CHEM95002: Orbitals in Organic Chemistry - Pericyclics

LECTURE 7 Cycloaddition Reactions

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Format & scope of lecture 7

• **Cycloaddition reactions**
  – Diels-Alder reaction
    • Rates
    • Regioselectivity
    • Stereoselectivity – the *endo* ‘rule’
  – 1,3-Dipolar cycloadditions
    • Ozonolysis
Cycloaddition: *the Diels-Alder reaction*

**Overall synthetic characteristics - summary:**

- **Reaction rates:** dependent on the HOMO-LUMO energy gap
  - Therefore varies as a function of reaction partner electronics
    - ‘Normal’ electron demand: accelerated by having an EDG on the diene & an EWG on the dienophile (cf. A vs. B vs. C/D)
    - ‘Inverse’ electron demand: accelerated by having an EWG on the diene & an EDG on the dienophile
- **Reaction regioselectivity:** dependent on the coefficients (=sizes) of the HOMO & LUMO reacting orbitals
  - can usually be anticipated by considering the ‘polarisation’ of the reaction partners
  - *ortho* and *para* products tend to predominate (cf. Ei vs Eii)
  - rate & selectivity often increased by catalysis
- **Reaction stereoselectivity:** dependent on secondary orbital interactions
  - *endo* products formed preferentially for normal electron demand reactions (*i.e.* involving EWG π-conjugated alkene dienophiles) (see: F)

![Reaction diagrams A-F](image)

- A: [Diels-Alder reaction](image) with thermal conditions: 165 °C, 17 h, 900 atm
- B: [Endo product](image) formed at 150 °C, 0.5 h
- C: [Substitution product](image) formed at 100 °C, 2 h
- D: [Substitution product](image) formed at 120 °C, 6 h
- E: [Ester formation](image) without (i) or with (ii) AlCl₃ catalysis
- F: [Endo ester](image) formed with AlCl₃ at -78 °C
Diels-Alder reactivity – HOMO-LUMO matching

**Reaction rates:**
- Reactivity is controlled by the relative energies of the FMOs.
- The key interaction is between the HOMO of one reactant and the LUMO of the other reactant:
  - the closer the two interacting orbitals are in energy the faster the reaction rate (cf. Klopman-Salem equation, lecture 1, slides 7/8).
  - consequently, 2 important types can be identified:
    - Recall from Lecture 1 (slides 9/10):
      - EWG (Z-substituents) lower HOMO & LUMO energies
      - EDG (X-substituents) raise HOMO & LUMO energies
      - conjugating systems (C-substituents) raise HOMO & lower LUMO.
    - Catalysis of ‘normal’ electron demand Diels-Alder reactions is generally by ‘LUMO-lowering’ catalysis’:
      - i.e. interaction of catalyst with a carbonyl conjugated to an alkene in the dienophile.

![Diagram showing HOMO-LUMO matching in Diels-Alder reactions]
**Diels-Alder regioselectivity – dienophile polarity**

*Can we understand how substitution on dienophile with an EWG changes orbital coefficients?*

- Consider *acrolein* as an average of allyl cation and butadiene:

  - In the presence of a Lewis acid (e.g. AlCl₃) acrolein will have more allyl cation character and hence the C-terminus coefficient of the LUMO will be larger, leading to greater selectivity (as well as higher rate).
Similarly, the effect on orbital coefficients of substituting the diene with electron donating groups

- consider 1-methoxybutadiene as an average of butadiene and a pentadienyl anion:

<table>
<thead>
<tr>
<th>HOMO</th>
<th>LUMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.37</td>
<td>-0.60</td>
</tr>
<tr>
<td>0.60</td>
<td>-0.37</td>
</tr>
<tr>
<td>0.60</td>
<td>0.37</td>
</tr>
<tr>
<td>0.37</td>
<td>0.60</td>
</tr>
</tbody>
</table>

HOMO of diene has a large orbital coefficient at the end of the diene.
Diels-Alder regioselectivity - summary

- Large-large and small-small overlap is best
- \( Z = \text{EWG (e.g. } \text{CO}_2\text{Me}), X = \text{EDG (e.g. } \text{OMe}), C = \text{conjugating group (vinyl, phenyl)} \)

Substituted dienophile orbital coefficients

1-Substituted diene orbital coefficients

2-Substituted diene orbital coefficients
Diels-Alder regioselectivity – in practice…

• Fortunately, for most synthetically useful D-A reactions, resonance-based polarity will correctly predict regioselectivity:

• BUT, not always. Sometimes, only the orbital coefficient approach correctly predicts the outcome.
  – However, these ‘exceptions’ are generally poor reactions from a HOMO-LUMO energy matching perspective (i.e. slow rates), e.g.
Diels-Alder stereoselectivity

- The *endo*-product is generally the major with dienophiles containing $\pi$-conjugation (e.g. a Z substituent)

- Secondary orbital overlap is a simple explanation for the kinetic preference for the *endo*-adduct

- Reversibility (as in D-A reactions with furan) can lead to the thermodynamically preferred *exo* adduct
Diels-Alder stereoselectivity

- Drawing and working out stereochemistry for Diels-Alder reactions

$$\text{BF}_3\cdot\text{OEt}_2, 50 \, ^\circ\text{C}$$

1. **Draw diene and dienophile in appropriate 3D arrangement**
2. **Decorate with substituents & draw arrows to form bonds**
3. **Draw product in 3D-arrangement like starting materials**
4. **Rotate to flat and transcribe stereochemistry**

**endo**
1,3-Dipolar cycloadditions

RECALL: Heteroaromatics Lectures
• Prof. Donald Craig, lectures 2 & 3:
1,3-Dipolar cycloadditions

- sp²-hybridized central atom

- sp-hybridized central atom

Azomethine ylid  Azomethine imine  Carbonyl oxide  Carbonyl ylid  Nitrone  Ozone

Nitrile ylids  Nitrile oxides  Diazooalkanes  Nitrile imines  Alkyl azides  Nitrous oxide
1,3-Dipolar cycloaddition: ozonolysis

1,3-dipolar Cycloaddition #1

1,3-dipolar Cycloaddition #2

W-H approach

FMO approach