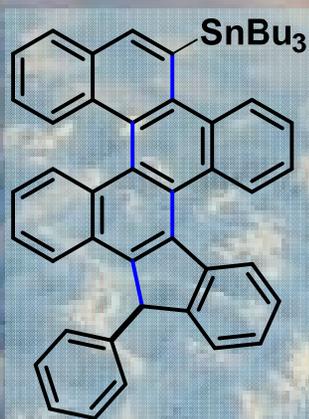


**Natural Bond Orbital Analysis:  
Rosetta Stone of computational organic chemistry.**

**Rediscovering hybridization and delocalization in  
order to understand organic structure and reactivity**

Igor Alabugin,  
*Florida State University*



Марковниковские чтения,  
*January 14, 2017, Krasnovidovo*

## Do quantum chemists and organic chemists think alike?

“The more accurate the calculations become,  
the more the concepts tend to vanish into thin air.”

R. S. Mulliken, J. Chem. Phys. S2, 43 (1965)

“It is nice to know that the computer understands the problem.  
But I would like to understand it too.”

E. P. Wigner (quoted in Physics Today, July 1993, p. 38)

“It is at least arguable that, from the point of view of quantum chemistry as  
usually practiced, the supercomputer has dissolved the bond.”

B. T. Sutcliffe, Int. J. Quantum Chem. 58, 645 (1996)

“The purpose of computing is insight, not numbers”

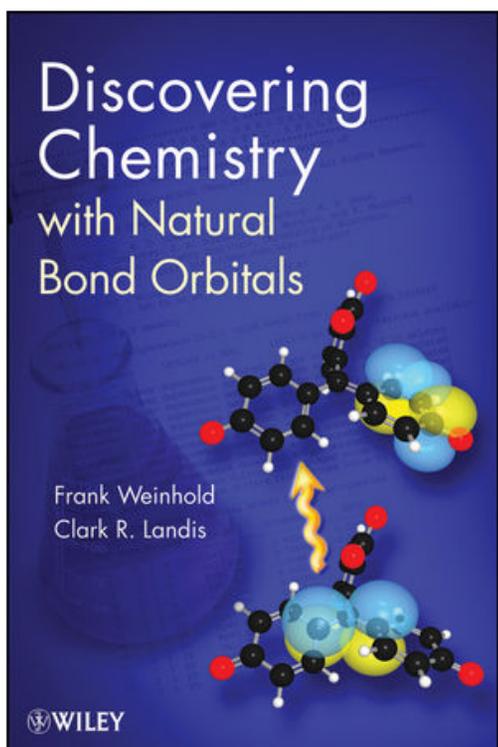
Richard Hamming (1962)

# Rosetta Stone

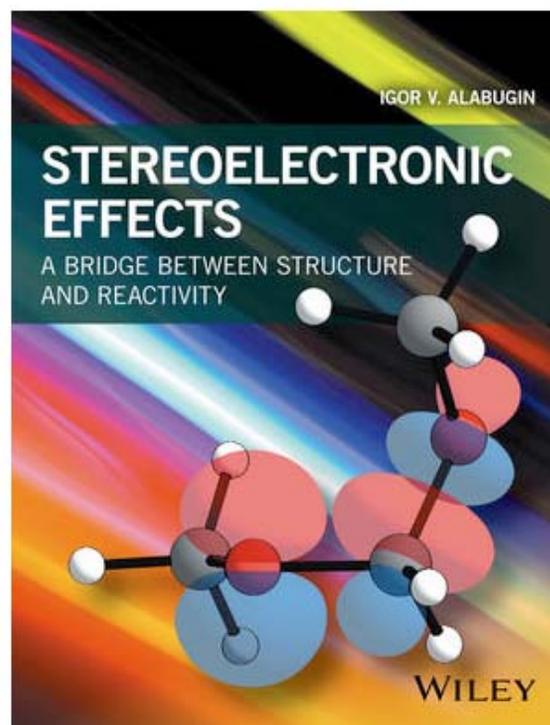
The Rosetta Stone was found in 1799. It has a decree issued at Memphis, Egypt, in 196 BC on behalf of King Ptolemy V. The decree appears in three scripts: the upper text is Ancient Egyptian hieroglyphs and the lowest is Ancient Greek. Hence, the stone provided the key to the translating Egyptian hieroglyphs.

# Rosetta Stone of computational chemistry

- NBO analysis



<http://eu.wiley.com/WileyCDA/WileyTitle/productCd-1118119967.html>



<http://eu.wiley.com/WileyCDA/WileyTitle/productCd-1118906349.html>

# NBO analysis as a key to understanding molecular structure

Title	1-20	Cited by	Year
<b>Electronic basis of improper hydrogen bonding: a subtle balance of hyperconjugation and rehybridization</b>	IV Alabugin, M Manoharan, S Peabody, F Weinhold Journal of the American Chemical Society 125 (19), 5973-5987	570	2003
<b>Stereoelectronic effects and general trends in hyperconjugative acceptor ability of <math>\sigma</math> bonds</b>	IV Alabugin, TA Zeidan Journal of the American Chemical Society 124 (12), 3175-3185	218	2002
<b>Cyclizations of alkynes: revisiting Baldwin's rules for ring closure</b>	K Gilmore, IV Alabugin Chemical reviews 111 (11), 6513-6556	214	2011
<b>Stereoelectronic Interactions in Cyclohexane, 1, 3-Dioxane, 1, 3-Oxathiane, and 1, 3-Dithiane: W-Effect, <math>\sigma</math>C-X<math>\leftrightarrow</math> <math>\sigma^*</math> CH Interactions, Anomeric Effect What Is Really Important?</b>	IV Alabugin The Journal of organic chemistry 65 (13), 3910-3919	196	2000
<b>Hyperconjugation</b>	IV Alabugin, KM Gilmore, PW Peterson Wiley interdisciplinary reviews: computational molecular science 1 (1), 109-141	147	2011

# Translating quantum chemistry to the language of organic chemists with NBO

## **Topics for today:**

Reemergence of Lewis structures from delocalized wavefunctions.

Rediscovering hybridization with NBO analysis

Quantifying delocalization with NBO analysis

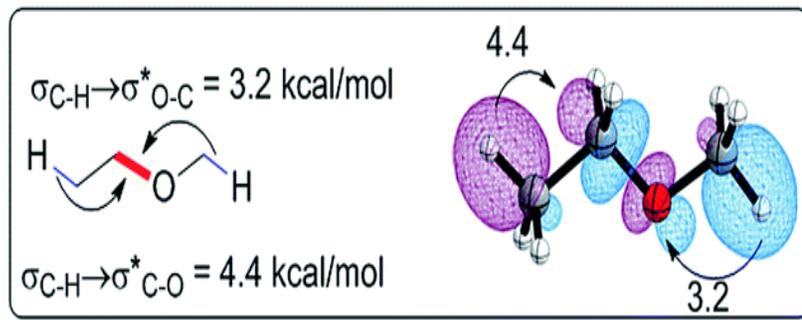
Understanding supramolecular interactions with NBO analysis: from improper H-bonding to radical bonding

NBO analysis of reactive intermediates and transition states

# Reconnecting quantum chemistry with the language of organic chemists with NBO:

Reemergence of Lewis structures from delocalized wavefunctions

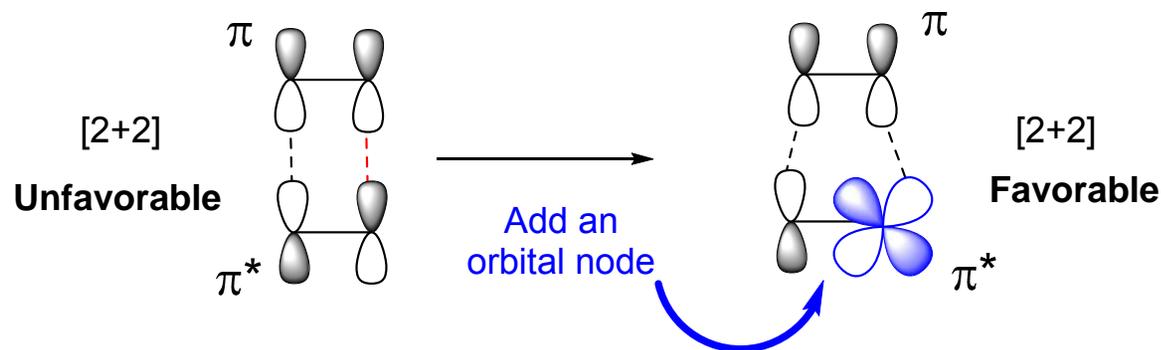
Two ways to look at the same molecule:



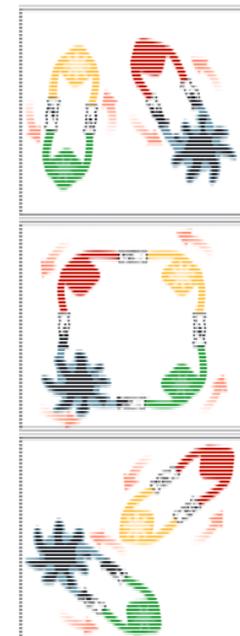
Which one do you prefer?

# Why understand orbital interactions?

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



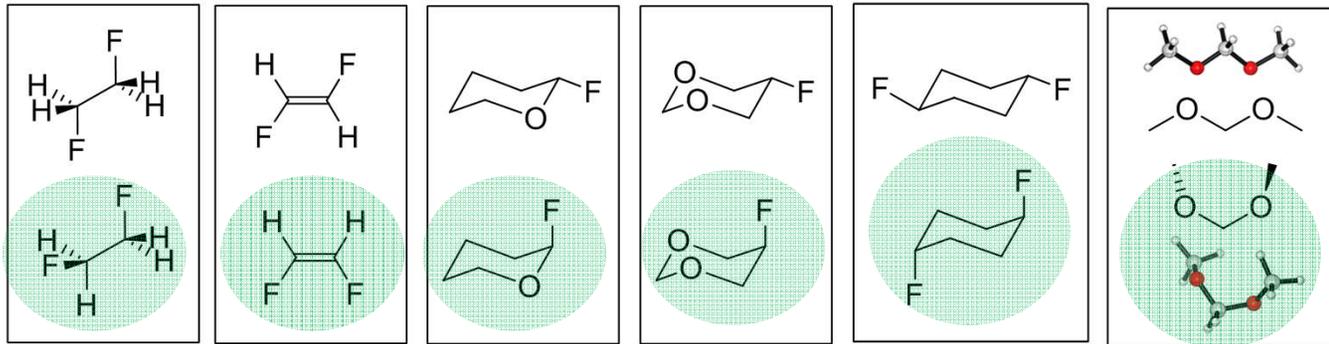
*An extra orbital node is the difference between a failed reaction and a Nobel Prize!*



## The importance of delocalization

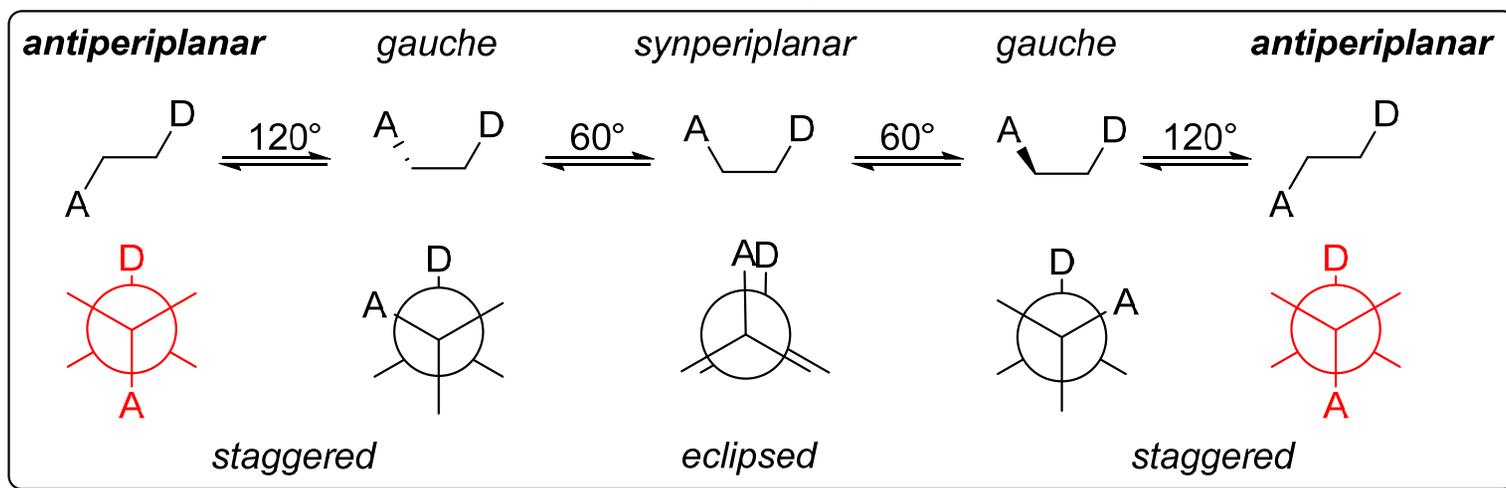
A little quiz from 2015:

choose the more stable structure from each of the pairs

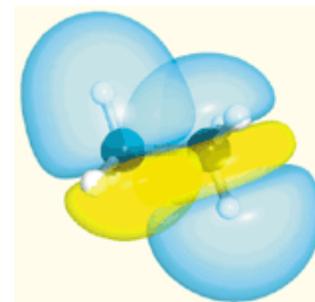
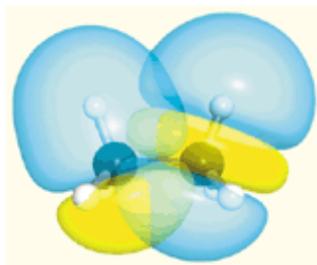
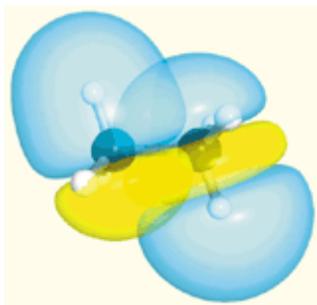


## “The main stereoelectronic rule”

“There is a stereoelectronic preference for conformations in which the best donor lone pair or bond is **antiperiplanar** to the best acceptor bond”



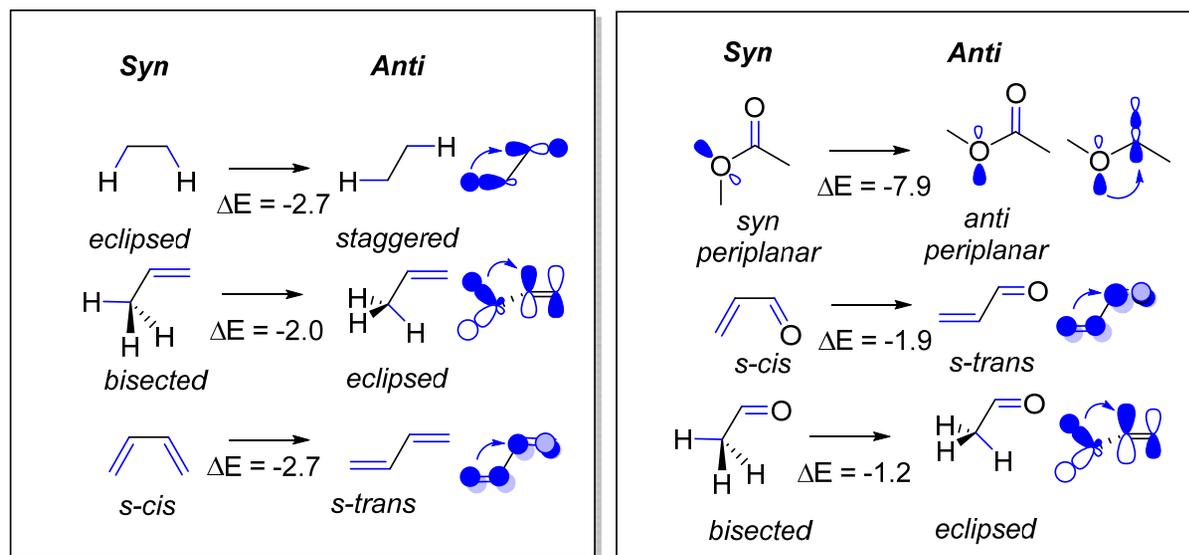
\*H's not shown



From Alabugin, “Stereoelectronic effects”

# Antiperiplanarity: “the main stereoelectronic rule”

The dependence of energies from rotation around single bonds is general.



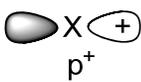
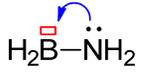
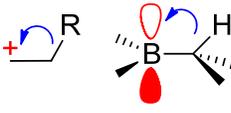
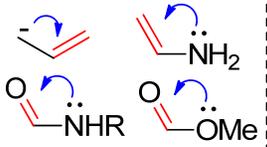
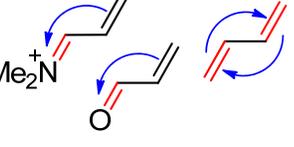
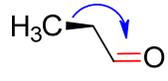
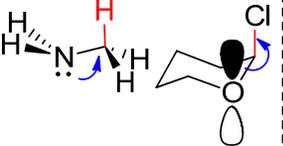
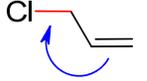
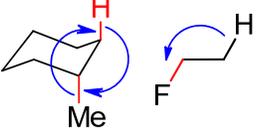
However, the differences in conformer energies can potentially originate from multiple sources, leaving room for controversies and the discussions regarding the relative importance of multiple components

M06-2X/6-311++G(d,p)  
Energies in kcal/mol

Stability is controlled by symmetry of orbital interactions. The optimal geometry is achieved when interacting donor and acceptor orbitals are antiperiplanar.

From Alabugin, “Stereoelectronic effects”

## Delocalizing interactions are diverse

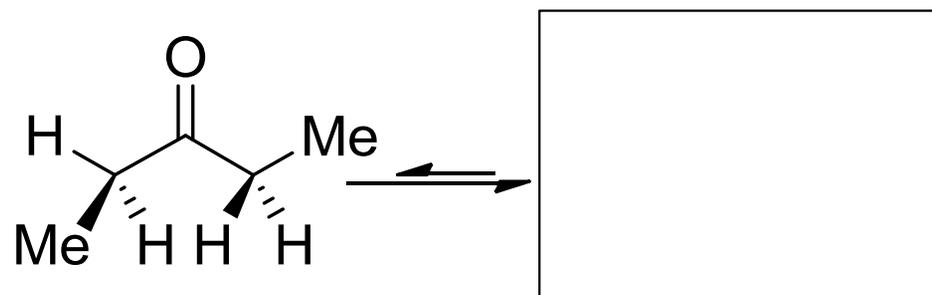
	non-bonding X:	$\pi$ -bond =Y	$\sigma$ -bond -Z	Donors
 $p^+$				
=Y $\pi^*$				
-Z $\sigma^*$				
Acceptors				

Can we really cover all of them by one rule?

The nine patterns correspond to different types of participating orbitals: non-bonding,  $\sigma$ - and  $\pi$ -. In each case, the interaction is mediated by two electrons from the donor orbitals.

From Alabugin, "Stereochemical effects"

**Test yourself: what is the most stable conformation of 3-pentanone?**

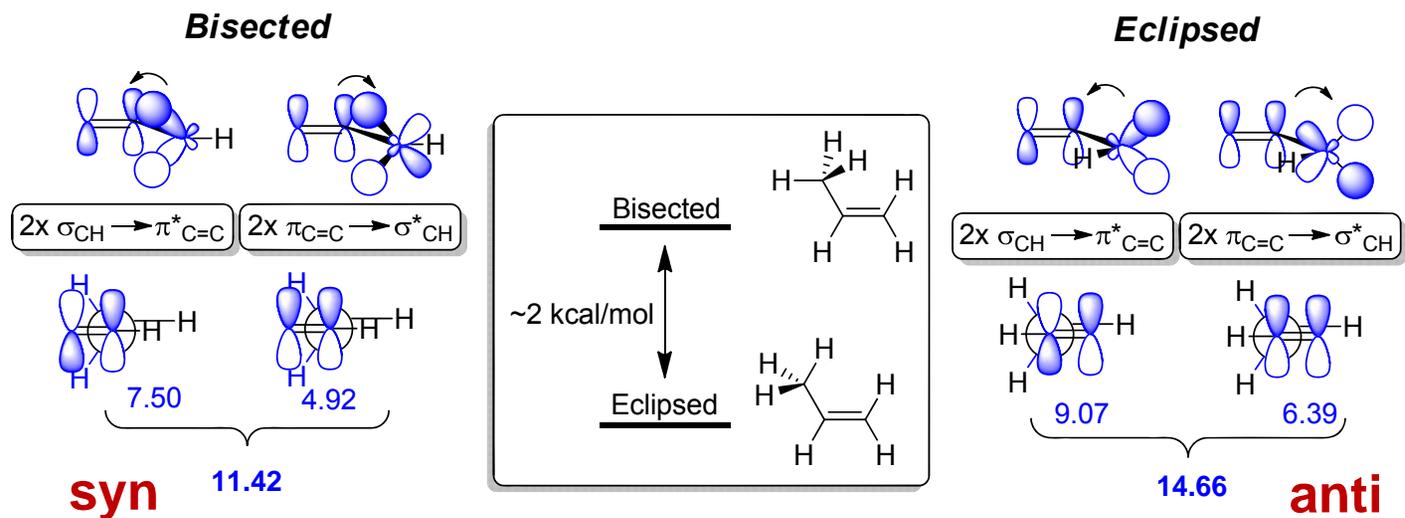


Doubly eclipsed

**Why?**

**A short explanation:** Preference for the two C-H bonds to be anti and ~coplanar to the carbonyl  $\pi^*$

## Stereoelectronic basis for the increased stability of the eclipsed conformation in propene

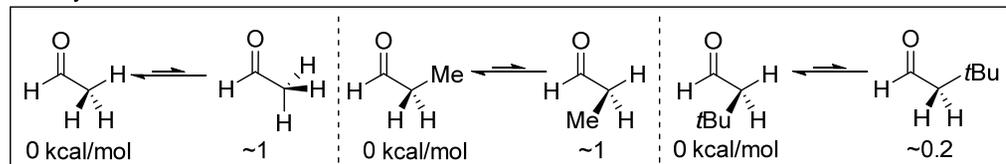


B3LYP/6-31G(d,p) NBO energies for the selected hyperconjugative interactions are shown in blue

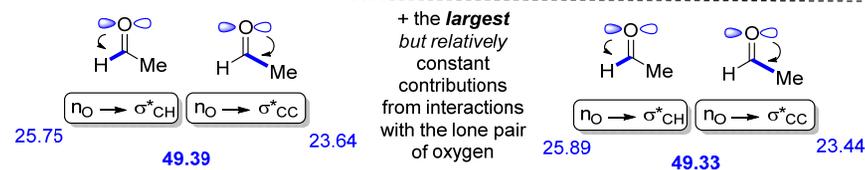
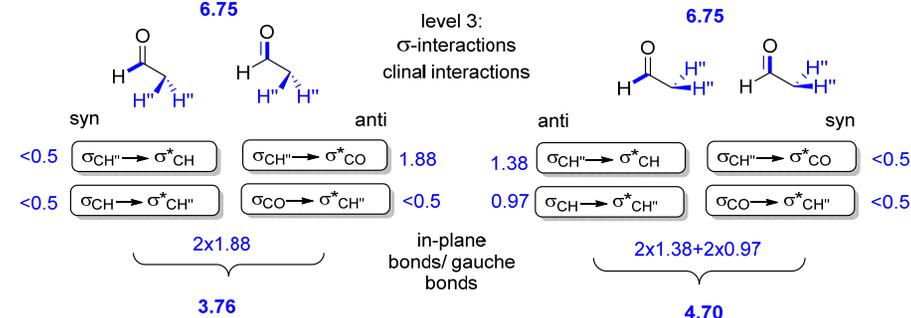
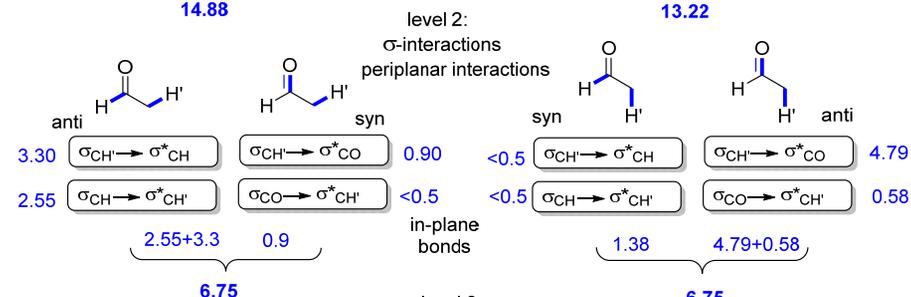
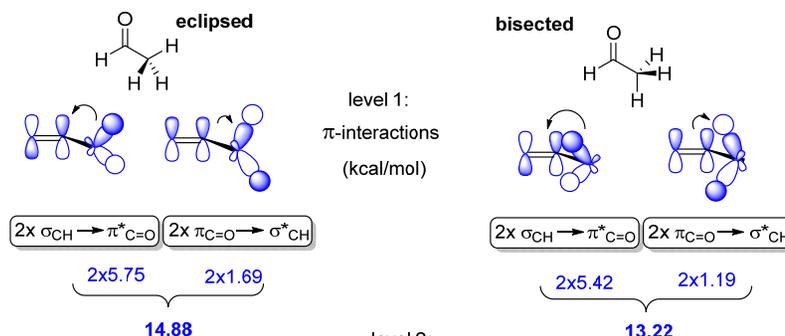
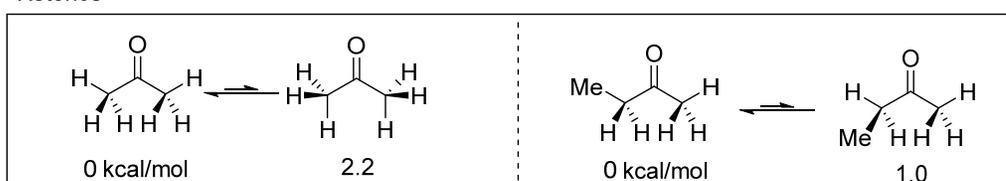
From Alabugin, "Stereoelectronic effects"

# Multiple layers of delocalizing interactions are present in the most common functional groups

## Aldehydes

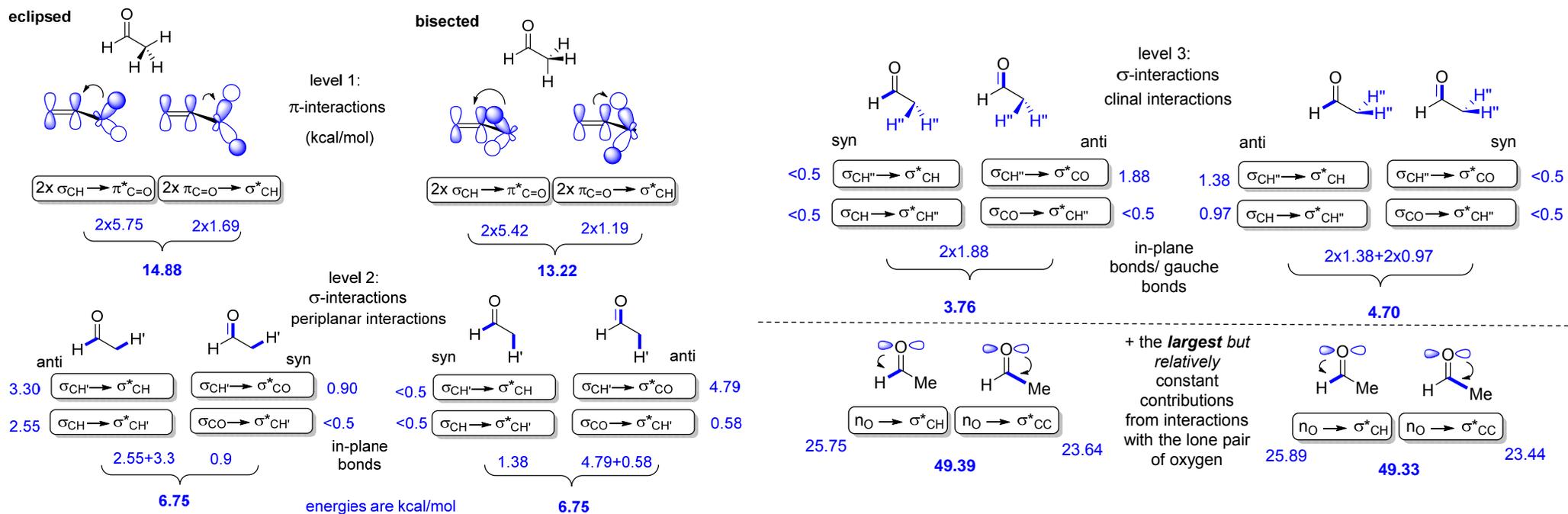


## Ketones



From Alabugin, "Stereochemical effects"

# It is helpful to know the relative importance of different delocalizing interactions



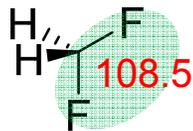
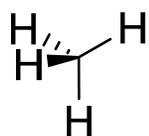
Where do the delocalizing energies (shown in blue) come from?

From Alabugin, "Stereochemical effects"

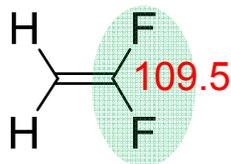
# Antiperiplanarity is not always the answer: more strange effects

Effects on structure:

What is the smallest  
valence angle in these  
two molecules?



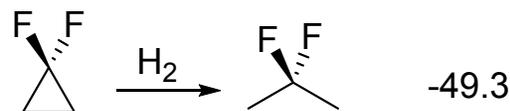
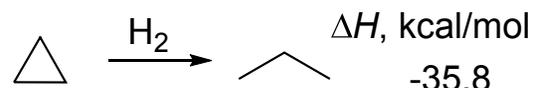
Two  $sp^3$  bonds at  
an "sp<sup>2</sup>-hybridized"  
carbon?



Hint: XCX angles are 108.5,  
109.5, and 113.9 degrees

Find two valence angle of 109.5  
degrees in these three molecules

Effects on stability/reactivity:



Which cyclopropane is  
more strained?

# Computational approaches to the study of electronic effects

Isogyric, isodesmic, hypohomodesmotic, homodesmotic, and hyperhomodesmotic equations

Dissecting electronic interactions using interactions between localized orbitals

From Alabugin, "Stereo-electronic effects"

## Isogyric, isodesmic, hypohomodesmotic, homodesmotic, and hyperhomodesmotic equations

In order to “isolate” a desired electronic effect, chemists often design hypothetical reactions of different degrees of sophistication

**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 within zooming in on the key electronic effect without introducing additional structural and electronic perturbations.

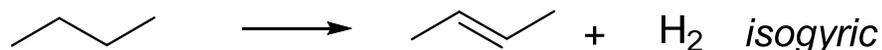
From Alabugin, “Stereo-electronic effects”

## Isogyric, isodesmic, hypohomodesmotic, homodesmotic, and hyperhomodesmotic equations

**The hierarchy of equations:** isogyric, isodesmic and homodesmotic (further divided into hypohomodesmotic, homodesmotic or hyperhomodesmotic).

The level of accuracy and sophistication increases in the following order, where each next category is a subclass of the previous one: isogyric (RC1)  $\supseteq$  isodesmic (RC2)  $\supseteq$  hypohomodesmotic (RC3)  $\supseteq$  homodesmotic (RC4)  $\supseteq$  hyperhomodesmotic (RC5)

Not all equations  
are created equal:

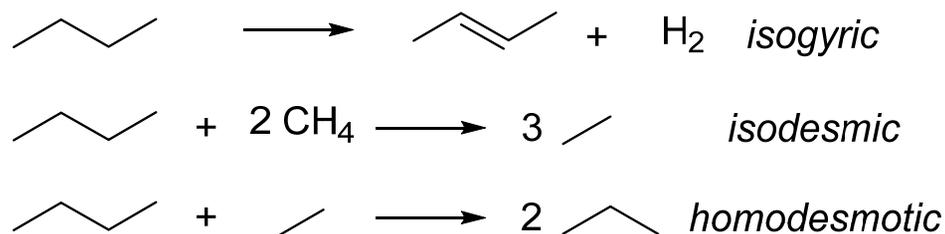


Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.*, 131, 2547–2560

## Isogyric equations

This is the least restrictive comparison.

In isogyric reactions (RC1) the **total number of electron pairs is conserved** but the number of specific bonds of a given type does not need to be balanced. Many reactions used in undergraduate chemistry textbooks (e.g., hydrogenation reactions) are isogyric.



Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.*, 131, 2547–2560

## Isodesmic equations

For hydrocarbons, the subset of isogyric reactions in which the number of C-C bonds of a given formal type (single, double, and triple) is conserved was defined as isodesmic (from Greek, *desmos* = bond) by Pople

Isodesmic reactions (RC2) are defined by preserving the number of bonds of each formal type (i.e., the single, double or triple C-C bonds) in both reactants and products, and they include “bond separation reactions”, a term for equations in which each bond between non-hydrogen atoms is separated into the simplest two-heavy-atom fragments with the same formal bond types

*Difference from isogyric equations:  
formal type of bonds (single, double, triple, etc.) is conserved*

Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.*, 131, 2547–2560

## Hypohomodesmotic equations

**Homodesmotic equations:** homodesmotic (“equal bonds”) equations are separated further in hypohomodesmotic (RC3), homodesmotic (RC4) and hyperhomodesmotic equations

### Hypohomodesmotic Reactions (RC3):

- (a) equal numbers of carbon atoms in their various states of hybridization in reactants and products, and;
- (b) equal number of carbon atoms (regardless of hybridization state) with zero, one, two, and three hydrogens attached in reactants and products. (i. e. CH, CH<sub>2</sub>, CH<sub>3</sub> groups)

*Difference from isodesmic equations:*

*The types of bonds are preserved, including heavy atom-hydrogen bonds. Carbon hybridizations are conserved*

Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. J. Am. Chem. Soc., 131, 2547–2560

## Homodesmotic equations

### (RC4):

(a) equal numbers of carbon-carbon [ $\text{Csp}^3\text{-Csp}^3$ ,  $\text{Csp}^3\text{-Csp}^2$ ,  $\text{Csp}^3\text{-Csp}$ ,  $\text{Csp}^2\text{-Csp}^2$ ,  $\text{Csp}^2\text{-Csp}$ ,  $\text{Csp-Csp}$ ,  $\text{Csp}^2=\text{Csp}^2$ ,  $\text{Csp}^2=\text{Csp}$ ,  $\text{Csp}=\text{Csp}$ ,  $\text{Csp}\equiv\text{Csp}$ ] bond types in reactants and products;

(b) equal number of each type of carbon atom ( $\text{sp}^3$ ,  $\text{sp}^2$ ,  $\text{sp}$ ) with zero, one, two, and three hydrogens attached in reactants and products.

*Difference from hypohomodesmotic equations:*

*The hybridization of partners in the individual C-C and C-H bonds is preserved*

Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.*, 131, 2547–2560

## Hyperhomodesmotic equations

**(RC5):**

(a) equal number of carbon-carbon [ $\text{H}_3\text{C}-\text{CH}_2$ ,  $\text{H}_3\text{C}-\text{CH}$ ,  $\text{H}_2\text{C}-\text{CH}_2$ ,  $\text{H}_3\text{C}-\text{C}$ ,  $\text{H}_2\text{C}-\text{CH}$ ,  $\text{H}_2\text{C}-\text{C}$ ,  $\text{HC}-\text{CH}$ ,  $\text{HC}-\text{C}$ ,  $\text{C}-\text{C}$ ,  $\text{H}_2\text{C}=\text{CH}$ ,  $\text{HC}=\text{CH}$ ,  $\text{H}_2\text{C}=\text{C}$ ,  $\text{HC}=\text{C}$ ,  $\text{C}=\text{C}$ ,  $\text{HC}\equiv\text{C}$ , and  $\text{C}\equiv\text{C}$ ] bond types in reactants and products;

(b) equal numbers of each type of carbon atom ( $\text{sp}^3$ ,  $\text{sp}^2$ ,  $\text{sp}$ ) with zero, one, two, and three hydrogens attached in reactants and products.

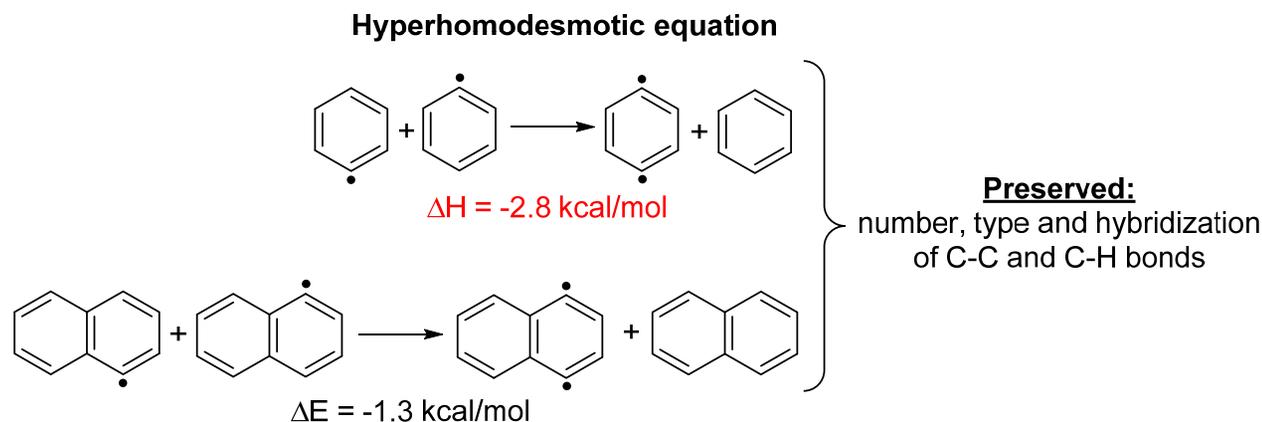
*Difference from homodesmotic equations:  
same number of C-H bonds at identically hybridized fragments*

Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. (2009) A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.*, 131, 2547–2560

## Example: Biradical stabilization energies

Biradical stabilization energies for the estimation of electronic interaction between the two radical centers in p-benzynes. Although the two radicals do not overlap in space, they couple the  $\sigma^*$  orbitals of the C-C bridges (“through-bond coupling”). All radical reactions of p-benzynes (i.e., H-abstraction, addition etc) have to pay a penalty for uncoupling the electrons, i.e., losing the through bond interaction.

How important is this coupling?

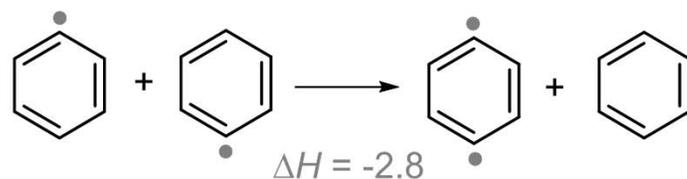


From Alabugin, “Stereochemical effects”

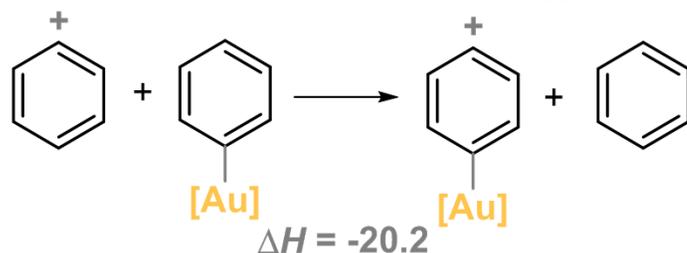
## Example: Zwitter-ion stabilization energies

Through-bond stabilization in the product of Au-catalyzed BC is dramatically larger than the one found in p-benzyne

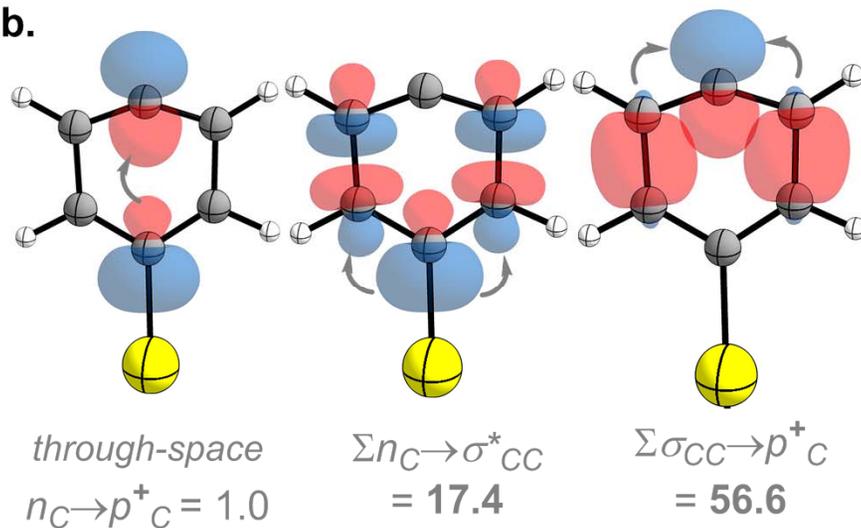
a. *Biradical stabilization energy:*



*$\gamma$ -Cation stabilization energy:*



b.



Selected NBO interactions (in kcal/mol) stabilizing the positive charge in the product.  $\text{PR}_3$  group omitted for clarity

*Drawing Catalytic Power from Charge Separation: Stereoelectronic and Zwitterionic Assistance in the Au(I)-Catalyzed Bergman Cyclization.* Gabriel dos Passos Gomes and Igor V. Alabugin, *under review*

# Homodesmotic equations are often avoided due to their complexity

Useful information can also be obtained when isodesmic or isogyric equations are combined

Let us analyze equations designed to evaluate stabilization provided to a carbonyl group by a cyclopropyl substituent.

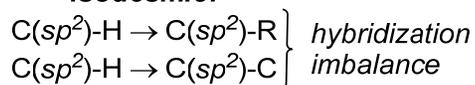
Because bent C-C bonds of cyclopropanes are good hyperconjugative donors, they are expected to lead to significant  $\sigma_{C-C} \rightarrow \pi^*_{C=O}$  donation.

Based on this hyperconjugative effect, the cyclopropyl esters have been suggested as potential prodrugs with enhanced hydrolytic stability.

“Replacement energies” from the equations suggest that a cyclopropyl group provides ~2 kcal/mol more stabilization to the carbonyl than a methyl.



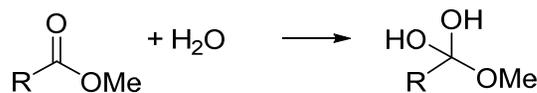
**isodesmic:**



$\Delta H(\text{CBS-QB3})$ , kcal/mol

-12.0 (R=cyclopropyl)  
-10.2 (R=methyl)

**Drawing increased stability from a strained functionality**

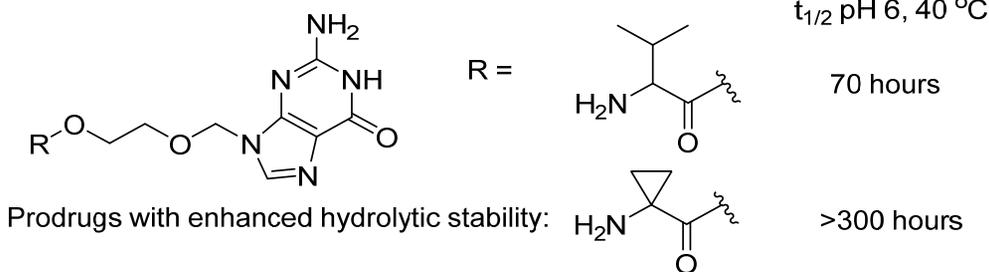


**isogyric:**

only the number of electrons is conserved

$\Delta H(\text{B3LYP})$ , kcal/mol

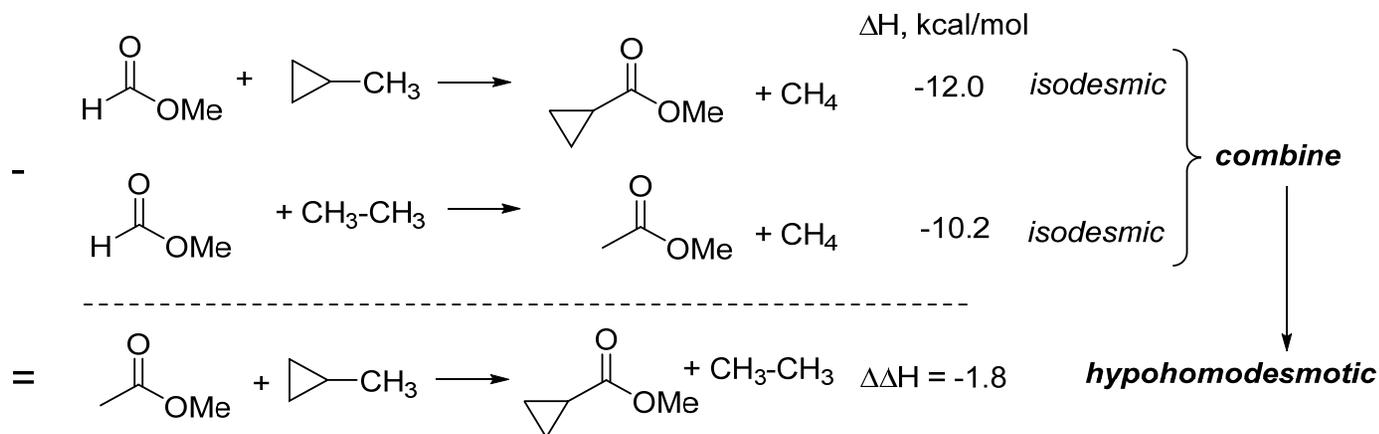
13.8 (R=cyclopropyl)  
11.1 (R=methyl)



Bender, D. M.; Peterson, J. A.; McCarthy, J. R.; Gunaydin, H.; Takano, Y.; Houk, K. N (2008), Cyclopropane-carboxylic Acid Esters as Potential Prodrugs with Enhanced Hydrolytic Stability. Org. Lett., 2008, 10, 509

## Combining equations

One can convert the above equations into a more accurate form by converting two equations into one in a way that can partially cancel the errors. For example, one can subtract the two equations as shown



*Converting a system of two isodesmic equations into a hypohomodesmotic equation by subtraction*

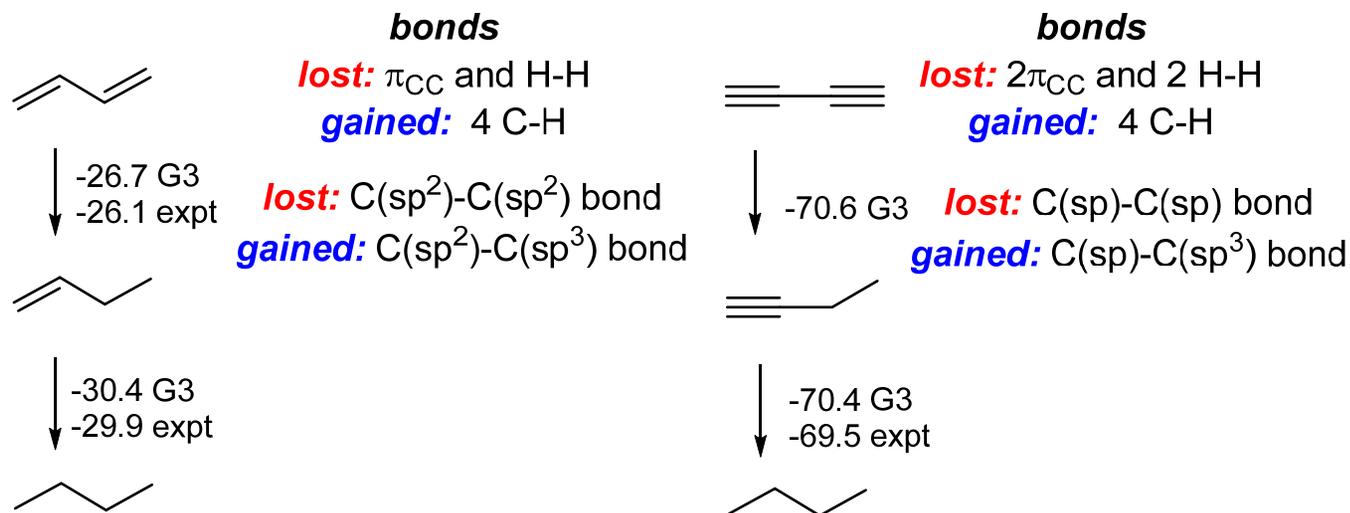
Gomes, G. d. P., Alabugin, I. V. Stereoelectronic Effects: Analysis by Computational and Theoretical Methods, Applied Theoretical Organic Chemistry

## The limitations of reaction equations: caveat emptor

It is important to design reaction equations aimed to evaluate a theoretical concept carefully. Otherwise, such equations can lead to puzzling results.

Let's compare, for example, "resonance energy" in dienes and diynes:

Hydrogenation  
equations are isogyric  
(the bond types are not  
conserved)



Gomes, G. d. P., Alabugin, I. V. Stereoelectronic Effects: Analysis by Computational and Theoretical Methods, in *Applied Theoretical Organic Chemistry*

# The Conjugation Stabilization of 1,3-Butadiyne Is Zero

Donald W. Rogers,<sup>\*,†</sup> Nikita Matsunaga,<sup>†</sup> Andreas A. Zavitsas,<sup>†</sup>  
Frank J. McLafferty,<sup>†</sup> and Joel F. Liebman<sup>‡</sup>

ORGANIC  
LETTERS

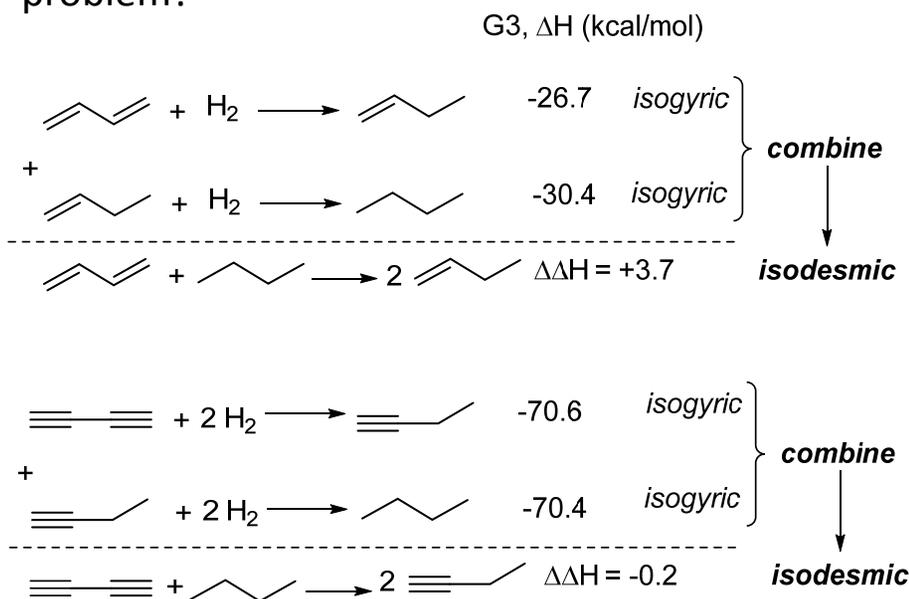
2003  
Vol. 5, No. 14  
2373–2375

“Every chemistry sophomore knows that the enthalpy (heat) of hydrogenation of 1-butene is -30 kcal/mol but the enthalpy of hydrogenation of 1,3-butadiene falls short of twice this amount by about 3.8 kcal/mol, a discrepancy ascribed to “conjugation stabilization”. Whatever the ensuing quantum mechanical argument may be to explain conjugation stabilization, the stability of conjugated double bonds relative to isolated double bonds is a thermochemical fact”

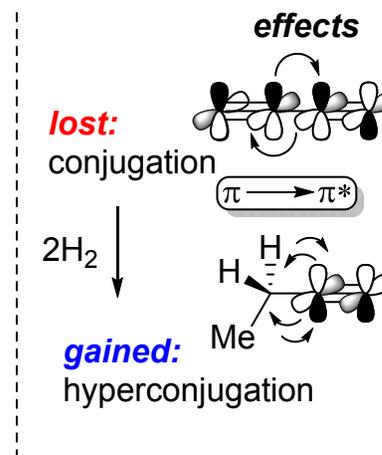
“But what of triple bonds? Naively supposing a triple bond to be two superimposed  $\pi$  bonds on an inert  $\sigma$  bond, one might think that the stabilization energy of 1,3-butadiyne (diacetylene) would be twice that of the  $\pi$  bonds in 1,3-butadiene or about 8 kcal/mol. **In fact this is wrong.** We show here that the **stabilization in diacetylene is at or near zero.**”

# More balanced *isodesmic* equations still suggest the “disappearance” of conjugative stabilization in butadiynes

So, why does a better equation still not solve the problem?



But the problem is deeper than a bond type imbalance!



The real issue with the above equations is much larger. The key omission is *its neglect of an important physical effect, i.e. hyperconjugation*

Gomes, G. d. P., Alabugin, I. V. Stereoelectronic Effects: Analysis by Computational and Theoretical Methods, Applied Theoretical Organic Chemistry



Dissecting electronic interactions  
Localized orbitals from delocalized wavefunctions

# Dissecting electronic interactions

## Localized orbitals from delocalized wavefunctions

The previous sections provided several indirect schemes for analyzing orbital interactions. One can see that isolating the desired effect is often difficult and sometimes impossible. In contrast, quantifying such electronic effects via a direct computational approach seems straightforward. Conceptually, all one needs to do is calculate the energy penalty for removing this interaction 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 as the interaction energy.

The main challenge lies in defining the appropriate localized state to serve as a reference point.

Three approaches have emerged as popular tools for isolating delocalizing interactions: Natural Bond Orbital (NBO) analysis, Energy Decomposition Analysis (EDA), and the Block-Localized Wavefunction method (BLW)

# From delocalized wavefunctions to NBO

## A little bit of quantum mechanics



Dirac: “The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known ...

- ... and the difficulty is only that the application of these laws leads to the equations much too complicated to be soluble”



“An FSU Physicist”

I do not like it, and I am sorry I ever had anything to do with it.

*Erwin Schrödinger (1887-1961) Austrian physicist. Speaking of quantum mechanics.*

Those who are not shocked when they first come across quantum mechanics cannot possibly have understood it.

*Niels Henrik David Bohr (1885-1962) Danish physicist.*

## From delocalized wavefunctions to NBO

A little bit of quantum mechanics

$$H\psi = E\psi$$

Wavefunction  $\psi = f(x, y, z, t) = f(r, \theta, \Phi, t)$

cartesian or spherical coordinates

$\psi$  by itself does not have any physical meaning but it returns allowed values of any physically measurable variable when plugged into an appropriate operator. For now, think about it **as an oracle which possesses a mystical power to give answers to any question.**

*But did we lose the connection with chemical bond?*

# Orbitals

An “orbital” refers to a one-electron wavefunction, and more specifically to the spatial part of a one-electron “spin-orbital.”

Fortunately, the rigorous theory of many-electron quantum mechanics justifies essential retention of orbital-type conceptions and their applications in bonding theory. The fundamental object underlying quantal measurement of a pure-state N-electron system is the “density matrix”:

$$\Gamma^{(N)} = \Psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) \Psi^*(\mathbf{r}'_1, \mathbf{r}'_2, \dots, \mathbf{r}'_N)$$

measurable properties of smaller subsystems of the N-electron system are expressed most rigorously in terms of corresponding pth-order “reduced” density matrices

$$\Gamma^{(p)} = [N!/p!(N-p)!] \int \Gamma^{(N)} d\tau_N d\tau_{N-1} \cdots d\tau_{N-p+1}$$

## What are Natural Orbitals?

Natural Orbitals are the eigenfunctions of the one-particle electron density matrix.

The electron density function,  $\rho$ , can be defined as:

$$\rho(\mathbf{r}) = n \int \Psi^*[\mathbf{r}(1), \mathbf{r}(2) \dots \mathbf{r}(n)] \Psi[\mathbf{r}(1), \mathbf{r}(2) \dots \mathbf{r}(n)] d\mathbf{r}(2) \dots d\mathbf{r}(n)$$

$\Psi$  is an electronic wavefunction and integration is made over the coordinates of all but the first electron (out of  $n$ ). The physical meaning that  $\rho d\mathbf{r}$  gives the probability of finding an electron in a volume element  $d\mathbf{r}$ , i.e., electron density in this volume.

An alternative description provides *the density matrix* formed by coefficients  $\alpha_{ij}$  in the following expansion:

$$\rho = \sum_i \sum_j \alpha_{ij} \Phi_i^* \Phi_j$$

The Natural Orbitals reduce the density matrix to a diagonal form where the coefficients  $b_k$  are occupation numbers of each orbital.

$$\rho = \sum_k b_k \Phi_k^* \Phi_k$$

## What are Natural Orbitals?

*“Natural Orbitals are determined by the wavefunction itself with no auxiliary assumptions and provide the most compact numerical description of the many electron molecular wavefunction”*

They are therefore “best possible” (most rapidly convergent, in the mean-squared sense) for describing the electron density. Compared to many other choices of orbitals that might be imagined or invented [e.g., the standard atomic orbital (AO) basis functions of electronic structure packages such as Gaussian], the natural orbitals are singled out by  $\psi$  itself as “natural” for its own description.

One might suppose that natural orbitals would also be “best possible” for teaching chemistry students about  $\psi$  in qualitative orbital language. This would be so, except for the fact that natural orbitals (like the canonical molecular orbitals of Hartree-Fock theory) are necessarily symmetry adapted

## Symmetry and spurious “delocalization”

Why is symmetry not always helpful?

Suppose, for example, that the quantum mechanical system of interest corresponds to two H atoms, one on earth and the other on the moon:

$$\psi_2 = \psi(H_{\text{earth}}, H_{\text{moon}})$$

On physical grounds we might expect that the orbital description of  $\psi_2$  is nearly identical to that for the corresponding localized wavefunctions

$$\psi_{1e} = \psi(H_{\text{earth}}), \quad \psi_{1m} = \psi(H_{\text{moon}})$$

However, due to the fact that  $\psi_2$  must incorporate the superposition symmetry between  $H_{\text{earth}}, H_{\text{moon}}$  (even if these atoms have no interactions of physical significance), the natural orbitals of  $\psi_2$  will be found to differ qualitatively from those of  $\psi_{1e}$  or  $\psi_{1m}$ . This has the unfortunate consequence of making the orbitals look “more delocalized” (and less transferable) than is physically meaningful, obscuring many simplicities of chemical bonding)

## Natural Bond Orbitals

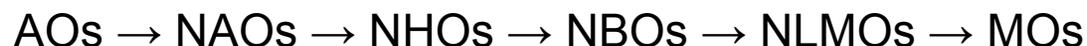
To remove spurious effects associated with symmetry adaptation, one can formulate a localized criterion for orbitals that have the analogous maximum-occupancy (natural) character in localized 1-center and 2-center regions of the molecule.

Localized orbitals of near-double occupancy can be found in the 1- and 2-center regions suggested by the elementary Lewis structure diagram. Such natural bond orbitals (NBOs) provide the most accurate possible “natural Lewis structure” picture of  $\psi$ , because all orbital details (polarization coefficients, atomic hybrid compositions, etc.) are mathematically chosen to include the highest possible percentage of the electron density.

This percentage gives an intrinsic measure of the accuracy of the natural Lewis structure picture, and is often found to be >99% for common organic molecules

## Progression of Natural Orbitals in NBO description

The NBOs are one of a sequence of natural localized orbital sets that include natural atomic (NAO), hybrid (NHO), and (semi-)localized molecular orbital (NLMO) sets, intermediate between basis AOs and canonical molecular orbitals (MOs)



All these natural localized sets are **complete and orthonormal**, able to exactly describe any property of  $\psi$ . Compared to standard AOs, e.g., the NAOs give a **much more condensed description of  $\psi$** , with only a small number (i.e., corresponding to the formal “minimal basis”) having appreciable occupancy.

## Progression of Natural Orbitals in NBO description

In accordance with the simple bond orbital picture, each bonding NBO  $\sigma_{AB}$  can be written in terms of two directed valence hybrids (NHOs)  $h_A$ ,  $h_B$  on atoms A and B, with corresponding polarization coefficients  $c_A$ ,  $c_B$ ,

$$\sigma_{AB} = c_A h_A + c_B h_B$$

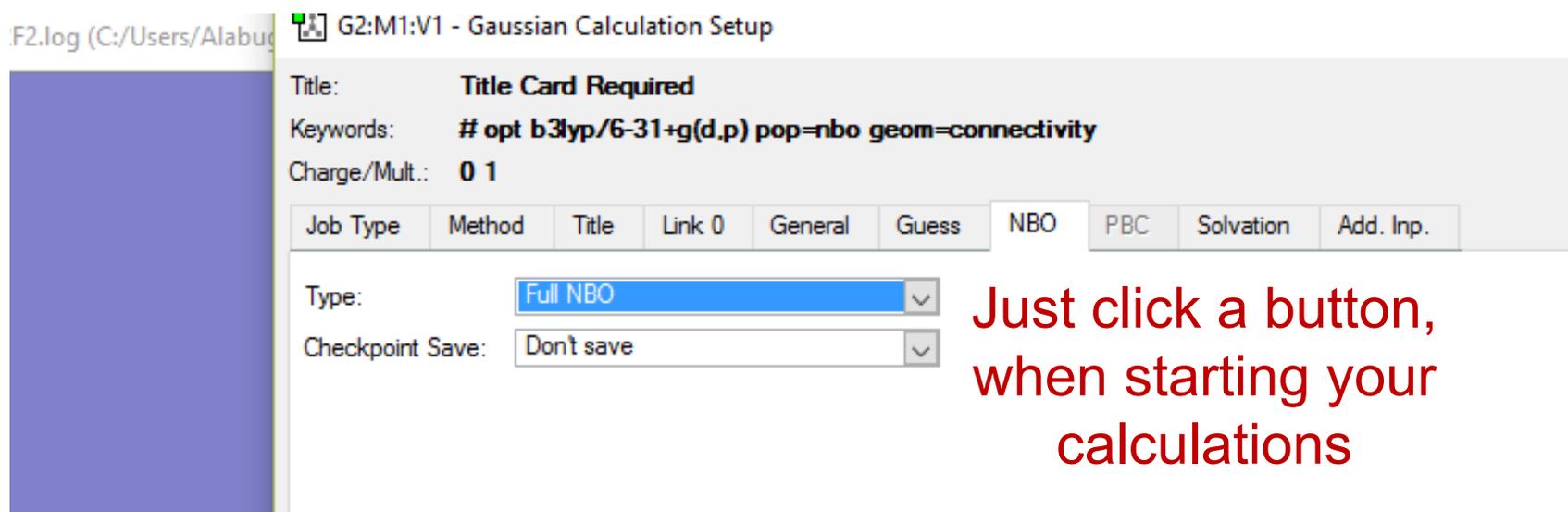
that vary smoothly from covalent ( $c_A = c_B$ ) to ionic ( $c_A \gg c_B$ ) limit.

Each valence bonding NBO (4a) must in turn be paired with a corresponding valence antibonding NBO

$$\sigma_{AB}^* = c_B h_A - c_A h_B$$

The “Lewis”-type (donor) NBOs are thereby complemented by the “non-Lewis”-type (acceptor) NBOs that are formally empty in an idealized Lewis structure picture.

## How to get NBO analysis for your molecule?



The screenshot shows the 'G2:M1:V1 - Gaussian Calculation Setup' dialog box. The 'Title' field is 'Title Card Required'. The 'Keywords' field contains '# opt b3lyp/6-31+g(d,p) pop=nbo geom=connectivity'. The 'Charge/Mult.' field is '0 1'. The 'NBO' tab is selected, showing 'Type: Full NBO' and 'Checkpoint Save: Don't save'. A red text overlay on the right says 'Just click a button, when starting your calculations'.

Title: **Title Card Required**

Keywords: **# opt b3lyp/6-31+g(d,p) pop=nbo geom=connectivity**

Charge/Mult.: **0 1**

Job Type Method Title Link 0 General Guess **NBO** PBC Solvation Add. Inp.

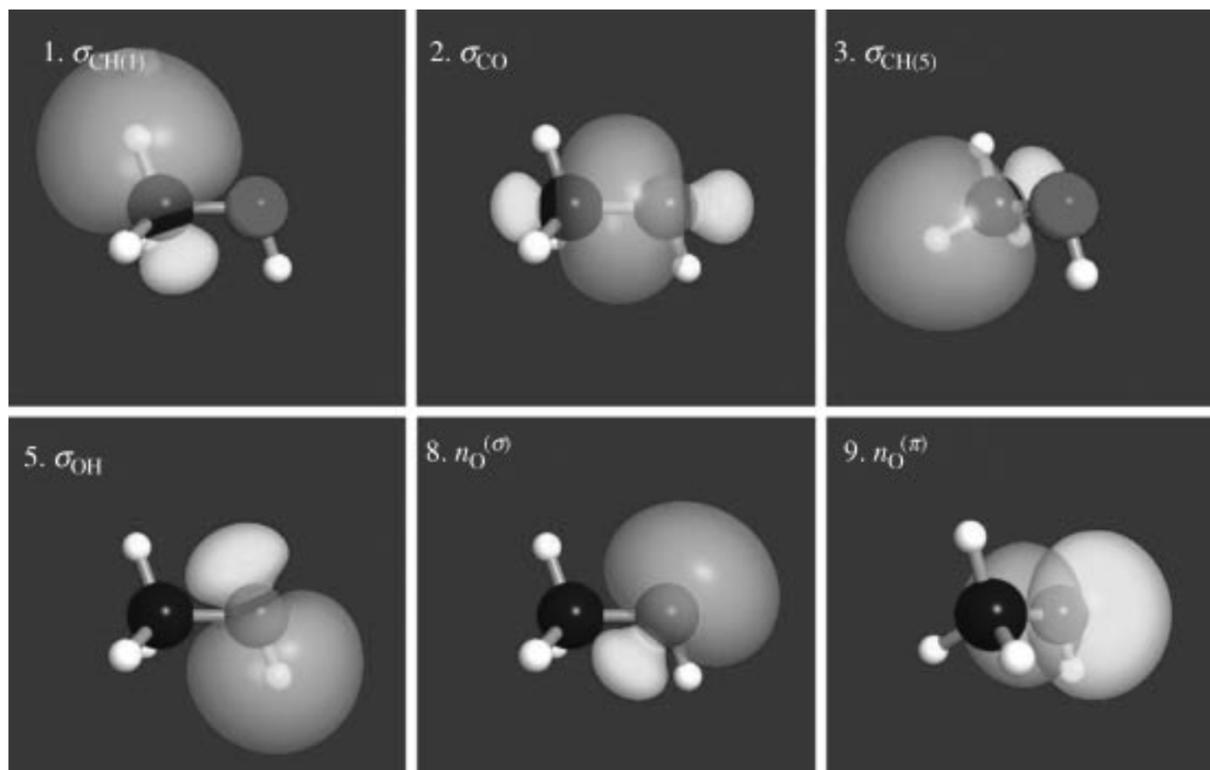
Type: **Full NBO**

Checkpoint Save: **Don't save**

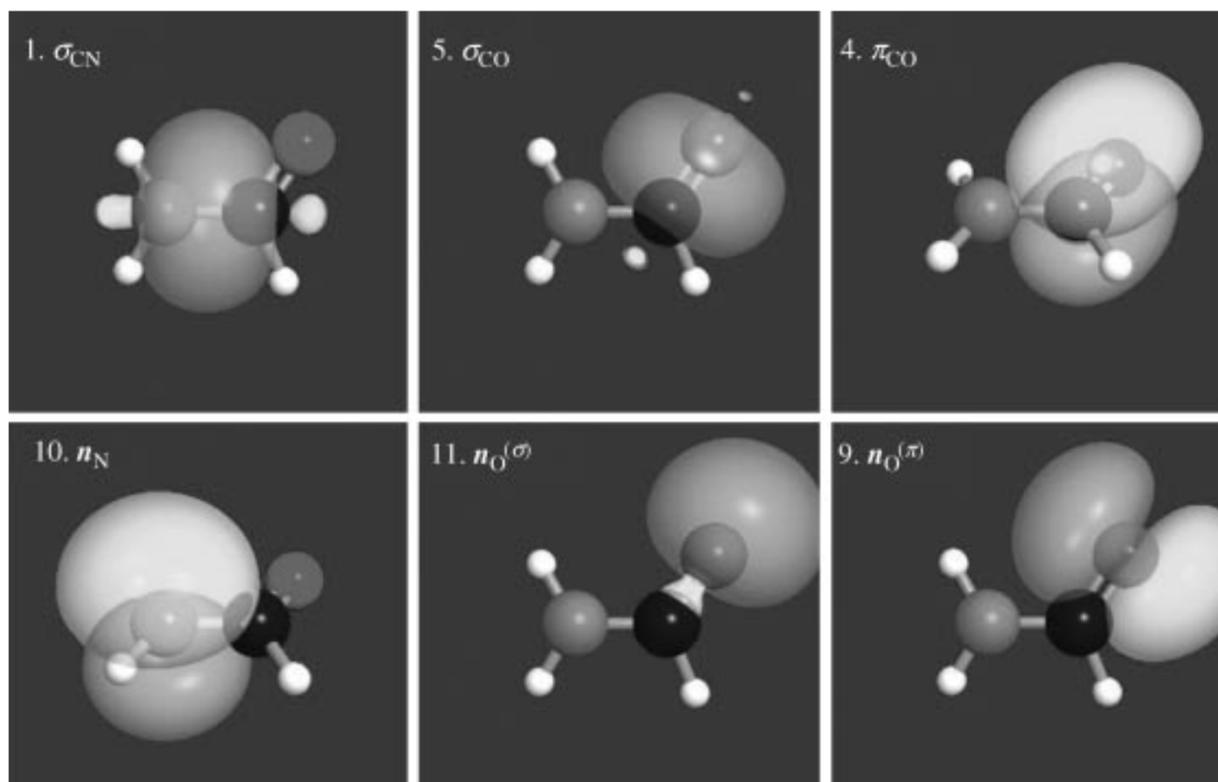
**Just click a button, when starting your calculations**

How do NBOs look?

## Methanol Natural Bond Orbitals



# Formamide Natural Bond Orbitals



# Anatomy of NBO output

## Natural Population Analysis

Natural atomic orbital occupancies

Summary of Natural Population Analysis (with **NBO charges**)

## Natural Bond Orbital Analysis

Summary

List of NBOs (**occupancy, polarization, hybridization**)

## NHO Directional Analysis ("Bond Bending")

## Perturbation Theory Energy Analysis

## NBO Summary

Principal NBOs, showing the occupancy, orbital energy, and the qualitative pattern of delocalization

## How well does the Lewis structure description work for CH<sub>4</sub>?

### NBO analysis from the Gaussian file

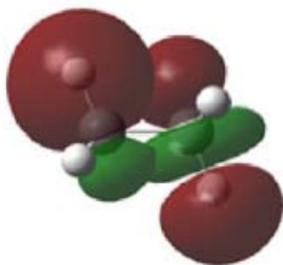
Core	1.99899	( 99.950%	of 2)
Valence Lewis	7.99500	( 99.938%	of 8)
=====	=====	=====	=====
Total Lewis	9.99400	( 99.940%	of 10)
-----	-----	-----	-----
Valence non-Lewis	0.00365	( 0.037%	of 10)
Rydberg non-Lewis	0.00235	( 0.024%	of 10)
=====	=====	=====	=====
Total non-Lewis	0.00600	( 0.060%	of 10)
-----	-----	-----	-----

**Works pretty well!**

# NBO analysis of ethane

Compare with methane

- Hybridization C-C vs C-H
- Population C-H vs. C-C
- Polarization C-H vs. C-C
- Total Lewis Density



BD ( 1) C1 - H2 / 67. BD\*( 1) C4 - H6  
3.47 kcal/mol

(1.99279) BD ( 1) C 1 - H 2  
 ( 61.04%) 0.7813\* C 1 s( 24.10%)p 3.15( 75.80%)d 0.00( 0.10%)  
 ( 38.96%) 0.6242\* H 2 s( 99.90%)p 0.00( 0.10%)  
 (1.99880) BD ( 1) C 1 - C 4  
 ( 50.00%) 0.7071\* C 1 s( 27.75%)p 2.60( 72.14%)d 0.00( 0.11%)  
 ( 50.00%) 0.7071\* C 4 s( 27.75%)p 2.60( 72.14%)d 0.00( 0.11%)

Core	3.99921 ( 99.980% of 4)
Valence Lewis	13.95549 ( 99.682% of 14)
=====	
Total Lewis	17.95470 ( 99.748% of 18)
-----	
Valence non-Lewis	0.03577 ( 0.199% of 18)
Rydberg non-Lewis	0.00954 ( 0.053% of 18)
=====	
Total non-Lewis	0.04530 (0.252% of 18)

**Four-fold increase! Compare with methane:**  
 Total non-Lewis 0.00600 (0.060% of 10)

## Lets add heteroatoms: 1) NBO quantifies bond polarity

- Ethane, EtNH<sub>2</sub>, EtOH, EtF
- Hybridization of C-X bonds
- Polarization of C-X bonds

Ethane:  
(1.99250) BD ( 1) C 1 - C 4  
( 50.00%) 0.7071\* C 1 s( 27.98%)p 2.57( 71.97%)d 0.00( 0.04%)  
( 50.00%) 0.7071\* C 5 s( 27.98%)p 2.57( 71.97%)d 0.00( 0.04%)

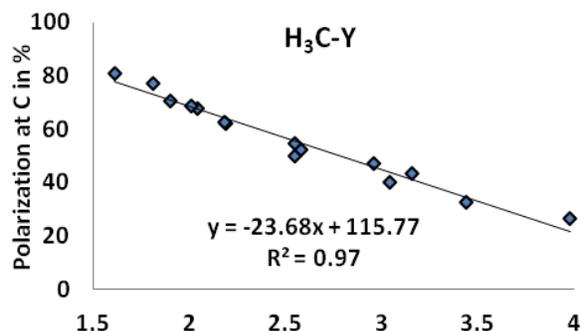
EtNH<sub>2</sub>:  
(1.99597) BD ( 1) C 5 - N 8  
( 40.72%) 0.6381\* C 5 s( 23.99%)p 3.16( 75.88%)d 0.01( 0.13%)  
( 59.28%) 0.7699\* N 8 s( 31.43%)p 2.18( 68.51%)d 0.00( 0.06%)

EtOH:  
(1.99643) BD ( 1) C 5 - O 8  
( 33.21%) 0.5763\* C 5 s( 21.07%)p 3.73( 78.68%)d 0.01( 0.25%)  
( 66.79%) 0.8172\* O 8 s( 29.14%)p 2.43( 70.78%)d 0.00( 0.09%)

EtF:  
(1.99674) BD ( 1) C 1 - F 8  
( 27.13%) 0.5209\* C 1 s( 18.55%)p 4.38( 81.17%)d 0.02( 0.28%)  
( 72.87%) 0.8536\* F 8 s( 25.90%)p 2.86( 74.00%)d 0.00( 0.10%)

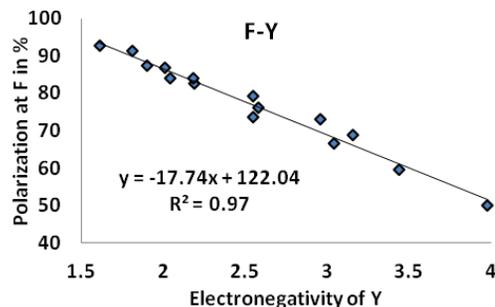
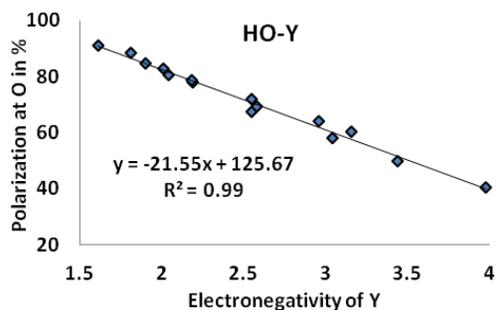
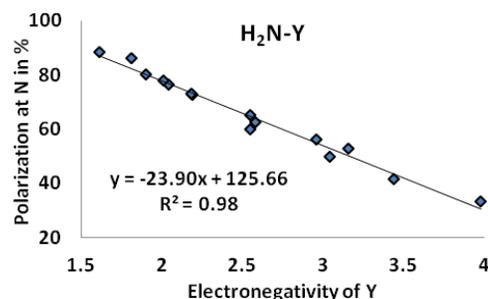
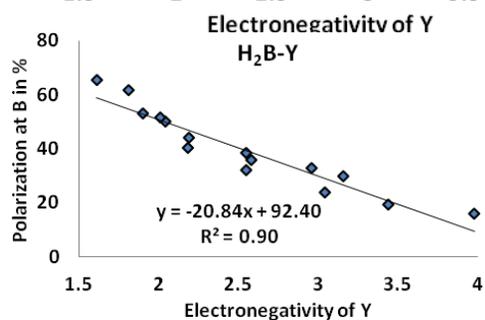
Let's plot C-X bond polarity via  
Pauling electronegativity of X

# Pauling's electronegativity vs. bond polarization



NBO bond polarization matches Pauling's electronegativity very well

How about other elements?



Bresch, Manoharan, Alabugin, J.  
*Phys. Chem. A* **2014**, *118*, 3663

## Lets add heteroatoms: 2) NBO quantifies hybridization

- Ethane, EtNH<sub>2</sub>, EtOH, EtF
- Hybridization of C-X bonds
- Polarization of C-X bonds

Ethane:  
(1.99250) BD ( 1) C 1 - H 2  
( 50.00%) 0.7071\* C 1 s( 27.98%)p 2.57( 71.97%)d 0.00( 0.04%)  
( 50.00%) 0.7071\* C 5 s( 27.98%)p 2.57( 71.97%)d 0.00( 0.04%)

EtNH<sub>2</sub>:  
(1.99597) BD ( 1) C 5 - N 8  
( 40.72%) 0.6381\* C 5 s( 23.99%)p 3.16( 75.88%)d 0.01( 0.13%)  
( 59.28%) 0.7699\* N 8 s( 31.43%)p 2.18( 68.51%)d 0.00( 0.06%)

EtOH:  
(1.99643) BD ( 1) C 5 - O 8  
( 33.21%) 0.5763\* C 5 s( 21.07%)p 3.73( 78.68%)d 0.01( 0.25%)  
( 66.79%) 0.8172\* O 8 s( 29.14%)p 2.43( 70.78%)d 0.00( 0.09%)

EtF:  
(1.99674) BD ( 1) C 1 - F 8  
( 27.13%) 0.5209\* C 1 s( 18.55%)p 4.38( 81.17%)d 0.02( 0.28%)  
( 72.87%) 0.8536\* F 8 s( 25.90%)p 2.86( 74.00%)d 0.00( 0.10%)

Note that hybridization of carbon in C-X bonds also correlates with electronegativity of X

sp<sup>4.4</sup> hybridization in the C-F bond?

## Lets add heteroatoms:

### 3) NBO quantifies delocalizing interactions

- Ethane, EtNH<sub>2</sub>, EtOH, EtF
- Hybridization of C-X bonds
- Polarization of C-X bonds
- Donation from  $\sigma_{C-H}$  to  $\sigma^*_{C-X}$**   
(from bonding to antibonding orbitals)

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

$F_{ij}$  is the resonance integral for orbitals  $i$  and  $j$ ,  $\epsilon_{\sigma}$  and  $\epsilon_{\sigma^*}$  are the energies of the  $\sigma$  and  $\sigma^*$  orbitals, and  $n_{\sigma}$  is the population of the donor

#### Second Order Perturbation Theory Analysis of Fock Matrix in NBO

Basis Threshold for printing: 0.50 kcal/mol

Donor NBO (i)	Acceptor NBO (j)	E(2) kcal/mol	E(j)-E(i) a.u.	F(i,j) a.u.
Ethane:				
BD ( 1)C 1 - H 3 / 68.	BD*( 1)C 4 - H 7	3.47	1.39	0.062
EtNH <sub>2</sub> :				
BD ( 1)C 1 - H 2 / 90.	BD*( 1)C 5 - N 8	3.76	0.84	0.050
EtOH:				
BD ( 1)C 1 - H 2 / 86.	BD*( 1)C 5 - O 8	4.05	0.79	0.050
EtF:				
BD ( 1)C 4 - H 5 / 79.	BD*( 1)C 1 - F 8	5.01	0.72	0.054

## NBO analysis and orbital hybridizations

*Why bother?*

*Haven't we learn everything about hybridization in the first month of organic chemistry?*

## Is It Time To Retire the Hybrid Atomic Orbital?

Alexander Grushow\*

Department of Chemistry, Biochemistry & Physics, Rider University, Lawrenceville, New Jersey 08648, United States

**ABSTRACT:** A rationale for the removal of the hybrid atomic orbital from the chemistry curriculum is examined. Although the hybrid atomic orbital model does not accurately predict spectroscopic energies, many chemical educators continue to use and teach the model despite the confusion it can cause for students. Three arguments for retaining the model in the chemical curriculum are presented. These arguments are then refuted and methods for teaching chemistry without invoking the hybrid atomic orbital model are presented to show how the model can be removed from the chemistry curriculum with little negative effect.

**KEYWORDS:** First-Year Undergraduate, Organic Chemistry, Physical Chemistry, Misconceptions/Discrepant Events, Theoretical Chemistry, VSEPR Theory, Valence Bond Theory, MO Theory, Covalent Bonding

### ■ ARGUMENTS

Despite significant experimental evidence and theoretical advances to indicate that hybrid atomic orbitals do not exist and do not appropriately describe molecular bonding, their description still permeates chemical education at many levels, and the model still finds its way into modern chemical literature.



[Retire the Hybrid Atomic Orbital? Not So Fast](#)

By: Tro, Nivaldo J.  
JOURNAL OF CHEMICAL  
EDUCATION Volume: 89 Issue: 5 Pages:  
567-568 Published: MAY 2012

[Retire Hybrid Atomic Orbitals?](#)

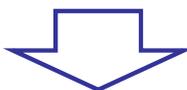
By: DeKock, Roger L.; Strikwerda, John R.  
JOURNAL OF CHEMICAL  
EDUCATION Volume: 89 Issue: 5 Pages:  
569-569 Published: MAY 2012

[Comments on "Is It Time To Retire the Hybrid Atomic Orbital?"](#)

By: Landis, C. R.; Weinhold, F.  
JOURNAL OF CHEMICAL  
EDUCATION Volume: 89 Issue: 5 Pages:  
570-572 Published: MAY 2012

[In Defense of the Hybrid Atomic Orbitals](#)

By: Hiberty, Philippe C.; Volatron, Francois;  
Shaik, Sason  
JOURNAL OF CHEMICAL  
EDUCATION Volume: 89 Issue: 5 Pages:  
575-577 Published: MAY 2012



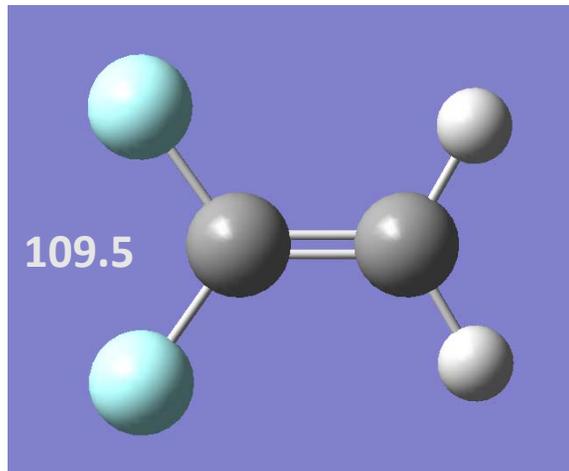
[In Response to Those Who Wish To Retain Hybrid Atomic Orbitals in the Curriculum](#)

By: Grushow, Alexander  
JOURNAL OF CHEMICAL  
EDUCATION Volume: 89 Issue: 5 Pages:  
578-579 Published: MAY 2012

## “Hybridization anomalies”

- Can you estimate the FCF angle?

F-C-F angle is “tetrahedral”  
because carbon uses  $sp^3$  hybrids  
to form the two C-F bonds

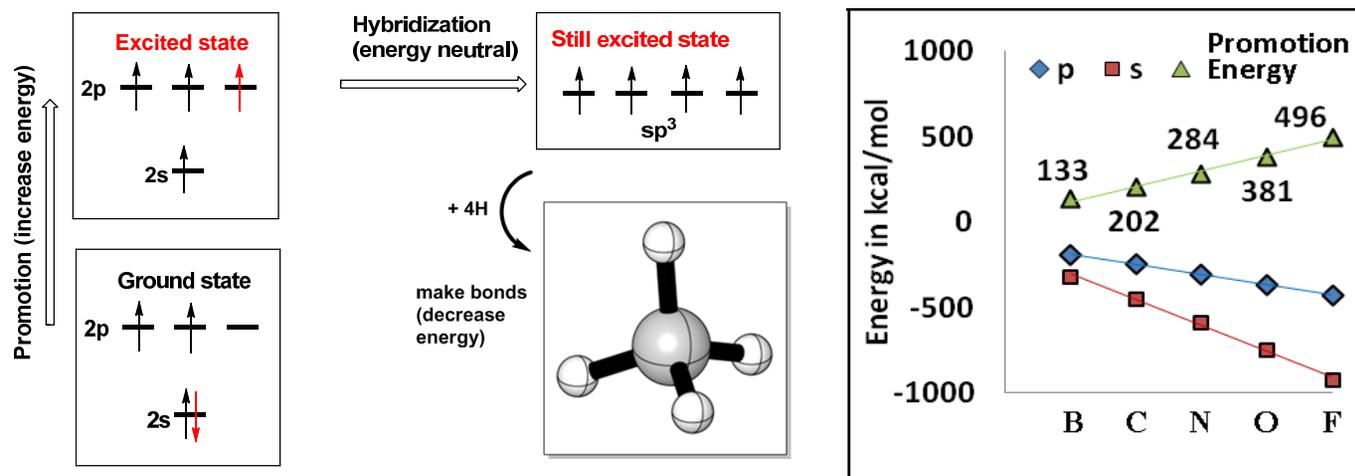


3. (1.99658) BD ( 1) C 1 - C 4  
( 50.24%) 0.7088\* C 1 s( 33.71%)p 1.97( 66.25%)d 0.00( 0.05%)  
( 49.76%) 0.7054\* C 4 s( 47.99%)p 1.08( 51.98%)d 0.00( 0.04%)

5. (1.99514) BD ( 1) C 4 - F 5  
(27.04%) 0.5200\* C 4 s(24.99%)p 2.99(74.69%)d 0.01( 0.32%)  
( 72.96%) 0.8542\* F 5 s( 28.74%)p 2.48( 71.14%)d 0.00( 0.12%)

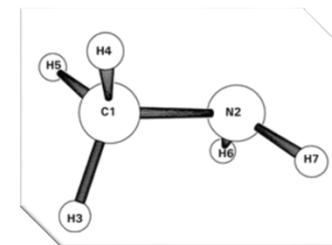
What hybrid does the C(F<sub>2</sub>) carbon use to form the C-C bond?  
What about the two C-F bonds?

## Revisiting hybridization



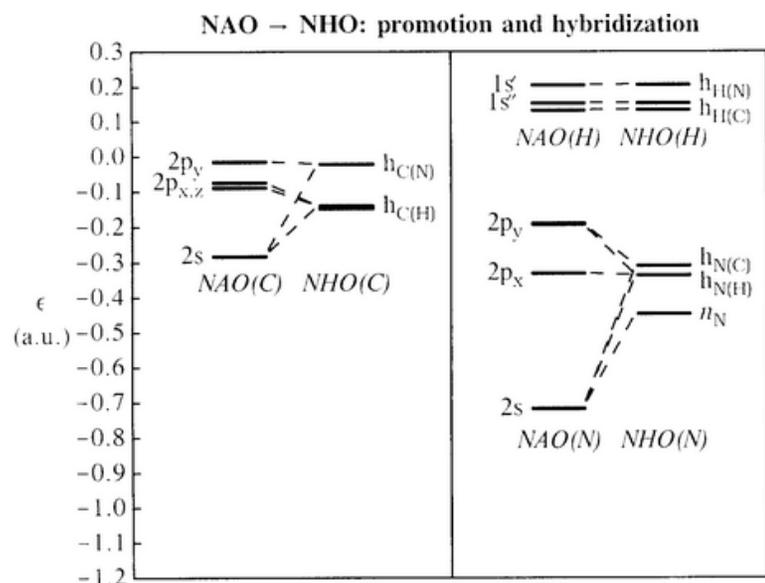
To “hybridize” (or mix) atomic orbitals, the carbon atom has to arrive to an excited state (one electron is promoted from 2s orbital to a 2p orbital) → *Organic chemistry is chemistry of excited state of carbon atoms*

# Rediscovering hybridization with NBO: example of methylamine



- Natural Hybrid Orbitals (NHOs) reveal many hidden hybridization effects on molecular structure and reactivity

Formation of directed hybrid NHOs from NAOs:  $\text{NAO} \rightarrow \text{NHO} \rightarrow (\text{NBO} = \text{Lewis structure} + \text{delocalization})$



Note that the starting { $p_x, p_y, p_z$ } valence NAOs of C, N show the expected slight breakdown of spherical symmetry in the molecular environment

Carbon, Nitrogen NAOs undergo promotion and hybridization to form directed hybrid NHOs of approximate  $sp^3$  character

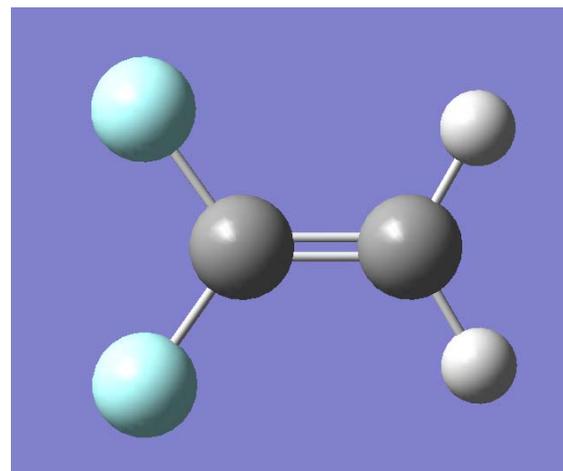
For the five H atoms, the "hybrid" NHOs are essentially identical to the starting 1sH NAOs, with orbital energies slightly separated into (1,2,2) splitting pattern by the asymmetric molecular environment

## Variable Orbital Hybridization

The hybridization parameter  $\lambda$  varies between 0 (pure s) and infinity (pure p), **with any integer or non-integer value in this range being physically allowed.**

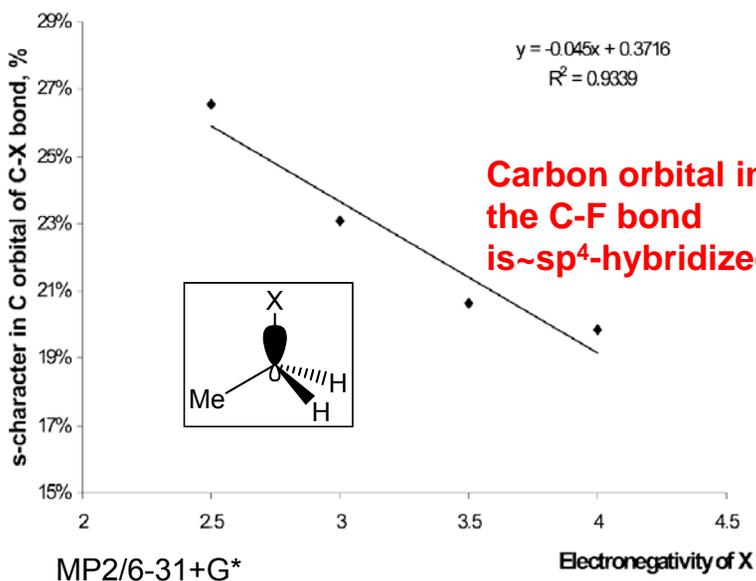
Atoms are not limited to the standard selection of  $sp^2$ ,  $sp^3$ ,  $sp$  hybridizations as long as total s% adds to 100% (and p% adds to 300%)

Carbon of $CF_2$ group:	s%:
Two $sp^3$ orbitals	2x25%
One sp	50%
One p	0%
Total:	100%



## Bent's rule: hybridization and electronegativity

“Atomic **s-character** concentrates in orbitals directed toward electropositive substituents” *Chem. Rev.* 1961, 61, 275 (Cited by 1123)



The **s-character** influences several observables:

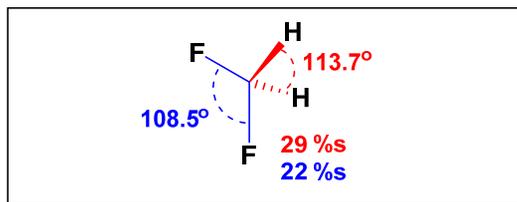
- Bond length
- Bond angle
- Bond polarity
- Bond-stretching force constants
- Bond-bending force constants
- NMR coupling constants
- Acid strength
- Base strength
- Dipole moments
- Kinetic isotope effects

Carbon orbital in the C-F bond is ~sp<sup>4</sup>-hybridized

Alabugin, I. V., Manoharan, M., Peabody S., Weinhold, F. *J. Am. Chem. Soc.*, 2003, 125, 5973

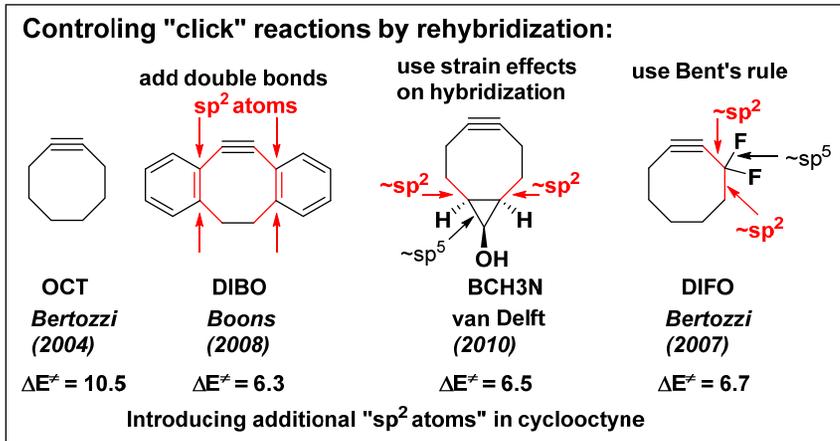
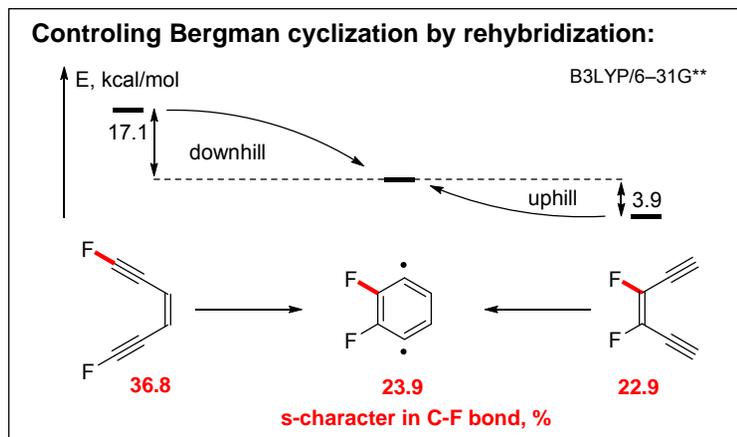
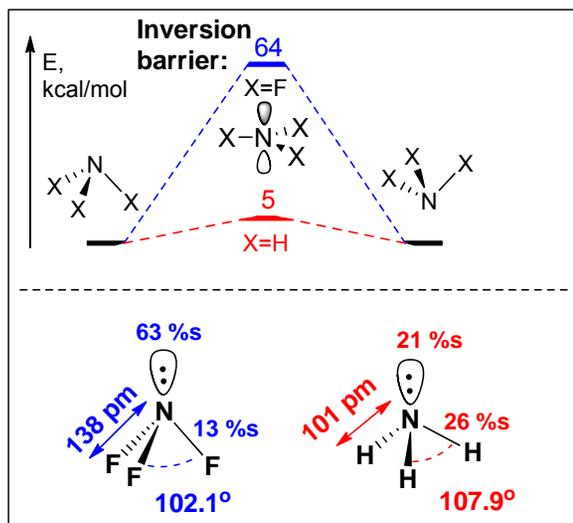


## Bent's Rule in Action



Can you explain geometry of difluoromethane?

Just look at s-character at in C-H and C-F bonds

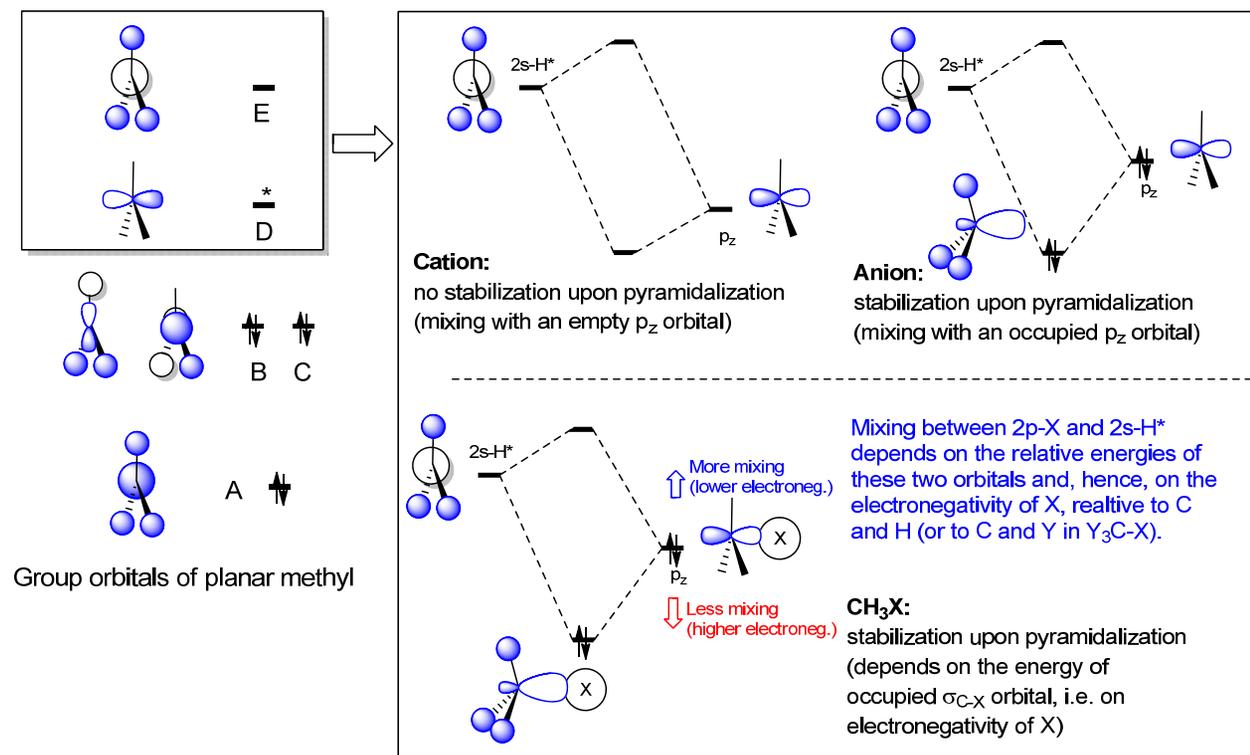


Orbital Hybridization: a Key Electronic Factor in Control of Structure and Reactivity. Alabugin, I. V.; Bresch S.; Gomes, G. P. *J. Phys. Org. Chem.*, **2015**, 28, 147-162. <http://onlinelibrary.wiley.com/doi/10.1002/poc.3382/abstract>

**Bent's Rule: is it general?**

**Can we expand it beyond carbon?**

## MO justification for Bent's rule

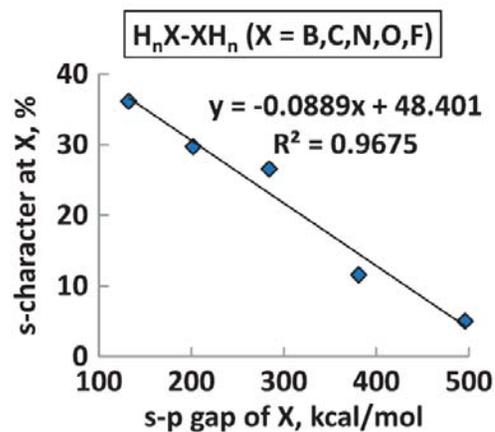
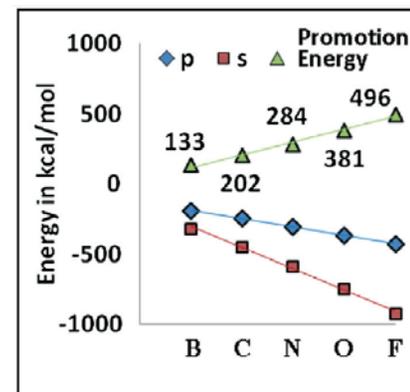
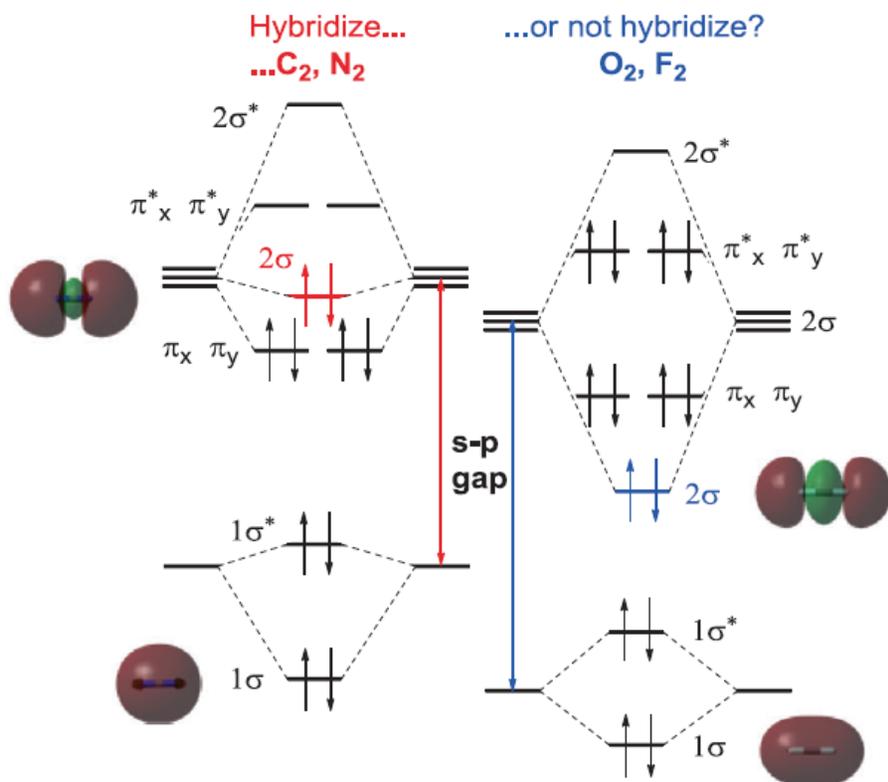


Wes Borden

Left: group orbitals of planar methyl. Right, top: Orbital interactions responsible for pyramidalization and hybridization (or lack of thereof) in methyl anion and cation. Right, bottom: MO model for the Bent's rule. An s-orbital is used for atom X for simplicity. It can be substituted by a p-orbital or an  $sp^n$ -hybrid

# Hybridization fades away across the Period (B → F)

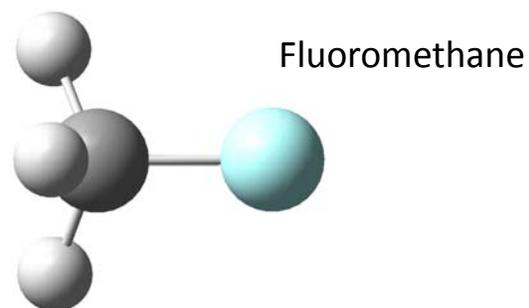
Why?



Look up hybridization of O-O and F-F bonds

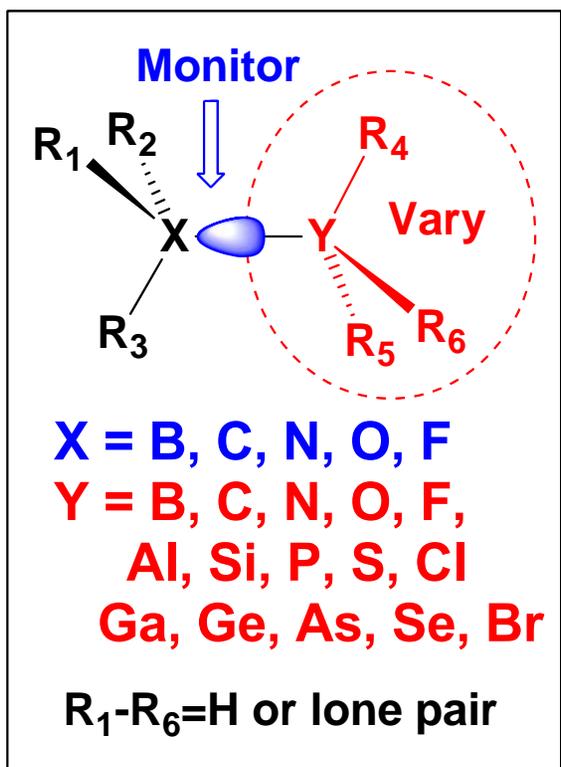
## Scope / Design

Calculate geometry and electronic structure



Use Natural Bond Orbital Analysis to find hybridization

```
1. (1.99867) BD (1) C 1 - F 2
  ( 27.66%) 0.5260* C 1 s( 20.69%)p 3.82( 79.01%)d 0.01( 0.30%)
    0.0000 -0.4477 0.0802 -0.0043 0.0002
    0.0000 0.0000 0.0000 0.0000 0.0000
    0.0000 0.0000 0.0000 -0.8862 0.0665
    0.0155 -0.0021 0.0000 0.0000 0.0000
    0.0000 -0.0550
  ( 72.34%) 0.8505* F 2 s( 25.46%)p 2.92( 74.45%)d 0.00( 0.09%)
    0.0000 -0.5044 0.0121 0.0005 0.0000
    0.0000 0.0000 0.0000 0.0000 0.0000
    0.0000 0.0000 0.0000 0.8628 -0.0127
    -0.0028 0.0001 0.0000 0.0000 0.0000
    0.0000 -0.0302
```

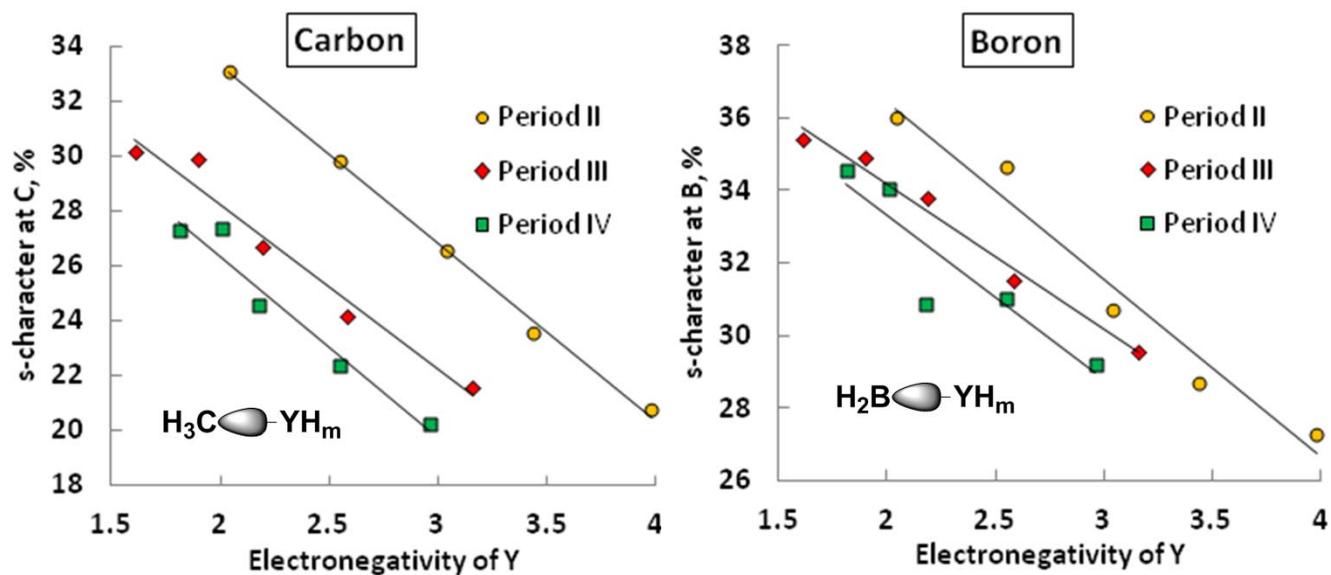


## 75 bond types



Stefan Bresch

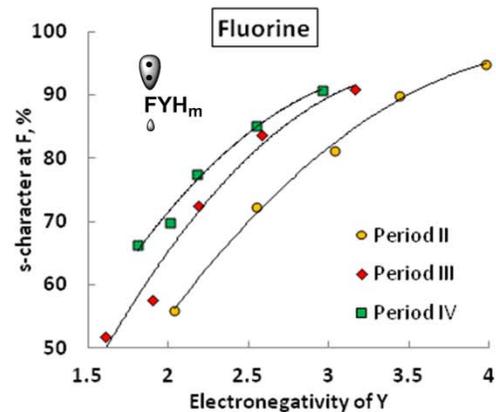
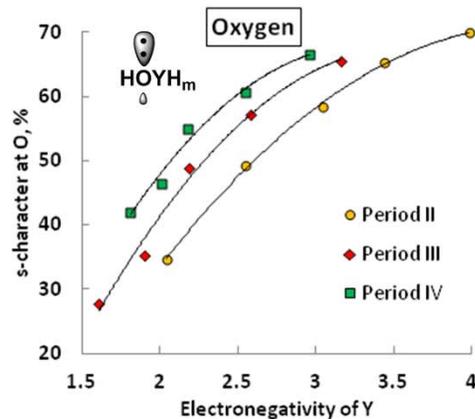
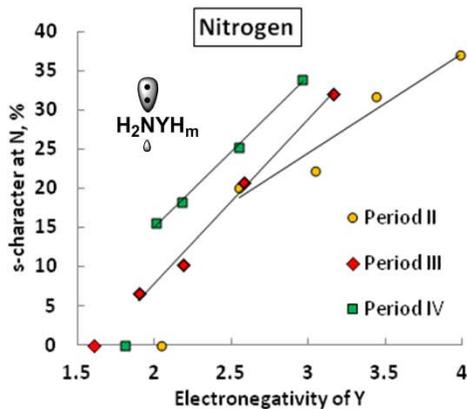
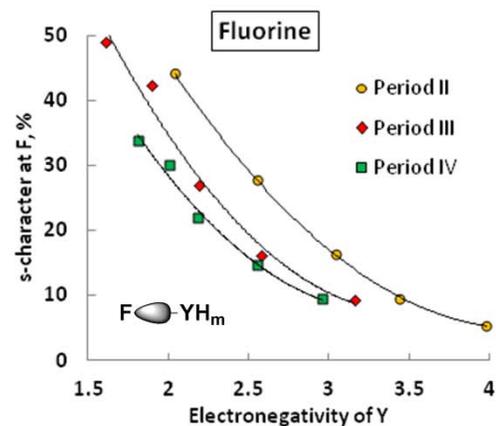
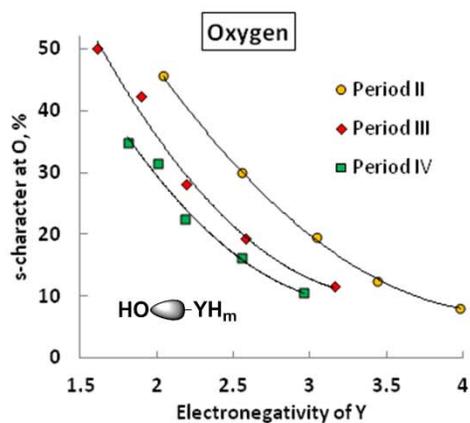
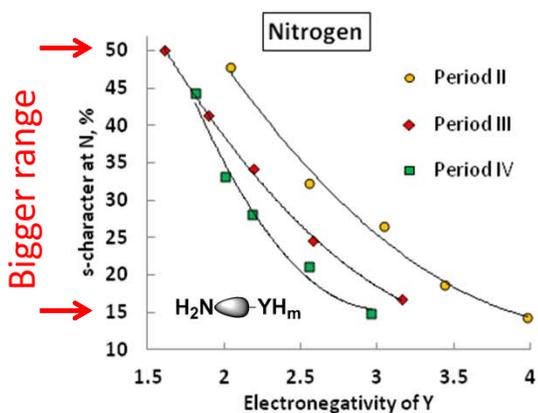
## How does hybridization depends on electronegativity?



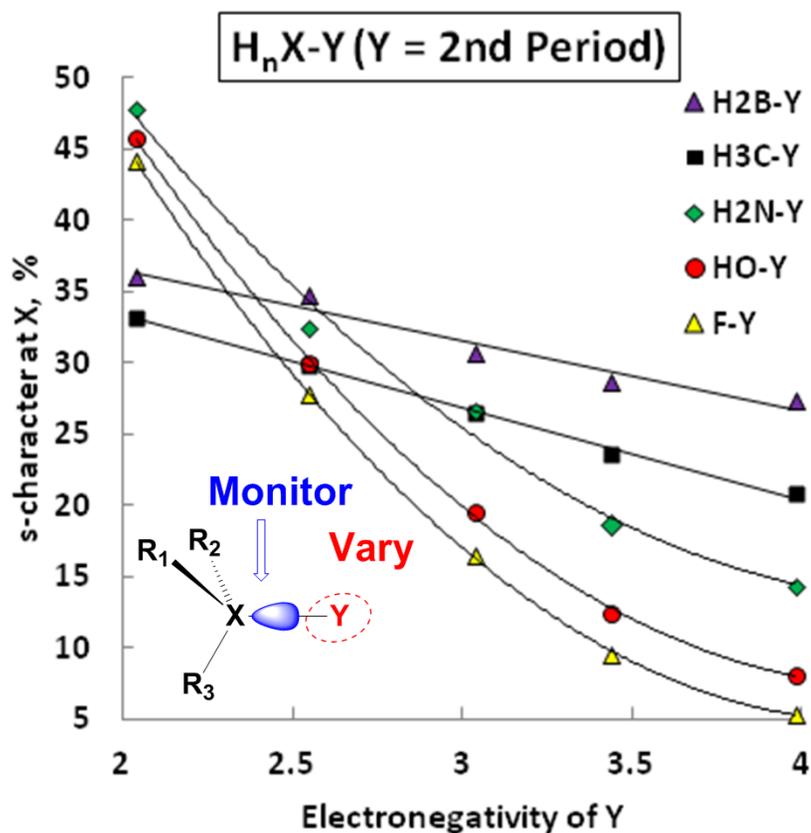
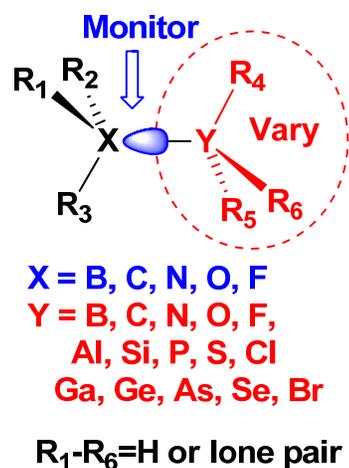
As expected from the Bent's rule?

# N,O,F are different

## Non-linear correlations

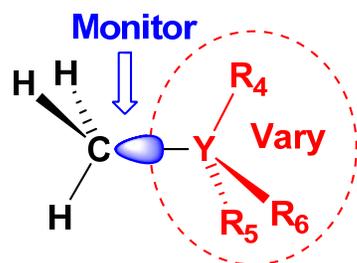


## Extension to other Groups: N,O,F are different



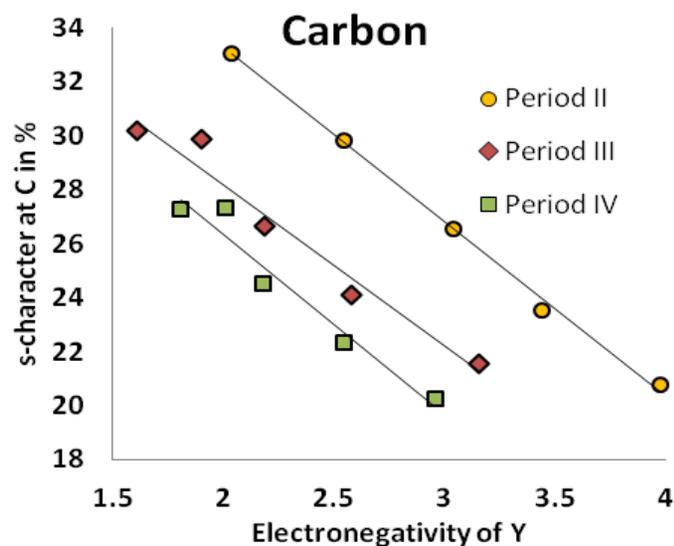
Bonds at atoms with lone pairs can rehybridize dramatically:  
**SUPER-rehybridization**

## Extension to other Periods



Y = B, C, N, O, F,  
Al, Si, P, S, Cl  
Ga, Ge, As, Se, Br

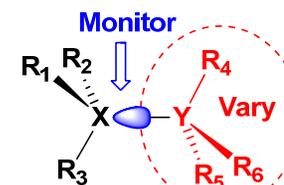
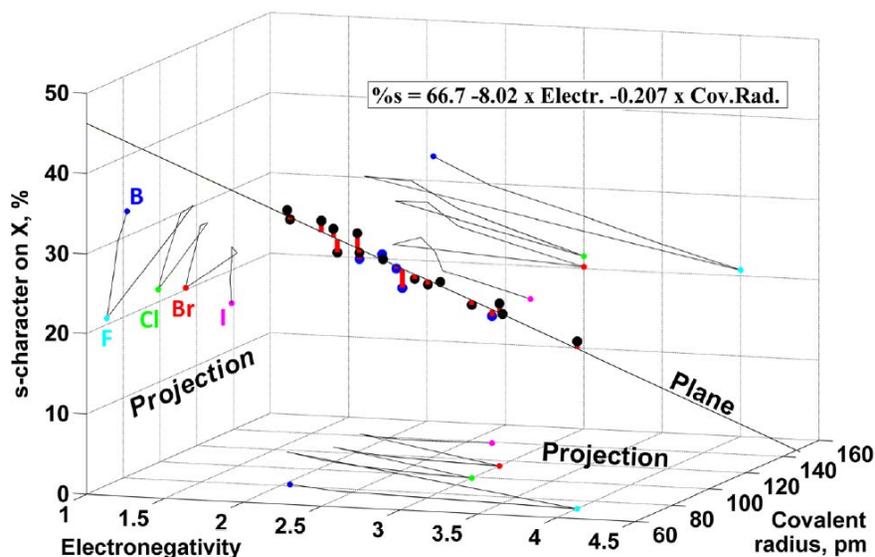
R<sub>4</sub>-R<sub>6</sub>=H or lone pair



Even for carbon, there is no single correlation with electronegativity – **there has to be an additional factor**

## Bent's rule applies across the Periodic Table if we add an additional parameter

**New Bent's Rule:** Carbon directs hybrids with **more p-character** towards **more electronegative** elements and to elements with **larger radii**.

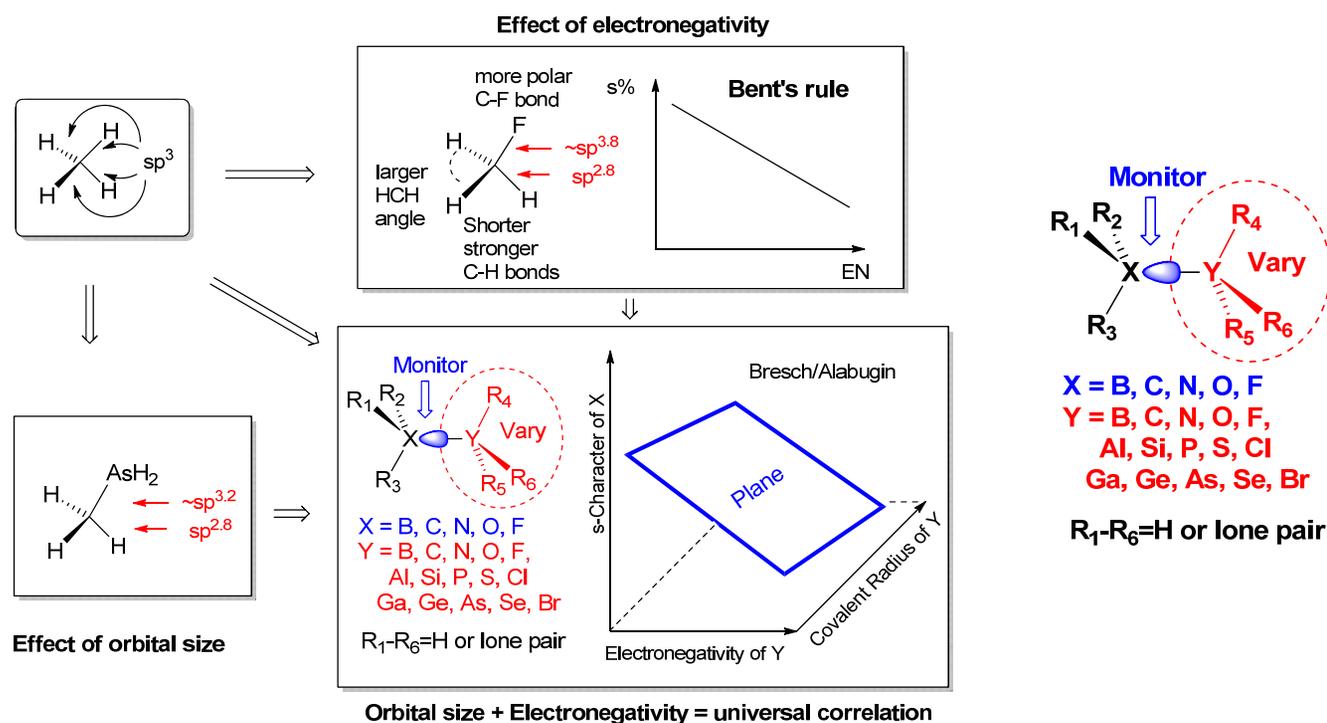


**X = B, C, N, O, F**  
**Y = B, C, N, O, F,**  
**Al, Si, P, S, Cl**  
**Ga, Ge, As, Se, Br**  
**R<sub>1</sub>-R<sub>6</sub>=H or lone pair**

s-Character (%) of the hybrid orbital of carbon in C–Y bonds of H<sub>3</sub>C–YH<sub>m</sub> compounds as a function of electronegativity (E) and covalent radius (R) of atom Y. View along the plane. The projections of the data points on the coordinate planes are shown as a zigzag chain of black line segments for the substituents Y = B, F, Cl, Br, I. None of the three projections (corresponding to a single parameter fit) can satisfactorily explain the hybridization trends

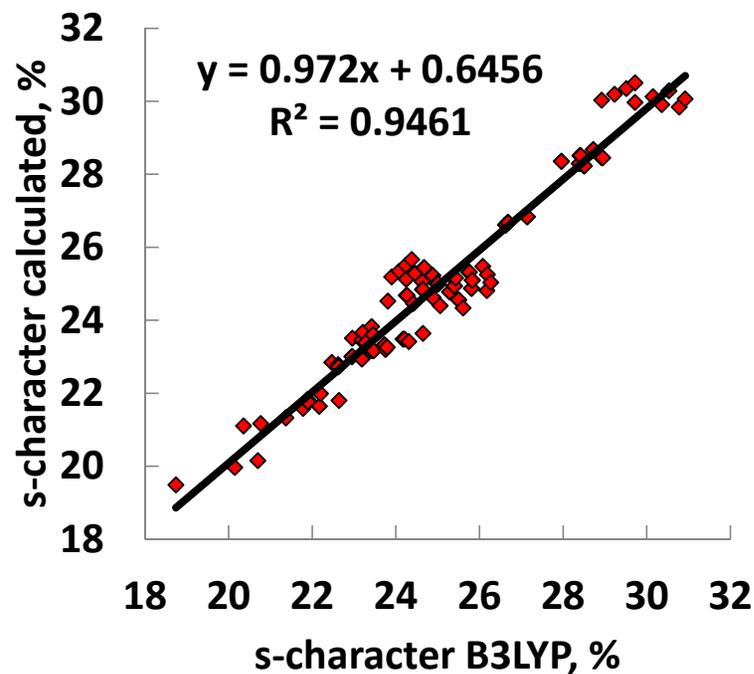
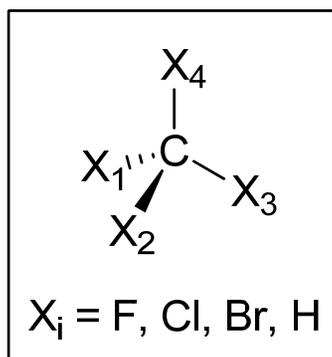
## Bent's rule applies across the Periodic Table

**Extension to other Periods:** Carbon directs hybrids with **more p-character** towards **more electronegative** elements and to elements with **larger radii**.



Bresch, Manoharan, Alabugin, *J. Phys. Chem.* **2014**, 3663

## Impact of multiple substituents



The tug-of-war equation:

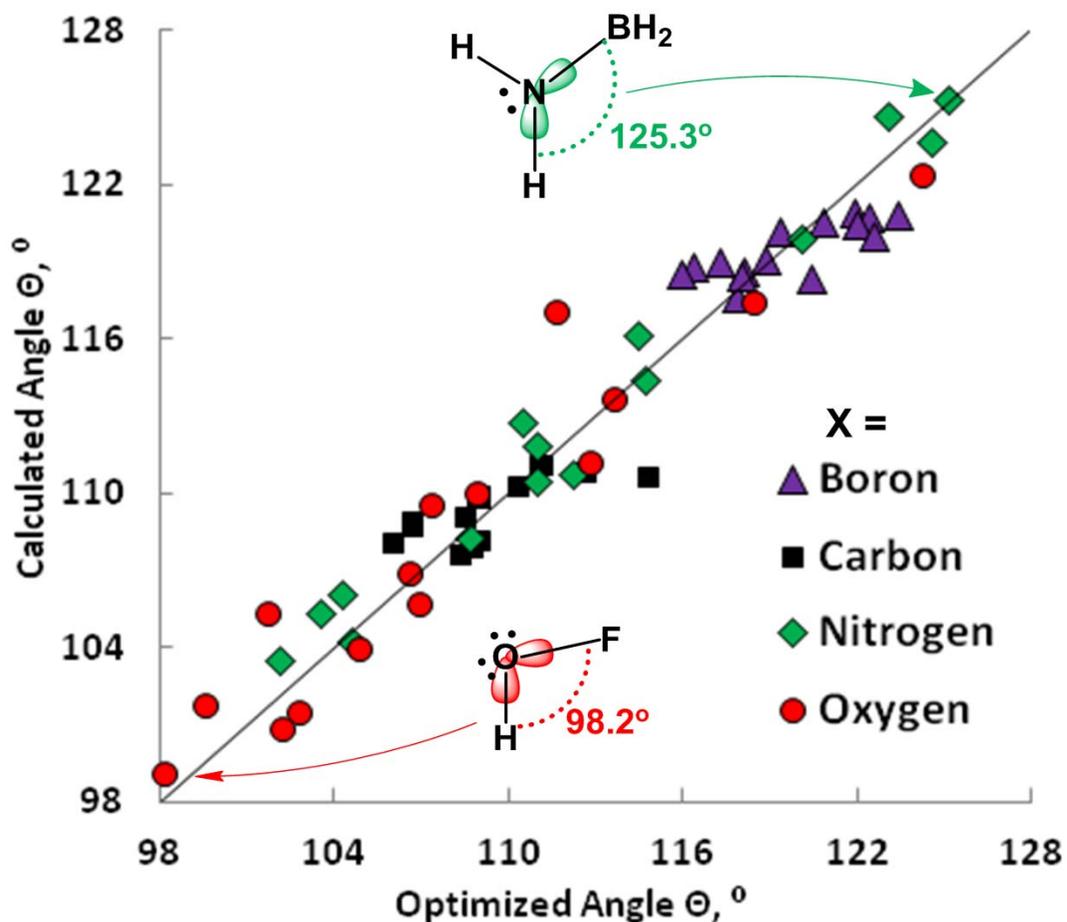
$$\%s_i = 25 - A \cdot \left( e_i - \frac{(e_j + e_k + e_l)}{3} \right) - B \cdot \left( c_i - \frac{(c_j + c_k + c_l)}{3} \right)$$

$i, j, k, l = 1, 2, 3, 4$

A & B depend on central atom

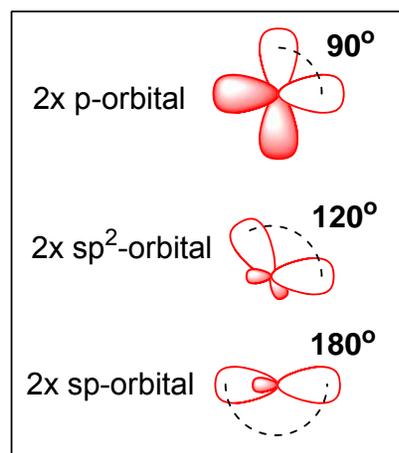
B3LYP/6-311++G(d,p)

# How can you tell that hybridization trends are real? Correlation with valence angles



MP2/6-311++G(d,p)

## Recall



$$1 + \sqrt{\lambda_1 \lambda_2} \cdot \cos(\Theta_{ij}) = 0$$

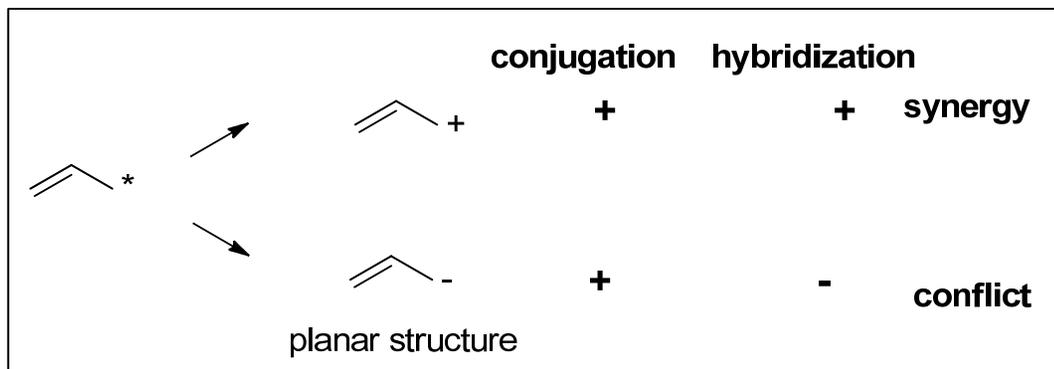
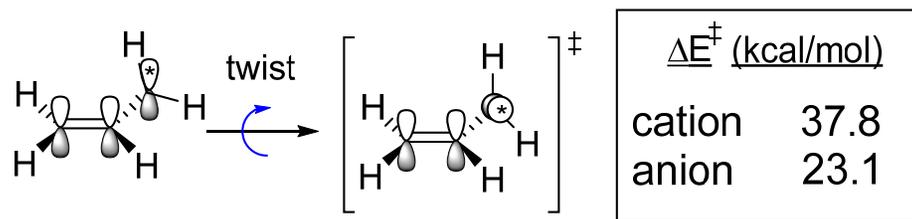
**Valence angles for the 2<sup>nd</sup> period elements change from 98 to 125 degrees in accordance with hybridization**

## Hybridization competing with resonance: allylic systems

Your have  
30  
seconds!

**Solve this riddle:** Why energy cost for twisting is for the allyl anion is only half of the twisting cost for the allyl cation?

*At the Huckel level, the allyl cation and anion should have the same delocalization energy*

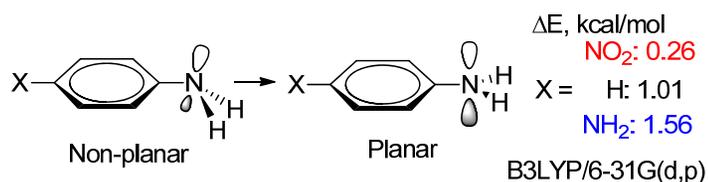


In the case of allylic anion, additional stabilization to the twisted form (~8-14 kcal/mol) is provided by rehybridization and pyramidalization from the planar geometry

# Hybridization competing with resonance: aniline

Stabilizing energy of resonance is smaller in neutral systems:

Is aniline planar?



substituent effects on the cost of planarization at the aniline nitrogen

Structure

vs.

Reactivity

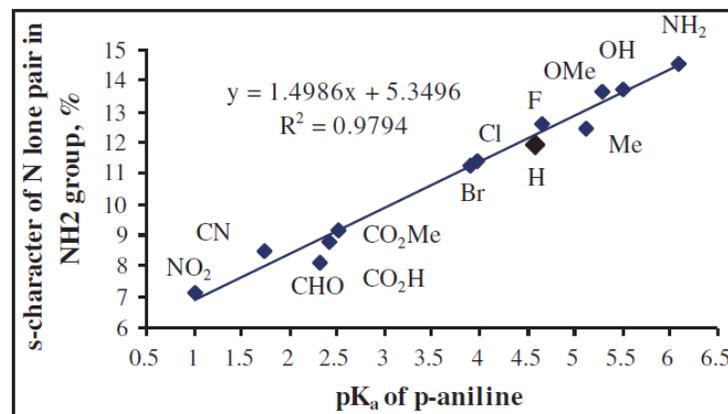
Geometries are controlled by the tug of war between hybridization and resonance

	$r$ (C-N)	$\theta_1$	$\theta_2$	$\varphi_1$	$\varphi_2$	s-Char (LP) <sub>N</sub>
R=NO <sub>2</sub>	1.378	117.7	114.4	19.6	144.4	7.1
R=H	1.398	114.9	111.5	25.8	132.9	11.9
R=NH <sub>2</sub>	1.409	113.5	110.1	29.2	128.6	14.6

$\theta_1 = [(C_1-N-H_a) + (C_1-N-H_b)] / 2$ ,  $\theta_2 = H_a-N-H_b$ ,  $\varphi_1 = [(C_6-C_1-N-H_a) + (C_2-C_1-N-H_b)] / 2$ ,  $\varphi_2 = C_1-N-H_a-H_b$ .

Analyze C-N bond lengths, H-N-C valence angles and deviations from planarity

*J. Phys. Org. Chem.*, 2015, 147

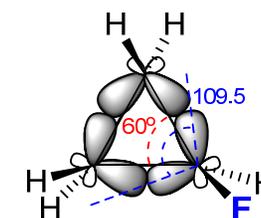
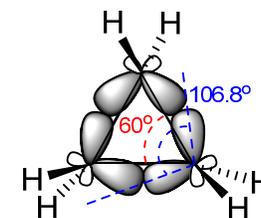
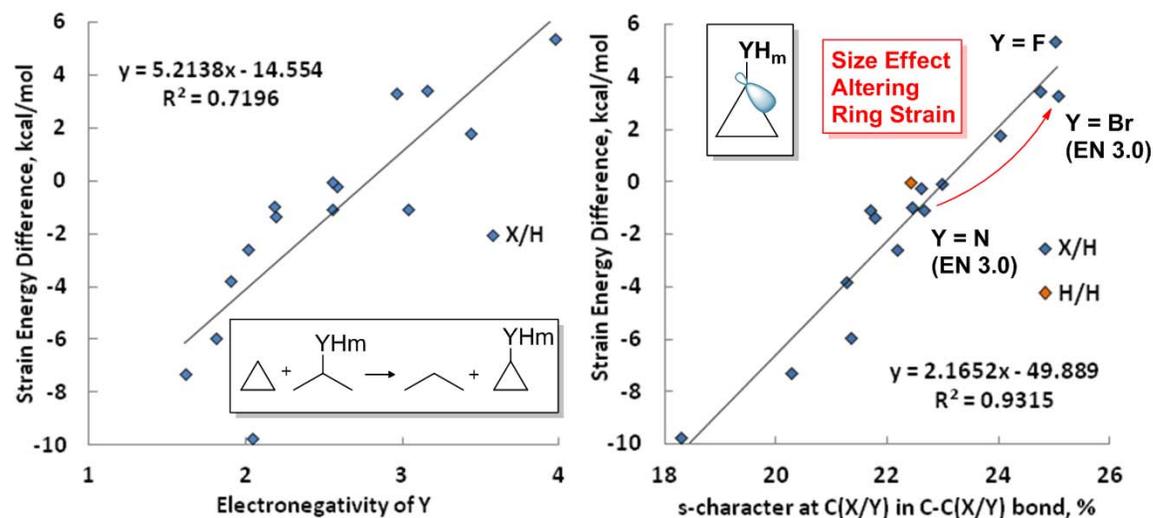


Correlations of s-character in the NH<sub>2</sub> lone pair with pK<sub>a</sub> of para-substituted anilines.

(How large are effects on basicity?)

## Hybridization can control strain

Exocyclic acceptors increase strain. Donors have the opposite effect.  
**p-Character in C-Y bond increases strain in the ring.**



Correlation with hybridization is stronger than correlation with electronegativity

Left: Correlation of relative strain energy in substituted cyclopropanes with electronegativity of Y in the exocyclic C-Y bonds

Right: The dependence of the strain energy difference on the s-character in the C-Y bonds in the cyclopropane cycle provides a clearer picture. **Note the differences in s-character and strain for Y = Br and N, two substituents with the same electronegativity but different size.**

B3LYP/6-311++G(d,p) data

If **exocyclic** acceptor C-X bonds **destabilize** small cycles, then what about **endocyclic** acceptor C-X bonds?

**“Hint”**: C-O and C-N bonds are shorter than C-C bonds



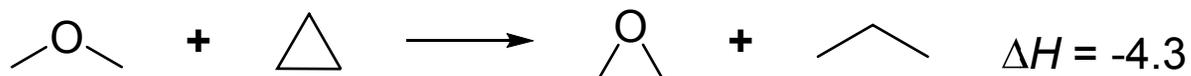
**Question**: are epoxides and aziridines more strained than cyclopropanes?

## Comparison of strain in cyclopropane, epoxide and aziridine

**Exo**cyclic acceptor C-X bonds **destabilize** small cycles



**Endo**cyclic acceptor C-X bonds **stabilize** small cycles

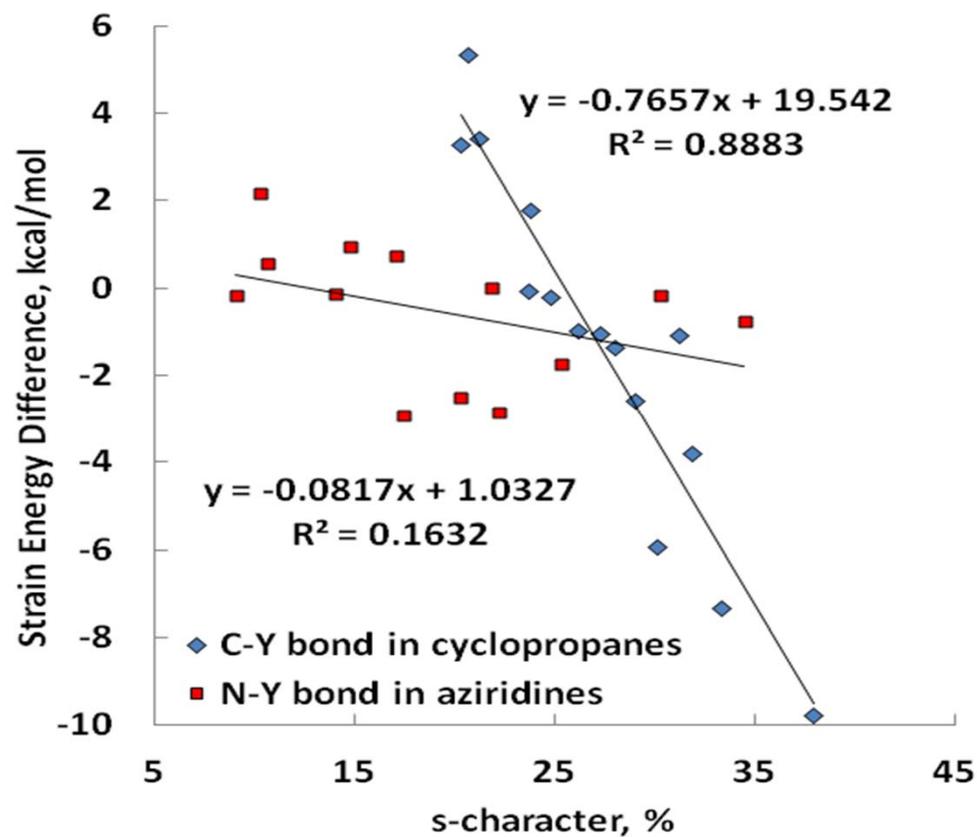
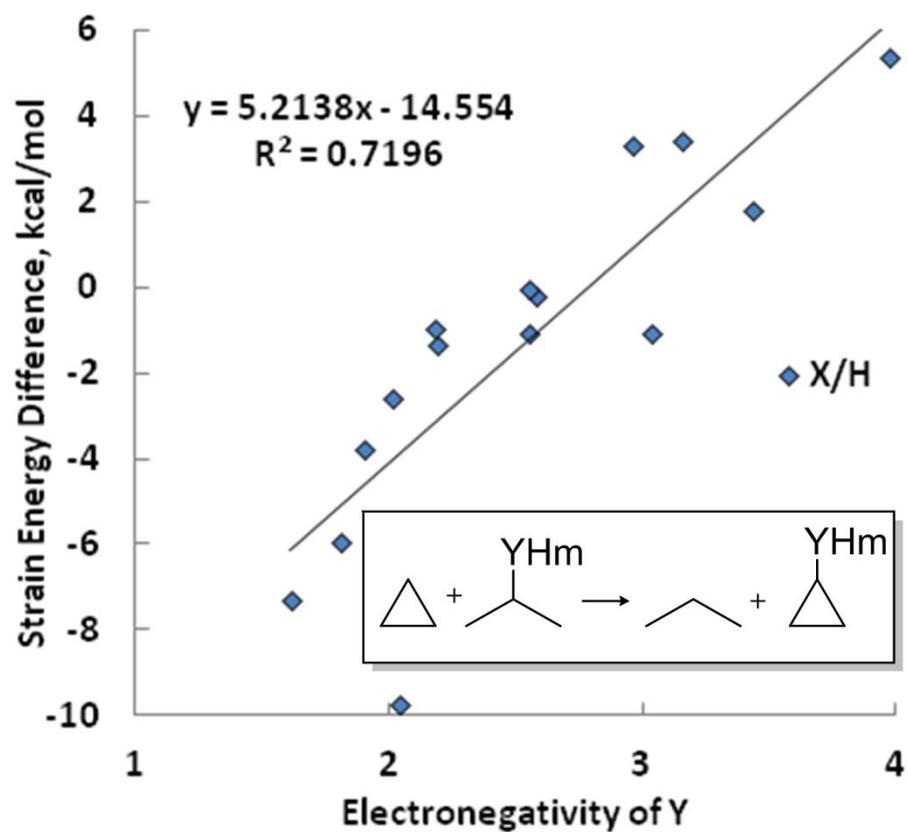


**Exo**cyclic C-F acceptor in aziridine does not make any difference

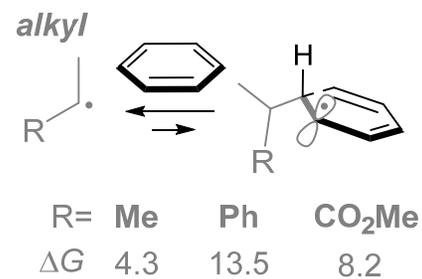
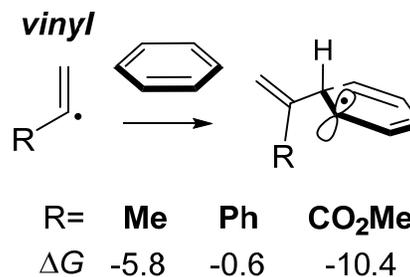
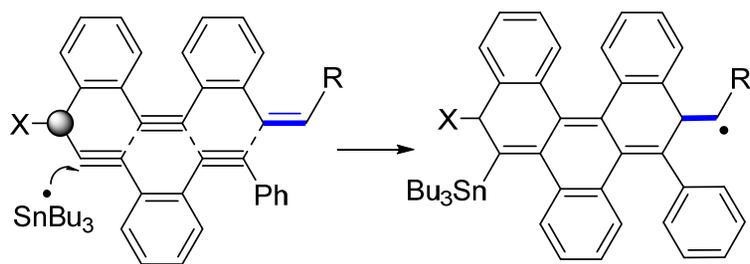
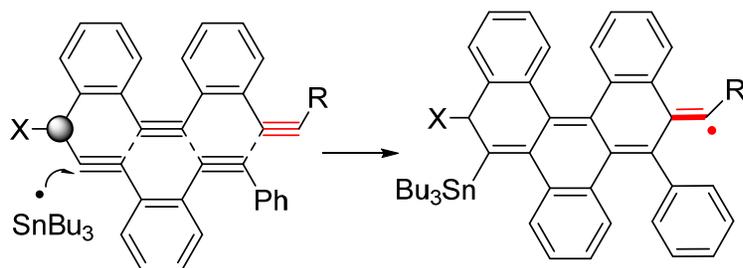


M06-2X(D3)/6-311++G(d,p), kcal/mol

These trends are general:

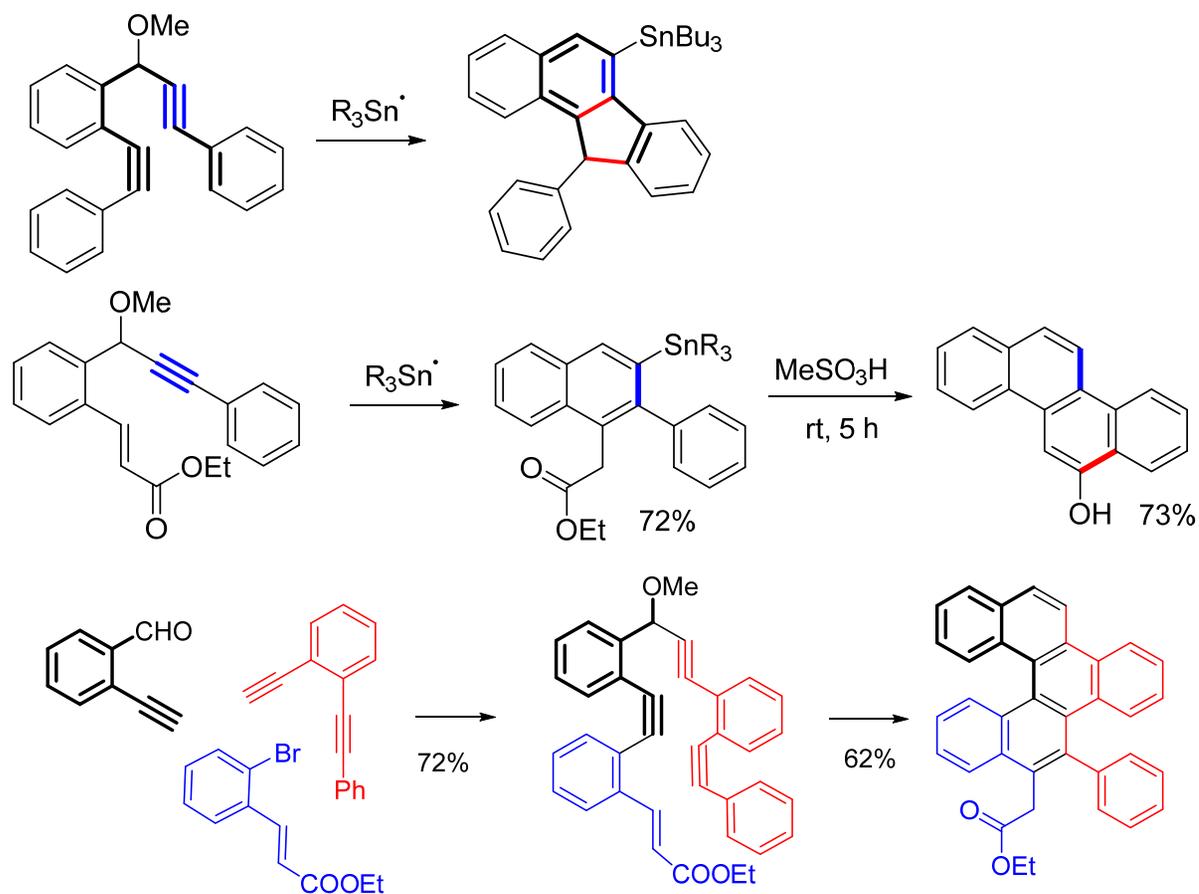


## Use of hybridization effects in synthesis



**Taming radicals**

## Alkene as a terminating point for radical cascades



Pati, K.; Gomes, G.; Alabugin, I. V. *Angew. Chem. Int. Ed.*, **2016**, *55*, 11633

## Emergence of delocalization in NBO description

Each bonding NBO  $\sigma_{AB}$ :

$$\sigma_{AB} = c_A h_A + c_B h_B$$

must in turn be paired with a corresponding valence antibonding NBO

$$\sigma_{AB}^* = c_B h_A - c_A h_B$$

The “Lewis”-type (donor) NBOs (4a) are thereby complemented by the “non-Lewis”-type (acceptor) NBOs (4b) that are formally empty in an idealized Lewis structure picture.

Weak occupancies of the valence antibonds signal irreducible departures from an idealized localized Lewis structure picture, i.e., true “delocalization effects.”

## “Antibonding orbitals” also contribute to chemical bonding

What IS this molecule?

What is special about NBO 24?

This C-H bond is antiperiplanar to the lone pair. Difference between NBO 24 and NBOs 25,26 reflects stereoelectronics of orbital interactions

NBO	Occupancy	Energy	Principal Delocalizations (geminal,vicinal,remote)
1. BD ( 1) C 1- N 2	1.99858	-0.89908	
2. BD ( 1) C 1- H 3	1.99860	-0.69181	
3. BD ( 1) C 1- H 4	1.99399	-0.68892	27(v),26(g)
4. BD ( 1) C 1- H 5	1.99399	-0.68892	28(v),25(g)
5. BD ( 1) N 2- H 6	1.99442	-0.80951	25(v),
6. BD ( 1) N 2- H 7	1.99442	-0.80951	26(v),
9. LP ( 1) N 2	1.97795	-0.44592	24(v),25(v),26(v)
23. BD*( 1) C 1- N 2	0.00016	0.57000	
24. BD*( 1) C 1- H 3	0.01569	0.68735	
25. BD*( 1) C 1- H 4	0.00769	0.69640	
26. BD*( 1) C 1- H 5	0.00769	0.69640	
27. BD*( 1) N 2- H 6	0.00426	0.68086	
28. BD*( 1) N 2- H 7	0.00426	0.68086	
-----			
Total Lewis	17.95048	( 99.7249%)	
Valence non-Lewis	0.03977	( 0.2209%)	
Rydberg non-Lewis	0.00975	( 0.0542%)	

Why are the antibonding NBOs populated?

# Quantifying delocalization by NBO

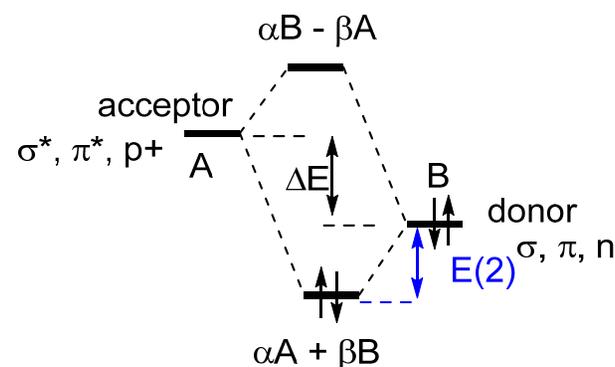
# Quantifying delocalization

## *NBO perturbative estimates*

The energetic stabilization due to such  $\sigma \rightarrow \sigma^*$  donor acceptor interactions can be estimated by 2nd-order perturbation theory, viz., for the  $\sigma_i \rightarrow \sigma_j^*$  interaction.

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

$F_{ij}$  is the resonance integral for orbitals  $i$  and  $j$ ,  $\varepsilon_{\sigma}$  and  $\varepsilon_{\sigma^*}$  are the energies of the  $\sigma$  and  $\sigma^*$  orbitals, and  $n_{\sigma}$  is the population of the donor

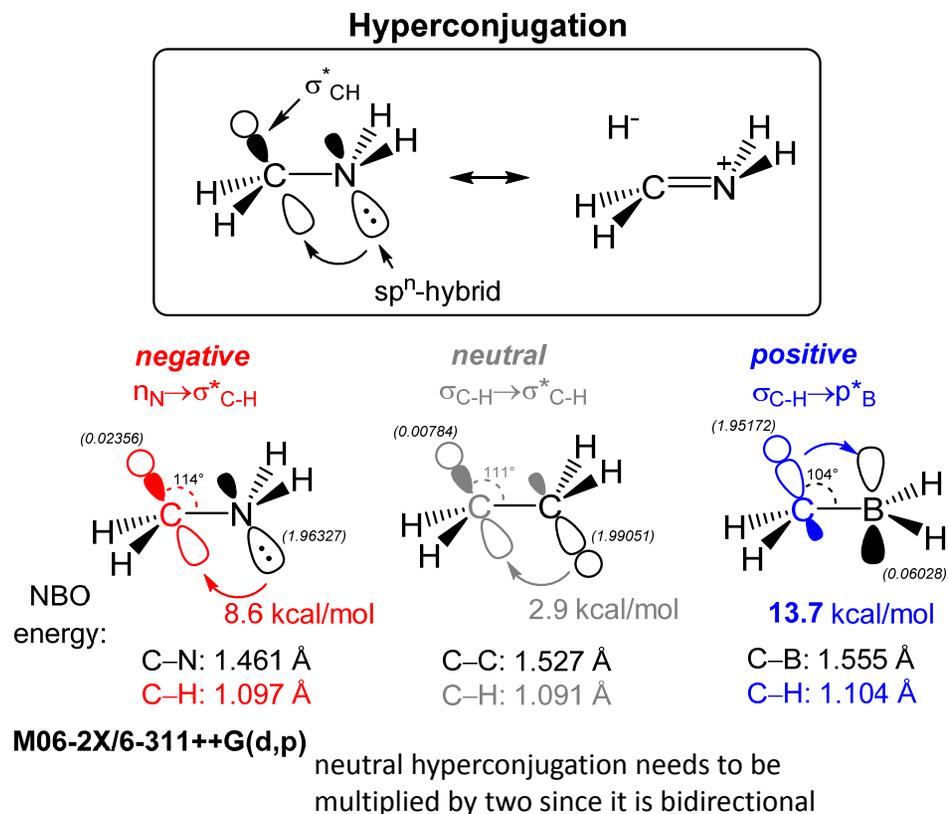


*Consideration of valence antibonds leads to the extension of elementary Lewis structure concepts to encompass delocalization corrections.*

## We can compare different types of delocalization: neutral, negative, positive

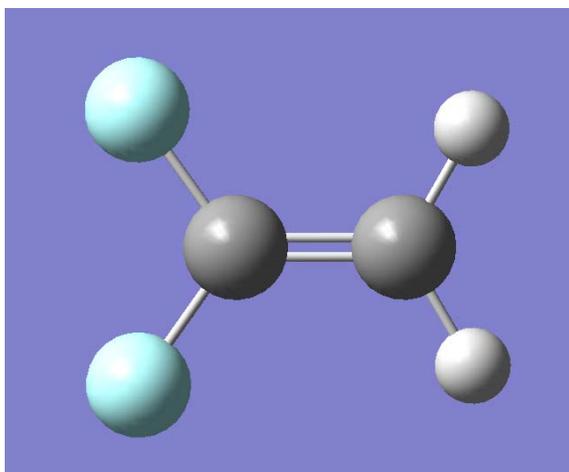
Let's start simple and analyze three parent  $H_3C-X$  systems of different electronic nature ( $X = NH_2, CH_3, BH_2$ ) to calibrate our perception of negative, neutral, and positive hyperconjugation

Let's analyze orbital populations and delocalizing energies



# NBO analysis of delocalization

- What are the greatest delocalizing interactions in 1,1-difluoroethene?



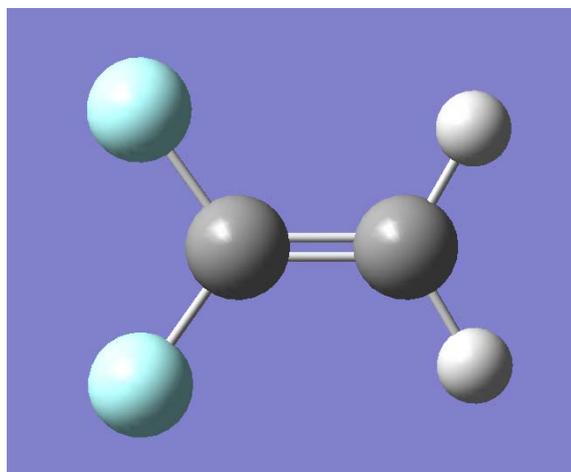
## Second Order Perturbation Theory Analysis of Fock Matrix in NBO

Basis Threshold for printing: 0.50 kcal/mol

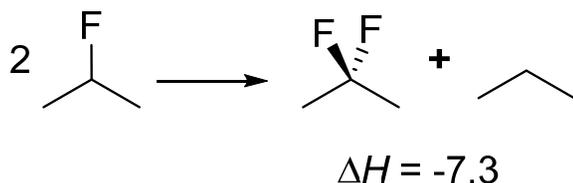
Donor NBO (i)	Acceptor NBO (j)	E(2) kcal/mol	E(j)-E(i) a.u.	F(i,j) a.u.
1. BD ( 1) C 1 - H 2	/ 83. BD*( 1) C 1 - C 4	1.02	1.14	0.030
1. BD ( 1) C 1 - H 2	/ 85. BD*( 1) C 4 - F 5	0.55	0.79	0.019
1. BD ( 1) C 1 - H 2	/ 86. BD*( 1) C 4 - F 6	9.58	0.79	0.079
3. BD ( 1) C 1 - C 4	/ 81. BD*( 1) C 1 - H 2	0.71	1.28	0.027
3. BD ( 1) C 1 - C 4	/ 82. BD*( 1) C 1 - H 3	0.71	1.28	0.027
5. BD ( 1) C 4 - F 5	/ 82. BD*( 1) C 1 - H 3	1.19	1.53	0.038
5. BD ( 1) C 4 - F 5	/ 83. BD*( 1) C 1 - C 4	0.51	1.65	0.026
5. BD ( 1) C 4 - F 5	/ 86. BD*( 1) C 4 - F 6	1.39	1.31	0.039
11. LP ( 1) F 5	/ 83. BD*( 1) C 1 - C 4	2.76	1.67	0.061
12. LP ( 2) F 5	/ 83. BD*( 1) C 1 - C 4	4.49	1.04	0.062
12. LP ( 2) F 5	/ 86. BD*( 1) C 4 - F 6	15.70	0.70	0.094
13. LP ( 3) F 5	/ 84. BD*( 2) C 1 - C 4	23.86	0.45	0.094

# NBO analysis of delocalization

- What are the greatest delocalizing interactions in 1,1-difluoroethene?



Explain this:



Second Order Perturbation Theory Analysis of Fock Matrix in NBO

Basis Threshold for printing: 0.50 kcal/mol

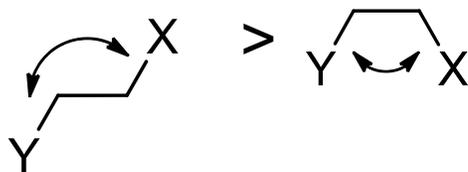
Donor NBO (i)		Acceptor NBO (j)		E(2)	E(j)-E(i)	F(i,j)
				kcal/mol	a.u.	a.u.
1. BD ( 1) C 1 - H 2	/ 83. BD*( 1) C 1 - C 4	1.02	1.14	0.030		
1. BD ( 1) C 1 - H 2	/ 85. BD*( 1) C 4 - F 5	0.55	0.79	0.019		
1. BD ( 1) C 1 - H 2	/ 86. BD*( 1) C 4 - F 6	9.58	0.79	0.079		
3. BD ( 1) C 1 - C 4	/ 81. BD*( 1) C 1 - H 2	0.71	1.28	0.027		
3. BD ( 1) C 1 - C 4	/ 82. BD*( 1) C 1 - H 3	0.71	1.28	0.027		
5. BD ( 1) C 4 - F 5	/ 82. BD*( 1) C 1 - H 3	1.19	1.53	0.038		
5. BD ( 1) C 4 - F 5	/ 83. BD*( 1) C 1 - C 4	0.51	1.65	0.026		
5. BD ( 1) C 4 - F 5	/ 86. BD*( 1) C 4 - F 6	1.39	1.31	0.039		
11. LP ( 1) F 5	/ 83. BD*( 1) C 1 - C 4	2.76	1.67	0.061		
12. LP ( 2) F 5	/ 83. BD*( 1) C 1 - C 4	4.49	1.04	0.062		
12. LP ( 2) F 5	/ 86. BD*( 1) C 4 - F 6	15.70	0.70	0.094		
13. LP ( 3) F 5	/ 84. BD*( 2) C 1 - C 4	23.86	0.45	0.094		

Good old anomeric effect:

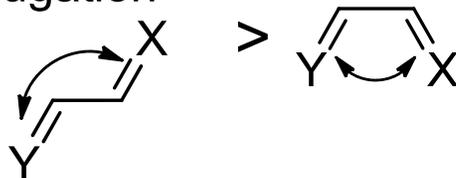
and lone pair/ $\pi$ -bond delocalization

## How to increase stabilization? Orbital Overlap and Antiperiplanarity

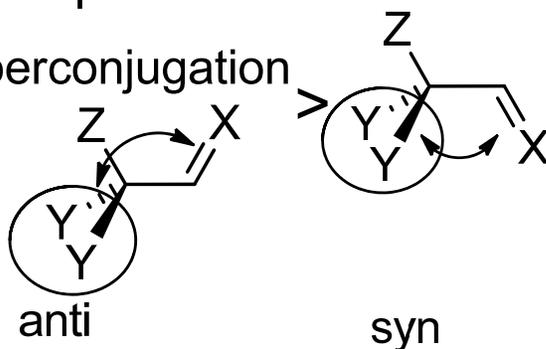
$\sigma$ -Conjugation



Conjugation



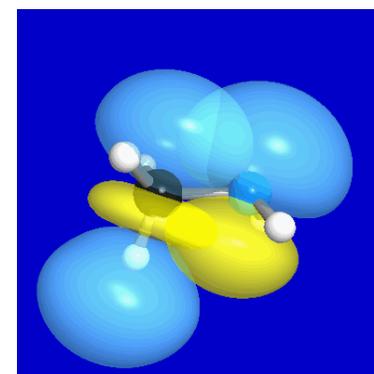
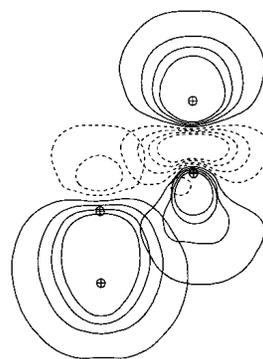
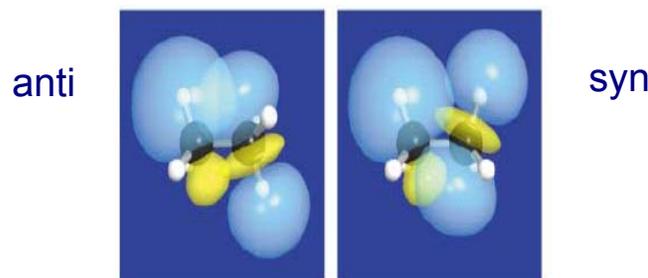
Hyperconjugation



Favorable symmetry for anti-periplanar interactions increases stabilizing orbital overlap:

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

$F_{ij}$  (the resonance integral for orbitals  $i$  and  $j$ ), is proportional to the orbital overlap

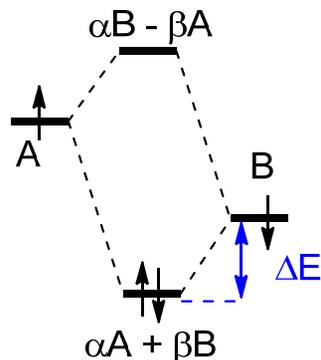


<http://nbo6.chem.wisc.edu/>

# What makes a good acceptor?

## Bond polarization

Opposite polarization  
for the antibond:



Bond polarization:  $\beta > \alpha$

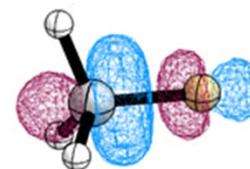
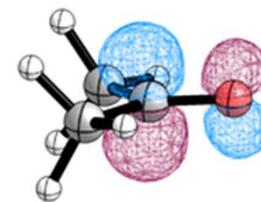
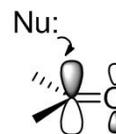
Polarization of antibonding orbitals explains regiochemistry of *intermolecular* nucleophilic reactions, such as generally observed attack at carbon atom in C-X bond of alkyl halides and C=O bonds of carbonyls

Alabugin, *Stereoelectronic Effects*

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

$F_{ij}$  is the resonance integral for orbitals  $i$  and  $j$ , is proportional to the orbital overlap

The bonding orbital has greater contribution from the more electronegative element B, whereas the antibonding orbital is polarized in the opposite direction with a greater orbital coefficient at the less electronegative element "A"



## How to increase stabilization?

### Additional factors controlling overlap

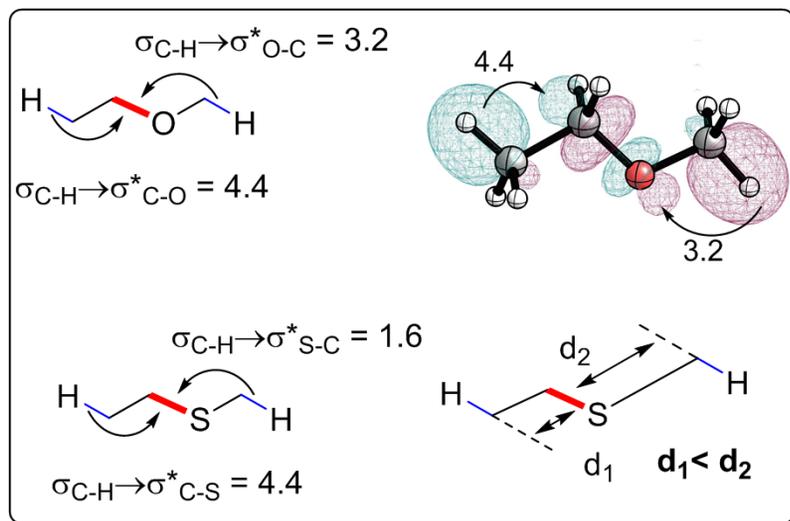
Directionality of interactions:

a) Effect of bond polarization

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

b) Effect of longer or shorter bonds

$F_{ij}$  is the resonance integral for orbitals  $i$  and  $j$ , is proportional to the orbital overlap



Energies are in kcal/mol

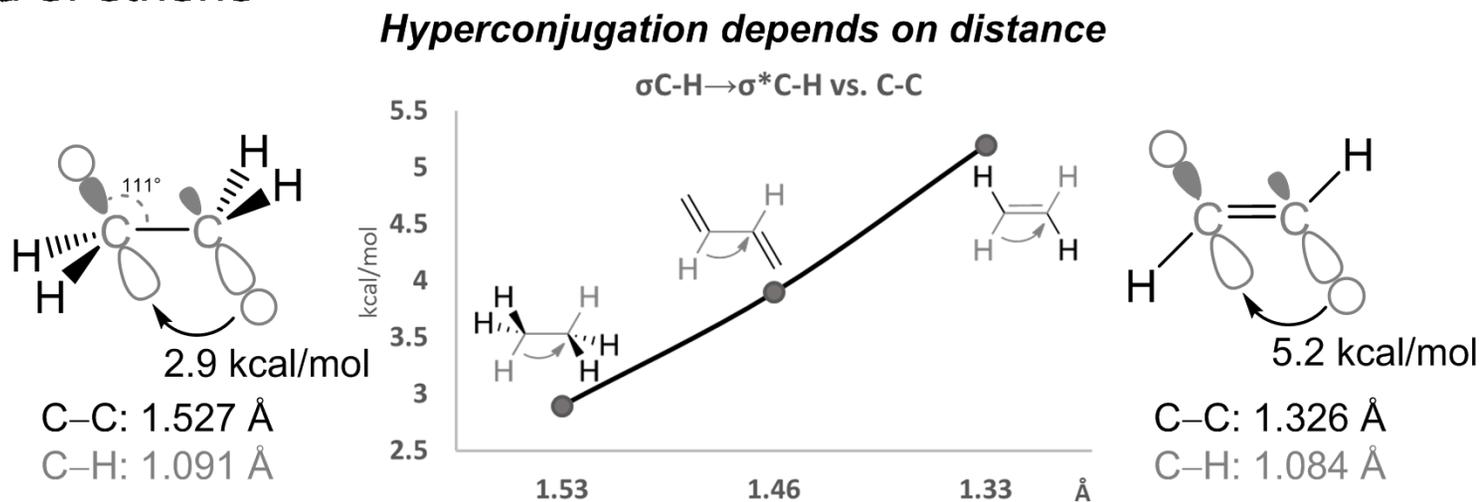
$\sigma^*_{O-C}$  is a weaker acceptor than  $\sigma^*_{C-O}$

$\sigma^*_{S-C}$  is a **MUCH** weaker acceptor than  $\sigma^*_{C-S}$

Alabugin, *J. Org. Chem.* **2000**, 3910

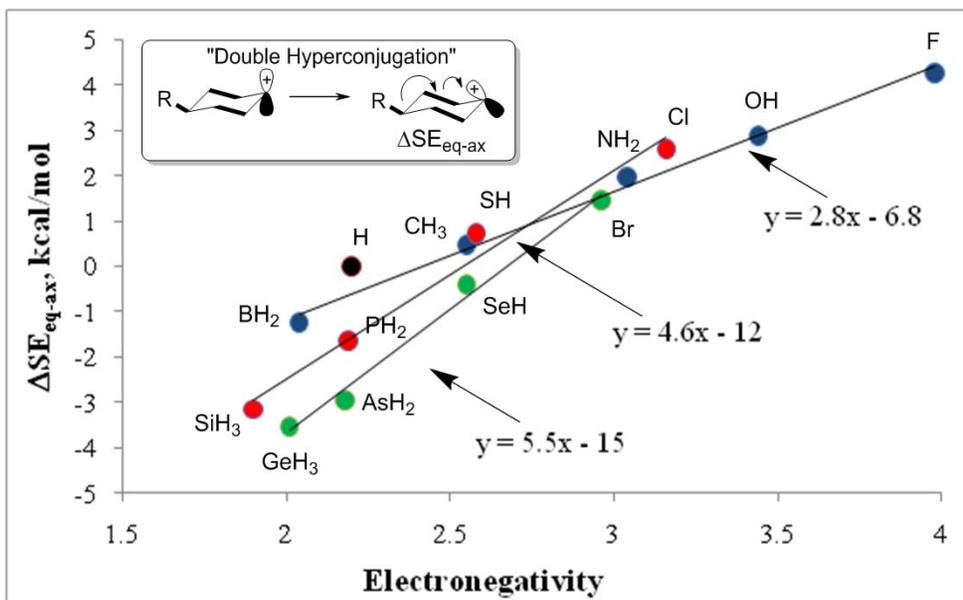
## The C-C distance, rather than hybridization, plays the dominating role

- the neutral C-H/C-H hyperconjugation can be increased by ~80% in magnitude when the interacting orbitals are separated by a shorter C=C bond of ethene



## Towards the general scale of sigma donor ability

The relative ability of many common sigma donors, including the most ubiquitous case of C-H vs. C-C bonds, is still debated



Interaction between the  $\sigma_{C-R}$  bond and the empty p-orbital is transmitted via double hyperconjugation

A balanced description of relative donor ability of s-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  $\delta$ -substituted cyclohexyl cations.

Alabugin, I. V.; Manoharan, M. (2004) Effect of Double Hyperconjugation on the Apparent Donor Ability of  $\sigma$ -Bonds: Insights from the Relative Stability of  $\delta$ -Substituted Cyclohexyl Cations. *Journal of Organic Chemistry*, 69, 9011-9024

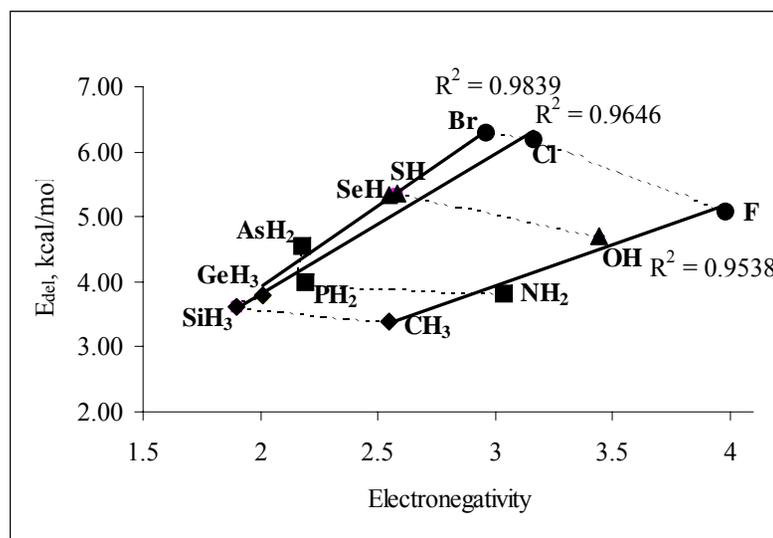
## Towards the general scale of sigma **acceptor** ability

### The opposing roles of electronegativity and orbital energies

No simple correlation  
with electronegativity

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

The acceptor ability of the C-X  $\sigma$ -bonds relative to the same donor (an antiperiplanar C-H bond) increases towards the end of a period and down a group.



The relative order of acceptor ability of  $\sigma^*_{C-X}$  bonds (the energies of  $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$  interactions are given in parentheses): X= Br (6.3) > Cl (6.2) > SH(1) (5.4) > F (5.1) > OH(1) (4.7)  $\approx$  SH(2) (4.7)  $\approx$  SeH (4.7)  $\approx$  PH<sub>2</sub>(1) (4.6)  $\approx$  AsH<sub>2</sub> (4.5)  $\approx$  NH<sub>2</sub>(1) (4.5) > OH(2) (4.2) > PH<sub>2</sub> (2) (4.0) > NH<sub>2</sub>(2) (3.8)  $\approx$  GeH<sub>3</sub> (3.8) > SiH<sub>3</sub> (3.6) > CH<sub>3</sub> (3.4) > H (3.2), where  $\approx$  means that the difference in the energy of  $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$  interactions is smaller than 0.1 kcal/mol

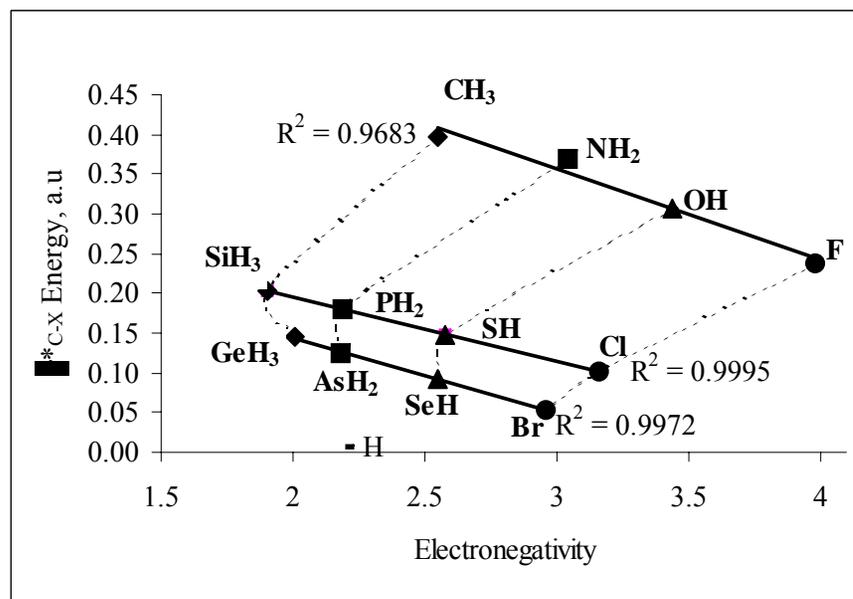
Alabugin, I. V.; Zeidan, T. A. (2002) Stereoelectronic Effects and General Trends in Hyperconjugative Acceptor Ability of  $\sigma$ -Bonds. *Journal of the American Chemical Society*, 124, 3175-3185

## Sigma acceptor ability

Both electronegativity and **energy gap** are important

No simple correlation  
with electronegativity

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



Correlation of energy of  $\sigma^*_{C-X}$  orbitals with electronegativity of element X in substituted ethanes,  $\text{CH}_3\text{CH}_2\text{X}$ .

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

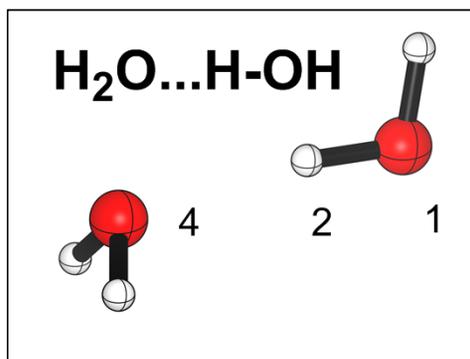
# **NBO analysis of supramolecular interactions**

# NBO analysis of supramolecular interactions

Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis

Threshold for printing: 0.50 kcal/mol

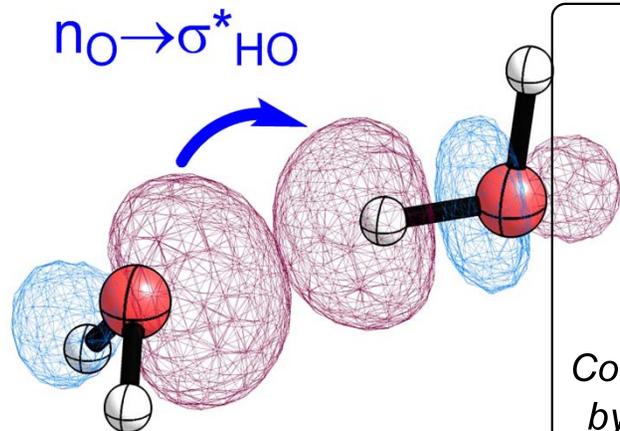
(Intermolecular threshold: 0.05 kcal/mol)



Donor NBO (i)	Acceptor NBO (j)	E(2) kcal/mol	E(j)-E(i) a.u.	F(i,j) a.u.
=====				
within unit 1	...			
from unit 1 to unit 2				
1. BD ( 1) O 1 - H 2	/ 58. BD*( 1) O 4 - H 6	0.22	1.22	0.015
from unit 2 to unit 1				
3. BD ( 1) O 4 - H 5	/ 55. BD*( 1) O 1 - H 2	0.07	1.33	0.008
10. LP ( 2) O 4	/ 55. BD*( 1) O 1 - H 2	9.15	1.15	0.092
within unit 2	...			

# Where does directionality of H-bonding come from?

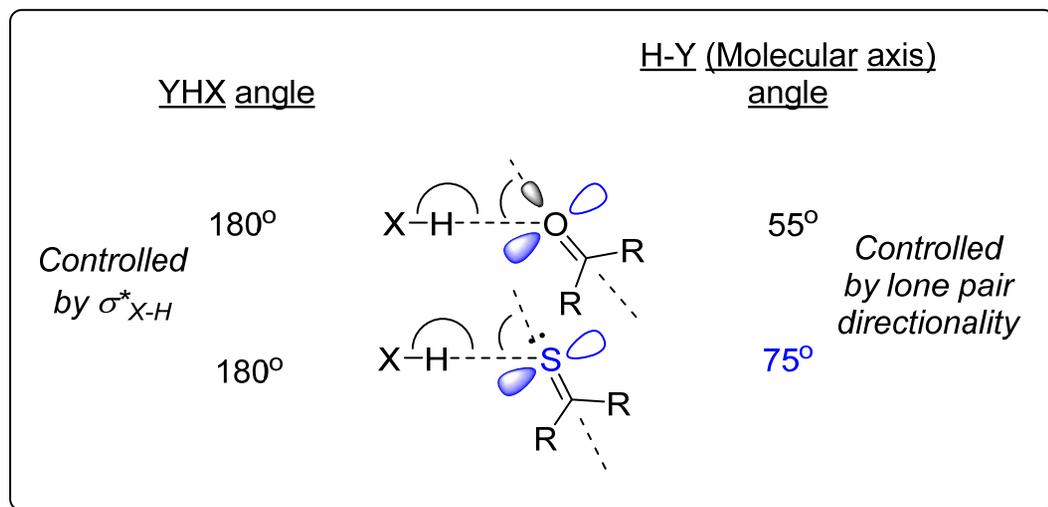
## Stereoelectronic effects on geometry of H-bonded complexes



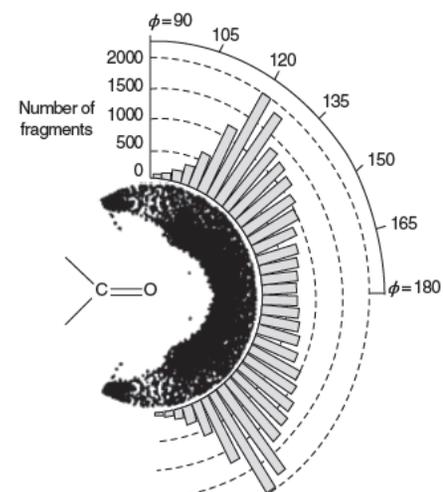
	<u>YHX angle</u>		<u>H-Y (Molecular axis) angle</u>	
	180°		180°	
<i>Controlled by <math>\sigma^*_{X-H}</math></i>	180°		180°	<i>Controlled by lone pair directionality</i>
	180°		55°	

From Alabugin, "Stereoelectronic effects"

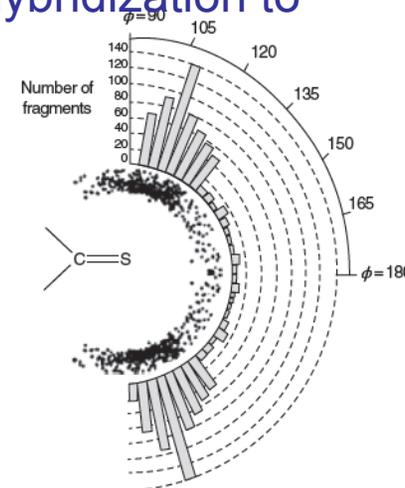
# Stereoelectronic effects on geometry of H-bonded complexes: a closer look



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



Why are thiocarbonyls different?  
Can you use hybridization to explain it?



## Hybridization in supramolecular chemistry: improper hydrogen bonds

A characteristic feature of H...Y hydrogen bond formation in an X-H...Y system is X-H bond lengthening with a concomitant **red shift** of the X-H stretching IR frequency.

The latter is widely regarded as the “**signature of H-bonding**”.

H-bonds always sign in red?  
...Or do they?

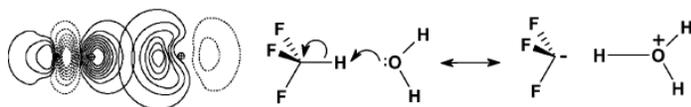
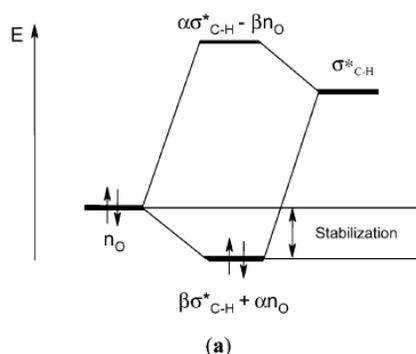
“Recent studies have reported the unusual class of “improper” or “blue-shifted” hydrogen bonds in which H-bond formation leads to X-H bond shortening and to a **blue shift** of the X-H IR stretching frequency.”

Are such “improper H-bonds” really H-bonds? Or is it a new supramolecular interaction?



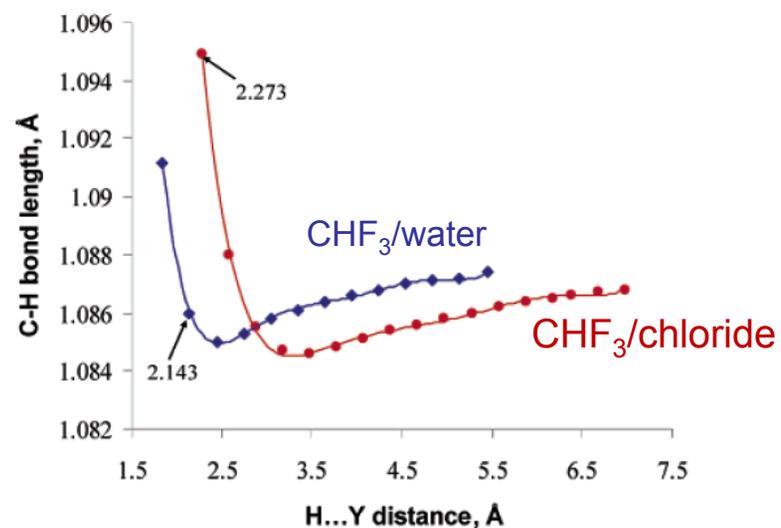
## Hybridization in supramolecular chemistry: improper hydrogen bonds (continued)

Where does the **red shift** of the X-H stretching IR frequency (the “signature of H-bonding”) come from?



The red shift and angular dependence of H-bonding share the same origin ( $n \rightarrow \sigma^*$  HX interactions).

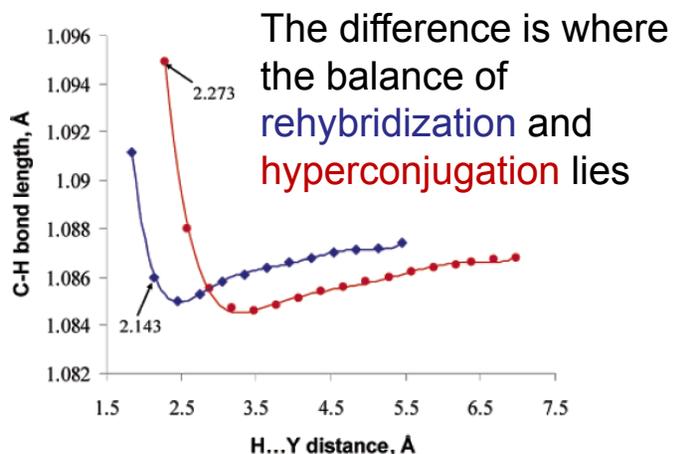
How to change it to the blue?



Correlation of C-H lengths with H...Y (Y = O or Cl) distance in CHF<sub>3</sub>/water (blue diamond) and CHF<sub>3</sub>/chloride (red circle) complexes. The equilibrium distances are shown with arrows

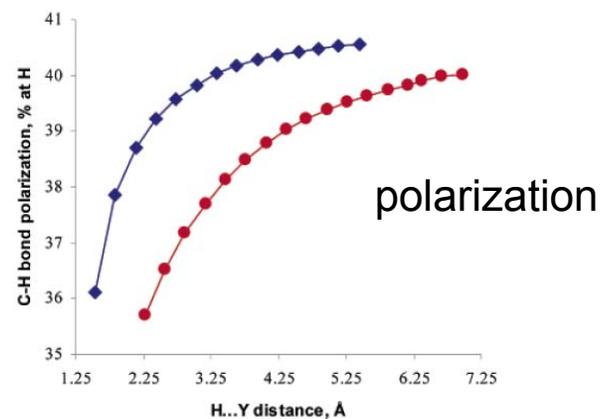
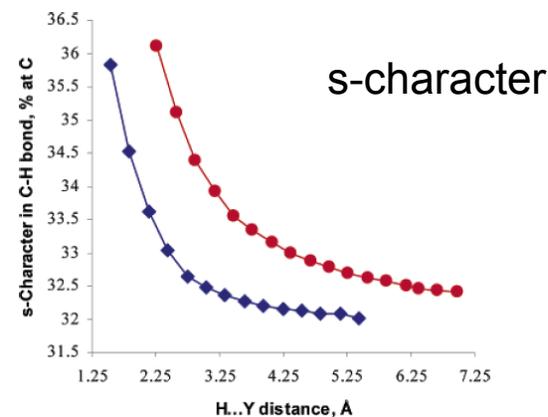
The two curves look very similar!

## Hybridization in supramolecular chemistry: improper hydrogen bonds (continued)



Correlation of C-H lengths with H...Y (Y = O or Cl) distance in CHF<sub>3</sub>/water (blue diamond) and CHF<sub>3</sub>/chloride (red circle) complexes. The equilibrium distances are shown with arrows

Blue and red-shifting H-bonds are very similar.



Title 1-20

Cited by Year

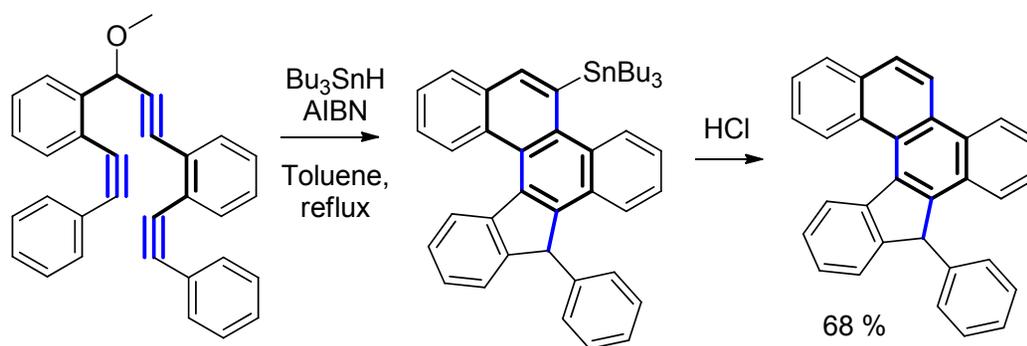
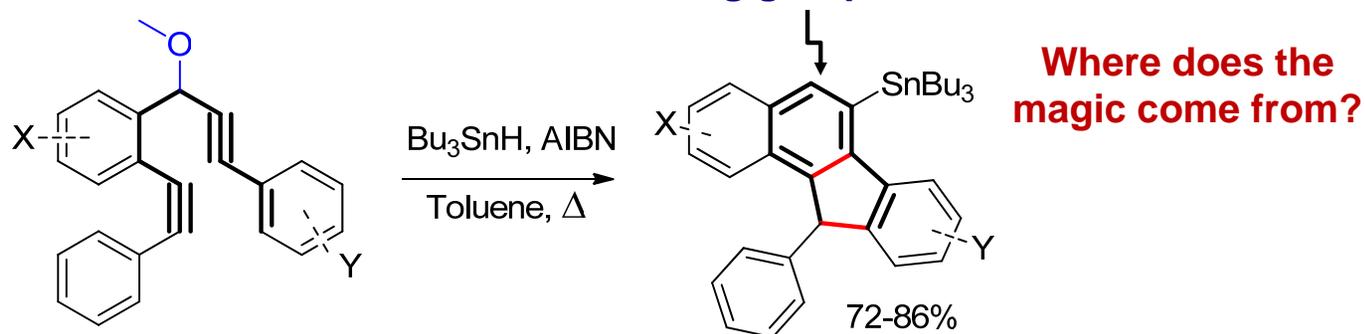
[Electronic basis of improper hydrogen bonding: a subtle balance of hyperconjugation and rehybridization](#)

IV Alabugin, M Manoharan, S Peabody, F Weinhold  
Journal of the American Chemical Society 125 (19), 5973-5987

570 2003

# Let's use the magic of **intermolecular** directing groups

The directing group is "traceless"



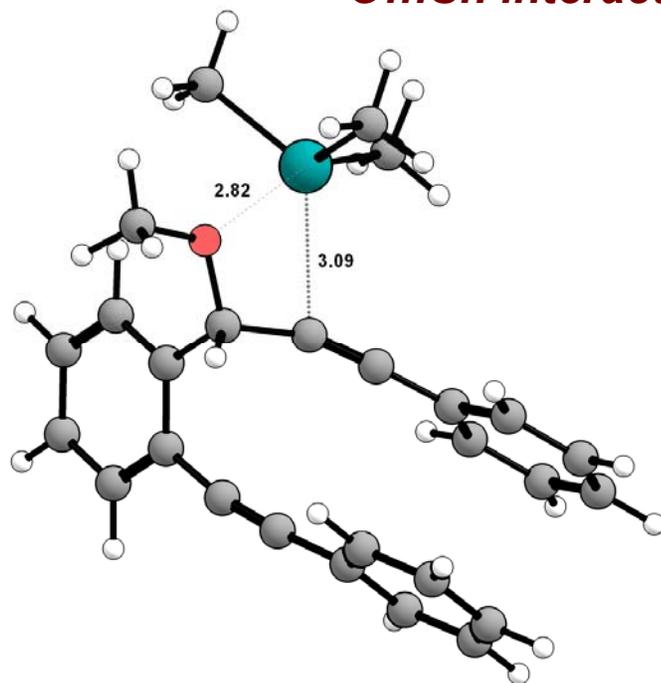


**From H-bonds to  
new supramolecular interactions:**

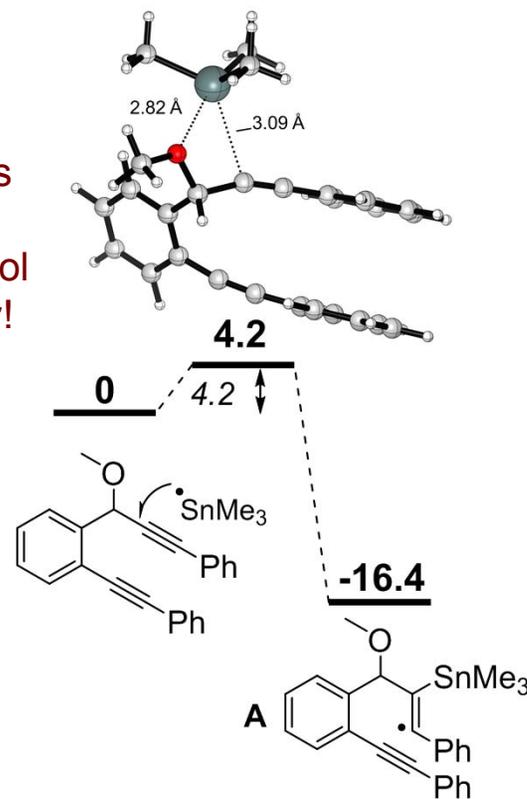
**The discovery of “R-Bonding”**

# Directing group: guiding radical addition through TS stabilization

## O...Sn interaction



$\Delta G^\ddagger$  is  
~12  
kcal/mol  
lower!



Gabriel dos  
Passos Gomes

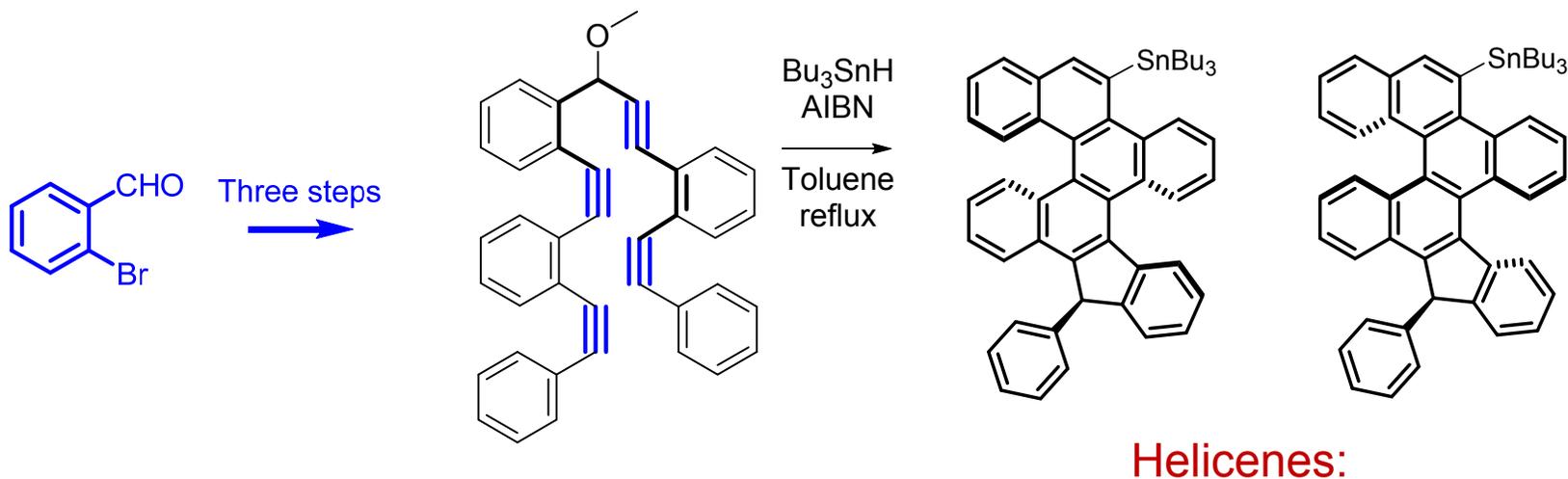
Mohamed, R.; Mondal, S.; Gold, B.; Evoniuk, C. J.; Banerjee, T.; Hanson, K.; Alabugin, I.V., *J. Am. Chem. Soc.*, **2015**, 6335

K. Pati, **G. Gomes**, T. Harris, A. Hughes, H. Phan, T. Banerjee, K. Hanson, I. Alabugin, *J. Am. Chem. Soc.*, **2015**, 1165.

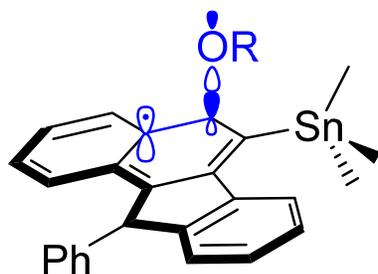


## Taking it further: tetraynes

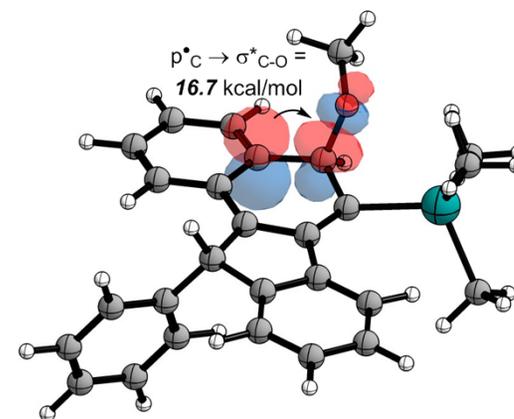
**Clean transformation into two products:** no triple bonds left, all spectral features are analogous to the fully cyclized structures



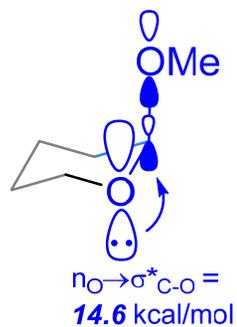
# NBO analysis guides us through other steps of this reaction sequence: Stereoelectronic assistance to radical C-O scission



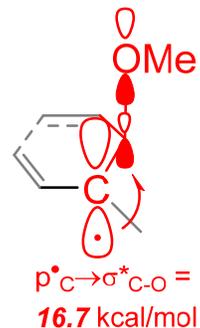
Radical orbital alignment with  $\sigma_{C-O}^*$  weakens the C-O bond



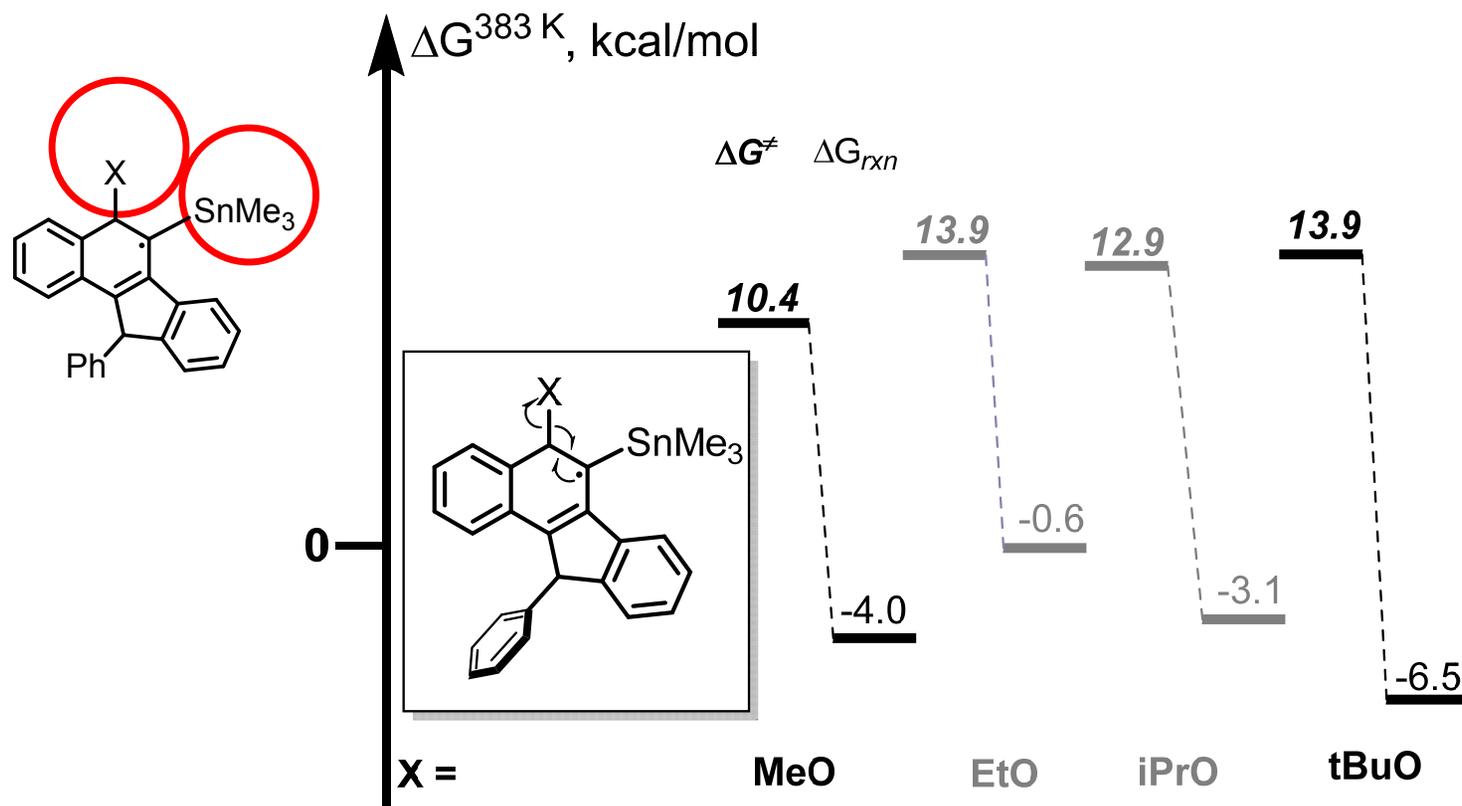
**Classical Anomeric Effect**



**Radical Assistance to C-O scission**



## Can steric decompression also assist in C-O scission?

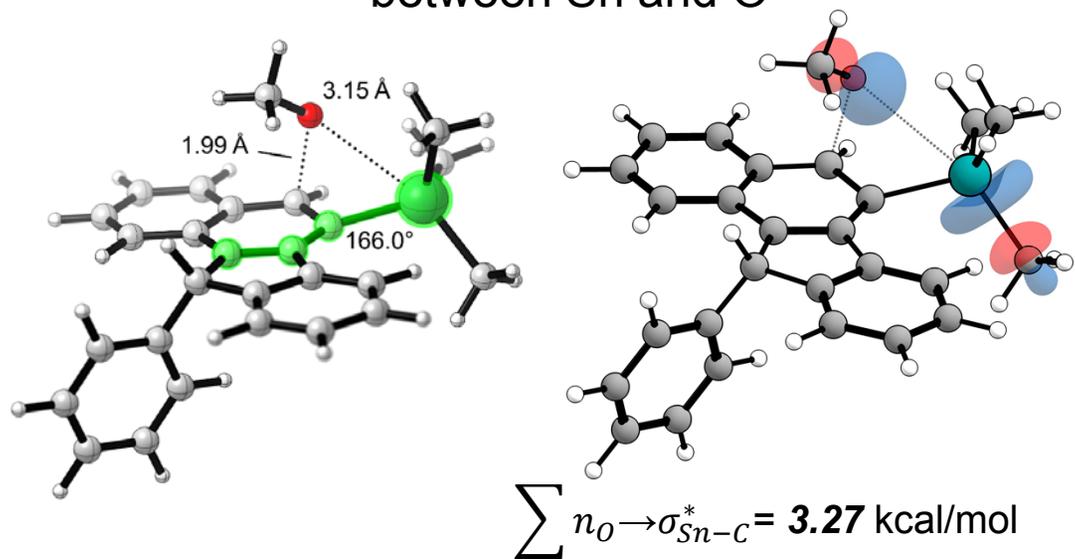
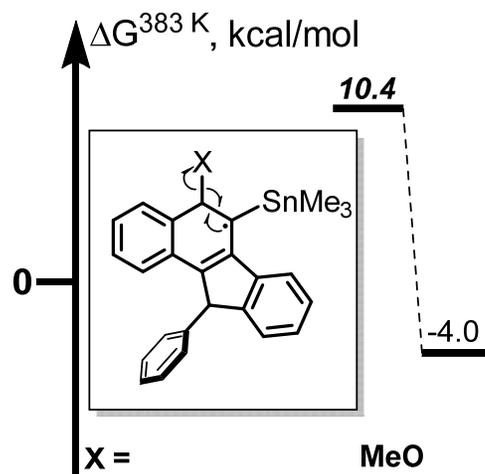


UM06-2X/LanL2DZ

T. Harris, G. P. Gomes, R. Clark, I. V. Alabugin, *J. Org. Chem.*, 2016, ASAP.

## Stereoelectronic analysis of TS

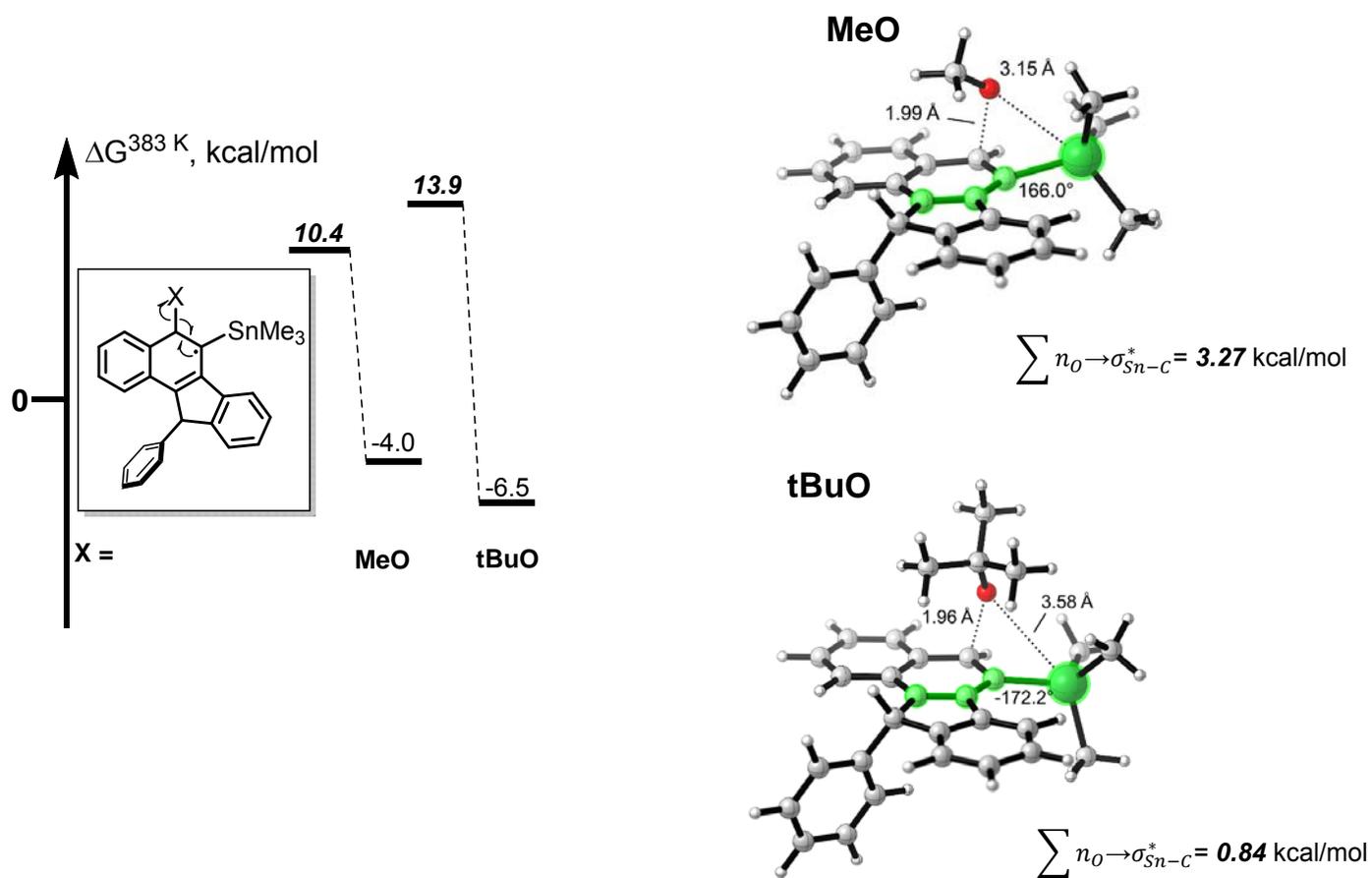
A new “supramolecular” interaction  
between Sn and O



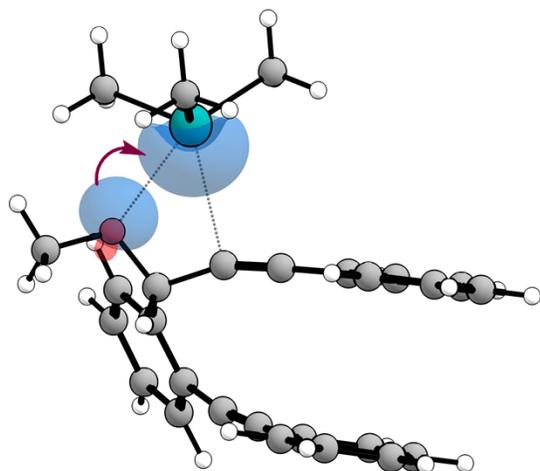
UM06-2X/LanL2DZ

T. Harris, G. P. Gomes, R. Clark, I. V. Alabugin, *J. Org. Chem.*, 2016, ASAP.

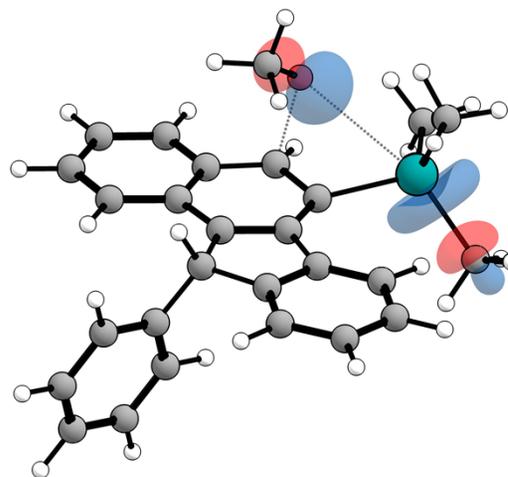
# Tug-of-war between attractive and repulsive interactions in TS



## Supramolecular effects in radical chemistry



$n_O \rightarrow n_{Sn}$  interaction  
controls arrival of  
 $SnBu_3$  radical



$n_O \rightarrow \sigma_{Sn-C}^*$  interaction  
controls departure of  
OR-radical

**How many more are there? Just waiting to be discovered?**

# Acknowledgments



\$\$\$:  
NSF  
National Science Foundation  
IBM