Chem 634

Pericyclic Reactions

Reading:
CS-B Chapter 6
Grossman Chapter 4
Pericyclic Reactions

Definition: Continuous, concerted reorganization of electrons

- cyclic transition state
- no intermediate, single transition state

Bond breaking & bond making occur at the same time.

Can be synchronous (equal extent of breaking & making in TS) or asynchronous (unequal extent of breaking & making in TS).

Fukui & Hoffmann: Nobel Prize in Chemistry, 1981, “for… their theories, developed independently, concerning the course of chemical reactions” (Woodward dies in 1979)
5 Types

1. Electroyclic
2. Cycloadditions
3. Sigmatropic
4. Chelatropic
5. Group Transfer
3 Theories

All 3 theories are correct!

1. Woodward–Hoffmann: Conservation of Orbital Symmetry
   • 1st historically
   • Uses correlation diagrams
2. Fukui: Frontier Molecular Orbital Theory
   • Easier than Woodward–Hoffmann (usually)
   • Based on HOMO/LUMO interactions
3. Dewar–Zimmerman: Aromatic Transition State
   • Easiest to apply for all reaction types, but not intuitive to understand why it’s valid
3 Things Matter

1. Number of electrons involved
2. Stereospecificity
3. Conditions: heat (Δ) vs. light (hu)
Type 1: Electrocyclic Reactions

- Ring openings and closures
- Exchange $\pi$-bond for $\sigma$-bond
- Classified by number of electrons

$\text{R} \xrightarrow{4e^-} \text{R} \xrightarrow{\text{Double bonds in configuration in SM or Pd}} \xleftarrow{\text{lb}e^-} \text{R} \xrightarrow{\text{R}} \xleftarrow{\text{lb}e^-} \text{R} \xrightarrow{\text{2e}^-} \xleftarrow{\text{2e}^-}$
Diastereoselectivity – Observations

Case 1:

\[
\text{R} - \text{R} \xrightarrow{\Delta \ 4e-} \text{R} \quad (\pm) \quad \text{R}
\]

Case 2:

\[
\text{R} - \text{R} \xrightarrow{h\nu \ 4e-} \text{R} \quad \text{R}
\]

Case 3:

\[
\text{R} \quad \text{R} \quad \xrightarrow{\Delta \ 6e-} \text{R}
\]

Case 4:

\[
\text{R} \quad \text{R} \quad \xrightarrow{h\nu \ 6e-} \text{R} \quad (\pm)
\]
General Phenomenon… Woodward–Hoffmann Rules

<table>
<thead>
<tr>
<th>Number of electrons</th>
<th>Thermal</th>
<th>Photochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>4n</td>
<td>Con</td>
<td>Dis</td>
</tr>
<tr>
<td>4n+2</td>
<td>Dis</td>
<td>con</td>
</tr>
</tbody>
</table>

\[(n = \text{integer})\]

6 points for a touchdown $\rightarrow$ 6e-, thermal, disrotatory

... But why???
Theory #1: Woodward–Hoffmann Correlation Diagrams


- Consider all molecular orbitals (MO’s) involved
- Consider symmetry of MO’s in starting material, product, and transition state.
- Orbitals of different symmetry can cross (orthogonal orbitals).
- Orbitals of same symmetry *cannot* cross (extreme energetic cost).
- We are about orbitals where electrons end up.
Example of W–H Correlation Diagrams

\[ \text{disrotatory TS} \quad \xrightarrow{\text{S-plane symmetry}} \quad \text{conrotatory TS} \]

$\sigma^*_{SM}$ \quad $\sigma_P$

$180^\circ \quad C_2$ axis of symmetry
Example of W–H Correlation Diagrams: Thermal Conditions

- **σ-plane of symmetry**
- **C₂ axis of symmetry**

**Disrotatory TS**
- \( \sigma_{SM} \) and \( \sigma_{P} \)
- \( \psi_1 \), \( \psi_2 \), \( \psi_3 \), \( \psi_4 \)

**Conrotatory TS**
- \( C_{2-sm} \) and \( C_{2-p} \)

*Favored*
Example of W–H Correlation Diagrams: Photochemical Conditions

- **σ**-plane of symmetry
- **C**<sub>2</sub> axis of symmetry
- **σ**<sup>SM</sup> and **σ**<sub>P</sub>
- **C**<sub>2-SM</sub> and **C**<sub>2-P</sub>

Disrotatory TS:
- **A** – Favorable
- **S** – Disfavorable

Conrotatory TS:
- **A** – Favorable
- **S** – Disfavorable

**ψ<sub>1</sub>**, **ψ<sub>2</sub>**, **ψ<sub>3</sub>**, **ψ<sub>4</sub>**

Con pathway: **disfavored**
**W–H Conservation of Orbital Symmetry Shortcut**

- **σ-plane of symmetry**
- **C₂ axis of symmetry**

**disrotatory TS**

**conrotatory TS**

Ψ₂
(HOMO)
Cycloadditions & Cycloreversions

- Union of 2 π-systems
- Exchange π-bonds for σ-bonds
- Classified by \([m+n]\), \(m \& n\) = # of conjugated atoms in each π-system

Diels–Alder Reaction!
Note: 6 e-
Great way to make cyclohexenes & cyclohexanes
Fukui: Frontier Molecular Orbital (FMO) Theory

The idea: Use FMO’s (HOMO + LUMO)

\[ \Delta E \propto \text{orbital overlap} \]

If closer in energy, then more stability by forming a covalent bond.

In this case, it doesn’t matter… HOMO/LUMO gaps are the same.

Which HOMO & LUMO?

diene
dienophile

nonbonding level
Types of Diels–Alder Reactions

Normal electron demand $= \text{HOMO of diene} + \text{LUMO of dienophile}$

Inverse electron demand $= \text{HOMO of dienophile} + \text{LUMO of diene}$
Net Bonding Interaction?

The idea: Use FMO's (HOMO + LUMO)

diene
dienophile
Diastereoselectivity: Endo vs. Exo

\[ \text{[4+2]} \]

- **Endo (favored):** Major
- **Exo:** Minor

**Syn → Stereospecific**

**Steroselectivity**
Why? ... Secondary Orbital Interactions
Regioselectivity & Rates: Substituent Effects

Rates depend on HOMO/LUMO gap.

<table>
<thead>
<tr>
<th>Perturbation</th>
<th>HOMO</th>
<th>LUMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>extra conjugation</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>electron-withdrawing group</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>electron-donating group</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Effects apply to both dienes & dienophiles.
Effect of substitution is biggest if on C1 of diene.
Examples

\[ \text{Example 1: } \text{rt, 24 h} \]

\[ \text{Example 2: } 165 ^\circ \text{C, 12,600 psi, 17 h} \]
Regioselectivity

Related to polarization of HOMO and/or LUMO

Quick prediction: “imaginary intermediate”
(push arrows to get maximum effect of substituents)

... but remember these reactions are **concerted**!!!
Lewis Acid Effects

One of the first Lewis acid-accelerated organic transformations!

Lewis acid increases rate, endo/exo selectivity & regioselectivity!

Yates, Eaton. *JACS* 1960, 82, 4436
Why???

MO perturbation!

More reactive, more like

Explains rates, but what about selectivity issues???

Houk *JACS* 1973, 95, 4094
Why???

Bigger difference in lobe size on C1 vs. C2 = better regioselectivity

Lower LUMO = faster rate

Bigger lobe on C=O carbon = bigger 2° orbital interactions = better endo/exo selectivity

Houk *JACS* 1973, 95, 4094
One More Consideration: S-cis vs. S-trans

S-cis reactive
S-trans not reactive!

\[
\begin{align*}
\text{cis} & \quad \text{trans} \\
& \quad \text{reactive!} \\
\end{align*}
\]

\[
\begin{align*}
& \quad + \\
& \quad \rightarrow \\
& \quad k_{rel} \\
& \quad 1 \\
& \quad 4 \\
& \quad 10^{-3} \\
& \quad 10^3
\end{align*}
\]

\[
\begin{align*}
& \quad + \\
& \quad \rightarrow \\
& \quad \text{Me}
\end{align*}
\]
[2+2] Cycloadditions

FMO Analysis:
- No net bonding… “forbidden”
- This geometry is suprafacial on both π bonds ⇒ [2πs + 2πs]

Suprafacial = same face of π-system
Antarafacial = opposite faces of π-system
Alternative Transition State Geometry

Problem: Steric Hindrance!

Solution: Remove steric hindrance!

Net bonding!  SUPRAFACIAL ON LUMO \( [2\pi + 2\pi] \)
ANTARAFACIAL ON HOMO \( \text{ALLOWED!} \)
Sigmatropic Reactions

- Reorganization of σ and π bonds (migration of a σ-bond)
- Number of σ and π bonds remains constant
- Classify by [m,n]-rearrangement or [m,n]-shift (m, n = number of atoms in fragment)
[1,3]-Sigmatropic Rearrangement

Does this rearrangement proceed under thermal conditions?
Supra- or antara-facial??

For FMO, break into HOMO and LUMO:

H° \rightarrow \text{LUMO}

\text{HOMO} \rightarrow \gamma

Suprafacial on allyl \text{Forbidden}

antara facial on allyl \text{Allowed}
[1,3]-Sigmatropic Rearrangements

Alkyl Shift?

FMO:

Forbidden

Antara inversion

Supra

Strained → rare
[3,3]-Sigmatropic Rearrangements

\[
\begin{align*}
\text{FMO Analysis:} & \\
\text{2 Allyl radicals:} & \\
\text{or} & \\
\text{Allyl cation & anion:} & \\
\text{Suprafacial on both components!} & \\
\text{Highly predictable TS \rightarrow “chair-like” (can predict stereochem)}
\end{align*}
\]
Claisen Rearrangement

$\Delta G < 0$

$C=O \pi > C-C \pi$
Oxy-Cope

2) Tautomerization of PhH: Oxy-Cope.

neutral: \( \text{PhH} \) \( k_1 \) \( \text{PhH} \) \( k_2 \) \( \text{PhOH} \) \( k_2 \) \( \text{Ph}^- \) 

anionic:

\[ \frac{k_2}{k_1} = 10^{10} - 10^{17} \]

\[ \text{JACS 1975, 97, 4465.} \]

why? Ground-state destabilization

\[ \varepsilon \]

TS stabilization

stabilizes radical character on allyl fragment

\[ \Rightarrow \text{Asynchronous (bond breaks more than bond forms in TS)} \]
Theory #3: Dewar–Zimmerman: Aromatic Transition State

Steps:
1. Choose basis set of 2p AO’s (or 1s for H atoms)
2. Assign phases (any phases)
3. Connect orbitals that interact in the starting material
4. Connect lobes that begin to interact in the reaction
5. Count the number of phase inversions
6. Identify topology
   1. Odd # of phase inversions = Möbius
   2. Even # of phase inversions = Hückel
7. Assign Transition State as aromatic (thermally allowed) or antiaromatic (photochemically allowed)

<table>
<thead>
<tr>
<th>System/Topology</th>
<th>Aromatic</th>
<th>Antiaromatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huckel</td>
<td>(4n+2) e-</td>
<td>(4n) e-</td>
</tr>
<tr>
<td>Mobius</td>
<td>(4n) e-</td>
<td>(4n+2) e-</td>
</tr>
</tbody>
</table>
Example of D–Z Theory

1 phase inversion
Mobius
4n (n=1)

Allowed