Pericyclic Reactions
6 Lectures • Year 3
Handout 2 • Michaelmas 2017

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Cycloadditions: oxyallyl cation

\[ \text{HOMO diene} \quad \text{constructive overlap} \quad ✓ \\
\text{LUMO allyl cation} \]

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
Total = 1
odd ✓
allowed

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\[ \text{HOMO \( \omega \)} \]
\[ \text{LUMO} \]

\[ \text{constructive overlap} \quad ✓ \]
\[ \text{disrotatory} \]
Cycloadditions: allyl cation & allyl anion

- **Allyl cation-diene**

  ![Diagram of allyl cation-diene reaction]

  - **Allyl anion-alkene and reverse process**

  ![Diagram of allyl anion-alkene and reverse process reaction]

- **HOMO allyl anion**

  - Constructive overlap ✓

- **LUMO alkene**

  - (4q + 2)_s = 1
  - (4r)_a = 0
  - Total = 1
  - Odd ✓
  - Allowed

Total = odd ✓ allowed
Cycloadditions: allyl cation & allyl anion

- Allyl anion-alkene (reverse process)

\[
\text{BuLi} \quad \text{Ph} \quad \text{PhCO}_2
\]

\[
\sigma^2 + \omega^2 = (4q + 2)_s = 3
\]

\[
(4r)_a = 0
\]

Total = 3

odd ✓ allowed

HOMO \(\omega\)

LUMO \(\sigma + \sigma\)

constructive overlap ✓

- It can be easier to analyse the reverse reaction.
1,3-dipolar cycloadditions

- **sp²-hybridized central atom**

\[
\begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\xrightarrow{\pi^4 s \pi^2 s}
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\xrightarrow{\pi^4 s \pi^2 s}
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\xrightarrow{\pi^4 s \pi^2 s}
\end{array}
\]

1,3-dipole

- **azomethine ylid**
- **azomethine imine**
- **carbonyl oxide**
- **carbonyl ylid**
- **nitrone**
- **ozone**

- **sp-hybridized central atom**

\[
\begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\xrightarrow{\pi^4 s \pi^2 s}
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\text{Z}
\end{array}
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\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\xrightarrow{\pi^4 s \pi^2 s}
\end{array}
\]

1,3-dipole

- **nitrile ylids**
- **nitrile oxides**
- **diazooalkanes**
- **nitrile imines**
- **alkyl azides**
- **nitrous oxide**
1,3-dipolar cycloadditions: ozonolysis

\[
\pi^2_s \quad \pi^4_s \\
\text{HOMO alkene} \quad \text{LUMO ozone} \quad \text{HOMO carbonyl} \quad \text{LUMO carbonyl ylid}
\]

\[
\text{(4q + 2)}_s = 1 \\
\text{(4r)}_a = 0 \\
\text{Total = 1} \\
\text{odd} \checkmark \quad \text{constructive overlap} \checkmark \\
\text{allowed}
\]

\[
\text{HOMO allyl anion}
\]

\[\psi_2\]
1,3-dipolar cycloadditions: azomethine ylids

\[(4q + 2)_s = 1\]
\[(4r)_a = 0\]
Total = 1
odd ✓ allowed
cconrotatory

\[\text{constructive overlap ✓ conrotatory}\]
Nitrone cycloadditions in synthesis

Nitrones are readily formed between aldehydes and substituted hydroxylamines

\[ \text{R-NHOH} + \text{R'C'HH} \rightarrow \text{R-N'O'R'} \]

Histrionicotoxin

Azomethine ylids in synthesis

Azomethine ylids in synthesis II

i) NaBH₄
ii) SOCl₂

i) Bu₃SnH, AIBN

i) DIBAL
ii) Ph₃P=CH₂

H⁺, H₂O

Na, NH₃, iPrOH

MeOH, MeOH
Cheletropic reactions

- A sub-class of cycloaddition/cycloreversion reactions in which the two $\sigma$ – bonds are made or broken to the same atom (compare with ketenes as vinyl cations)

Addition of singlet carbenes (stereospecific) is most important: side on approach necessary:
The addition of sulfur dioxide to polyenes is a reversible process.
Cheletropic reactions: sulfur dioxide and polyenes

With trienes the extrusion process dominates but considering the reverse process, the reaction must be antarafacial with respect to the triene component.

\[
\text{HOMO SO}_2 \xleftarrow{\text{constructive overlap}} \text{LUMO SO}_2
\]

too strained; \( \text{ca. } 10^4 \text{ times less reactive than } \text{so}_2 \)
Cheletropic reactions: sulfur dioxide and polyenes

The cheletropic extrusion of SO₂ is often used in synthesis to unmask a diene, as a prelude to a Diels-Alder or other cycloaddition.

Application in the synthesis of a steroid core

Application in the synthesis of columbiasin
Electrocyclic reactions

Thermal electrocyclic processes will be conrotatory if the total number of electrons is $4n$ and disrotatory if the total number of electrons is $(4n + 2)$.

This is reversed for photochemical reactions.

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
\[ \text{Total} = 1 \]
\[ \text{odd} \checkmark \]
\[ \text{allowed disrotatory} \]

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
\[ \text{Total} = 1 \]
\[ \text{odd} \checkmark \]
\[ \text{allowed disrotatory} \]

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
\[ \text{Total} = 1 \]
\[ \text{odd} \checkmark \]
\[ \text{allowed conrotatory} \]

Symmetry allowed but geometrically constrained

Does not occur
Electrocyclic reactions

\[ (4q + 2)_s = 0 \]
\[ (4r)_a = 0 \]
\[ \text{Total} = 0 \]
\[ \text{even} \checkmark \]
\[ \text{allowed conrotatory} \]

\[ \text{Cyclopropyl cation / allyl cation interconversion} \]

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
\[ \text{Total} = 1 \]
\[ \text{odd} \checkmark \]
\[ \text{allowed disrotatory} \]

Lewis acid, low temperature
The ionisation of cyclopropyl halides and tosylates is a concerted process to give allyl cations (i.e. discrete cyclopropyl cations are not formed). The reaction can be viewed as an internal substitution in which the electrons in a σ-bond (HOMO) feed into the C-X σ* (LUMO).

The reaction is disrotatory and the sense of rotation (torquoselectivity) is specified – this dictates the geometry of the allyl cation and can have a large influence on reaction rate.

Influence on rates – solvolysis in acetic acid
Electrocyclic reactions: Nazarov cyclization

The analogous anionic pentadienyl anion cyclization is also electrocyclic

The analogous anionic pentadienyl anion cyclization is also electrocyclic
Pericyclic reactions & natural products: the endiandric acids

endiandric acid A methyl ester

endiandric acid B methyl ester

endiandric acid C methyl ester

endiandric acid D methyl ester

endiandric acid E methyl ester

endiandric acid F methyl ester

endiandric acid G methyl ester

Diels–Alder

Diels–Alder

Diels–Alder

6π electrocyclic

6π electrocyclic

6π electrocyclic

8π electrocyclic

8π electrocyclic

Pericyclic reactions & natural products: the endiandric acids

**H₂ Lindlar**

heat 100 °C

**exo-Diels Alder reaction**

**endiandric acid A methyl ester**

**endiandric acid E methyl ester**

**endiandric acid D methyl ester**

8π electrocyclic conrotatory

6π electrocyclic disrotatory

6π electrocyclic disrotatory
Pericyclic reactions & natural products: the endiandric acids

endiandric acid B methyl ester
heat, 100 °C → exo-Diels Alder reaction
endiandric acid F methyl ester

endiandric acid C methyl ester
endiandric acid G methyl ester

endo-Diels Alder reaction

6π electrocyclic disrotatory

8π electrocyclic conrotatory

H₂ Lindlar
Synthetically the most important sigmatropic rearrangements are the Cope and Claisen rearrangements and variants thereof.

The Claisen/Cope rearrangements can proceed via chair-like or boat-like transition states – the chair-like transition state is strongly favoured unless there are steric constraints that force a boat-like transition state.

Where possible, substituents generally adopt equatorial sites in the chair-like transition state.
Claisen rearrangements

(4q + 2)s = 3
(4r)a = 0
Total = 3
odd ✓
allowed

Diequatorial
trans, trans - major
diaxial
cis, cis - minor

cis, trans
Claisen and Cope variants

- Johnson-Claisen rearrangement - synthesis of γ,δ-unsaturated esters.

- Eschenmoser-Claisen rearrangement

- Carroll rearrangement

- Ireland-Claisen rearrangement
**Cope and Oxy-Cope rearrangement**

- **Cope rearrangement**: high temperatures usually required (>200°C)

- **Bullvalene**: valence isomers interconvert by degenerate Cope rearrangements.

- The anionic oxy-Cope can be conducted at low temperature (0 °C).

- A useful method for the synthesis of *cis*-decalins

\[
k_2/k_1 \approx 10^{10} - 10^{17}
\]
I,\(n\)-hydride shifts

- A suprafacial I,\(n\)-hydride shift involves the hydrogen moving from one end of the conjugated system to the other across one face of the conjugated system.

- An antarafacial I,\(n\)-hydride shift involves the hydrogen moving from one end of the conjugated system to the other and moving from one face of the conjugated system to the opposite face.

\[\text{(4q + 2)}_s = 1 \quad (4r)_a = 0 \quad \text{Total} = 1 \quad \text{odd} \checkmark \quad \text{allowed}\]

\[\text{(4q + 2)}_s = 0 \quad (4r)_a = 1 \quad \text{Total} = 1 \quad \text{odd} \checkmark \quad \text{allowed}\]
1,5-Hydride shifts occur readily when the two ends of the diene are held close.

In acyclic systems, 1,5-hydride shifts can be much slower.
1,2-shifts of alkyl groups can also be pericyclic.

Allowed, concerted 1,2-shifts of carbanions are geometrically impossible.

1,2-Shifts of carbanions occur by a radical mechanism – 1,2-Wittig & 1,2-Stevens rearrangements.
1,3 & 1,4-shifts

- Thermal [1,3]-alkyl shifts occur with inversion of configuration in the migrating group.

- Thermal 1,3-shift of hydrogen is only geometrically reasonable in a suprafacial (thermally disallowed).

- In the following [1,4]-shift, migration occurs with inversion of configuration with D always on the concave face of the bicyclic structure.
**I,n-shifts**

- 1,5-Alkyl shift with retention of configuration in the migrating group.

- [2,3]-Wittig rearrangement – most likely proceeds via an envelope transition state; large groups at the allylic position will tend to occupy a pseudo-equatorial position.

- Sommelet-Hauser rearrangement.

\[ (4q + 2)_s = 1 \]
\[ (4r)_a = 0 \]
\[ Total = 1 \]
\[ odd \checkmark \]

\[ (4q + 2)_s = 3 \]
\[ (4r)_a = 0 \]
\[ Total = 3 \]
\[ odd \checkmark \]
2,3-rearrangements

- Meisenheimer Rearrangement.

\[
\begin{align*}
\text{Rearrangement of allyl sulfoxides,} \\
\text{sulfinimines and sulfonium ylids.}
\end{align*}
\]

- A [9,9]-sigmatropic shift.

\[
\begin{align*}
(4q + 2)_s &= 1 \\
(4r)_a &= 0 \\
\text{Total} &= 1 \\
\text{odd} &\checkmark \\
\text{allowed}
\end{align*}
\]
Group transfer reactions

- Group transfer – appear to be a mix of a sigmatropic rearrangement and a cycloaddition. They are bimolecular and so are not sigmatropic rearrangements, and no ring is formed so they are not cycloadditions.

- Conia-ene reaction.
Group transfer reactions

- Carbonyl-ene reaction - frequently catalysed by Lewis acids.

  ![Chemical structure](image)

  180 °C, 48 h
  SnCl₄, 0 °C

  92 2.5
  8 97.5

- Thermal carbonyl ene reaction: sterics are important.

- In the Lewis acid-catalysed reaction significant positive charge develops in the “eneophile”.

- Retro-ene and retro group transfer reactions are common.

retro group transfer: X = S, Se, or NR (Cope elimination)
Summary of pericyclic reactions

Four classes: Cycloadditions (chelotropic reactions); Electrocyclic reactions; Sigmatropic rearrangements; Group transfer.

A ground state pericyclic reaction is symmetry allowed when the total number of \((4q + 2)_s\) and \((4r)_a\) components is odd (q and r must be integers).

A pericyclic change in the first electronically excited state (i.e. a photochemical reaction) is symmetry allowed when the total number of \((4q + 2)_s\) and \((4r)_a\) components is even.

For thermal cycloadditions and group transfers:

1. If the total number of electrons is \((4n + 2)_s\), both components can be used in a suprafacial manner.
2. If the total number of electrons is \((4n)_s\), one of the components is suprafacial and the other antarafacial.

For electrocyclic reactions:

3. Thermal electrocyclic processes will be *conrotatory* if the total number of electrons is \(4n\) and *disrotatory* if the total number of electrons is \((4n + 2)_s\).