The Activation Strain Model

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The Activation Strain Model (ASM)

- Also referred to as Distortion Interaction Model
- The Activation Strain Model:
 - A fragment based approach which decomposes the potential energy surface into strain and interaction portions in an effort to understand the physical properties that are responsible for energy barriers.
 - Leads to rational design of efficient reactions
- Developed independently by Houk and Bickelhaupt



Before Using the ASM

- Before using ASM, first:
 - Locate transition state of interest
 - Scan From Reactant
 - Perform a steepest descent calculation to obtain the intrinsic reaction coordinate (IRC)
 - Scan back to Local Minima on each side



reaction coordinate

Using the ASM

- ASM decomposes energy into two terms:
 - $\odot \Delta E = \Delta E_{strain} + \Delta E_{int}$
 - ΔE_{strain} = geometric
 deformation of fragments
 (reactants) from a
 reference geometry
 - ΔE_{int} = interaction
 between fragments
 - The transition barrier occurs when the slope of $\Delta E_{strain} = \Delta E_{int}$



Interpreting the Activation Strain Diagram (ASD)



- Two hypothetical
 reactions A (black) and B
 (blue).
- Interaction energy is for reaction B is more stabilizing at any given point along the reaction coordinate
- Single point analysis would yield opposite conclusion!

Fernandez, I.; Bickelhaupt, F.M. Chem Soc Rev, 2014, 43, 4953 - 4967

Using Molecular Orbital Theory to Explain ΔE_{strain}

- ΔE_{strain}: MO theory can explain why structural deformation destabilizes a chemical species.
 - Walsh Diagram

$$H^{O_H} \longrightarrow H^{-O-H}$$



Using Energy Decomposition Analysis to Explain ΔE_{int}

- Energy Decomposition Analysis:
 - Adapted from Morokuma, Ziegler, and Rauk

$$\Delta E_{int} = \Delta V_{elstat} + \Delta E_{Pauli} + \Delta E_{oi} (+ \Delta E_{disp})$$

- $-\Delta V_{elstat}$ = Electrostatic Potential Energy
 - Usually attractive (negative) at chemically relevant distances
- ΔE_{Pauli} = Pauli Repulsion: Responsible for Steric Repulsion
 - Repulsive (positive)
- ΔE_{oi} = Orbital Interaction: Includes charge transfer and polarization
 - Stabilizing (negative)
- ΔE_{disp} = Dispersion Energy (arising from induced instantaneous polarization)
 - Repulsive at < 3.5 Å, attractive beyond 3.5 Å

Bickelhaupt et al., Comput. Mol. Sci., 2015, 5, 324-343

Frontside vs Backside $S_N 2$

• Bimolecular Nucleophilic Substitution



Purpose: To elucidate a causal relationship between the reactants' electronic structure and S_N2 reactivity



Bento, A.P.; Bickelhaupt, F.M. J. Org. Chem. 2008, 73, 7290-7299



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Applying ASM

- Activation Strain Model addresses the following questions:
 - 1. Why does the energy barrier increase when the nucleophile progresses from F to I?
 - 2. What physical properties of the reactants result in backside attack being favored over frontside attack?

Applying ASM to Assess Nucleophilicity



Bento, A.P.; Bickelhaupt, F.M. J. Org. Chem. 2008, 73, 7290-7299



Dominant orbital interaction is between occupied AO on X⁻ and CH₃Y σ^*_{C-Y}

Bento, A.P.; Bickelhaupt, F.M. J. Org. Chem. 2008, 73, 7290-7299

 $S_N 2$: Factors Controlling ΔE_{int}



- ΔE_{oi} becomes more negative due to weakening of C-Y bond
- ΔV_{elstat} becomes more negative because of positive charge buildup on the carbon.

Steeper Descent of ΔE_{int}

- = Earlier Transition State
 - = Lower Energy Barrier

Bento, A.P.; Bickelhaupt, F.M. J. Org. Chem. 2008, 73, 7290-7299

Activation Strain Analysis for Frontside vs Backside Attack



Bento, A.P.; Bickelhaupt, F.M. J. Org. Chem. 2008, 73, 7290-7299

Summary of $S_N 2$

- 1. Orbital Interaction term dictates nucleophilicity
 - Enhances stabilization from ΔV_{elstat}
- 2. Frontside attack is disfavored because Pauli repulsion makes the slope of E_{int} less steep

Case I: Oxidative Addition



Bickelhaupt, F.M.; J. Comput. Chem. 1999, 20, 114-128

Pd(0) Catalyzed Bond Activation Through Oxidative Insertion

					$\Delta E^{\pm/E_a}$ (kcal/mol)	ΔE _{strain} /E _{int} (kcal/mol)
Н—Н	+	Pd		H-Pd-H	-21.7 / 2.7	55.6 / -77.3
H ₃ C-H	+	Pd		H ₃ C-Pd-H	-1.6 / 6.4	53.5 / -55.1
H₃CH₂C−H	+	Pd	>	H ₃ CH ₂ C-Pd-H	-0.7 / 7.5	<mark>54.7</mark> / -55.4
H ₃ C-CH ₃	+	Pd		H_3C -Pd-C H_3	12.6 / 21.2	39.4 / -26.8
H ₃ C-Cl	+	Pd		H ₃ C-Pd-Cl	-4.3 / 9.6	<mark>8.8</mark> / -13.1

Strain and C-(H/C/Cl) Bond Stretch



Strain and C-(H/C/Cl) Bond Stretch



 ΔE_{strain} correlates with % stretch, but ΔE^{\dagger} does not!

 ΔE_{int} must be more thoroughly investigated to understand reaction barrier.

Energy Decomposition Analysis

 $\Delta E_{int} = \Delta V_{elstat} + \Delta E_{Pauli} + \Delta E_{oi} (All in kcal / mol)$



Analysis of ΔE_{oi}





Insertion into H-H

		номо	Номо	HOMO LUMO		
Orbital	σ* _{H-H}	4d	σ _{H-H}	5s		
E _{orbital} (eV)	-2.854	-4.193	-8.438	-3.423		
Overlap	0.3	00	0.5	566		
Population (e [−])	0.43	9.28	1.73	0.45		

E_{oi} = -102.3 kcal / mol

Insertion into C-H

	LUMO	номо	HOMOL	Jumo
Orbital	σ* _{C-H}	4d	σ_{C-H}	5s
E _{orbital} (eV)	-1.625	-4.193	-7.435	-3.423
Overlap	0.3	27	0.4	401
Population (e ⁻)	0.36	9.32	1.71	0.38
			· · · ·	

E_{oi} = -95.8 kcal / mol

Insertion into C-C LUMO HOMO HOMO LUMO Orbital σ^*_{C-C} 4d 5s $\sigma_{\text{C-C}}$ E_{orbital}(eV) -0.391 -4.193 -7.303 -3.423 Overlap 0.136 0.213 Population (e⁻) 0.25 9.42 1.83 0.22

E_{oi} = -79.9 kcal / mol

Insertion into C-Cl



E_{oi} = -48.7 kcal / mol

Summary of Pd(0) Catalyzed Bond Activation

				<u>ΔE[‡] / ΔE_{strain} / E_{int} (kcal/mol)</u>	$\frac{\Delta E_{Pauli} + \Delta E_{elstat} / E_{oi}}{(kcal/mol)}$
H-H	+	Pd	 H-Pd-H	-21.7 / <mark>55.6</mark> / -77.3	25 / -102.3
H ₃ C-H	+	Pd	 H₃C-Pd-H	-1.6 / <mark>53.5</mark> / -55.1	40.7 / -95.8
H₃C−CH₃	+	Pd	 H_3C -Pd-C H_3	12.6 / <mark>39.4</mark> / -26.8	53.5 / -93.3
H ₃ C-CI	+	Pd	 H ₃ C-Pd-Cl	-4.3 / <mark>8.8</mark> / -13.1	35.6 / -48.7

Anion Assistance



H-H Bond Insertion



H-H Bond Insertion



Reactivity with C-X bond

 $H_3C-CI + Pd \longrightarrow H_3C-Pd-CI$



Reactivity with C-X bond



Summary of Oxidative Addition

- The interplay between Strain and Interaction Dictate Reaction barriers:
 - H-H has highest strain energy, but lowest activation energy while C-Cl has second lowest barrier with lowest interaction energy
- Anion assistance steepens ΔE_{int} curve, resulting in an earlier transition state and a lower energy barrier.

Intermission

Case IIa: Exo Selective Diels Alder



Gouverneur, V; Houk, K. et al. JACS, 2009 ,131, 947-195

Exo vs Endo Selectivity



Distortion – Interaction Analysis



The reactants in the *endo* pathway are more distorted than the *exo* pathway, resulting in *exo* selectivity.

Strain in Transition State



Higher distortion in *endo* pathway is due to a more asynchronous TS





Summary of Exo Selective Diels Alder



Case IIb: MO₄ Cylcoaddition to Ethylene



M = Os, Re, Tc, Mn

• 3+2 vs 2+2

- It was known that 3+2 was the operative pathway
- It was also knows that Amine bases catalyzed the reaction
- Distortion / Interaction Analysis and Energy Decomposition Analysis employed to explain:
 - The mechanism of amine base catalysis
 - Reactivity differences between selected metals

32TS vs 22TS (OsO₄)



Ess, D. J. Org. Chem., 2009, 74, 1498-1508

32TS vs 22TS (OsO₄): uncatalyzed



	ΔE^{\pm}	$\Delta E_{\rm d}^{\pm}$	$\Delta E_{\rm d}$ [‡]	
	$[\Delta E_{\rm rxn}]$	(MO_4)	(C_2H_4)	ΔE_{i}^{*}
uncatalyzed	l			
32TS	4.9 [-33.4]	10.2	4.3	-9.5
22TS	44.9 [6.2]	21.3	10.9	12.7

- OOsO bond angles equally distorted
- Os-O bond in 22TS more distorted
- 22TS later than 32TS

Ess, D. J. Org. Chem., 2009, 74, 1498-1508

32TS vs 22TS (OsO_4): catalyzed



NH3-32TS	4.2 [-41.0]	5.9	3.9	-5.5
NH ₃ -22TS	44.7 [14.8]	34.1	18.2	-7.6

- case
- 22TS more distorted ۲ than uncatalyzed case

Distortion Interaction Analysis: 32TS Uncatalyzed Case



OsO₄ remains approx 5kcal / mol distorted than ethylene throughout the entire surface

Distortion Interaction Analysis: Uncatalyzed Case



 Positive Interaction Energy!

Current Analysis

• Answered Questions:

Q: Why is the 3+2 TS preferred over the 2+2 TS?

A: The 3+2 pathway has an earlier, less distorted TS.

Q: Why does the presence of an amine ligand catalyze the reaction?

A: The amine NH_3OsO_4 complex is distorted less in the TS, resulting in a lower energy barrier

- Unanswered Questions:
 - How do we interpret positive interaction energy?
 - Can the reactivity of Osmium be understood in terms of its electronic structure?
 - Can similar analysis explain the reactivity of other metals?

Absolutely Localized Molecular Orbital Interaction Decomposition Analysis

• ALMO-EDA:

$\Delta E_{int} = \Delta E_{FRZ} + \Delta E_{POL} + \Delta E_{CT} + \Delta E_{HO}$

- ΔE_{FRZ} : Frozen Electron Densities: Includes Coulombic interaction and exchange / correlation.
- ΔE_{POL} : Polarization
- $-\Delta E_{CT}$: Charge Transfer
- $-\Delta E_{HO}$: Higher order orbital relaxation effects (includes all induction effects)

Positive interaction energy



	(I KE)	(101)	(01)	2 1	•	(110)	(111)
32TS	41.7	-2.4	-61.3	-7.2	-54.1	15.6	-6.4
22TS	89.7	-25.7	-41.8	-17.5	-24.2	-5.5	16.7

Comparison Across Metals: Distortion, Interaction and Energy Barrier



Ess, D. J. Org. Chem., 2009, 74, 1498-1508

EDA at Nonstationary Points

				$MO_4 \rightarrow$	$C_2H_4 \rightarrow$		
	$\Delta E_{(FRZ)}$	$\Delta E_{(POL)}$	$\Delta E_{(\rm CT)}$	C_2H_4	MO_4	$\Delta E_{\rm (HO)}$	$\Delta E_{(INT)}$
$\overline{\mathrm{OsO}_4 + \mathrm{C}_2\mathrm{H}_4}$	44.1	-3.3	-62.5	-7.5	-55.0	15.4	-21.7
$\operatorname{ReO_4^-} + \operatorname{C_2H_4}$	53.0	-6.8	-23.8	-12.5	-11.2	-3.2	22.4
$T_{0}O_{1}^{-} \perp C_{1}U_{1}$	95.4 128.0	-14.3 -21.7	-63.5 -115.8	-25.8 -36.8	-37.6 -79.0	$-3.4\\10.5$	17.7 —9.5
$100_4 + 0_2 n_4$	52.2	-6.9	-27.6	-12.9	-14.8	-3.8	17.6
$MnO_4^- + C_2H_4$	127.2	-22.6	-156.5	-38.0	-118.5	35.4	-51.8
	50.9	-7.7	-35.6	-13.7	-21.9	-4.5	7.6

Ess, D. J. Org. Chem., 2009, 74, 1498-1508

Distortion / Interaction Curve



MO₄ Cylcoaddition to Ethylene: Summary

- Charge transfer from ethylene to OsO₄ is most efficient because low-lying LUMO of OsO₄
- MnO₄⁻ is an active oxidant because of its early TS

 Low strain
- TcO₄⁻ and ReO₄⁻ are less active because of their later TS.
 - $-\Delta E_{\text{int}}$ develops more slowly due to less stabilization from charge transfer

Summary

 ASM or Distortion / Interaction analysis can be used in a variety of ways to show the physical origin of energy barriers

Frequently used with EDA

- The PES can be decomposed in multiple different ways:
 - Method of decomposition is at the discretion of the practitioner