Energy Decomposition Analysis

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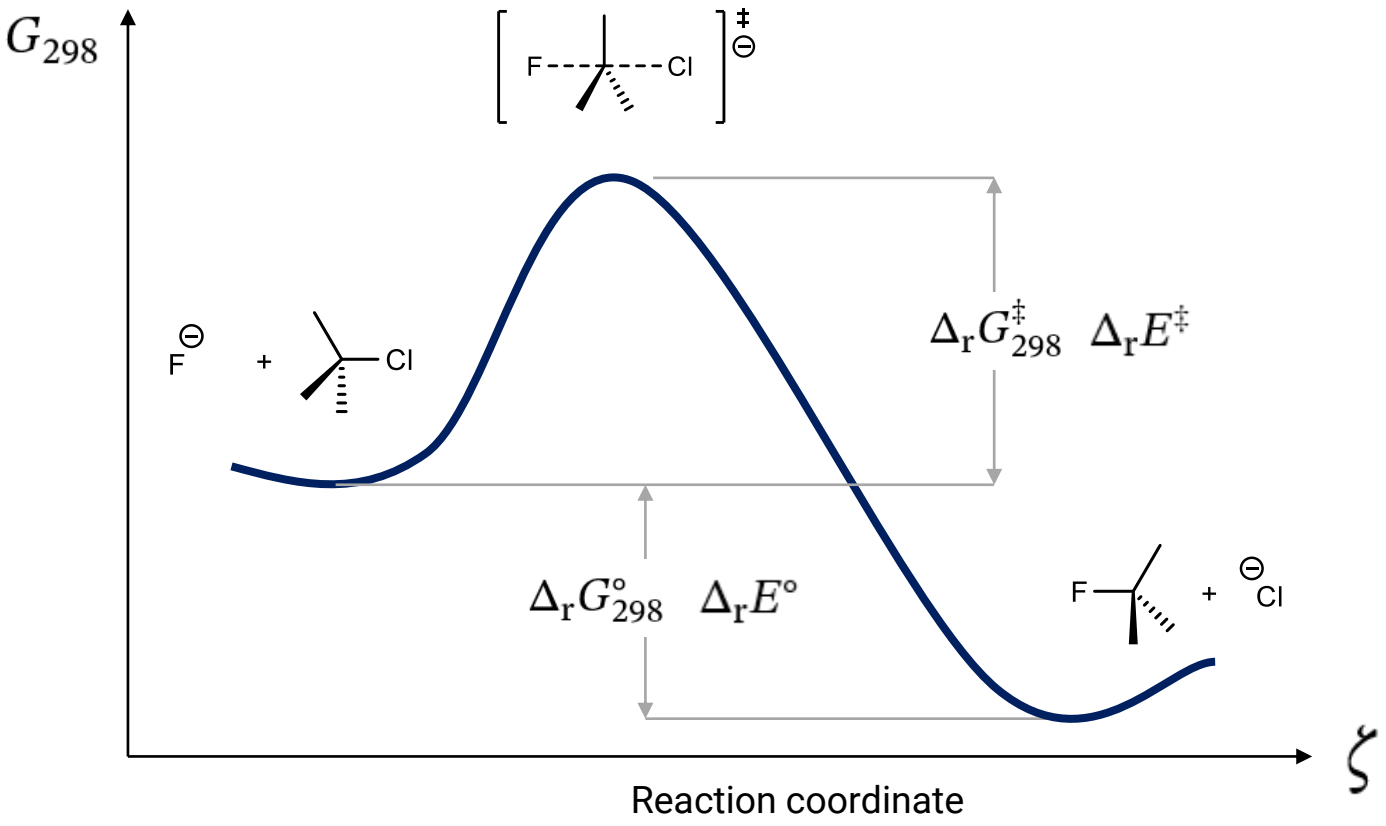
Purpose of this presentation

- Summarize and get acquainted with commonly employed terminology
  - This helps understand the intent of computational sections in modern publications
- Show the unique opportunity of computational methods to break down the overall result into constituents
  - This cannot be done experimentally
- Show how these results may inform us of fundamental reactivity principles
  - The results of this analysis may inform reaction optimization decisions

Explanation of Selectivity

Distortion-Interaction analysis ***focuses on E, the total electronic energy***.



Largest (in absolute values) contributor

$$G_T = \underbrace{E + \mathrm{ZPVE} + h(T)}_{H_T} - T \cdot S_T$$

Definitions

- Energy Decomposition Analysis

Partitioning of the energy in the *ab initio* quantum chemistry calculations into chemically meaningful origins

  - Geometry distortion
  - Electrostatics
  - Exchange-Repulsion
  - Polarization
  - Charge Transfer
  - Dispersion
  - *etc*

- [+] Powerful analytic tool that provides interpretable models
- [+] Generally inexpensive to carry out
- [–] Answers may be highly sensitive to the choice of model and should be interpreted with care
- [–] Contributions from *entropy* and *enthalpy* need to be studied separately.

S. Phipps MJ, Fox T, S. Tautermann C, Skylaris C-K. *Chemical Society Reviews* **2015**, *44* (10), 3177–3211.

Part 1.
Distortion-Interaction Analysis

Basics of energy partitioning

Activation Strain Model

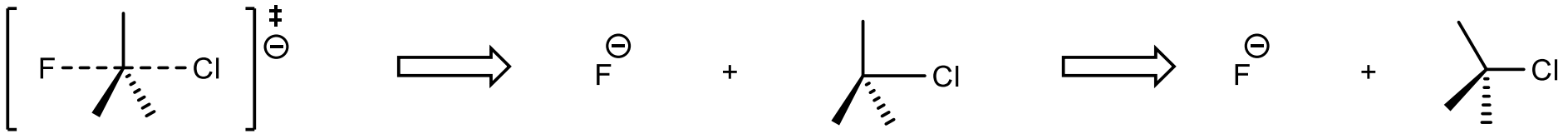
$$\boxed{E_{\mathbf{AB}(\zeta)} = E_{\mathbf{A}(\zeta)} + E_{\mathbf{B}(\zeta)} + \Delta E^{\mathrm{int}}_{\mathbf{AB}}}$$

$$\Delta_{\mathrm{r}} E^{\ddagger} = E_{\mathbf{AB}(\ddagger)} - E_{\mathbf{A}(0)} - E_{\mathbf{B}(0)} = \Delta E^{\mathrm{int}}_{\mathbf{AB}(\ddagger)} + \underbrace{\left(E_{\mathbf{A}(\ddagger)} - E_{\mathbf{A}(0)}\right)}_{\Delta E^{\mathrm{dist}}_{\mathbf{A}(\ddagger)}} + \underbrace{\left(E_{\mathbf{B}(\ddagger)} - E_{\mathbf{B}(0)}\right)}_{\Delta E^{\mathrm{dist}}_{\mathbf{B}(\ddagger)}}$$

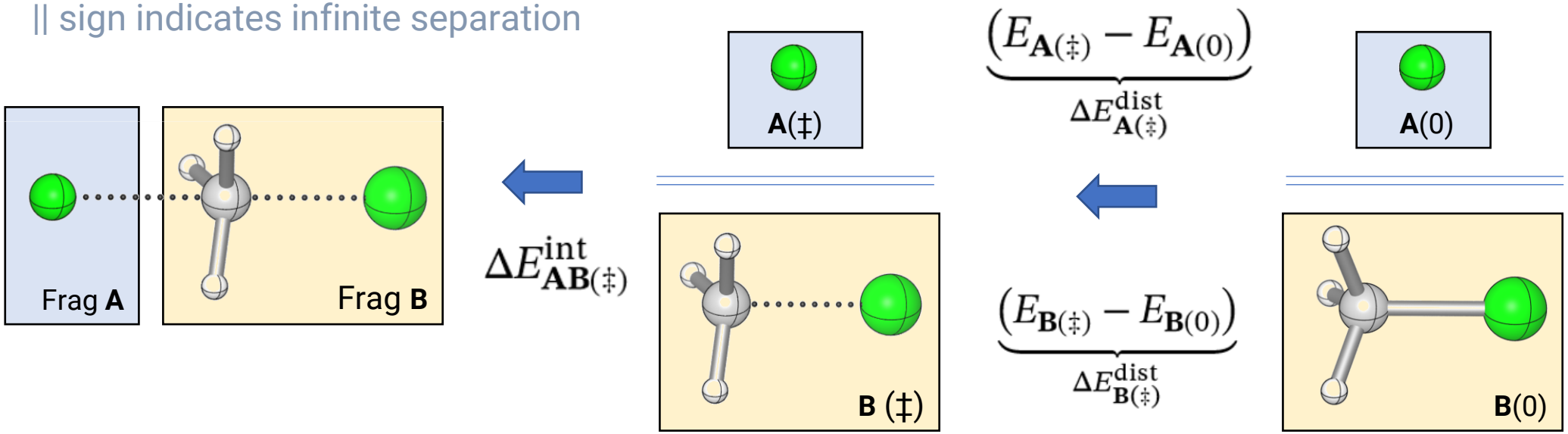
$$\Delta_{\mathrm{r}} E^{\ddagger} = \Delta E^{\mathrm{int}}_{\mathbf{AB}(\ddagger)} + \Delta E^{\mathrm{strain}}_{\mathbf{A}(\ddagger),\mathbf{B}(\ddagger)}$$

- Distortion = Strain (different terminology)
- Most successful applications are elucidating the transition states
- The model is simplistic, but powerful
  - It is as accurate, as the overall model [*note: further sections will show why this is important*]
- Commonly used as the first step in EDA approach

Basic Example: S_N2 Transition State

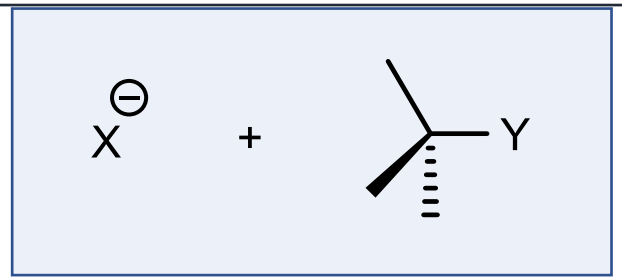


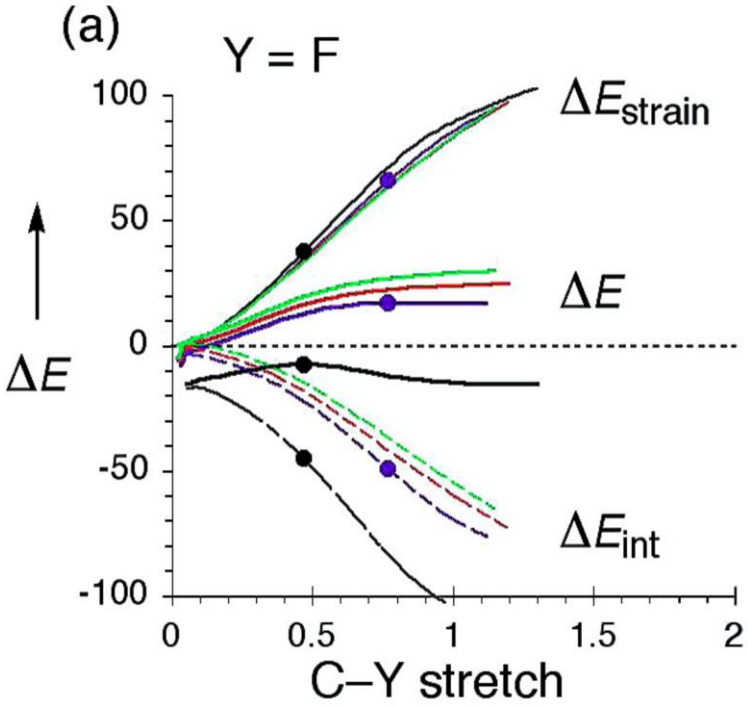
|| sign indicates infinite separation



In this example only fragment **B** has geometry reorganization,
but in principle both fragments undergo reorganization

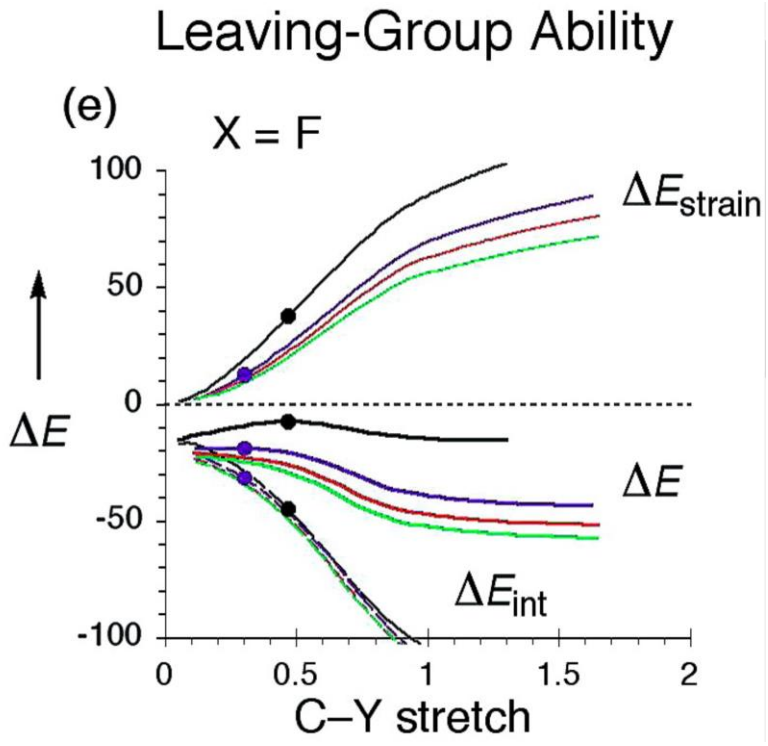
S_N2 Reaction





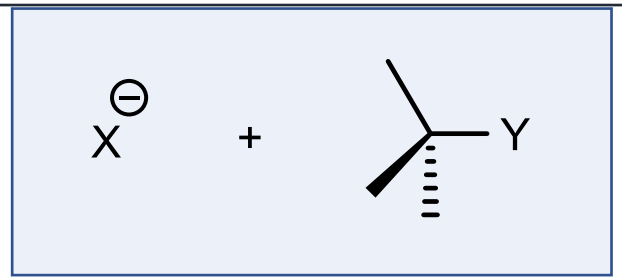
X = F
X = Cl
X = Br
X = I

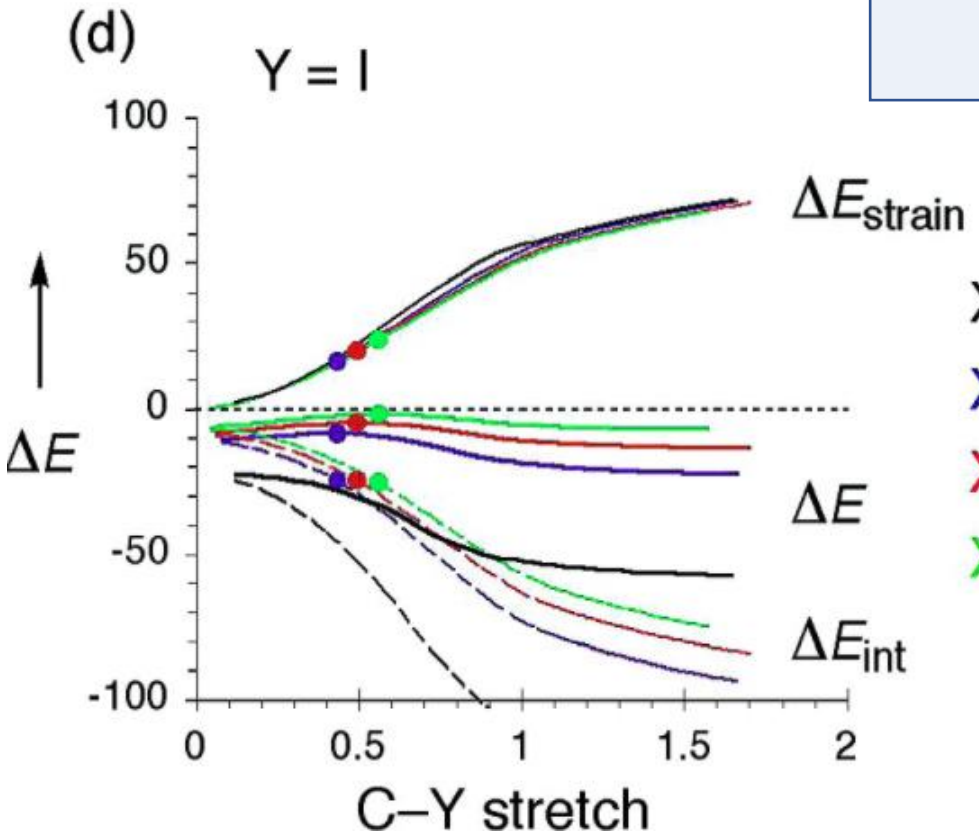
Y = F
Y = Cl
Y = Br
Y = I



Bento AP, Bickelhaupt FM. *J. Org. Chem.* **2008**, *73* (18), 7290–7299.

S_N2 Reaction





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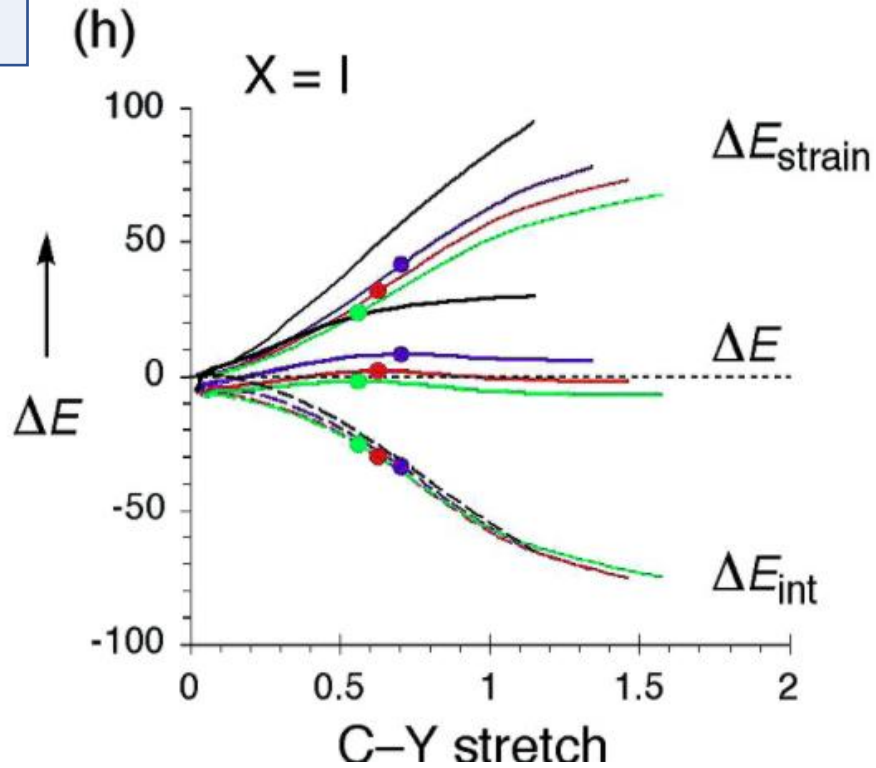
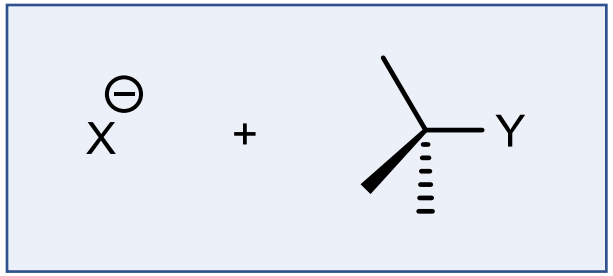
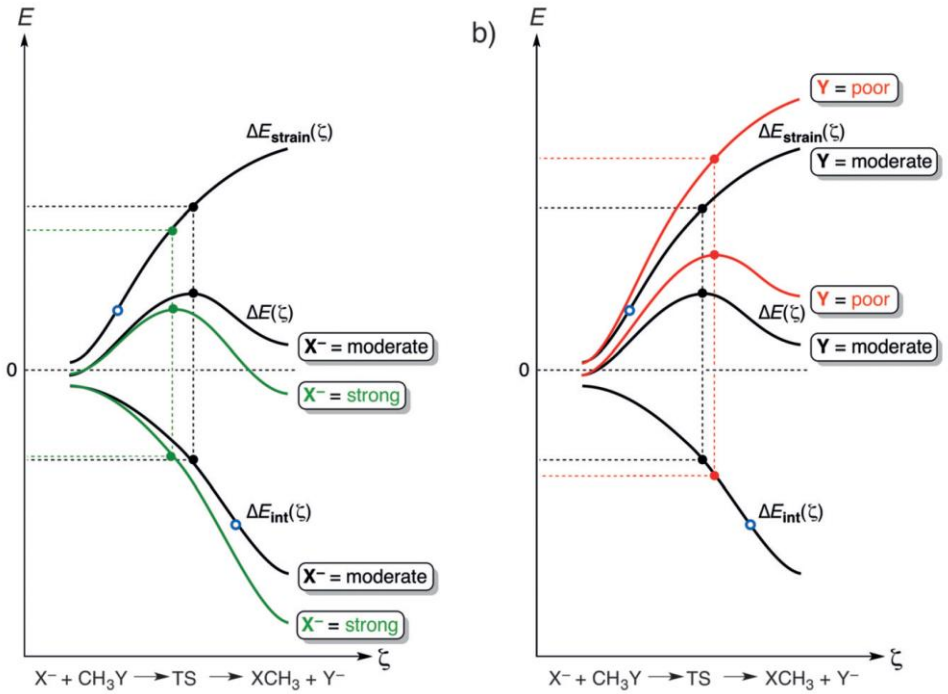


Bento AP, Bickelhaupt FM. *J. Org. Chem.* **2008**, *73* (18), 7290–7299.

S_N2 Reaction: Conclusion





- Cautionary tale: full reaction DIA profile analysis is normally more informative
- SN2 transition state is strongly dependent on the **position of the TS on the coordinate**:
  - earlier TS with lower strain due to good LG ability
  - Projection of IRC onto individual coordinates
- DIA values are more useful in comparative studies. Absolute values can be misleading.

Bento AP, Bickelhaupt FM. *J. Org. Chem.* **2008**, *73* (18), 7290–7299.

Part 2.
The Importance of Distortion

1,3-Dipolar cycloadditions (including bio-orthogonal)

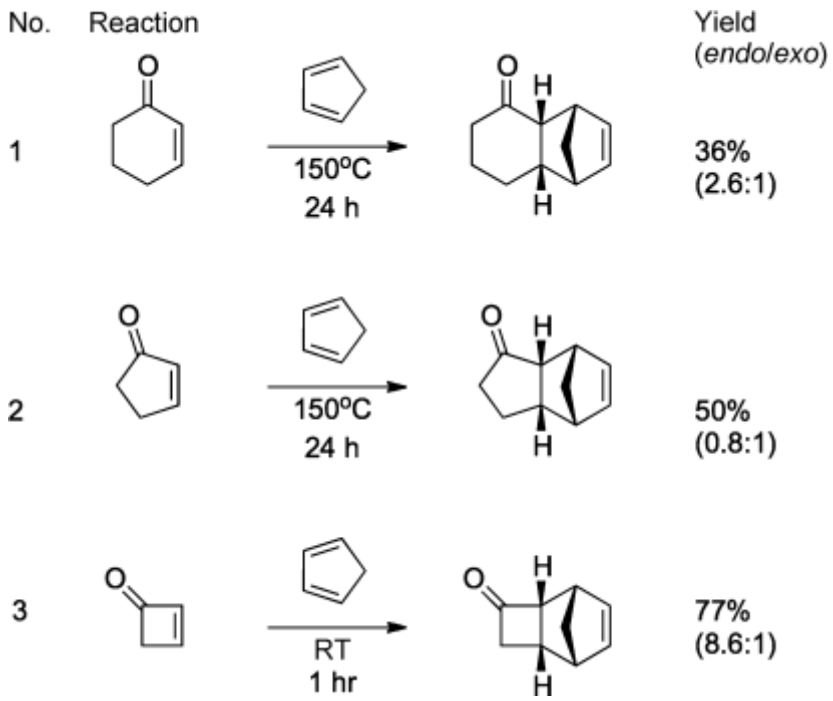
Diels-Alder reaction

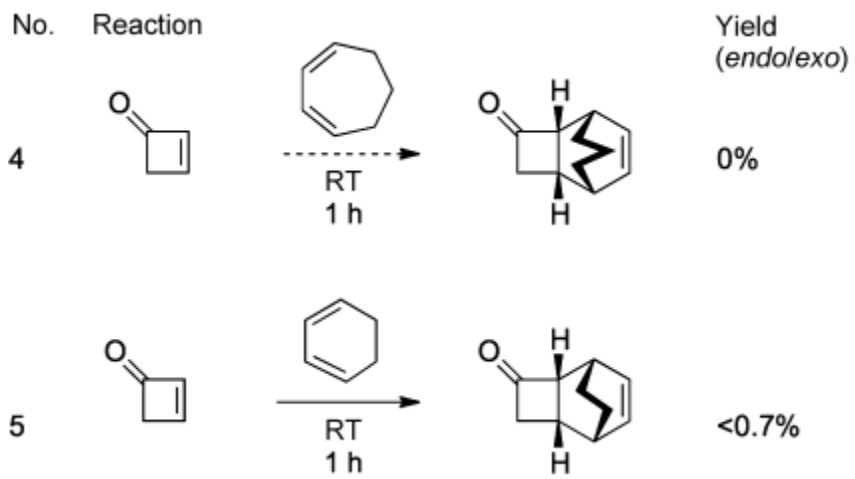
Benzyne AdN regioselectivity

Pop-up Question

What is the most widely accepted predictive model
in both 1,3-dipolar cycloaddition and Diels-Alder reactions?

Diels-Alder Reactions

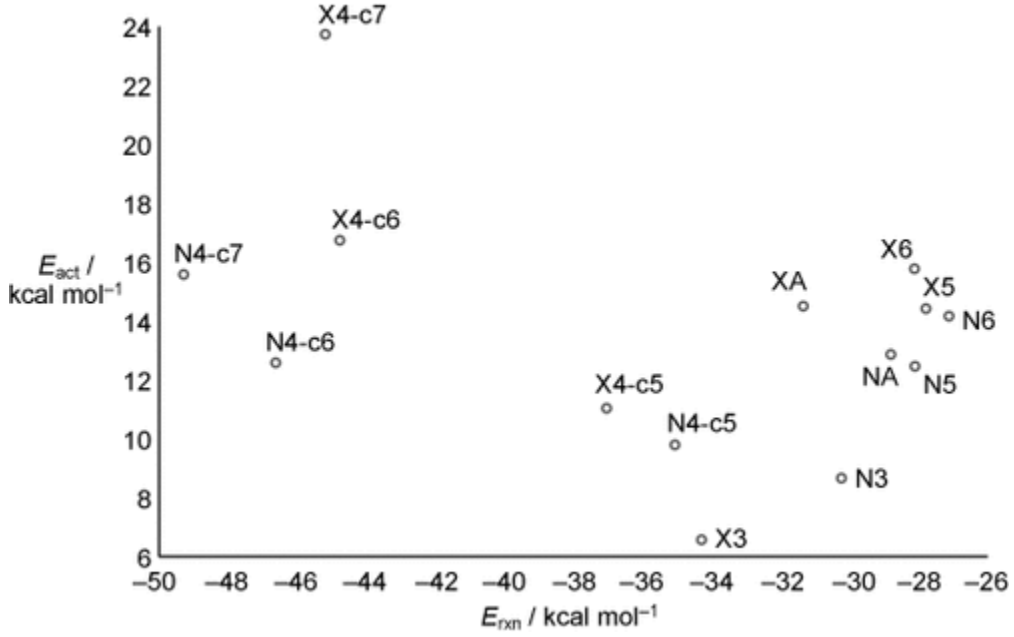


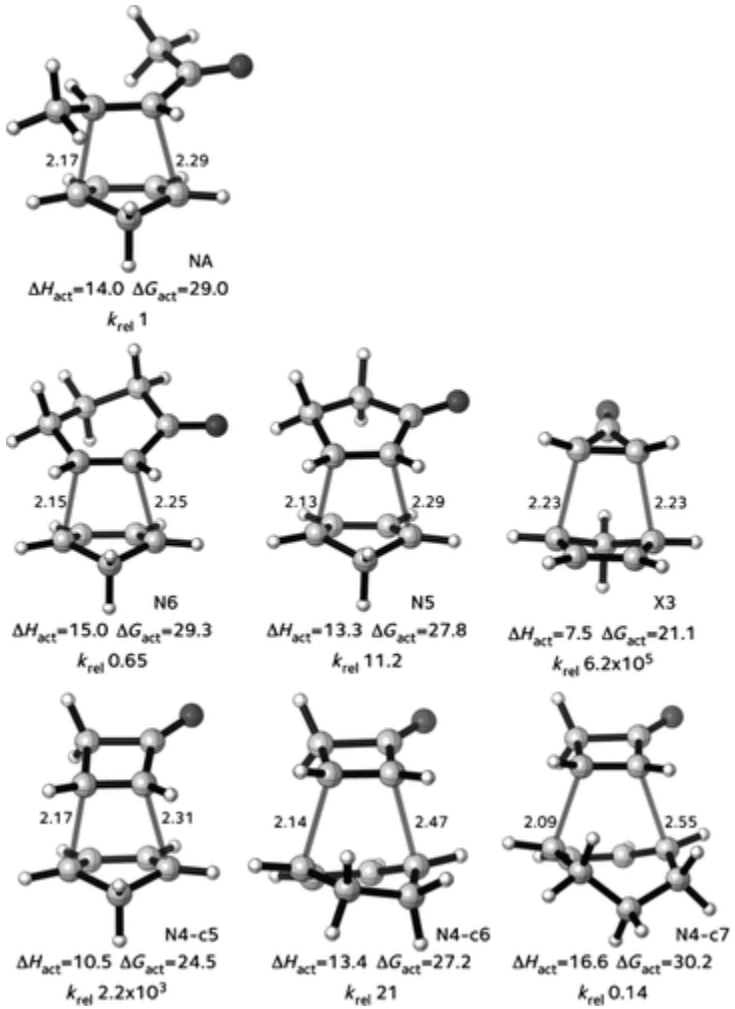


Paton RS, Kim S, Ross AG, Danishefsky SJ, Houk KN. *Angewandte Chemie International Edition* **2011**, *50* (44), 10366–10368.

Diels-Alder Reactions

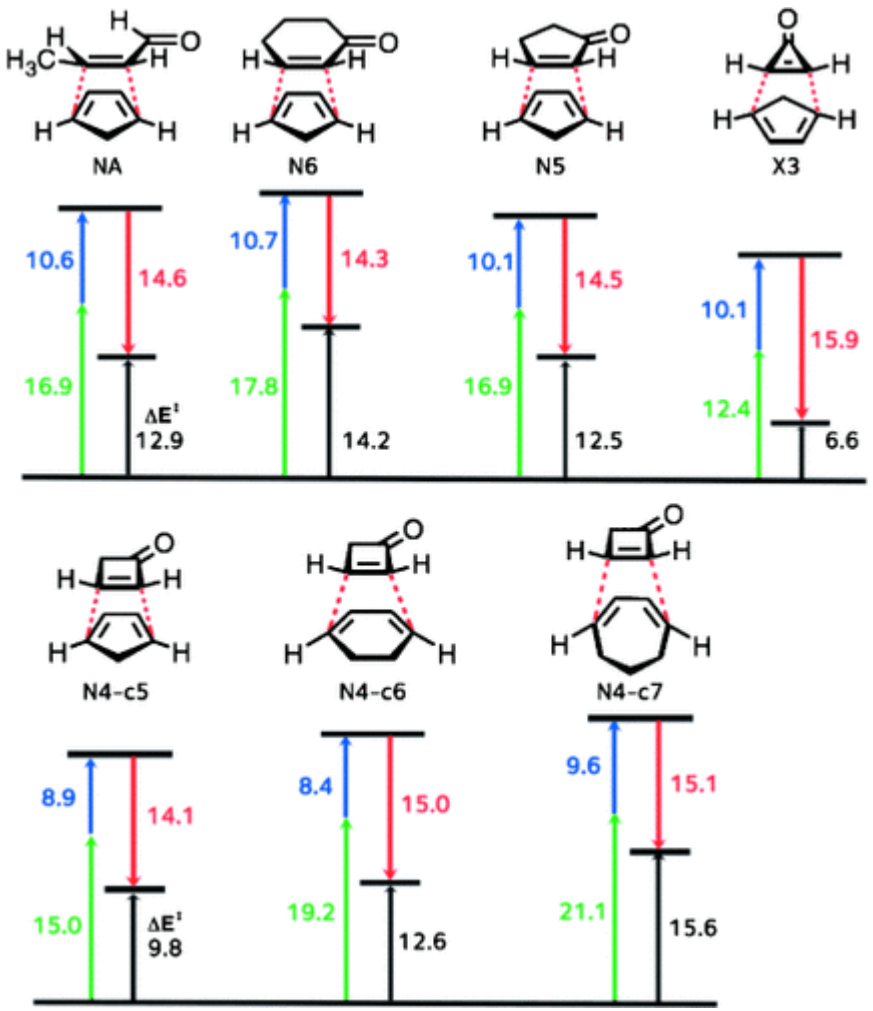
Hammond's postulate not operational



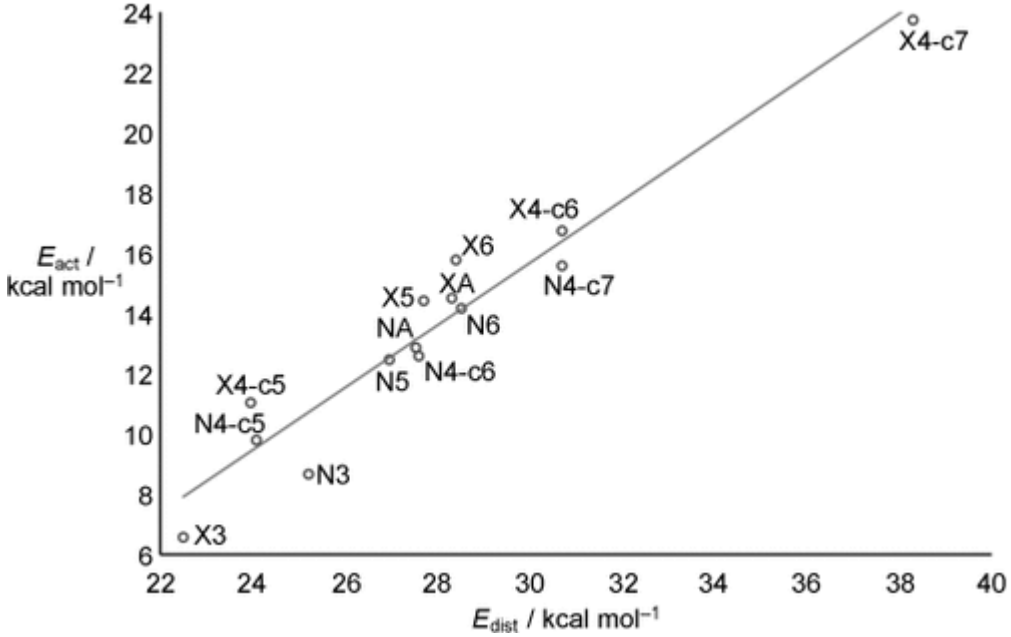


Paton RS, Kim S, Ross AG, Danishefsky SJ, Houk KN. *Angewandte Chemie International Edition* **2011**, *50* (44), 10366–10368.

Diels-Alder Reactions

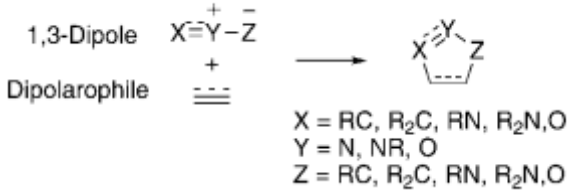


Distortion energy plays the largest contribution



Paton RS, Kim S, Ross AG, Danishefsky SJ, Houk KN. *Angewandte Chemie International Edition* **2011**, *50* (44), 10366–10368.

1,3-Dipolar Cycloadditions



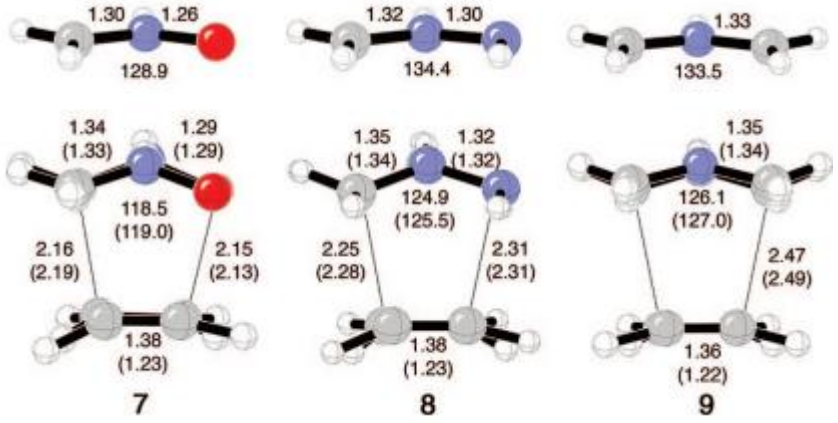
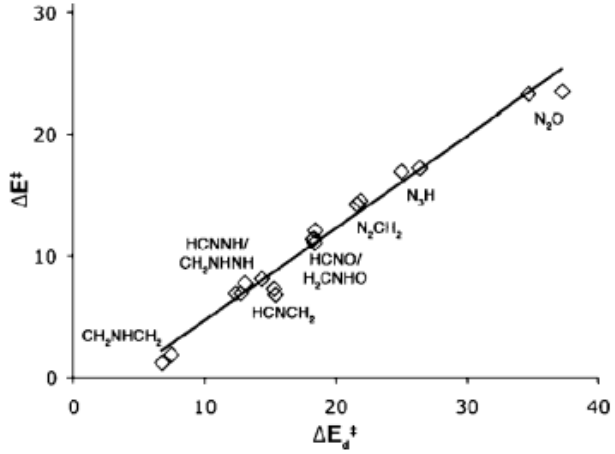


Table 5. B3LYP/6-31G(d) Activation, Distortion and Interaction Energies for Reaction of Dipoles **1**–**9** with Ethylene (ENE) and Acetylene (YNE)[a]

	$\Delta E^{\ddagger}$		$\Delta E_d^{\ddagger}$		$\Delta E^{\ddagger}$	
dipole	ENE	YNE	ENE	YNE	ENE	YNE
1	23.5	23.3	37.3	34.7	−13.8	−11.4
2	17.2	16.9	26.4	25.0	−9.2	−8.1
3	14.3	14.5	21.6	21.9	−7.3	−7.4
4	11.4	12.1	18.3	18.4	−6.9	−6.3
5	6.9	7.8	12.4	13.1	−5.5	−5.3
6	6.9	8.1	12.8	14.4	−5.9	−6.3
7	11.4	11.1	18.3	18.4	−6.9	−7.3
8	7.3	6.8	15.3	15.4	−8.0	−8.6
9	1.2	1.9	6.8	7.5	−5.6	−5.6

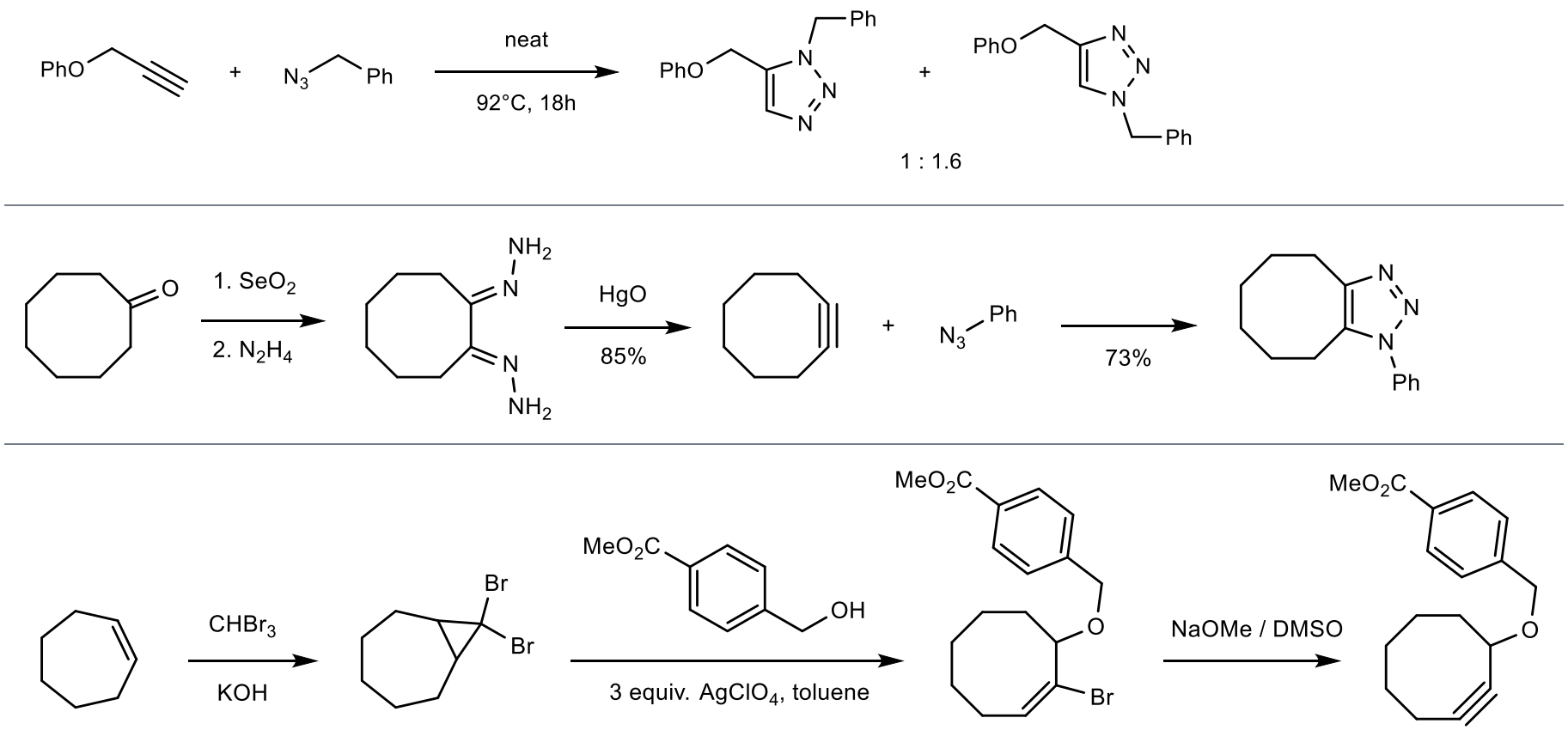
[a] Values reported in kcal/mol.



Ess DH, Houk KN. *J. Am. Chem. Soc.* **2008**, *130* (31), 10187–10198.

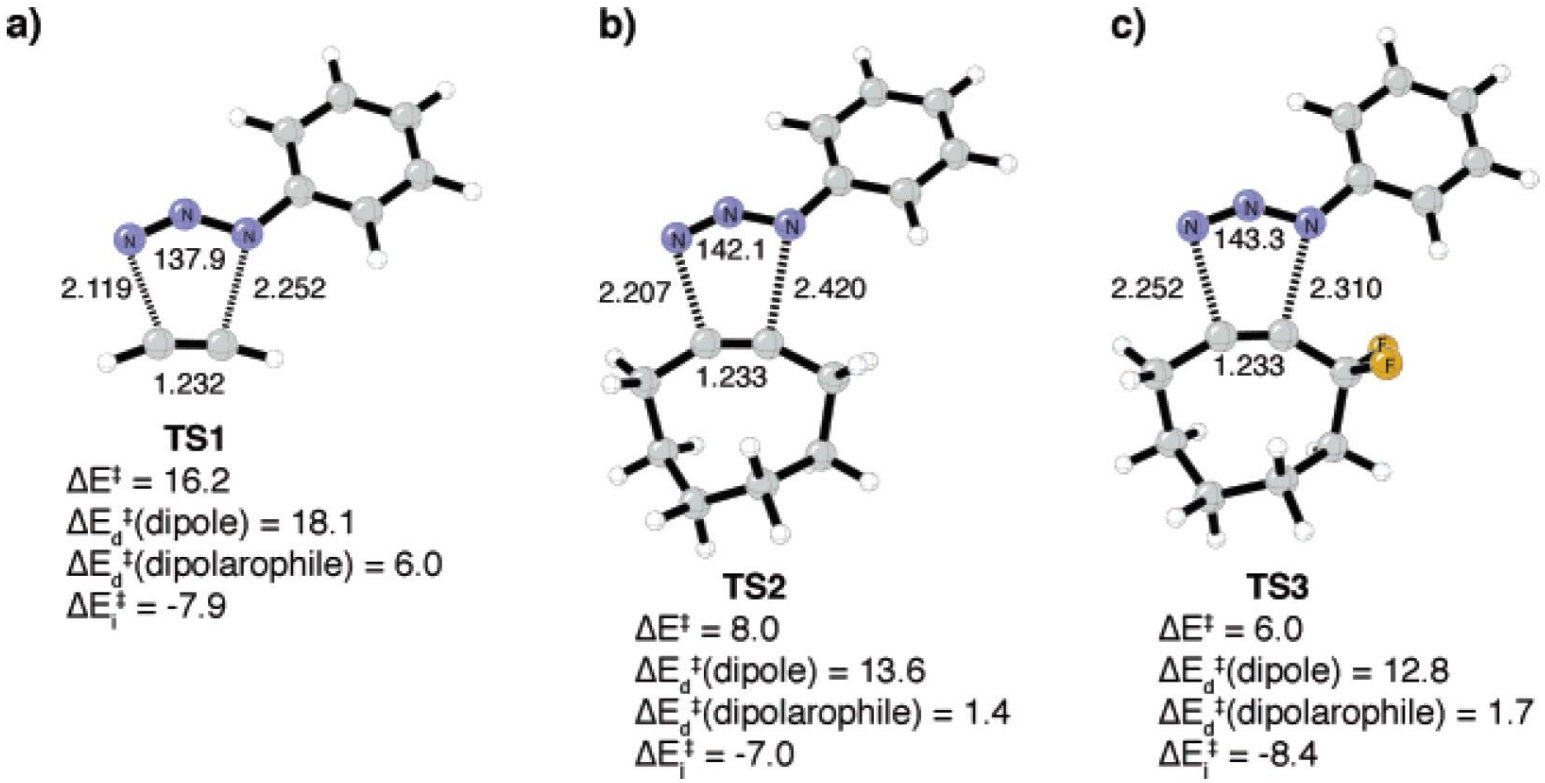
Bio-Orthogonal Cycloadditions

- Strained alkynes participate in Huisgen cycloaddition without heat or catalysis



Wittig G, Krebs A. *Chemische Berichte* **1961**, *94* (12), 3260–3275. | Agard NJ, Prescher JA, Bertozzi CR. *J. Am. Chem. Soc.* **2004**, *126* (46), 15046–15047. | Scinto SL, Bilodeau DA, Hincapie R, Lee W, Nguyen SS, Xu M, am Ende CW, Finn MG, Lang K, Lin Q, Pezacki JP, Prescher JA, Robillard MS, Fox JM. *Nat Rev Methods Primers* **2021**, *1* (1), 1–23. | Carell T, Vrabel M. *Top Curr Chem (Z)* **2016**, *374* (1), 9. | Ramil CP, Lin Q. *Chem. Commun.* **2013**, *49* (94), 11007–11022. | Devaraj NK. *ACS Cent. Sci.* **2018**, *4* (8), 952–959.

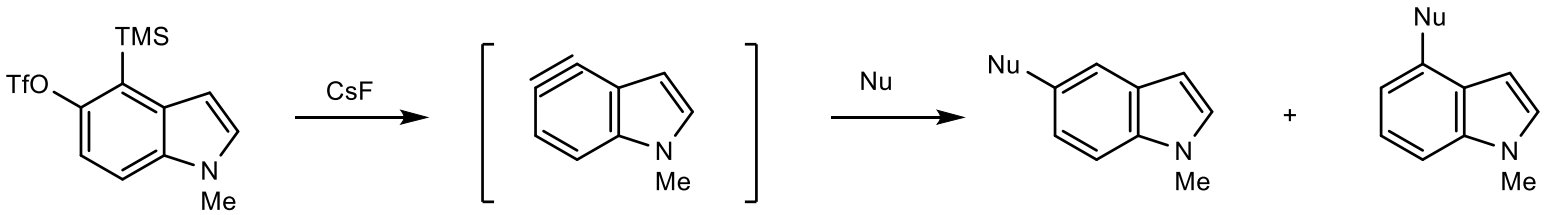
Bio-Orthogonal Cycloadditions

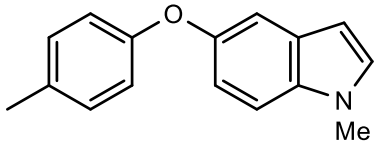


Ess DH, Jones GO, Houk KN. *Org. Lett.* **2008**, *10* (8), 1633–1636.
Xu L, Doubleday CE, Houk KN. *Angewandte Chemie International Edition* **2009**, *48* (15), 2746–2748.
Dommerholt J, van Rooijen O, Borrmann A, Guerra CF, Bickelhaupt FM, van Delft FL. *Nat Commun* **2014**, *5* (1), 5378.

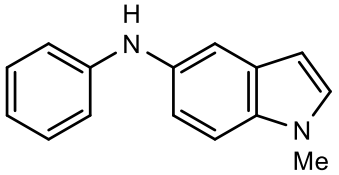
Aryne Distortion Reactivity Model

- Nucleophilic additions or cycloadditions with arynes is one of the most successful predictive application of reaction strain model.

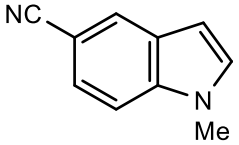




80%, 3 : 1



91%, 12 : 1

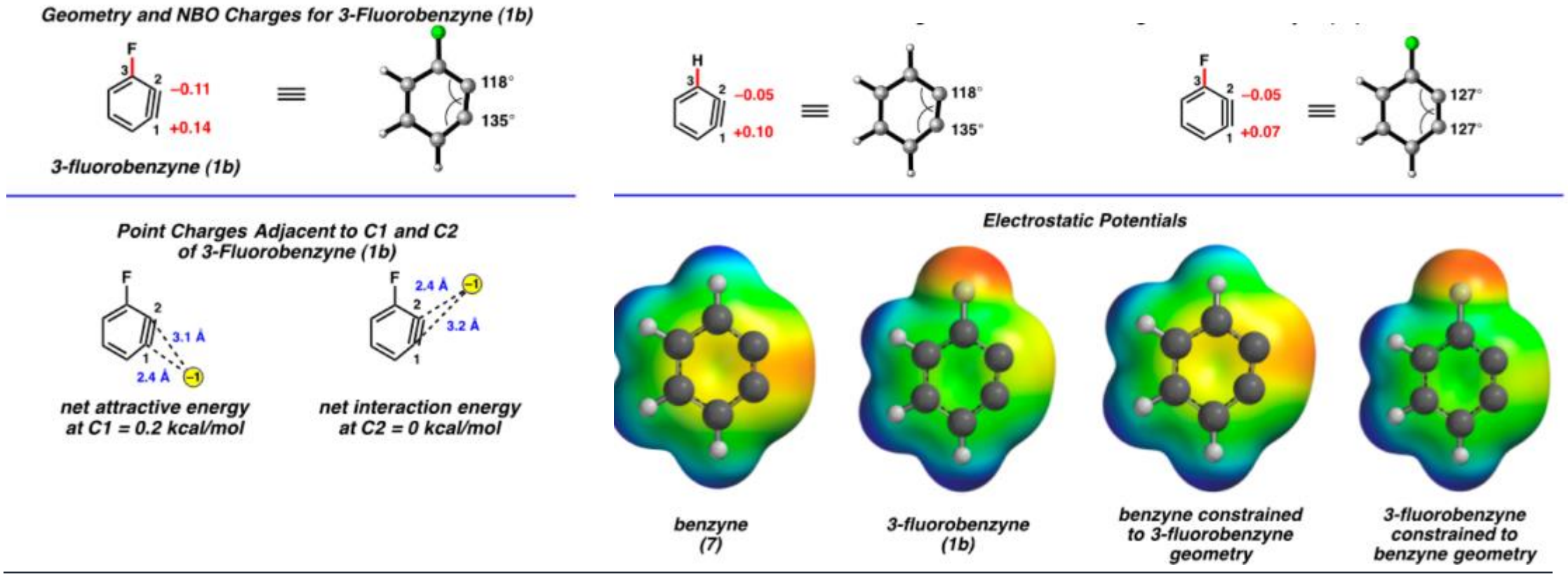


85%, 3 : 1

Cheong PH-Y, Paton RS, Bronner SM, Im G-YJ, Garg NK, Houk KN. *J. Am. Chem. Soc.* **2010**, *132* (4), 1267–1269.
Yamano MM, Kelleghan AV, Shao Q, Giroud M, Simmons BJ, Li B, Chen S, Houk KN, Garg NK. *Nature* **2020**, *586* (7828), 242–247.
Medina JM, Mackey JL, Garg NK, Houk KN. *J. Am. Chem. Soc.* **2014**, *136* (44), 15798–15805.

Aryne Distortion Reactivity Model

- Nucleophilic additions or cycloadditions with arynes is one of the most successful predictive application of reaction strain model.



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Yamano MM, Kelleghan AV, Shao Q, Giroud M, Simmons BJ, Li B, Chen S, Houk KN, Garg NK. *Nature* **2020**, *586* (7828), 242–247.
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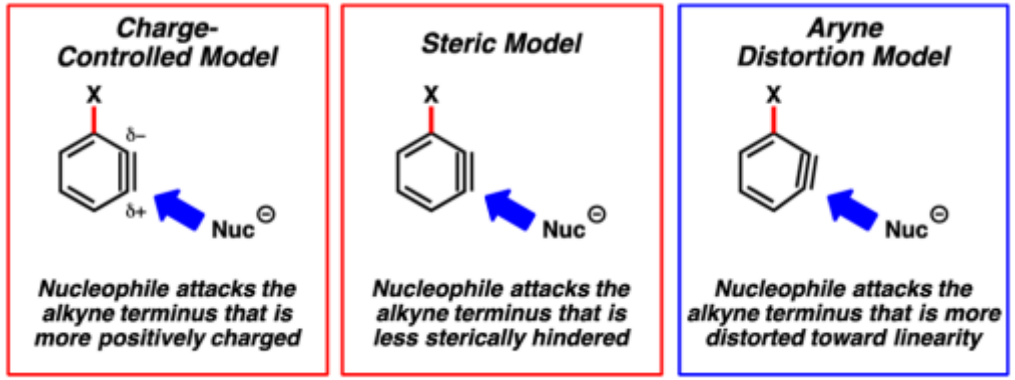

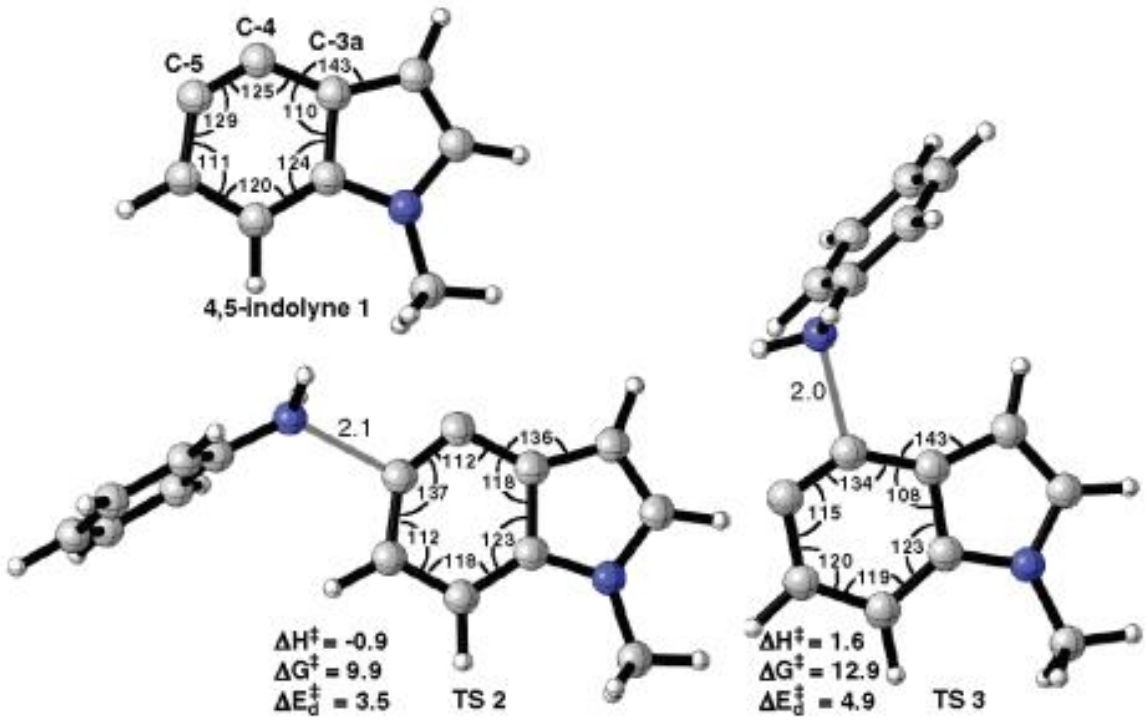

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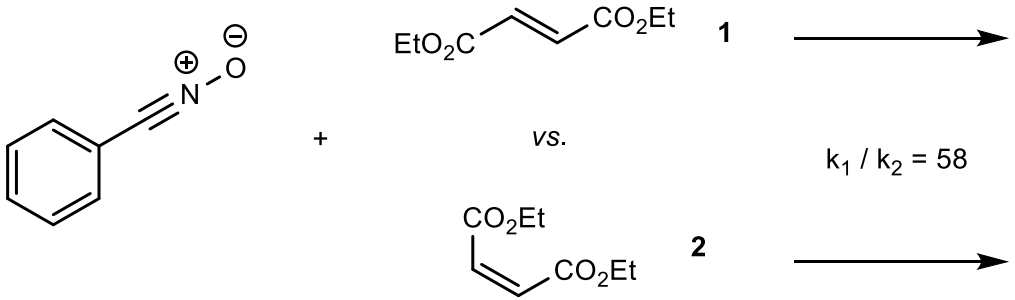
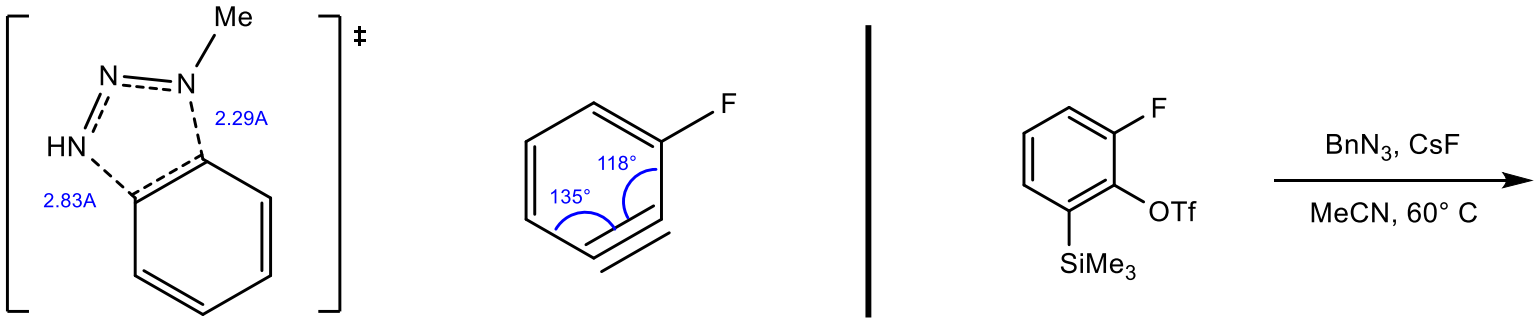
Medina JM, Mackey JL, Garg NK, Houk KN. *J. Am. Chem. Soc.* **2014**, *136* (44), 15798–15805.

Group Problem

1. In cycloadditions of 1,3-dipoles with EWG-alkenes, *cis* alkenes react considerably **slower** than *trans*. Propose an explanation for this effect. Show the product structure. How does one generate nitrile oxides?



2. Predict and rationalize the selectivity of aryne-azide cycloaddition, given the optimized equilibrium aryne geometry and a model TS geometry. Show the aryne formation mechanism.



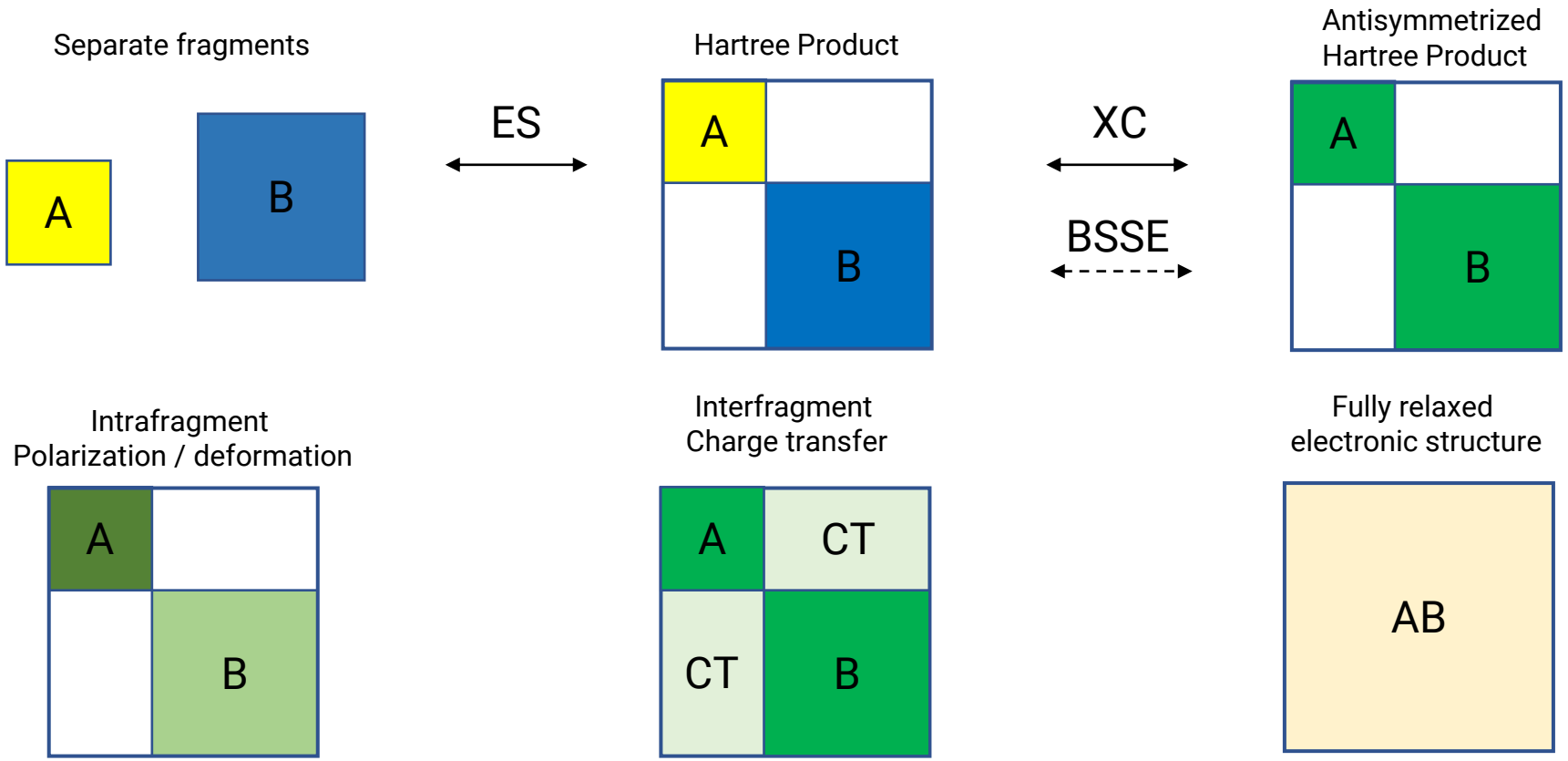
Huisgen R. *Angewandte Chemie International Edition in English* **1963**, *2* (11), 633–645.
Medina JM, Mackey JL, Garg NK, Houk KN. *J. Am. Chem. Soc.* **2014**, *136* (44), 15798–15805.

Part 3.
Interaction Energy Partitioning

Definition of Terms

Explanation of common binding effects

Principles of Interfragment interaction



The key to EDA is deletion of certain types of interactions, then comparing the energies

This is a very, very crude approximation to what the Fock matrices look like. But it is better than nothing.

Keiji Morokuma (1934–2017)

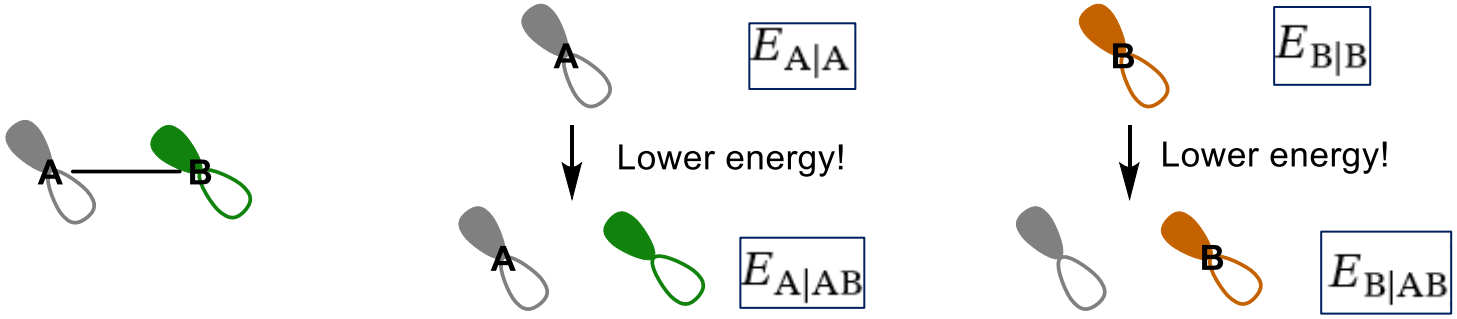
- PhD 1963 (Kyoto University with Kenichi Fukui)
- Known for
  - Kitaura-Morokuma EDA
  - ONIOM methods
    - Multiscale approaches that allow to treat different regions of molecules with different methods
    - Can be used to tackle reactivities with as large as protein structures, incorporating part of QM
  - Artificial Force Induced Reactions
    - Methods that allow automatic determination of reaction pathways
    - Used extensively

Sameera WMC, Maeda S, Morokuma K. *Acc. Chem. Res.* **2016**, *49* (4), 763–773.
The ONIOM Method and Its Applications | Chemical Reviews https://pubs.acs.org/doi/10.1021/cr5004419 (accessed 2021 -09 -21).

Basis Set Superposition Error

For simplicity this section will address a big problem that contaminates the interaction energies heavily (and won't be mentioned subsequently)

- Small basis sets contaminate results due to *incompleteness* and *superposition error*.
  - *This is a general rule, not particular to EDA*
- As an example, BSSE typically leads to overestimated interaction energies



Solutions:

1. Use *large* basis sets (at least TZ, better QZ)
   Not always possible, plus may affect polarization
2. **Explicitly calculate *counterpoise correction***
   This is the preferred way

$$\Delta E_{\mathrm{BSSE}} = \left(E_{\mathrm{A|AB}} - E_{\mathrm{A|A}}\right) + \left(E_{\mathrm{B|AB}} - E_{\mathrm{B|B}}\right)$$

van Duijneveldt FB, van Duijneveldt-van de Rijdt JGCM, van Lenthe JH. *Chem. Rev.* **1994**, *94* (7), 1873–1885.

Kitaura-Morokuma (KM) EDA

- One of the earliest systematic ways of partitioning energy [HF only] (into 5 components)

$$\Delta E^{\mathrm{int}} = \Delta E_{\mathrm{ES}} + \Delta E_{\mathrm{EX}} + \Delta E_{\mathrm{POL}} + \Delta E_{\mathrm{CT}} + \Delta E_{\mathrm{MIX}}$$

Term	Symbol	Meaning	Comment
Electrostatic interaction	ES	Interaction of undisturbed electron densities	
Exchange Repulsion	EX	Repulsion of electrons due to Pauli exclusion principle	
Polarization	POL	Distortion of charge distributions *within fragments*	At short distances becomes mixed with charge transfer
Charge transfer	CT	Electron transfer *between fragments*	^^^
	MIX	Residual	Has no exact physical meaning: all residual interactions just fall in this category

Morokuma K, Kitaura K. Energy Decomposition Analysis of Molecular Interactions. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials: Reactivity, Structure, Scattering, and Energetics of Organic, Inorganic, and Biological Systems*; Politzer, P., Truhlar, D. G., Eds.; Springer US: Boston, MA, 1981; pp 215–242.

Extended Transition State (ETS) EDA

An attempt to improve KM-EDA. Popular due to simplicity. Orbital picture can be interpreted.

Term	Symbol	Meaning	Comment
Electrostatic interaction	ES	Interaction of undisturbed electron densities between fragments	
Pauli Repulsion	Pauli	Repulsion of electrons due to Pauli exclusion principle	
Orbital Interaction	Orb, oi	All changes due to orbital reorganization	

S. Phipps MJ, Fox T, S. Tautermann C, Skylaris C-K. *Chemical Society Reviews* **2015**, *44* (10), 3177–3211.

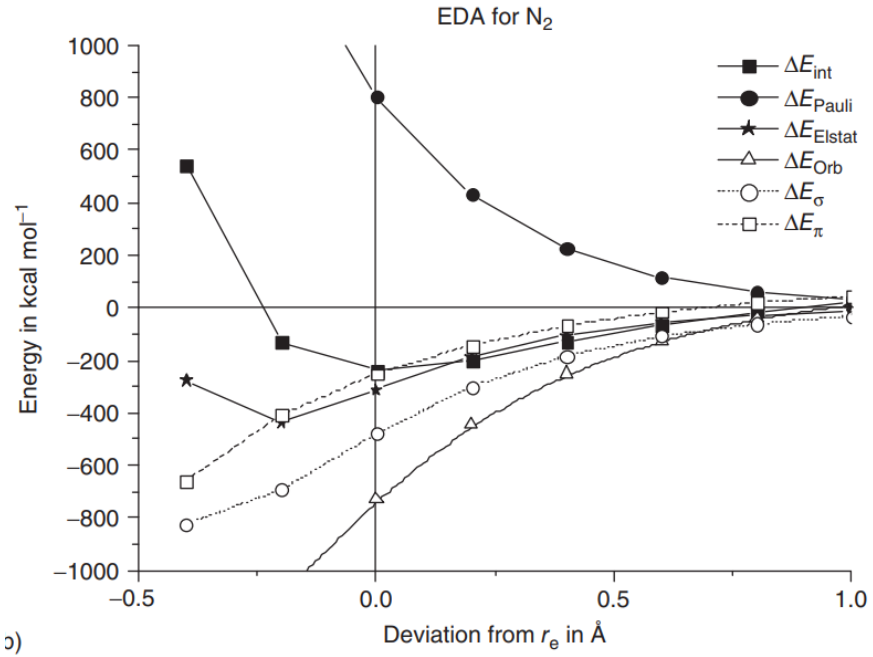
Natural Orbitals for Chemical Valence (ETS-NOCV)

An extension of ETS method allows to **visualize orbital reorganization**.

Orbitals are transformed into a basis that naturally corresponds to valence.

Very useful in the analysis of bonding orbitals and their relative contributions to the interaction energy.

	N_2	CO
Symmetry[b]	$D_{\infty h}$	$C_{\infty v}$
ΔE_{int}	−232.2	−258.4
ΔE_{Pauli}	791.7	575.8
ΔE_{elstat}[c]	−308.5 (30.1%)	−240.0 (28.8%)
ΔE_{orb}[c]	−715.4 (69.9%)	−594.2 (71.2%)
ΔE_{σ}[d]	−470.0 (65.7%)	−301.7 (50.8%)
ΔE_{π}[d]	−245.4 (34.3%)	−292.5 (49.2%)



Frenking G, Bickelhaupt FM. The EDA Perspective of Chemical Bonding. In *The Chemical Bond*; John Wiley & Sons, Ltd, 2014; pp 121–157.

Restricted Variational Space (RVS) EDA

An attempt to improve KM-EDA by taking into account the

Term	Symbol	Meaning	Comment
Electrostatic interaction + exchange	ESX	Interaction of undisturbed electron densities + Repulsion of electrons due to Pauli exclusion principle	
Polarization	POL	Distortion of charge distributions *within fragments* upon mixing of orbitals	Differs from KM-EDA: antisymmetrized wavefunction
Charge transfer	CT	Electron transfer *between fragments*	
	MIX / RES	Residual	Has no exact physical meaning: all residual interactions just fall in this category

Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

Natural Energy Decomposition Analysis (NEDA)

Developed by Frank Weinhold in context of Natural Bond Orbital theory [HF/DFT/correlated].

The interpretation required HIGHLY biased localization function (1-2 center, 2 electron localization).

Controversial perception, not very popular.

Term	Symbol	Meaning	Comment
Electrostatic	ES	Interaction of undisturbed densities between fragments	Electrostatic + Exchange-Correlation
Polarization	POL	Distortion of charge distributions *within fragments*	Differs: use localized orbitals
Charge transfer	CT	Dynamic electron transfer *between fragments*	
Exchange-Correlation	EX/XC	Interaction of undisturbed electron densities + Repulsion of electrons due to Pauli exclusion principle	
Deformation	DEF	Distortion of electron density distribution *within fragments*	

Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

Absolutely Localized Molecular Orbital (ALMO) EDA

Currently the most popular EDA scheme. Developed by Head-Gordon group, Implemented in Q-Chem ($$$).

Term	Symbol	Meaning	Comment
Frozen Density Component	FRZ	Interaction of frozen electron densities	Electrostatic + Exchange-Correlation
Polarization	POL	Distortion of charge distributions *within fragments* upon mixing of orbitals	Differs from KM-EDA: used antisymmetrized wavefunction
Charge transfer	CT	Dynamic electron transfer *between fragments*	CT Directionality

Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

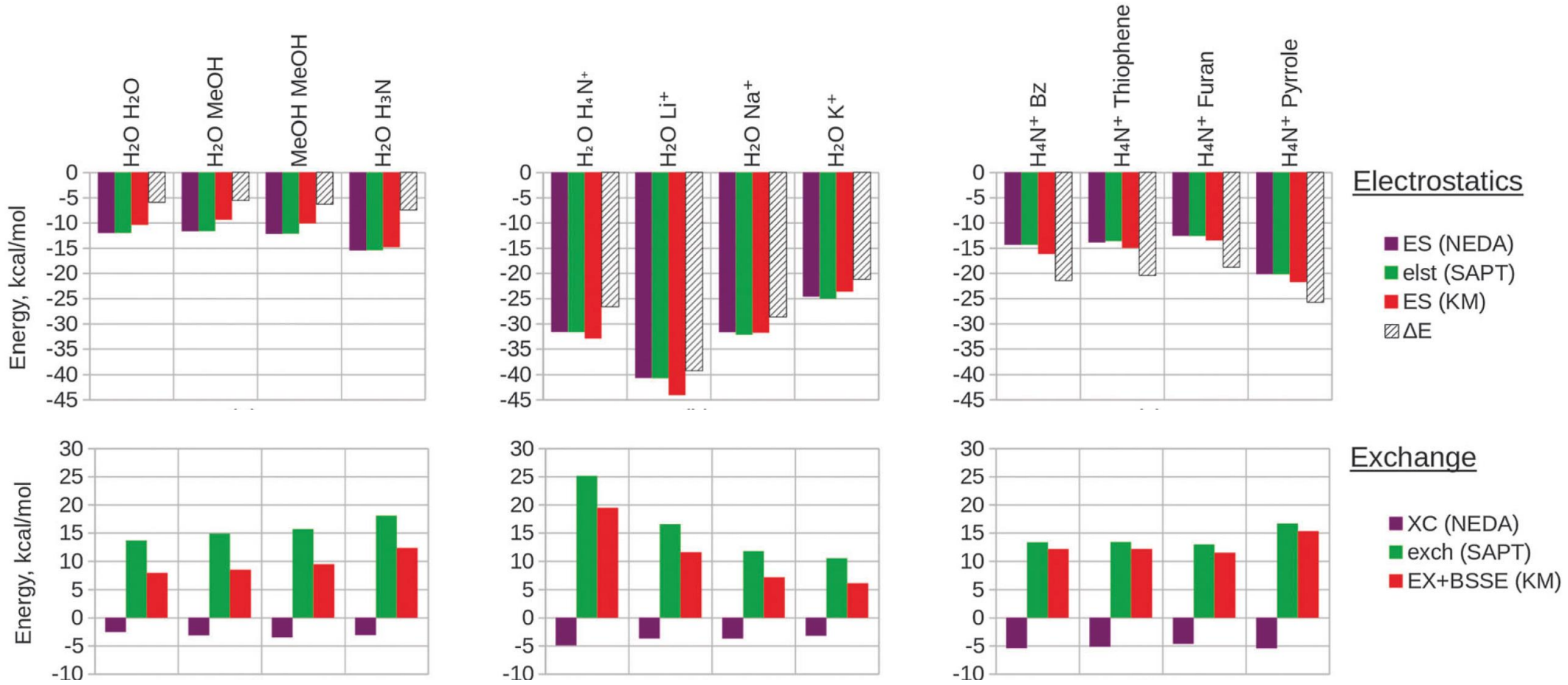
2nd Generation ALMO-EDA

Currently the most popular EDA scheme. Developed by Head-Gordon group, Implemented in Q-Chem.

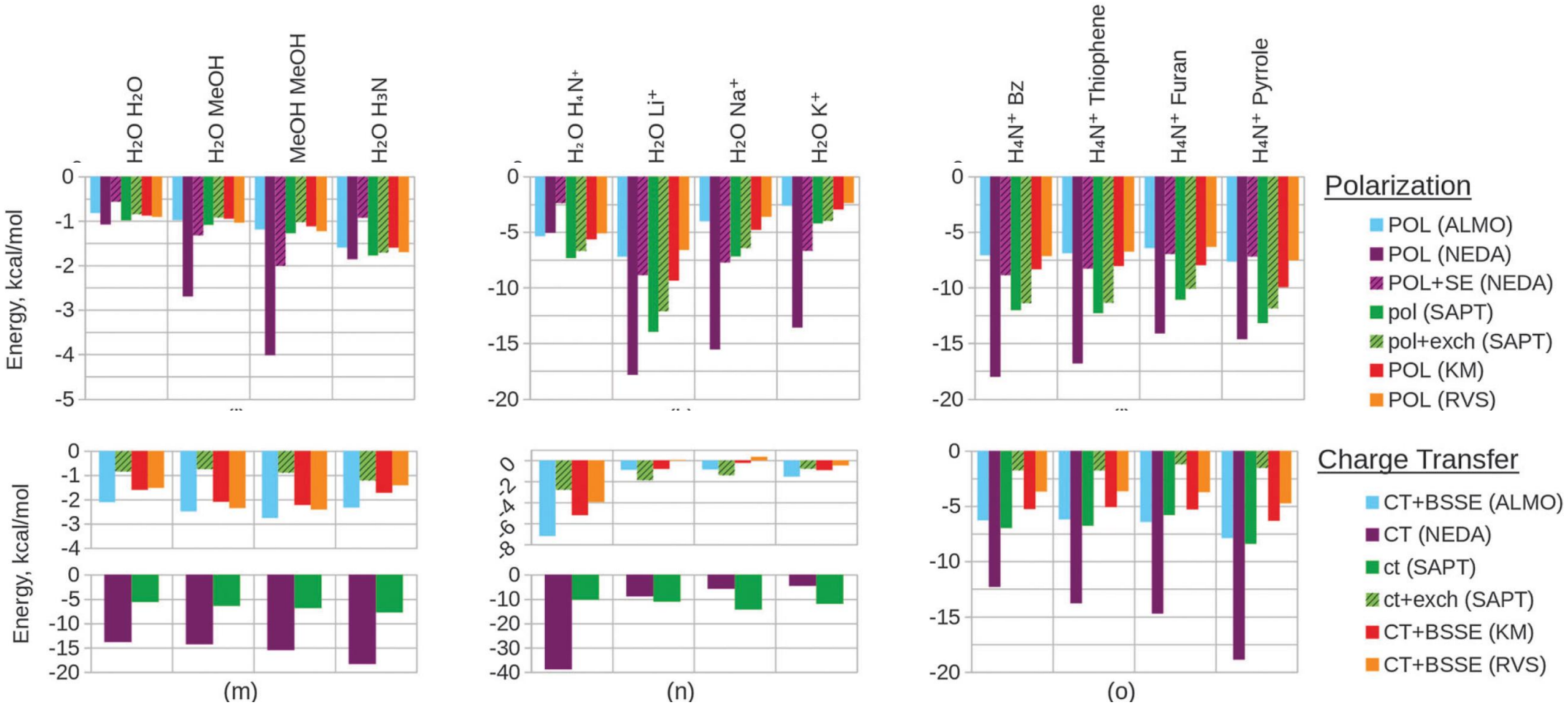
Term	Symbol	Meaning	Comment
Pauli repulsion	Pauli	Exchange repulsion of electrons	Split
Electrostatic	elstat	Electrostatic interaction of frozen fragments	
Polarization	POL	Distortion of charge distributions *within fragments* upon mixing of orbitals	
Charge transfer	CT	Dynamic electron transfer *between fragments*	CT Directionality
Dispersion	Disp	Weak noncovalent electron correlation effect	TBD later

Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

Differences Between Partitioning Methods



Differences Between Partitioning Methods



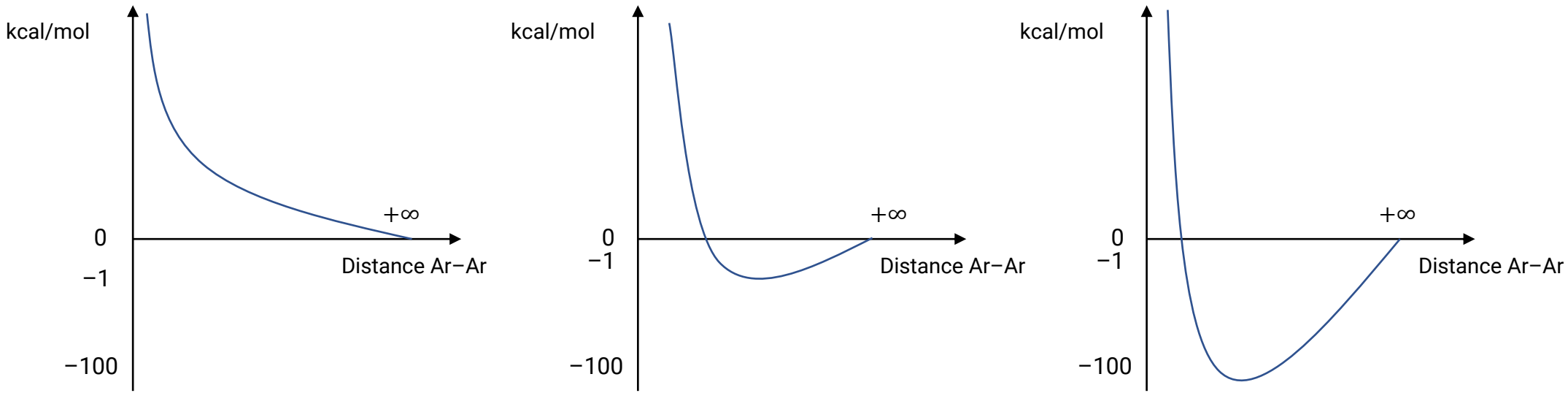
Part 4.
Understanding Interactions in TM Catalysis

Interfragment charge transfer

Dispersion interaction

Pop-up question

- Which of the three graphs represents a correct total energy curve for two argon atoms?

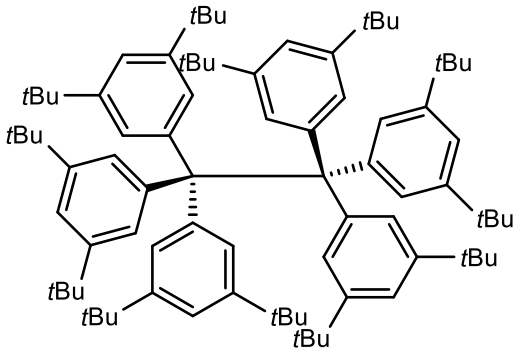


We normally recognize that *e*-density interaction is repulsive, but it can also exhibit attraction due to dynamic correlation (weak, but additive!)

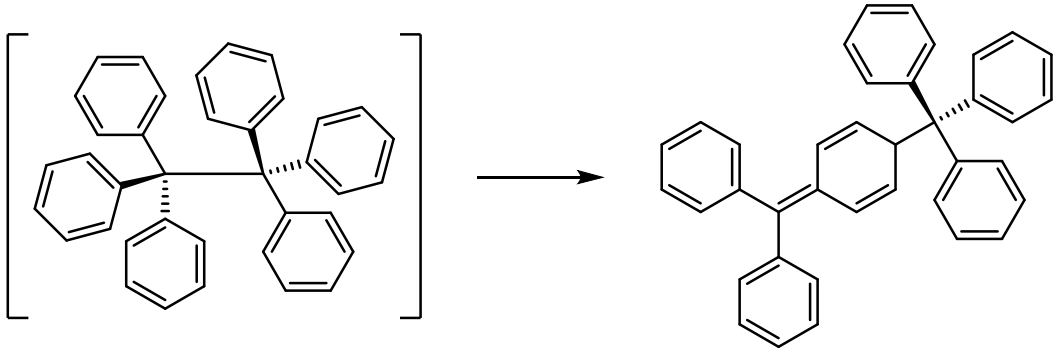
Please excuse my poor drawings

Treatment of Dispersion Effects

- Dispersion is a dynamic electron correlation effect. It cannot be modeled in a self-consistent field (HF/DFT/CASSCF).
- Most accurate treatment is through MP2 or CCSD(T)
  - (insanely expensive for large systems, but there is light with approximations)
- There are *empirical* corrections (D2, D3, D4, VV10) that can reintroduce dispersion into DFT
- Why bother?



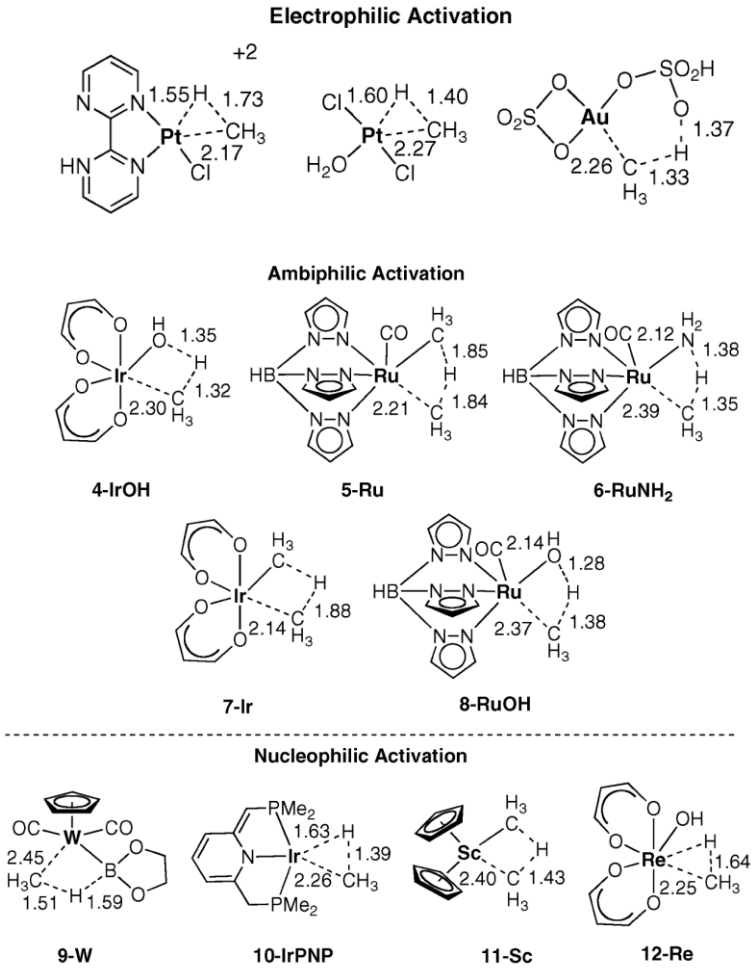
Stable!



Unstable

Wagner JP, Schreiner PR. *Angewandte Chemie International Edition* **2015**, *54* (42), 12274–12296.
Liptrot DJ, Power PP. *Nat Rev Chem* **2017**, *1* (1), 0004.
Goerigk L. A Comprehensive Overview of the DFT-D3 London-Dispersion Correction. In *Non-Covalent Interactions in Quantum Chemistry and Physics*; Elsevier, 2017; pp 195–219.

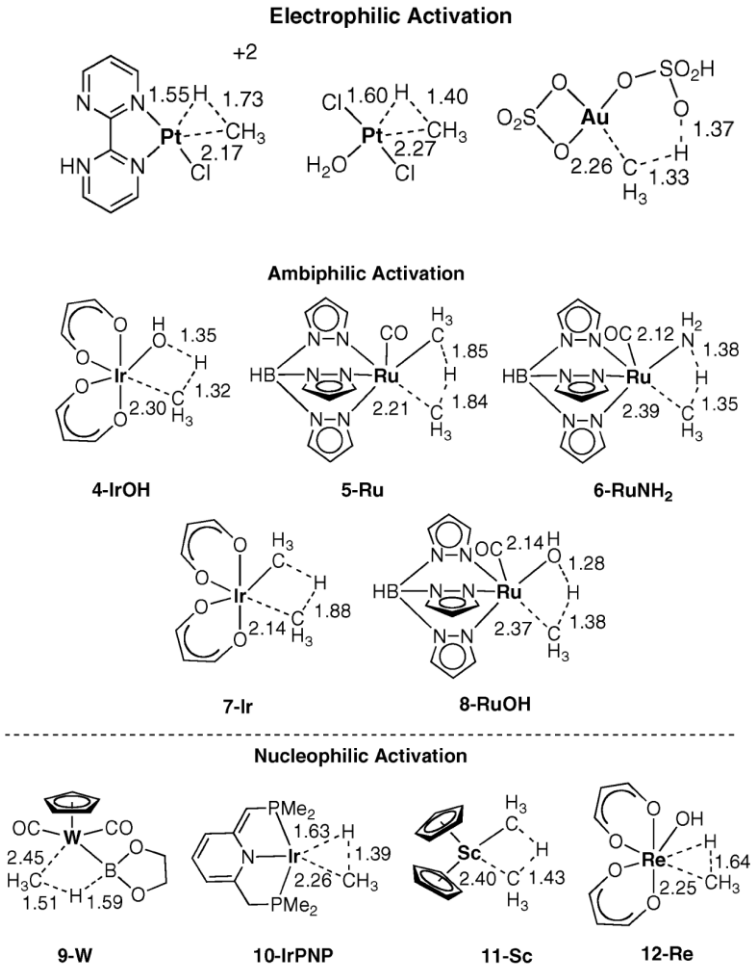
ALMO-EDA: Probing C-H Activation

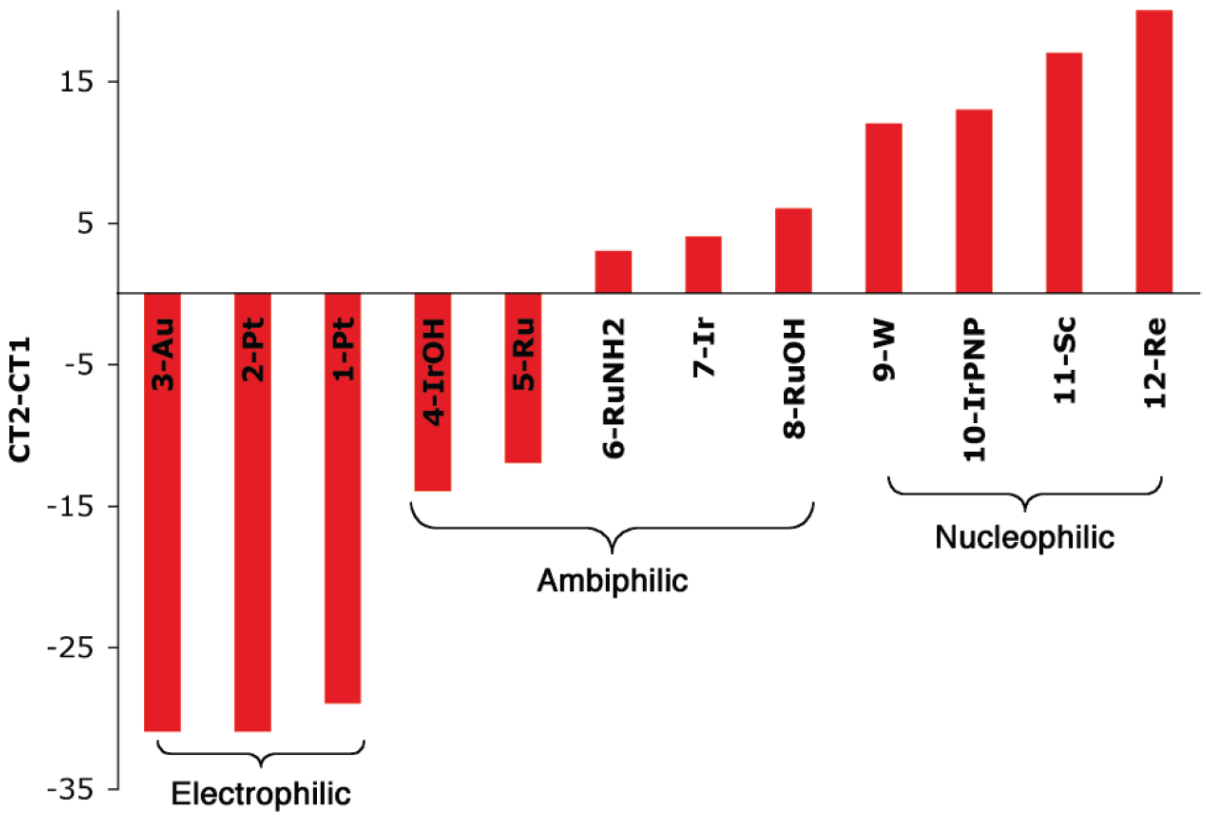


TS	E_{CT1}[a]	E_{CT2}[b]	E_{FRZ}	E_{POL}	E_{SE}[c]	E_{HO}[d]	E[e]
1-Pt[f]	**−40**	**−70**	53	−27	3	−1	−83
	(−52)	**(−60)**	(62)	(−27)	(3)	(−1)	(−74)
2-Pt	**−37**	**−55**	50	−19	3	−3	−60
3-Au	**−21**	**−52**	73	−43	3	6	−34
4-IrOH	**−25**	**−39**	90	−46	2	−1	−19
5-Ru	**−56**	**−68**	84	−48	2	1	−86
6-RuNH$_2$	**−28**	**−25**	84	−41	3	−2	−9
7-Ir	**−58**	**−54**	68	−26	3	0	−66
8-RuOH	**−32**	**−26**	88	−47	4	−2	−15
9-W	**−47**	**−35**	66	−25	3	−1	−40
10-IrPNP	**−40**	**−27**	47	−18	2	−1	−37
11-Sc	**−45**	**−21**	80	−32	2	−1	−17
12-Re	**−70**	**−44**	79	−28	3	3	−57

Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

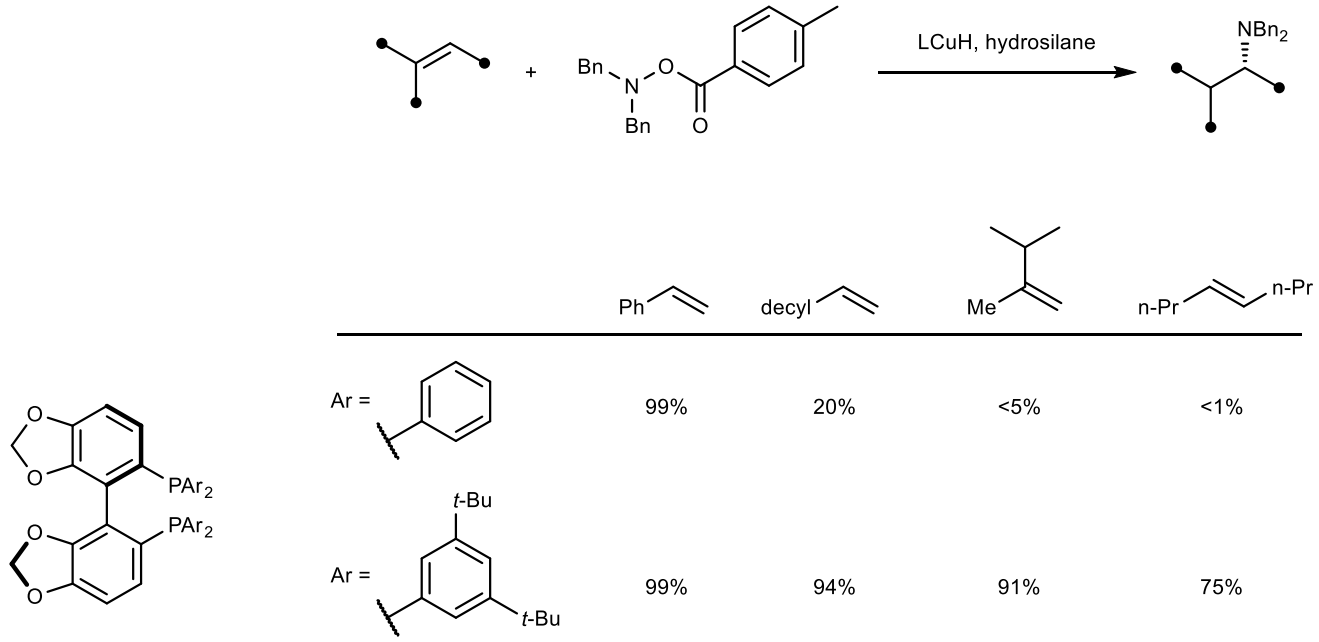
ALMO-EDA: Probing C-H Activation





Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.

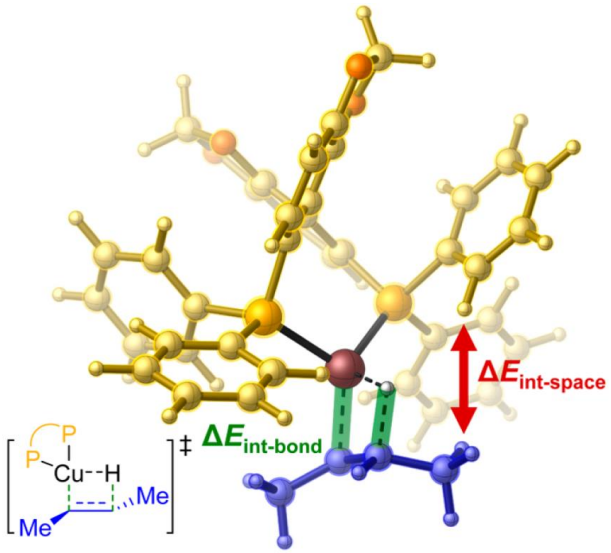
Ligand-Substrate Interaction: [Cu]-hydrocupration

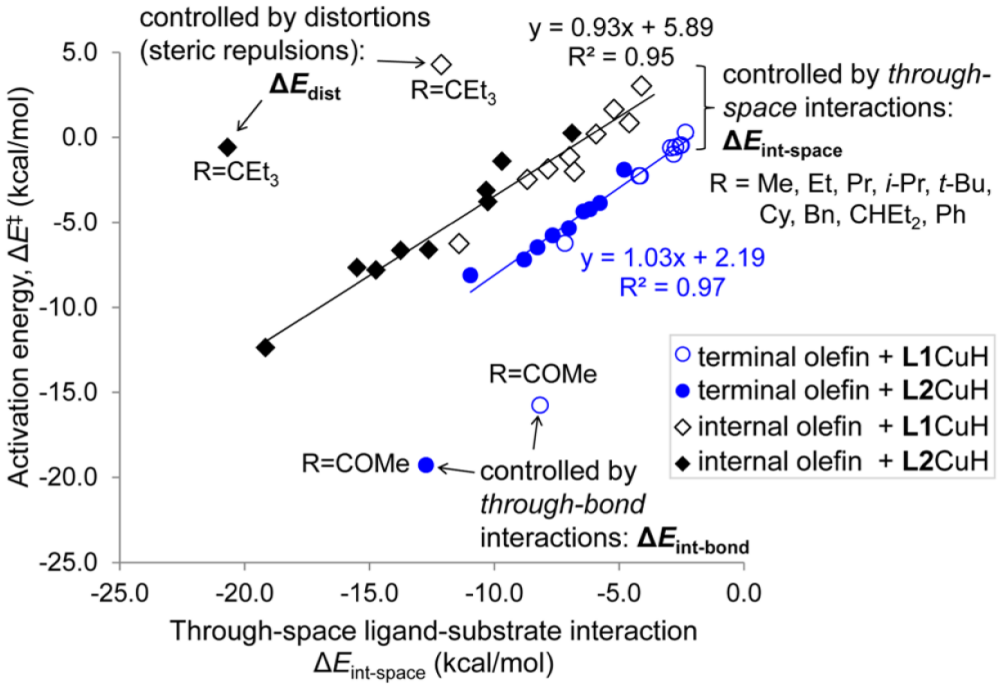


Term	Symbol	Meaning	Comment
Through space interaction	Int-space	Interactions between distorted ligand and substrate (CuH deleted)	Repulsion, polarization, charge transfer and dispersion
Through bond interaction	Int-bond	Residual when Distortion and through-space interactions are accounted for	

Lu G, Liu RY, Yang Y, Fang C, Lambrecht DS, Buchwald SL, Liu P. *J. Am. Chem. Soc.* **2017**, *139* (46), 16548–16555.

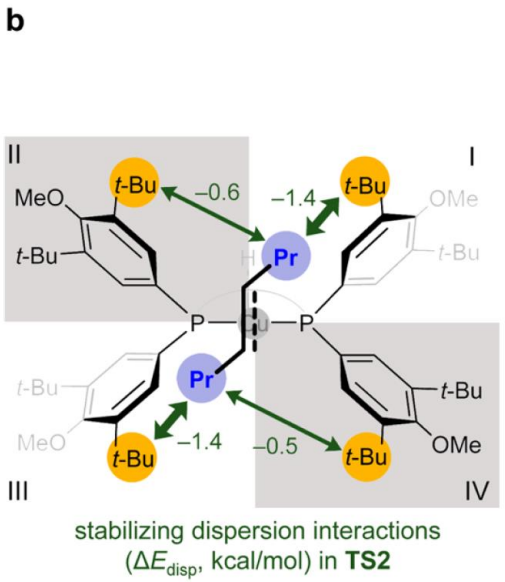
Ligand-Substrate Interaction: [Cu]-hydrocupration



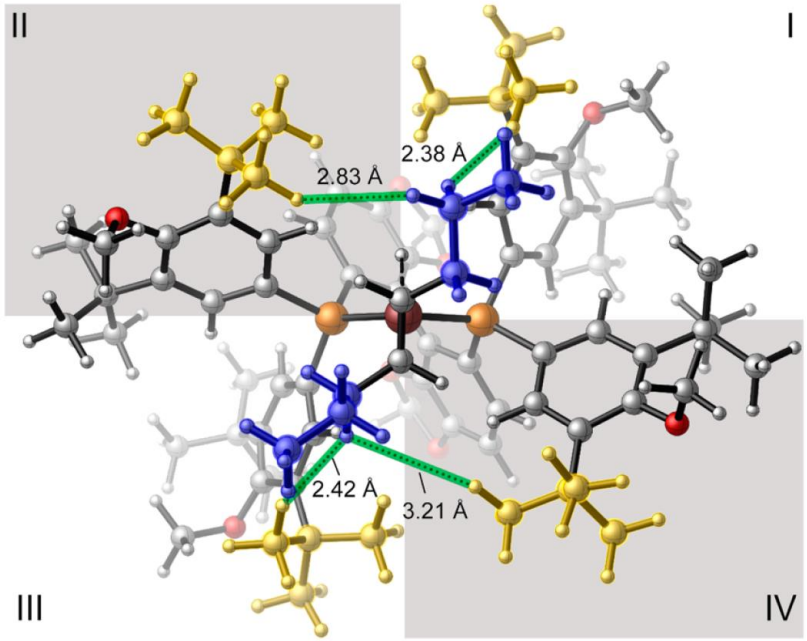


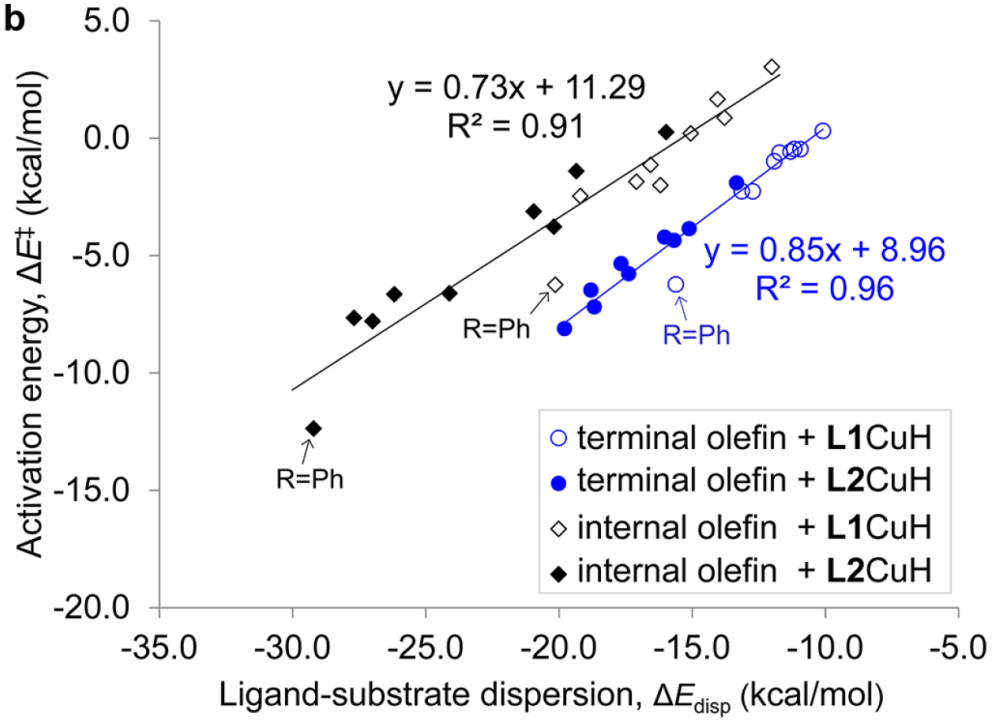
Lu G, Liu RY, Yang Y, Fang C, Lambrecht DS, Buchwald SL, Liu P. *J. Am. Chem. Soc.* **2017**, *139* (46), 16548–16555.

Ligand-Substrate Interaction: [Cu]-hydrocupration



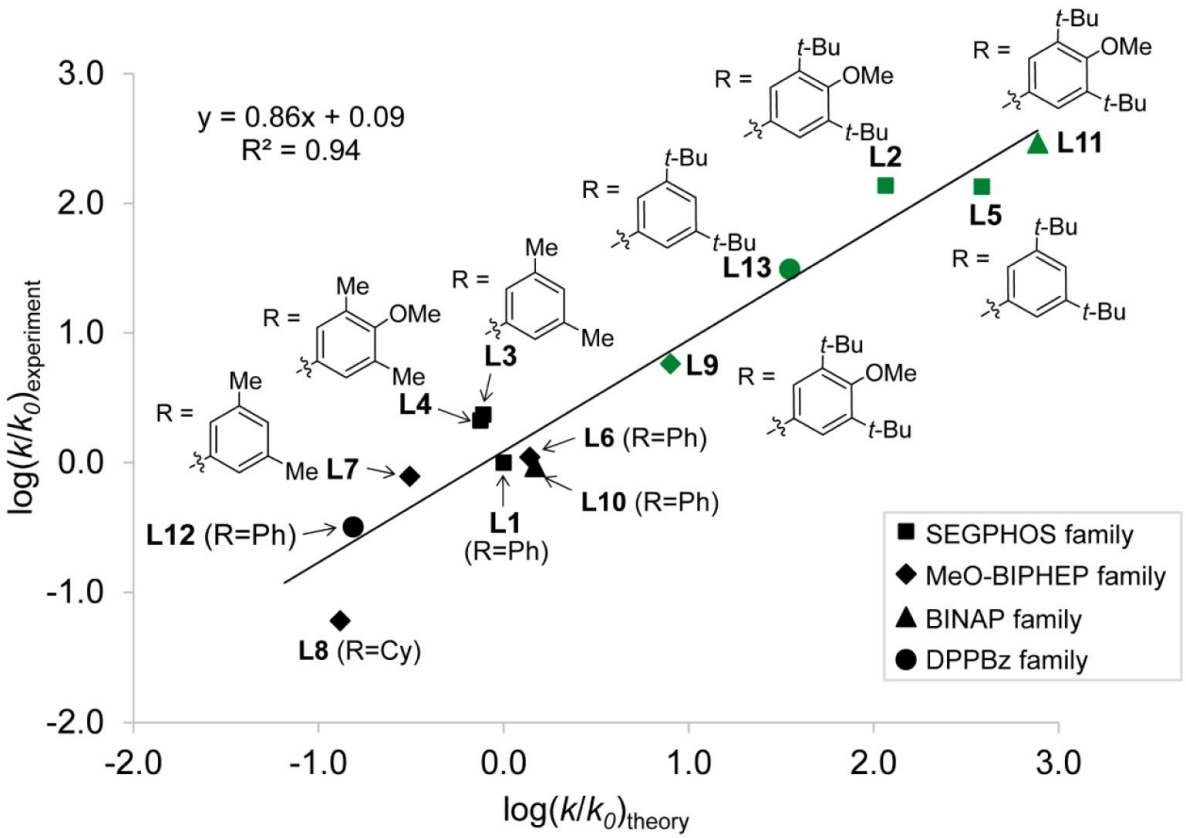
stabilizing dispersion interactions (ΔE_{disp}, kcal/mol) in **TS2**





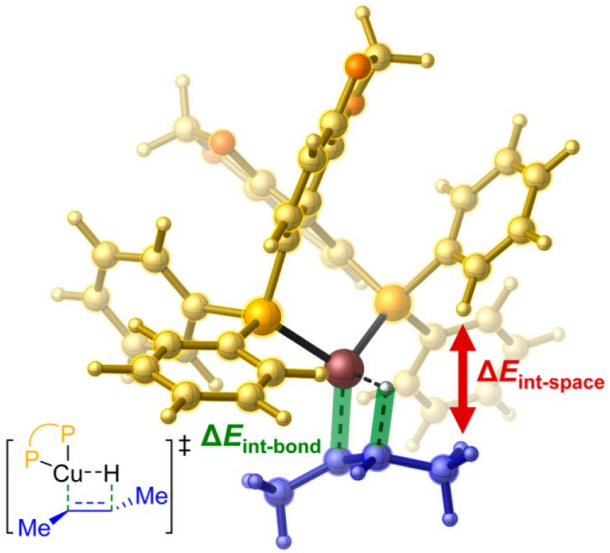
Lu G, Liu RY, Yang Y, Fang C, Lambrecht DS, Buchwald SL, Liu P. *J. Am. Chem. Soc.* **2017**, *139* (46), 16548–16555.

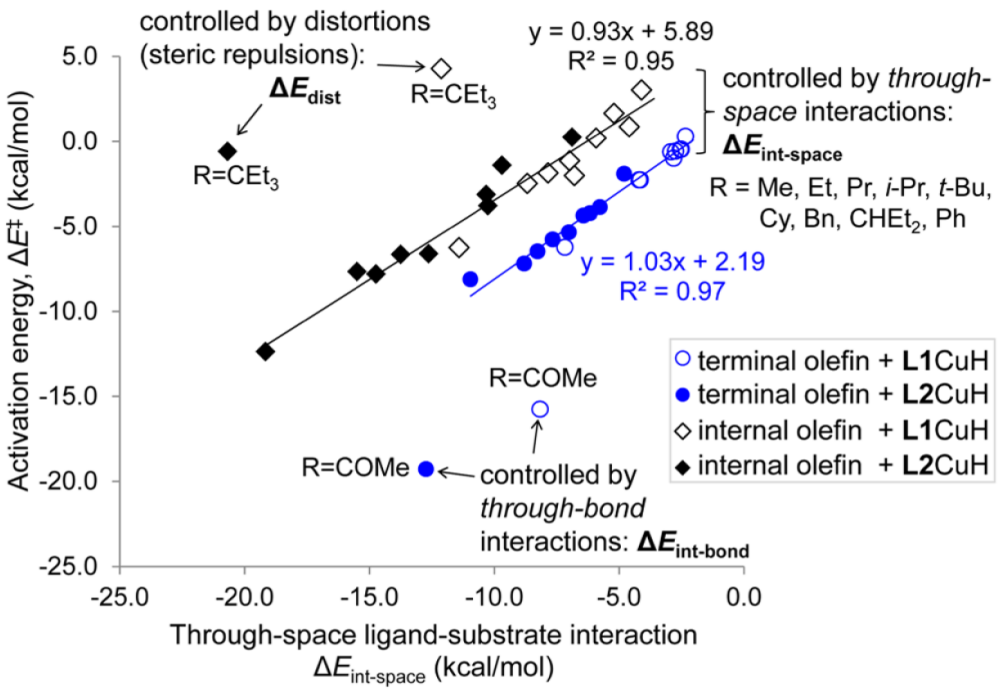
Ligand-Substrate Interaction: [Cu]-hydrocupration



Lu G, Liu RY, Yang Y, Fang C, Lambrecht DS, Buchwald SL, Liu P. *J. Am. Chem. Soc.* **2017**, *139* (46), 16548–16555.

Ligand-Substrate Interaction: [Cu]-hydrocupration

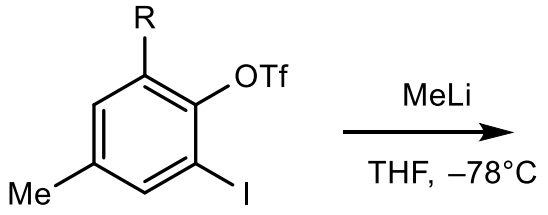




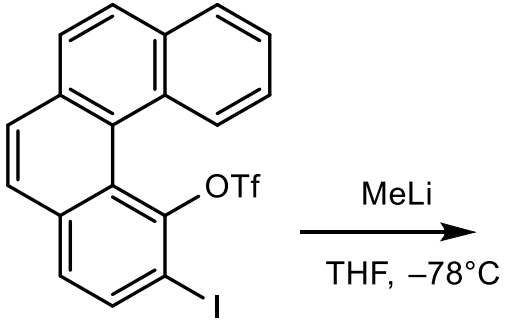
Thomas AA, Speck K, Kevlishvili I, Lu Z, Liu P, Buchwald SL. *J. Am. Chem. Soc.* **2018**, *140* (42), 13976–13984.

Group Problem

1. In a recent *JACS* publication it was reported that certain benzyne (2 + 2)-cycloadditions are highly regioselective. Attempt to guess the major isomer of the products and rationalize the selectivity. Propose a theoretical study that can corroborate your hypothesis.



R	ratio of isomers
Me	1.1 : 1
i-Pr	7.7 : 1
t-Bu	16 : 1
1-Ad	> 20 : 1



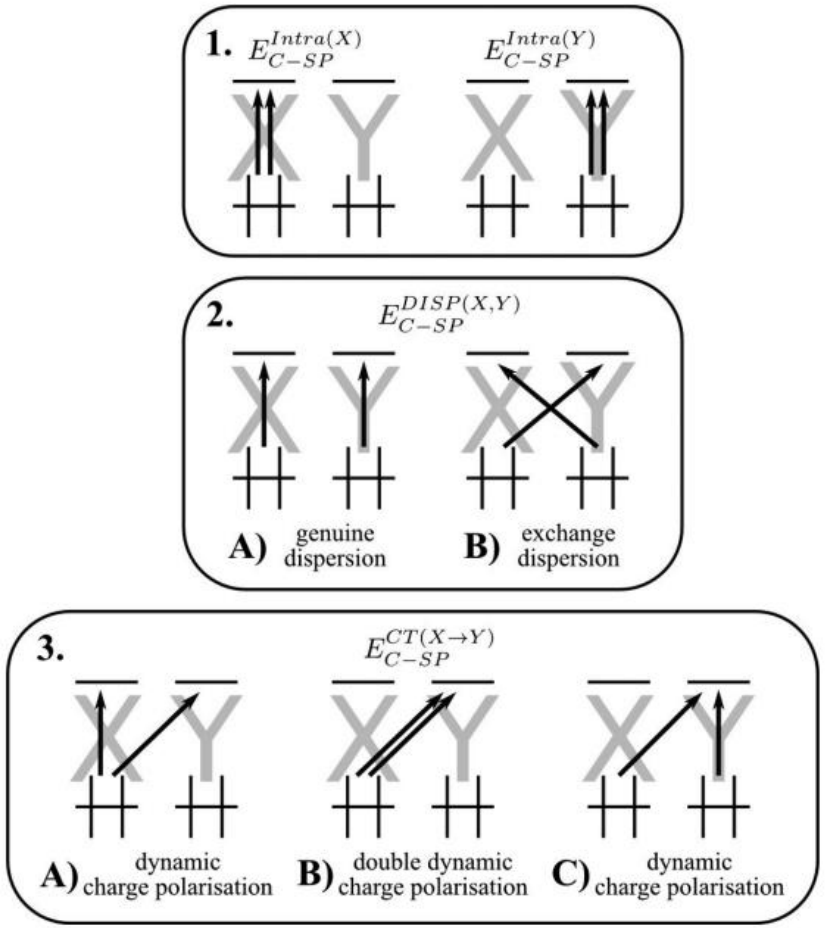
Ikawa T, Yamamoto Y, Heguri A, Fukumoto Y, Murakami T, Takagi A, Masuda Y, Yahata K, Aoyama H, Shigeta Y, Tokiwa H, Akai S. *J. Am. Chem. Soc.* **2021**, *143* (29), 10853–10859.

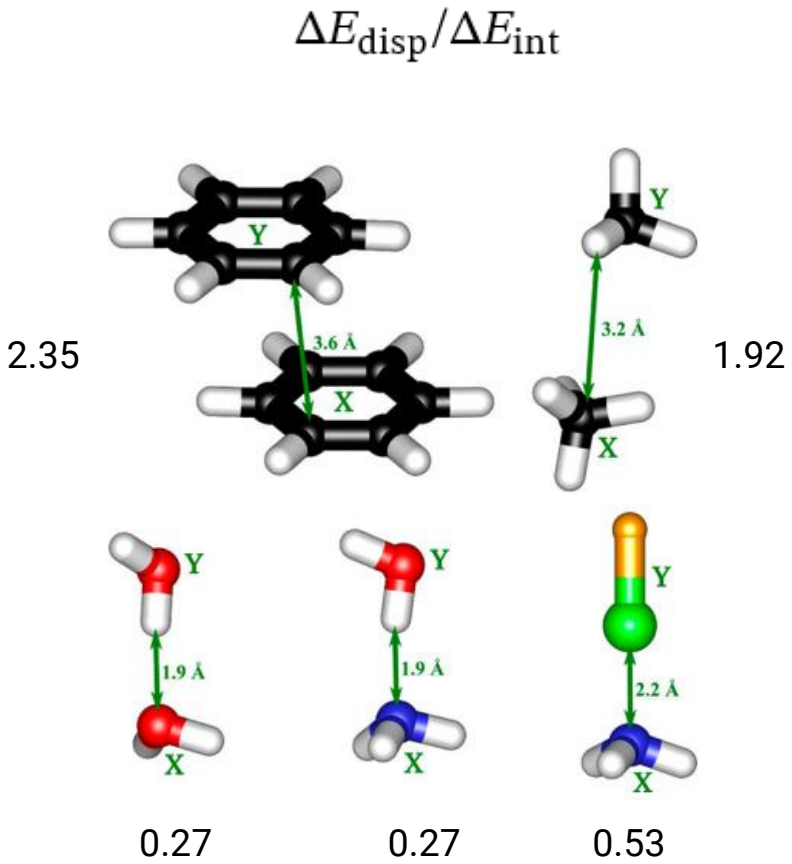
Part 5.
Outlook & Conclusion

Weak Non-Covalent Interaction Descriptions

Perspectives of EDA Methods

Partitioning of Dynamic Correlation





Schneider WB, Bistoni G, Sparta M, Saitow M, Riplinger C, Auer AA, Neese F. *J. Chem. Theory Comput.* **2016**, *12* (10), 4778–4792.

Take Home Messages

- There is a multitude of approaches
- There is a multitude of opinions about what does or does not give the *right* picture

- EDA is NOT about right/wrong or full/incomplete analysis.
  - All partitioning schemes are (±)-arbitrary, there are no true strictly separable elements.
  - Transferability of knowledge is more important
  - *Don't forget: "Computers don't solve problems people do". Not denying the importance and desire to obtain accurate numbers: don't forget that in the end it is the molecule and its chemistry or spectroscopy that we want to learn something about. The fact that you may be able to compute one or the other number a little more accurate doesn't mean that this helps us understanding the physics and chemistry of our target system any better. The danger of getting locked into technicalities and miss the desired insight is real!* [ORCA MANUAL]

- EDA components should be compared in terms of their *consistency/stability* with respect to method/basis/system.
  - So long as this can be ensured, there are enough tools

Reading Suggestions

Primary review sources

1. Bickelhaupt FM, Houk KN. *Angew. Chem. Int. Ed.* **2017**, *56* (34), 10070–10086.
2. S. Phipps MJ, Fox T, S. Tautermann C, Skylaris C-K. *Chemical Society Reviews* **2015**, *44* (10), 3177–3211.
3. Zhao L, Hopffgarten M von, Andrada DM, Frenking G. *WIREs Computational Molecular Science* **2018**, *8* (3), e1345.

Outlook and future directions

1. Andrés J, Ayers PW, Boto RA, Carbó-Dorca R, Chermette H, Cioslowski J, Contreras-García J, Cooper DL, Frenking G, Gatti C, Heidar-Zadeh F, Joubert L, Pendás ÁM, Matito E, Mayer I, Misquitta AJ, Mo Y, Pilmé J, Popelier PLA, Rahm M, Ramos-Cordoba E, Salvador P, Schwarz WHE, Shahbazian S, Silvi B, Solà M, Szalewicz K, Tognetti V, Weinhold F, Zins É-L. *Journal of Computational Chemistry* **2019**, *40* (26), 2248–2283.

Thanks for your attention!

Questions?