the parent cyclooctyne (OCT) reported by Bertozzi and coworkers.²⁶ Subsequently, it was shown that the stereoelectronic nature of the stabilizing interactions leads to amplification once the optimal orbital overlap between the α -C-F bond and the in-plane alkyne π -system is achieved.²⁷ As generally occurs for breaking bonds,^{14,15} the in-plane π -bond of the alkyne moiety becomes a better donor when it is distorted, making hyperconjugative interactions with the appropriately positioned substituents stronger. This strengthening is illustrated by the symmetric bending of 2-butyne relative to fluoro-2-butyne (Figure 9.15), with a decreasing energy cost of bending in the following order: 2-butyne > 1-fluoro-2-butyne (gauche) > 1-fluoro-2-butyne (syn-periplanar) > 1-fluoro-2-butyne (antiperiplanar).

An intramolecular stereoelectronic TS stabilizing effect

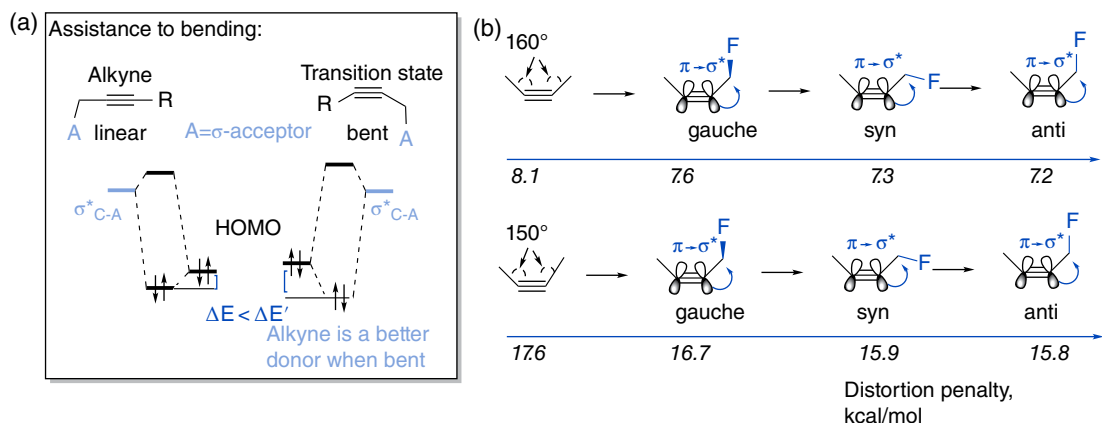


Figure 9.15 (a) Stereoelectronic basis for assistance to alkyne bending utilized in transition state stabilization in azide-alkyne cycloadditions. (b) Symmetric bending scan of butyne and 2-fluorobutyne in the gauche, syn-periplanar, and anti conformations.²⁵

The stabilizing effect increases even further in the full TS, where azide is present in close proximity to the bent alkyne. This increase indicates that the propargylic acceptor facilitates bond formation in the transition state (Figure 9.16). According to NBO analysis, π^* of the alkyne (its LUMO) becomes populated as the azide approaches. The high energy π^* -orbital is usually empty but in the cycloaddition TS it has sufficient electron density (transferred from the azide in the bond forming interaction) to serve as a very strong donor. Figure 9.16 illustrates that orbital mixing in the TS leads to greater stabilization when delocalization into a propargylic acceptor ($\pi + \pi^* \rightarrow \sigma^*_{CF}$) is possible. This qualitative analysis is fully supported by NBO dissection of the individual stereoelectronic contributions.

An intermolecular stereoelectronic TS stabilizing effect

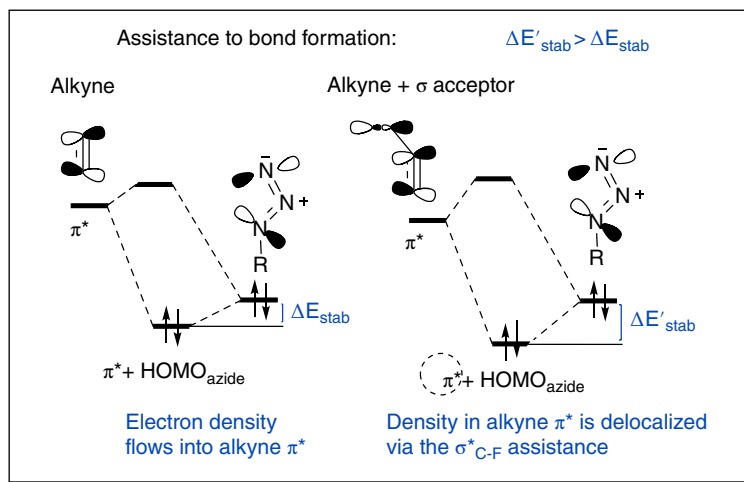


Figure 9.16 Stereoelectronic basis for assistance to bond formation provided by acceptors in azide-alkyne cycloadditions. This example illustrates how intermolecular transfer of electron density and stereoelectronic effects can amplify each other.

While exocyclic fluorine substituents are blocked by ring C-C bonds from achieving the antiperiplanar orbital arrangement in DIFO, acyclic alkynes and cyclooctynes bearing endocyclic acceptors allow for much stronger interactions and enhanced reactivity.²⁸ In addition to assisting in bending linear alkynes to the TS geometry, when acceptors are contained within a cycle, they alleviate strain in bent alkynes. Despite the premature activation of this interaction as a reactant-stabilizing effect, alkynes with endocyclic acceptors are still predicted to be more reactive than the parent cyclooctyne by DFT calculations (Figure 9.17). Such increase in reactivity is possible because the stabilizing interactions grow even stronger in the TS. This increase illustrates the power of TS stabilization as an element of reaction control.

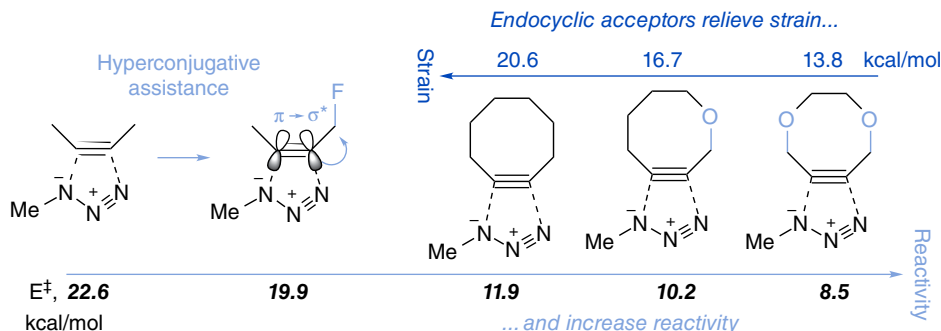


Figure 9.17 Simultaneous stereoelectronic alleviation of strain and enhancement of reactivity in cyclooctynes for metal-free click chemistry.

9.5 Negative conjugation – donation from oxygen lone pairs to breaking bonds

Oxyanionic assistance to Cope rearrangements In the previous example, we utilized acceptor substituents to stabilize bond breaking in the TS. In this section, we will illustrate how to use donors to impose large effects on pericyclic reactions.

The oxy-Cope rearrangement is dramatically (10^{17} !) accelerated by deprotonation of the OH group at the central C-C bond (Figure 9.18).²⁹ Even when significant electron assistance is available in the neutral state (e.g. an OR group is present at the other carbon of the breaking C-C bond), the effect weakens but does not disappear – the deprotonation still leads to 10^{12} -fold acceleration. The electronic origin of this effect is in the dramatic increase of the donor ability of the lone pairs at anionic oxygen.

The bis-anionic oxy-Cope³⁰ rearrangement of bis-alkynes produced by the reaction of acetylides with benzil occurs below room temperature (Figure 9.19).³¹ Computational studies confirm a significant barrier decrease for the rearrangement where the central C-C bond is weakened by the four radical stabilizing groups (Ph and O⁻). The two Ph groups introduction leads to ~12 kcal/mol barrier lowering, and two deprotonations add another 15–16 kcal/mol of TS stabilization. As a result, the calculated Cope rearrangement barrier falls from >30 to ~5 kcal/mol. The bond dissociation energy (BDE) for the central bond is so low that the anionic Cope rearrangements are diverted into a dissociative process³² with the cleavage of the central C-C bond in the presence of bulky TIPS substituents at the alkyne termini.

Vinylogous anomeric effect in Claisen rearrangement Another example of stereoelectronic assistance via negative hyperconjugation is provided by the ~10–25-fold accelerating effect of O-atom at the γ -allylic position on rate of the Claisen rearrangement reported by Curran and Suh.³³ The effect of oxygen is not a ground

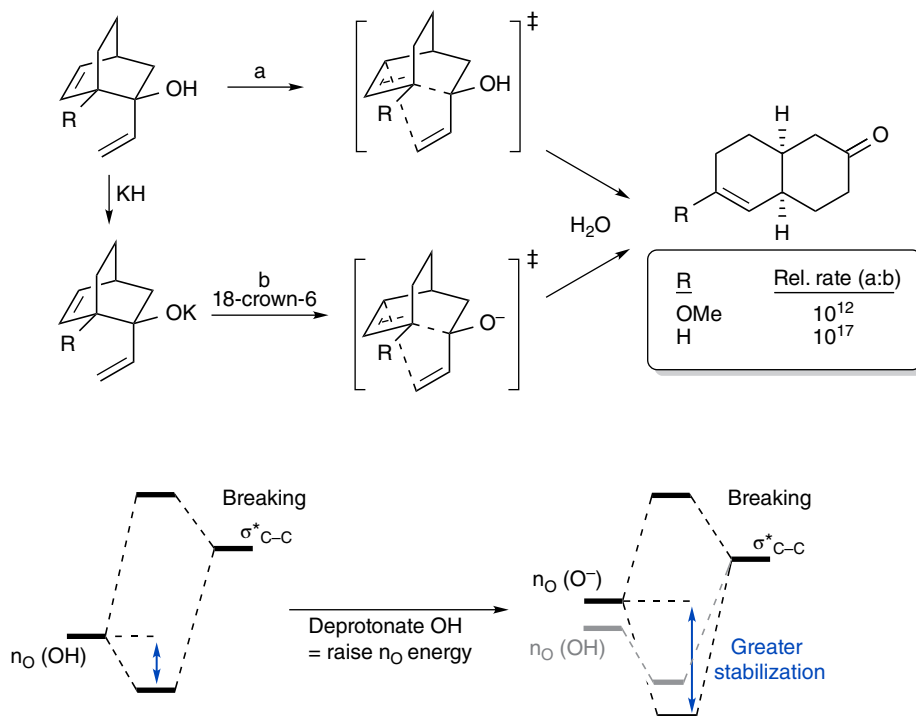


Figure 9.18 Large rate enhancements of the oxy-Cope rearrangement provided by anionic TS stabilization.

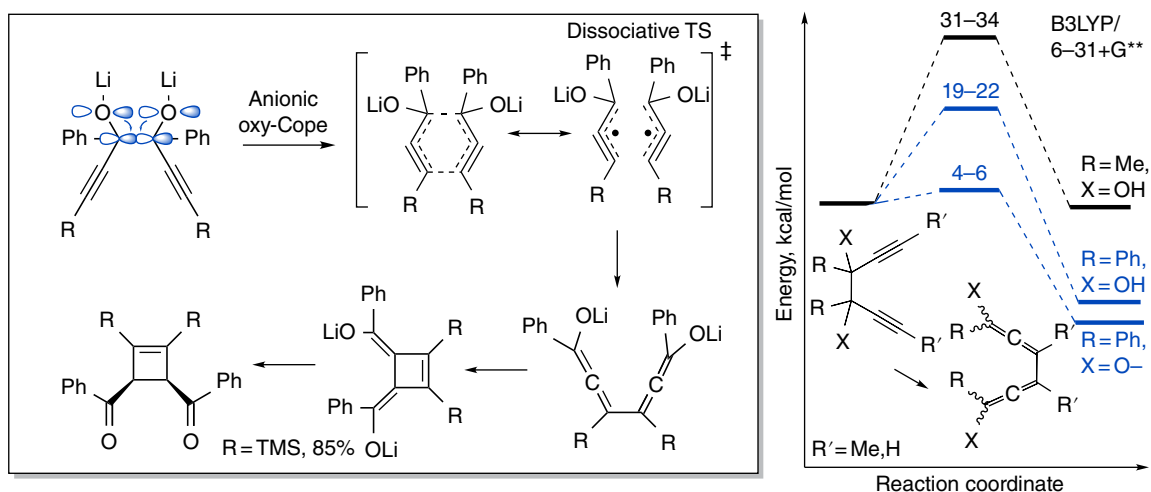


Figure 9.19 Lone pair/radical stabilization dramatically accelerates the anionic oxy-Cope rearrangement.

state conformational effect. The authors suggest that there is no inherent conformational bias because both carbo- and heterocyclic six-membered substrates in Figure 9.20 exist in conformations with the migrating group preferentially axial, as required for the Claisen rearrangement.

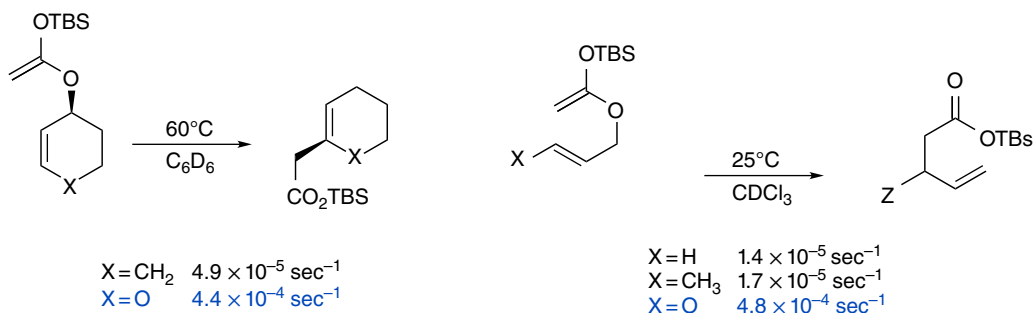


Figure 9.20 The accelerating effect of the γ -allylic O-atom on the Claisen rearrangement rate.

The stereoelectronic underpinnings of the observed reactivity difference are associated with the oxygen substituent at C6. This substituent lowers the energy of the transition state by facilitating the cleavage of the weakened O3C4 bond. The O3C4 bond in this system may be considered to be vinylogously anomeric. The exocyclic O atom at C6 assists in the Claisen rearrangement by weakening (via vinylogous anomeric effect) the same bond (O3C4) that is breaking in the Claisen TS (Figure 9.21).

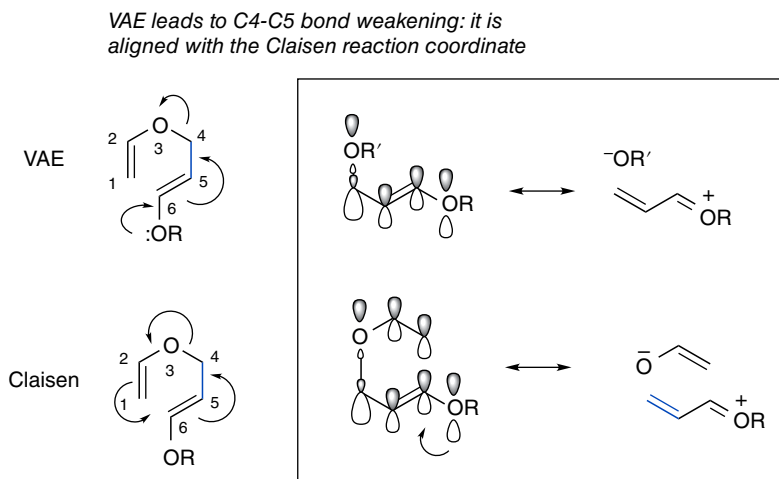


Figure 9.21 Connection between the vinylogous anomeric effect and substituent effects in the Claisen rearrangement.

Hetero Diels–Alder – intermolecular case – donor and acceptor are in different molecules (but interact via two orbital subsets) Intermolecular delocalization is not limited to the earlier discussed alkyne/azide cycloadditions. It has been reported to provide significant contribution to the observed electronic effects in other cycloadditions. For example, Boger and coworkers reported that the Diels–Alder reaction of

N-sulfonyl-1-aza-1,3-butadienes with vinyl ethers provided a single diastereomeric cycloadduct arising from an endo approach at the transition state (Figure 9.22).³⁴ In this geometry, the lone electron pair on nitrogen and the σ^* C-O orbital of the dienophile lie antiperiplanar to each other. The absence of a similar stabilizing $n \rightarrow \sigma^*$ interaction in the exo transition state helps to explain the unusually large >20:1 endo:exo diastereoselectivity of this reaction.

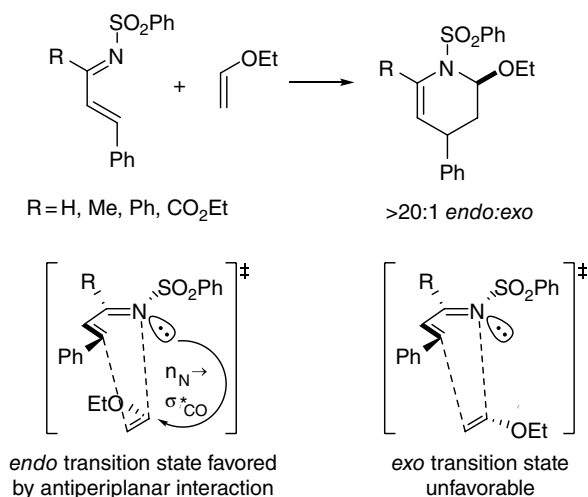


Figure 9.22 The interplay of delocalizing effects in the Diels–Alder reaction of 1-aza-1,3-butadienes: the $\pi_{\text{alkene}}/\pi_{\text{diene}}^*$ interactions are responsible for the regioselectivity whereas the orthogonal $n_{\text{N}}/\sigma_{\text{C-O}}^*$ interactions are responsible for the observed endo-selectivity.

The two layers of donor-acceptor interactions in this reaction play distinctly different roles – the formation of new σ -bonds in the cycle and the observed regioselectivity of cycloaddition are controlled by the $\pi_{\text{alkene}} \rightarrow \pi_{\text{diene}}^*$ interactions whereas the stereoselectivity is controlled by the $n_{\text{N}} \rightarrow \sigma_{\text{C-O}}^*$ interaction. The oxygen and nitrogen bearing functionalities participate in both interactions but switch their donor-acceptor character (i.e. the N-containing component is the acceptor and the O-containing component is the donor in the π -interaction, but the N-containing component is the donor and the O-containing component is the acceptor in the σ -interaction).

9.6 Remote lone pairs in radical reactions: fragmentations

In the final example, we will switch to bond cleavage reactions (fragmentations). We can apply the same stereoelectronic concepts because, according to the principle of macroscopic reversibility, bond formation and scission proceed through the same transition state.

A new stereoelectronic interaction was found in fragmentations that complete radical cascades which convert aromatic enynes into α -Sn-substituted naphthalenes (Figure 9.23). After a sequence of reactions that provide the formal 6-endo-trig product, the penultimate species of this cascade, the final step involves a C-C bond scission. The efficiency of fragmentation can be enhanced by stabilizing the rational design of radical leaving groups.³⁵

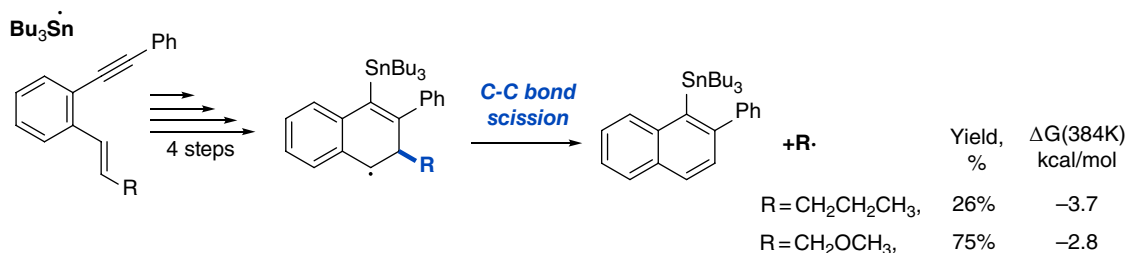


Figure 9.23 Efficiency of fragmentation can be increased by proper substitution at the alkene terminus.

Paradoxically, fragmentation leading to the formation of the *more* stable α -oxy radical (CH_2OMe) is *less* exergonic than the analogous fragmentation that forms the propyl radical. The lower thermodynamic driving force for the formation of a *more* stable product can be explained by the presence of a selective reactant stabilization for the O-containing reactant. Stabilizing through-bond (TB) interaction between benzylic radical and the lone pair at the δ -position was identified as the source of this reactant stabilization. Such TB coupling between two non-bonding orbitals populated with three electrons (the lone pair of X and the radical center) can rationalize the calculated fragmentation exergonicities by providing additional stabilization to the benzylic radical with a β -X group. From the practical point of view, such stabilization should deactivate the reactant and make this fragmentation less efficient. However, the experimental data clearly suggests the opposite.

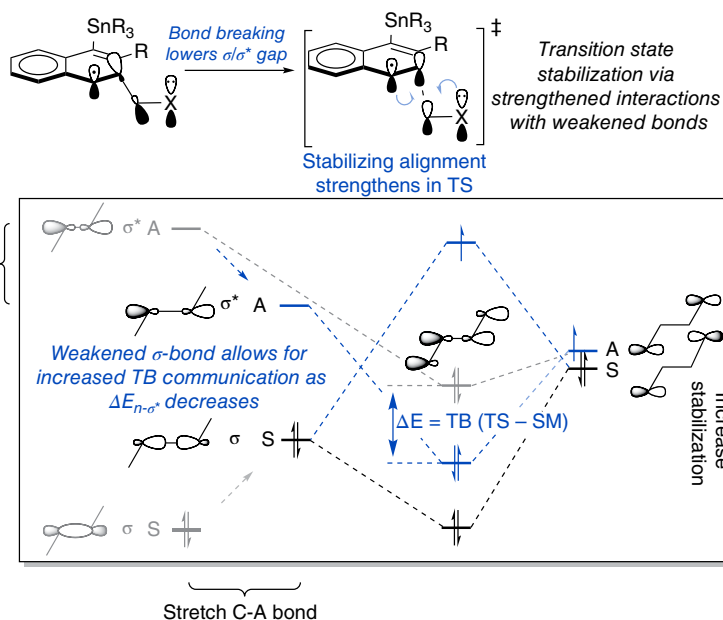
The above paradox can only be resolved if the presence of oxygen leads to selective TS stabilization that exceeds such stabilization of the reactant. Indeed, the odd-electron TB communication between the radical and the lone pair through the σ -bridge is increased at the transition state.

The increase in TB interaction through stretched bonds is documented by NBO orbital interaction energies. In the fragmentation process, the energy of the σ^* -antibonding bridge orbital is lowered, decreasing the ΔE_{ij} term for the stabilizing interaction that couples the non-bonding orbitals (i.e. the radical and lone pair). In addition, as the fragmentation progresses, the $\sim \text{sp}^3$ σ -bond is transformed into two p-orbitals (one π -bonded in naphthalene and the other in a 2c-3e “half-bond”), increasing overlap between interacting orbitals (Figure 9.24). Together these interactions are responsible for selective TS stabilization for the fragmentation process.

The validity of NBO insights is confirmed by the relation between reaction exothermicities and reaction barrier using Marcus theory.^{36,37} This analysis shows that intrinsic reaction barriers for the fragmentation are decreased by the presence of heteroatoms with lone pairs and illustrates the utility of Marcus dissection for finding selective TS stabilization effects such as the through-bond interaction described above. This interaction serves as a stereoelectronic conduit for kinetic acceleration of the bond scission. Along the reaction path, the calculated molecular geometry in the CCOH moiety changes to adopt the coplanar arrangement between the radical center and the p-type lone pair on oxygen.

In summary, this chapter has provided several examples of transition state stabilization enabled by the unusual properties of breaking and forming bonds. Although transition states can challenge the usual chemical intuition, the focus on TS stabilization often provides the most direct way to design efficient chemical transformations. It is clear that the general stereoelectronic concepts can be used successfully for the understanding of such effects and for the rational control of reaction rates. We will provide further examples of such control in the following chapters.

(a)



(b)

Relative to X = H:			
X	$\Delta\Delta E^\ddagger$	$\Delta\Delta E$	$\Delta\Delta E^\ddagger/\Delta\Delta E$
CH ₂ Et	-11.7	-13.2	0.89
CH ₂ OMe	-13.5	-14.1	0.96
CH ₂ OH	-13.7	-12.7	1.08
CH ₂ NMe ₂	-22.0	-21.4	1.03
CH ₂ Ph	-19.6	-22.2	0.88

Surprisingly large kinetic effects

Marcus dissection

$$\Delta E_0^\ddagger = \frac{\Delta E^\ddagger - \frac{1}{2}(\Delta E_{\text{rxn}}) + \sqrt{(\Delta E^\ddagger)^2 - \Delta E^\ddagger \Delta E_{\text{rxn}}}}{2}$$

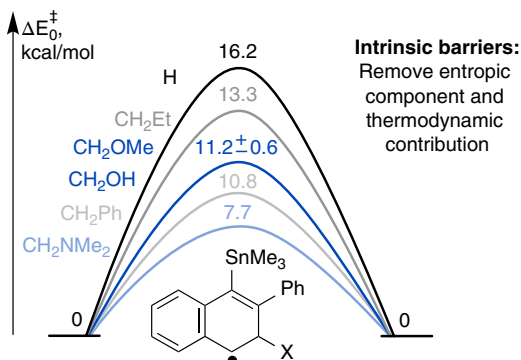


Figure 9.24 (a) Electronic coupling between non-bonding orbitals in 1,4-diradicals and β -heteroatom substituted radicals strengthens in the TS, facilitating C-C bond fragmentation. Additional stabilization due to TB coupling through the breaking bridging bond is shown as ΔE (blue). The σ and σ^* energies in the starting radical are shown in gray. (b) Stereoelectronics of the fragmentation viewed through the prism of Marcus theory. The top part summarizes differences in reaction and activation free energies caused by the substituents. The bottom insert shows intrinsic reaction barriers for the fragmentation.

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10

Stereoelectronic Effects in Reaction Design

We have illustrated the diversity and power of stereoelectronic effects in the previous sections. In this section, we provide a general outline of concepts that can be used to implement the stereoelectronic principles in practice in order to design and control chemical reactions and processes.

Two types of control Broadly, the applications of stereoelectronics in chemistry can be separated into two types.

1. *Static stereoelectronics*, i.e. the control of molecular shape
This approach defines molecular conformation by utilizing stereoelectronic interactions that are *not directly involved in the reaction*. This control is often used efficiently for achieving selectivity in a chemical process by enforcing a desired geometry.
2. *Dynamic stereoelectronics*, i.e. the control of reactivity.
This approach uses stereoelectronic effects to directly control the bond-forming and bond-breaking steps. It can lead to changes in reaction rates, chemo- and regioselectivities, as well as new reactivity patterns.

10.1 Static stereoelectronics

The essence of this approach is to use a stereoelectronic effect (or a combination of several effects) to control molecular shape and conformation. We will illustrate the basics of this concept using a stereoselective synthesis of mono- and disubstituted β -amino acids developed by Juaristi and coworkers (Figure 10.1).¹

The initial feature of this approach is the elegant double use of allylic A^{1,3} strain (imposed by amide resonance at the two nitrogen atoms flanking the C1 carbon) to force the bulky *tert*-butyl group into the axial

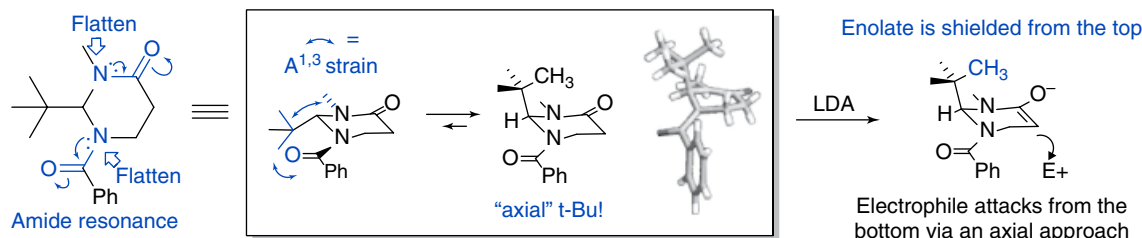


Figure 10.1 Stereoelectronic components for the highly selective synthesis of substituted β -amino acids.

orientation (Figure 10.1, left). The steric shielding provided by this group provides stereodifferentiation between the two possible directions of electrophilic attack by selectively blocking the top side of the enolate. Note that the axial (or "pseudoaxial", to be precise, since this is not a perfect chair conformation) approach of the electrophile stems from another stereoelectronic effect: the preferred trajectory for the attack on an enolate π -system. Overall, the reaction outcome results from harmonious interplay between three stereoelectronic effects (amide resonance, $A^{1,3}$ strain, and alignment of electrophile with the target π -system) that work together to accomplish a highly selective transformation.

Furthermore, the product of the enolate reaction with the electrophile can be converted into a new, more substituted enolate that can be introduced into a reaction with another electrophile (Figure 10.2). Overall, this symphony of stereoelectronic effects opens synthetic access to both (*R*) and (*S*) isomers of a variety of β -amino acids from a common chiral starting material.

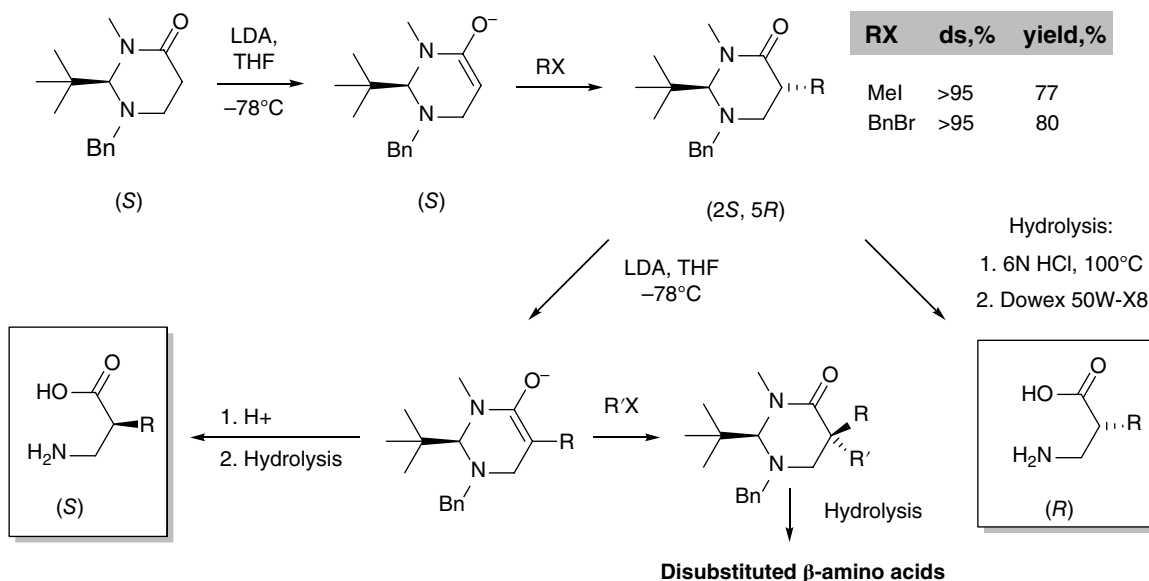


Figure 10.2 Successful use of stereoelectronic control over molecular shape for the design of selective synthesis of β -amino acids.

Preference for the gauche conformations was used for reliable assignments of absolute configuration of chiral 1,2-diols by NMR spectroscopy. By combining calculations, circular dichroism and NMR spectroscopy, it was found that the conformational preference around the C(1)-C(2) bond in the aromatic esters of

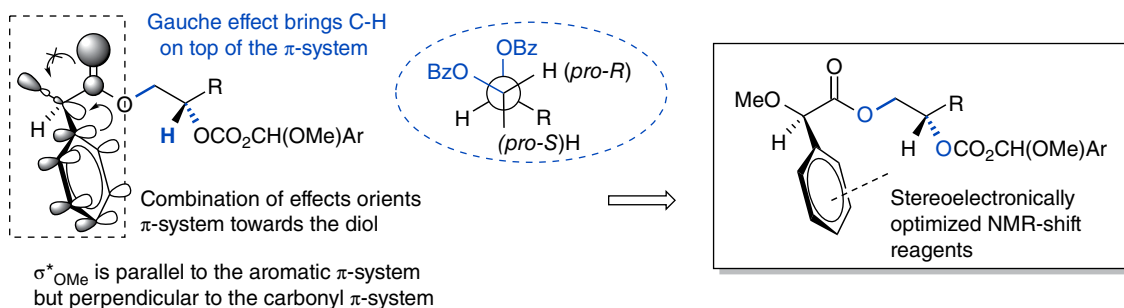


Figure 10.3 Combination of stereoelectronic effects in propane-1,2-diol derivatives responsible for the reliable shielding effects in $-\text{OCH}_2\text{CH(R)O}-$ moiety.

(S)-propane-1,2-diol favors one of the gauche conformers (Figure 10.3.). The overall conformational profile depends on both the gauche effect and a combination of other stereoelectronic effects discussed in this chapter. For example, in one of the key conformers shown below, the benzylic σ^*_{OMe} orbital is aligned with the aromatic π -system but perpendicular to the carbonyl π -system. The combination of these two effects orients the aromatic π -system in a proper way for exerting its shielding NMR effects at the $-\text{OCH}_2\text{CH(R)O}-$ moiety.²

10.2 Dynamic stereoelectronics

In the other common scenario, stereoelectronic control of reactivity originates from a delocalizing interaction that comes into play dynamically, often by being amplified only at a certain stage of the reaction path. Such situations are interesting because they can take advantage of effects that play a minor role in the starting material but manifest themselves at the right moment, i.e. in the transition state for one of the alternative reaction paths.

Stereoelectronic influences in reactant, TS, and products A common way of identifying a stereoelectronic effect on reactivity is to detect it in the starting material (either via a spectroscopic observation or by geometry modification) and extrapolate this effect onto either transition state for a reaction of interest if the reaction is under kinetic control, or the product if the reaction is under thermodynamic control. A common misconception is to equate ground state stabilization with increased reactivity, i.e. $\text{n} \rightarrow \sigma^*\text{C-X}$ donation at the anomeric position to the increased lability of the C-X bond. It is important to understand that any *reactant* stabilization effect decreases reactivity. However, this effect may also identify “a weak spot” in the molecular structure that is converted upon the evolution of molecular structure along the reaction path into an even *stronger* delocalizing effect that stabilizes the TS and/or the product much more than the reactant. The evolution of delocalizing interactions that leads to their amplification in the TS resolves the seeming paradox (that sometimes confuses students) of how a *stabilizing* interaction can be associated with the *increase* in reactivity. It also illustrates why the focus on TS stabilization is needed for gaining deeper understanding of stereoelectronic effects on reactivity, even though this understanding is difficult and complicated by the intrinsically delocalized nature of transition states.

The interplay between TS- and product-stabilizing effects is illustrated by the evolution of the anomeric effect along the reaction coordinate for the C-Cl bond ionization shown in Figure 10.4. Importantly, the magnitude of this effect increases as an axial C-X bond at the anomeric position starts to break and thus this effect has the necessary qualities to provide TS stabilization for bond breaking.

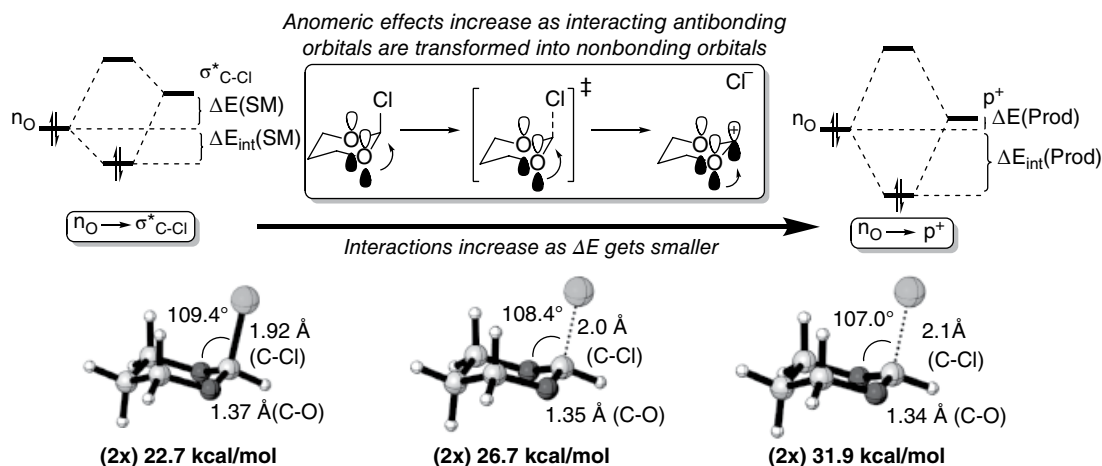


Figure 10.4 Quantification of the evolution of anomeric effect throughout the reaction path for the dissociation of 2-chloro-1,3-dioxane in the gas phase. Optimized geometries (full optimization and optimizations with fixed bond lengths) and NBO analysis at the B3LYP/6-311++G(d,p) level of theory. Interaction energies are only given for p-type lone pairs of the oxygens.

Ground state (reactant) effects An alternative way of connecting electronic structure of reactants and transition states involves analysis of structural distortion in the reactants and correlating them with the distortion needed for reaching alternative transition states. For example, the correlation of inherent distortion present in unsymmetrical arynes with the transition state distortion energies was used to predict regiochemistry of nucleophilic addition to these systems.³ We will discuss o-benzynes in more detail closer to the end of this chapter. “Distortional asymmetry” of π -bonds was shown to correlate with high stereoselectivity in sterically unbiased bicyclic alkenes where the distortion energy potentials favor distortion away from the preferred face of attack.⁴

While analyzing the ground state geometries, one has to bear in mind that they have predictive power only when they point out to an emerging electronic effect that will be amplified in the TS of interest. For example, in the case of arynes, the regioselectivity is controlled by progressive evolution of negative hyperconjugation from a moderate $\pi_{in} \rightarrow \sigma^*_{CO}$ interaction to a strong $n_C \rightarrow \sigma^*_{CO}$ interaction (Figure 10.5). Because the ground

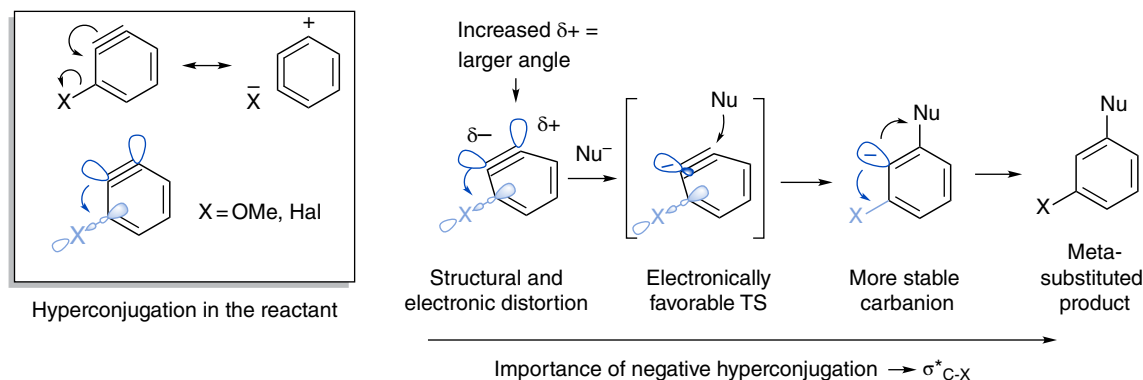


Figure 10.5 The ground state structural distortion and dominant force of TS stereoelectronic stabilization are the same: ground state geometry predicts correct reaction product.

state structural distortion and the dominant force of TS stereoelectronic stabilization coincide, trends in the ground state geometry correctly predict the observed reaction product.

The ground state distortion effects can be subtle and often require a computational analysis to reveal themselves. Although such effects are useful for a posteriori analysis and rationalization of results, their predictive power can be limited.

Stereoelectronic control by deactivation of unproductive stabilization The alternative way to analyze chemical reactivity is based on the comparison of ground state structures with the structural distortions needed to satisfy the electronic demands of transition states and/or evolution of delocalizing effects on route from the starting material to the product (Figure 10.6). This analysis can readily reveal the stereoelectronic approaches to efficient control of reactivity in a direct and specific way.

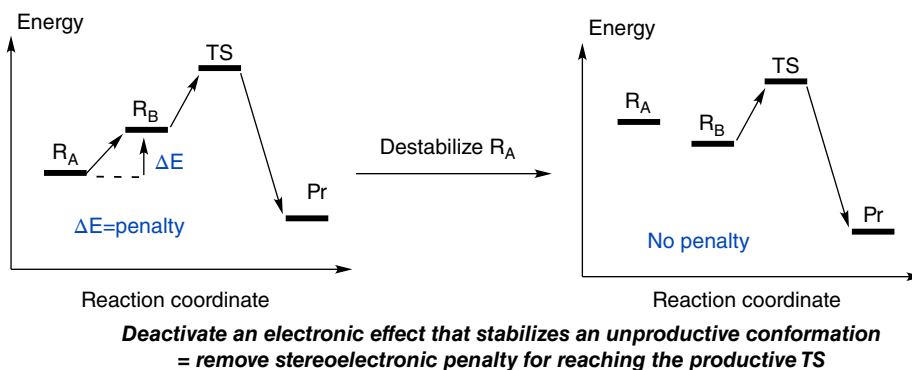


Figure 10.6 Deactivation of unproductive ground state stabilization.

The following sections will discuss examples of such effects. They can involve either appearance/strengthening or disappearance/weakening of a stereoelectronic interaction in the course of a reaction. Both approaches can be useful for the control of reactivity and selectivity. A particularly elegant implementation of this strategy involves deactivation or activation of precisely chosen electronic interactions that are directly associated with the targeted reaction.

Even though stereoelectronic effects are usually associated with increased reactivity, this is only true when such effects are displayed in the TS. When considered more broadly, stabilizing effects can also be unproductive when they operate in starting materials but not the transition states. For example, the barrier of the elusive radical 5-endo-dig cyclization in Figure 10.7a, exceeds 20 kcal/mol because benzylic stabilization of the reactant is lost upon the 90° rotation of the radical orbital needed to reach the cyclization TS. On the other hand, 5-endo-dig cyclization in a constrained polycyclic system in Figure 10.7b⁵ does not suffer from reactant stabilization and shows ~9 kcal/mol lower activation barrier.⁶

Similar control of unproductive reactant destabilization can be accomplished by other structural effects. Examples below illustrate that once unproductive stabilization is removed, it can be traded for a productive stereoelectronic interaction that leads to enhanced reactivity along a desired reaction path.

Stereoelectronic control by steric constraints Several examples provided in the following sections describe the application of steric factors for shaping the reactant conformational profile towards productive, stereoelectronically activated geometries. We will illustrate the generality of these principles by providing an example of such control in cationic, anionic (both benzylic carbanion and enolates), radical, and pericyclic processes.

Vinyl cations Solvolysis of arylvinyl bromides and tosylates provides an example of energetic penalty that has to be paid for reaching a conformation where stereoelectronic effect is activated (Figure 10.8).⁷ Generally,

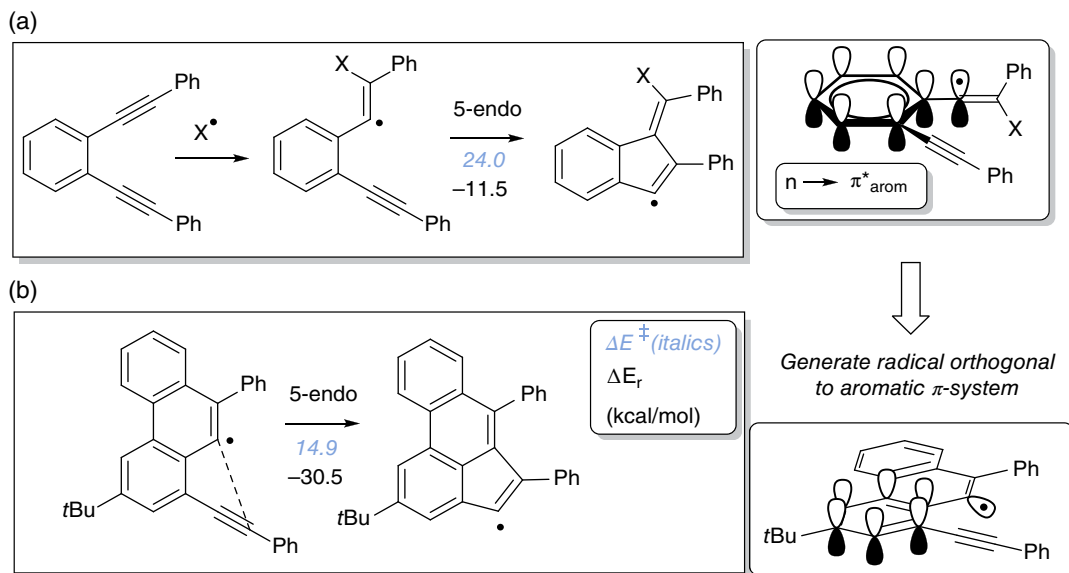
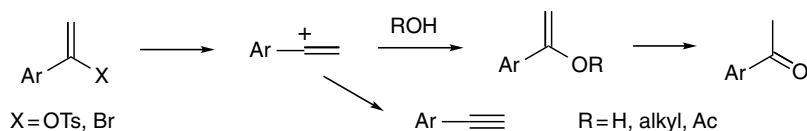


Figure 10.7 (a) Loss of a stabilizing stereoelectronic effect (i.e. benzylic stabilization of the vinyl radical) imposes additional penalty on the 5-endo-dig cyclization. (b) The penalty can be removed via conformational constraints in the reactant.



Stereoelectronic effect		Electronic effect of Me		
		Relative rates		
X = OTs	4.2×10^5	7300	23	1 ($1.9 \times 10^{-8} \text{ s}^{-1}$) ^a
X = Br	1.8×10^5	3000	40	1 ($8.7 \times 10^{-10} \text{ s}^{-1}$) ^b
		Activation parameters		
X = OTs ^a				
ΔH , kcal/mol	18.4	21.4	24.5	24.2
ΔS , cal/mol $\cdot$ T	-8	-10	-8	-18

a: MeOH-H₂O (1:1), 36.5°C; b: EtOH-H₂O (4:1), 88°C

Figure 10.8 Conformational effects on the relative rate of solvolysis for vinyl tosylates and bromides.

vinyl halides and related molecules are reluctant to participate in solvolysis due to the great strength of the $C(sp^2)-X$ bonds. Rate enhancements of up to 4×10^5 over the parent 1-phenylvinyl systems have been observed in the presence of two ortho-methyl substituents. This dramatic effect is much greater than the combination of purely electronic effects expected from the methyl substituent as illustrated by the only modest acceleration provided by the p-Me group.

What is the origin of these large changes in reactivity? Hyperconjugation between an adjacent π -system and a $C-X$ bond could assist in the $C-X$ bond breaking but, for the parent 1-phenylvinyl systems, the necessary orbital alignment comes at a price – it requires the reactants to sacrifice the coplanarity between the phenyl and the vinyl π -systems. The accompanying penalty for the loss of π -resonance (estimated to be of the order of 4–5 kcal/mol) is included in the energy cost for reaching the $C-X$ fragmentation transition state. On the other hand (Figure 10.9), the steric hindrance to coplanarity produced by the ortho-substituents switches the unproductive reactant stabilization off and imposes a geometry that is effectively preorganized for the conjugation of the aromatic π -system with the breaking $C-X$ bond in the TS (and with the newly formed vacant p-orbital in the vinyl cation intermediate).

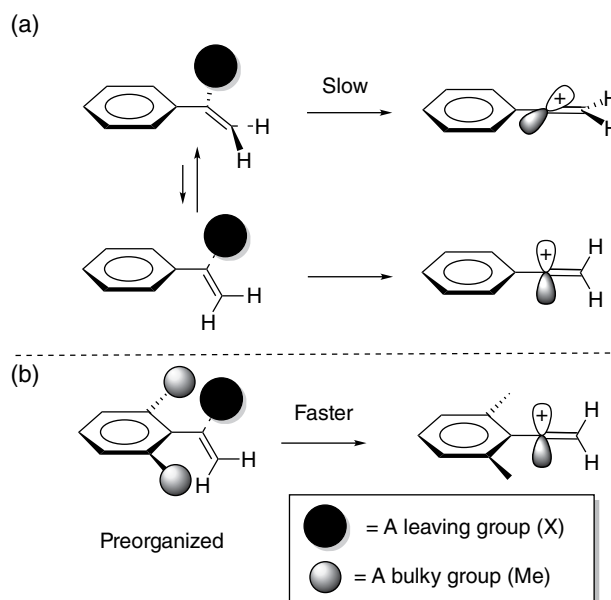


Figure 10.9 (a) Reactant stabilization between vinyl and phenyl systems sacrifices reactivity necessary for $C-X$ bond breaking. (b) Preorganization of starting material induced by bulky ortho substituents accelerates $C-X$ bond breaking.

An interesting feature of the above system is that, despite the high penalty for breaking a relatively strong $C(sp^2)-X$ bond and the intrinsic instability of vinyl cations, solvent participation in the formation of a vinyl cation was shown to be weak, suggesting that the positive hyperconjugation with the aromatic π -system does most of the work.

Anions via selective deprotonation An umpolung of the above interaction illustrates that the negative hyperconjugation with the aromatic π -system can have a large impact on reactivity as well.⁸ Although benzylic $C-H$ bonds are usually more reactive toward deprotonation than vinylic $C-H$ bonds,⁹ twisting of methyl-substituted styrene derivatives results in the selective activation of vinyl hydrogens towards deprotonation. The observed correlation between the reactivity of the vinyl hydrogens and the magnitude of the twist suggest that the

stereoelectronic origin of the observed effects lies in the orbital interaction between the π^* orbital of the benzene ring and the σ orbital of the vinylic C–H bond. The vinyl anion can be trapped via protonation (or deuteration, Figure 10.10) or via the Brook rearrangement. Significant amount of vinylic deprotonation was found for only the highly twisted *o*-substituted *Z*-styrenes. In contrast, the respective *E*-isomers underwent deprotonation exclusively at the benzylic position, further confirming that twisting serves as the stereoelectronic origin of the observed vinyl C–H activation.

(a)

	Vinyl	Allylic	Benzylic	Vinyl and allylic
pK _a :	50	44	43	41
ΔH_{H^+} :	-	409	391	382
				381 (Gas phase, kcal/mol)

(b)

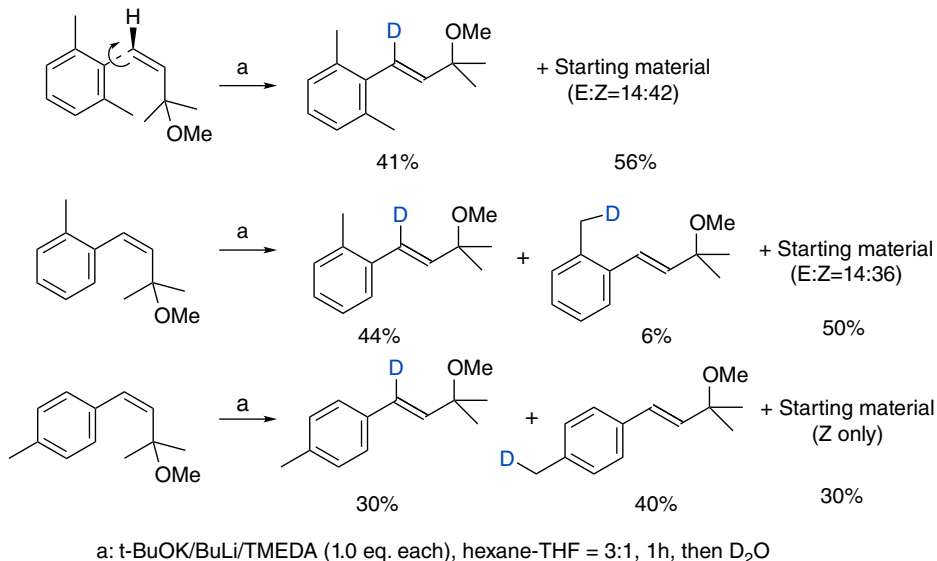


Figure 10.10 (a) pK_a and hydride affinities for selected hydrocarbons. (b) Deprotonation/deuteration experiments for substituted styrenes as a function of conformational constraints.

After the stereoelectronically favorable vinyl anion is formed from the twisted *Z*-alkene, an additional feature of this system (presence of a spatially close OR group) facilitates *Z* → *E* isomerization assisted by the formation of a new chelating O...Li interaction (Figure 10.11).

Note that the sp^2 C–H bonds from the aromatic ring do not react because they are perpendicular to the aromatic π -system and the products of respective deprotonation cannot enjoy $n \rightarrow \pi^*$ delocalization.

Enolates vs. allenolates Transformation of carbonyl compounds into enolates by regio- and stereoselective deprotonation of α -C(sp^3)-H bonds is a powerful strategy for generating nucleophilic species for C–C bond formation. In these processes, the proton removal can be accomplished readily because it is assisted by the overlap of the C–H bond with the carbonyl π^* orbital (Figure 10.12). In contrast, the generation of corresponding enolates

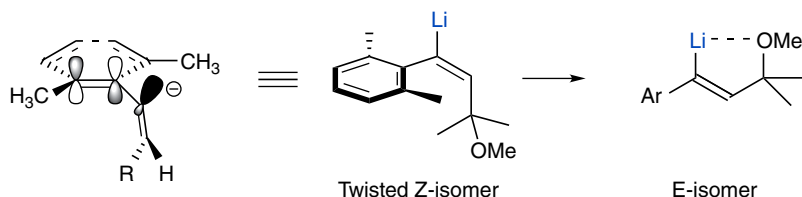


Figure 10.11 A pendant OR group close to vinyl anion assists $Z \rightarrow E$ isomerization.

(allenolates) from unsaturated carbonyl compounds with α -C(sp²)-H bonds is scarcely documented because the α -C-H bonds in the π -conjugated enones and enals are close to orthogonality with the π^* C=O orbital.

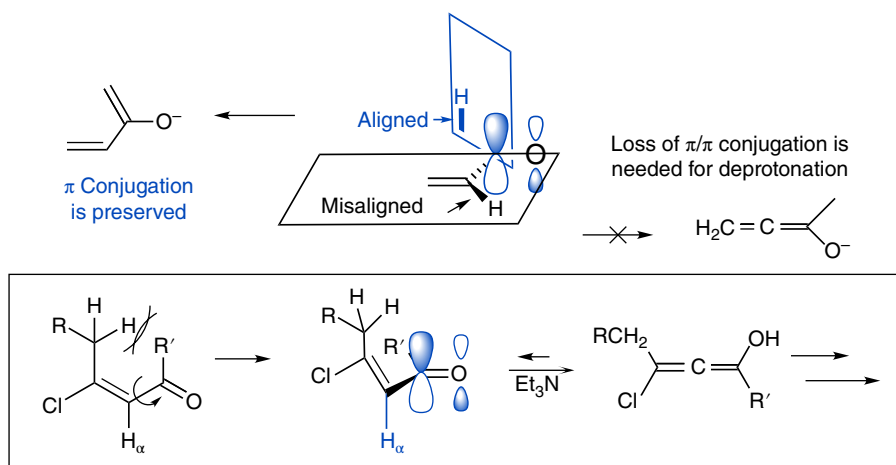


Figure 10.12 Generation of enolates from α -C(sp³)-H bonds is assisted by C-H overlap with the carbonyl π^* system.

The lack of favorable overlap with the carbonyl π -system makes the α -vinyl deprotonation challenging. However, once a non-planar conformation is enforced, the situation changes dramatically. This is illustrated by facile α -vinyl enolization of (E)- β -chlorovinyl ketones by a base as weak as Et₃N.¹⁰ The mild α -vinyl enolization of these compounds was suggested to originate from their non-planar conformation which, unlike the planar conformation of respective (Z)-isomers, leads to a good orbital overlap between the carbonyl π -system and the α -C-H bond. The enolization to allenol is preferred over the α -C(sp³)-H bond deprotonation from R.

Radical C-H abstraction Alignment of C-H bonds with a π -system can also be used for the control of radical reactions. An elegant example of competition between radical S_H2 ring opening and H-abstraction in aryl cyclopropanes was reported by Tanko and coworkers.¹¹ Generally, C-H bonds of cyclopropanes are *deactivated* towards H-abstraction by hybridization effects (i.e. increased s-character in the carbon hybrid of the C-H bond), whereas the C-C bonds are *activated* by the ring strain. As a result, reactions of phenyl and naphthyl cyclopropanes with bromine atoms under free radical conditions (once the ionic processes are carefully excluded) exclusively lead to formation of ring-opened dibromides via radical C-C bond cleavage. Unlike the analogous C-H bonds of toluene, the benzylic C-H bond in aryl cyclopropanes remains unreactive (Figure 10.13).

However, the selectivity is dramatically changed for 9-cyclopropylanthracene where a C-H bond becomes the main target for the radical attack and >70% of 1-(9-anthryl)cyclopropyl bromide is formed (Figure 10.13). Stereoelectronic reasons for this striking differences in selectivity are revealed by the conformational

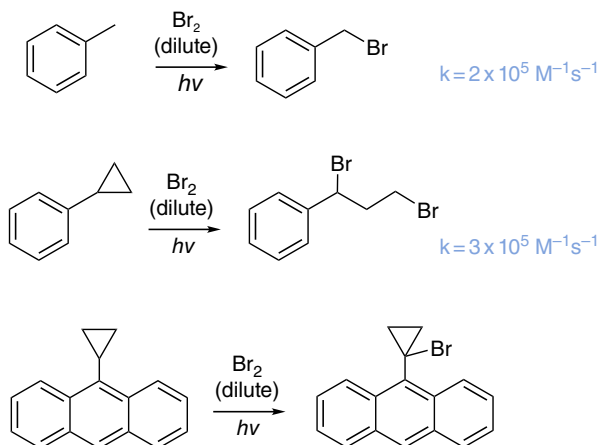


Figure 10.13 Radical brominations of phenyl and naphthyl cyclopropanes.

preferences of the reactants and transition states. For phenylcyclopropane, β -cyclopropyl- naphthalene and other compounds where the bisected conformation is more stable, the cyclopropyl methine C-H bond is orthogonal to the π -system (Figure 10.14). At the same time, the cyclopropyl C-C bonds are aligned with the aromatic systems and activated towards the radical ring opening. In contrast, the bisected conformation is *disfavored* in 9-cyclopropylantracene by repulsive interaction with the peri-hydrogens of the annealed aromatic rings. The preferred perpendicular conformation aligns the C-H bond with the aromatic π -system. Abstraction of this hydrogen by bromine atom leads to a favorable transition state with considerable degree of benzylic stabilization.

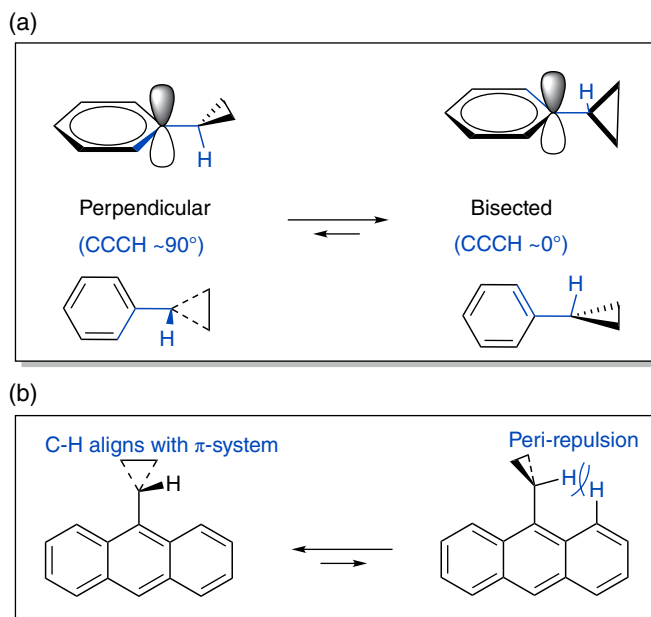


Figure 10.14 (a) Cyclopropyl C-C bonds aligned with aromatic system lead to radical ring opening. (b) Steric repulsion favors methine C-H alignment of cyclopropyl group with aromatic system.

Pericyclic process – ene reactions Abstraction of allylic hydrogen with singlet oxygen proceeds as a concerted pericyclic process (the ene reaction) that leads to the formation of allylic hydroperoxides (Figure 10.15). The reaction of substituted 1,3-dienes generally involves the sp^3 C-H bonds at the allylic position. However, this reaction can target selective vinylic C-H bonds once the diene moiety is sufficiently twisted.¹² When the reacting diene is forced closer to the perpendicular geometry ($C=C-C=C$ dihedral angle in the vicinity of 70°) where C-H bond at an internal diene carbon is aligned with the adjacent π -system, the respective allenes are formed in synthetically useful yields.

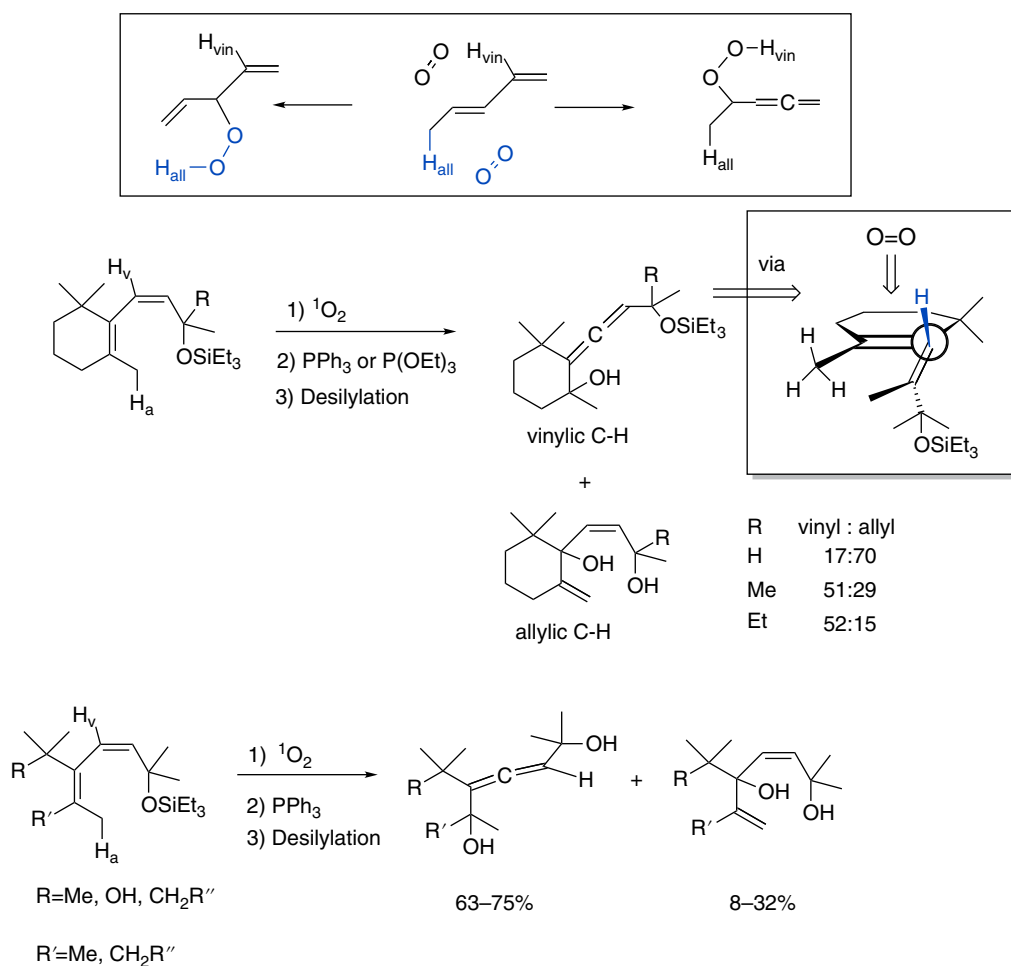


Figure 10.15 Ene reactions of 1,3-dienes generally involve allylic hydrogens but can target vinyl hydrogens when proper structural constraints are introduced.

Summary The recurring theme in the above examples is that a minor delocalizing interaction can be inactive at the most stable ground state geometry defined by an alternative stronger interaction that moves the system “perpendicularly” to the desired reaction coordinate. The stereoelectronic “readjustment” requires a conformational change and comes with a thermodynamic cost. When such readjustment is unnecessary, the role of stereoelectronic effects is revealed clearly and their accelerating power is utilized fully.

Once the correct stereoelectronic effect can take over, it can provide significant acceleration to a reaction by stabilizing its TS. In each case, this minor interaction is manifested in an alternative, usually less stable geometry and starts to grow in importance as the molecule moves along a reaction coordinate trajectory. In this process, the relative power of delocalizing interactions changes somewhere between the initial (ground state) and reacting (transition state) geometries. Such changes are indicative of the greater ability of breaking bonds (which can be considered as incipient cationic, radical or anionic centers) to participate in delocalization in comparison to fully developed chemical bonds at the equilibrium geometries. For the fully developed bonds, the σ -orbital is low and σ^* is high in energy. As the bond is stretched, both orbitals start to approach non-bonding MOs and their donor and acceptor abilities increase at the same time. Due to this general feature, cations, anions, radicals alike can be chaperoned along the desired reaction path.

Formation and reactivity of *o*-benzynes *o*-benzynes serve as illustrative stereoelectronic models due to two features: a) structural rigidity that restricts orbital interactions exclusively to syn-periplanar geometries and b) distortion of the in-plane π -system. These features are translated in the interplay of two related stabilizing effects controlling the structure of substituted benzynes and their reactivity towards nucleophiles: 1) interaction of σ -acceptors with bent bonds and 2) interaction of σ -acceptors with anionic centers.

Reactivity of *o*-benzynes is often analyzed through the ground state distortions. We have mentioned the evolution of delocalizing effects in *o*-benzynes earlier (Figure 10.5). In the following discussion, we will illustrate how stereoelectronic analysis provides an alternative simple description of the rich reactivity of such compounds.

The stereoelectronic influence on stability of benzynes is illustrated by the rates of benzyne generation via lithium halide elimination from aryl halides (Figure 10.16).

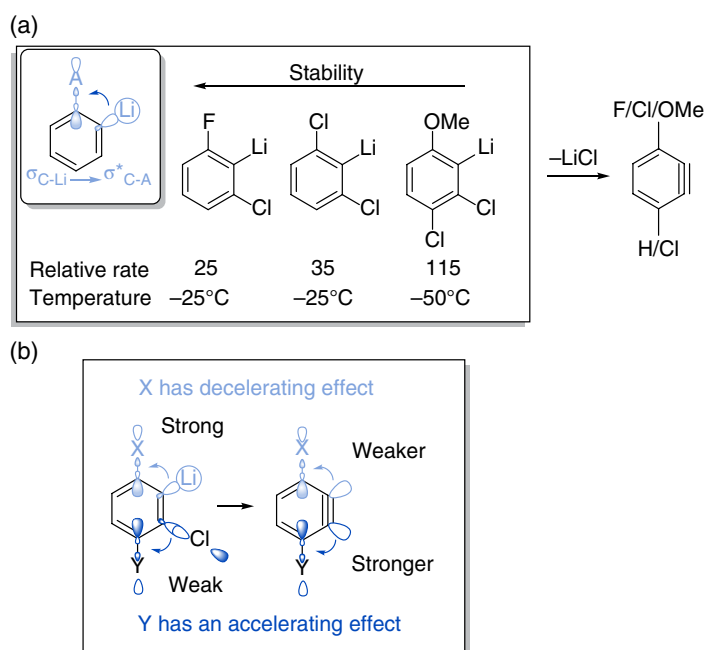


Figure 10.16 Effect of negative hyperconjugation on the relative rate constants for benzyne formation determined in reference 13b. (a) relative rates of LiCl elimination from the substituted aryl anions. (b) Strong negative hyperconjugation of carbanionic center with σ_{CX}^* in the reactant evolves into a weaker interaction of bent benzyne π -bond with σ_{CX}^* . The overall effect is decelerating. In contrast, the σ_{CY} bond is a much weaker donor than the benzyne π -bond, so σ_{CY}^* acceptor can enjoy stronger donor-acceptor interaction in benzyne. Such σ -acceptors near the leaving Cl-group are accelerating.

Although these reactions are affected by subtle changes in reaction conditions (the nature of oligomeric Li-species, solvation, ion-pairing etc.), the underlying stereoelectronic preferences are still displayed clearly (Figure 10.16). On one hand, σ -acceptor substituents *next to the anionic center* make formation of *o*-benzynes slower by stabilizing the carbanionic reactant. The loss of this strong interaction is not compensated by the weaker interaction with the bent π -bond in the *o*-benzyne product and the respective TS. The moderate σ -acceptor (the methoxy group) near the anionic center does not overstabilize the aryl lithium intermediate as much as the C-F and C-Cl bonds.¹³ On the other hand, introduction of a σ -acceptor *near the leaving halide* accelerates the reaction because the elimination removes the weak σ -donor (C-X bond) and introduces a stronger π -donor (bent alkyne).

These effects explain the highly regioselective formation of *o*-benzynes from substituted precursors. For example, both 2- and 3-chloroanisole gave the same *o*-benzyne as the sole product in transition-metal-free alkynylation of aryl chlorides (Figure 10.17).¹⁴ While deuterium incorporation experiments suggest that H/D exchange is observed at the 4-position, the nature of observed products suggests that only 3-methoxybenzyne is formed in both cases, in accordance with the earlier reports of more facile benzyne generation from 2,6-dihaloaryllithiums and haloanisoles.¹³ Stabilization of bent alkynes with σ -acceptors can also facilitate benzyne generation for subsequent use in the hexadehydro-Diels–Alder reaction.¹⁵

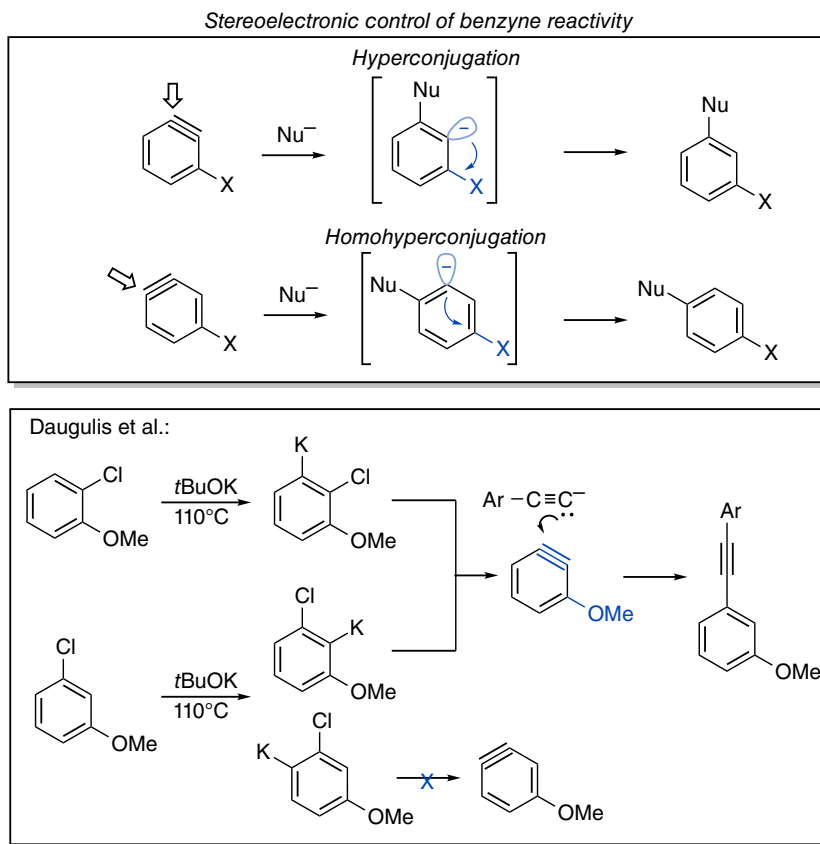


Figure 10.17 Stereoelectronic effects on generation and reactivity of *o*-benzynes.

The principle of microscopic reversibility brings the above stereoelectronic effects back into play in the reactions of *o*-benzynes with nucleophilic trapping species (Figure 10.17).¹⁶ For example, control of relative stabilities of aryl lithiums by substitution allows selective preparation of halosubstituted biphenyls.¹⁷ In the

preferred direction of nucleophilic attack, the developing anion is able to benefit from increasing hyperconjugative stabilization of the vicinal C-O acceptor. When the substituent is removed one atom further from the *o*-benzynes moiety, the nucleophilic attack proceeds in a way where the resulting anion can be stabilized by homohyperconjugation (see Chapter 8 for a more detailed discussion of such effects).

The regioselective generation of *o*-benzynes (i.e. via TMSOTf elimination) removes any uncertainty about the nature of these species and facilitates analysis of stereoelectronic effects in nucleophilic addition to these strained alkynes (Figure 10.18). A thoroughly investigated case of *o*-benzynes with an annealed pyrrole ring (indolynes),¹⁸ illustrates the effects of stabilizing delocalization via $\pi \rightarrow \sigma^*_{C-A}$ hyperconjugation in the syn-periplanar arrangement. As in the previous example, presence of a σ -acceptor *ortho* to the triple bond directs nucleophilic attack at the alkyne carbon removed from the substituent, providing an anionic intermediate strongly stabilized by vicinal hyperconjugation. When the triple bond is further from the C-N acceptor (4,5- and 5,6-indolynes), the stabilization and selectivity are consistent with the influence of through space interaction between the back lobes of σ -donor and σ -acceptor (i.e. homohyperconjugation, Chapter 8). These stabilizing interactions correlate well with distortion energies needed for the reactants to reach the TS geometry.¹⁹ The greater electronic stabilization translates into lower distortion energy (for an analogous effects on a different reaction of strained alkynes, see discussion of alkyne/azide cycloaddition in Chapter 9).

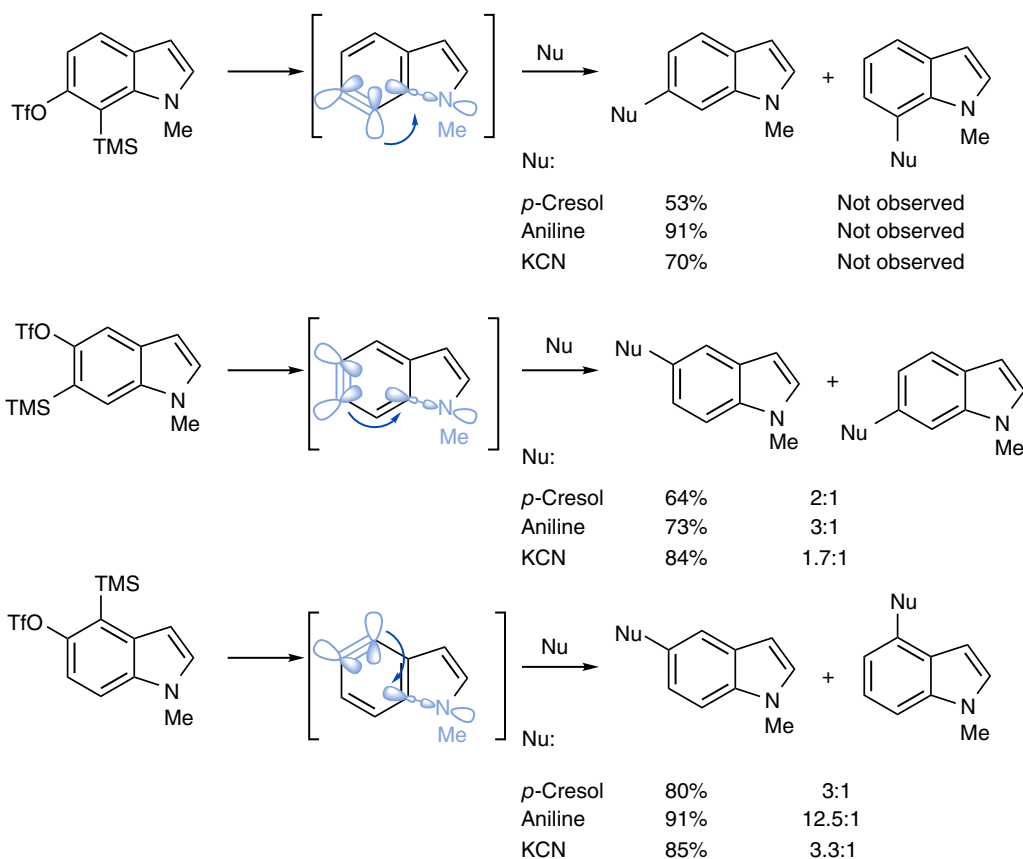


Figure 10.18 Hyperconjugation and homohyperconjugation in control of regioselectivity of nucleophilic additions to *o*-benzynes.

“ α -Effects” in nucleophiles with vicinal lone pairs – transition from an unproductive four-electron interaction to strong anomeric interactions along the reaction path Molecules with lone pairs at two adjacent atoms have unusual combination of basicity and nucleophilicity, often referred to as “ α -effect”.²⁰ Originally, this effect was defined as “the enhancement of nucleophilicity that is found when the atom adjacent to a nucleophilic site bears a lone pair of electrons”.²¹ In the literature, this definition is often refined as a positive deviation from Brønsted-type nucleophilicity plots in comparison with a reference nucleophile of the same basicity.²³ Such deviations ($k_{\alpha\text{-Nu}}/k_{\text{normal-Nu}}$) vary significantly in magnitude (in the range of 5–1000) for different reactions and sometimes mysteriously disappear.

For example, when analyzing the relative reactivity of $\text{NH}_3/\text{N}_2\text{H}_4/\text{NH}_2\text{OH}$ (and many substituted analogues) in water, Mayr and coworkers found that acceleration in reactions with benzhydrylium ions and quinone methides due to the change of H to NH_2 ($\text{NH}_3 \rightarrow \text{N}_2\text{H}_4$) is significant (~ 100 -fold) but not as large as acceleration by a Me group ($\text{NH}_3 \rightarrow \text{CH}_3\text{NH}_2$; >200 -fold). Acceleration by an OH group in hydroxylamines ($\sim$ factor of 10) is also significantly smaller than the effect of a methyl group.²²

Analysis below will focus on the first order effects of α -lone pair on *both* kinetics and thermodynamics instead of the second order effects such as the deviations from the Brønsted plots. We will illustrate how basic stereoelectronic considerations can explain why *both* basicity and nucleophilicity are significantly different in the $\text{HOO}/\text{HO}\cdot$, $\text{t-BuOO}/\text{t-BuO}\cdot$, $\text{H}_2\text{O}_2/\text{H}_2\text{O}$, $\text{NH}_3/\text{N}_2\text{H}_4$ pairs.

A stereoelectronic description of the α -effect is based on the evolution of anomeric interactions in this system along the reaction path. We will describe them by analyzing the simplest case with one lone pair on each atom X and Y (Figure 10.19).

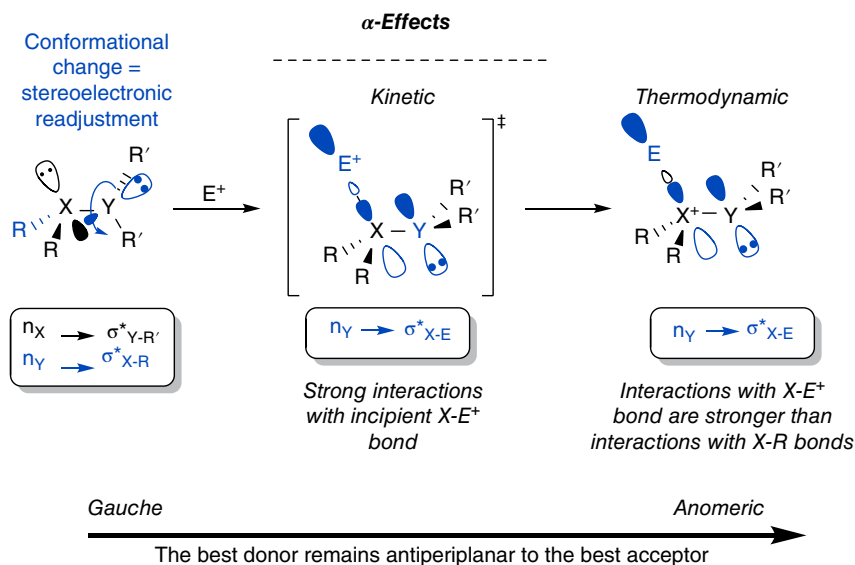


Figure 10.19 The α -effects occur when a relatively weak stereoelectronic interaction in the reactant is transformed to a stronger anomeric effect during the reaction. Kinetic effects correlate with nucleophilicity, while thermodynamic effects correlate with basicity. The “excessive” α -effects associated with the positive deviations from the Brønsted correlation result from stronger interactions in the TS than in the product.

In the starting materials, the gauche effect is utilized, the best donors (lone pairs of X and Y) align antiperiplanar to the best acceptors (σ_{Y-R}^* and σ_{X-R}^* -orbitals, respectively). In the TS for nucleophilic attack of X on E^+ , strong anomeric effects ($n_Y \rightarrow \sigma_{X-E}^*$) develop between the high energy lone pair and the low energy antibonding orbital associated with the incipient bond. In the product, the lone pair of Y has the choice to align itself with either the X-E or X-R bonds. If the X-Y reactant was neutral, X is positively charged at this stage and both of these σ^* -orbitals are strong acceptors. Depending on the acceptor ability of the X-E bond, a thermodynamic α -effect may be present on the stability of reaction (e.g. S_N2) products. The evolution of ($n_Y \rightarrow \sigma_{X-H}^*$ / $n_Y \rightarrow \sigma_{X-H}^* / n_Y \rightarrow \sigma_{X-H}^*$) interactions along the protonation path describes additional stereoelectronic activation of this process that accounts for the relatively high basicity of such compounds.

Further contribution to increased nucleophilicity and basicity in reactions with electrophiles containing low energy LUMOs is associated with the extent of electron transfer in the TS that is responsible for varying degrees of radical character on the nucleophilic atom.²³ Recall that an α -lone pair can stabilize radicals via 2-center, 3-electron half-bonds (as discussed in Chapter 3).

Thermodynamic control of reactivity – control of reactivity by an external switching off a stereoelectronic effect

The simple comparison of electronic effects in reactant and product is sufficient for reactions that proceed under thermodynamic control. It is common for chemical reactions to proceed from reactants that have relatively weak stereoelectronic stabilization to products where such stabilization is stronger. In such situations, switching off a stereoelectronic effect can be used to reverse position of equilibrium between two common functional groups. As is well-known, amides are more stable than esters due to the greater magnitude of the $n_N \rightarrow \pi_{C=O}^*$ interaction in amides in comparison to the $n_O \rightarrow \pi_{C=O}^*$ interaction in esters. The relative magnitude of stereoelectronic stabilization is responsible for both the ubiquity of reactions that transform esters into amides and for the scarcity of the reverse process. However, coordination of amide nitrogen to a strong Lewis acid switches off this interaction, and the amide can be easily transformed into the ester when the $n_N \rightarrow \pi_{C=O}^*$ interaction is switched off, e.g. by coordination to an external Lewis acid (Figure 10.20).²⁴

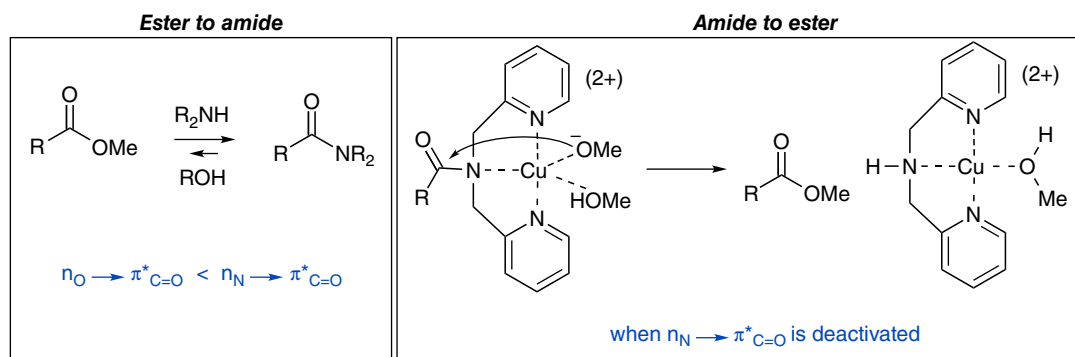


Figure 10.20 Reversal of equilibrium by switching off a stereoelectronic effect.

Control of reactivity by activating a strong stereoelectronic effect The differences in the donor ability of heteroatoms can be used in a variety of ways. For example, it leads to a convenient synthesis of diaza[4] helicenes from tris(2,6-dimethoxyphenyl)methyl cation and primary amines (Figure 10.21).²⁵ Again, the transformation is driven by favorable thermodynamics originating from a delocalizing donor-acceptor interaction between nitrogen lone pairs and benzylic cations.

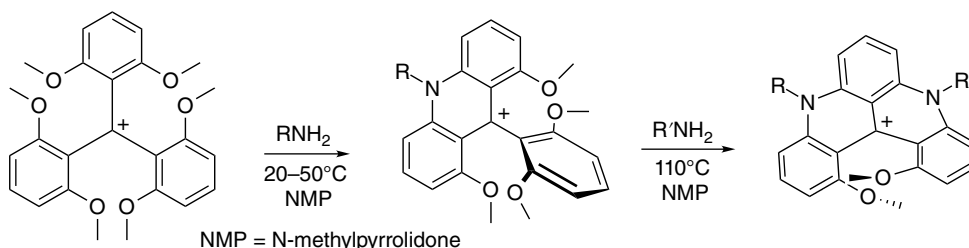


Figure 10.21 Synthesis of diaza[4]helicenes driven by thermodynamics of cation stabilization.

A more subtle example for the use of electronic effects for the control of chemical equilibria is given by stereospecific synthesis of 1,2-diamines via diaza-Cope rearrangement (Figure 10.22).²⁶ This efficient process illustrates how the strength of H-bonds can control the reaction equilibrium. Both reactants and products are stabilized by the H-bond between phenolic oxygen and imine nitrogen. However, in the product, the H-bond is made stronger by the synergistic contribution of π -delocalization (the so-called resonance-assisted hydrogen-bond (RAHB) effect²⁷).

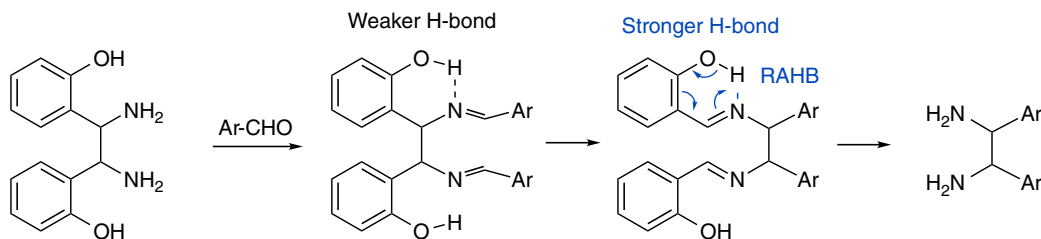


Figure 10.22 The RAHB effect seen in the synthesis of 1,2-diamines.

Summary The collection of examples and concepts provided in this chapter illustrates that timing of stereoelectronic interaction determines their effects on reactivity. Delocalizing interactions can be counterproductive when they fade out of existence along the reaction path or productive/accelerating when they are amplified in the transition state. In the following sections, we will provide further examples of dynamic stereoelectronic interplay between structure and reactivity in a variety of chemical areas.

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11

Stereoelectronic Effects in Action: The Many Doors Opened by Orbital Interactions

The scope and applications of stereoelectronic concepts have increased so dramatically in the recent decades that providing a comprehensive coverage of this ever-expanding field is impossible within the confines of this book. This chapter will aim to illustrate the generality of stereoelectronic concepts, their interplay with other factors and their broad applicability to different areas of chemistry, biochemistry and materials science. We will provide examples of how recognizing the orbital interactions ability to play many different roles and serve many different purposes has led to the discovery of practically useful chemical processes.

We will organize our discussion according the three key patterns ($\sigma \rightarrow \sigma^*$, $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$) of orbital interactions as a guiding principle. In doing so, let's not forget that some overlap between these patterns is unavoidable, as the dominant interactions may interconvert during chemical reactions.

11.1 Gauche effect ($\sigma \rightarrow \sigma^*$ interactions)

In the first of these sections, we will discuss a broad selection of examples related to organic reaction control, catalyst design, fatty acid mimics, conformations of biopolymers, structure of oligosaccharides that constitute part of the bacteria cell walls, and initiation of enzymatic processes associated with sensing hypoxia. Remarkably, each example from this diverse array originates from a common stereoelectronic source, the gauche effect.

Control of reactive conformations We have outlined the electronic origins and conformational consequences of the gauche effect in Chapter 6 and already illustrated its utility for the design of NMR probes of chirality (Chapter 10). However, the list of applications of the gauche effect in the control of chemical structure and reactivity is much more diverse.¹ For example, the gauche effect has been utilized to achieve efficient and “strain-free” conformational control in the first example of the elusive 5-endo-dig cyclization of

carbon-centered radicals.² The gauche arrangement of the two hydroxy groups in hexa-1,5-diyne-3,4-diol preorganizes the two alkyne moieties in the “near attack” conformation without potentially deactivating cyclic constraints (Figure 11.1).

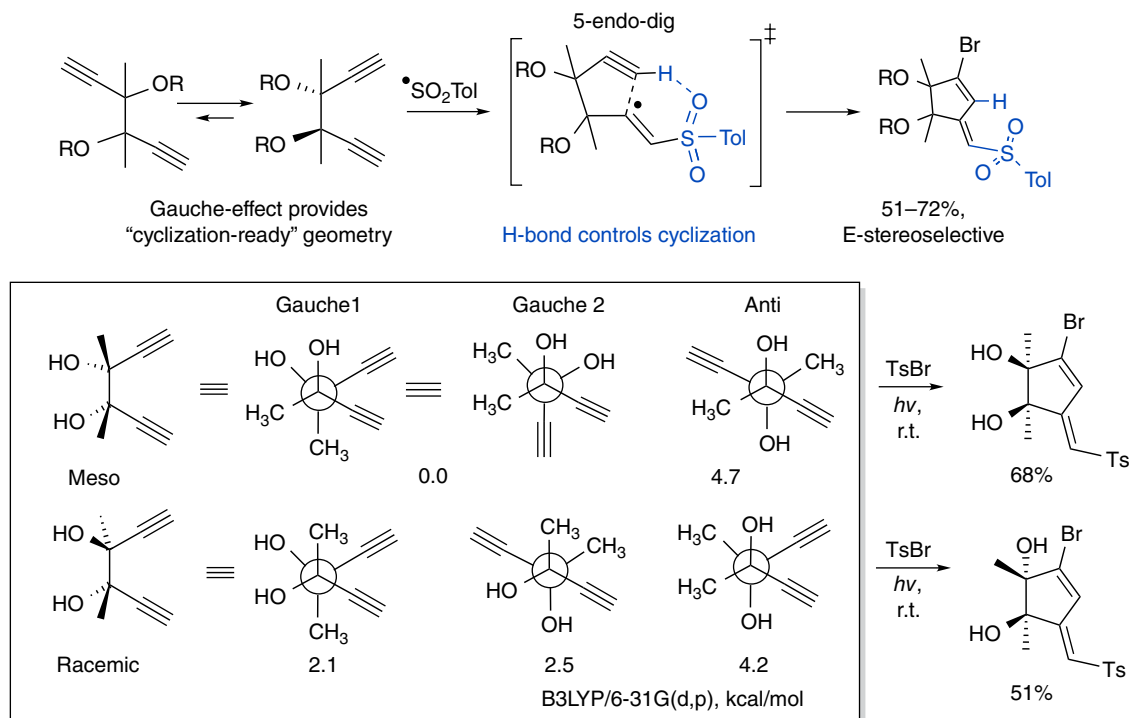


Figure 11.1 The combination of the preorganizing gauche effect and the TS-stabilizing C-H...O interaction required for the successful design of the first efficient radical 5-endo-dig cyclization. Calculated energies are given below the Newman projections in kcal/mol.

Similar stereoelectronic effects can be utilized for the control of stereoselectivity. For example, the “inside fluoro effect”³ that accounts for the high level of stereocontrol in iodolactonization and iodoetherification of allylic fluorides has been traced back to the same donor/acceptor properties. The computational analysis of the most favorable transition states and intermediates revealed that, for the fluoromethyl-substituted iodonium complex, the fluorine atom prefers the inside position by 3 kcal/mol with respect to the outside, and 5 kcal/mol with respect to the anti arrangements (Figure 11.2). In the anti conformation, the acceptor $\sigma_{\text{C-F}}^*$ orbital aligns with one of the C-I bonds, leading to destabilization of the iodonium ion. As expected from the degree of electron deficiency, the “inside fluoro effect” is stronger for the positively charged iodonium ion than for the neutral I_2 - π complexes. The authors also suggested that the “inside” fluorine substituent can also use its lone pairs of electrons to stabilize the partial positive charge of the I_2 - π complex, via a homoanomeric-like interaction.

Control of conformational space in catalyst design Gilmour and coworkers introduced chiral pyrrolidino pyridines bearing a β -fluoroamine where molecular space is defined by a fluorine gauche effect.⁴ An elegant feature of this design is that the effect is amplified when protonation or acylation generate an electropositive nitrogen (Figure 11.3). This chemical change drastically decreases the conformational mobility of the F-C-N⁺ “molecular hinge” – the flexible catalyst is rigidified in the first step of the catalytic process. This change was compared to the structural consequences of “substrate binding” in the induced fit process in enzymatic systems.

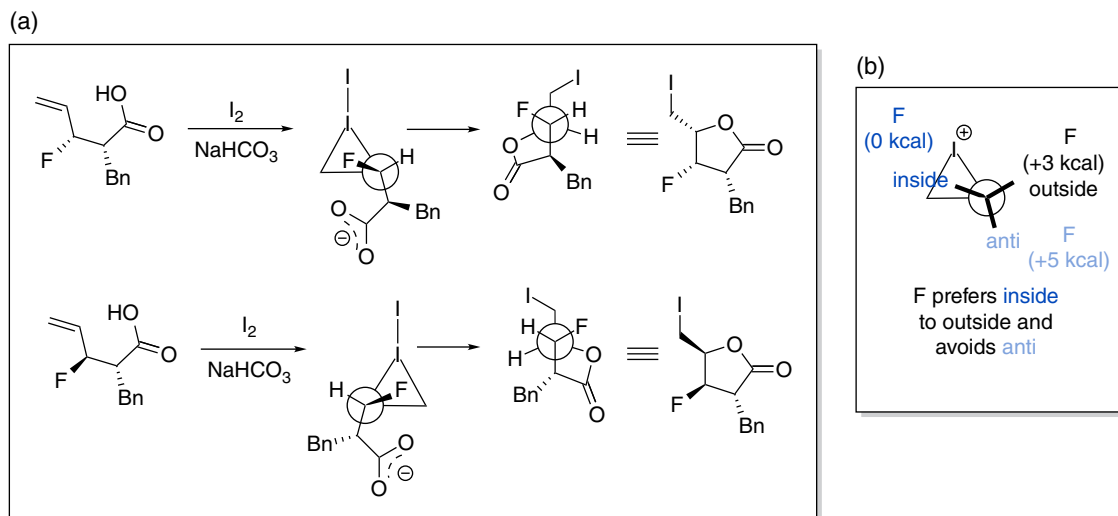


Figure 11.2 (a) The mechanism of the iodolactonization of diastereomeric allylic fluorides via the most stable rotamers of the I_2 -alkene π -complexes. (b) definition for the inside, outside, and anti positions and relative energies for the corresponding rotamers of fluoromethyl-substituted iodonium ion.

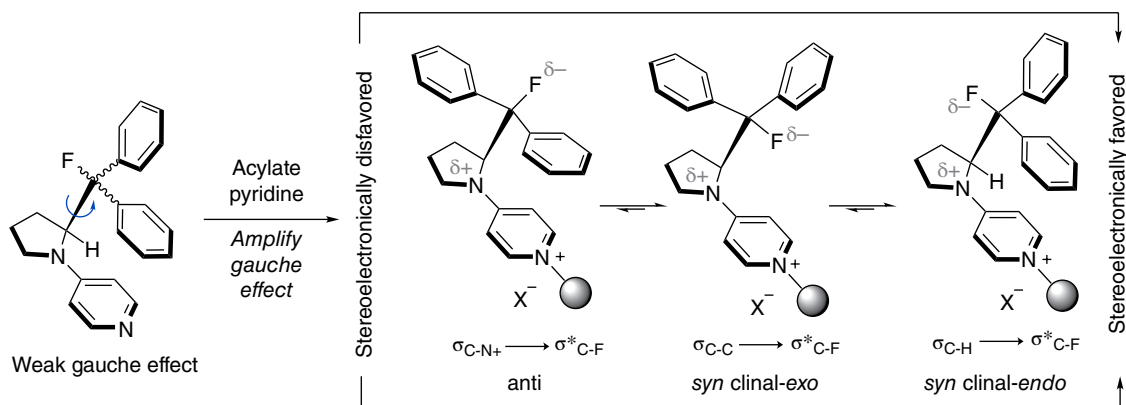


Figure 11.3 Gauche effect in catalyst design.

Precise and reliable folding of acyclic compounds Reliable design of folded molecular shape is challenging in the absence of rigid structural elements such as cis-substituted rings and cis-double bonds. Gauche effect allows conformational control without unsaturation. *Erythro* and *threo* diastereoisomers of 2,3-difluorosuccinic amides have drastically different conformations.⁵ Analogous control is applicable to the free *erythro*- and *threo*-9,10-difluorostearic acids. The *threo* diastereomers adopt extended conformation similar to that of trans-fatty acids whereas the *erythro* isomers were suggested to prefer a folded conformation similar to that of cis-fats (Figure 11.4).⁶

This concept for the cycle- and unsaturation-free control of molecular shapes is likely to find multiple applications. For example, four stereoisomeric vicinal difluorinated analogues of the natural cyclic heptapeptide unguisin A were found to adopt dramatically different secondary structures as a function of stereoelectronic and steric interactions.⁷ The preferred conformations of PEG (polyethylene glycol) groups (popular solubilizing substituents for many biomedical applications) are likely to be affected by the gauche effect as well.

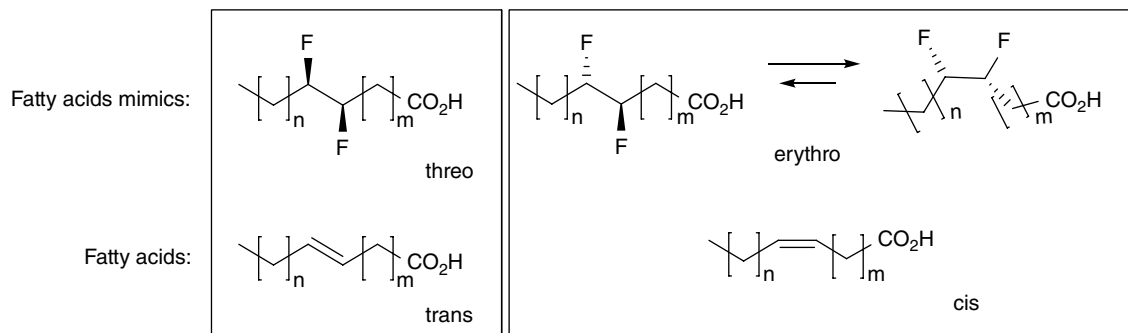


Figure 11.4 Use of gauche-effect for conformational control and folding of long alkyl chains in fatty acids.

Fliposomes/flipids Samoshin and coworkers developed amphiphilic trans-3,4-bis(acyloxy)-1-benzylpiperidines that are able to perform a pH-triggered conformational flip (flipids) and suggested their use as components of a new type of pH-sensitive liposomes (fliposomes). The protonation-generated change in molecular structure makes the conformer with axial acyloxy groups predominant and drastically increases the separation of hydrocarbon chains (Figure 11.5). In addition to intramolecular hydrogen bond and electrostatic interactions suggested by the authors, it is clear that the dominating conformation of the non-protonated form is disfavored by the antiperiplanar arrangement of the relatively strong vicinal C-N and C-O acceptors. This ring flip changes relative orientation of these acceptor bonds to the more stereoelectronically favorable gauche arrangement. From a structural point of view, this process perturbs the liposome membrane causing rapid (within a few seconds) release of the liposome cargo in response to increased acidity of the media.⁸

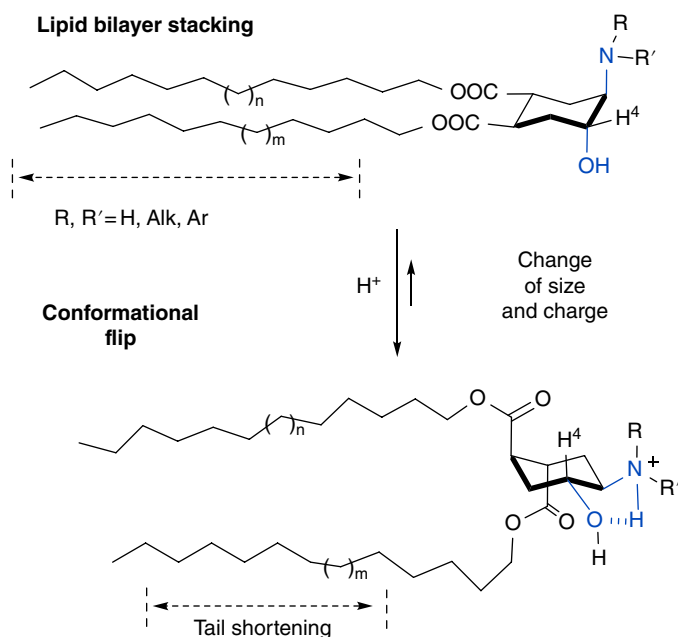


Figure 11.5 A pH-triggered conformational flip in amphiphilic trans-3,4-bis(acyloxy)-1-benzylpiperidines (flipids) increases the separation of hydrocarbon chains.

Due to the prevalence of vicinal diol and aminoalcohol functionalities in biomolecules, the gauche effect is likely to contribute to a variety of biochemical properties and phenomena. Stability of supramolecular structures formed by fats and lipids depends on the energy cost (or lack thereof) of projecting multiple OR groups to the desired direction.

For example, the most common head groups found in biological lipid membranes are phosphorylcholine (PC) and phosphoryl-ethanolamine (PE).⁹ The principal dihedral angle, O-C-C-N, for the two model compounds in vacuum and in bulk water were calculated and compared with experimental NMR estimates. In vacuum, the anti conformation is strongly disfavored with respect to the gauche conformation where strong intramolecular electrostatic interactions are synergistic with the gauche effect. In bulk water, the influence of solvent results in a stabilization of the anti conformation but the gauche conformation still remains more stable (Figure 11.6, +1.5 and +0.02 kcal/mol for the model compounds, PC and PE, respectively).

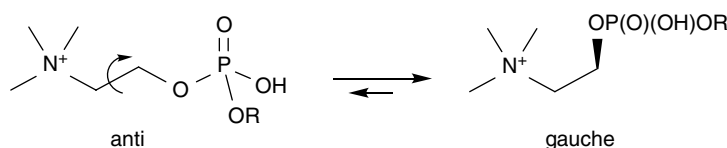


Figure 11.6 Preferred conformation of phosphorylcholine (PC).

Deviations from the all-anti conformations occur even when only one C-X bond is present in a 1,2-disubstituted ethane moiety. For example, solutions of dopamine provide mixtures of *trans* and *gauche* conformers in the protonated forms whereas the isolated molecules prefer the *gauche* conformation.¹⁰ The conformational equilibrium in such species often depends on a number of factors but understanding their interplay is important because the shape of neurotransmitters influences their transport properties and plays a key role in the molecular recognition at the receptor site.

Peptides The gauche effect can also be used to control the conformation of proline residues in peptide chains.¹¹ The relative energies of the *endo* or *exo* ring pucker of the pyrrolidine rings relative to the peptide bonds (Figure 11.7) depend strongly on the presence and position of an acceptor C-X bond. Raines and coworkers found that the *endo* pucker can be enforced by the electron withdrawing substituents in the *trans* isomer (*S* configuration at C(X)), whereas the *exo* pucker is favored by the *cis*-withdrawing substituents (*R* configuration). In both cases, the more stable conformers achieve antiperiplanarity of C-N and C-F σ^* -acceptors with C-H donors and avoid the mutual antiperiplanarity of C-N and C-F bonds.¹²

As typically happens in multifunctional molecules, where multiple interactions are possible, other stereoelectronic effects can clash or cooperate with the gauche effect, either hiding or reinforcing its consequences. In particular, the ring pucker can either enforce or inhibit the through-space $n \rightarrow \pi^*$ interaction between the two carbonyl groups. Such interplay of the two effects was suggested to define the relative stabilities of the *cis* and *trans* conformations of the amide moiety in the substituted prolines (Figure 11.8).^{13,14} The stabilizing through-space $n \rightarrow \pi^*$ interaction only operates in the *trans*-amides, stabilizing them and also inducing chirality by pyramidalizing this usually planar group. The *trans/cis* ratio is important because all of the peptide bonds in triple-helical collagen reside in the *trans* conformation.¹⁵ In the 4*R*-isomers, the *exo* ring pucker places the electronegative substituent on the opposite side of the ring from the carbonyl but in the 4*S*-isomer, the substituent is on the same side, thereby introducing steric interactions in the *trans* amide configuration. While the *trans* is still favored, the $K_{cis/trans}$ is much smaller than analogous *R*-prolines. This modification preorganizes the helical structure, assisting in the overall thermodynamics of protein folding in addition to the hydrophobic and dispersive interactions.

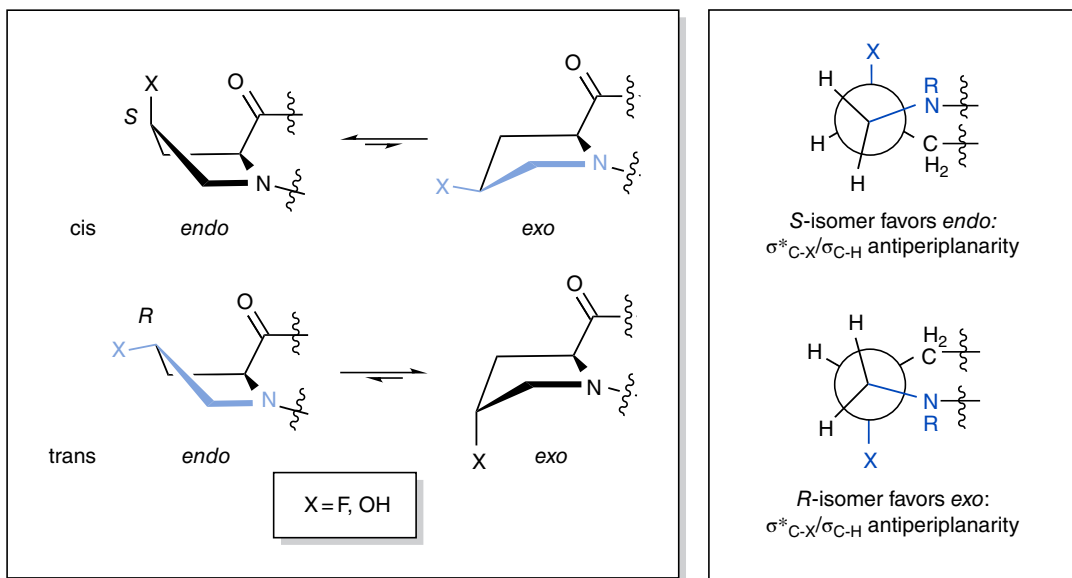


Figure 11.7 Control of proline ring pucker via the gauche effect explains the different shapes of the cis- and trans-substituted rings.

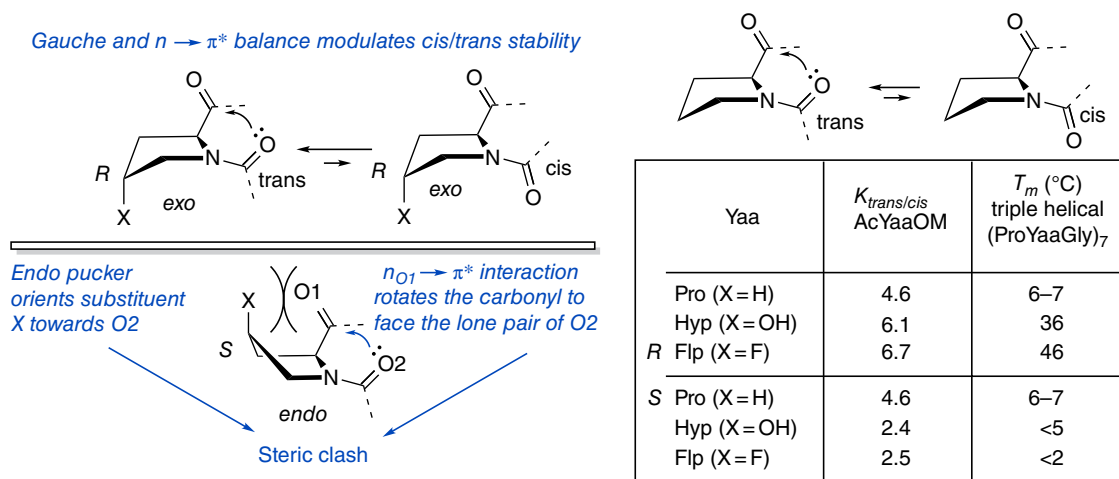


Figure 11.8 Anticooperativity between gauche effect and $n \rightarrow \pi^*$ interaction in the cis (4R) isomer of 4-X-substituted prolines.

Wennemers and coworkers reported that the azido group can be used as a conformation-directing element in 4-azidoproline containing polyprolines (Figure 11.9). In agreement with the above analysis, the polyproline PPII helix is stabilized by (4R)-azidoproline and destabilized by (4S)-azidoproline. Efficient functionalization of such polymers by click chemistry renders azido-containing polyprolines attractive molecular scaffolds.¹⁶

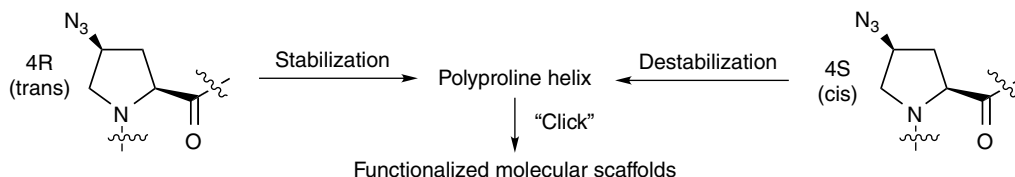


Figure 11.9 Azido group as a conformation-directing element in 4-azidoproline containing polyprolines.

This stereoelectronic approach can be used for the rational design of conformations and stability of proteins where these units are incorporated. For example, the sequence ProHypGly (Gly=glycine, Pro=proline and Hyp=4(*R*)-hydroxyproline) occurs approximately 300 times in collagen's triple helix. The *trans* configuration is required for triple helix formation, thus stabilization relative to *cis* should increase the folded proteins stability. The stability of the helices can be increased by incorporation of Flp (4(*R*)-fluoroproline), which enforces the *trans* conformation.

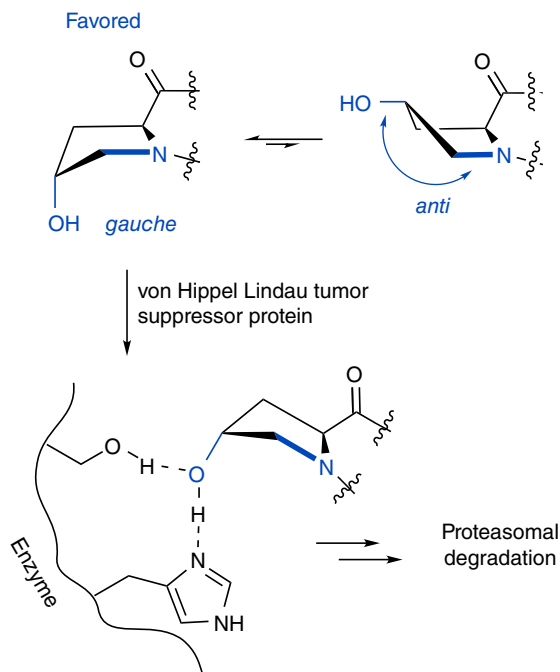


Figure 11.10 Recognition of hydroxylated prolines by prolyl hydroxylases.

The biased pucker of the proline residue significantly influences conformational stability when additional interactions are absent. However, it has been shown that preorganized proline units can also weaken native interactions in certain cases.¹⁷ While most studies have focused on the folding kinetics and stability of the resulting proteins, effects of proline derivatives on protein function (i.e. ligand-binding) have also been investigated.¹⁸

It was shown that hydroxylation of prolyl moieties can mark important proteins for proteasomal degradation.¹⁹ This structural modification, accomplished by prolyl hydroxylase enzymes, induces a conformational bias into the protein 3D-structure that is crucial for protein-protein recognition involved in oxygen sensing/hypoxia response (Figure 11.10).

The azido-gauche effect also manifests itself in the preferred backbone conformation of β -azidoalanine-containing dipeptide and tripeptide²⁰ and was implicated in helical peptide foldamers containing a cyclic amino acid with two azido groups (Figure 11.11).²¹ Of the 25 bis-azido-substituted proline residues analyzed by X-ray crystallographic analysis, 13 N–C–C–N torsion angles showed gauche or synclinal ($-30^\circ \sim -90^\circ$) conformations.

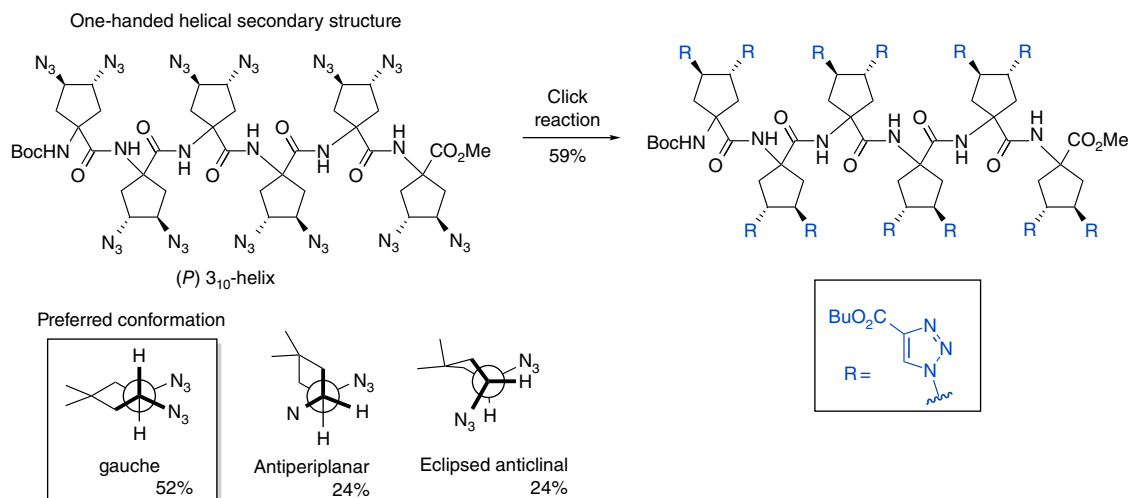


Figure 11.11 Click reactions of azido-substituted helical peptide foldamers.

Carbohydrates The gauche effect also manifests itself in sugars. For example, rotamer populations about the C4–C5 bond in arabinofuranose and its oligomers are also influenced by the gauche effect.²² In respective disaccharides, the relative abundance of gg and gt isomers reaches 80–90% in each of the rings (Figure 11.12).²³ The shape and flexibility of such oligosaccharides were suggested to be important for the packing of mycolic acids that constitute part of the unique cell wall characteristic for *Mycobacterium tuberculosis*.

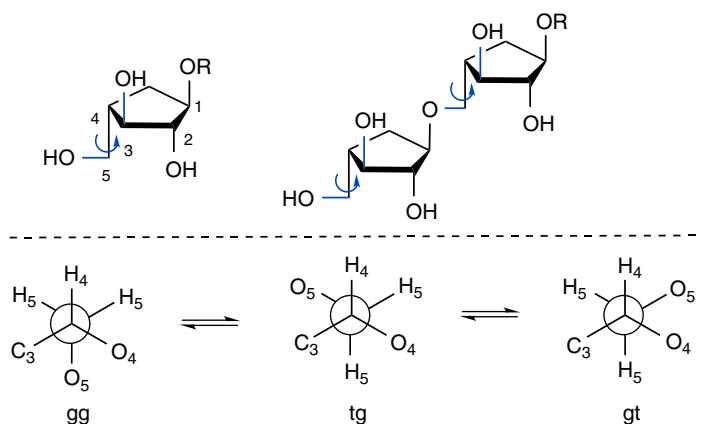


Figure 11.12 Gauche effect in arabinofuranose (g = gauche, t = trans arrangement of large groups). Numbers at the H and O atoms in the bottom part indicated to which carbon atom of arabinofuranose these atoms are connected.

11.2 Trans-effect – the cousin of gauche effect in organometallic chemistry

For the design of organometallic catalytic reactions, one can apply stereoelectronic effects that are specific to the metal centers, such as the trans-effect. An interesting manifestation of this effect in the Rh-catalyzed Claisen rearrangement of propargyl vinyl ethers (Figure 11.13) was found in the computational analysis of this process.²⁴

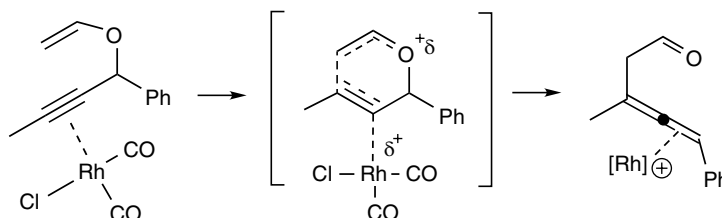


Figure 11.13 Rh-catalyzed Claisen rearrangement of propargyl vinyl ethers.

Both the reactant-complex and the transition states for the “cyclization-mediated” rearrangement pathway were significantly stabilized when the π -acceptor CO ligand was *trans* to the alkyne donor but the transition state is stabilized to a far greater extent (9.0 kcal/mol) than the reactant complex (4.0 kcal/mol, Figure 11.14). This effect increases the electrophilicity of the metal and lowers the activation barrier, providing a catalytically important contribution to transition state stabilization.

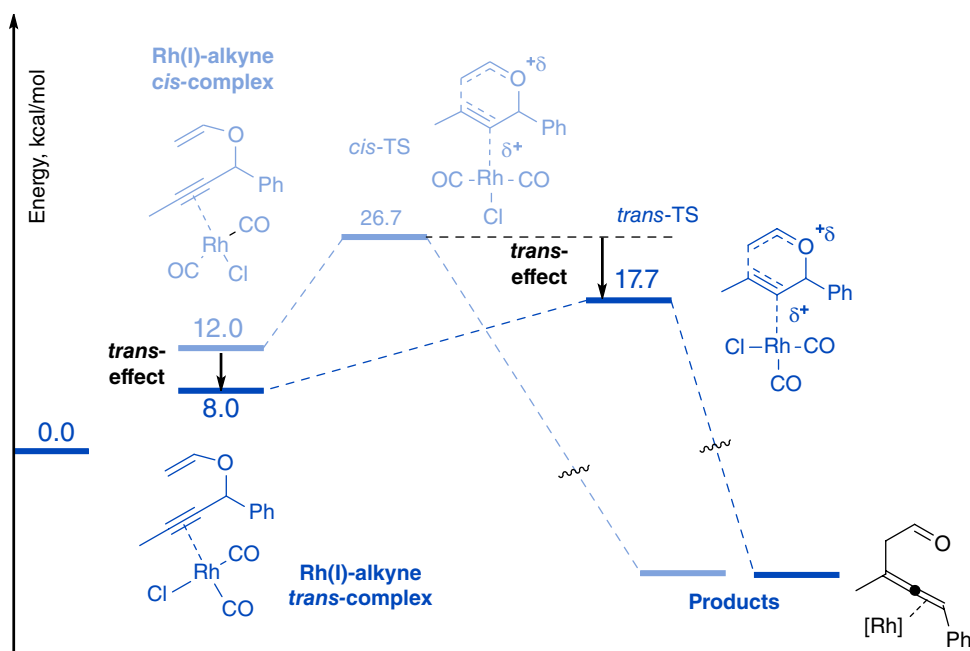


Figure 11.14 Energy profile of the Rh-catalyzed Claisen rearrangement of propargyl vinyl ethers initiated by coordination at the alkyne. Red and gray depict the cis and the trans orientations, respectively, of CO relative to substrate at the Rh center. Energies were calculated relative to the most stable Rh(I)-vinyl ether complex at the M05-2X/LANL2DZ level.

The electronic origin of the observed effect lies in the greater transfer of electron density from the catalytic metal center to the CO ligand oriented *trans* to the alkyne. This change facilitates the process where electron density is transferred from the vinyl ether to the alkyne, allowing the TS to benefit more from the *trans* CO acceptor ligand than the starting alkyne-Rh complex.

The *trans*-effect was also invoked to explain enantioselectivity in the Rh-catalyzed intermolecular hydroacylation (Figure 11.15).²⁵ The preferred *S*-enantiomer formation is consistent with the product-determining ketone insertion step where the ligand cooperatively renders the hydride more nucleophilic and the ketone more electrophilic. This synergy facilitates formation of the *S*-stereoisomer of the product in Figure 11.15. Conversely, the alternative complex is stabilized by the *trans*-effect, and the barrier to migratory insertion is increased as a consequence of this ground state stabilization.

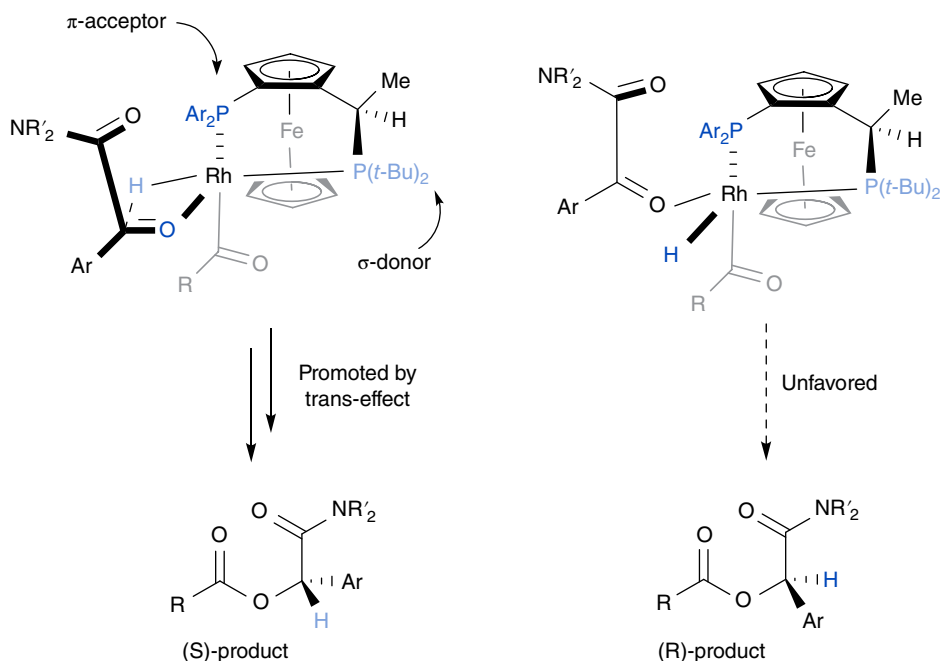


Figure 11.15 Proposed role of *trans*-effect in enantioinduction in Rh(I)-catalyzed cross-coupling of aldehydes and ketoamides.

11.3 Anomeric effects ($n \rightarrow \sigma^*$ interactions)

The anomeric effect provides multiple examples to illustrate the power of $n \rightarrow \sigma^*$ delocalization. As illustrated in Chapter 6, the classic definition of anomeric effect as the axial preference for an acceptor group at the anomeric position can be expanded to a variety of systems that contain lone pairs. Because lone pairs are potent donors, they impose a particularly strong stabilizing effect on processes that create adjacent electron deficiency. Comparison of hydride affinities of methyl and hydroxymethyl carbonium ions illustrates that, in the gas phase, this stabilization (69 kcal/mol) approaches the strength of a covalent bond. It provides greater stabilization than allylic resonance (56 kcal/mol) and hyperconjugation with a methyl group (39 kcal/mol, see Chapter 5 for a detailed discussion). In condensed media, such differences are less dramatic but still significant.

Anomeric effect in carbohydrates Anomeric stabilization is easiest to detect in conformationally well-defined cyclic systems with two polar heteroatoms at the same carbon. Considering the above, it is not surprising that acetals are the central functionality for studies of anomeric effect and that carbohydrates (i.e. cyclic acetals) played the key historic role in the discovery of this effect (Chapter 6). The anomeric effect is particularly important in hydrolysis of acetals, where the oxygen atom is available for providing stabilization to the developing cationic centers (Figure 11.16). The stereoelectronic factors in the acetal reactions reveal multiple ways for modification of the electron-donating ability of an oxygen atom by changing orientation of its lone pairs.

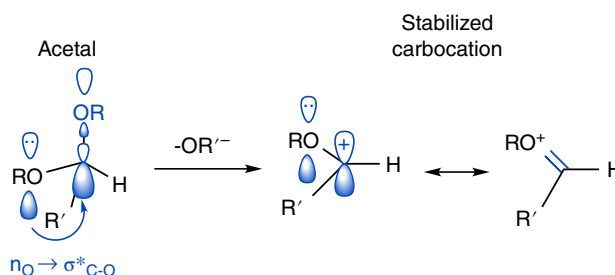


Figure 11.16 Anomeric effect in ionization of acetals.

However, carbohydrates also possess additional polar substituents that combine with the anomeric effect to yield new stereoelectronic patterns. In fact, the chemistry of carbohydrates provides a great testing ground for the design of cooperative stereoelectronic patterns. In Chapter 6, we briefly discussed the competition between gauche and anomeric effects. We will expand our discussion of the interplay between stereoelectronic effects in carbohydrates in the following section.

For a simple system, the situation is straightforward: the axial leaving group at the anomeric carbon is more labile – formation of the oxocarbenium ion via its departure from an α -glycoside is facilitated relative to the analogous departure in the equatorial β -conformer. Due to the principle of microscopic reversibility, the reverse process (i.e. the addition of nucleophiles to the oxocarbenium ion) proceeds through the same transition state and preferentially provides the axial product (i.e. the 1,2-cis glycoside in Figure 11.17).²⁶

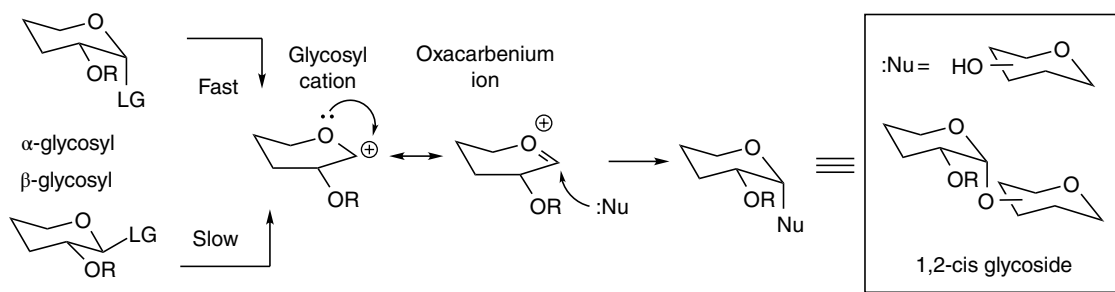


Figure 11.17 Difference in reactivity between α - and β -glycosides in formation of glycosyl cation and reactions with nucleophiles.

A more realistic mechanistic picture involves species with varying degrees of charge separation. For example, reactions of glycosyl donors promoted by TfOH was suggested to involve transient formation of anomeric triflates mediated by the usual interplay between the contact and solvent separated ion pair formation. Due to the strong anomeric assistance, the calculated $\Delta G^\ddagger$ value for breaking the C-O bond is only 10.4 kcal/mol. Ionization of the equatorial leaving group is slower (13.5 kcal/mol, M06-2X activation barrier, Figure 11.18).²⁷

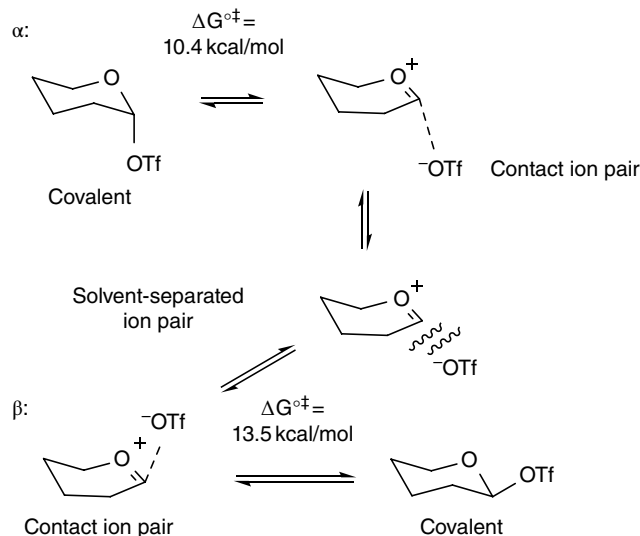


Figure 11.18 The spectrum of intermediates involved in ionization and solvolysis of the two isomers of anomeric triflates.

However, this simple picture can be significantly complicated by structural distortions that are available to flexible molecules, allowing them to reach alternative stereoelectronic arrangements of similar magnitude. Such effects were analyzed in details by Kirby and coworkers who designed several families of bicyclic acetals with the increasingly strict structural constraints. These studies provided a number of interesting insights in the nature of stereoelectronic control of reactivity.

Surprisingly, hydrolysis of a group of tetrahydropyranyl acetals derived from oxadecalin revealed that the non-catalyzed hydrolysis of the axial isomer is actually slower than that of the equatorial isomer by the factor of 3.6. Only under the acid-catalyzed conditions (below pH 4), the axial compound is hydrolyzed more rapidly (the corrected rate factor of 13), as predicted by the stereoelectronic theory.²⁸

It was suggested that, for the slow reaction, the equatorial isomer can react via an alternative conformation that is only slightly higher in energy than the ground state. Because one end of the tetrahydropyran ring is locked by the trans-ring junction, the free end of the chair can still twist to position a lone pair of electrons antiperiplanar to the leaving group (Figure 11.19).

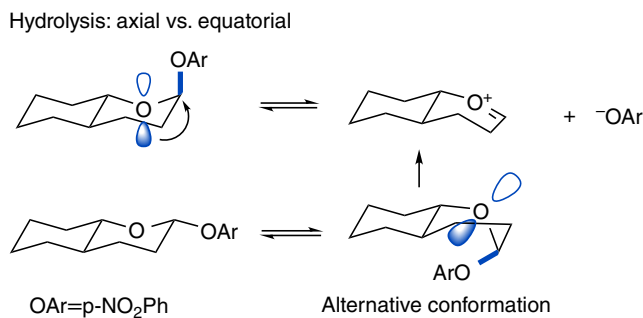


Figure 11.19 Structural distortions allow reaching a stereoelectronically favorable conformation.

However, when the conformation is further constrained, the expected effects do appear.²⁹ If the leaving group is fixed equatorial by the stiffer trans-ring junction, it is hydrolyzed slower relatively to its axial anomer. Although the difference is moderate for the spontaneous hydrolysis (factor of 2), it increases greatly in acid (factor of 60). Interestingly, the non-catalyzed hydrolysis of the axial anomer appears to be slow because of a change in the rate-determining step. The bicyclic molecular structure enforces rapid internal return from the initial product of C-O cleavage (Figure 11.20). Indeed, the solvent deuterium isotope effect indicates that intermolecular hydration of the oxocarbenium ion is slow in comparison with the intramolecular recyclization (via the axial phenoxide attack, which is also a stereoelectronically favorable path according to the macroscopic reversibility principle).

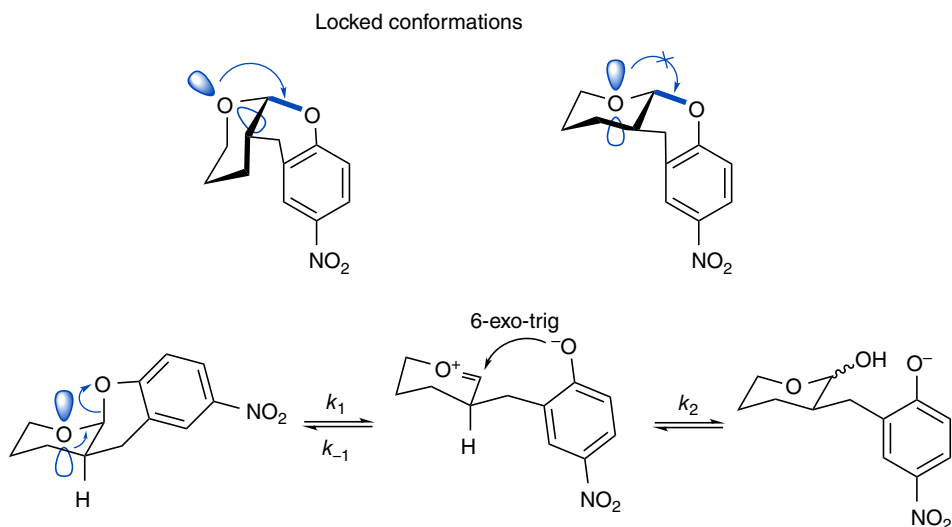


Figure 11.20 Greater rigidity makes structural distortions more difficult but increases the rate of intramolecular recapture of the oxocarbenium cation.

These findings led to the choice of even more rigid acetals. In the derivatives of 9-oxabicyclo[3.3.1]nonane, the bicyclic system enforces the perpendicular geometry where the cation p-orbitals and the oxygen p-lone pair in a putative oxocarbenium ion are nearly orthogonal (Figure 11.21).

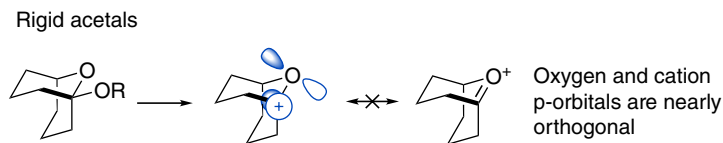


Figure 11.21 Inefficiency of resonance in anti-Bredt oxocarbenium ions.

As a result the lone-pair electrons on the ring oxygen cannot assist C-OR cleavage, and the compound is hydrolyzed ca. 10^{13} times more slowly than a comparable axial tetrahydropyranyl acetal, allowing an estimate of 19 kcal/mol for the stereoelectronic barrier to the cleavage of an equatorial tetrahydropyranyl acetal (a model β -glucoside), in its ground-state chair conformation.³⁰

Variations in reaction conditions and substrate structure may impose additional effects on the reactivity and selectivity. In particular, factors such as ion pair formation, substituent effects, involvement of the boat

conformation, and participation of neighboring groups complicate this picture. As a result, the overall result is often more difficult to predict and interpret in comparison to the examples of radical reactivity described later in this chapter. Such complexity makes reaction design more challenging but it also opens the door to many creative solutions.

11.3.1 Cooperativity and anticooperativity in anomeric systems

Cooperativity/competition among acceptors (armed/disarmed carbohydrates) Cleavage of the C-X bond at the anomeric position proceeds via evolution of the anomeric $n_{\text{O}} \rightarrow \sigma^* \text{C-X}$ interaction that culminates in the oxocarbenium ion. This carbocation is so strongly stabilized by $n_{\text{O}} \rightarrow p^+$ interaction that this interaction is commonly described as a dative π -bond. Because oxocarbenium ions are strongly stabilized, their formation is relatively facile. In cross-coupling glycosylation reactions, however, it is beneficial to differentiate the reactivity of two saccharides for the selectivity reasons. The competition and cooperativity between stereoelectronic effects can be used to fine-tune the reactivity of anomeric systems.

It is well-known that the position of substituents adjacent to the anomeric carbon can affect the conformational equilibrium. For example, the axial hydroxyl group at C(2) in D-mannopyranose increases the contribution of the axial conformer (“ α -anomer”) at the equilibrium in comparison to that in D-glucopyranose (69 vs. 36%, respectively, Figure 11.22). In this case, the β -C-O axial acceptor increases the acceptor ability of the α -C-O group in the anomeric $n_{\text{O}} \rightarrow \sigma^*_{\text{C}\alpha-\text{O}}$ interaction.

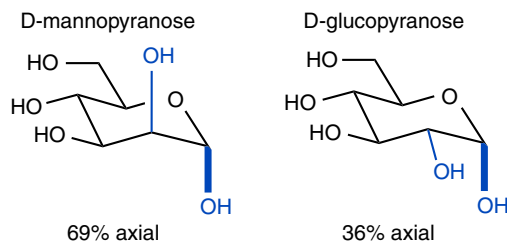


Figure 11.22 Cooperativity among acceptors in the anomeric conformational equilibrium.

An elegant approach to control reactivity in glycosides and related compounds for selective cross-couplings in oligosaccharide synthesis is based on “arming” or “disarming” of the anomeric reactants by the introduction of a σ -acceptor with a tunable acceptor power.³¹ The presence of α -OR substituent adjacent to the cationic center disfavors the oxocarbenium formation. The destabilization imposed on the cationic intermediate by an ester ($\text{R}=\text{COR}$) is much larger than the destabilization imposed by an ether ($\text{R}=\text{alkyl}$, benzyl, Figure 11.23a). The stronger acceptor abilities of the ester group disfavors oxocarbenium formation and “disarms” the sugar.

Fraser-Reid and coworkers applied this concept in the one-pot di- and trisaccharide synthesis shown in Figure 11.23b. They reacted an armed glycoside with a disarmed glycoside (deprotected at one of the hydroxyls) under conditions that promoted the transformation of O-pentenyl protected anomeric position to a cationic center. Because the armed OBn-substrate is considerably more reactive, it can be chemoselectively activated in the presence of the OBz-sugar, leading exclusively to the desired heterocoupling of the two glycosides. Addition of another glycoside and another equivalent of the promoter yielded a trisaccharide with no need for an intermediate purification and deprotection steps.

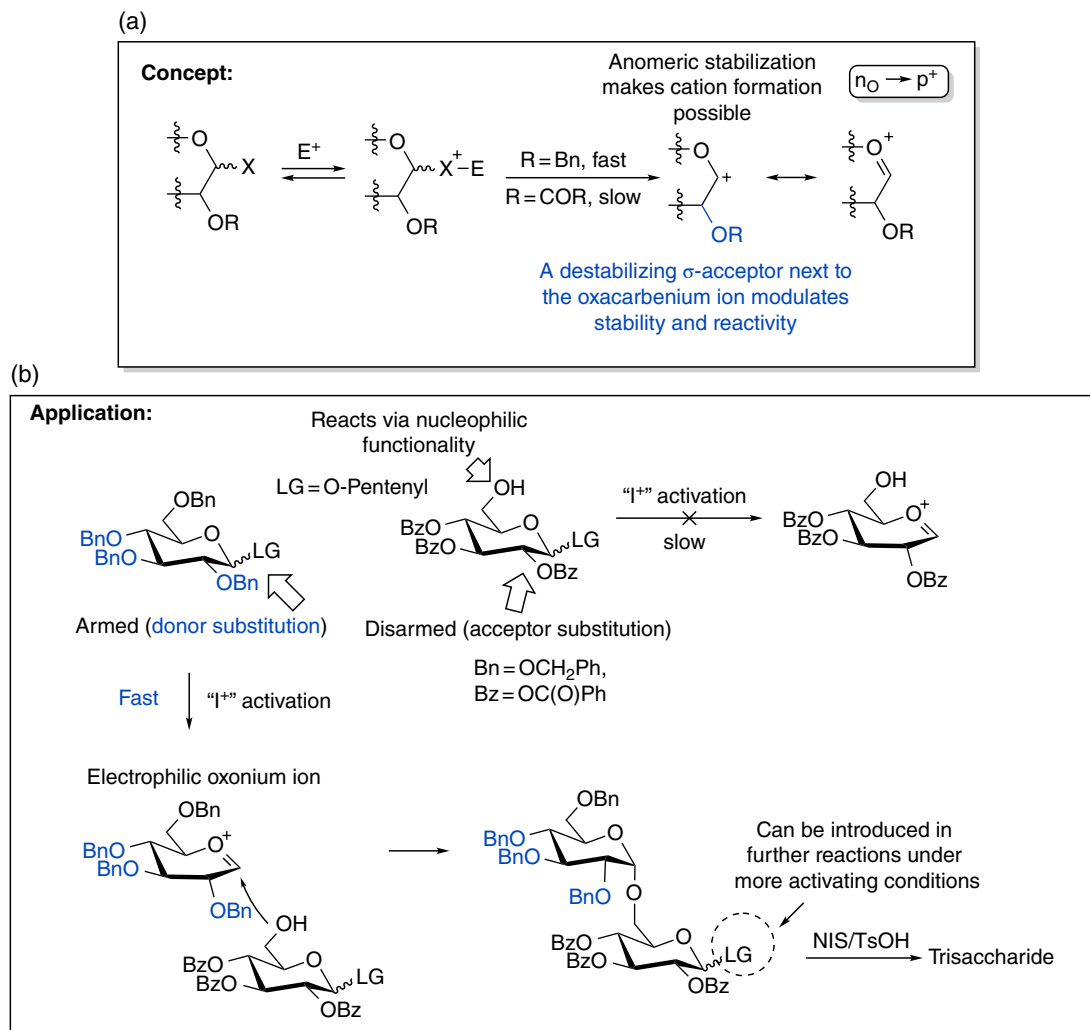


Figure 11.23 (a) Glycosides armed/disarmed by two competing stereoelectronic effects, one stabilizing and one destabilizing the cationic intermediate. The stronger acceptor abilities of the ester substituents slow bond cleavage at the anomeric position. (b) Application of armed/disarmed substrates for selective one-pot synthesis of di- and trisaccharides.

11.3.2 Spectrum of armed and disarmed glycosides

Many other substitution patterns can be used to control the reactivity of anomeric substrates in glycoside synthesis. Such substrates are often, somewhat misleadingly, referred to as “donors”, a term that we will avoid in order to prevent possible confusion, because such compounds are acceptors from the electronic point of view, as the sources of electrophilic cationic species. Considering the variety of choices, substrate reactivity can be viewed as a continuum of tunable reactivity values.³² In a comprehensive study, Wong and coworkers outlined approaches for molecular design that led to reactivity values spanning more than five orders of magnitude (Figure 11.24).³³ The key feature of successful application of this concept is the sequential

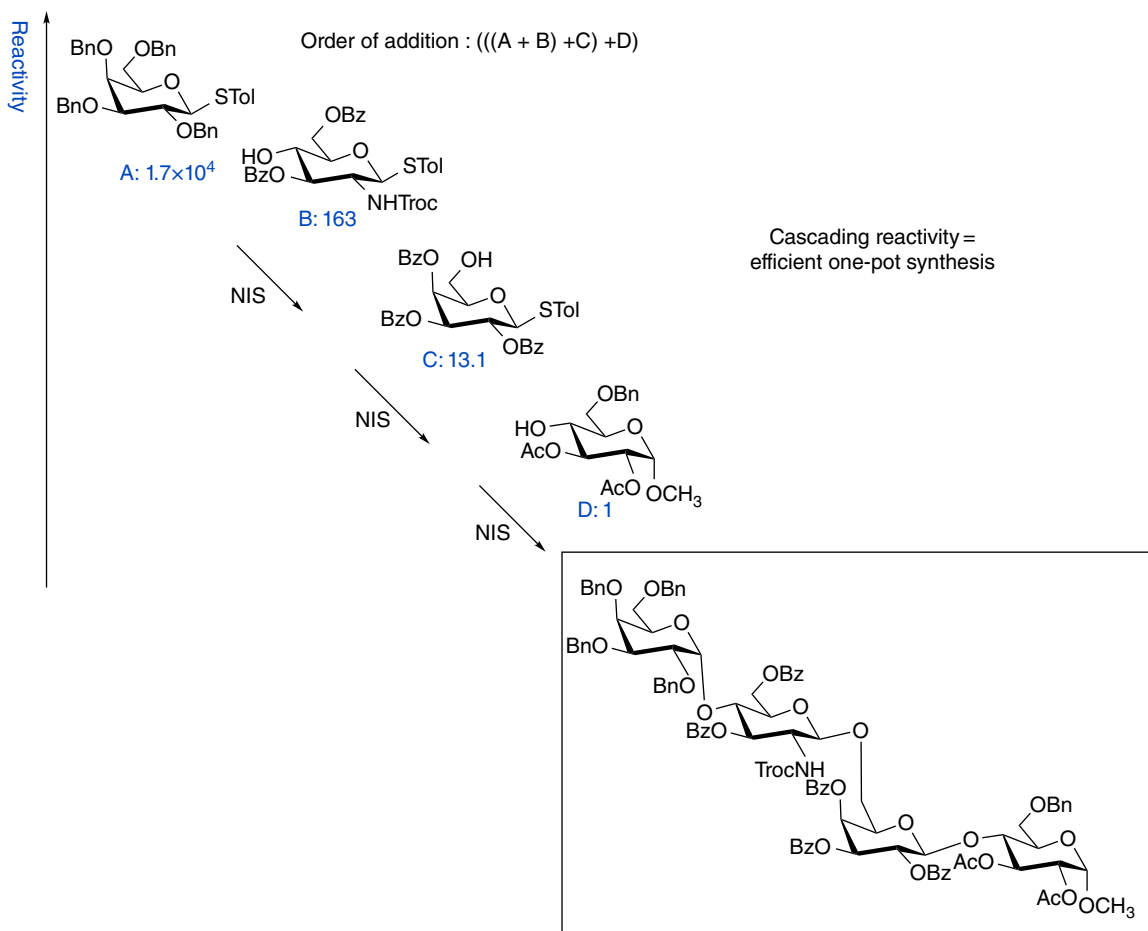


Figure 11.24 Wong's one-pot approach for the preparation of oligosaccharides using sequential addition of descending reactivity. Relative reaction rates are shown in blue.

addition of substrates of decreasing reactivity. Unlike the traditional oligosaccharide synthesis, this approach allows combining multiple coupling steps in a one-pot procedure, which avoids isolation of intermediates and manipulation of protecting groups.

“Super”-armed glycosides In an astute observation that illustrates the power of stereoelectronic thinking, Jensen and Bols used a 0.4 pK_a units difference in the basicity of two similar hydroxylated piperidines as an inspiration for the design of “super”-armed glycosides (Figure 11.25).³⁴ The all-*cis* galacto-isofagomine was found to be more basic than its corresponding *trans-trans* analogue. Considering the importance of double hyperconjugation discussed in the earlier chapters, it is not surprising that an axially oriented σ -acceptor OH group was found to be less electron-withdrawing than its equatorial counterpart.

From the analogy between the cationic structure of the protonated piperidine and the oxacarbenium ion-like transition state in glycoside hydrolysis, one can explain why galactosides were ~ 5 -fold more reactive than glucosides and why the removal of the OH group leads to a further increase in reactivity towards hydrolysis.

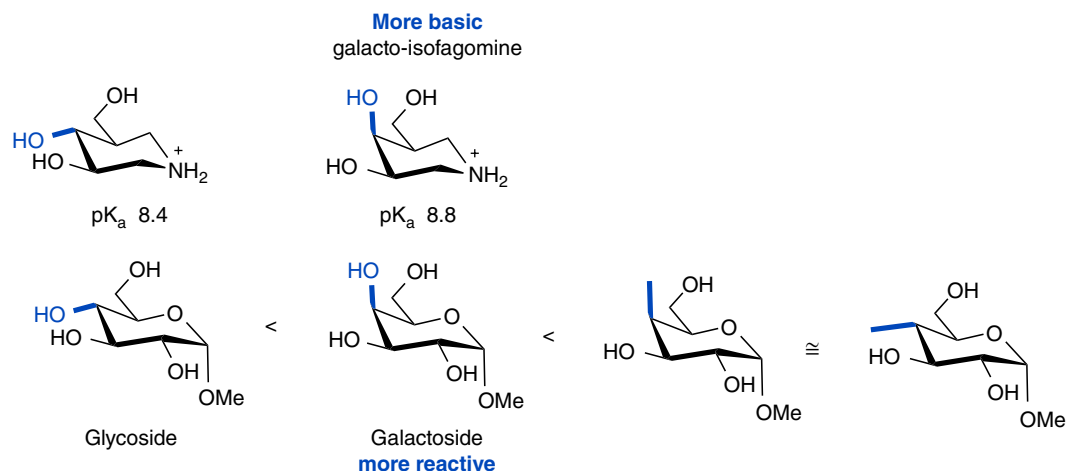


Figure 11.25 Connection between thermodynamics of amine protonation and kinetics of acetal ionization is provided by stereoelectronic concepts.

Furthermore, the orientation of the hydroxyl groups can be controlled by sterically bulky substituents and by additional structural constraints. In both cases, a significant increase in reactivity was observed. For example, the 3,6-anhydrosugar where all normally equatorial hydroxyl substituents are placed in an axial orientation, is >400-fold more reactive than the corresponding non-constrained glycoside (Figure 11.26).³⁵ This combined effect is especially remarkable since the axial OR group vicinal to the leaving group should destabilize the forming oxocarbenium ion (relative to the axial C-H bond in the other conformer).

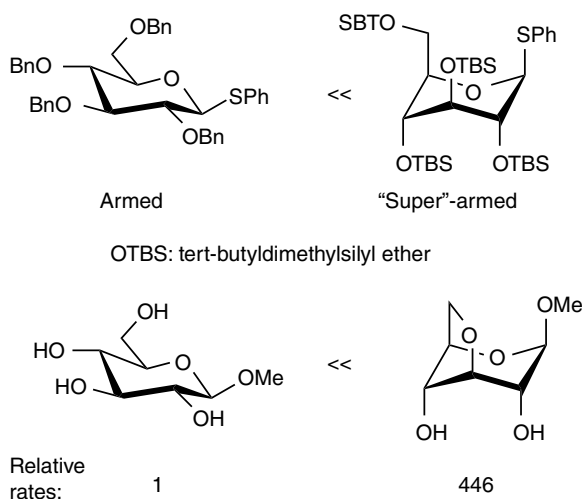
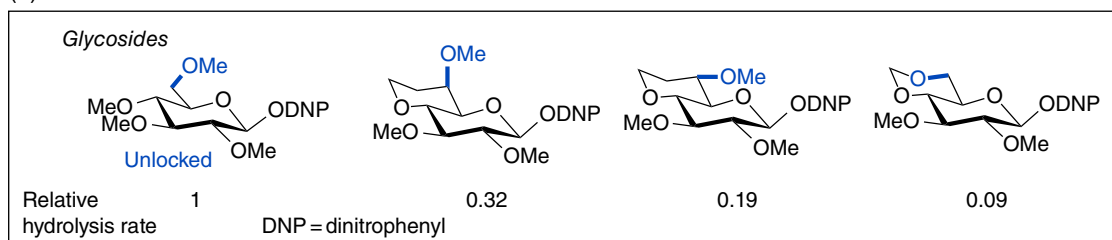


Figure 11.26 Forcing a glycoside into an all-axial conformation by steric or structural constraints dramatically increases reactivity towards hydrolysis (note: the chair conformation of “super”-armed donor is a simplification – steric hindrance leads to considerable distortions).

The destabilization of oxocarbenium ions (“disarming of saccharide”) can also arise from the loss of anomeric stabilization imposed by structural effects in rigid polycyclic structures. Formation of oxocarbenium

(a)



(b)

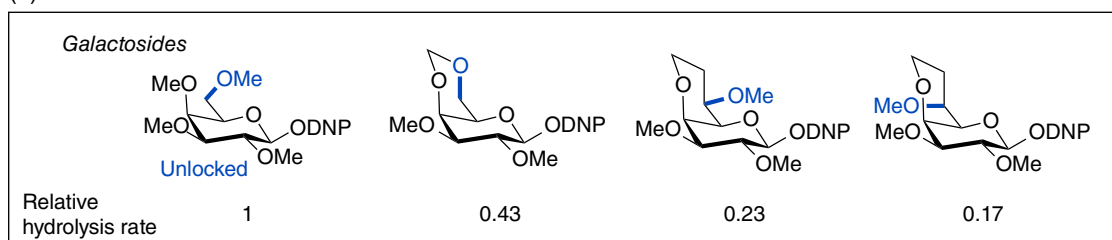


Figure 11.27 Disarming effects by constraining position of a remote C–O bond (shown in blue) in glycosides (a) and galactosides (b).

ion leads to flattening at the anomeric position, a structural deformation that is resisted by rigid cyclic protecting groups in the “disarmed” structure in Figure 11.27.

The disarming effect of a *trans*-fused benzylidene ring was rationalized by Bols as a combination of torsional effects and electronic disarming effects with the latter predominating and arising from the different reactivity of hydroxymethyl rotamers (Figure 11.27a).³⁶ Crich and coworkers expanded this analysis to the galactopyranose series and revealed that the *cis*-fused alkylidene ring system is also disarming (Figure 11.27b).³⁷ The importance of remote electronic interactions is illustrated by deactivation via introduction of the appropriately positioned acceptors. Such effects can be used for selective synthesis of disaccharides. The formation of oxacarbenium ion proceeds much faster from the monocyclic substrate than from the “disarmed” bicyclic substrate.

Cooperativity between donors The effects on reactivity can be amplified when several donors work together. For example, the high reactivity of orthoesters and related compounds (1; X = any leaving group, Y and Z = O or N, Figure 11.28) originates from the stabilization derived by the carbonium ion from the lone pairs of the two heteroatoms. As a result, substitutions at the acetal centers are generally dissociative S_N1 -like processes where the assistance from the solvent and nucleophile participation can be quite small.³⁸ The key stereoelectronic feature of such processes is the increased efficiency of the departing C–X bond cleavage when the lone pairs of the remaining heteroatoms Y and Z reach antiperiplanarity to the leaving group X. Such compounds can be readily ionized and the resulting cations are sufficiently stable to be studied by X-ray crystallography.

The high reactivity of orthoesters can be used for initiation of cationic reactions under relatively mild conditions.³⁹ Acid hydrolysis of *myo*-inositol 1,3,5-orthoformates proceeded within 15 min in 10:1 mixture of TFA:water at room temperature. The resulting bridged ions can be trapped in a variety of inter- and intramolecular reactions (Figure 11.29).

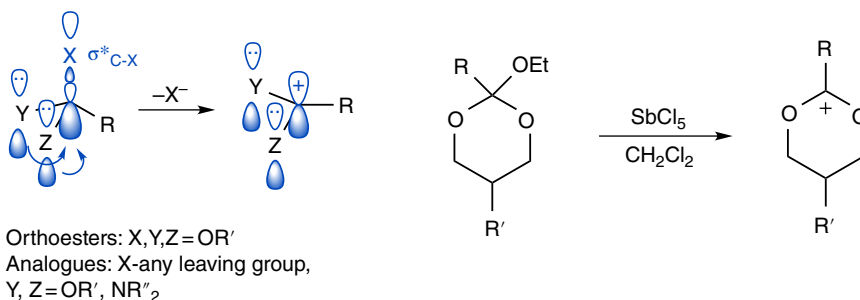


Figure 11.28 Cooperative anomeric assistance to ionization of orthoesters and related compounds.

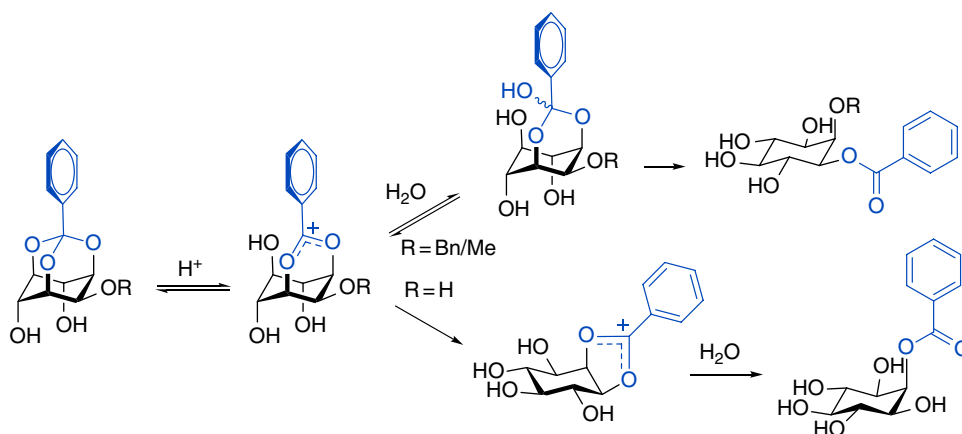


Figure 11.29 Combining mild generation of cationic intermediates from orthoesters with inter- and intramolecular trapping.

Stereoelectronic factors clearly play a role in this increased reactivity. For example, Eliel and Nader reported that orthoesters in the conformationally constrained 1,3-dioxane systems show a striking preference for cleavage of an axial exocyclic C-O bond compared to an equatorial C-O bond (Figure 11.30).⁴⁰ Whereas the axial 2-methoxy-1,3-dioxane reacts smoothly with Grignard reagents to give the corresponding axially substituted 2-alkyl-1,3-dioxane, the equatorial isomer is unreactive under these conditions. In order to explain the difference in reactivity and the observed retention of configuration, it was suggested that both the C-O bond scission and C-R bond formation are assisted by their antiperiplanarity to lone-pair orbitals on the ring oxygens.

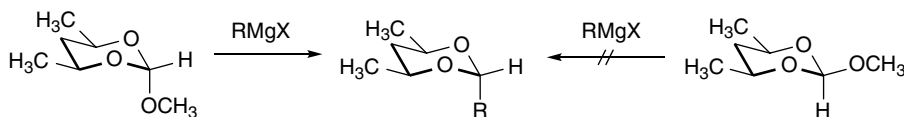


Figure 11.30 Contrasting reactivity of axial and equatorial 1,3-dioxane-based orthoesters.

The stereoelectronic factors in acetals can be modified by changing the relative orientation of the p-type lone pairs of the two oxygens. In an illustrative example, Deslongchamps and Li reported that out of the two epimeric cyclic acetals shown in Figure 11.31 only the one with an axial 2-H is oxidized by ozone

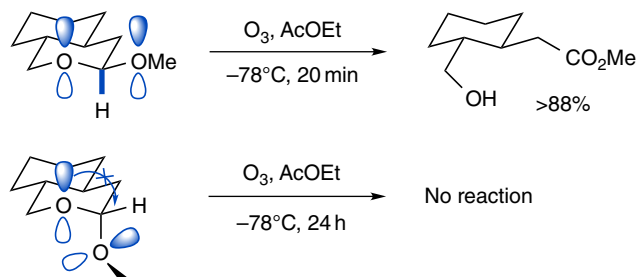


Figure 11.31 Cooperativity among donors in reactions at the anomeric position.

(Figure 11.31).⁴¹ Note that in this case, lone pairs from both oxygen atoms can assist in the axial C-H bond oxidation. For the second reaction, only the exocyclic oxygen can align its p-type lone pair with the C-H bond. A more detailed analysis of such effects is available in the classic book of Deslongchamps⁴² and a more recent review.⁴³

11.3.3 Restoring exo-anomeric effect in carbasugars

Modifications of the sugar moiety via the replacement of one of the acetal oxygen atoms by a carbon is a valuable way to produce sugar mimics that can fool cellular receptors and be used for the design of carbohydrate-based drugs. However, the conformational behavior of such molecules changes as the result of the O → C replacement. In particular, more flexibility is observed in the interglycosidic linkage due to removal of the exo-anomeric effect (Figure 11.32). Such a change can be detrimental for the binding of such designed molecules to the target proteins due to the entropic penalty it induces.

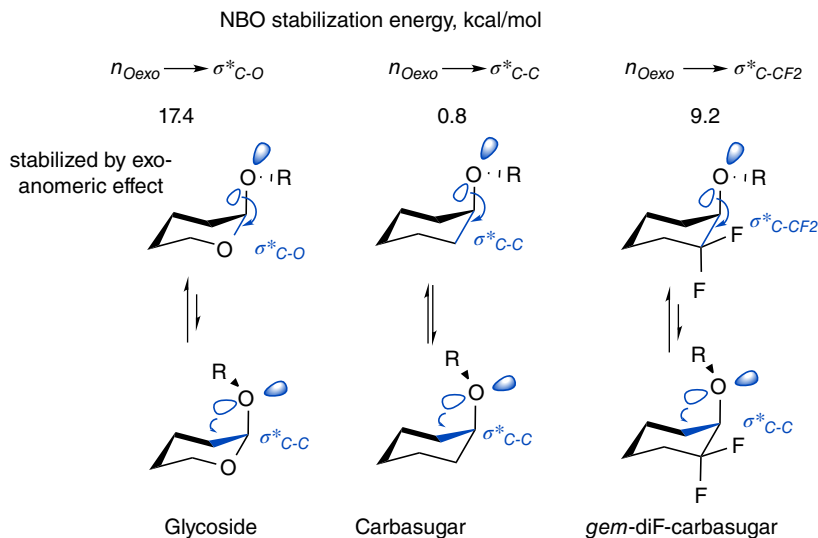


Figure 11.32 Restoring exo-anomeric effect in carbasugars.

Using the stereoelectronic component of the exo-anomeric effect as the inspiration for structural design, a family of carbosugars was developed where the anomeric effect was restored by replacing the endocyclic oxygen atoms with a stronger σ -acceptor moiety, such as a CF_2 group (Figure 11.32).⁴⁴ Additional polarization of the C-C bond induced by this group provides the needed stereoelectronic bias that restores the exo-anomeric effect, which has been mostly abolished in the simple carbosugar analogues of maltose.

The vinylogous anomeric effect (VAE) can also display itself in reactivity. For example, VAE is the key stereoelectronic interaction in the Ferrier rearrangement (also called Ferrier I reaction, Figure 11.33).⁴⁵ This reaction transforms glycols into 2,3-unsaturated glycosyl derivatives in a process that can be described as a nucleophilic substitution with allylic rearrangement. The reaction is greatly facilitated when the leaving group adopts the pseudoaxial position where it is aligned with the endocyclic oxygen lone pair via the π -system.

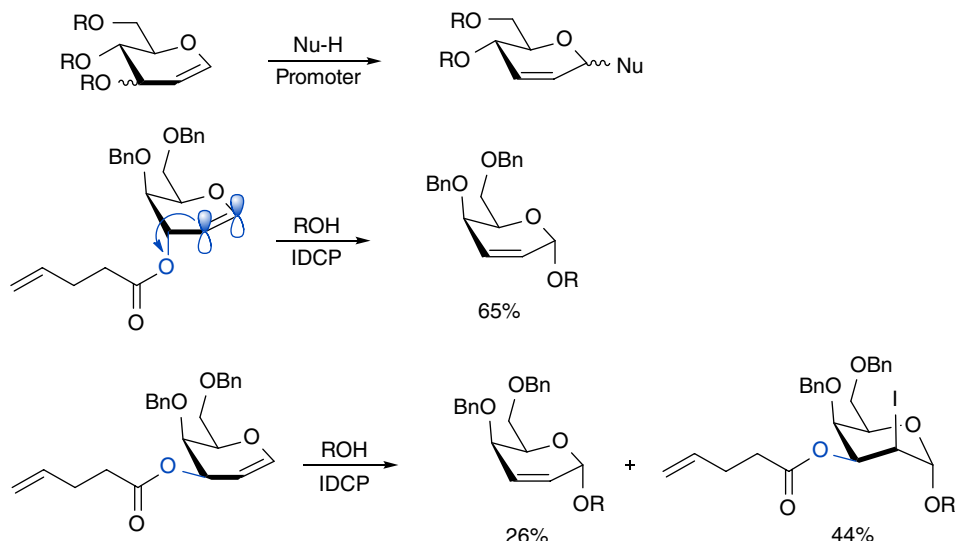


Figure 11.33 Effect of the configuration at the allylic center on the iodonium-catalyzed Ferrier rearrangement (IDCP=iodonium dicollidinium perchlorate).

The VAE has also been used to generate nitrosoalkenes from α -chloro ketoximes⁴⁶ and to accelerate Claisen rearrangements of appropriately substituted substrates.⁴⁷ An interesting example of the remote effect on reactivity was found in the epoxidation of 4-deoxypentenosides (4-DPs) by dimethyldioxirane (DMDO) where competing directing effects can be imposed by the anomeric and allylic substituents.⁴⁸

Vinylogous armed/disarmed systems Glycols can be armed and disarmed analogously to glycosides (see the earlier sections). Just as the formation of an oxacarbenium ion is disfavored for esters relative to ethers in glycosides, the same trend is observed for halonium formation at the double bond of glycols (Figure 11.34).

Anomeric reactivity in radical reactions Effects are strongest for the formation of cationic centers but they are also significant for bonds stretching and breaking, including homolytic cleavage that leads to the formation of radicals next to the lone pair. As discussed earlier, stretched bonds are relatively strong acceptors (Chapter 9) and radicals form 2c,3e-bonds with adjacent lone pairs (Chapter 3).

The anomeric weakening of C-H bonds by hyperconjugation significantly increases the rate of homolytic C-H bond cleavage in cyclic ethers (a good reason for not distilling old THF samples to dryness!). For example, Malatesta and Ingold reported that the tetrahydrofuran (THF) oxygen makes adjacent hydrogens ~2860 times as reactive as the hydrogens in cyclopentane towards *t*-butoxy radicals at -60°C .⁴⁹ The effects are clearly stereoelectronic and occur only upon the proper alignment of the breaking C-H bond with the p-type lone pair of the activating oxygen. For example, no radical formation was detected from oxanobornane whose two C-H bonds are orthogonal to the oxygen p-type lone pair ($\theta=90^\circ$). Another interesting example, the dioxo [3.2.1] bicyclooctane, only gave the radical formed by abstraction of H_a , ($\theta=30^\circ$) with no trace of the radicals which

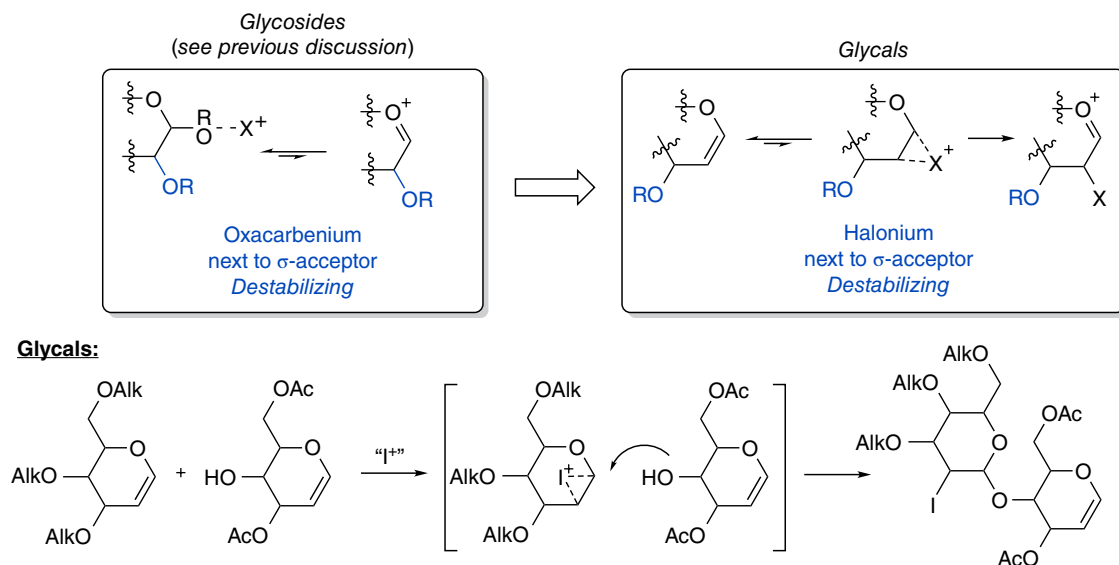
Arming/Disarming Sugar Reactivity

Figure 11.34 Vinylogous “arming” and “disarming” of glycals through a double bond.

would be formed by loss of H_b ($\theta=70^\circ$) or loss of H_c , though the latter has two neighboring oxygens ($\theta=50^\circ$ and 70°) (Figure 11.35a).

In parallel, Beckwith and Easton reported stereoelectronic preferences for H-atom abstraction in 1,3-dioxanes (Figure 11.35b).⁵⁰ As expected, the compound with three lone pairs aligned with the target C-H is the most reactive. The difference in reactivity, however, is less pronounced than in the previous example.

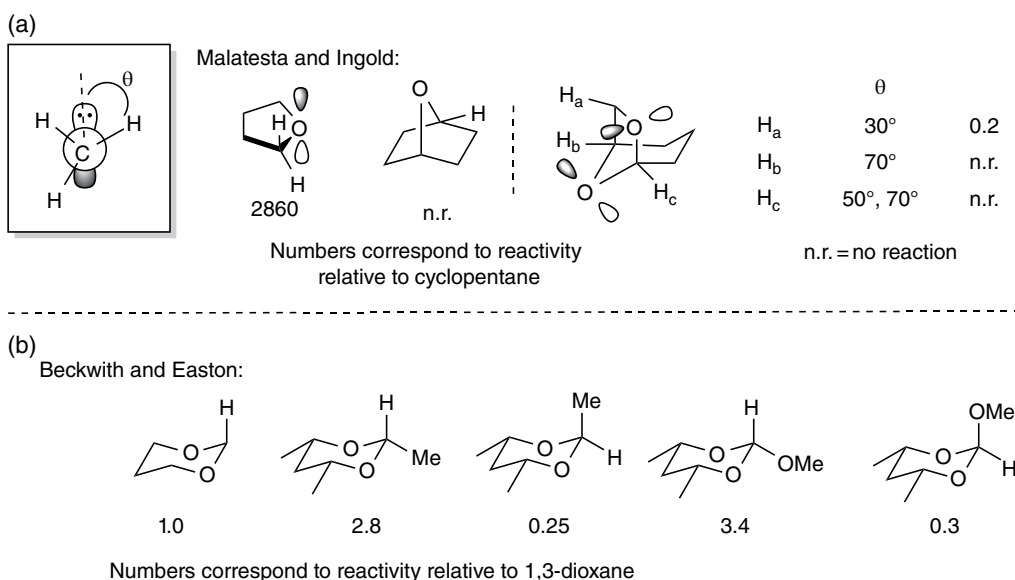


Figure 11.35 Selected stereoelectronic effects on H-atom abstraction by *t*-BuO radical.

Carbene C-H insertion reactions Lee and coworkers described an array of intriguing stereoelectronic effects involved in the insertion of alkylidene carbenes into C-H bonds (Figure 11.36).⁵¹ This transformation, which is a useful tool for constructing quaternary carbon centers, has been known to proceed faster when an oxygen atom is adjacent to the reacting C-H bond.⁵² The authors examined how the cyclic nature of for the C-H insertion transition state changes stereoelectronic assistance when the activating oxygen atoms are placed inside (endo) and outside (exo) of the forming cycle. Furthermore, the reaction of the respective acetal was used to shed light on the possible cooperativity between the endo- and exocyclic oxygen atoms.

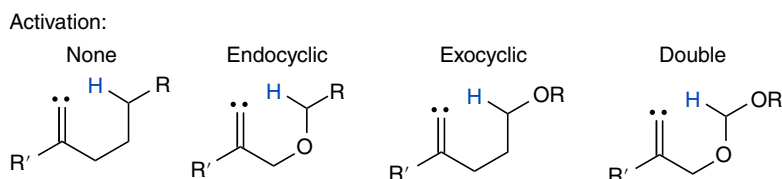


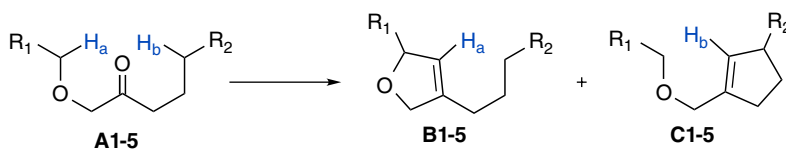
Figure 11.36 Possible activation modes for the insertion of alkylidene carbenes into C-H bonds adjacent to an oxygen atom.

The observed selectivity did not always reflect the intrinsic bond strength. Instead, it revealed an interesting response to structural effects (Figure 11.37). For example, even though the insertion reactions of substrates with an endocyclic oxygen occurred exclusively at the C-H_a bonds adjacent to the oxygen atom, the selectivity eroded in the presence of the exocyclic oxygen (a 10:1 ratio of products, 96%). Not only was the less pronounced effect of the exocyclic oxygen intriguing, but the “doubly activated” substrate with both endo- and exocyclic oxygen substituents also provided a 10:1 ratio of the two product in a slightly lower 86% yield. This result suggested that only one of the oxygens plays an activating role for the C-H insertion.

Substrates	Products	Yield
		90%
		74%
		96%
		86%

Figure 11.37 The observed selectivity of C-H insertion reactions revealed the differences in the activating ability of endo- and exocyclic oxygen atoms.

Direct competition between endo- and exocyclic oxygens showed the same trend – insertion next to the endocyclic oxygen was favored by a factor of 2. Furthermore, when substitution at the exo oxygen was kept constant (OBn) while the endo oxygen substituent was varied, the selectivity was further perturbed by the other delocalizing interactions to a different extent (Figure 11.38). The deactivating effect of the exo oxygen substituent (a methoxy group) in the acetal fragment was particularly surprising.



Compound	R ₁	R ₂	Yield(B+C)	Ratio B:C
1	MeO		86%	10:1
2		OBn	96%	2:1
3		OBn	89%	1.5:1
4		OBn	82%	0.7:1
5	MeO	OBn	80%	0.5:1

Figure 11.38 Effect of additional delocalizing substituents on regioselectivity of C-H insertion.

The exact origins for the inefficiency of the exocyclic oxygen are still unknown. However, from selectivities observed in the presence of steric and structural constraints, it was clear that the activating effect of the endocyclic oxygen is stereoelectronic in nature. Only the axial C-H bond aligned with the p-type lone pair of endocyclic oxygen was activated whereas the equatorial C-H bond was deactivated relative to the analogously positioned C-H bonds in the oxygen-free regions of the molecules (Figure 11.39).

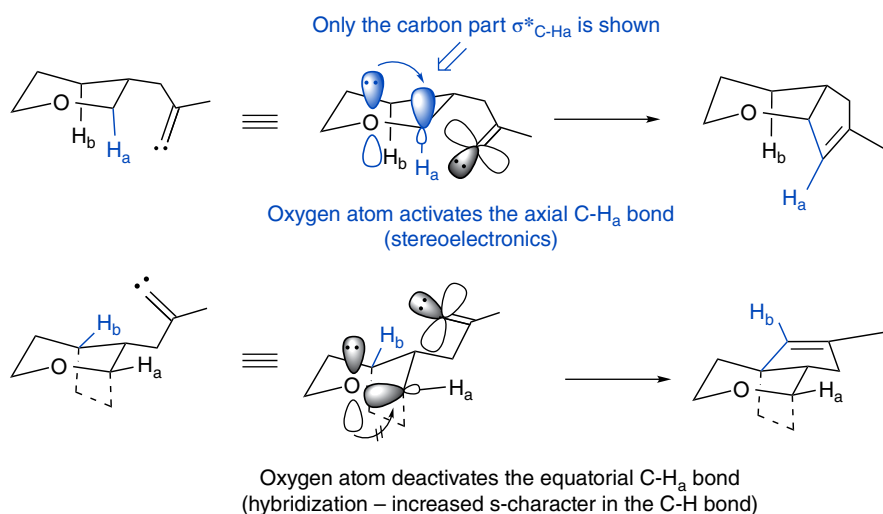


Figure 11.39 In the cyclic substrates, the axial C-H bonds are activated stereoelectronically by an adjacent oxygen atom. The analogous equatorial C-H bonds are deactivated via a rehybridization effect. Only the carbon part of the targeted $\sigma^*_{\text{C-H}}$ orbital is shown for clarity.

Furthermore, the observed reactivity trends illustrated the interplay of anomeric effect with two other electronic factors described earlier in this book. In particular, the loss of activation associated with the poor lone pair/C-H overlap in the bicyclic system is an example of Bredt's rule (restriction on π -overlap at the bridgehead position) whereas the additional deactivation of H_a is a consequence of Bent's rule. Because the bridgehead carbon directs a hybrid orbital with increased p-character towards the adjacent oxygen, it leaves more s-character for the bond with the hydrogen, thus increasing the C-Ha bond dissociation energy.

Such effects are likely to be general. For example, rhodium-catalyzed intramolecular C-H insertion with diazo compounds, which are tethered by alkoxyamines, afforded either 1,5- ($Z=CH_2$) or the unusual 1,7-insertion products ($Z=O$, Figure 11.40).⁵³

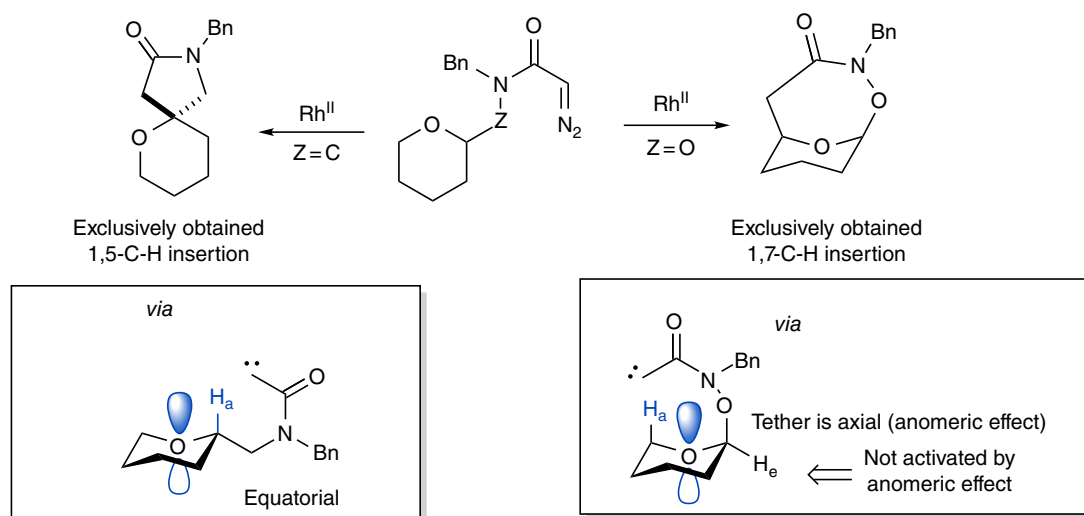


Figure 11.40 Two roles for anomeric effect in rhodium-catalyzed intramolecular C-H insertion: control of conformation of the reactant and activation of the target C-H bond.

When the carbene “warhead” is connected to the cyclohexane ring via a carbon atom, the tethered carbene precursor occupies the equatorial position, forcing the axial C-H bond to the activated anomeric position (Figure 11.40, left). Of the two axial C-H bonds, the one closest to the pendant carbene is attacked. On the other hand, when the tether starts with an oxygen atom, the anomeric $n_o \rightarrow \sigma^*_{C-O}$ interaction comes into play, forcing the carbene-bearing functionality to the axial position. This structural change has two consequences for the observed reactivity. First, it deactivates the C-H at the point of attachment, thus preventing the formation of spiro-product of 1,5-insertion. Second, it places the carbene moiety in the direct vicinity of the remote axial C-H bond, allowing the unusual 1,7-functionalization. Note that the other axial C-H bond, which is not activated by the anomeric effect, remains unreactive.

It is important to note that these reactions proceed with retention of the configuration, as shown by Wardrop for the insertion of alkylidenes at the anomeric C-H bond of carbohydrates (Figure 11.41).⁵⁴

Deactivating nucleophiles Anomeric effect shows how to activate electrophiles. The opposite side of $n \rightarrow \sigma^*$ hyperconjugation is that it can decrease donor ability of the lone pair and deactivate the nucleophile. For example, the reactivity of cyclic phosphites where the lone pair of phosphorus is aligned with the acceptor O-C bonds is drastically decreased in comparison with triethyl phosphite.⁵⁵ The bicyclic phosphite was also found to be less donating than PMe_3 , PPh_3 , and $P(OMe)_3$ in $Ru(II)$ complexes (Figure 11.42).⁵⁶

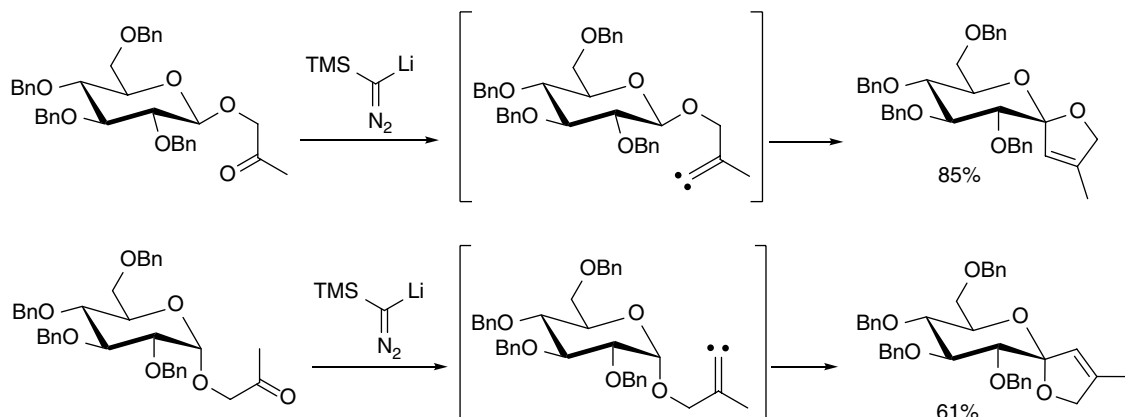


Figure 11.41 Retention of the configuration for insertion of alkylidenes at the anomeric C-H bonds.

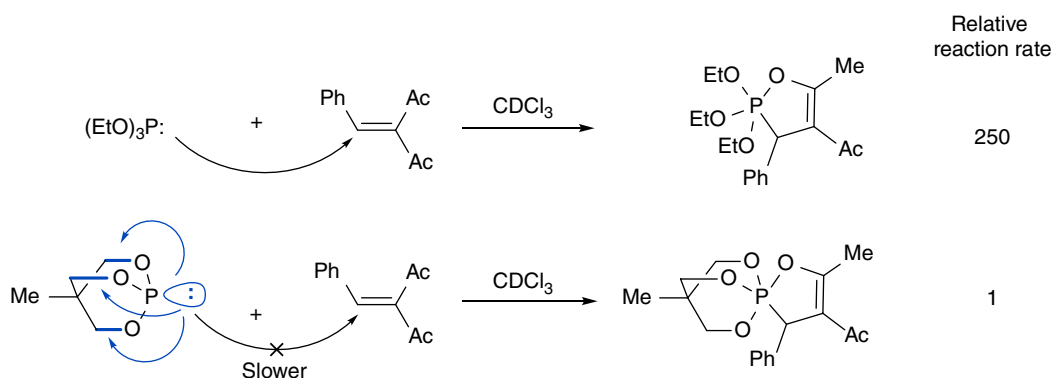


Figure 11.42 Decreased nucleophilicity of phosphites with antiperiplanar arrangements of phosphorus lone pair and $\sigma^*_{\text{O-C}}$ orbitals.

Anomeric and “double anomeric” effects in phosphates The unusual stereoelectronic properties of negatively charged oxygen as a source of donor orbitals play a role in the formation of tetrahedral intermediates in nucleophilic addition/substitution at carbonyl. It also has important consequences for phosphate transfer reactions – one of the key types of chemical events in biology.

Although phosphate is a familiar structural and functional unit of chemistry and biology, its hidden secrets and paradoxes explain why discussions of “why nature chose phosphate”⁵⁷ still continue. The diversity of features and reactivity patterns is remarkable for such a seemingly simple combination of atoms. For example, phosphate diesters are the most stable biology building blocks that won the evolutionary competition as the links that safely keep the units of genetic information together. At the same time, they can be readily hydrolyzed in the presence of a suitable enzyme catalyst while phosphate “dimer and trimer” constitute the high-energy bonds in adenosine diphosphate (ADP) and adenosine triphosphate (ATP). Some of these properties result from the relatively high acidity of the PO-H bonds that allows ionization and significant charge accumulation in phosphates and oligophosphates. This charge can provide an electrostatic shield against negatively charged nucleophiles. However, there is increasing evidence that orbital interactions play many roles in phosphate reactivity as well.

We refer the reader to the recent perspective by Kirby and Nome for an educational and insightful analysis of the surprisingly rich reactivity patterns in phosphates.⁵⁸ We will highlight only a small selection of these features below, after summarizing the key mechanistic features of phosphate hydrolysis.

Reactions of phosphate triesters and phosphate diester anions proceed via different mechanisms (Figure 11.43). Whereas the triesters can react through a stepwise mechanism with the formation of a penta-coordinated intermediate (similar to the tetrahedral intermediates from the chemistry of carboxylic acid derivatives), such species are disfavored for diester anions and monoester dianions.

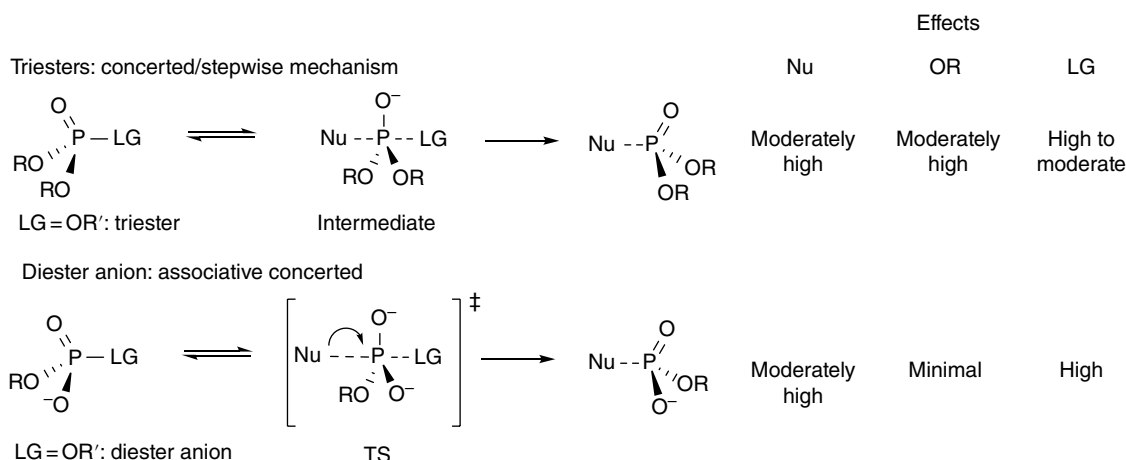


Figure 11.43 Selected mechanistic features for hydrolysis of phosphate triesters and diester anions.

As expected, both the nucleophile and the leaving group nature have a strong effect on these reactions – the substitutions proceeds faster with the stronger nucleophiles and the better leaving groups. Even though peculiarities exist – e.g. nucleophilic anions react fast with neutral triesters whereas neutral amines are more reactive toward diester anions – the latter correlations are not overall surprising.

However, not everything is straightforward. For example, it may not be immediately obvious why the non-leaving groups at the P atom would also strongly affect hydrolysis of triesters. Both experimental and computational data suggest that an increase in the electron-withdrawing ability of the “spectator” groups can accelerate the reaction by many orders of magnitude (Figure 11.44). For example, change from Me to CH₂CF₃ decreases experimental free energy of activation by ~5 kcal/mol.⁵⁹

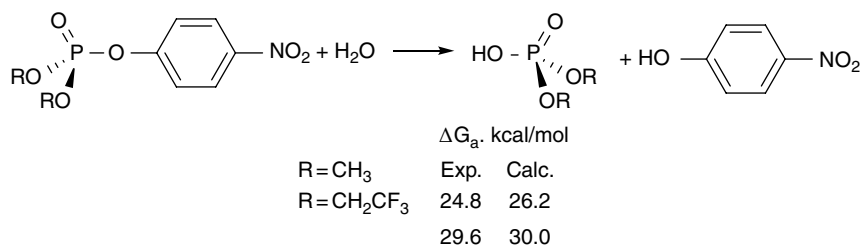


Figure 11.44 Comparison of the rates of spontaneous hydrolysis of 4-nitrophenyl dialkyl triesters with the alkyl groups of different acceptor ability.

According to computational analysis, electron-accepting non-leaving groups stabilize both the activated complex and the pentacovalent intermediate. Furthermore, the lower reactivity of the diester anions in relation to the triesters readily follows from this dependence if the negatively charged oxygen of the diester anion is recognized as a powerful electron donor substituent. Indeed, the point for the hydrolysis of the related bis-4-nitrophenyl diester (BPNPP) falls on the extrapolated line when the pK_{NLG} for the P-O⁻ oxygen is used (Figure 11.45).

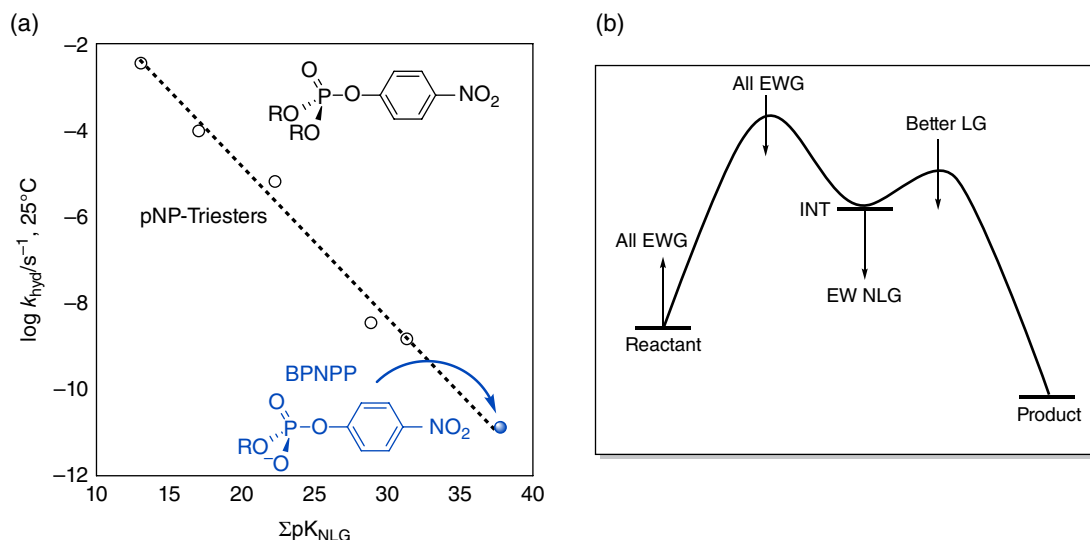


Figure 11.45 (a) dependence of the rates of spontaneous hydrolysis of 4-nitrophenyl triesters and one diester on the sum of the pK_a 's of the non-leaving groups ROH. (b) Effects of leaving group capability on the energy surface for the reaction of phosphate triesters with nucleophiles according to Kirby and Nome.⁵⁸

This is a fascinating finding because it indicates that the stability of phosphate diester linkers in DNA towards hydrolysis is derived to a considerable degree from the deactivating effect of the P-O⁻ substituent. It well-known, of course, that the electrostatic effect of the negatively charged substitution plays a role in protecting oligophosphates from anionic nucleophiles. However, the electrostatic protection should be relatively inefficient against non-charged nucleophiles such as water, amines, and thiols. As the result, the very existence of reliable genetic code that can be passed to the next generations relies on the deactivating effect of a bystander group on the reactivity of phosphates.

So, where does all of this mechanistic richness come from? In the following discussion, we will outline the key stereoelectronic features of phosphate substitution reactions and illustrate how the unique features of anionic oxygen and pyramidal intermediates/transition states explain the abovementioned idiosyncrasies of this functional group and combine to make the key reactions of biology possible.

We have discussed stereoelectronics of oxygen in detail in this book but we have not extended this analysis to anionic oxygen. It is time now to correct this omission. Phosphate OH groups are acidic and ionized under the biological conditions to form O-centered anions. Furthermore, even the neutral “P=O” moiety of triesters can be better described as a P⁺O⁻ group. In contrast to the neutral divalent oxygen which has only one p-type lone pair (along with a sp^3 hybrid), the alkoxide group RO⁻ has the two stereochemically important p-type lone pairs on oxygen. Both of the p-type lone pairs can interact with the suitably positioned s-acceptors, potentially creating the possibility of *two mutually orthogonal anomeric interactions* (Figure 11.46). The two effects can play different roles, and indeed they do. A number of interesting features of phosphate chemistry stem from this “double anomeric effect”.

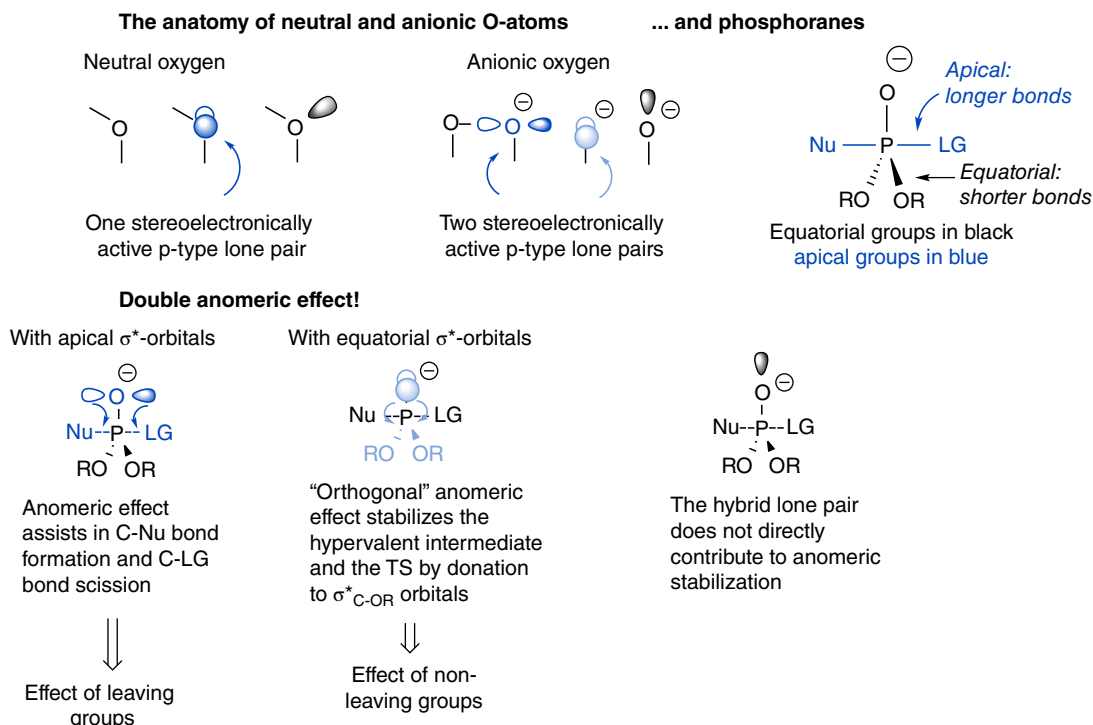


Figure 11.46 Two anomeric effects cooperate in hydrolysis of phosphate triesters.

In particular, the combination of two anomeric effects readily explains the above effect of non-leaving groups on the hydrolysis of phosphate triesters. The nucleophilic attack leads to the development of negative charge at the phosphoryl oxygen increasing the donor potency of both of its p-type lone pairs. The first of the two pairs (shown in blue in Figure 11.46) aligns with the $\sigma^*_{\text{P-LG}}$ orbital assisting in the leaving group departure. At the same time, the same lone pair also interacts with the $\sigma^*_{\text{C-Nu}}$ orbital of the collinear forming bond. Both effects are stabilizing and decrease the overall potential energy of the reacting system, similar to other kinetic anomeric effects described earlier.

However, there is an additional effect unique to the pentacoordinate system. It involves the interaction of the second lone pair (shown in red) with the two σ^*_{OR} orbitals of the non-leaving bystander groups. This effect also serves as a stabilizing force for the pentacoordinate intermediate and the adjacent TS and is responsible for the excellent correlation with the acceptor ability of the OR groups and the rate of nucleophilic attack. The two orthogonal anomeric effects operate separately but in synergy, stabilizing the key part of the potential energy surface for phosphate transfer.

The interplay between the two anomeric effects has other consequences in the chemistry of pentacoordinated phosphorus. For example, acidity of apical and equatorial OH bonds is known to be different and to correlate with the lengths of the apical (longer) and equatorial (shorter) C-OP bonds.⁶⁰ The differences between the two types of OH groups are remarkably large (the $\text{p}K_{\text{a}}$ values of 13.5 ± 1.5 and 8.6 ± 1.9 , respectively). This structural effect leads to almost a 10,000-fold difference in the acidity of the same substituents at the same atom (Figure 11.47)!

Why would the bond length affect acidity so strongly? The modulation of the anomeric effect readily explains this difference. The lone pair of the conjugate base is a strong donor in the $n_{\text{O}} \rightarrow \sigma^*_{\text{P-O}}$ interactions, the key

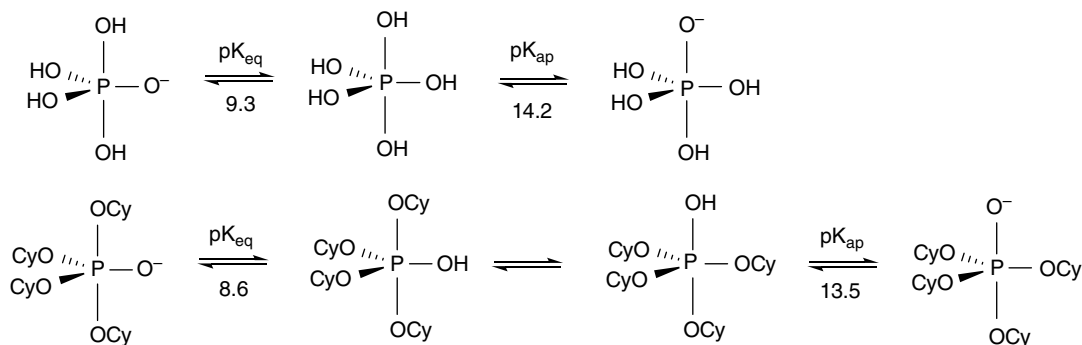


Figure 11.47 Two estimates for pK_a 's of axial and equatorial OH groups in hydroxyphosphoranes.⁶¹

stabilizing force for the anion. These hyperconjugative interactions are stronger for the equatorial OR groups where the donor lone pair and the acceptor σ^* orbitals are brought closer as a result of the shorter P-O distances. As the P-O distance between the donor and the acceptor decrease for the apical substituent, the stabilizing effect of anomeric interaction greatly decreases as well. As a consequence, the formation of an apical anion is less favorable.

The effect of the spectator groups gets much smaller for diester anions.⁶² In phosphate monoester dianions (which represent a considerable portion of the monoester at the physiological pH), the balance between the two anomeric effects shifts even further. Here, the usual anomeric stabilization is still significant whereas the orthogonal anomeric stabilization with the participation of non-leaving group is considerably weakened. Both of these effects, of course, originate from the accumulation of negative charge at the P-O oxygen atoms.

The triple $n_O - \sigma^*_{P-OR^*}$ interactions in the dianions of Figure 11.48 provide the major nucleophilic “push” for the displacement of the leaving group, to the extent that for a good leaving group reactivity depends little on the basicity of the nucleophile. With a very good leaving group, such processes can occur with no measurable involvement of the nucleophile in the bond-breaking step, in a preassociation-concerted reaction where the highly reactive metaphosphate is formed transiently, and immediately trapped with a closely positioned nucleophile.

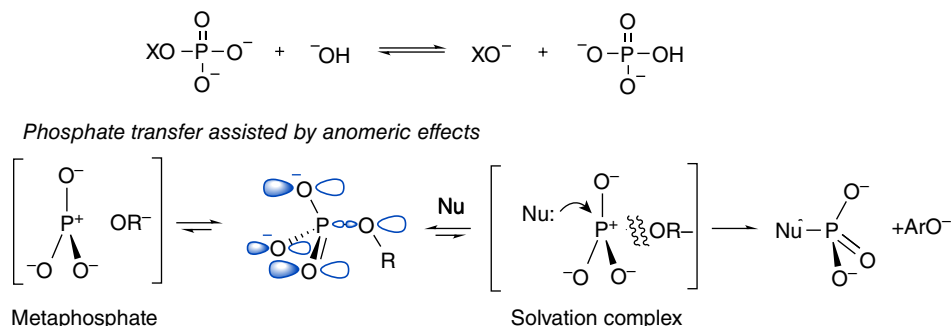


Figure 11.48 The triple $n_O - \sigma^*_{P-OR^*}$ interaction assists in the displacement of leaving group and the formation of transient and highly reactive metaphosphate species.

The insensitivity of the ester dianion reaction to the nature of nucleophile can be used for trapping of unreactive nucleophiles in “high energy bonds” such as P-O-P in ATP. For these reactions, all one needs to do is to stabilize the departing group! This stabilization provides the key mechanistic insights into the key phosphate transfer in biology, the ATP synthase reaction. This reaction produces ATP in the human body from

ADP and inorganic phosphate on the >kilogram scale. The ^{18}O labeling experiments show that the terminal bridge oxygen of the ADP molecule is transferred to the ATP product. The simplest plausible mechanism involves the inorganic phosphate as the phosphorylating agent, likely activated at one of the hydroxyl groups by coordination with a cationic (acidic) residue in the active site (Figure 11.49). In this situation, even such a weak nucleophile as pyrophosphate works well!

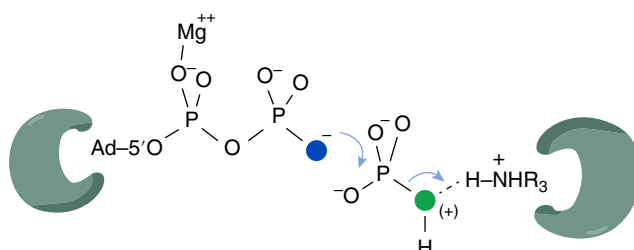


Figure 11.49 A plausible mechanistic scheme for the ATP synthase promoted phosphorylation of ADP.

The opposite process is the conversion of high energy phosphoanhydride bonds into usable energy via hydrolysis. The ease of hydrolysis in adenosine 5'-triphosphate has long been attributed to factors such as electrostatics and charge transfer effects based on the electronegativity of substituents polarizing the O-P σ bond.⁶³ The anomeric bond weakening when an oxygen lone pair is antiperiplanar to the O-P bond is the electronic component in the combination of factors that accelerate the P-O bond scission.⁶⁴

Indeed, NBO analysis suggests that the anomeric effect significantly activates the P-O bonds. In particular, the NBO energy dissection reveals strong correlation between $n_{\text{O}} \rightarrow \sigma_{\text{O-P}}^*$ anomeric interactions and such structural and energetic parameters as P-O bond lengths and free energy of hydrolysis in substituted phosphates.⁶⁵ Calculations of the equilibrium geometries and geometries during rotation in phosphates confirm the preference for geometries which maximize the anomeric effect.⁶⁶

The quantitative estimates of such effects in biological systems become more complicated, because environmental factors can alter the strengths and importance of stereoelectronic effects. Solvent interactions play an important role in the rates of P-O cleavage, and thus alter the strength of the anomeric effect.⁶⁷ The hyperconjugative $n_{\text{O}} \rightarrow \sigma_{\text{H-OH}}^*$ hydrogen bonding interaction between phosphates and water withdraws electron density from the donor involved in the anomeric weakening of the phosphate bond. Interestingly, rotation of an H-bonded water molecule about the P-O bond did not have a large effect on the overall strength of the anomeric effect, as the other lone pair was able to compensate (Figure 11.50).

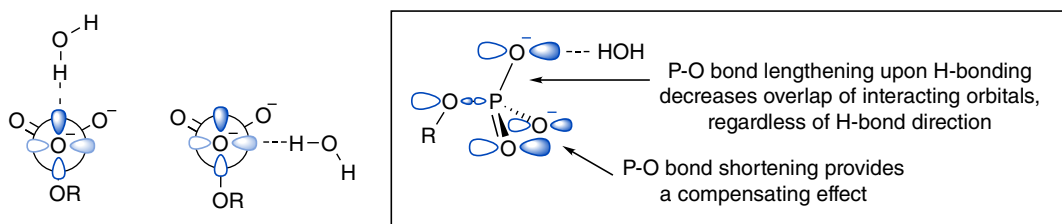


Figure 11.50 H-bonding effects on anomeric effect in phosphate monoesters.

These changes were analyzed in detail using NBO analysis. H-bonds decrease the anomeric effect locally by depleting electron density at the H-bonded oxygen. As expected, these electronic changes are accompanied

by P-O bond lengthening. At the same time, however, the anomeric effect increased for the oxygen lone pairs not involved directly in H-bonds, with a concomitant decrease in the bond length of “free” oxygen P-O bonds. This shortening of the bystander geminal bonds reflects the resilience of anomeric interactions – as one anomeric interaction gets weaker due to H-bonding, the other interactions partially compensate for this weakening.

Numerous studies have utilized quantum/molecular mechanical techniques to investigate enzyme mechanisms involved in ATP hydrolysis,⁶⁸ finding P-O bond lengthening in the active conformation of the protein under examination. It would be interesting to check in the future if this structural effect originates from the anomeric weakening of the P-O bonds. If such effects are amplified in the TS, they may be able to provide selective stabilization to the transition state while simultaneously assisting in the P-O bond scission.

Overall, this section provides multiple examples of the power of negative $n \rightarrow \sigma^*$ hyperconjugation (which sometimes evolves into conjugation) in control of stability and reactivity. In the following section, we will show that $n \rightarrow \pi^*$ conjugation can have multiple consequences for reactivity as well by analyzing the variety of chemical phenomena that take advantage of delocalization (or lack of thereof) with the amide π -system.

Modification of amide resonance In α -peptides, the α -C-N bond cannot avoid an interaction with either a $\pi^*_{C=O}$ or a $\sigma^*_{C=O}$ orbitals of the carbonyl. The resulting conformational profile can be complex since it aims to find a compromise between multiple attractive and repulsive interactions of different origin (Figure 11.51).

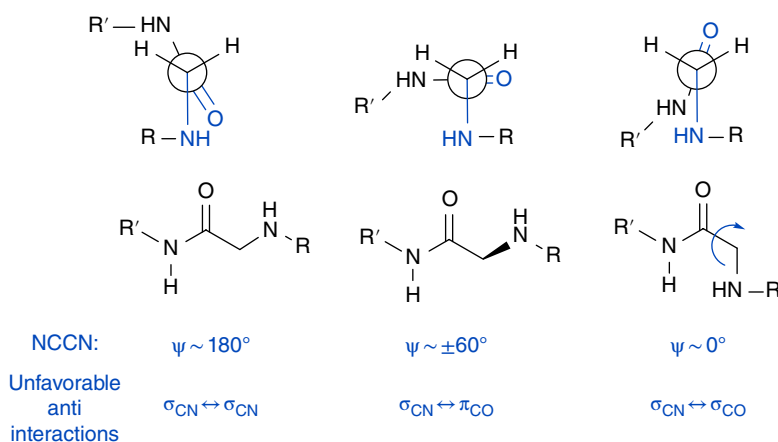


Figure 11.51 Selected conformations of α -peptides.

Strieter and Andrew have thoroughly analyzed the relationship between conformation and stereoelectronic effects of a scissile amide bond in order to understand the interesting interplay between geometries and binding between ubiquitin and ubiquitin-like proteins with deubiquitinases/ubiquitin-like proteases.⁶⁹ For example, the C-terminal glycine of ubiquitin is confined to ψ angles that fluctuate between syn and gauche conformation in the complexes with deubiquitinases, whereas the syn-conformer rapidly isomerizes back to the anti geometry in the absence of a protease. Interestingly, NBO analysis found that, in the syn-conformation, the carbonyl orbitals change into two banana bonds made out of sp^3 -like hybrid orbitals (Figure 11.52). Furthermore, the carbonyl carbon and the amide nitrogen experience out-of-plane deformations (pyramidalizations) in the syn-conformation. These changes weaken the canonical amide resonance and increase reactivity.

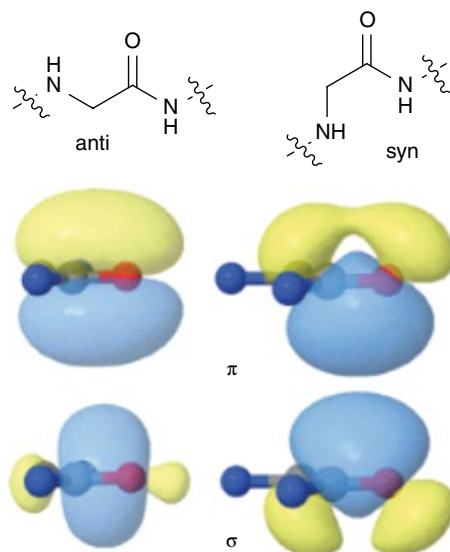


Figure 11.52 The anti and syn-conformations of glycine fragment and different NBO descriptions of the carbonyl groups in the two conformations.

H-transfer in amides Several earlier examples illustrated increased reactivity of C-H bonds at the anomeric position (i.e. due to negative hyperconjugation). One can ask whether the lone pair “deactivated” by donation into a strong $\pi^*C=O$ acceptor can still provide an activating effect to an adjacent C-H bond. Such activation is expected if one considers the N-C=O moiety as an extended allyl-like π -system. Indeed, it was found that C-H bonds aligned with the amide π -system are activated for the radical hydrogen atom transfer (HAT) reactions (Figure 11.53).⁷⁰

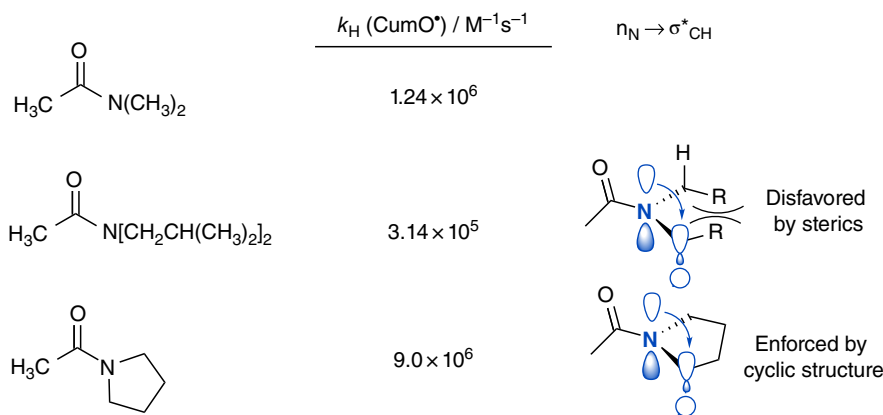


Figure 11.53 Steric and structural effects can modify the amide effect on the rate of α -C-H bond abstraction.

The highest rates of HAT were measured for the reactions of cumyloxy radicals with N-acylpyrrolidines. In these substrates, the α -C-H bonds from the ring are held in a conformation that is optimally aligned with

the amide π -system, thus allowing for the relatively facile HAT reaction. The lowest rates were found for the reaction of N,N-diisobutylacetamide, where the steric bulk associated with the N-isobutyl groups imposes an energy penalty for reaching the most suitable conformation for HAT.

The above examples illustrate the importance of resonance that involves the amide π -system. When the electronic unity of amides is disrupted by a structural change (i.e. rotation), amides behave in unusual ways. Below, we will provide several additional examples of the anti-Bredt's amides distorted by the constraints imposed by their bicyclic structure. The usually robust $N=C$ partial double bonds of amides become very sensitive towards hydrolysis and polymerization when the nitrogen atom is placed at a bridgehead position.

Towards anti-Bredt's amides The first hint of decreased stability comes from the fact that such twisted amides are hard to prepare. For example, the early efforts of Lukeš to incorporate a nitrogen at a bridgehead position in a bicyclic ring system were unsuccessful (Figure 11.54).⁷¹

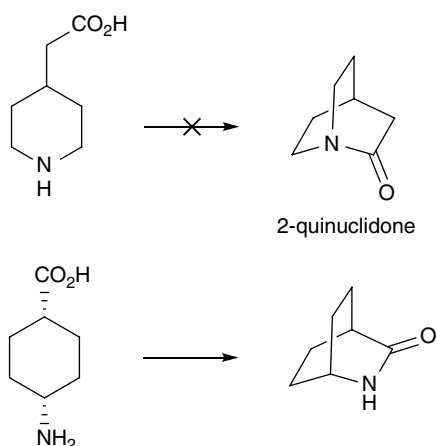


Figure 11.54 Unsuccessful synthesis of 2-quinuclidone, an anti-Bredt amide, contrasts the facile preparation of its structural isomer.

Several other twisted amides were prepared subsequently.⁷² However, Tani and Stoltz synthesized 2-quinuclidone, the same elusive twisted amide pursued by Lukeš, only in 2006 (Figure 11.55). Remarkably for an amide, it was isolated as a tetrafluoroborate salt – an indication of an amine-like reactivity. An intramolecular Schmidt ring expansion, where dinitrogen (N_2) release serves as a driving force, was used for the construction of the strained bicyclic core.⁷³

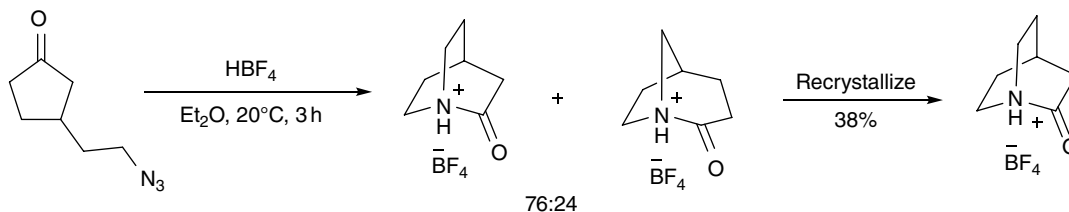


Figure 11.55 Synthesis of 2-quinuclidonium tetrafluoroborate by Tani and Stoltz.

Bredt's amides are very reactive Twisted amides display enhanced sensitivity to hydrolysis and a host of other interesting chemical peccadillos. For example, Kirby reported the formation of stable tetrahedral intermediates from 1-aza-2-adamantanone (Figure 11.56).⁷⁴ This compound combines amine reactivity (it can be rapidly protonated) with ketone reactivity (it undergoes Wittig olefination).⁷⁵

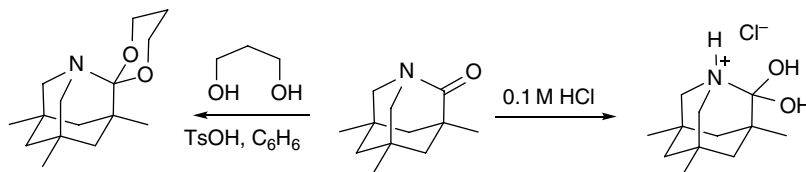


Figure 11.56 1-aza-2-adamantanone can be converted into stable tetrahedral intermediates.

The inhibition of the amide $n \rightarrow \pi^*$ resonance came into play in another fascinating example from the history of science – the structure of penicillin.⁷⁶ For a number of years after the discovery of antibiotic activities of this ground-breaking molecule, its structure eluded elucidation (Figure 11.57). Part of the problem was the discrepancy between spectroscopic hints and observed reactivity. Based on the unusually high reactivity of penicillin in hydrolysis reactions, Robertson suggested that penicillin could not have been an amide because amides were well-known to be stable to hydrolysis (for the stereoelectronic reasons of this stability, see Chapter 6). However, R. Woodward suggested that this discrepancy can be resolved if the amide moiety is included in a four-membered cycle where the constraints imposed by the small cycle twist the lone pair out of conjugation with the carbonyl. Hence, the classic β -lactam structure of the important antibiotic was born of stereoelectronic thinking. This change leads to the marked increase in electrophilicity of penicillin in comparison to normal amide and explains why β -lactams do not exhibit classic amide reactivity.

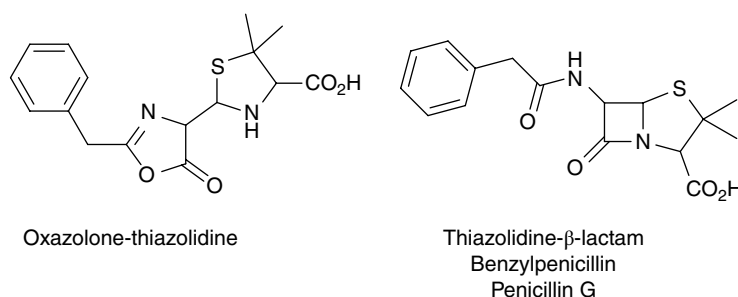


Figure 11.57 The two possible penicillin structures from 1944.

The inefficiency of amide resonance in β -lactams and their spring-loaded reactivity associated with the release of angle and electronic strain played a defining role in the development of the key step in the Holton's synthesis of Taxol (Figure 11.58).⁷⁷

In their efforts to develop stable anti-Bredt N-heterocyclic carbenes (NHCs), Bertrand and coworkers showcased the fundamental differences between strained bridgehead amidinium salts and their non-strained counterparts.⁷⁸ It can be expected that remaining inductive effect of nitrogen atoms would result in a functional group featuring both a "superelectrophilic" carbon center and basic amino groups, a combination of properties which may allow for dihydrogen activation.

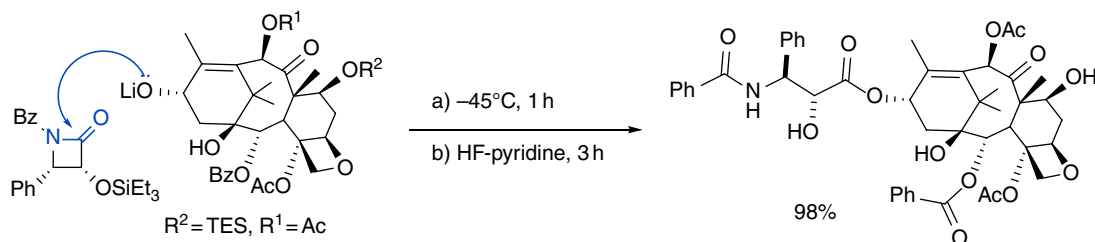


Figure 11.58 Holton's synthesis of Taxol was assisted by the inefficiency of amide resonance in β -lactams.

The role of structural constraints on properties of α -amino cations is illustrated in Figure 11.59. The first α -amino-group provides dramatic stabilization to the cationic center (~ 55 kcal/mol). The additional stabilization by the second amino group is weaker but still very large (~ 24 kcal/mol). However, when the second amino group is at a bridgehead position, its introduction actually destabilizes the adjacent cation by 5.5 kcal. This destabilization suggests that inductive effect of nitrogen is not compensated by the orbital interaction between the cationic center and the nitrogen lone pair.

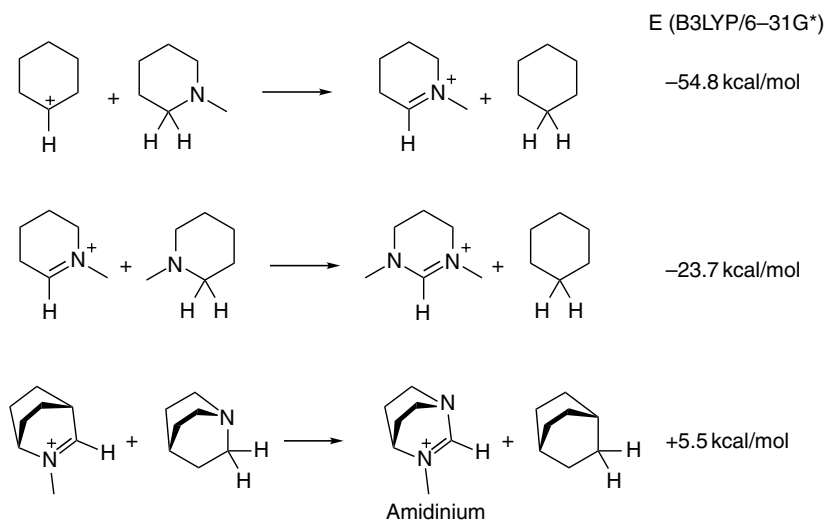


Figure 11.59 Isodesmic reactions for the evaluation of the stabilization of carbocations by amino groups.

These unusual electronic properties lead to unusual reactivity. For example, in deprotonation of such amidinium salts with a strained bridgehead amino group with lithium hexamethyldisilazide (LiHMDS), the corresponding carbene could not be observed by ^{13}C NMR spectroscopy even at the low temperature. Instead, deprotonation at a NCH_2 carbon led to an azomethine ylide. Although potassium hexamethyldisilazide (KHMDS) deprotonates the amidinium salt at the vinyl position at -78°C , the resulting carbene is highly unstable and readily reacts with the concomitantly formed hexamethyldisilazane. These results agree well with the computed relative stabilities of the two isomeric deprotonated forms of normal and highly strained amidinium ions (Figure 11.60).

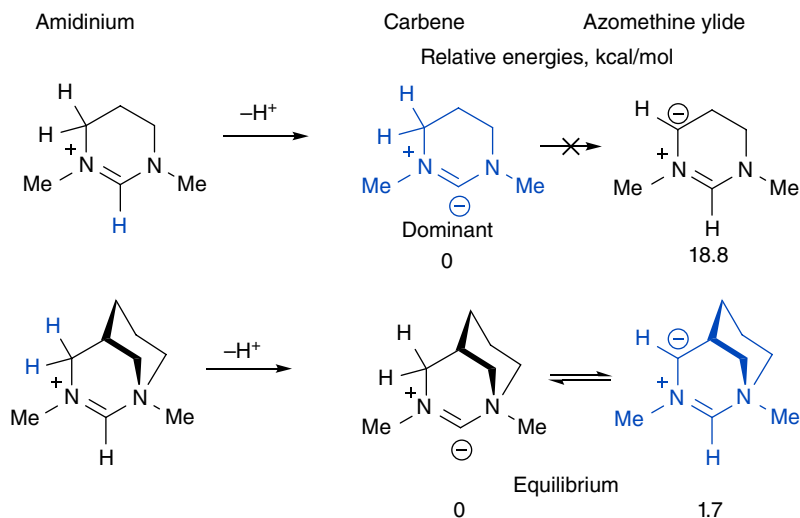


Figure 11.60 Structural effects on deprotonation of amidinium ions.

11.4 Bioorganic chemistry and enzyme reactions

There is always a hidden penalty in using stereoelectronic catalysis. Albeit reaching the optimal conformation for the stabilizing orbital overlap can significantly decrease activation enthalpy, it comes at the price of restricting molecular degrees of freedom and hence an unfavorable entropic contribution. One can argue that in flexible systems where multiple conformations are possible, the true power of stereoelectronic activation is never realized. The entropic disadvantage can be as large as 8 e.u. (2.4 kcal/mol at 298 K) per lost degree of freedom, potentially corresponding to ~100-fold rate difference.⁷⁹

One of the interesting aspects of enzyme catalysis is that it can potentially utilize the intrinsic binding energy for restricting the substrate into the stereoelectronically optimal geometry and, thus, helping the full enthalpic advantage of stereoelectronic activation to be realized without the masking entropic penalty. Aligned with this scenario is the concept of “orbital steering” that suggests that small structural changes that weaken the optimal overlap can have dramatic kinetic consequences (10^3 – 10^5 -fold drop in reaction rates for a 20° rotation of a reacting substrate).⁸⁰

An even more interesting scenario is when the enzyme, instead of simply increasing the fraction of the reactive ground state conformation, changes the preferred substrate conformation in a way which distorts the substrate closer in structure and energy to the desired TS. Such high energy conformation cannot be accumulated under the equilibrium conditions outside of the enzyme. This scenario corresponds to ground state destabilization and can be considered a unique advantage of enzyme catalysis. Furthermore, the destabilization of alternative stages of a multistep mechanism can be beneficial for avoiding unproductive deep potential energy minima. Interestingly, recent high-resolution X-ray data found a number of examples where substrate structural distortion and scissile bond elongation suggest that this mechanism does indeed contribute to the catalytic power of enzymes.⁸¹

Finally, enzymes have the special ability of stabilizing the transition state of the reaction. There are multiple ways for this mechanism to operate, depending on the nature of electronic density accumulation and dissipation in the activated complex. It is important to note that this approach, albeit powerful, has its limitations for multistep reactions where several transition states are encountered on route from the substrate to the product.

Lowering the barrier for the rate-limiting step will only accelerate the reaction to a point where the other elementary step becomes rate limiting. In this situation, the enzyme must confront the problem by finding a path that lowers the barrier to each of the elementary steps. Evolutionary pressure can lead to an enzyme-catalyzed reaction where all of the barriers are similar in height and no one step is rate limiting.

In the above situation, a perfect enzyme should function by organizing all kinetically important species, including the substrate and the possible intermediates, in a stereoelectronically favorable conformation. This scenario would require a conformationally flexible enzyme active site with the multiplicity of conformational states, each suited for a different intermediate/transition state combination.

The mechanistic studies of enzyme catalysis constitute a very large field where rapid progress has been fueled by the recent advances in X-ray crystallography techniques and new spectroscopic methods. We will restrict ourselves to a small number of illustrative examples and refer the reader to an earlier thorough discussion of stereoelectronic effects in biomolecules by Gorenstein.⁸²

Stabilization of a reactive conformation An example of how an enzyme can overcome unfavorable ground state conformations is provided by the enzymatic cleavage of β -glucosides by the enzyme lysozyme.⁸³ After careful analysis of conformational effects at the anomeric carbons (discussed at the beginning of this chapter), Kirby pointed out that the 19 kcal/mol stereoelectronic barrier to C-OR cleavage of the model β -glucoside where the leaving group is held in the equatorial conformation would be inconsistent with the rapid C-OR cleavage catalyzed by an enzyme unless the enzyme can induce a conformational change that improves the anomeric overlap. He also pointed out that the binding site can accommodate oligosaccharides containing up to six sugar residues, as long as one of them, the fourth sugar from the non-reducing end, is twisted into the half-chair conformation. Remarkably, this is precisely the residue where the cleavage of the glycosidic bond occurs (Figure 11.61).

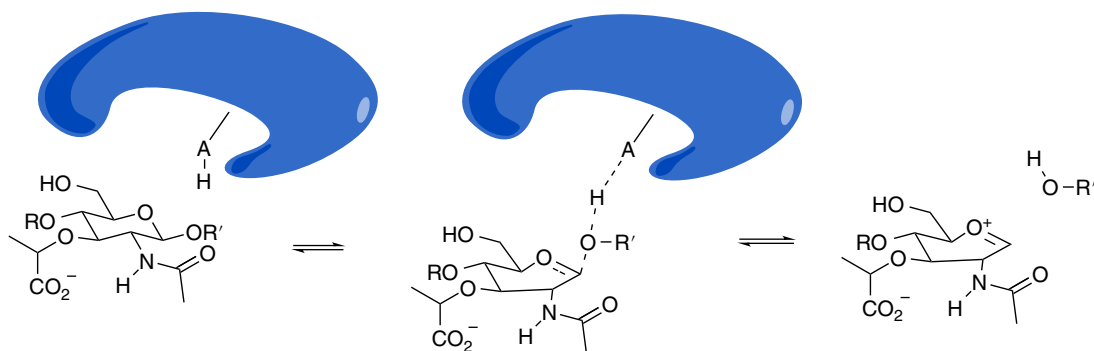


Figure 11.61 Stabilization of reactive conformation in the enzymatic cleavage of β -glucosides by the lysozyme.

The mechanistic work on the hydrolysis of acetals provides a stereoelectronic rationale for the earlier suggestions that this essential conformational change should be involved in the enzyme-catalyzed β -glycosyl transfer reactions either as a part of the initial binding process or in one of the subsequent isomerization steps.⁸⁴ The lone pair- σ^*_{OR} overlap gradually increases as the ring flattens into the half-chair conformation and an alternative mode of stereoelectronic assistance becomes possible.

Destabilization of ground state (removal of a kinetic trap): Hydrogenases are a group of enzymes that catalyze the reversible cleavage of molecular hydrogen. One of the most interesting members of this family is the [Fe]-hydrogenase, used by certain microorganisms to reduce carbon dioxide to methane.⁸⁵ This enzyme catalyzes the reversible hydrogenation of the tetrahydromethanopterin cation (H_4MPT^+) which contains an

amidinium functionality, to give methylenetetrahydromethanopterin (H_4MPT) and a proton. The overall process is mildly exergonic ($\Delta G^\circ = -1.3$ kcal/mol), which is consistent with its reversibility (Figure 11.62).

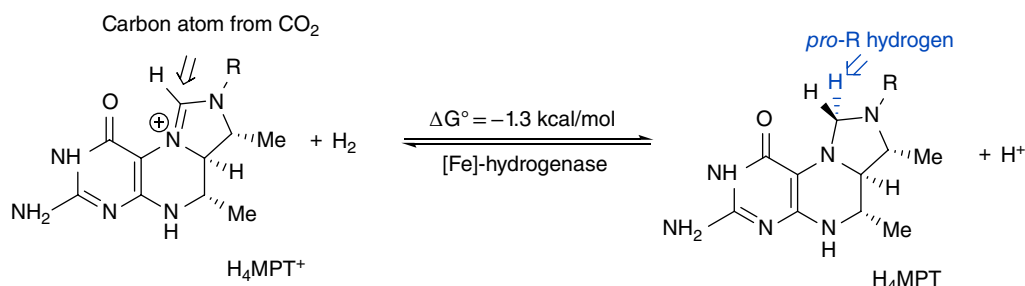


Figure 11.62 Reversible reduction of H_4MPT^+ to H_4MPT by [Fe] hydrogenase.

To explain this process, Berkessel and Thauer proposed the mechanism outlined in Figure 11.63. In this proposal, they extended, for the first time, the idea of superelectrophilic activation, a concept that had previously been postulated only under superacidic conditions, into the realm of enzymatic reactions.⁸⁶ Furthermore, this mechanism has a number of interesting stereoelectronic features that we will discuss below.

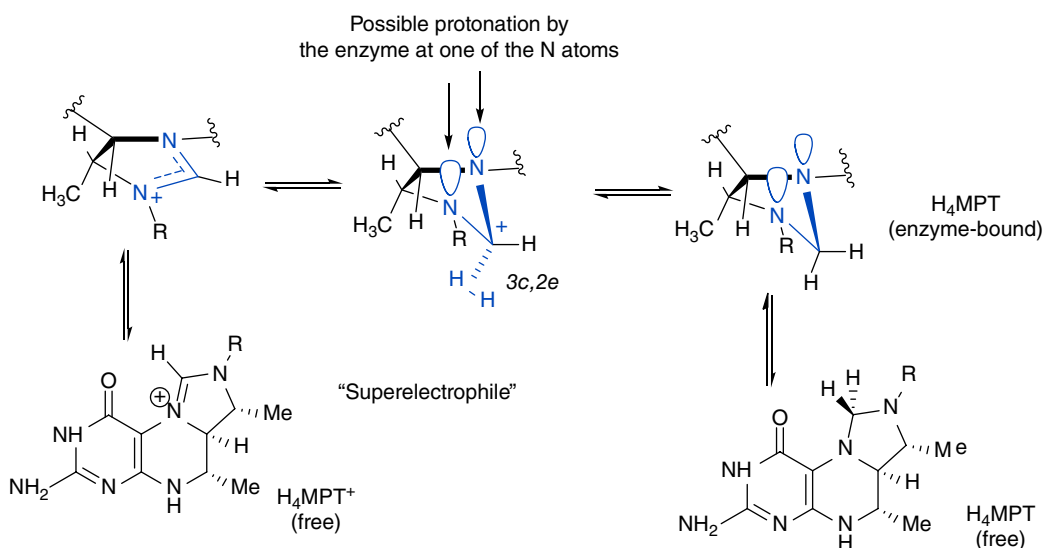


Figure 11.63 Stereoelectronic model for the [Fe] hydrogenase-catalyzed reduction of H_4MPT^+ to H_4MPT .

It was suggested that the imidazolidine ring in the reacting species is locked in a non-planar conformation by the enzyme. In the non-planar conformation of substrate H_4MPT^+ , the resonance stabilization of the cationic center by the lone pairs is diminished, and such species have much increased electrophilicity. Furthermore, it was suggested that acidic functional groups from the enzyme active site can lead to additional protonation at one of the nitrogen atoms. Strong coordination is consistent with the stereoselective delivery of the hydride to H_4MPT^+ from the pro-R direction. The process is reversible, and the axial hydrogen center is also

stereoselectively removed when H_4MPT is transformed into H_4MPT^+ and dihydrogen. This ionization is assisted by donation from the antiperiplanar nitrogen lone pairs and, according to the principle of microscopic reversibility, the reverse reaction will be accelerated by this stereoelectronic effect as well.

Conversion of H_4MPT into H_4MPT^+ and H_2 by protonation has had an ample precedent. For example, triazaphenalene, an ortho amide structurally related to H_4MPT , readily provides the respective guanidinium cation and dihydrogen when treated with HBF_4 at 110°C (Figure 11.64). This transformation is greatly facilitated by the high stability of nitrogen substituted carbenium ions and the favorable antiperiplanar arrangement of the C-H bond and the three lone pairs at the nitrogen centers. Hence, a comparable reaction may take place when H_4MPT is locked by the enzyme in an analogous conformation and an acidic site of the enzyme protonates the C-H bond with the formation of H_4MPT^+ .

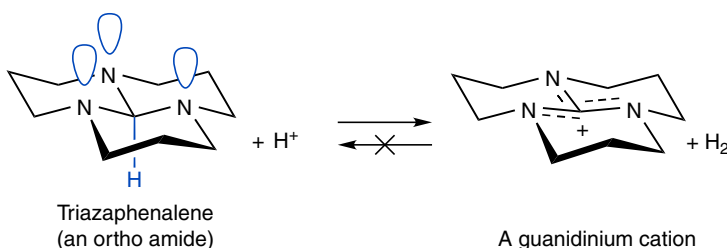


Figure 11.64 Hydride-removal assisted by three anomeric interactions in triazaphenalene.

However, this proposal had an apparent weakness – unlike the *reversible* enzyme reaction, the guanidinium ions *do not* react with molecular hydrogen to give back the ortho amides. Because the high stability of planar nitrogen substituted carbenium ions makes their hydrogenation much more difficult, it was suggested that the enzyme fixes H_4MPT^+ in a folded envelope conformation where conjugative stabilization with the nitrogen lone pairs is diminished, and electrophilicity of the carbocationic center is greatly increased. In other words, stabilization is needed to form the cation but excessive stabilization would be detrimental for its reactivity. As a result, the enzyme moderates stereoelectronics by distorting the cation from planarity (Figure 11.65).

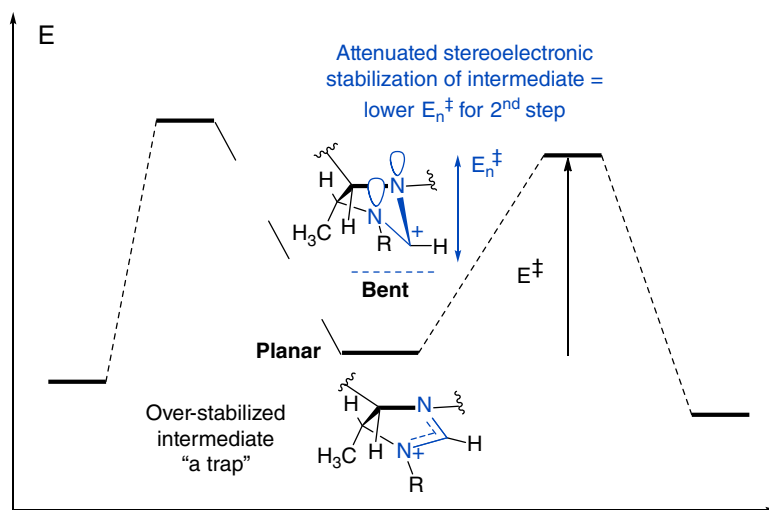


Figure 11.65 Preventing over-stabilization of reactive intermediate in a stepwise enzymatic pathway.

It was also suggested that the turned-off conjugation can allow one of the nitrogen centers of the imidazolidine ring to be protonated by the acidic enzyme sites. This combination of factors can generate a highly electrophilic reaction center which may be sufficient to form a pentacoordinated non-classic carbonium cation by coordination with H_2 via a 3c,2e-bond. Proposal of such intermediates in an enzymatic transformation is remarkable because this chemistry usually occurs only under the exotic superacidic conditions.

In summary, this mechanistic hypothesis has a number of stereoelectronic features that are tightly coordinated to create an efficient enzymatic process. Formation of H_4MPT^+ via removal of the axial C-H is favored by the combined stereoelectronic assistance of the lone pairs of the three nitrogen atoms. However, the full power of such assistance in an enzyme would be counterproductive because it would overstabilize the cationic part of the catalytic cycle. Instead, the enzyme imposes a non-planar conformation where excessive stereoelectronic stabilization is avoided. This system illustrates an interesting connection between geometry, reactivity and enzymatic function.

Redirecting reactions via conformational control In the final example of this chapter, we will show how understanding of enzyme stereoelectronics allows one to redirect reactivity of known substrate into a new direction. When the structural constraints of enzyme active sites are removed, a new set of stereoelectronic constraints can be imposed on the same substrate to enforce a different reactivity. For example, the effect of stereoelectronic factors on the relative order of steps in the deprotonation/decarboxylation sequence were recently analyzed for an enzyme-catalyzed vs. Cu-catalyzed reactions of the similar substrates (Figure 11.66).⁸⁷ The first process is involved in the biosynthesis of polyketides and fatty acids where enzymatic activation of

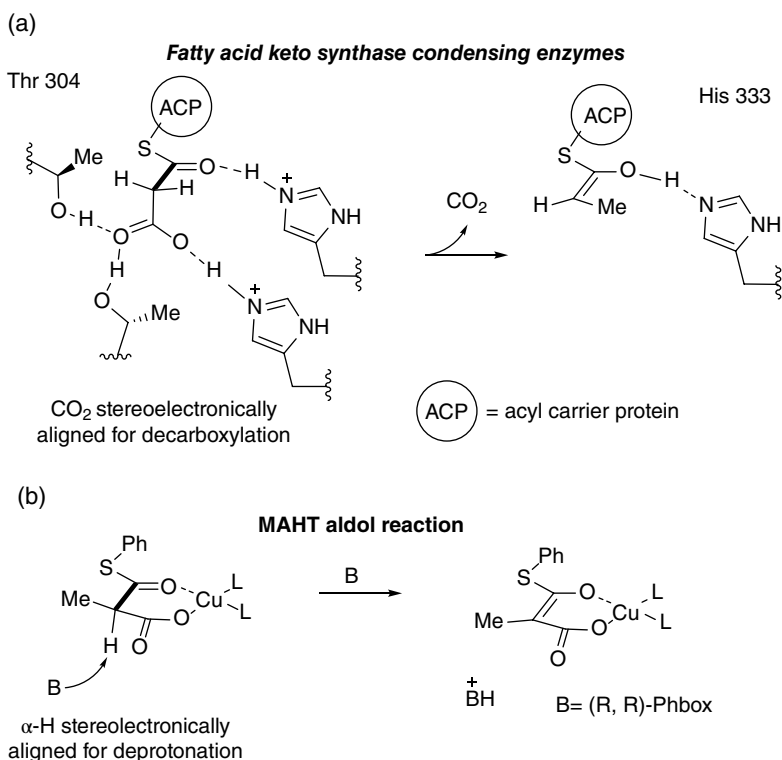


Figure 11.66 Decarboxylation precedes condensation in the enzyme mechanism whereas the Cu-catalyzed reaction starts with deprotonation.

malonic acid half thioesters (MAHTs) proceeds via decarboxylation to provide thioester enolates that undergo Claisen condensation with thioesters. In contrast, the Cu(II)-catalyzed aldol reaction of MAHTs involves decarboxylation *after* addition to aldehydes.

Fortner and Shair provide the following stereoelectronic explanation to the mechanistic dichotomy between Cu(II)-catalyzed and enzyme-catalyzed reactions of MAHTs. As suggested earlier by Holden and coworkers, the enzymes activate MAHTs by polarizing the thioester group while orienting the carboxylate orthogonally to enforce overlap between the breaking C-C σ -bond and π^* of the thioester carbonyl, which is stereoelectronically required for decarboxylation (Figure 11.66a).⁸⁸ In this geometry, deprotonation is prevented because the C-H bond cannot be aligned with the thioester carbonyl. In contrast, in the Cu-catalyzed aldol reaction, the bidentate coordination of MAHT by Cu(II) locks the $-\text{CO}_2$ -moiety in the molecular plane and aligns the C2-H bond with the π -system, allowing deprotonation but not preventing decarboxylation (Figure 11.66b).

Summary The few selected examples in this chapter have illustrated the ever-expanding scope of stereoelectronic concepts across molecular sciences, from chemistry to biochemistry and materials science.

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12

Probing Stereoelectronic Effects with Spectroscopic Methods

In earlier chapters, we discussed how to gain knowledge of stereoelectronic effects from a structural change, an increase in stability, or an enhancement of reactivity. We will conclude this book with a brief discussion of spectroscopic methods that can provide additional insights into stereoelectronic effects. Spectroscopy often allows glimpses of change in molecular parameters that complement and enhance structural data obtained from X-ray crystallography. The advantages of spectroscopic methods are that they are generally non-destructive, fast, often sensitive, and can be used across the large span of possible space timescales, potentially providing dynamic information from a remote location regarding an evolution of molecular structure along a reaction path or after application of an external stimulus. Furthermore, photons of different energies can be used to probe a variety of molecular properties that manifest themselves at different energy scales.

For example, photoelectron spectroscopy can measure the energies of occupied MOs, whereas UV-visible (UV-Vis) spectroscopy reveals important information about electronic states within a molecule, including HOMO-LUMO transitions. Infrared (IR) radiation resonates with molecular vibrations, assisting in identification of various functionalities and in the fingerprinting of specific molecules of interest. Furthermore, vibrations and respective IR frequencies are sensitive to electronic interactions that directly influence chemical bonding, as reflected in the bond strength and valence angles. Microwave spectroscopy provides information about rotational energy levels and, because the measured rotational constants depend upon the moments of inertia of a molecule, they can be used to determine the bond lengths and valence angles.¹ Nuclear magnetic resonance (NMR) spectroscopy is an extremely useful tool for organic chemists, as both the ^1H and the ^{13}C nuclei have non-zero spins, and their chemical shifts and spin-spin coupling are highly sensitive to electronic structure and geometry. In cases where unpaired electrons are present, electron paramagnetic resonance (EPR) can provide information regarding radical delocalization in a molecule. As a result of interactions of the spin of the unpaired electron with that of the nucleus, hyperfine splitting can be observed in EPR spectra.² In addition

to coupling strength dependence on bond lengths and dihedral angles in organic radicals,³ hyperfine coupling provides direct estimate of hyperconjugation with odd-electron centers.⁴

A comprehensive discussion of the advantages of different spectroscopic techniques goes beyond the scope of the present work. An excellent description of the applications of photoelectron and UV-Vis spectroscopies for the analysis of conjugative effects, is given in a recent monography by Gleiter and Haberhauer.⁵ An excellent online resource for the key aspects of NMR spectroscopy for organic chemists has been developed by Reich.⁶ We will focus subsequent discussion on the selected aspects of IR and NMR spectroscopies that provide indirect but valuable structural information at the level of individual bonds and functional groups. Although these methods are of particular use in the study of molecular geometry in relation to electronic structure, one has to keep in mind that these methods provide an *indirect* insight into electronic structure. Thus, a way to get reliable stereoelectronic insights from such methods is to correlate them with either experimentally measurable chemical reactivity or with computational data.

12.1 Infrared spectroscopy

Caveat When extracting structural information from IR spectra, one has to keep in mind that not all bands correspond to simple bond stretching or bending. The presence of overtones, combination bands, Fermi resonances, etc. can lead to absorption lines that are shifted from the expected positions. However, interesting structural information can still be extracted from IR spectra, and ingenious experimental techniques have been developed for this purpose. For example, the above difficulties can be removed by the deuterating all of the hydrogens except for the one under investigation. For example, the CHD2 “isotopomer” can be used instead of a methyl group. This substitution decreases the importance of Fermi resonances in the CH stretching region as well as the importance of the coupling to other motions of the CH stretching. McKean and coworkers, who used this technique in a number of comprehensive studies, referred to such frequencies as ‘isolated’ frequencies, $\nu_{\text{C-H}}^{\text{is}}$.⁷

12.1.1 Bohlmann effect

The connection between the bond length, bond strength, and IR-stretching frequencies is the basis of the Bohlmann effect, a historically important tool for studies of stereoelectronic effects.⁸ The first mention of unusual IR-stretching frequencies goes back to the 1957 work of Bohlmann,^{8a} who noted that characteristic red-shifted bands appeared in conformationally confined amines ($\sim 2800\text{--}2700\text{ cm}^{-1}$, as a reference point, the C-H stretching frequency in methane is $\sim 3000\text{ cm}^{-1}$). An analogous effect was observed in methylamine where the lower 2880 cm^{-1} stretching frequency is observed for the C-H bonds that is antiperiplanar to the lone pair of nitrogen, and thus is lengthened and weakened by the anomeric $n_{\text{N}} \rightarrow \sigma_{\text{CH}}^*$ hyperconjugative interaction. Characteristic absorption bands for such C-H bonds can be used for structural and stereochemical assignments in amines (Figure 12.1).⁷ Furthermore, this spectroscopic feature can also be detected for C-H bonds located near the oxygen atom of alcohols and ethers.

There is evidence of analogous hyperconjugative interaction in F-substituted compounds. In particular, the $\nu(\text{C-H})^{\text{is}}$ for methyl fluoride is 16 cm^{-1} red-shifted relative to methane (2976 vs. 2992 cm^{-1}).⁷ Because hybridization effects imposed by Bent’s rule should increase s-character in the C-H bonds and lead to the blue-shift,¹⁷ the experimental red-shift observation indicates the importance of $n_{\text{F}} \rightarrow \sigma^* \text{C-H}$ interactions. Additional fluorine substituents remove most of the red-shift ($\nu(\text{C-H})^{\text{is}}$ for CH_2F_2 and CHF_3 are 2984 vs. 2990 cm^{-1} , respectively) suggesting the increasing importance of rehybridization (progressive s-character increase in the C-H bond(s)) and, possibly, the importance of $n_{\text{F}} \rightarrow \sigma^* \text{C-F}$ interactions that partially “neutralize” the donor capacity of the fluorine lone pairs. Small blue-shifts are observed for the chloro- and bromoderivatives of methane.

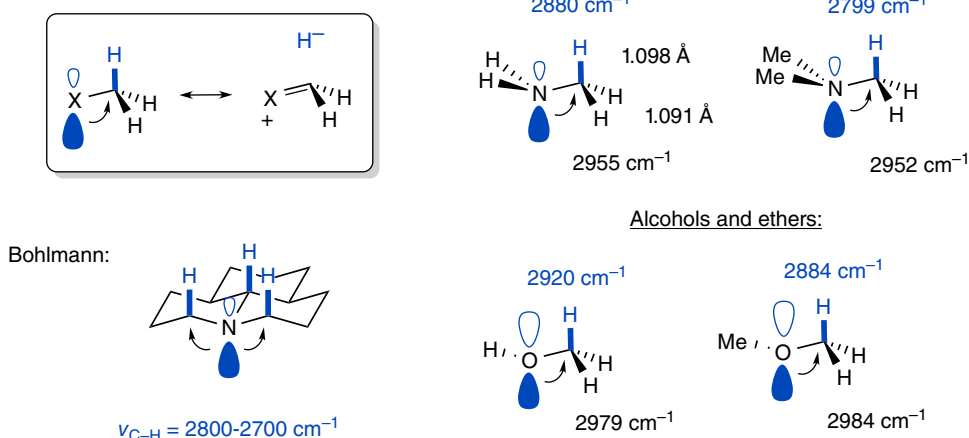
Bohlmann effect: lower IR-stretching frequency for the antiperiplanar C-H bond


Figure 12.1 Bohlmann effect reflects stereoelectronic effects in amines, alcohols, and ethers. C-H bonds with the red-shifted IR stretching frequencies are shown in blue. Bond lengths calculated at the B3LYP/6-311G++(d,2p) level of theory. $\nu(\text{C-H})^{\text{is}}$ values from reference 7.

The Bohlmann effect is also observed in C-H bonds antiperiplanar to lone pairs in systems where the lone pair containing heteroatom is doubly bound to the C-H carbon (i.e. aldehydes, imines, etc.). The additional stereoelectronic feature of imines is the presence of geometric isomers that allow clear distinction between syn- and antiperiplanarity effects (Figure 12.2).⁹ The stretching IR frequencies for the C-H bonds antiperiplanar to the nitrogen lone pair are noticeably red-shifted.

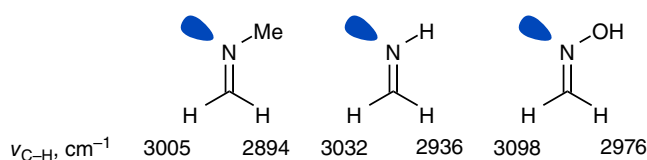


Figure 12.2 Bohlmann effect observed in the $\nu(\text{C-H})^{\text{is}}$ “isolated” frequencies due to stereoelectronic effects in imines.

The weakening of C-H and N-H bonds oriented *trans* or antiperiplanar to vicinal lone pairs leads to red-shifted IR vibrations (Figure 12.3). While the N-H stretches are undetectable in *trans*-diimide, the unstable *cis* isomer shows much lower stretching frequencies than methyleneimine (3070 cm^{-1} vs. 3280 cm^{-1} , respectively). In dimethylhydrazine, two N-H stretching frequencies are present with the red-shift associated with interaction of the N-H bonds with the antiperiplanar lone pair from NMe_2 moiety. In *cis*-methyl diazene, the $n_{\text{N}} \rightarrow \sigma_{\text{N-D}}^*$ interaction simultaneously strengthens the N-N bond and weakens the N-D bond relative to the *trans*-isomer.¹⁰

Similar effects are observed in aldehydes and formic acid derivatives where the stretching frequencies for C-H bonds at the sp^2 carbons are significantly red-shifted in comparison to the C-H bonds of ethylene. Acceptor substituents aligned with the in-plane p-type lone pair of the carbonyl oxygen weaken the Bohlmann effect by attenuating the $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ interactions, leading to higher C-H stretching frequencies. This behavior is observed for acyl halides, esters, and amides. The order of C-H blue-shift parallels the σ -acceptor ability

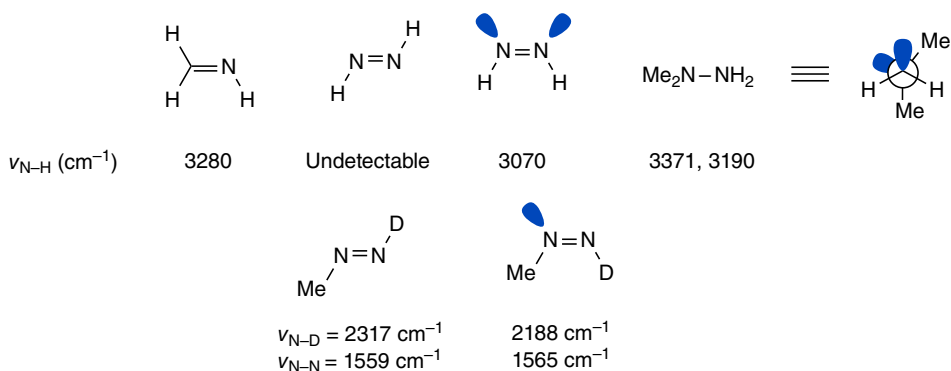


Figure 12.3 Bohlmann effect observed in N-H IR-stretching frequencies due to stereoelectronic effects.

of X ($\text{F} > \text{O} > \text{N}$). An extreme version of this effect is observed upon Lewis acid coordination at the carbonyl. Such coordination shifts C-H IR frequencies back to higher frequencies, as the lone pair cannot participate in the $n_{\text{O}} \rightarrow \sigma^*$ interactions anymore.⁷

The similarity of the C-H stretching frequencies for acetaldehyde, acrolein, and benzaldehyde ($2770\text{--}2800 \text{ cm}^{-1}$) suggests that σ -effects dominate and additional π -conjugation has minimal perturbative effect. However, the C-H stretching frequency in propargylic aldehyde is significantly blue-shifted in comparison to that in acrolein (2858 vs. 2800 cm^{-1}), reflecting the “in-plane” π -acceptor capacity of alkyne (Figure 12.4).

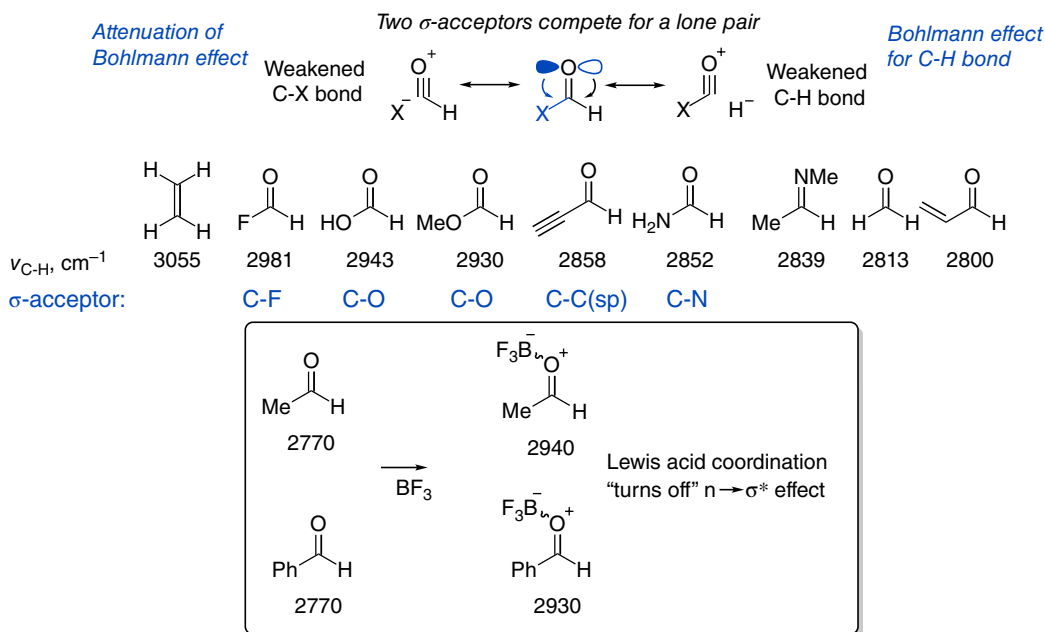


Figure 12.4 Bohlmann effect observed in C-H IR-stretching frequencies reflect stereoelectronic effects in the carbonyl containing compounds and their chemical relatives. Bond lengths calculated at B3LYP/6-311G++(d,2p). Values from ref. 7. Insert: Deactivation of $n_{\text{O}} \rightarrow \sigma^*_{\text{C-H}}$ interactions by coordination of a Lewis acid at the carbonyl.

The key important IR-active functionality of the carbonyl family, the C=O group, responds to structural changes in a more complex way as it reflects the interplay of two orthogonal sets of delocalizing interactions: the in-plane $n_O \rightarrow \sigma^*_{C-X}$ and out-of-plane $p_X \rightarrow \pi^*_{C=O}$ interactions (see Chapter 6 for a detailed discussion). The first of these interactions strengthens the C=O group with a concomitant blue-shift whereas the other one has the opposite structural and spectroscopic consequences.

For example, as the $n_O \rightarrow \sigma^*_{C-X}$ interactions become more important for the highly electronegative substituents X, the C=O group contracts due to the increase in interactions between the lone pair and the σ^* -acceptor that lead to the partial triple bond character and the blue-shift of the C=O IR stretching frequencies (Figure 12.5).¹¹

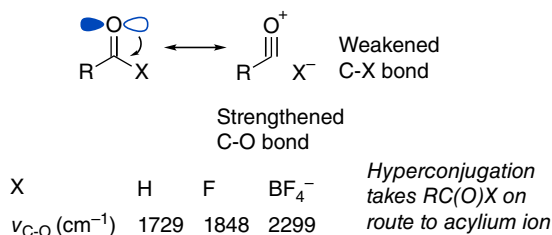


Figure 12.5 Removal of the $n_O \rightarrow \sigma^*_{C-H}$ hyperconjugative effects can explain the blue-shift of the IR stretching frequency of carbonyl compounds as X becomes more electronegative. (X = H from ref 7a. X = F, BF₄⁻ from 7b.)

On the other hand, transfer of electron density *from* the substituent to the antibonding π^* orbital of the carbonyl renders the C=O bond weaker and leads to the red-shift. Such shifts are obvious in aryl and vinyl ketones in comparison to their dialkyl counterparts (Figure 12.6). Of course, one has to be cognizant of other electronic effects that can influence the carbonyl group as well. For example, hybridization effects can mask stereoelectronic trends. In particular, strained cycles made of the p-rich banana bonds have to allocate more s-character in the exocyclic bonds. Increased s-character makes bonds stronger and shorter, which is reflected in the blue-shifted carbonyl stretching frequencies for the strained cycloalkanones.

The red-shifting effect of ester oxygen atom is weak and strongly dependent on substitution, possibly because the competition between the aforementioned stereoelectronic effects is closely balanced. The carbonyl stretch in amides is very sensitive to substitution and its analysis is further complicated by the presence of combination bands (only the blue-shifted of the two bands is shown in Figure 12.6).

The spectroscopic signature of carboxylic acids is strongly dependent on H-bonding and ionization. The H-bonded dimers are red-shifted in comparison to the monomers whereas the deprotonated carboxylate anions display even greater red-shift (down to ~1550–1610 cm⁻¹). Such effects have been studied experimentally and computationally. For example, the carbonyl band of the acetic acid monomer was calculated to be ~50 cm⁻¹ above that of its dimer, while the carbonyl band of the salt monomer was ~60 cm⁻¹ below that of its dimer (Figure 12.6).¹³ The role of stereoelectronic effects in these spectroscopic features can be understood from a simple model based on weakening of the $n_O \rightarrow \pi^*_{C=O}$ hyperconjugation by H-bonding in the dimers (Figure 12.7). The even greater red-shift in the carboxylate anions is clearly the result of very strong $n_O \rightarrow \pi^*_{C=O}$ conjugation.

Depending on the nature of H-bond, either blue- and red-shifting can be observed for the C=O bonds in hydrogen-bonded esters.¹⁴ The majority of ester H-bonds are formed with the carbonyl oxygen. Such H-bonding makes $n_O \rightarrow \pi^*_{C=O}$ interaction stronger by activating the acceptor and leads to the red-shift in the C=O frequency (Figure 12.8). In contrast, H-bonding at the OR group renders $n_O \rightarrow \pi^*_{C=O}$ interaction weaker by deactivating the donor and results in the blue-shift of the C=O frequency. In other words, the red- or blue-shifts in the IR frequencies result, respectively, from strengthening or weakening of $n_O \rightarrow \pi^*_{C=O}$ resonance (Figure 12.8).

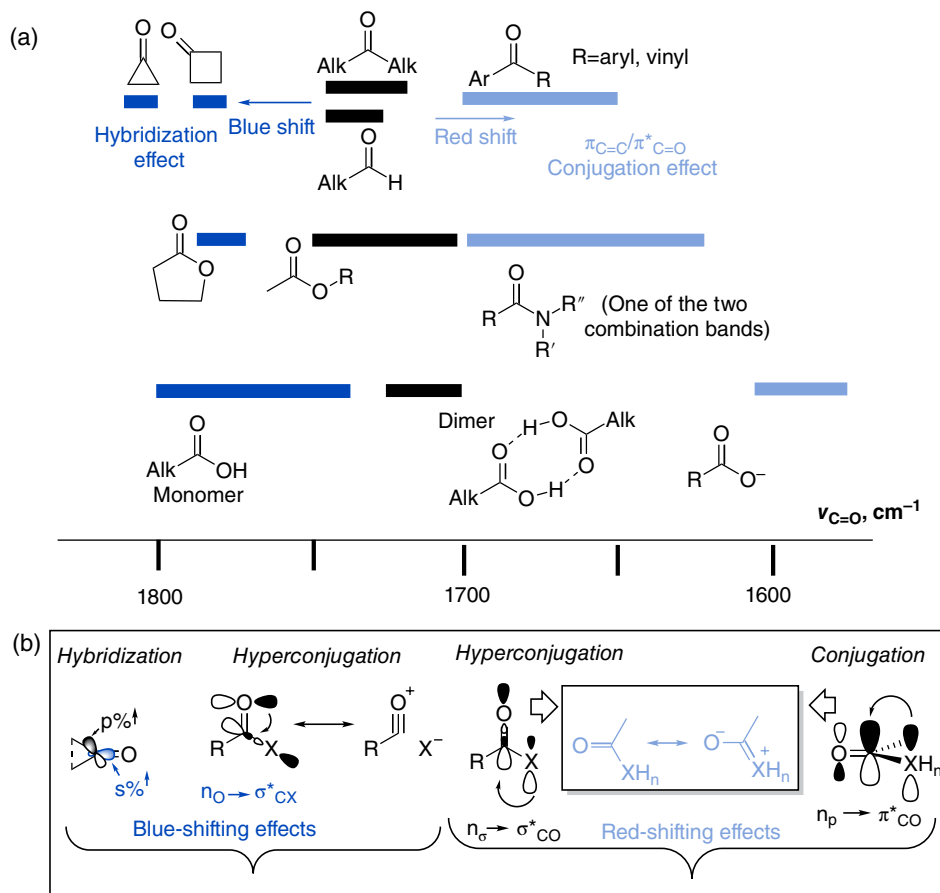


Figure 12.6 (a) The approximate ranges for the C=O stretch in selected carbonyl derivatives.¹² (b) The competition between blue- and red-shifting stereoelectronic effects on the C=O stretch.

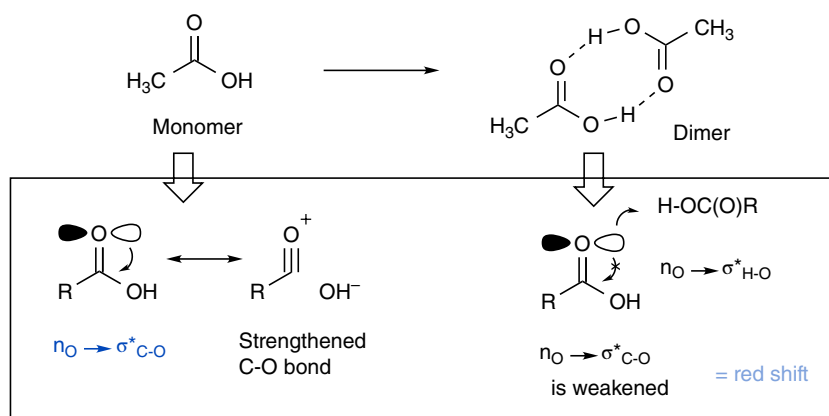


Figure 12.7 Weakening of the $n_{\text{O}} \rightarrow \sigma_{\text{C-X}}^*$ hyperconjugation by H-bonding explains the red-shift of the C=O stretching frequency upon dimerization of carboxylic acids.

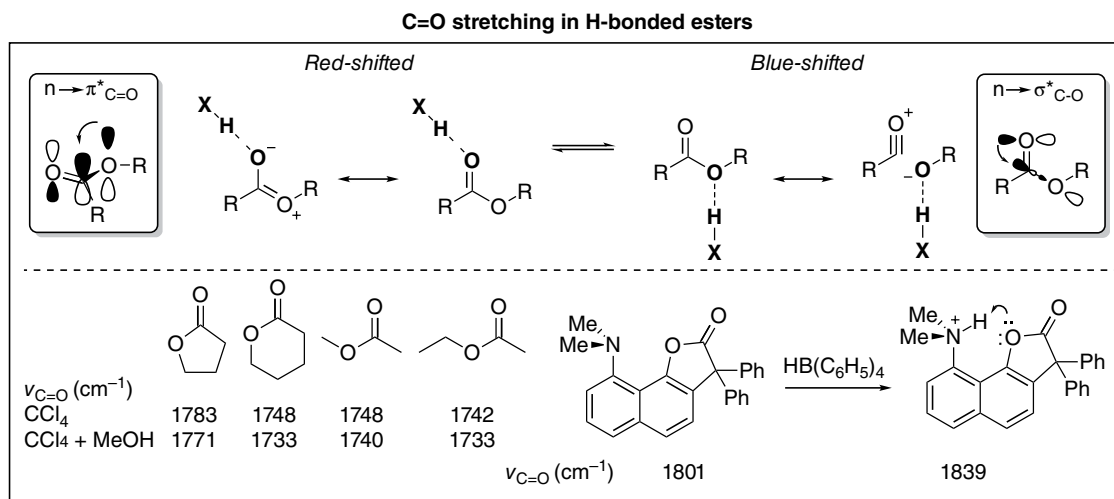


Figure 12.8 Red- and blue-shifted C=O stretching frequencies in esters stem from H-bonding at different oxygen atoms. Values from ref. 14. Data in CCl_4 provide the reference point (no H-bonds between solvent and carbonyls).

$\sigma \rightarrow$ cations The “umpolung” of the classical negative hyperconjugation pattern of the Bohlmann effect is provided by the effects of positive hyperconjugation on the IR-frequencies associated with α -C-H bonds in a cation. Those C-H bonds that are aligned with the empty p-orbital are significantly weakened. For example, the *t*-butyl cation shows a significantly red-shifted C-H stretching frequency in both the gas phase ($\sim 2800 \text{ cm}^{-1}$)¹⁵ and in the solid state ($\sim 2900 \text{ cm}^{-1}$)¹⁶ relative to neutral hydrocarbons (methane $\nu_{\text{C-H}} \sim 3000 \text{ cm}^{-1}$, Figure 12.9). Interestingly, the C-H bonds that are misaligned with the cationic p-orbital have more s-character than the sp^3 bonds of methane and $\text{sp}^{3.3}$ C-H bonds of 2,2-dimethylpropane.¹⁷ These rehybridization trends should lead to noticeable blue-shifts for the misaligned C-H bonds relative to that for the C-H bonds aligned with the cationic center.¹⁸

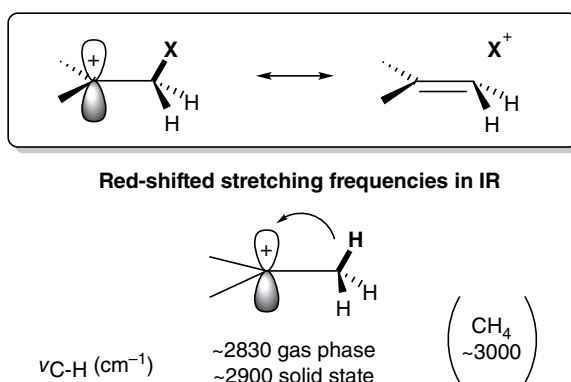


Figure 12.9 Red-shifted C-H stretching frequencies in the *t*-butyl cation. Values from refs. 15 and 16.

C-Sn and C-Si bonds can stabilize the positive charge so efficiently (see the earlier discussion of β -effects in Chapter 6) that it allows for the isolation and structural characterization of the respective vinyl cations.¹⁹

The observed $C=C^+$ stretch in the disilyl-substituted vinyl cation is significantly blue-shifted relative to commonly observed $C=C$ stretching frequencies ($\sim 2000\text{ cm}^{-1}$ vs. $\sim 1600\text{ cm}^{-1}$). The efficient $\sigma_{C-Si} \rightarrow p^+$ stabilization of the cationic center strengthens the bridge bond giving it significant triple bond character (Figure 12.10).

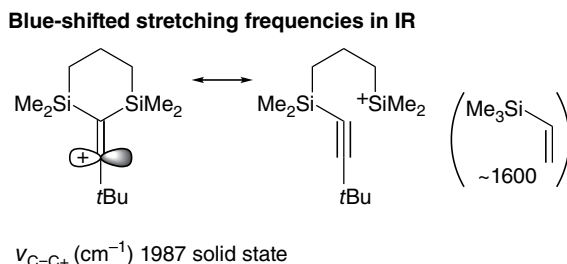


Figure 12.10 Blue-shifted $C=C$ frequencies in silyl substituted vinyl cation originate from positive hyperconjugation. Values from ref. 20.

It is important to keep in mind that other effects, both intra- and intermolecular, can be involved in the spectroscopic features. As discussed already, the intramolecular stabilization of carbocations provided by $\sigma_{CH} \rightarrow p^+$ positive hyperconjugation leads to significantly red-shifted stretching frequencies for the aligned C-H bonds. Recent studies of the X-ray crystal structure of a series of carbocations with carborane counter anions attributed the red-shift of antiperiplanar hydrogens to H-bonding rather than hyperconjugation.²¹ This is a “chicken vs. egg” argument, as H-bonding is amplified by hyperconjugative transfer of positive charge from the cationic center to β -hydrogens, whereas the hyperconjugative interaction of C-H bond with the empty p-orbital is enhanced by H-bonding that supplies additional electron density to the C-H bond and renders it a better donor (see Chapter 6 for a more detailed description of stabilization in cations). The two synergistic effects rely on and reinforce each other (Figure 12.11).

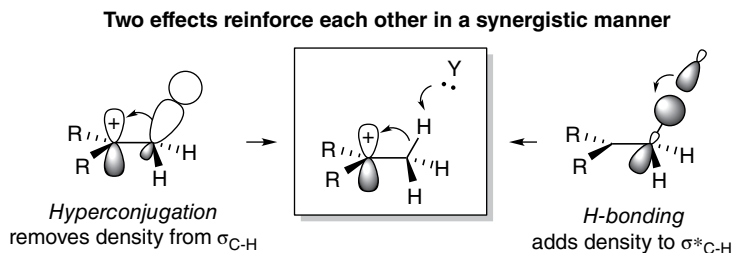


Figure 12.11 Hyperconjugation and H-bonding: two synergistic effects leading to the red-shift of the IR stretching frequency.

C-H bonds adjacent to π -bonds When a vicinal π -system is present, allylic C-H bonds are weakened and elongated by $\sigma_{C-H} \rightarrow \pi^*_{C-X}$ and $\pi_{C-X} \rightarrow \sigma^*_{C-H}$ interactions. As a result, C-H stretching frequencies in allylic, propargylic, and α -C-H bonds next to carbonyls, cyanides, and isocyanides, are often red-shifted (Figure 12.12).⁷ In allylic and heteroallylic positions, the out-of-plane C-H bonds display lower frequency stretches than the in-plane C-H bonds, whereas all three C-H bonds adjacent to a triple bond are equivalent.

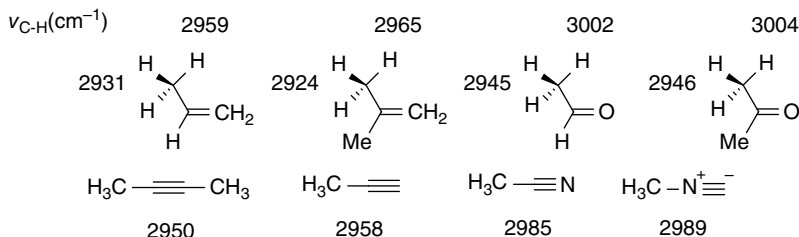


Figure 12.12 C-H Bonds adjacent to π -bonds displaying red-shifted IR frequencies.

Although it may seem surprising that the C-H bonds in acetaldehyde and 2-propanone are stronger than in propene and 2-methylprop-1-ene, it can be readily explained by Bent's rule.²² Hybrid orbitals with increased p-character are directed towards the electronegative carbonyl groups, leading to greater s-character in orbitals directed towards hydrogens. Such hybridization effects strengthen both the in-plane and out-of-plane C-H bonds relative to those in propene and 2-methylprop-1-ene. Still, the observed $\Delta\nu$ values are larger in the carbonyl compounds in comparison to the alkenes (58 vs. 28 cm⁻¹), illustrating the importance of $\sigma_{\text{C-H}} \rightarrow \pi_{\text{C=O}}^*$ hyperconjugation. The same effect is observed for the propargylic C-H frequencies in alkynes relative to those in nitriles and isonitriles.

Interactions between σ -bonds Even the ubiquitous consequences of such common effect as $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-H}}^*$ hyperconjugation can be dissected via the use of the $\nu_{\text{CH}}^{\text{is}}$ method of McKean.⁷ For example, C-H frequencies in ethane are 42 cm⁻¹ red-shifted in comparison to those in methane (Figure 12.13). The C-H bonds at the secondary carbon of propane (potentially antiperiplanar to *two* C-H bonds from the Me groups) display additional 30 cm⁻¹ red-shift whereas the tertiary C-H of isopropane (potentially antiperiplanar to *three* C-H bonds from the Me groups) is red-shifted by 30 cm⁻¹ more.

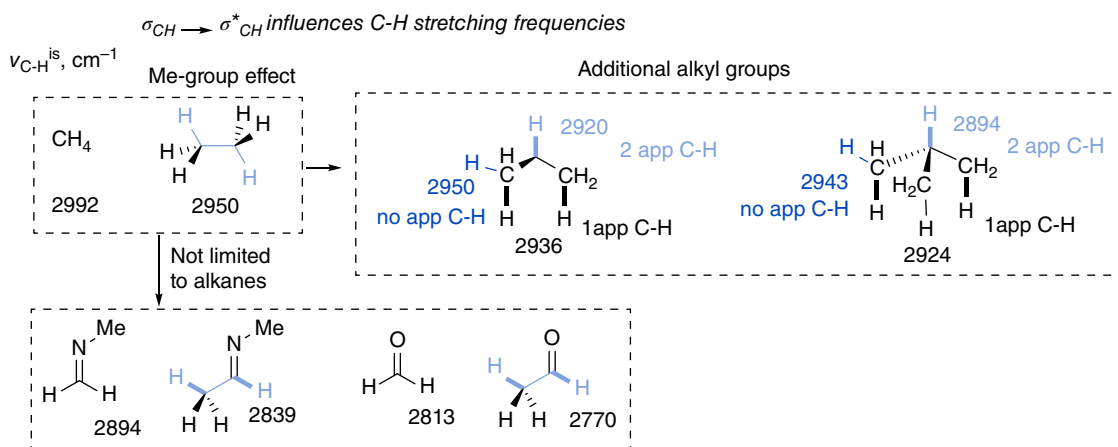


Figure 12.13 Selected effects of CH/CH hyperconjugation on C-H IR-stretching frequencies (app=antiperiplanar).⁷

In monosubstituted ethanes, β -substituents impose a larger effect on the antiperiplanar C-H bonds than on the gauche C-H bonds (Figure 12.14).⁷ The observed $\text{F} < \text{Cl} < \text{Br} < \text{I}$ trend is consistent with the relative acceptor abilities of the respective $\sigma^* \text{C-X}$ orbitals ($\text{F} < \text{Cl} < \text{Br} < \text{I}$ ²³, see Chapter 5 for a discussion).

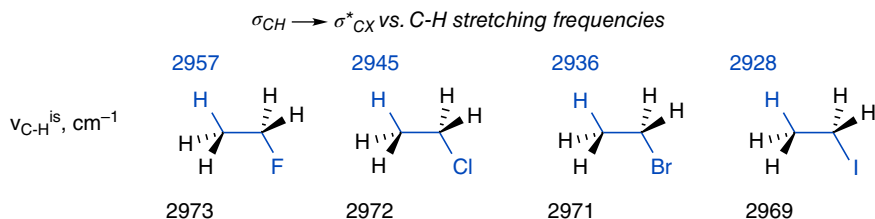


Figure 12.14 Selected effects of CH/CX hyperconjugation on C-H IR-stretching frequencies (app=antiperiplanar).⁷ Red-shifted H-bonds are shown in blue.

12.1.2 Red-shifting hydrogen bonds – an intermolecular version of the Bohlmann effect

The intermolecular version of the Bohlmann effect is the well-known spectroscopic signature of H-bonding (the red-shift of X-H frequency in the X-H...Y complex). The commonly observed weakening of X-H bonds in X-H...Y complexes, a consequence of $n_Y \rightarrow \sigma_{X-H}^*$ negative hyperconjugation (Figure 12.15),²⁴ is generally detected via the concomitant red-shift in the IR X-H stretching frequencies. This structural and spectroscopic effect can be readily understood as a consequence of increased population of the antibonding σ_{X-H}^* orbital.

Intermolecular Bohlmann effects: hydrogen bonding

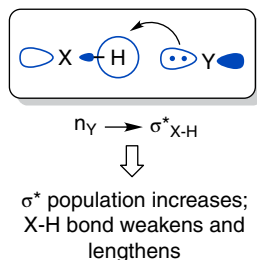


Figure 12.15 Intermolecular hyperconjugation in H-bonding usually leads to a red-shift in the H-X frequency analogous to that observed in the Bohlmann effect.

Factors responsible for H-bonding have been debated for some time, with a consensus that a balance of electrostatics, polarization, charge transfer, and dispersion is responsible for the formation of H-bonds and for the structural consequences of these interactions.²⁵

Red-shifted H-bonds These are the most common and well-documented type of H-bonds. The hyperconjugative factor ($n \rightarrow \sigma^*$), responsible for H-bonding, also results in bond weakening and the observed red-shift and broadening in the IR spectrum.²⁶ When H-bonds are disfavored, i.e. upon heating or dilution, the “associated” broad O-H stretching bands of an alcohol or an acid disappear, and sharp high-energy “non-associated” bands reappear.²⁷

As early as 1937, it was found that a linear relationship exists between H-bond strength and the shift in the IR H-X stretching frequency, termed the Badger–Bauer rule (Figure 12.16).²⁸ Although, the qualitative correlation between H-bond strengths and stretching frequencies has been observed in many chemical and biological systems,²⁹ it has been recognized that a single linear relationship does not hold throughout the many diverse types of H-bonding.³⁰ However, for structurally related compounds, satisfactory linear correlations

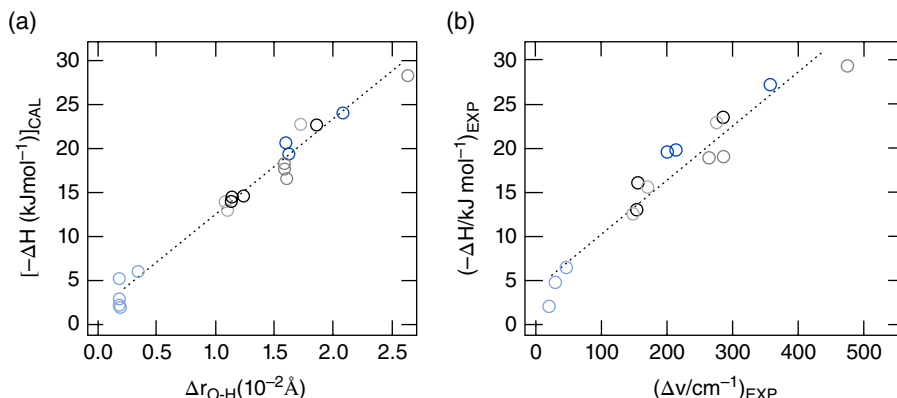


Figure 12.16 Badger–Bauer rule: Linear relationship between H-bond strength and magnitude of red-shifting in O–H stretching frequency. (Source: Bhatta 2014 (31). Reproduced with permission of World Scientific Publishing.)

between enthalpy of H-bond formation, the shift in the IR stretching frequency, and the X–H bond elongation were indeed found.³¹

It is generally accepted that a red-shifted frequency and lengthened X–H bond are related to the covalent aspect of in the X–H...Y complex (e.g. intermolecular hyperconjugation between the lone pair of Y and the $\sigma^*_{\text{H-X}}$).^{25,26} For X–H...Y-bonds (X=O, N, Cl), the magnitude of the observed X–H(D) shift correlates with the strength of the H-bond acceptor (Y, measured by base strength).^{25a} More basic H-bond partners Y participate in stronger H-bonds with much larger $\Delta\nu$ X–H values.

C–H...X hydrogen bonds The early notion that H-bonds can only be formed with H–X species where X is highly electronegative (e.g. N, O, F), has been expanded to include C–H bonds and other relatively non-polar X–H bonds.^{25a} In fact, Allerhand and Schleyer wrote in 1962:²⁶ “That chloroform and acetone form a complex has been known for a long time; as early as 1914, attempts were made to calculate an association constant.”³² While many C–H...Y hydrogen bonds have only moderate hyperconjugative $n_Y \rightarrow \sigma^*_{\text{C-H}}$ contribution to the C–H frequencies, many do in fact show the red-shifted spectroscopic signature of a classical H-bond.

This type of H-bonding was originally accepted for the case of strong H-bond acceptors and relatively acidic C–H species such as hydrogen cyanide, acetylenes, aldehydes, and halogenated alkanes.^{25a} Electron withdrawing groups at carbon facilitate H-bond formation by increasing acceptor ability of the $\sigma^*_{\text{C-H}}$ orbitals. The magnitude of shifts in the C–H stretching frequencies (Figure 12.17) suggests that the ability of hydrocarbons to serve as H-bond donors is hybridization dependent, following the order $sp > sp^2 > sp^3$.²⁶

Even such weak H-bond acceptors as π -bonds and aromatic systems were shown to form C–H... π H-bonds (Figure 12.18).³³ Furthermore, the common edge-to-face geometry for the interaction of aromatic systems can be described as a weak H-bond with relatively small but not negligible contributions from $\pi \rightarrow \sigma^*_{\text{C-H}}$ and $\sigma_{\text{C-H}} \rightarrow \pi^*$ interactions.

Blue-shifted H-bonds The reversal of the trademark behavior of H-bonds is the seemingly paradoxical C–H bond shortening and the blue-shift in the respective IR stretching frequency observed in the so-called “improper” or blue-shifting H-bonds.³⁴ This behavior reflects rehybridization as the second structural force

Red-shifted C-H H-bonding in alkyl C-H groups

	R_3C-H (CCl_4)	$R_3C-H \cdots O^--S^+(CD_3)_2$ (0.95 M)			$R_3C-H \cdots N$ (2.0 M)		
	ν_{CH}	$\nu_{CH(free)}$	$\nu_{CH(H-bond)}$	$\Delta\nu_{CH}$	$\nu_{CH(free)}$	$\nu_{CH(H-bond)}$	$\Delta\nu_{CH}$
	2998	shoulder	2918	80	2996	2883	113
	2987	shoulder	2921	66	2983	2891	92
Br_3C-H	3031	shoulder	2981	50	3029	2963	66
I_3C-H	3011	3008	2968	40	3007	2952	55
Cl_3C-H	3020	shoulder	2991	29	shoulder	2974	46
F_3C-H	3036	shoulder	3008	28	3037	none	—

Figure 12.17 Examples of red-shifted C-H stretching frequencies in C-H...X H-bonds cm^{-1} . (Data from ref. 26.)

ν_{CH}	3289	3289	3289
$\nu_{CH(H-bond)}$	3240	3276, 3273	3286, 3270
$\Delta\nu_{CH}$	49	~15	3, ~20

Figure 12.18 Red-shifting observed for acetylene C-H stretching frequency ($\Delta\nu$, cm^{-1}) as a result of H-bond formation with water, benzene, and ethylene.

controlling the evolution of X-H bond length in the process of X-H...Y bond formation (Figure 12.19).³⁵ Blue-shifting is observed when the hyperconjugative component is relatively weak, allowing rehybridization effects to dominate. Importantly, there is no fundamental difference between the two types of H-bonds, as all structural changes associated with H-bond formation stem from a balance of both effects.

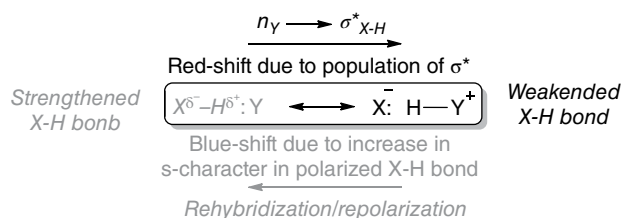


Figure 12.19 Factors responsible for structural and spectroscopic consequences of H-bond formation. Different dominating effects give “normal” red-shifted H-bonds and “improper” blue-shifted H-bonds.

Blue-shifted H-bonds were originally thought to be reserved for C-H...Y H-bonds, but it has been suggested that blue-shifting can be much more general.³⁶ While many physical descriptions of blue-shifting in H-bonds are available,^{34,37} a readily understandable chemical description of these seemingly anomalous observations is available within the framework of classic organic structural theory.³⁵

As already mentioned, both electrostatic attraction of dipoles (inherent and induced) and $n_Y \rightarrow \sigma^*_{X-H}$ interactions are responsible for the attraction that gives rise to H-bonds. In contrast, to the strong hyperconjugative interactions that cause the proper red-shifted H-bond, rehybridization/repolarization becomes important when hyperconjugative interactions are relatively weak. According to Bent's rule,^{17,22} X will direct hybrid orbitals with increased s-character towards hydrogen as it becomes more electropositive,³⁸ giving a shorter, stronger, and more polarized X-H bond, resulting in a blue-shift in the IR spectrum.³⁵

The delicate balance of charge transfer and rehybridization becomes apparent when examining the H-bonds between F₃C-H and water (blue-shifted) and F₃C-H and Cl⁻ (red-shifted, Figure 12.20).³⁵ Relative to the “free” C-H bond, the C-H-bonds in the two complexes show an increase in s-character, C-H bond polarization, and σ^*_{C-H} population. Interestingly, the F₃C-H...Cl⁻ H-bond actually shows a greater percentage of s-character (36.1% vs. 33.6%) and a more polarized bond (64.3% vs. 61.3%), relative to the blue-shifted F₃C-H...OH₂ H-bond. Despite these larger changes in hybridization and polarization, the hyperconjugative charge transfer acts as a dominating force leading to the red-shifted F₃C-H...Cl⁻ H-bond. Interestingly, at the greater F₃C-H...Cl⁻ separations, the C-H bond initially undergoes a contraction (which should lead to a blue-shift in the respective IR stretching frequency) and only at the distances that the direct orbital overlap with the chloride lone pair is sufficiently large to make the $n_{Cl} \rightarrow \sigma^*_{C-H}$ interaction sufficiently strong, is the C-H bond contraction replaced by C-H bond elongation. This analysis illustrates that the same factors are involved in the two H-bond types and it is the balance of them which controls the observed shift in the C-H stretching frequency.

		Blue-shifted	Red-shifted
Blue-shifting factors:			
s-character, %	31.9	33.6	36.1
C-H polarization, % at C	59.3	61.3	64.3
Red-shifting factors:			
σ^*_{C-H} population, a.u.	0.0351	0.0375	0.0619
$n \rightarrow \sigma^*_{C-H}$, kcal/mol	—	8.6	24.9
		Hybridization dominates	Hyperconjugation takes over as the main factor
C-H bond length, Å	1.088	1.086	1.095
Interaction energy, kcal/mol	—	5.2	16.6

Figure 12.20 Structures, energies, and NBO analysis of blue- and red-shifted H-bonds at the MP2/6-31+G* level of theory (from ref. 35).

“No-shift” H-bonds The logical consequence of the existence of blue- and red-shifted H-bonds is that at the proper distance, the factors responsible for the red- and blue-shift in X-H stretching frequencies may cancel and no shift will be observed.³⁹ Such nearly exact cancellation was found in cage molecules where

O-H...F contacts are forced to remain in close proximity (Figure 12.21). While NMR and proton exchange experiments suggest a strong H-bonding interaction, the IR shifts in solvents that do not act as H-bond acceptors were nearly identical when the O-H group is positioned *in* or *out*. In solvents that are able to participate in H-bonds (i.e. DMAP) the orientation where the OH group is *out* shows a significant red-shift, while the *in* orientation shows no significant shift.

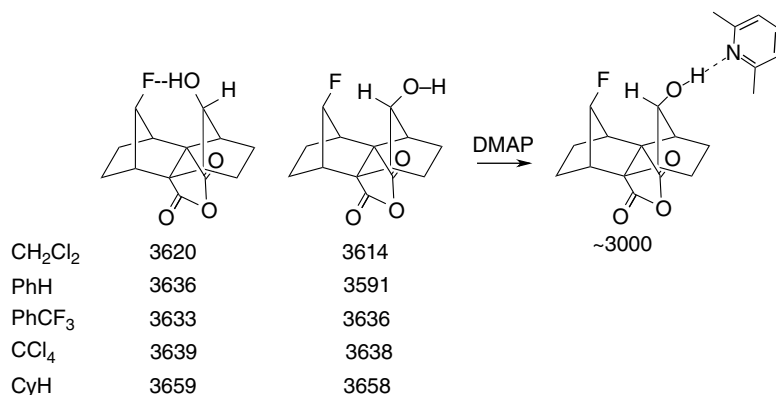


Figure 12.21 No-shift H-bonds where stereoelectronic and hybridization effects nearly cancel to give virtually no shift in the O-H stretching frequency (cm⁻¹).

12.2 Nuclear magnetic resonance spectroscopy

The value of NMR spectroscopy is that it provides information directly related to chemical structure.^{40,41} As stereoelectronic effects redistribute electron density within a molecule, parameters measured by NMR are extremely sensitive to such electronic perturbations. In this section, we focus on the NMR aspects that are directly associated with stereoelectronic effects. From electron density surrounding specific atoms given by chemical shifts to bond lengths and dihedrals provided by coupling constants between nuclei, NMR provides invaluable information about orbital interactions. The caveats do exist, however, especially in the analysis of carbon NMR data where paramagnetic terms can lead to counterintuitive consequences and in the anisotropic spatial response of many functional groups to external magnetic fields. Our discussion will be relatively short due to the existence of an excellent treatise of structural effects in NMR spectroscopy of organic molecules by H. Reich at UW Madison. This free resource is available online.⁶ It is written with organic chemists in mind, and provides a thorough discussion that does not need to be duplicated in the present work.

12.2.1 Stereoelectronic effects on chemical shifts

Factors responsible for chemical shifts can be quite complex, stemming from a combination of diamagnetic contributions from both directly bound electrons and neighboring group electrons (neighboring group anisotropy), as well as paramagnetic effects caused by electron promotion from ground state to excited state orbitals. Stereoelectronic effects influence all of these terms and, while the specific factors contributing to observed chemical shifts are not always clear-cut, we will provide examples where molecular structure and orbital directionality plays a large role in observed chemical shifts.

We will start with a short discussion of the origin of NMR chemical shift. The observed chemical shift is determined by the net magnetic field “felt” by each nucleus in a molecule. The net magnetic field at an atom, B_{net} , can be related to the applied magnetic field, B_0 , using the following relationship:

$$B_{net} = B_0(1 - \sigma) \quad (12.1)$$

where σ is the screening constant, which accounts for shielding. The screening constant depends on many factors, three of which are given below.

$$\sigma = \sigma_{diam} + \sigma_{para} + \sigma_{nl} \quad (12.2)$$

The diamagnetic contributions σ_{diam} come directly from induced magnetic fields of electrons directly bound to the atom, while the non-local term σ_{nl} stems from through-space interactions and anisotropic effects of neighboring atoms or functionalities. Paramagnetic contributions σ_{para} are not easily understood within simple models. We will discuss them later.

The most obvious way for orbital interactions to affect the observed NMR spectra is through delocalization of electron density. As electron density is redistributed via stereoelectronic effects, nuclei will be either shielded or deshielded depending on the specific effects that dominate. As a result, stereoelectronic effects can significantly alter NMR chemical shifts.

12.2.2 Diamagnetic effects in ^1H NMR

The diamagnetic contributions from 1s hydrogen electrons dominate in ^1H NMR chemical shifts. The closer electrons are to the nucleus, the stronger the diamagnetic shielding. Consequently, the electronegativity of directly bound atoms plays a large role in ^1H chemical shifts. For example, the chemical shift of the methylene protons are observed much further upfield in tetraethylsilane than in fluoroethane (0.6 vs. 4.4 ppm).⁴⁰ This effect, however, is not absolute and can be overridden by other factors (vide infra). Even for simple ethyl halides, the chemical shifts at the **Me** group do not follow the trends expected from the relative electronegativity of β -halogens (the chemical shift increases from F to I: $\text{MeCH}_2\text{F} < \text{MeCH}_2\text{Cl} < \text{MeCH}_2\text{Br} < \text{MeCH}_2\text{I}$).

Diastereotopic protons As diastereotopic protons reside in different chemical environments, different chemical shifts and splitting patterns are observed. We will discuss this in more detail in the part dedicated to spin-spin coupling constants.

Anomeric effects Hyperconjugative electron transfer into σ^* C-H orbitals can lead to increased shielding and decreased chemical shift of protons antiperiplanar to unshared electron pairs. This effect in tris-amines is illustrated in Figure 12.22.⁴² In the acyclic compound, where free rotation is possible, the methyl resonance appears at 3.02 ppm. When lone pairs are forced to be syn-periplanar, the relative inefficiency of anomeric effects allows

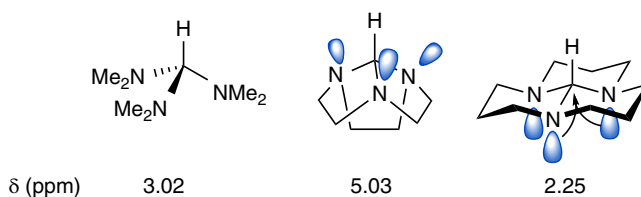


Figure 12.22 Effects of the adjacent lone pairs' orientation on the chemical shift of C-H bond protons.

inductive electron withdrawing effects to cause a significant downfield shift (~ 5 ppm). However, when lone pairs are constrained to the antiperiplanar orientation, $n_{\text{N}} \rightarrow \sigma_{\text{C-H}}^*$ interactions redirect electron density to the C-H bond, effectively shielding the methane proton, which now displays a chemical shift of 2.25 ppm.⁴³

Such effects are useful for distinguishing between axial and equatorial protons as long as their position relative to the adjacent lone pairs is reliably established. For example, Anderson and coworkers illustrated that the relative chemical shift values of the axial and equatorial C2-H hydrogens in 1,3-diazacyclohexanes can be inverted when orientation of the lone pairs is changed by structural constraints (Figure 12.23).⁴⁴ In 1,3-di-*tert*-butyl-5-methyl-1,3-diazacyclohexane the bulky *tert*-butyl groups are oriented equatorially, leaving the nitrogen lone pairs axial. Strong shielding of the axial proton (~ 2.4 ppm) is consistent with the contribution of the $n_{\text{N}} \rightarrow \sigma_{\text{C-Hax}}^*$ interactions. Axial/equatorial proton assignments in these systems are reliably confirmed by the presence of W-constants (vide infra) with the equatorial protons at C5. Conversely, the lone electron pairs on nitrogens in 1,5-diazabicyclo[3.2.1]octane are directed equatorially. A much smaller difference in the proton chemical shifts is observed, with the equatorial proton being slightly more shielded.

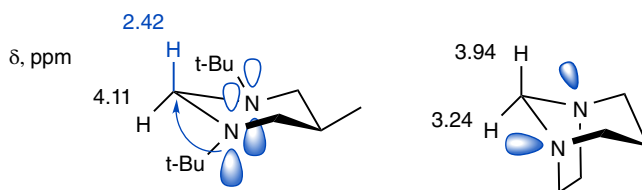


Figure 12.23 Effects of the adjacent lone pairs' orientation on the chemical shift of axial and equatorial protons in conformationally constrained 1,3-diazacyclohexanes.

C-H bonds adjacent to π -systems Hyperconjugative interactions can also change chemical shifts for C-H bonds adjacent to π -systems. For instance, the chemical shifts of the methyl groups of toluene, propene, acetone, and 2-butyne are shifted downfield relative to aliphatic protons (Figure 12.24). While such effects have been attributed to the anisotropic effects of neighboring groups, the stereoelectronic contribution becomes apparent when examining specific substituent effects more closely (with the added caveat that stereoelectronics can also alter neighboring group anisotropic effects). For instance, π^* -orbitals in esters and amides are weaker acceptors than π^* -orbitals in ketones. This difference is reflected in the upfield chemical shift of the CH_3 -carbonyl groups in ethyl acetate (2.04 ppm) and *N,N*-dimethylacetamide (2.08 ppm) relative to acetone (2.17 ppm). Analogous trends are observed when donor and acceptors are attached *para* to benzylic protons: donors cause upfield shifts and acceptors cause downfield shifts. When comparing such effects, it is prudent to keep the interacting species separated in space in order to avoid contributions from non-local interactions.

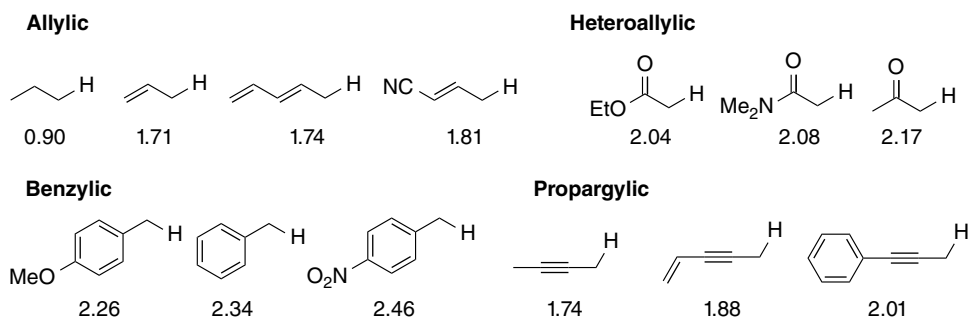


Figure 12.24 Selected effects of conjugation on ^1H NMR chemical shifts.

The effects of π -conjugation are illustrated by the large changes in the chemical shifts of vinyl protons as a function of substitution. Whereas the geminal hydrogens are deshielded by both the OEt and the NO_2 group, the effects on the vicinal protons do follow expectations based on the dominant delocalizing interactions – shielding by the vicinal p-donor groups (e.g. OR, NR_2) and deshielding by the π -acceptor (e.g. NO_2). However, note that cis-protons are deshielded relative to the trans protons in both the OEt- and NO_2 -substituted ethylenes, suggesting that the chemical shifts have a significant contribution from the local through-space interactions between the cis-protons (Figure 12.25).

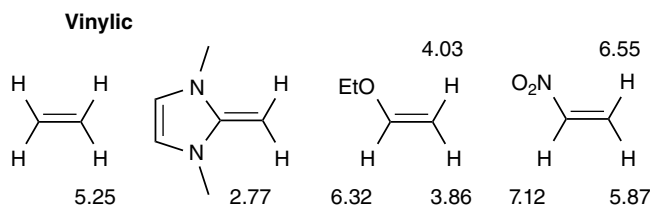


Figure 12.25 Substituent effects on the chemical shifts of vinyl protons.

Another example of how considerations based solely on electronegativity can be misleading is provided by chemical shifts of alkyne protons. Despite the greater electronegativity of sp^2 -hybridized carbons in comparison to sp^3 -hybridized carbons, alkynes show C-H bonds that are significantly shielded in comparison with alkenes. These effects originate from anisotropy of local currents in such molecules (Figure 12.26).

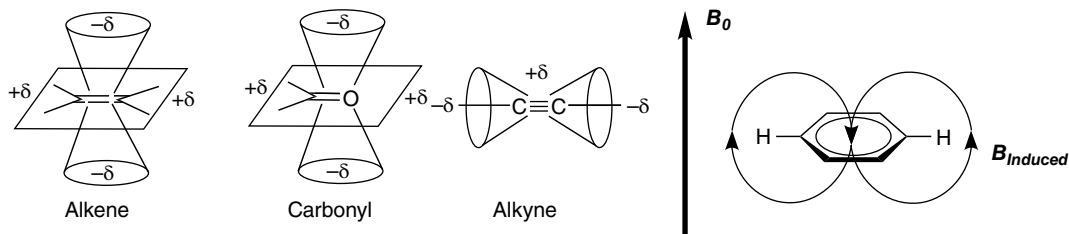


Figure 12.26 Anisotropic effects on local fields on the NMR shielding of protons in π -functionalities.

Furthermore, symmetry of orbital interactions in cyclic systems can lead to either diamagnetic (aromatic) or paramagnetic (antiaromatic) ring currents. Such effects have been discussed extensively in chemical textbooks and will not be analyzed here.

12.2.3 Paramagnetic effects in ^{13}C NMR

While diamagnetic contributions act to shield nuclei from the applied magnetic field (B_0), paramagnetic contributions are deshielding. Paramagnetic contributions stem from electronic promotion from the ground state to the excited state. Of course, the energy difference between the ground and excited states are much larger than the energy of magnetic field. However, even a very small contribution from the excited state structure in a multiconfigurational ground state wavefunction can have a very large effect on the observed NMR parameters. This term is unimportant for s-orbitals of ^1H nuclei but becomes dominant for ^{13}C NMR, due to the presence of p-orbitals on carbon. Their contributions can lead to puzzling behavior with counterintuitive stereoelectronic consequences.

For ^{13}C NMR, paramagnetic contributions described by Eq. (12.3), outweigh the effect of the diamagnetic term.

$$\sigma_{\text{para}} \propto \Sigma Q / \Delta E(r^3) \quad (12.3)$$

where ΔE is the difference between filled and vacant molecular orbitals (i.e. the electronic excitation energy), r^3 is the average of (non s) orbital radii, and ΣQ is derived from charge density and bond orders (increases for multiple bonds).

Particularly strong paramagnetic deshielding is observed when the HOMO orbitals are orthogonal to LUMO orbitals (e.g. when a lone pair is orthogonal to a π -system). It is the contribution from $n_{\text{O}} \rightarrow \pi_{\text{C=O}}^*$ excitation that serves the key underlying force for the large downfield shifts in carbonyl compounds. The secondary role of electron density removal by the acceptor oxygen atom is illustrated by the similar large downfield shift in aryl systems containing an orthogonal lone pair, such as pyridine and phenyl lithium (Figure 12.27).⁴⁵

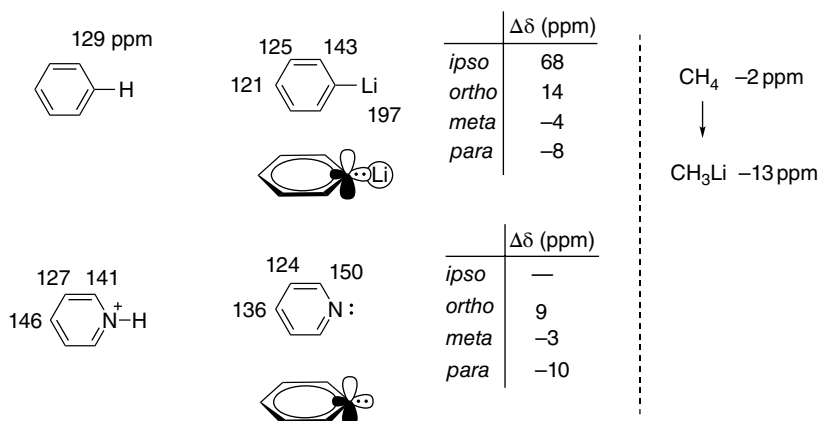


Figure 12.27 Large paramagnetic contributions to ^{13}C chemical shifts in phenyllithium and pyridine. Values from refs. 45a and 45c.

For Ar-Li, the downfield shift goes against expectations based on electron density. This observation illustrates the danger of using ^{13}C NMR for the analysis of stereoelectronic effects using logic directly transferred from ^1H NMR. It is especially surprising considering the opposite trends observed in comparison to methyl lithium.

Excitation of the triple bond is harder than that of the double bond, thus the paramagnetic term is less important, leading to more shielded ^{13}C in alkynes. Distortion of the triple bond in strained alkynes decreases the HOMO/LUMO gap, thus increasing the importance of the paramagnetic term and resulting in a downfield shift (Figure 12.28).

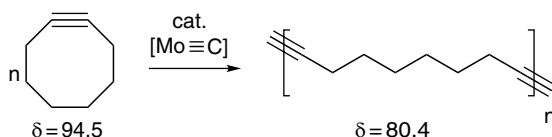


Figure 12.28 Conversion of strained cyclooctyne to the acyclic alkyne product can be conveniently monitored by NMR.⁴⁶

Another illustrative example where carbon NMR does not follow expectations based on electron density is the difference in the carbon chemical shifts for the stable carbene and the corresponding carbenium ion. In solution, the carbon atom at the *neutral* carbene center is significantly more deshielded (214 ppm) in comparison to the carbon atom at the *positively* charged carbenium center (135 ppm, Figure 12.29).⁴⁷ The explanation to this unexpected behavior is similar to that for the Ph-Li example analyzed above – carbenes also contain two orthogonal orbitals (the in-plane lone pair and the out-of-plane empty p-orbital), accounting for a large contribution to the paramagnetic term in their NMR.

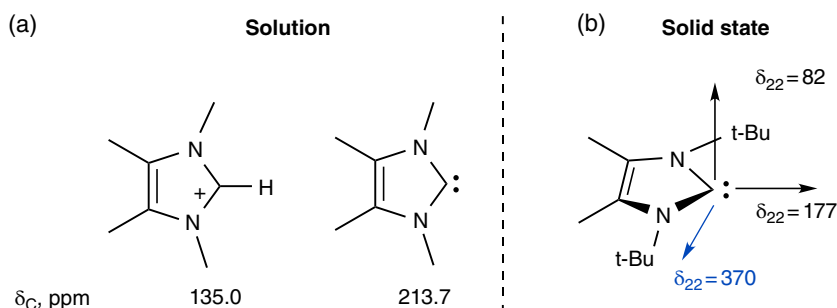


Figure 12.29 Why carbene carbon is more deshielded than carbenium ion carbon: (a) comparison of carbenium ion and carbene carbon chemical shifts. (b) anisotropic contributions to carbene carbon chemical shift tensor in the solid state.

Additional information can be obtained in the solid state where conversion of the isotropic chemical shift into a tensor opens additional opportunities for stereoelectronic insights inherent to the directionality components of the tensor. Calculations indicate that the orientation of the chemical shielding tensor of the carbene is such that the most shielded component is perpendicular to the molecular plane, whereas the least shielded component is perpendicular to the directions of both the lone pair and the p-orbitals.

12.2.4 Through-space interactions – γ -substituent effects

Additional structural effects on ^{13}C NMR chemical shifts originate from the spatial proximity of groups that are not directly connected. In particular, these effects are observed when hydrogen atom is changed to a substituent at the γ -carbon (i.e. $\text{C}^*-\text{C}-\text{C}-\text{H} \rightarrow \text{C}^*-\text{C}-\text{C}-\text{X}$). If $\text{X}=\text{Me}$, and the spatial proximity is enforced by structural constraints or conformational energies, the upfield shift at C^* is ~ 6 ppm. For conformationally flexible systems, the observed upfield shift reflects the relative abundance of such spatially close conformations (e.g. gauche or eclipsed) at the equilibrium.

The γ -effects can be useful in conformational assignments if the γ -carbon is close to the observed carbon in one conformer but not in the other, e.g. in E- and Z-isomers of alkenes. A carbon group that is cis-to a substituent will be generally upfield from the same carbon in the other isomer where this group is cis to a hydrogen. For a theoretical analysis of this phenomenon, see ref. 48 (Figure 12.30).

Similar local anisotropic effects can mask the effect of bond polarization in diaryl acetylenes (tolanes). A number of *ortho*- and *para*-substituted tolanes have been examined to test the effect of alkyne polarization on the ^{13}C chemical shifts.⁴⁹ While bond polarization controls the relative chemical shifts in *p*-tolanes (more positive carbon displays a downfield shift), the trends in *o*-tolanes are complicated by the close proximity of the substituent to the alkyne (Figure 12.31). Local anisotropic contributions of *ortho*-substituents caused the *alpha*-alkyne carbon to display an upfield shift despite π -effects on alkyne polarization.

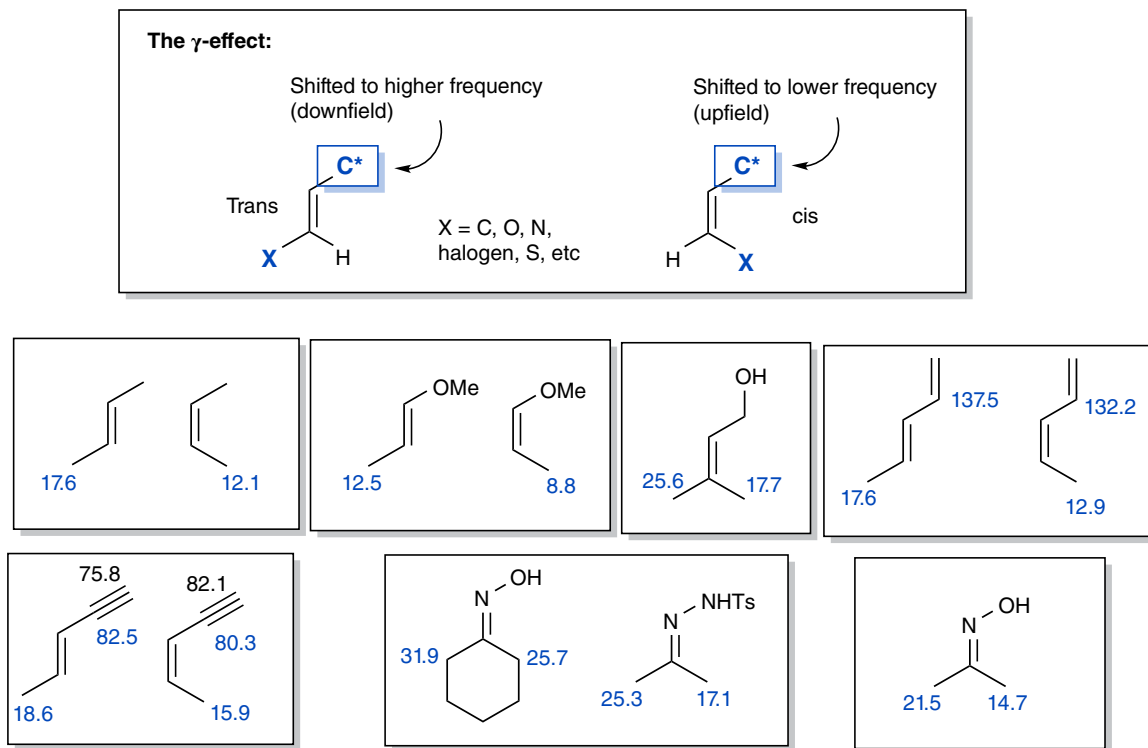


Figure 12.30 γ -Effects in ^{13}C NMR chemical shifts are useful for conformational assignments.

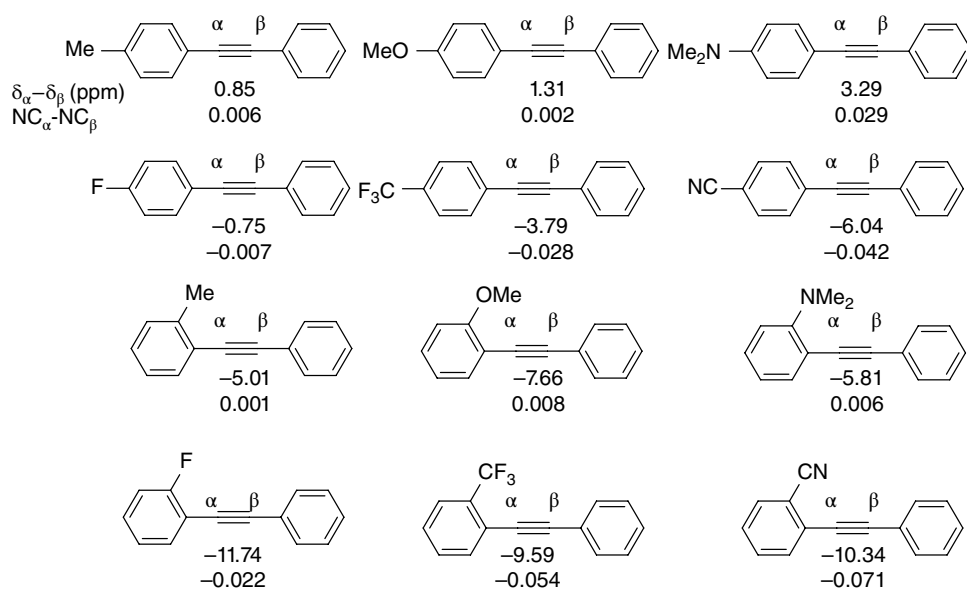


Figure 12.31 Local anisotropic effects in tolanes can mask the polarization effects on ^{13}C NMR.

Analogous effects can be observed in conformationally well-defined saturated compounds. The substituent effect on the γ -carbon of cyclohexane ring depends on the conformation. Because an axial substituent is gauche to the γ -carbon of the ring, it causes a significant upfield shift of ~ 4 – 7 ppm. On the other hand, an equatorial substituent is trans to the γ -carbon and causes a much smaller upfield shift of 0–3 ppm (Figure 12.32).

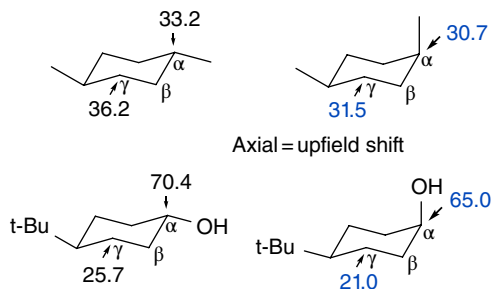


Figure 12.32 γ -Effects in ^{13}C NMR of cyclohexanes.

The introduction of a double bond anti to the C7-F bond of norborn-7-yl fluorides induces a large downfield fluorine shift that has been attributed to the $\pi \rightarrow \sigma_{\text{C-F}}^*$ homohyperconjugation.⁵⁰ These through-space interactions also have a significant effect on the direct $^1J_{\text{CF}}$ coupling. When the double bond is syn to the C-F bond, the corresponding effects are small (Figure 12.33).

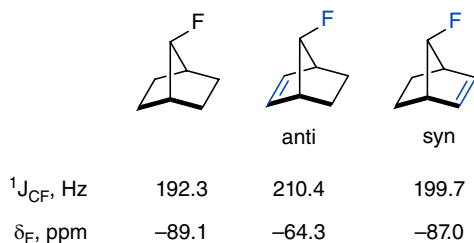


Figure 12.33 Effect of through-space $\pi \rightarrow \sigma_{\text{C-F}}^*$ interactions on selected NMR parameters.

12.2.5 Stereoelectronic effects on coupling constants

Spin–spin interactions, expressed as “coupling constants” or “J values”, have been widely applied in structure determination and conformational analysis of organic, inorganic, and biological molecules. Although NMR reports on the spins of nuclei, the nuclear spin–spin interactions are mediated by bonding electrons. Even though the use of the coupling constants in defining the three-dimensional structure has declined because of the success of the nuclear Overhauser effect (NOE) based techniques that can give precise interatomic distances, the coupling constants continue to play an important role by providing the torsion angle restraints for the structural calculations. In RNA and DNA, where the number of NOEs is fewer than in proteins, the couplings between protons of the furanose rings and other nuclei in the polynucleotide backbone play important role for the determination of the overall conformation. Similarly, polysaccharide conformation can often be deduced from vicinal and remote coupling constants. For the smaller chiral organic compounds, stereoelectronic effects on coupling constants are useful for the assignment of diastereotopic protons in methylene groups.

In the classic book on the theory of NMR, Pople and coworkers stated that “the existence of such coupling constants, therefore, is an indication of intrinsic delocalization of the bonding orbitals.”⁵¹ This statement directly follows from Eq. (12.4) that evaluates spin-coupling constants by MO theory:

$$J_{NN'} \sim (\beta\gamma)^2 h(\Delta E)^{-1} \sum_{st} \psi_s^*(N) \psi_t^*(N') \psi_t(N) \psi_s(N') \quad (12.4)$$

where β is the Bohr magneton, γ is the proton magnetogyric ratio and $\psi_s(N)$ is the value of molecular orbital ψ_s at the nucleus N , and ΔE is the energy gap between occupied and empty orbitals.

If MOs can be substituted by a set of delocalized or localized orbitals that would strictly correspond to bonds, lone pairs, and inner electrons, the equation above would predict no coupling constant for the protons in different bonds.

Therefore, spin coupling is the product of delocalization and should reflect stereoelectronic effects. Below, we will illustrate the use of the coupling constants in identification and study of stereoelectronic effects. Historically, each of the common J-constants (one-bond, two-bond, three-bond, and long range interactions, Figure 12.34) had its own specific role that we will touch upon below. However, due to the complexity of this important topic, this discussion will be selective rather than comprehensive.

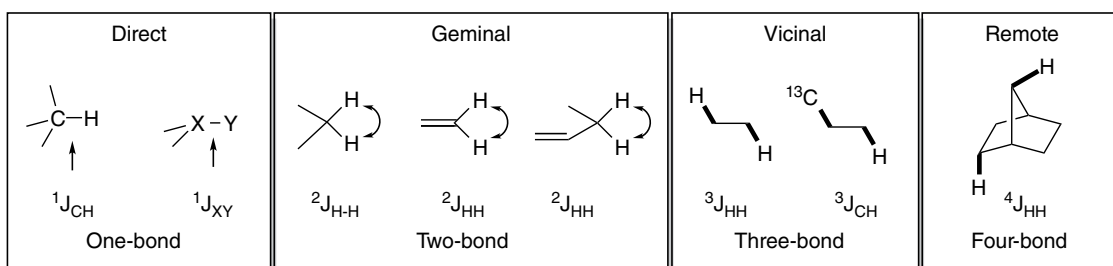


Figure 12.34 Representative coupling patterns.

12.2.5.1 One-bond (direct) coupling constants

For the chemically bonded nuclei, this coupling constant provides information related to the nature of the chemical bond as well as a variety of other effects related to electronic distribution, bond length and bond angles, substituent and conformational effects, etc.

For example, the general connection between $^1J_{C-H}$ and C-H bond strength/length leads to the strong dependence of these coupling constants from hybridization expressed by the well-known equation that connects spin-coupling constants with hybridization:

$$^1J_{C-H} = 500 s(i), \quad (12.5)$$

where $s(i)$ is the fractional s-character for the sp^n carbon hybrid forming the C-H bond.

This equation predicts ~2-fold difference in the magnitude of C-H coupling constants at an sp - and sp^3 -hybridized carbons with 50% and 25% of s-character in the C-H forming hybrids: ($500 \times (0.5) = 250$ Hz and $J = 500 \times 0.25 = 125$ Hz, respectively).

In order for a comparison to provide meaningful information regarding one of these effects, the contribution of all local effects, except for the one that is investigated, should change as little as possible. When

molecular connectivity is the same (i.e. for a pair of diastereotopic hydrogens in molecules of general YCH_2X type), the longer C-H bond is usually associated with the lower one-bond C-H coupling constant.⁵² Such correlations serve as the basis of the well-known phenomenon known as the Perlin effect.

Perlin effect In cyclohexane, the direct ^1H - ^{13}C coupling constants are smaller for axial hydrogens.⁵³ This phenomenon, commonly referred to as the normal Perlin effect,⁵⁴ reflects the greater length of the axial C-H bonds. Because bond lengthening in the axial position occurs as a result of hyperconjugative $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-H}}^*$ interactions of antiperiplanar C-H bonds in the axial position (Figure 12.35), the normal Perlin effect provides a connection between NMR spectroscopy and stereoelectronic effects.⁵⁵

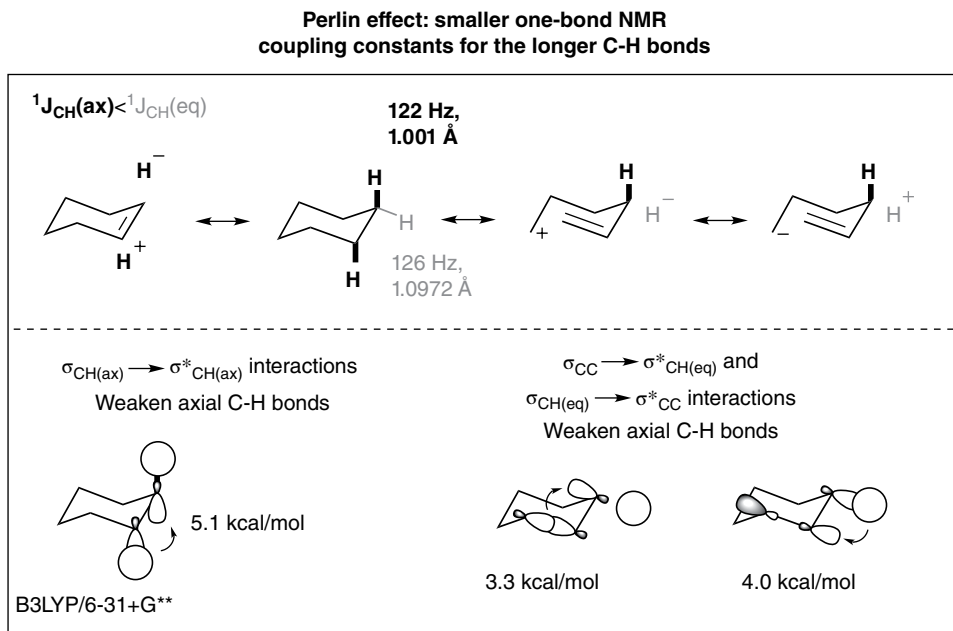


Figure 12.35 The Perlin effect, where smaller $^1J_{\text{CH}}$ values are observed experimentally for axial protons in cyclohexane, results from $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ interactions. The longer and weaker bonds are shown in bold. (All data is from ref. 55.)

These connections are easier to detect in molecules with stronger stereoelectronic interactions. The sensitivity of the direct H-C coupling constants to the stereoelectronic factors is widely used for stereochemical assignments, especially in carbohydrate chemistry.⁵⁶ The differences in the direct coupling constants are manifestations of elongation and weakening of C-H bonds participating in hyperconjugative interactions. All three previously discussed types of negative and neutral hyperconjugation ($\text{n} \rightarrow \sigma^*$, $\text{p} \rightarrow \sigma^*$, and $\sigma \rightarrow \sigma^*$ interactions) have been implicated in spectroscopic consequences of the Perlin effect.

Anomeric effects on C-H coupling The effects of negative hyperconjugation on the C-H coupling in six-membered saturated heterocycles was systematically investigated by Juaristi and coworkers (Figure 12.36).⁵⁷ The axial lone pairs of O- and N-atoms increase the magnitude of the Perlin effect by selectively weakening the axial C-H bond. The effect is clearly stereoelectronic because, once the lone pair of azacyclohexane is oriented equatorially, the difference between axial and equatorial $^1J_{\text{C-H}}$ values decreases to its value in

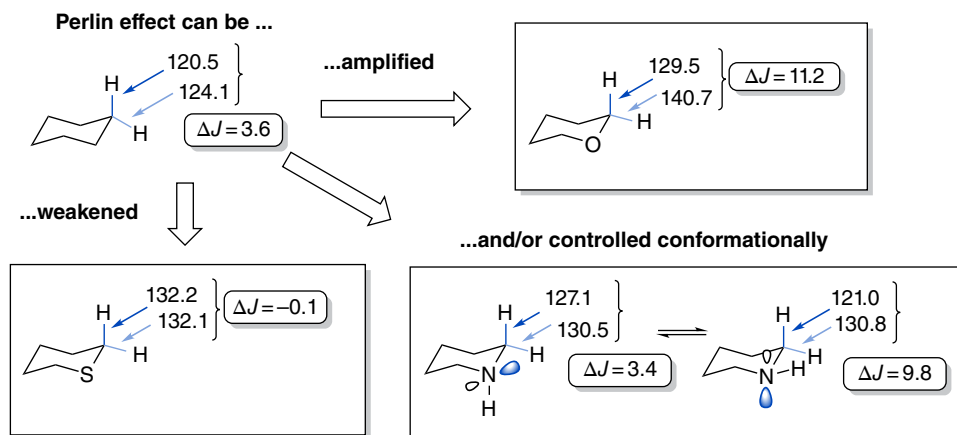


Figure 12.36 Selected direct C-H coupling constants calculated at B3LYP/6-31G(d,p) level.⁵³

cyclohexane. Interestingly, the lone pair of S-atom does not impose a similar effect, suggesting either the weakness of sulfur anomeric effect or presence of alternative delocalizing interactions that selectively weaken and elongate the equatorial C-H bond (vide infra) (Figure 12.36).

Another interesting feature of heteroatom substituted cyclohexane analogues is that the absolute values of the $^1J_{\text{C-H}}$ values are greater than they are in cyclohexane, even for the elongated axial C-H bonds. This feature may be attributed to the hybridization effects. As carbon atoms at the anomeric positions direct more p-character towards the heteroatoms to satisfy Bent's rule, more s-character has to be directed to the C-H bonds.

Spin coupling found application in studies of carbohydrate derivatives where the anomeric carbon-proton coupling is very sensitive to the configuration at C-1. For example, in the α - and β -anomers, the $^1J_{\text{C-H}}$ values for C-1 are 170 and 161 Hz respectively (Figure 12.37).⁵⁸ The smaller C-H coupling for the β -anomer reflects the relative weakening of the axial C-H bond. In making stereochemical assignments, one should be aware that the inversion of the relative magnitudes for axial/equatorial C-H coupling constants can be observed at the β -carbons relative to heteroatoms. This phenomenon reflects the alternative family of stereoelectronic effects and will be analyzed in the subsequent section.

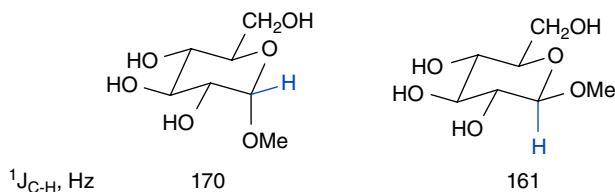


Figure 12.37 Manifestation of the Perlin effect, where anomeric C-H coupling is larger for the equatorial hydrogen than for the axial hydrogen.

Analogous effects were reported for N-containing saturated heterocycles (Figure 12.38) where a similar ~ 10 Hz decrease in the $^1J_{\text{CH}}$ value was observed for the axial C-H bond.⁴⁴ In rigid tricyclic orthoamides reported by Weisman, $^1J_{\text{CH}}$ for the C-H bonds antiperiplanar to three nitrogen lone pairs was much smaller (141 Hz) in comparison to C-H bonds syn to the lone pairs (184 Hz), suggesting a ~ 18 Hz per interaction decrease in the $^1J_{\text{CH}}$ value (Figure 12.38).⁴³

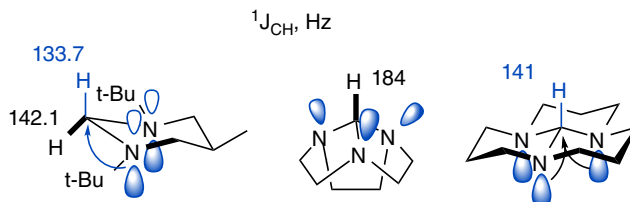


Figure 12.38 The effect of the adjacent lone pairs on the axial and equatorial $^1J_{CH}$ values in 1,3-di-tert-butyl-5-methyl-1,3-diazacyclohexane and on the $^1J_{CH}$ value for the central C-H bond in rigid tricyclic orthoamides.

The NMR consequences of the anomeric effect has been extensively studied for methylamine and methanol.^{41,59} Analysis of the electronic aspect of this effect suggested that it is generally dominated by the Fermi contact (FC)⁶⁰ term.^{41,61} The most common model is based on the observation that the $n \rightarrow \sigma^*$ interactions shorten the N/O-C bonds and lengthen the vicinal C-H bonds. Because the C-H bond antiperiplanar to the lone pair is longer than for the two gauche C-H bonds, this observation is consistent with the smallest $^1J_{CH}$ for the C-H bond antiperiplanar to the N/O lone pair. However, Contreras and coworkers⁴¹ reported that the spin coupling constant retained its dependence on the dihedral angle even if the three C-H bond lengths were kept identical. The calculated difference of ~ 16.6 Hz was similar to experimental data measured for geometric isomers of imines (Figure 12.39).

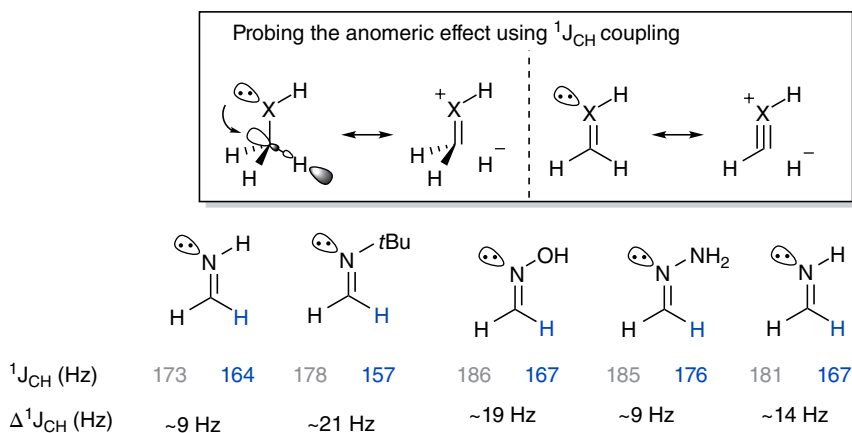


Figure 12.39 Anomeric effects on $^1J_{CH}$ couplings in N-containing molecules.^{41,62}

The stereoelectronic nature of the observed trends in the $^1J_{C-H}$ values is consistent with the conformational dependence of this NMR parameter in formate esters. For seven alkyl formates, the more abundant s-cis rotamer had $^1J_{C-H} \sim 7$ Hz greater relative to that in the minor s-trans conformer. In the s-trans geometry, the $n_O \rightarrow \sigma_{C-H}^*$ interaction weakens the C-H bond and decreases the magnitude of C-H spin coupling (Figure 12.40).⁶³

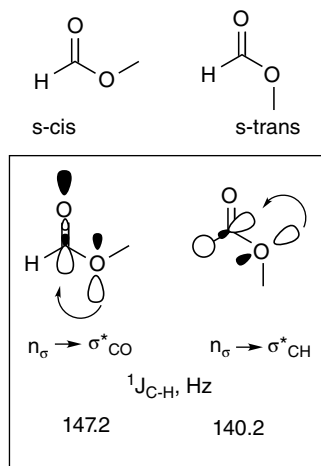


Figure 12.40 Conformational effects on direct C-H coupling in esters.

It is also interesting to compare the effects of hyperconjugative effects on direct C-H coupling constants with the effects of the C-H IR stretching frequency discussed earlier in this chapter. Gratifyingly, the earlier discussed competition between donation from the in-plane p-type lone pair of carbonyl oxygen to the $\sigma_{\text{C-H}}^*$ and $\sigma_{\text{C-X}}^*$ orbitals manifests itself in a similar way in NMR and IR parameters. Increase in the σ -acceptor ability of the C-X bond leads to the increase of $^1J_{\text{C-H}}$ and an attenuation of the Perlin effect. However, the correlation between IR and NMR parameters breaks down when carbonyl derivatives are compared to alkenes, suggesting the importance of local anisotropy effects for the NMR features of the carbonyl moiety (Figure 12.41).

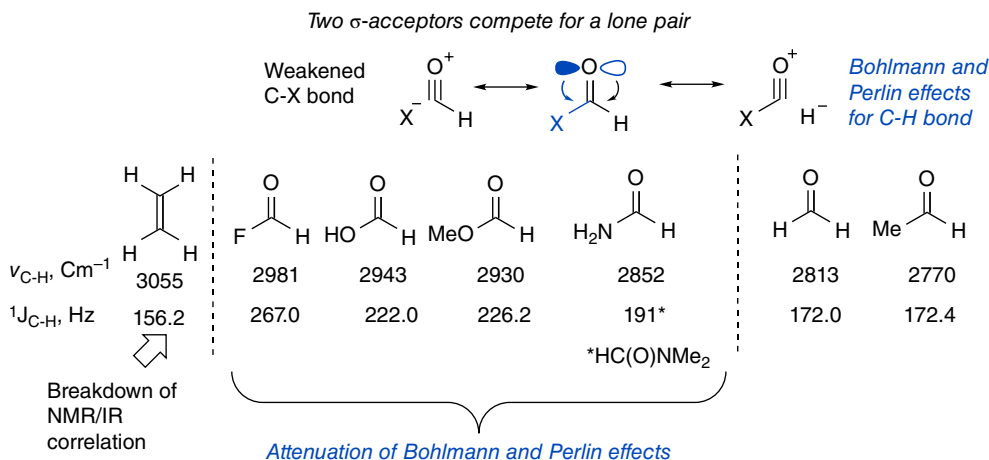


Figure 12.41 Comparison of Bohlmann and Perlin effects in carbonyl compounds. (NMR data is from ref. 64.)

However, the seemingly perfect unison of hyperconjugation and direct C-H coupling constants is not general. More recently, however, Cuevas, Perrin, Juaristi, and coworkers showed the simple picture suggested

by the above data needs to be reconsidered. Computational analysis of structures with systematic variations in the HCOC dihedral angle τ in ethers revealed that, although the maximum $n_{\text{O}} \rightarrow \sigma_{\text{CH}}^*$ delocalization and minimum $^1J_{\text{CH}}$ ought to be at $\tau=90^\circ$, there is no minimum at this geometry ($^1J_{\text{CH}} \approx 135$ Hz). Instead, the $^1J_{\text{CH}}$ values monotonously decrease from $\tau=180$ to 0° (138.6 to 129.3 Hz).⁶⁵ Similar analysis based on experimental data suggested that direct C-C coupling constant at the anomeric carbons of ethers also cannot be primarily derived from $n_{\text{O}} \rightarrow \sigma_{\text{CC}}^*$ delocalization.⁶⁶ Although the contribution of negative hyperconjugation is not negligible, the electronic origin of these intriguing observations seems to be mostly based on polarization effects associated with the local dipole-dipole interactions. Such caveats are important to keep in mind when proceeding to the further discussion of the stereoelectronic features in NMR analysis.

Reverse Perlin effect In contrast to cyclohexane, axial protons at the β -carbons of heterosubstituted cyclohexanes may have coupling constants larger than those of the equatorial protons (i.e. the *reverse* Perlin effect).^{67,68} In 1,3-dioxanes and 1,3-dithianes, equatorial C-H bonds at the five-position have been shown to display this behavior (Figure 12.42).

The term “reverse” can be misleading for these systems, because the normal and the reverse Perlin effects share the same structural origin – the shorter C-H bond has a greater C-H coupling constant. In this sense, the “reverse” Perlin effect is perfectly normal!

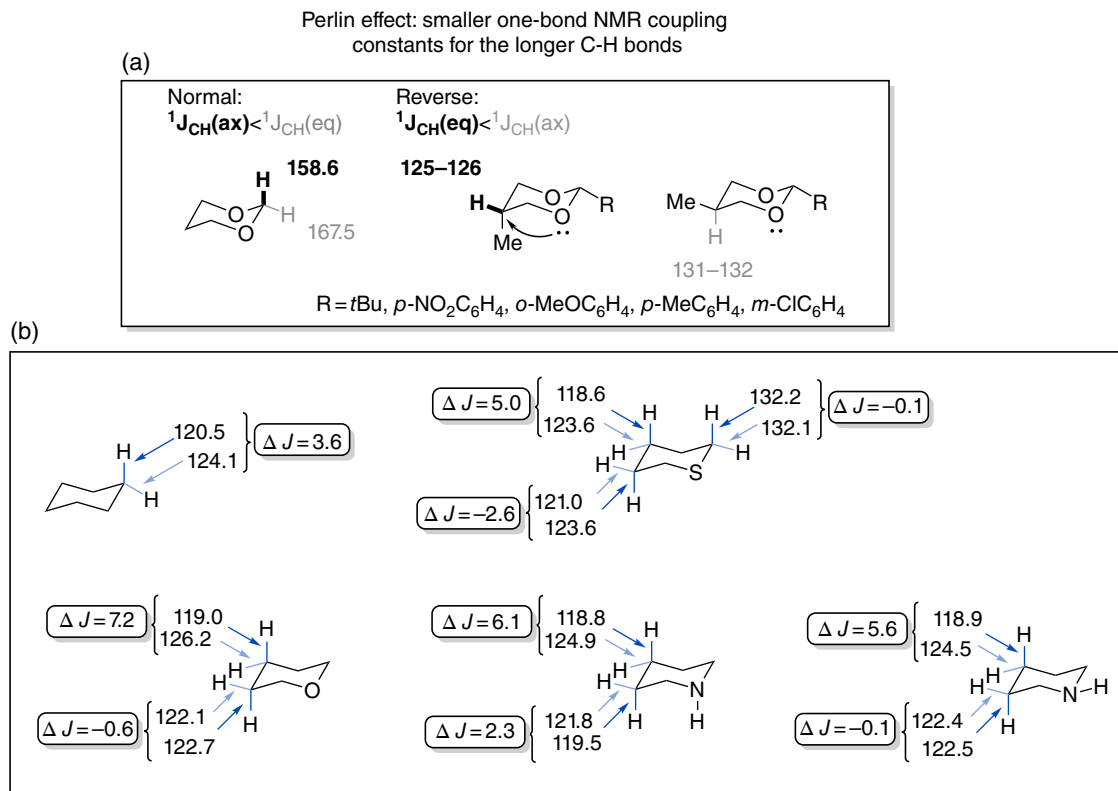


Figure 12.42 Experimental (a) and theoretical (b), calculated at B3LYP/6-31G(d,p) level⁵³ data illustrating the differences between axial and equatorial C-H couplings constants in cyclohexane and its heteroatomic analogues.

The discovery of the reverse Perlin effect led to subsequent refinement of the general picture for homoanomeric effects. For example, the earlier suggestion that the W-arrangement of interacting orbitals⁶⁶ (pseudoequatorial lone pair $\rightarrow \sigma_{\text{CH}(\text{eq})}^*$) is responsible for the reverse Perlin effect in 1,3-dioxanes has been tested using NBO analysis. It was found that the W-effect is weak in this molecule (<0.1 kcal/mol, B3LYP/6-31+G**) and cannot be the primary interaction responsible for the reverse Perlin effect. Instead, the equatorial C-H bond elongation and weakening originates from interaction with the higher energy p-like pseudoaxial lone pair (2.7 kcal/mol, B3LYP/6-31+G**, Figure 12.43).⁶⁷ The balance of other vicinal interactions that involve the equatorial C-H bonds does not change strongly. Even though $\sigma_{\text{CH}(\text{eq})} \rightarrow \sigma_{\text{CO}}^*$ interactions are stronger in dioxanes than in cyclohexane as a result of the better acceptor ability of the C-O bond, the reverse $\sigma_{\text{CO}} \rightarrow \sigma_{\text{CH}(\text{eq})}^*$ is decreased. The remote homoanomeric effect is a relatively small contribution but, when all other effects are nearly balanced, it can serve as the final drop needed to shift the balance towards the reversal of normal Perlin effect.

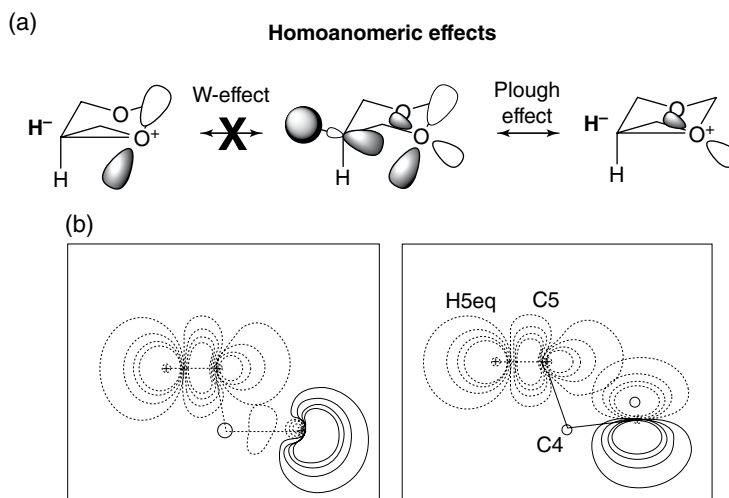


Figure 12.43 (a) Reverse Perlin effect originates from homoanomeric effects in saturated heterocycles. (b) Overlap between the high energy p-like pseudoaxial lone pair and σ_{C5}^* is larger than the overlap with the pseudoequatorial lone pair and is responsible for the lengthened $\text{C}_5\text{-H}_{\text{eq}}$ bonds.⁶⁷

In 1,3-dithianes, the homoanomeric effects, while present, are of lesser importance than in 1,3-dioxanes. Interestingly, the C-S bonds in dithianes are better donors and acceptors than the C-C bonds in cyclohexane and C-O bonds in dioxanes, giving stronger interactions with equatorial protons at C-5 (Figure 12.44, also see Chapter 5 for a discussion of donor and acceptor ability of σ -bonds).⁶⁷

Umpolung of anomeric effect – NMR consequences of positive hyperconjugation Hyperconjugative interactions involving $\sigma_{\text{C-H}}$ bonds and the π -systems (carbonyl, thiocarbonyl, and alkene) were evaluated from computed C-H coupling constants. Large effects were observed at the α -positions. $\sigma_{\text{C-Hax}} \rightarrow \pi_{\text{C=Y}}^*$ and/or $\pi_{\text{C=Y}} \rightarrow \sigma_{\text{C-Hax}}^*$ hyperconjugative interactions were the largest for the thiocarbonyl group, followed by the carbonyl and, finally, the methyldene group (Figure 12.45). Interestingly, no inverse Perlin effects were found at the β -carbons.⁶⁹

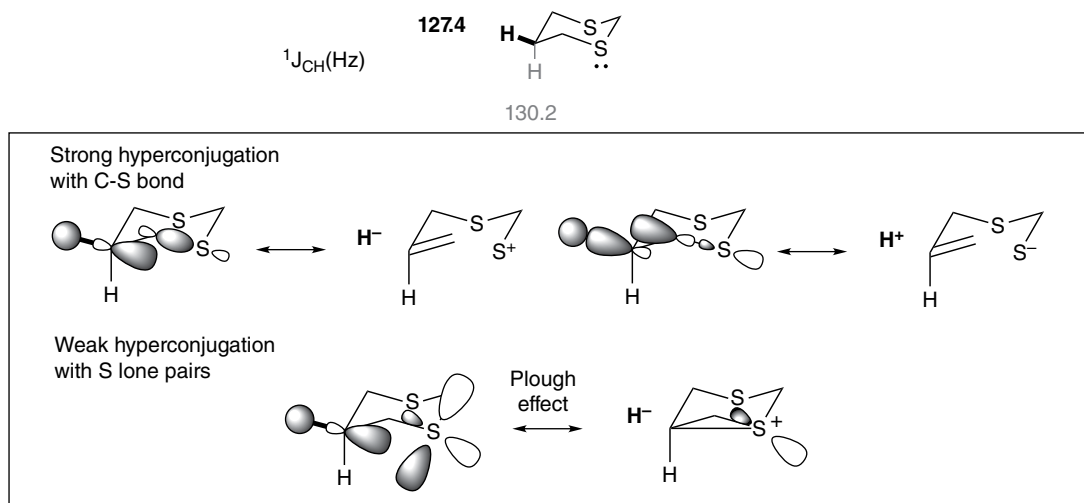


Figure 12.44 Reverse Perlin effect in 1,3-dithianes. $^1J_{\text{CH}}$ values (Hz) from ref. 55.

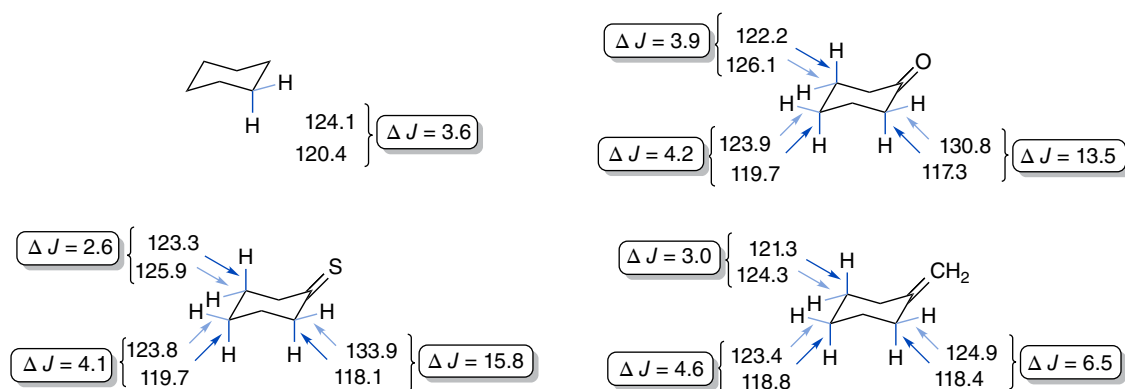


Figure 12.45 Effect of interactions between $\sigma_{\text{C-H}}$ bonds and π -systems on the direct C-H coupling constants, calculated at B3LYP/6-31G(d,p) level⁵³

Anomeric effects on C-C coupling Although the probability of two ^{13}C atoms to be directly connected at the natural abundance is exceedingly low (i.e. $\sim 0.01\%$, or one molecule out of 10,000!), methods based on the observation of ^{13}C satellites in the ^{13}C NMR spectra with the concomitant “suppression” of the signals of the principal isotopomers (i.e. the INADEQUATE technique) greatly facilitated the measurement of C-C coupling constants in samples with a natural isotopic content.⁷⁰ Such constants provide valuable information about the nature of carbon hybridization, overlap, bond strength, etc.⁷¹ In this section, we will provide a short selection of examples that describe how the direct C-C constants respond to changes in the orientation of the substituents at the respective C-C bond.

For example, significant effects are observed in the heteroanalogues of cyclohexane. In such systems, C-C coupling is noticeably decreased for the axial C-C bonds adjacent to heteroatoms. The effect can be cumulative, e.g. at the C2 of 1,3-dioxane where lone pairs of the two oxygen atoms can interact with the axial substituent (Figure 12.46).⁷²

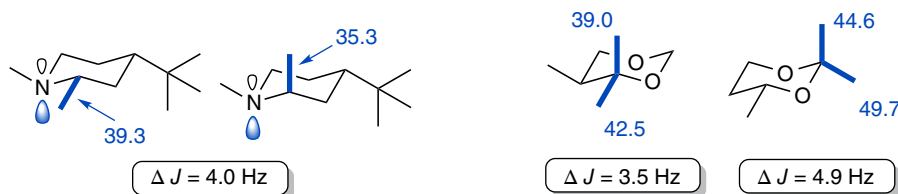


Figure 12.46 Effects of negative hyperconjugation at the direct C-C coupling at anomeric positions.

Krivdin and coworkers reported that one-bond C-C coupling constants at the sp^2 carbon of oximes were ~ 7 Hz smaller for the C-C bonds anti to the lone pair.⁷³ Analogously, the coupling constant for C-C bonds that are anti to the nitrogen lone pair was always about 10 Hz smaller (Figure 12.47).⁷⁴

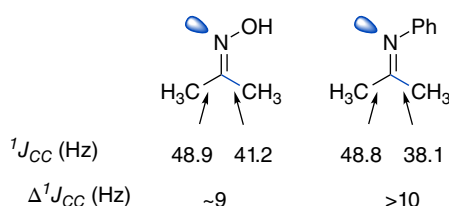


Figure 12.47 Representative $^1J_{CC}$ values for syn and anti substituents in oximes and imines.

C-C Coupling constants calculated using second order polarization propagator approach (SOPPA) are in a good agreement with the available experimental data and can be used for conformational analysis in the N-containing carbonyl derivatives (Figure 12.48).⁷⁵

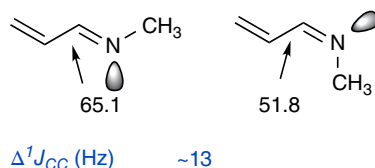


Figure 12.48 Effects of imine stereochemistry on the C-C coupling constants.

The shift from the s-trans-conformer of alkyl vinyl ethers to the s-trans geometry where the σ -type oxygen lone pair is antiperiplanar to the $\sigma_{C=C}^*$ orbital the double bond leads to a ~ 4 Hz decrease in the respective direct C-C constant (Figure 12.49).⁷⁶

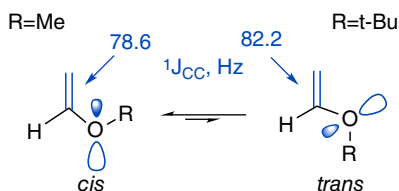


Figure 12.49 Conformational effects of on C-C coupling constants in vinyl ethers.

Increased C-C coupling constants at allylic carbons with electron acceptor substituents can be potentially attributed to the importance of $\pi_{C=C} \rightarrow \sigma_{C-X}^*$ hyperconjugation that increases the $=C-C-X$ bond order.⁷⁷ A similar effect is observed for carbons that connect two π -systems where increase in the $=C-C=$ bond order parallels the increase in the CC NMR coupling (Figure 12.50).

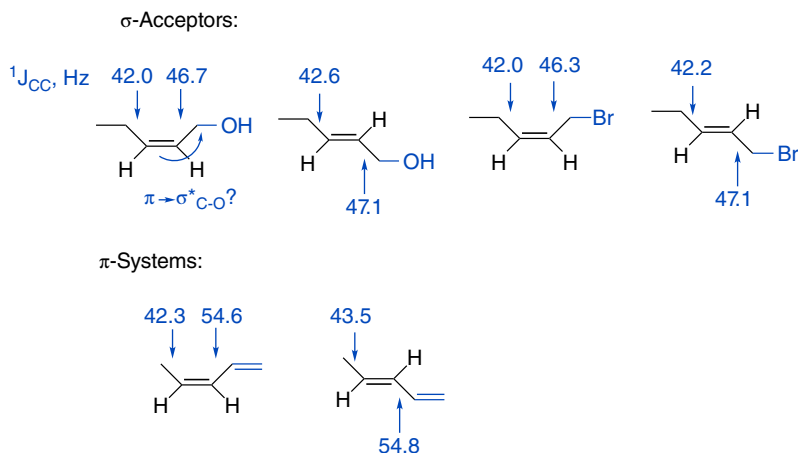


Figure 12.50 Increased C-C coupling constants in allylic and dienyl systems can reflect the importance of hyperconjugation and conjugation. (Source: Contreras 2000 (41a). Reproduced with permission of Elsevier.)

The stereoelectronic aspects of interactions between π - and σ -systems is illustrated by the differences between axial and equatorial 2-methyl cyclohexanones. The lower C-C constant is observed for the axial C-C bond that is aligned better with the carbonyl π -system (Figure 12.51).⁷⁸

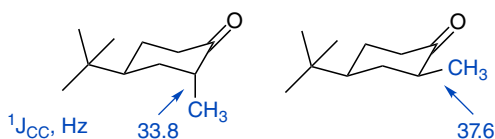


Figure 12.51 Stereoelectronic effects on C-C coupling constant in axial and equatorial 2-methyl cyclohexanones.

Although the effects of anti- lone pairs and π -systems seem to be consistent with stereoelectronic models, the trends with other geometries are not always clear cut. For example, the syn-vicinal lone pair of pyridine imposes an apparent increase in the magnitude of C-C coupling constant at the ortho carbon. It would be interesting to analyze stereoelectronic contributions of $\sigma_{C-Me} \rightarrow \sigma_{N-H}^*$ interactions as well as the relative contributions of the syn-anomeric and homoanomeric $n_N \rightarrow \sigma_{C-Me}^*$ effects to the observed trend (Figure 12.52).⁶⁹

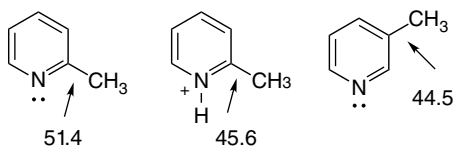


Figure 12.52 Selected C-C coupling constants in pyridine derivatives.

Other direct coupling constants Structural effects of neutral hyperconjugation are often small and can be masked by other structural effects.⁷⁹ For example, Basso and coworkers found that even when calculated structural parameters (bond lengths, valence, and dihedral angles) 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, $^1J_{\text{C-C}}$, in these systems correlated with the structural parameters.⁸⁰

Lambert and coworkers explored the possibility of using NMR coupling constants as a probe of structural and electronic consequences of hyperconjugation and observed that variations of M in benzylic systems in Figure 12.53 did not produce a monotonous increase in the coupling constant between the benzylic and ipso-carbons doubly bonded in the contributing no-bond, double bond structure. This result illustrates that separating local effects from the analyzed phenomena is essential, and that the NMR couplings depend not only on the bond lengths but also on other factors, such as bond polarity or rehybridization.⁸¹

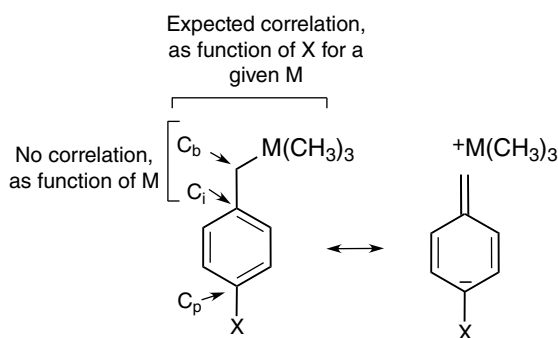


Figure 12.53 Effects of neutral hyperconjugation on the direct NMR coupling constants.

However, when such factors are kept constant (via varying electron demand of a π -substituent X for the same hyperconjugative donor M at the benzylic position) and when the substituent and the probe are separated in space – so that local anisotropic contributions are avoided – the monotonic decrease in the direct M-C coupling constants has been observed with increasing electron withdrawal for ^{13}C - ^{29}Si and ^{13}C - ^{119}Sn bonds (Figure 12.53).⁸² This change is consistent with the increased importance of hyperconjugation.

Hyperconjugation $\pi \leftarrow \rightarrow \sigma$ effects on C-H coupling An angular dependence on $^1J(\text{C}, \text{H}_i)$ is also found for C-H bonds adjacent to π -bonds, with magnitudes of effects on coupling constants mirroring the π -bond acceptor strength (Figure 12.54). In propene, acetaldehyde, and fluoroacetaldehyde $\sigma_{\text{CH}} \rightarrow \pi^*$ interactions lengthen C-H bonds, with maximized overlap of interacting orbitals when the C-H bond is aligned with the π -bond. In all three cases, this geometry corresponds to the minimum $^1J(\text{C}, \text{H}_i)$ value.⁴⁰

Analysis of such systems leads to interesting observations. The first is in the large difference in the magnitude of effects based on the relative strengths of the acceptor π -bond. A change of only ~ 2 Hz is observed for propene, while a much larger change of ~ 12 Hz is observed for both acetaldehyde and fluoroacetaldehyde. Also interesting is the fact that significant differences are present between $\phi = 0^\circ$ and $\phi = 180^\circ$. In both cases the C-H bond is orthogonal to the neighboring π -bond, suggesting that differences must stem from alternative effects. This asymmetry has been attributed to differences in electrostatic interactions, especially for acetaldehyde, where the hydrogen is close to either an oxygen lone pair or vinyl C-H bond.⁴⁰ However, one would not expect this difference to be large in propene. In the $\phi = 180^\circ$ geometry, either an sp^2 C-C or C-O bond lies antiperiplanar to the C-H bond, allowing for $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CC/CO}}^*$ interactions to weaken the C-H bond. The better acceptor ability of a π -bond relative to a σ -bond accounts for the smaller coupling constant at $\phi = 90^\circ$ than at $\phi = 180^\circ$ (Figure 12.54).

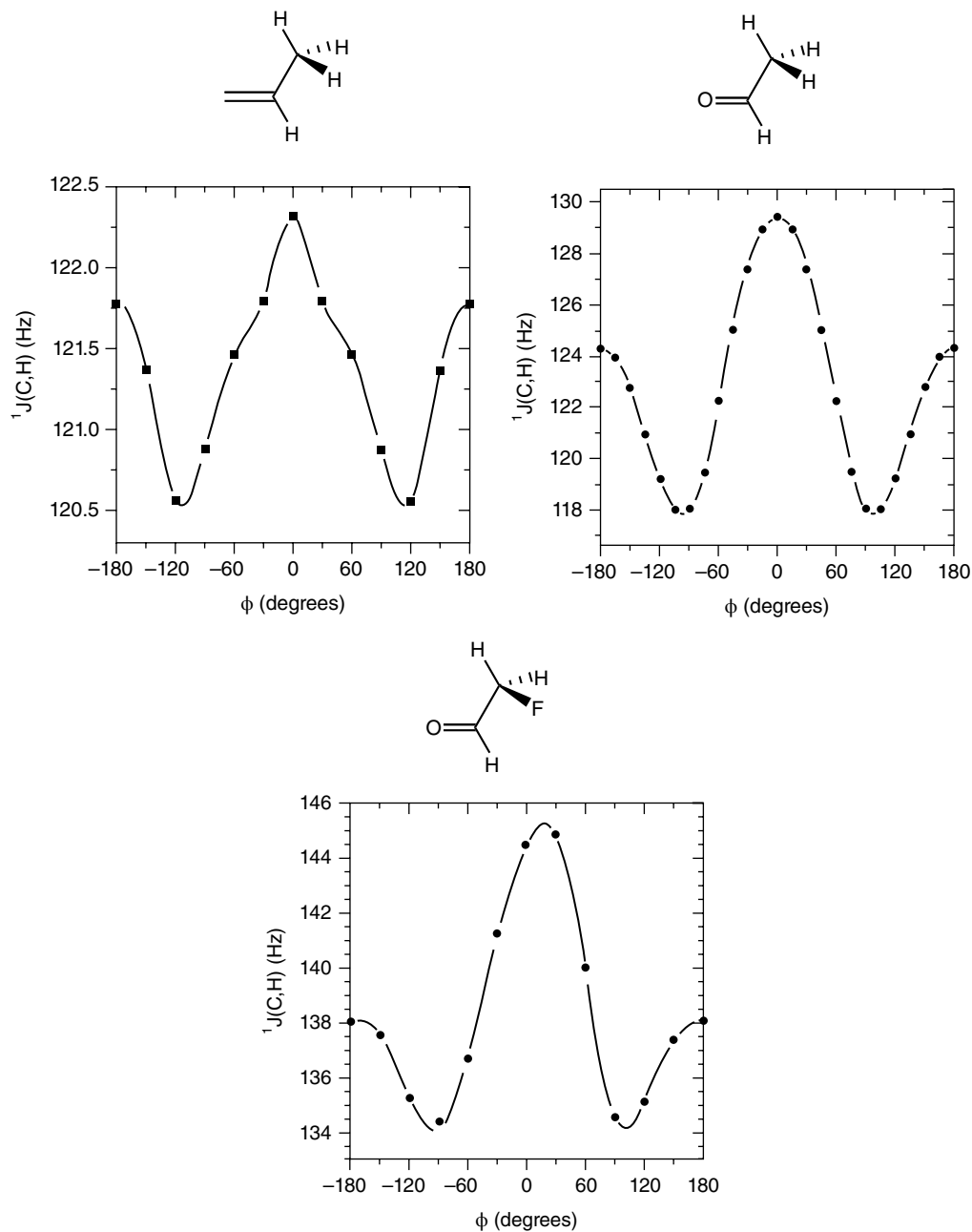


Figure 12.54 Dependence of the calculated Fermi contact term of the $^1J(\text{C},\text{H})$ on the rotation around the C-C single bond in propene, acetaldehyde, and fluoroacetaldehyde. $\phi = 0^\circ$ corresponds to the eclipsed conformation. (Source: Contreras (2000). Reproduced with permission of Elsevier.)

Finally, interesting effects are observed upon replacement of one hydrogen with a fluorine atom. According to Bent's rule, carbon allocates additional p-character in the bond towards the electronegative fluorine atom, giving more s-character to the C-H bonds. As a result, C-H bonds become stronger and shorter, leading to increased coupling.

12.2.5.2 Two-bond (geminal) coupling constants⁸³

Even for two hydrogens at the same carbon, the H-H couplings can adopt a remarkably large range from $\sim +42$ to -25 Hz. The exact value of $^2J_{HH}$ depends on a rather complicated interplay of effects that modify both the magnitude and the sign of the coupling constant. These extreme effects illustrate complications arising from the use of ^{13}C as the NMR probe for stereoelectronic effects. For example, whereas geminal constants for a CH_2 group at an sp^3 hybridized carbon in non-strained acyclic systems are in the range -10 to -13 Hz, the coupling becomes more negative, i.e. larger in magnitude (from -16 to -25 Hz) when the CH_2 group is substituted with a π -acceptor, i.e. a carbonyl or cyano group.⁸⁴ Whereas geminal constants at an sp^2 hybridized carbon are usually much smaller (from 0 to -5 Hz), such couplings exhibit large variations as illustrated by the extremely large (and positive) $^2J_{HH}$ in formaldehyde (Figure 12.55).⁸⁵

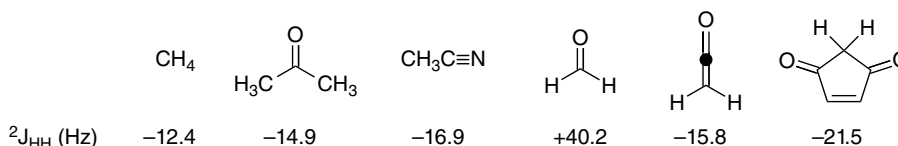


Figure 12.55 Large variations in $^2J_{HH}$ stem from a delicate balance of effects.

The electronic effects of substituents can be understood based on the PMO (perturbation MO) analysis of Pople and Bothner-By.⁸⁶ When the interacting nuclei are protons, the spin constant is given by:

$$J_{HH'} = h(4\beta\gamma_H/3)^2 s_h^4(0) \pi_{h,h'} \quad (12.6)$$

where β is the Bohr magneton, γ_H is the magnetogyric ratio of the proton, and $s_h(0)$ is the magnitude of a hydrogen 1s atomic orbital at the nucleus. $\pi_{h,h'}$ is the “mutual polarizability coefficient”⁸⁷ for the hydrogen 1s orbitals h and h' given by:

$$\pi_{h,h'} = -4 \sum_i^{\text{occ}} \sum_j^{\text{unocc}} (\epsilon_j - \epsilon_i)^{-1} c_{ih} c_{ih'}' c_{jh} c_{jh'}' \quad (12.7)$$

This analysis concentrates on the interaction between filled and empty CH_2 group orbitals, giving the largest role to the HOMO-LUMO ($\psi_2 \rightarrow \psi_3$) transition (transition with the largest $1/\Delta E$ term, Figure 12.56). Excitation between orbitals of the same symmetry has a *negative* effect on J , while excitation between orbitals of opposite symmetry has a *positive* effect. Substituents that reduce the energy gap between ψ_2 and ψ_3 (i.e. raise ψ_2 or lower ψ_3) will increase the size of $1/\Delta E$ and thus have a (+) effect on the coupling, whereas those which increase the energy gap (i.e. lower ψ_2 or raise ψ_3) will have a (−) effect. The magnitude of the coupling can be further modified by variations in the orbital coefficients (Figure 12.56).

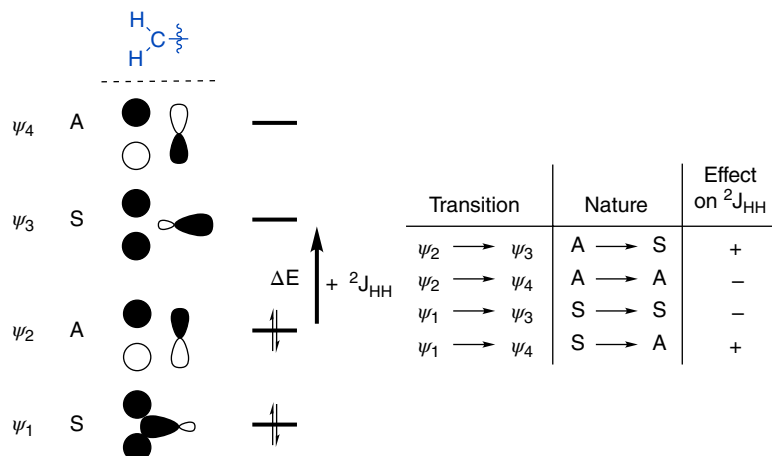


Figure 12.56 Molecular orbitals of a methylene group along with sign of contribution to the coupling constant from electronic excitations. The largest contributing transition (HOMO $\rightarrow$ LUMO) has a positive contribution to the $^2J_{HH}$.

Symmetry considerations suggest both σ -acceptor substituents (electronegative atoms like F, O, N) and σ -donor substituents (e.g. Si or Li) interact mainly with ψ_3 and ψ_1 . The major interaction responsible for changes in coupling constants come from the changes in ψ_3 . A decrease in the $1/\Delta E$ term (smaller energy gap as ψ_3 is lowered) is observed as a result of σ -acceptor substituents and thus have a (+) effect. The opposite is observed for σ -donors, where ψ_3 is raised, and thus a (-) effect on the coupling is observed (Figure 12.57).

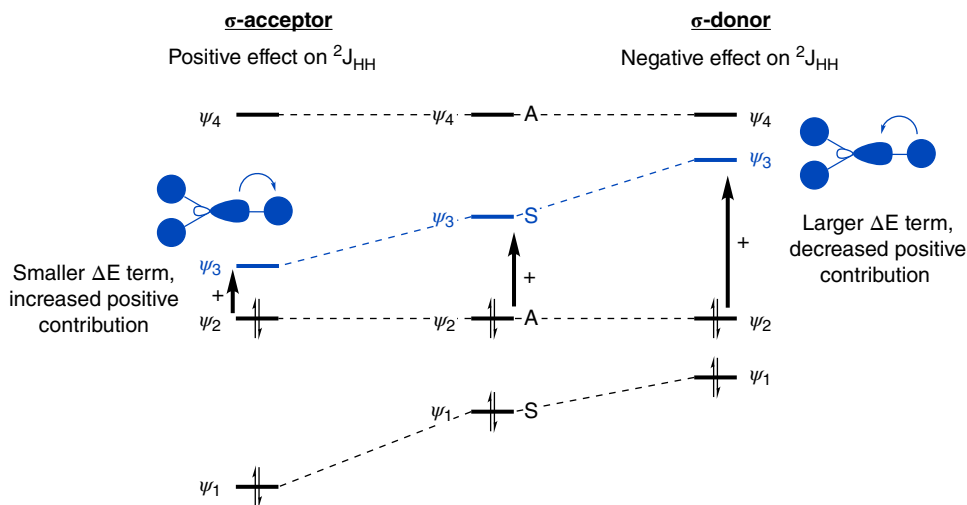


Figure 12.57 Effect of σ -donors (right) and σ -acceptors (left) on the relative energies of methylene MOs from Figure 12.66 and effects on $^2J_{HH}$.

The effects of σ -donors and acceptors on the $^2J_{HH}$ can be seen in Figure 12.58. Relative to methane, $^2J_{HH}$ values for methanol and fluoromethane are less negative, due to the positive contribution from the σ -acceptor abilities of the more electronegative O and F atoms. Geminal H-H coupling in tetramethylsilane is more negative than methane, due to the σ -donor properties of C-Si bonds.

	<u>σ-acceptors</u>		<u>σ-donor</u>	
	CH ₃ OH	CH ₃ F	CH ₄	(CH ₃) ₄ Si
$^2J_{HH}(\text{Hz})$	-10.8	-9.6	-12.4	-14.1

Figure 12.58 Effects of σ -donors and acceptors on $^2J_{HH'}$ where acceptors have a positive contribution and donors have a negative contribution, as a consequences of MO interactions presented in Figure 12.57.

Symmetry restrictions dictate that π -donors and acceptors have the largest effects on ψ_2 and ψ_4 , with the major effect on coupling constants being the change in energy of ψ_2 . Donors (lone pairs or electron-rich π -bonds) will raise the energy of ψ_2 , decreasing the HOMO-LUMO gap and increasing the $1/\Delta E$ term, giving an increased (+) contribution to the coupling constant. Acceptors have the opposite effect, lowering the energy of ψ_2 , increasing the HOMO-LUMO gap, and decreasing the $1/\Delta E$ term, having a negative effect on the coupling constant (Figure 12.59).

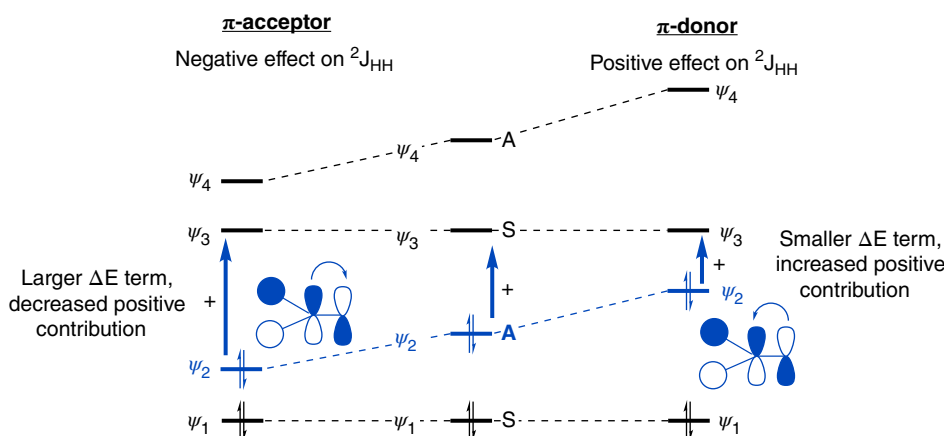


Figure 12.59 Effect of π -donors (right) and π -acceptors (left) on the relative energies of methylene MOs from Figure 12.66 and effects on $^2J_{HH'}$.

The effects of π -donors and acceptors on the $^2J_{HH}$ can be seen in Figure 12.60. Relative to ethylene, $^2J_{HH}$ values for 1,1-difluoroethylene, ketenes, and cyclopentenone are more negative, while the effects of α lone pairs (π -donors) give more positive values.

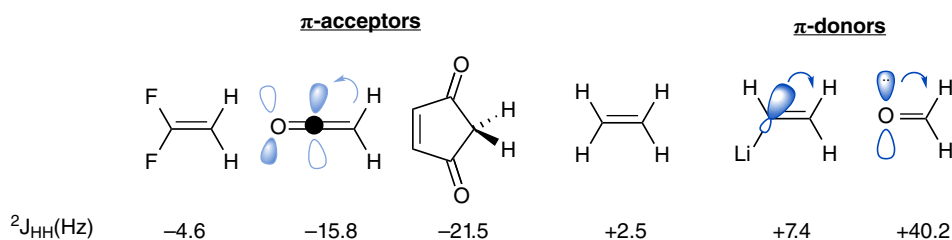


Figure 12.60 Effects of π -donors and acceptors on $^2J_{HH'}$ where acceptors have a negative contribution and donors have a positive contribution, stemming from MO arguments presented in Figure 12.59.

Geminal H-H coupling in saturated carbons (sp^3): $^2J_{HH}$ values in methane and other aliphatic systems range from -10 to -13 Hz but can change as the result of factors discussed above. In addition to π -acceptors, conjugated π -systems also have a negative effect on coupling constants, bringing $^2J_{HH}$ between -16 and -25 Hz (Figure 12.61). Furthermore, these values can be modified by changes in the dihedral angle between the methylene group and the carbonyl π -system.⁸⁸

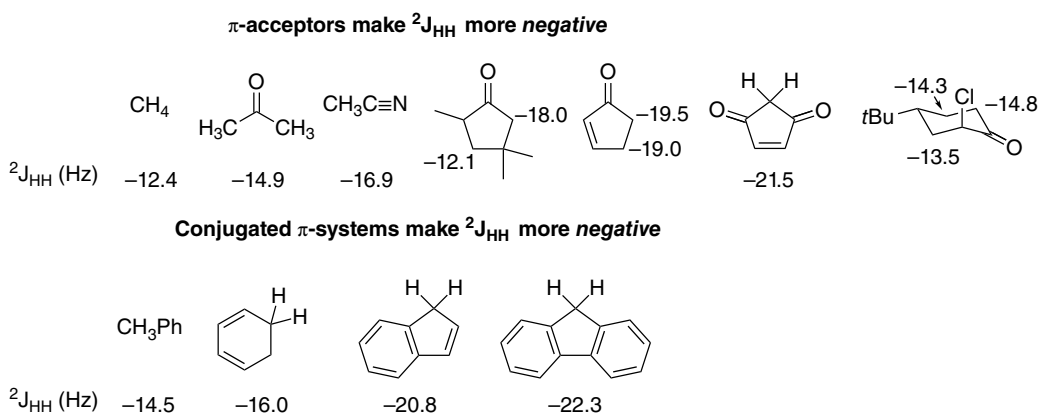


Figure 12.61 Negative effects of π -acceptors and conjugated π -systems on $^2J_{HH}$ in saturated methylene groups.

Electronegative elements (N, O, F, Cl, etc.) act as σ -acceptors, but these atoms also contain lone pairs, which have π -donating effects. As both of these effects display a positive contribution to $^2J_{HH}$, all values in Figure 12.62 are more positive than methane, and some values start to approach zero.

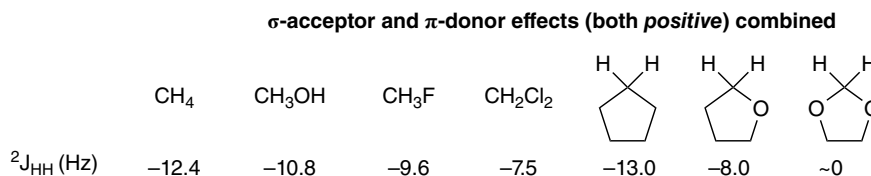


Figure 12.62 Positive effects of σ -acceptors and π -donors on $^2J_{HH}$ in saturated methylene groups.

Similar to the effects of σ -acceptors, strained rings use hybrid orbitals with increased s-character in the exocyclic bonds and effectively act as an inductively withdrawing group towards the exocyclic substituents. As a result, a positive effect on the geminal coupling constant is observed (Figure 12.63). In aziridines and oxiranes, the additional effects of σ -acceptors and π -donors give even more positive values.

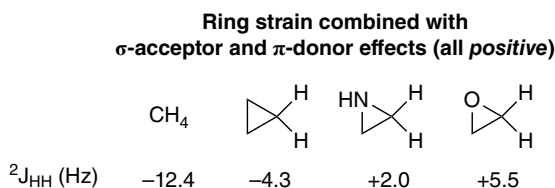


Figure 12.63 Positive effects of ring strain, σ -acceptors, and π -donors on $^2J_{HH}$ in strained rings.

Geminal coupling at unsaturated carbons (sp^2): In unsaturated carbon systems, vicinal substituents act as either π -donors or acceptors in hyperconjugative interactions. Coupling in ethylene is relatively small (+2.5 Hz), thus weak π -acceptors bring this value close to zero, while stronger π -acceptors will display negative couplings (Figure 12.64). The π -donors give more positive values, especially for α -trimethylsilylvinyl lithium, while competing effects can give undetectable coupling constants, as is the case in α -ethoxyvinyl lithium. Note the different role of fluorine substitution in comparison to the previous section – it served as a σ -acceptor and a π -donor in CH_3F but, in $CF_2=CH_2$, fluorine is removed further from the CH_2 group where it can only interact with the latter by the vicinal hyperconjugation ($\sigma_{C-H} \rightarrow \sigma_{C-F}^*$), accounting for the π -acceptor effect.⁸⁹

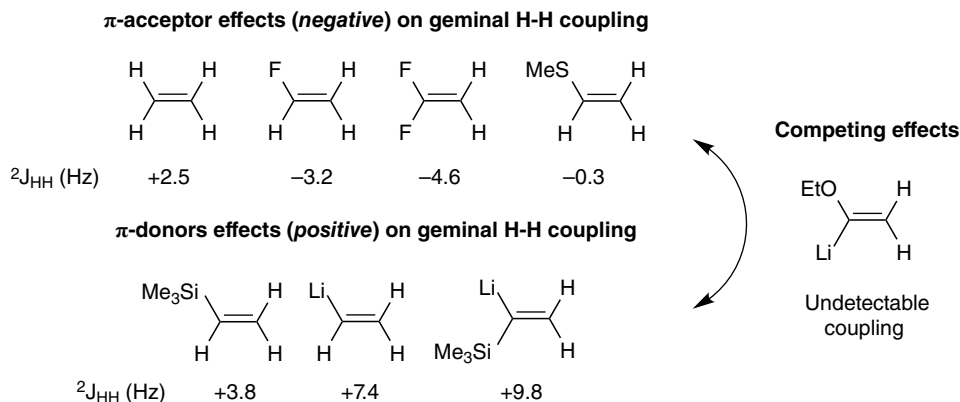


Figure 12.64 Effects of vicinal substituents, acting as π -donors and acceptors, on $^2J_{HH}$ in terminal alkenes. (Source: Reich 2015 (93). Reproduced with permission of <http://www.chem.wisc.edu/areas/reich/nmr/index.htm>.)

Unusually large positive couplings are observed for formaldehyde and to a lesser extent, but due to the same factors, in imines (Figure 12.65). This dependence stems from the strong σ -acceptor strength of the electronegative oxygen (or nitrogen) in combination with the π -donating lone pairs. Furthermore, the synergistic positive effects on coupling are amplified as a result of the short bond lengths.

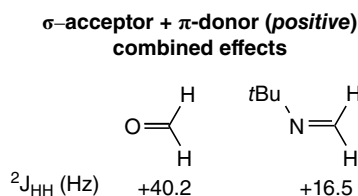


Figure 12.65 Large couplings in formaldehyde and *N*-*t*-butylmethanimine as a result of combined positive effects.

It has been shown that geminal coupling constants can also be influenced by hyperconjugative interactions. A useful generalization for the role of stereoelectronic effects on geminal couplings between atoms A and B has been proposed as follows: “Interactions which transfer charge into the antibonding orbitals will increase the $^2J_{AB}$, while interactions that transfer charge from bonding orbitals will decrease $^2J_{AB}$.”⁹⁰

This rule can rationalize the differences in *cis*- and *trans*-4-*t*-butylcyclohexanol, namely $^2J_{C1-H_{ax}}$ in *cis*-4-*t*-butylcyclohexanol (Figure 12.66). NBO analysis found a large hyperconjugative $\sigma_{C2-H_{ax}} \rightarrow \sigma_{C1-O}^*$ interaction (5.2 kcal/mol, along with 1.4 kcal/mol back-donation) mainly responsible for the decreased coupling constant for the stereoelectronically aligned axial hydrogen in *cis*-4-*t*-butylcyclohexanol.

Furthermore, the rule explains the role of lone pairs on one of the coupled nuclei on the geminal coupling constant. The anti $\sigma_{\text{C-H}}^*$ is involved in a strong $n_{\text{N}} \rightarrow \sigma_{\text{C-Hanti}}^*$ interaction, which yields a positive contribution to the coupling constant.⁸⁹

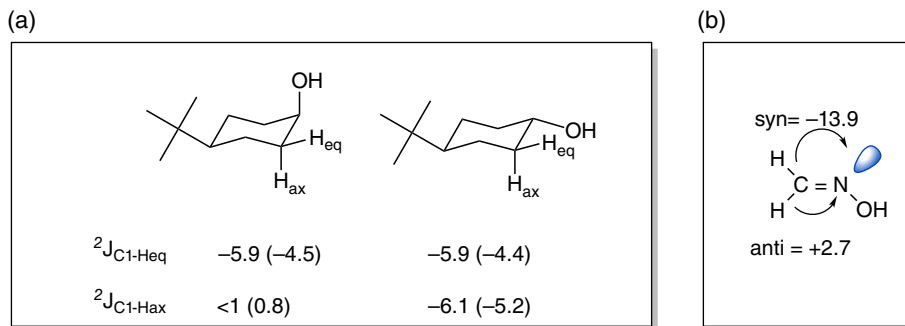


Figure 12.66 (a) $^2J_{\text{CH}}$ terms (in Hz) for cis- and trans-t-butylcyclohexanol. Both experimental and calculated (in parentheses) are given. (b) Comparison of $^2J_{\text{NH}}$ terms for the syn and anti hydrogens in formaldehyde oxime.

Orbital overlap on geminal coupling It is also useful to investigate effects of geometry and orbital overlap on observed couplings, in systems where rotation around a single bond is possible. It was found that the magnitude of geminal H-H coupling in CH_2 groups connected to an sp^2 -hybridized atom (X) depends on $\cos^2\phi$, where ϕ is the rotation angle around the $\text{H}_2\text{C-X}$ bond.⁹¹ The geminal $\text{C}=\text{C-C}$ coupling constant in propene is sensitive to rotation around the single bond, with the smallest values for geometries where one of the C-H bonds is eclipsed with the C-C double bond (when hyperconjugative interactions are the strongest). This is due to decreased π -bonding character as a result of $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ interactions. This correlation can be applied towards the conformation of glycyl residues in the backbone of peptides and proteins.⁹²

12.2.5.3 Three-bond (vicinal) coupling constants

The main application of these constants in studies of stereoelectronic effects is focused on the correlation between vicinal constants and geometry rather than on the electronic consequences of delocalization per se. The conformational dependence of the three-bond coupling constants in NMR has been widely explored and well-documented.⁹³ In good agreement with the previously discussed preference for the orbital interactions to be maximized in the antiperiplanar geometry and vanish at the orthogonal spatial arrangement, the vicinal coupling constants also show marked increase when the orbitals are aligned well for the overlap (anti > syn > orthogonal).

The most well-known stereoelectronic analysis of the $^3J_{\text{AB}}$ vicinal coupling dependence from the respective dihedral AXYB angle is exemplified by the famous equation suggested by Karplus.⁹⁴

$$J(\varnothing) = A \cos^2 \varnothing + B \cos \varnothing + C \quad (12.8)$$

Where J is the ^3J , 3-bond coupling constant, $\varnothing$ is the dihedral XCCY dihedral angle, and A , B , and C are empirically derived substituent-dependent parameters. The effects of orbital overlap on coupling constants become obvious by examining the geometric dependence of vicinal H-H coupling in ethane (Figure 12.67).

$$J(\varnothing) = 4.22 \cos^2 \varnothing - 0.5 \cos \varnothing + 4.5 \quad (12.9)$$

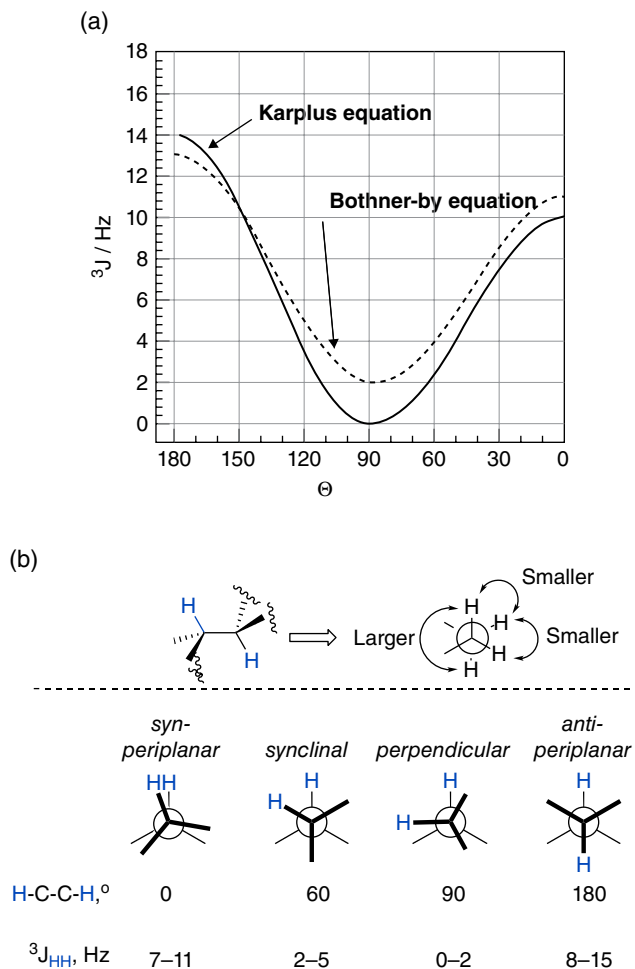


Figure 12.67 (a) A simplified version of the Karplus relation for ethanes $^3J_{HH} = J_0 \cos^2(\text{HCCH})$, ($J_0 = 14$ (HCCH = 90–180°, $J_0 = 10$ (HCCH = 0–90°)) and an even simpler curve suggested by Bothner-By that does not require different J_0 values (Source: Reich 2015. Reproduced with permission of <http://www.chem.wisc.edu/areas/reich/nmr/index.htm>).

As illustrated by the Karplus relationship, orbital overlap plays a large role in determining the strength of vicinal coupling. This dependence would make vicinal constants ideal for studying conformational effects induced by polar groups, but there is an important complication: the constants are also sensitive to electronegativity of substituents, valence angles, hybridization, and hyperconjugative effects.⁹⁵ Improved correlations that account for these effects were expanded to other types of bonds and continue to be of wide utility in studies of molecular conformations.⁹⁶

In particular, the geometric dependence of vicinal coupling constants is useful for the conformational analysis of cyclohexanes and their heteroanalogues. In the chair cyclohexane, the axial-axial constant, J_{aa} , is generally much larger (9–13 Hz) than the constants that involve the equatorial protons, J_{ee}/J_{ea} (~3–4 Hz each, Figure 12.68).⁹⁷ In applying this analysis to heterocyclohexanes (such as sugars), one has to keep in mind the effects of electronegativity on the magnitude of the constants. The relative trends, however, still remain valid as long as the structures are not significantly distorted from the chair geometry.

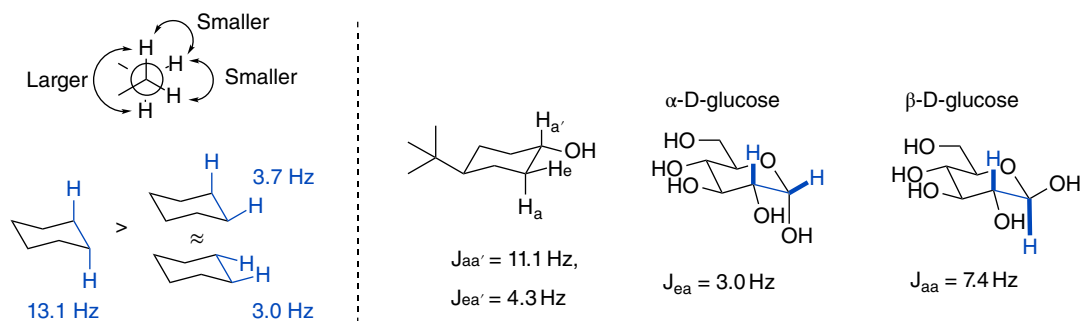


Figure 12.68 The conformational dependence of vicinal coupling constants and conformational analysis of cyclohexanes and heterocyclohexanes.

The conformational profiles of substituted cyclopentanes is quite different and reliable stereochemical assignments are often complicated by the presence of several low energy conformations, each with its own dihedral relationship. In many cyclopentanes, *cis*-couplings (8–10 Hz) are larger than *trans* (2–9 Hz). This feature usually indicates that at this part of the cyclopentane envelope, the *cis* hydrogens have H-C-C-H dihedral angles close to 0° , whereas the *trans* protons are near 120° . However, smaller conformational regions exist where *trans*-couplings can be identical to or larger than the *cis*-couplings. Furthermore, *trans* vicinal constants can increase between protons in the $-\text{CH}_2\text{CH}_2-$ parts of the near-planar five-membered rings containing heteroatoms with a lone pair.^{98,99} The situation is more simple in rigid bicyclo[2.2.1]heptanes where the *cis* constants (both endo-endo and exo-exo) are always greater than endo-exo constants (Figure 12.69).⁹³

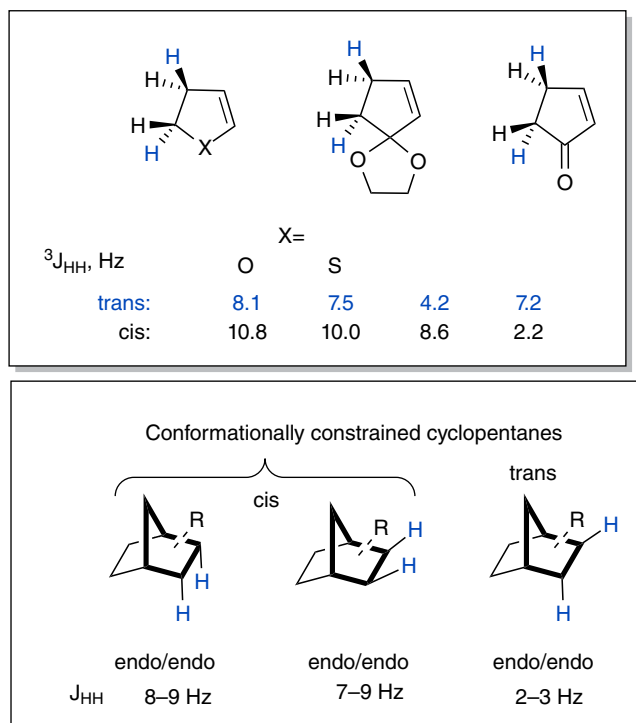
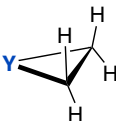


Figure 12.69 Substituent and structural effects on vicinal H-H coupling in cyclopentanes.

Cis coupling constants in cyclobutanes are almost always larger (6–9 Hz) than trans (2–8) with the exception of strongly puckered rings.¹⁰⁰ Geometries of cyclopropanes are well-defined due to their structural rigidity and, as a result, the cis constants are always larger than their trans counterparts (7–10 Hz vs. 2–6 Hz). The same trend is observed for the saturated heterocyclic cyclopropane analogues (epoxides, aziridines, etc., Figure 12.70).¹⁰¹



Y=	CH₂	O	NH	S	S=O
$^3J_{\text{cis}}$	9.0	4.5	6.3	7.2	11.5
$^3J_{\text{trans}}$	5.6	3.2	3.8	5.7	10.5

Figure 12.70 Vicinal H-H coupling in cyclopropane and its heterocyclic analogues.

The vicinal couplings of vinyl protons to the adjacent allylic hydrogens follow the Karplus behavior as well. Fast rotation in the flexible acyclic system averages the observed values. When alkene is included into a cycle, the antiperiplanar arrangement that corresponds to the greatest $^3J_{\text{HH}}$, is not possible, and smaller constants are observed (Figure 12.71). On the other hand, when conformational profile is biased via A^{1,3}-strain towards the geometry where allylic and vinyl hydrogens are antiperiplanar, the vicinal constant increases (e.g. 9.55 Hz in (Z)-4-Me-2-hexene).¹⁰²

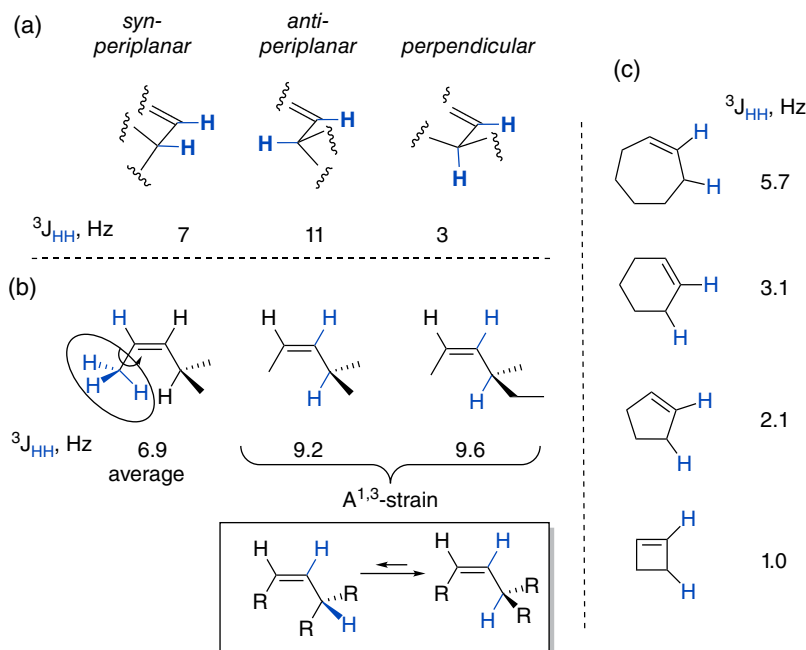


Figure 12.71 (a) Selected vicinal constants from Karplus relation for allylic systems $^3J_{\text{HH}} = J_0 \cos^2(\text{HCCH}) + 2.6 \sin^2(\text{HCCH})$, ($J_0 = 11.6$ for $\text{HCCH} = 90^\circ\text{--}180^\circ$; $J_0 = 6.6$ for $\text{HCCH} = 0^\circ\text{--}90^\circ$).⁹³ (b) Vicinal coupling between vinylic and allylic protons in constrained acyclic systems. (c) Vicinal coupling between vinylic and allylic protons in cyclic systems of varying size.

Differences in the cis and trans coupling constants can also be taken as a manifestation of the general Karplus relationships. These differences are commonly used as indicators of stereochemistry because, for the same combination of substituents, $^3J_{\text{trans}}$ is always greater than $^3J_{\text{cis}}$ (Figure 12.72).

		X,Y =		
		Me, CN	Ph, COOH	H, CH=CH ₂
	$J_t = 12\text{--}24\text{ Hz}$	16.0	15.8	17.1
	$J_c = 3\text{--}19\text{ Hz}$	11.0	12.3	10.7

Figure 12.72 Illustrative differences in the *cis* and *trans* coupling constants.

The absolute values of the constants are sensitive to electronegativity of substituents and structural constraints. For example, the $^3J_{\text{cis}}$ values decrease significantly in smaller cycloalkenes (compare 10.4 Hz in cyclooctene with 1.3 Hz in cyclopropene, Figure 12.73!).⁹³

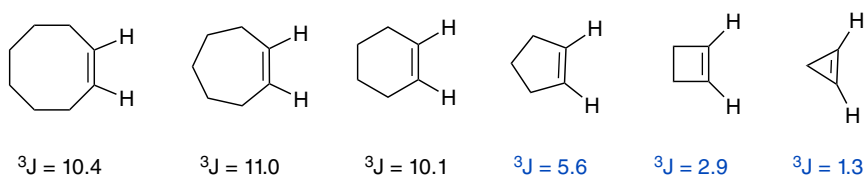


Figure 12.73 Vicinal C-H constants in cycloalkenes are sensitive to the ring size.

Even more subtle, but conceptually interesting, are the correlations between spin-spin coupling and the apparent bond order. The *cis* coupling in ethene is significantly larger than in benzene. Increased vicinal couplings at selected positions of polyaromatic hydrocarbons (e.g. the central ring of phenanthrene) reveal the more “olefinic” parts of the molecule (Figure 12.74).¹⁰³

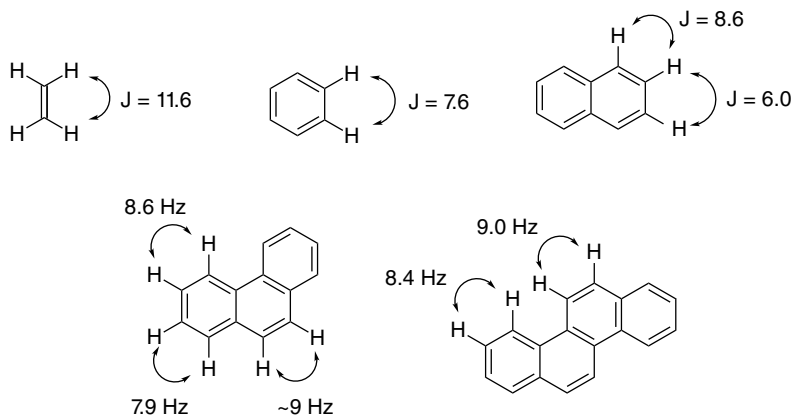


Figure 12.74 Vicinal C-H constants in aromatics and polyaromatics reflect C/C bond order.

The combination of ring size and bond order effects explain the notable decrease in the magnitude of vicinal coupling constants in heterocyclic molecules, especially those with a five-membered ring (Figure 12.75).

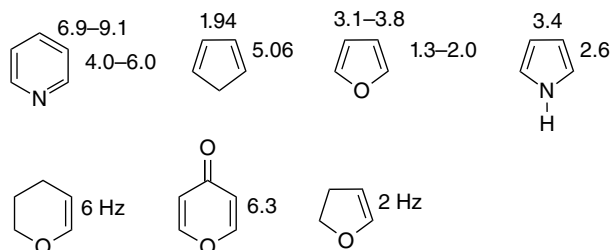


Figure 12.75 Decreased vicinal coupling constants in heterocyclic molecules.

Vicinal protons at C2 and C3 of 1,3-butadiene show a quite large coupling (10.4 Hz) that is indicative of the predominantly *s-trans* conformation of this molecule.¹⁰⁴ Presence of additional factors that stabilize the *s-trans* conformation lead to a further increase in the J_{23} coupling in 1,3-butadienes¹⁰⁵ whereas constraining a 1,3-diene moiety into a cycle (i.e. the *s-cis* conformation) makes the vicinal coupling constants smaller. Inserting the diene into a smaller cycle decreases these constants even further. For example, the respective J_{23} constant in cyclopentadiene is only 1.9 Hz (Figure 12.76).⁹³

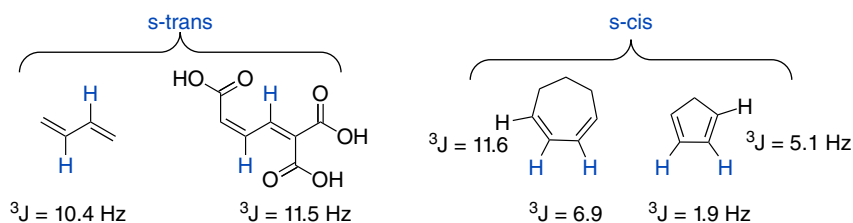


Figure 12.76 Vicinal H-H coupling in *s-trans* and *s-cis* dienes are dramatically different.

The combined effect of stereoelectronics and electronegativity is illustrated by vicinal coupling constants in aldehydes where the ^3J coupling is typically very small (1–3 Hz) because the interacting C-H bonds are misaligned in the dominant eclipsed conformation. Once this stereoelectronic preference is changed, the coupling becomes considerably larger. Such increase is observed, for example, in conjugated aldehydes. As these molecules adopt a planar *s-trans* conformation in order to maximize the π -overlap, the H-CC(O)-H dihedral angle approaches 180° (Figure 12.77).⁹³

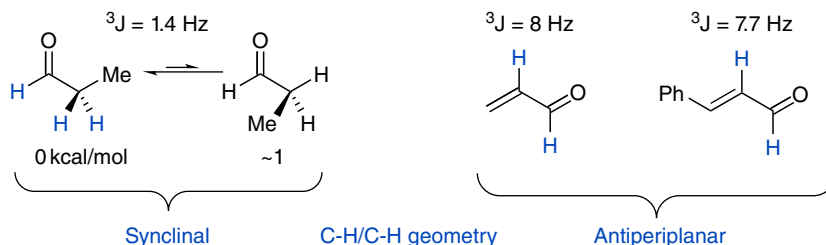


Figure 12.77 Vicinal H-H coupling in aldehydes increases when the interacting protons correspond to antiperiplanar C-H bonds.

Couplings via connecting atoms other than carbon also follow Karplus-type relationships. In particular, such relationship for the vicinal couplings of protons with ^{13}C , ^{15}N , ^{19}F , and ^{31}P can provide a useful tool for conformational analysis. Much effort has been put into studies of the $\text{HN}-\text{CH}\alpha$ coupling in peptides and proteins, which is crucial in defining part of the backbone conformation. Wang and Bax have extended this analysis to the four coupling constants that fully define the peptide backbone conformation (i.e. $^3J_{\text{HNCH}\alpha}$, $^3J_{\text{HNCC}'}^{\prime}$, $^3J_{\text{HNCCb}}^{\prime}$, $^3J_{\text{HCaNC}'}^{\prime}$, where C' represents the amide carbonyl carbon).¹⁰⁶ The J values corresponding to $\text{H}-\text{C}-\text{O}-\text{P}$ couplings can be used to define geometry of the $-\text{C}-\text{O}-\text{P}-\text{O}-\text{C}-$ unit of RNA and DNA.¹⁰⁷ The magnitude of the coupling depends on the nature of the bridge – decreased coupling can be observed for atoms more electronegative than carbon. Additional contributions from through-space interactions exist for the small dihedrals when the interacting groups are in the close proximity.

The stereochemical features of $^3J_{\text{HC}}$ coupling has been utilized for analysis of the interglycosidic bond geometry¹⁰⁸ as well as aminoacid, peptide, and protein conformations.¹⁰⁹ Vicinal J_{HC} coupling generally has a range of 0 to 10 Hz and is sensitive to the electronic effects of substituents (Figure 12.78).¹¹⁰

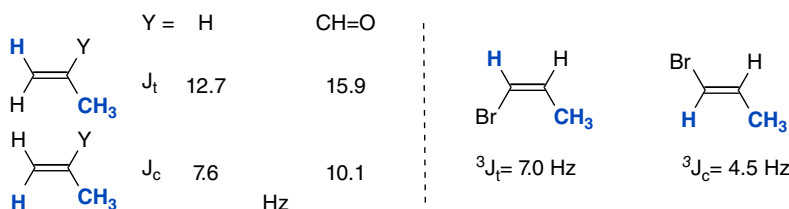


Figure 12.78 The stereochemical features of $^3J_{\text{HC}}$ coupling (J_t and J_c correspond to coupling between *trans*- and *cis*-groups, respectively).

For example, the coupling between the equatorial H_2 and C_6 in 4-*tert*-butyl cyclohexanone is only 3.1 Hz whereas the similarly aligned equatorial H_3 and the carbonyl carbon display a much larger coupling constant (8.4 Hz, Figure 12.79).¹¹¹

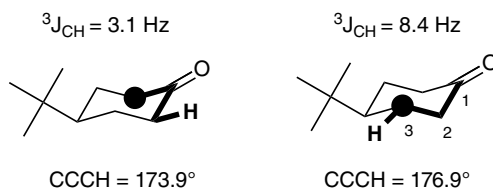


Figure 12.79 Nature of the bridge changes the magnitude of remote $\text{C}-\text{H}$ coupling.

12.2.5.4 Long-range coupling constants

These spin interactions can occur either through bonds or through space. A particularly useful and reliable remote coupling is $^4J_{\text{HH}}$ observed for $\text{H}-\text{C}-\text{C}-\text{C}-\text{H}$ fragments in a planar *W* conformation.¹¹² The 2–3 Hz couplings between the meta hydrogens in substituted benzenes are the most commonly encountered example of this interaction. It is also often observed in saturated six-membered rings between equatorial protons separated by four bonds and in rigid bicyclic molecules (Figure 12.80).

Even larger ^4J couplings were observed in systems where direct orbital overlap is possible. For example, Padwa and coworkers reported that, in substituted bicyclo[1,1,1]pentanes¹¹³ where the distance between the bridgehead atoms is only 1.89 Å, the coupling constant between the bridgehead protons reaches 18 Hz!

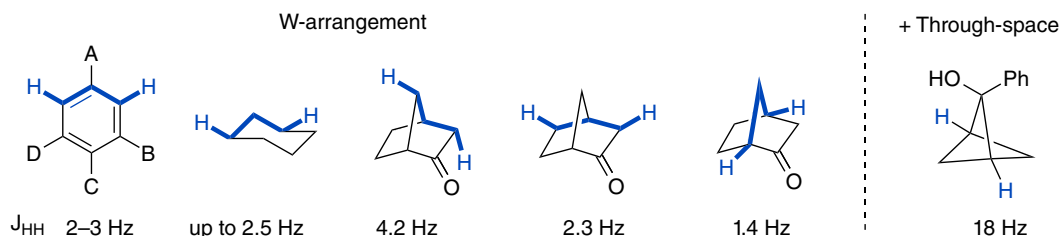


Figure 12.80 Examples of long-range coupling H-H constants.

Interaction between even more remote spins is possible in conjugated systems such as alkynes and allenes. $^5J_{HH}$ is also commonly observed in homoallylic fragments ($H-C-C=C-C-H$). Large couplings of this type are observed in 1,4-cyclohexadienes.¹¹⁴ Small homoallylic coupling is also observed across amides. Its magnitude is a function of conformations across peptide bonds (Figure 12.81).¹¹⁵

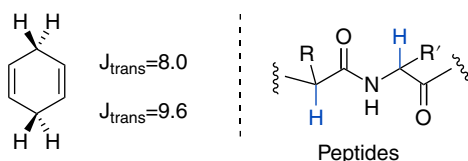


Figure 12.81 Remote coupling in homoallylic fragments.

12.2.5.5 Combining multiple spin-coupling constants for stereochemical determinations

Despite their obvious utility, the proton–proton vicinal coupling constants are inadequate when two H/H gauche rotamers have similar H-H coupling. However, additional information from carbon–proton constants can greatly facilitate stereochemical analysis as outlined in detail by Murata and coworkers for identification of the predominant staggered rotamer(s) out of the six choices possible for a pair of threo and erythro diastereomers.¹¹⁶ This elegant method for elucidating the relative configuration of acyclic organic compounds is based on the combination of three types of spin-spin coupling: vicinal $^3J_{HH}$ coupling between protons and vicinal and geminal carbon–hydrogen couplings, $^2J_{CH}$ and $^3J_{CH}$.

The vicinal $^3J_{HH}$ and $^3J_{CH}$ couplings follow the Karplus-type dependence discussed in detail earlier whereas the geminal $^2J_{CH}$ coupling provides conformational information that can identify the position of an oxygen functionality. When the latter is gauche to its geminal proton, $^2J_{CH}$ becomes large, and when it is anti, the coupling becomes small (Figure 12.82).

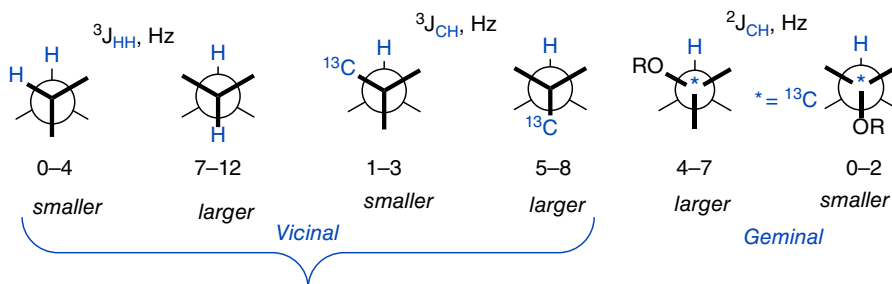


Figure 12.82 Dihedral angle dependence of $^3J_{HH}$, $^3J_{CH}$ and $^2J_{CH}$ in typical acyclic systems. Narrower ranges of the coupling constant values can be defined for specific patterns (e.g. 1,2-dioxygenated systems).

Taken together, these three parameters allow comprehensive stereochemical analysis of complex natural products. Each diastereomer can be described as a combination of three staggered rotamers, a reasonable approximation for a variety of hydroxy and methyl substituted chains, in the absence of bulky substituents. Four out of the six rotamers for a *threolerythro* pair of diastereomers can be determined unambiguously solely from the three coupling constants discussed therein. The remaining pair of conformations can be distinguished on the basis of NOEs.

12.3 Conclusion

Even though we have just scratched the surface of the possible applications of spectroscopic techniques in studies of stereoelectronic effects, we hope that we have illustrated the diversity of possible outcomes and the value of such analysis. The correlation between stereoelectronic effects and spectroscopy is sometimes indirect but often reliable. In particular, IR-stretching frequencies and direct coupling constants for X-Y bonds can be useful in detecting stereoelectronic effects that are associated with the X-Y bond weakening with the caveat that the masking effects of hybridization, usually via the connection of the latter with electronegativity, should be taken into account. The tug-of-war between hybridization and delocalization is a common scenario that can mask stereoelectronic trends.

NMR coupling constants provide rich stereoelectronic information but not in a pure form. On many occasions, the stereoelectronic contributions have to be extracted carefully via a combination of conformational effects and computational dissections. It is possible that a few of classic correlations of stereoelectronics and spectroscopy need to be critically reevaluated with the help of modern computational techniques.

However, unprecedented opportunities also exist. Sometimes, these opportunities masquerade as problems but such situations are temporary. For example, carbon NMR effects are sensitive to both ground and excited state properties. Although excited state contributions to paramagnetic shielding can obstruct the clear view of ground state effects, they can also provide a rare glimpse in the still underinvestigated excited state properties.

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