Lecture 25 Agenda...
Pericyclic Reactions (30.1)
Cycloadditions (30.5, 30.6)
Diels-Alder (14.4, 14.5)

Suggested Problems:
Ch 30: 30.5, 30.6, 30.20 – 30.22, 30.38, 30.41

Make-Up Exam on Tuesday, July 15 in lecture. Sign-up now ‘til Friday.
Pericyclic reactions involve the interaction of p and s orbitals. (No direct participation of electrophilic/nucleophilic centers.)

3 Main Varieties:
1. Electrocyclizations
2. Cycloadditions
3. Sigmatropic Shifts

• In each case, a mixture of stereo- and/or regioisomers are possible, but in general, a strong preference is observed for any one of the possible products.

• This control of stereo/regiochemistry render these reactions extremely valuable in organic synthesis & C-C bonds are made!

• The basis for selectivity can be seen mechanistically, namely the molecular orbitals undergoing the transformation.
Molecular orbitals are mathematically constructed by the combination of atomic orbitals.

Basic info:
1. # of M.O.s must equal # of A.O.s

2. The square of the orbital is a region of space about the nucleus where an electron might be found

3. M.O.s are 4 dimensional constructs:
   - 3 dimensions of geometry
   - 1 dimension of energy - spreads the orbitals out; they are at different energies and therefore do not “see” or “interfere” with each other

4. The better 2 given orbitals match in these 4 dimensions, the Stronger the interaction. This interaction can be stabilizing (2 electrons to share) or destabilizing (4 electrons in total to Share → filled orbitals/2 electrons in each orbital = steric).
Electrocyclization reactions involve a single starting material. They involve the rearrangement of $\pi$ bonds to form one new $\sigma$ bond.

Example of an electrocyclization:

A conjugated triene $\xrightarrow{\text{Heat}}$ A cyclohexadiene
Sigmatropic rearrangements involve a shift of a sigma-bonded atom or group across a pi system. The sigma bond breaks, pi bonds move, a new sigma bond forms.

Example of a sigmatropic rearrangement:

A [3,3] sigmatropic rearrangement

An allylic vinylic ether $\Rightarrow$ Cyclic transition state $\Leftrightarrow$ An unsaturated ketone
Cycloaddition reactions involve the combination of two separate $\pi$ systems to form a ring. Two new bonds are formed at once - powerful for synthesis!

Example of a cycloaddition:

2-Cyclohexenone  +  2-Methylpropene  \(\xrightarrow{hv}\)  Product  (40%)
There are two major classes of cycloadditions:
(a) $2\pi + 2\pi$
(b) $4\pi + 2\pi$ (known as a Diels-Alder reaction)

(a) $2\pi + 2\pi$:

- Done under photochemical conditions
- The stereo/regiochemistry is controlled by steric and electronic effects (beyond the scope of this class)
- Can be done intramolecularly
- Can be reversible

\[\text{2-Cyclohexenone} + \text{2-Methylpropene} \xrightarrow{h\nu} \text{(40%)}\]
2 + 2 Cycloadditions are done under photochemical conditions. If subjected to thermal conditions, no reaction.
(b) \(4\pi + 2\pi\) (known as a Diels-Alder reaction)

- more prevalent cycloaddition
- \(4\pi\) system is the diene
- \(2\pi\) system is the dienophile
- the product is known as a Diels-Alder adduct
- Can be reversible
- Can be intramolecular

To consider:
- **Regiochemistry** - use resonance to rationalize selectivity
- **Stereochemistry** with substituted dienes and/or substituted dienophiles:
  1. Intracomponent control
  2. Intercomponent control
In Diels-Alder reactions, when using substituted dienes and dienophiles, one must consider the following when predicting the major product that will be formed:

**Regiochemistry:** that is, where groups coming off the cyclohexene ring will be with respect to each other.

We’ll use resonance to predict the major regioisomer that will form.

**Stereochemistry:** that is, what is the relative stereochemistry of the groups coming off the cyclohexene ring (cis or trans).

Two things to consider for this:
1. Intracomponent control
2. Intercomponent control
Diels-Alder Regioselectivity...

When considering all possible products of a Diels-Alder reaction, first consider the major regioisomer. To do this, use resonance.

Regioisomers:
*Groups are either 1,2 or 1,3 with respect to each other
Diels-Alder Stereochemistry...
There are two essentially independent stereochemical issues which arise when substituted dienes combine with substituted dienophiles:

1. **Intracomponent control:**

\[
\text{cis} \quad \text{OR} \quad \text{trans}
\]

2. **Intercomponent control:**

\[
\text{cis} \quad \text{OR} \quad \text{trans}
\]

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Intracomponent control...
The Diels-Alder reaction is a concerted reaction without intermediates. Both new C-C bonds form simultaneously. Thus, there is no opportunity for the alkene geometry to be lost or scrambled.

With intracomponent control, the product stereochemistry directly follows from alkene geometry. Groups that are cis in the starting material will be cis in the product. Groups that are trans in the starting material will be trans in the product.

\[ \text{cis only!} \]
More intracomponent examples...

\[ \text{trans only!} \]

\[ E + E \]

\[ CH_3 \text{ groups are cis} \]

\[ E \]

\[ CH_3 \text{ groups are trans} \]

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Intercomponent control...

Consider the following reaction:

\[
\text{CH}_3 + \text{CHO} \rightarrow \text{cis} \quad \text{OR} \quad \text{trans}
\]

Each product arises from different transitions states: endo or exo.

To analyze the transition states, one must consider the HOMO of one starting material and the LUMO of the other. Typically, it is the HOMO of the diene and the LUMO of the dienophile.

Typically, the endo transition state is preferred since it yields the most stable transition state, has a lower activation energy and is kinetically favored.

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A generalization about Diels-Alder stereochemistry (endo TS):

\[ \text{A} \text{B} \text{C} \text{D} + \text{W} \text{Y} \text{Z} \text{X} \rightarrow \text{B} \text{A} \text{X} \text{W} \text{Y} \text{Z} \text{C} \text{D} \]
**Hetero-DA reactions** are commonly used in natural product synthesis. It is a way to incorporate heteroatoms into a six-membered ring.