Unit 2

Molecular Orbitals and Pericyclic Reactions

2.10 Molecular Orbital Theory - 1

9/27:

- See Georgia's notes on Canvas (also included below).

Lecture 10: MO Theory (1/2)

DATE 27 Sept 2024

Exam Reflections

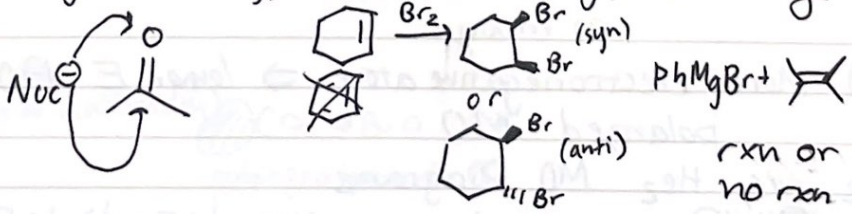
- You all did great
- "How did I do?"
  - 90-100 excellent
  - 80-90 good
  - <80 adequate, reach out
- exams hand back in recitations
- these guidelines are exam specific
  - ↳ first exam typically best
- You learned structure determination!

What's Next?

- how do you go from 2D structure to where are e⁻ where do they react

Unit 2 Molecular Orbitals & Pericyclic Reactions

- deeper look at e⁻ movement
- new types of reactions, new class of mechanism
- use molecular orbitals (MO's) to predict reaction outcomes
  - ↳ regioselectivity, diastereoselectivity, reactivity



- MO's provide insight into structure & reactivity

Background/Review & Study

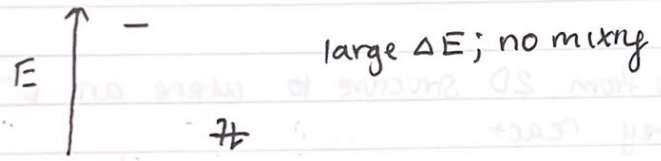
- review gen chem (5.11/5.12) & Orgo I (5.12)
- Clayden: ch. 4, 5, 6

27 Sept Lecture 10 : Cont

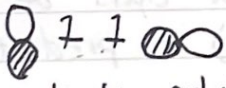
- orbitals are wavefunctions that describe the ability to find an electron in space
  ↳ they interact constructively & destructively

Rules:

1. # atomic orbitals (AOs) in = # MO's out
2. interacting orbitals must have similar energy
   - if large ΔE ; no mixing
   - if same E ; best mixing



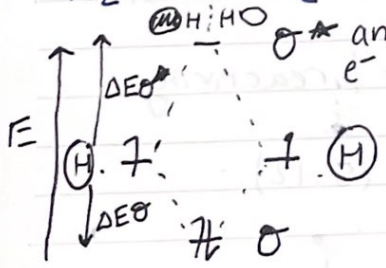
3. interacting orbitals must overlap efficiently and have similar ~~energy~~ symmetry



perpindicular orbitals
- poor overlap
- no mixing

4. More electronegative atom ⇒ lower E AO = more polarized MO

H_2 vs He_2 MO Diagrams

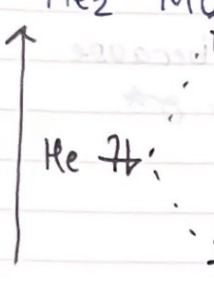


HOH
bonding; e⁻ in middle

Note: $|\Delta E_{\sigma^*}| > |\Delta E_{\sigma}|$
antibonding is more destabilizing than the bonding is stabilizing
H_2 MO more stable than 2× H· AO
↳ why H_2 bond forms

Lecture 10 Cont

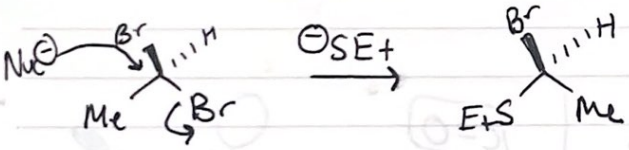
He_2 MO Diagram



- antibonding MO filled!
- this is less stable than two individual H atoms
- forming He-He requires filling σ^* (which is more destabilizing) than

- this is the MO explanation for the full octet rule

S_N2 MO Picture

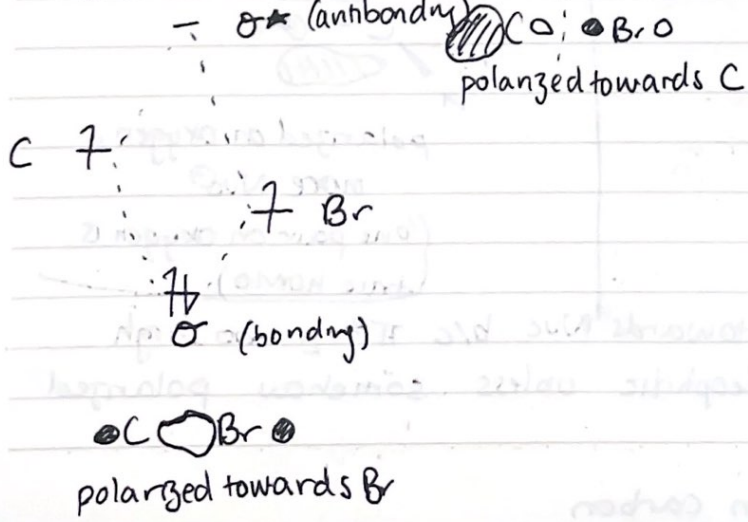


Why backside attack?
- identify HOMO & LUMO

HOMO highest occupied MO = π orbital, ⊖SEt nucleophile, filled orbitals, lone pair

LUMO lowest unoccupied MO = electrophile = empty orbitals = π^* or σ^* orbital, cations, C of C-Br bond

MO of C-Br



NO. 4

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Lecture 10: Cont

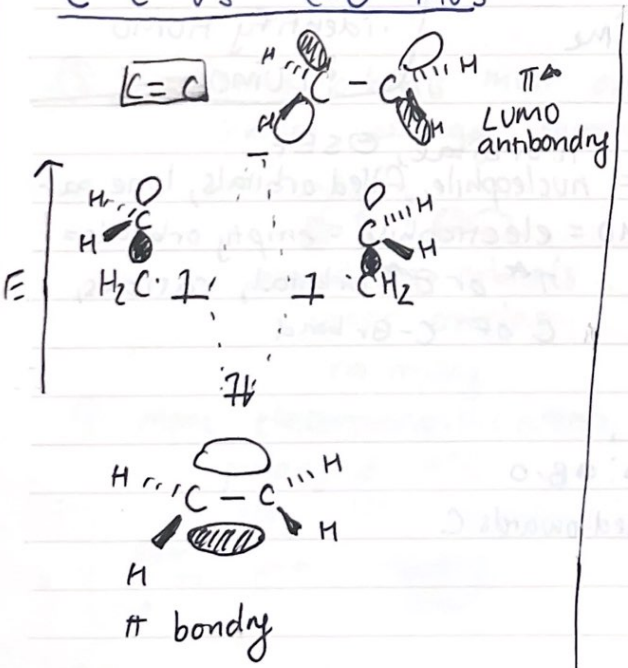
backside attack because there is a larger σ^* lobe there

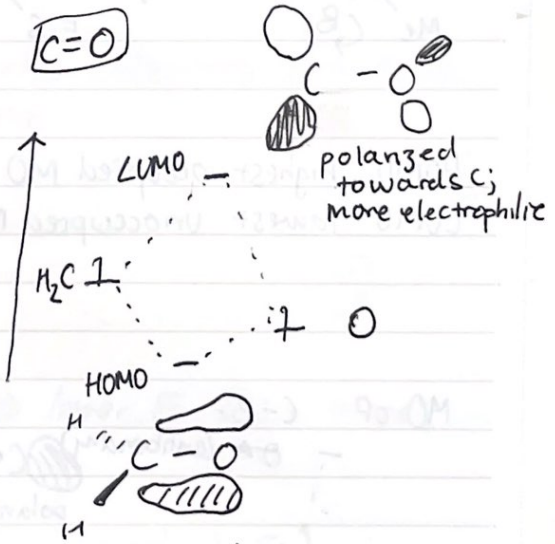
Meanwhile

σ bond breaks because σ^* populated

Our mechanistic arrows show this

C=C vs C=O MOs





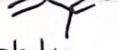
polarized on oxygen, more Nuc⊖

(lone pair on oxygen is true HOMO)

Consequences:

C=C less reactive towards Nuc b/c π* E too high

C=C generally nucleophilic unless somehow polarized

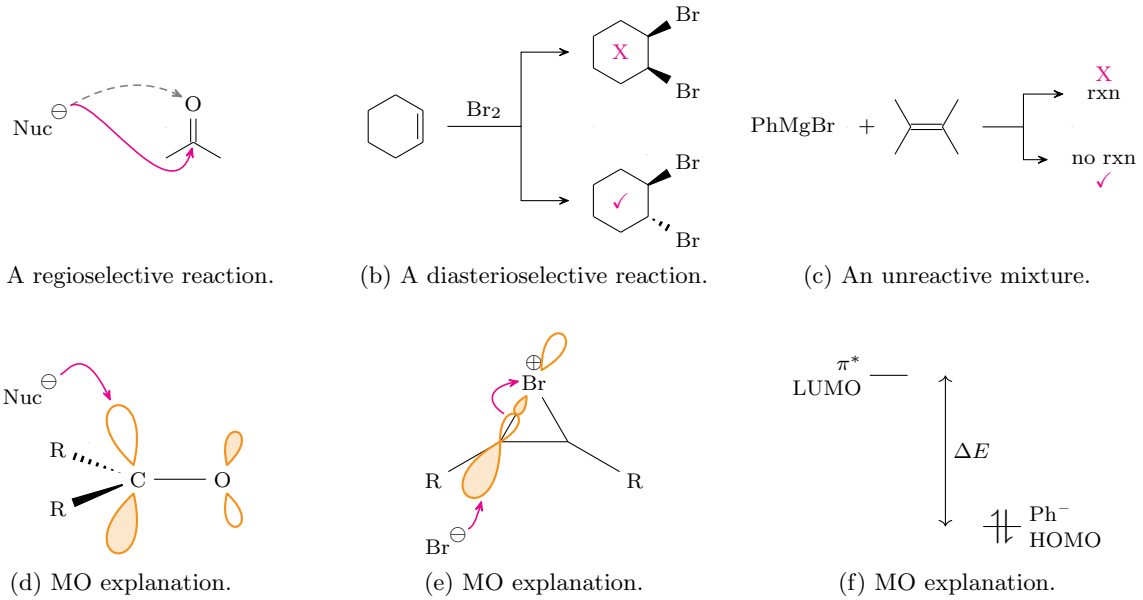
ex: 

C=O electrophilic on carbon

2.11 Molecular Orbital Theory - 2

9/30:

- Lecture 10 recap: What MO theory can explain.



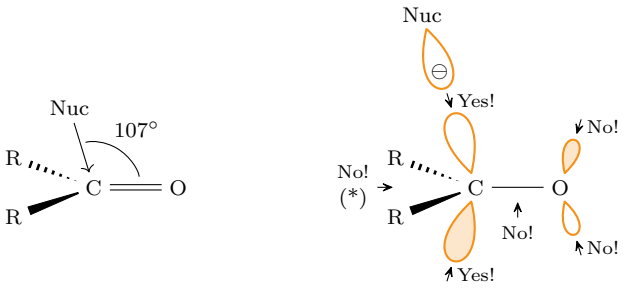
(a) A regioselective reaction. (b) A diasterioselective reaction. (c) An unreactive mixture.

(d) MO explanation. (e) MO explanation. (f) MO explanation.

Figure 2.1: MO theory explains these phenomena.

- Regioselectivity.
  - Consider a nucleophile adding into a carbonyl (Figure 2.1a).
    - Experimentally, we observe that the nucleophile attacks the carbon atom (magenta arrow) instead of the oxygen atom (grey dashed arrow).
  - To understand why, we must consider the carbonyl's molecular orbitals (Figure 2.1d).
    - Specifically, we must consider the carbonyl's LUMO, since this will be the MO that interacts with the nucleophile's HOMO. Here, the LUMO is the carbonyl's π^*-orbital.
    - The carbonyl's LUMO has big lobes on carbon and small lobes on oxygen; in other words, this LUMO is **polarized** toward carbon.
    - The difference in lobe size explains why the nucleophile attacks carbon instead of oxygen.
- Diastereoselectivity.
  - Consider the bromination of an alkene (Figure 2.1b).
    - Experimentally, we observe that the *anti* adduct is formed instead of the *syn* adduct.
  - To understand why, we consider the MOs of the bromonium ion intermediate (Figure 2.1e).
    - For the same reason as before, we must consider the bromonium ion's LUMO. Here, the LUMO is the C–Br σ^*-orbital.
    - The bromonium ion's LUMO has its largest lobe behind carbon.
    - Thus, this is the lobe that will be attacked by the Br^- nucleophile. Such an attack is called a "backside attack" and induces the *anti* product.
- Reactivity.
  - Consider a Grignard reagent adding into an olefin (Figure 2.1c).
    - Experimentally, we observe no reaction here.
  - To understand why, we must consider the relative energies of the reacting MOs (Figure 2.1f).
    - Essentially, the alkene's LUMO (a π^*-orbital) is much higher in energy than the phenyl anion's HOMO. Thus, the ΔE gap is too big, i.e., there is a lack of energy symmetry.
    - Therefore, by Rule 3 from Lecture 10, no reaction occurs.

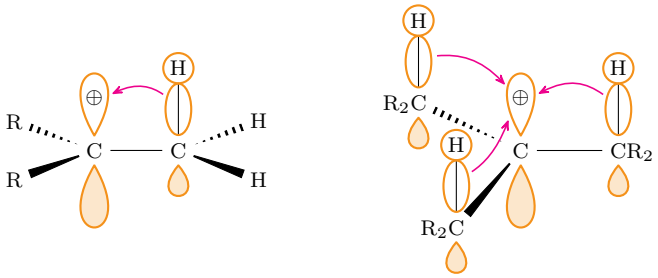
- Today: More MO theory.
- Lecture outline.
  - The Bürgi-Dunitz angle.
  - Hyperconjugation.
  - The anomeric effect.
  - Stereoelectronic effects and the rate of reaction.
- **Bürgi-Dunitz angle**: The angle at which nucleophiles typically add to carbonyls. *Given by* 107°.



(a) Definition. (b) Effective overlap.

Figure 2.2: Bürgi-Dunitz angle.

  - This is the angle between the new C–Nuc bond and the carbonyl's σ-plane (Figure 2.2a).
  - Nucleophiles attack at this angle because it's the location of the π^*-lobe on carbon (Figure 2.1d).
  - Let's elaborate a bit on Figure 2.1d now (Figure 2.2b).
    - Once again, consider the carbonyl π^*-orbital (its LUMO) and its "butterfly" lobes.
    - The nucleophile must approach the π^*-orbital with the right symmetry. This is why we see its HOMO's lobe approach the carbon atom's π^*-lobe dead-on at exactly the right angle.
      - ➢ This angle leads to efficient overlap, and hence an effective sharing of electron density.
      - ➢ This is an example of Rule 3 from Lecture 10.
    - Are there any other locations at which we can add into the carbonyl?
      - ➢ We can also add into the shaded carbon π^*-lobe on the other side of the σ-plane by reversing the shading of the nucleophile's lobe!
      - ➢ However, any other angle of attack will *not* work.
      - ➢ Note (*): A backside attack is good for interacting with the σ^*-orbital, but bad for interacting with the π^*-orbital that we need for carbonyl chemistry.
- **Hyperconjugation**: The mixing of filled and empty orbitals to stabilize a system.
- Example (from 5.12): Stabilizing carbocations.



(a) 1° carbocation. (b) 3° carbocation.

Figure 2.3: Hyperconjugation stabilizes carbocations.

  - Consider a primary (1°) carbocation (Figure 2.3a).
    - In a carbocation, the positively charged carbon localizes its lack of electron density to an empty p-orbital.
    - However, adjacent to this empty p-orbital is a full σ-orbital, namely, the adjacent C–H bond. Moreover, this bond has the right *geometry* to donate into the empty p-orbital.
    - Thus, the σ-orbital of the C–H bond will donate electron density into the empty p-orbital, delocalizing both positive and negative charges and thereby stabilizing the system.
  - We denote hyperconjugation interactions using a special **notation**; the particular hyperconjugation in Figure 2.3 is denoted $\sigma_{CH} \to p_C$.[1]
  - In a tertiary (3°) carbocation, we get electron donation from *three* adjacent σ_{CH} orbitals.
    - These *three* stabilizing interactions explain why 3° carbocations are more stable than 1° ones!
    - Such effects are also why more substituted cations are more stable in general.

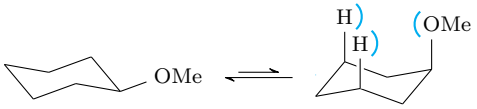
- **Hyperconjugation notation**: The concise method for denoting a certain hyperconjugative orbital interaction. *Given by*

$$\text{orbital}_{\text{atoms}} \to \text{orbital}_{\text{atoms}}$$

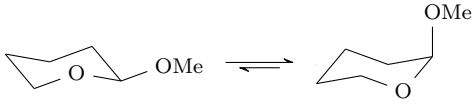
  - The arrow means "donates into."
    - Indeed, we always write the filled orbital first (before the arrow) and the empty orbital second (after the arrow).
  - Possible orbitals: $\sigma, \sigma^*, \pi, \pi^*, p, n$.
    - Note that n denotes a nonbonding lone pair.

- **Anomeric effect**: The tendency of heteroatom substituents adjacent to heteroatoms in cyclohexane derivatives to prefer the axial orientation.

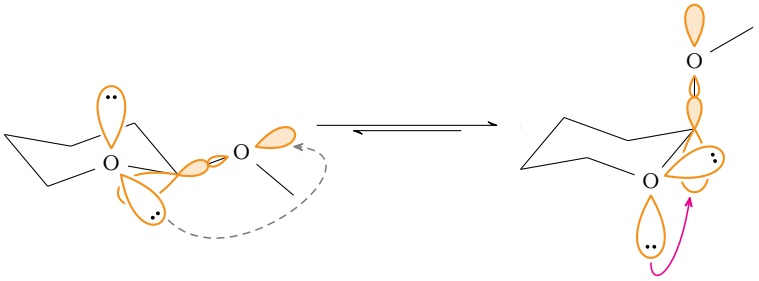
- Let's break this rather complicated definition down through an example.



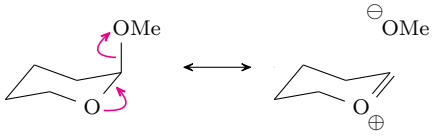
(a) Sterics win in methoxycyclohexane.



(b) Anomeric wins in 2-methoxytetrahydropyran.



(c) MOs explain the anomeric effect.



(d) Resonance explains the anomeric effect.

Figure 2.4: Anomeric effect.

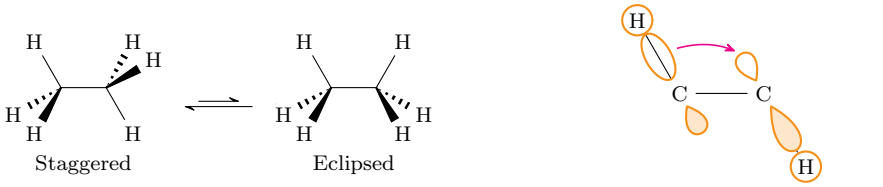
[1] This is pronounced "sigma C–H to p C donation" or (very explicitly) "sigma see aech to pee see donation."

- In methoxycyclohexane, the methoxy group prefers to be equatorial to avoid 1,3-diaxial interactions (Figure 2.4a).
  - This leads to a 70 : 30 distribution in favor of the equatorial conformer.
- However, in 2-methoxytetrahydropyran, the methoxy group prefers to be *axial* due to the anomeric effect (Figure 2.4b).
  - This *also* leads to a 70 : 30 distribution, but this time in favor of the axial conformer.
  - Notice how this empirical observation reflects the definition of the anomeric effect: We have a heteroatom substituent (the methoxy group) adjacent to a heteroatom in cyclohexane (the oxygen in the six-membered ring), and it is prefering the axial orientation!
- What causes the anomeric effect? Let's investigate the stabilization of the axial conformer further using molecular orbitals (Figure 2.4c).
  - In 2-methoxytetrahydropyran's equatorial conformation, we get poor overlap between the oxygen lone pair's orbital and the C–OMe antibonding orbital. This poor overlap is due to the *gauche* orientation of said orbitals.
  - In 2-methoxytetrahydropyran's axial conformation, we get really nice overlap between the oxygen lone pair and the σ^*-orbital of the C–OMe bond. This is because both orbitals have large lobes pointing axial down. Because of this favorable geometry, $n_O \rightarrow \sigma^*_{CO}$ hyperconjugation occurs.[2]
- Another way of showing how the anomeric effect stabilizes the axial conformer is by using resonance diagrams (Figure 2.4d).
  - Indeed, starting from the typical picture, we can push the lone pair into an O=C π-bond and formally break the C–OMe σ-bond.
  - The result is called a **no-bond resonance form**.
  - Something should feel off to you here, though.
    - ➢ When you learned to draw resonance structures, you learned that you can't break σ-bonds.
    - ➢ However, we are now telling you that sometimes, you *are* allowed to break σ-bonds. This is "next-level resonance structures."
  - Note that 2-methoxytetrahydropyran doesn't go all the way to the no-bond resonance form, but said resonance form *is* a major contributor.
    - ➢ This also means that the no-bond resonance form affects the reactivity of the molecule.

- Both hyperconjugation and the anomeric effect fall under the broader category of **stereoelectronic effects**.
  - Note that they are not the only examples of such effects, though.
- **Stereoelectronic effect**: An effect on structure or reactivity of a molecule caused by the spatial orientation of its orbitals.
  - We've previously learned that everything in Orgo can be explained by steric and electronic effects, but stereoelectronic effects are like a secret third option!
- Let's now look at some more places where stereoelectronic effects crop up.

[2]Note that there is no particular reason why overlap with a σ^*-orbital, in particular, is stabilizing. Rather, the point is that we have a filled orbital (the lone pair) adjacent to an empty orbital (which just happens to be a σ^* orbital), so hyperconjugation can occur to spread out the negative and positive charges. This delocalization — like any — is then inherently stabilizing.

- Example: Hyperconjugation in noncationic species.



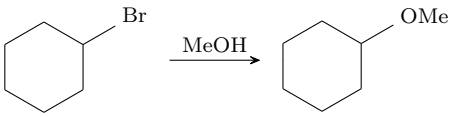
(a) Ethane's conformers.

(b) $\sigma_{CH} \rightarrow \sigma^*_{CH}$ stabilization.

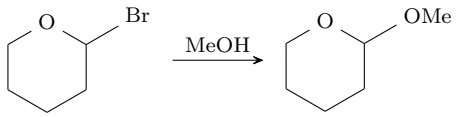
Figure 2.5: Hyperconjugation stabilizes staggered ethane.

  - We may have learned that ethane prefers the staggered conformer over the eclipsed conformer (Figure 2.5a) due to sterics.
    - This is not true!
    - We know this because H is really tiny.
  - In fact, this preference is due to hyperconjugation, a stereoelectronic effect (Figure 2.5b).
    - Staggered ethane is stabilized by electron donation from the σ-bond of one C–H bond into the adjacent, antiperiplanar C–H bond's σ^* orbital: $\sigma_{CH} \rightarrow \sigma^*_{CH}$.
    - This is a small interaction, but it occurs six times, once for each C–H σ-bond!
  - Takeaway: Electron delocalization is stabilizing, and more delocalization is more stabilizing.

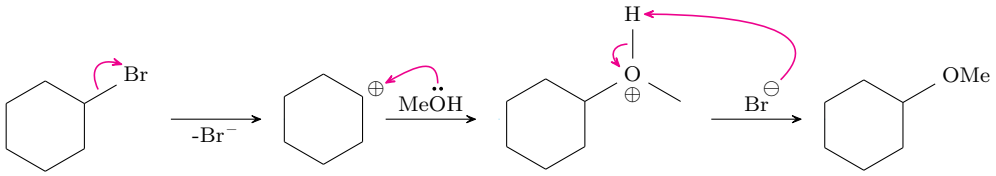
- Example: Stereoelectronic stabilization can accelerate reactions.



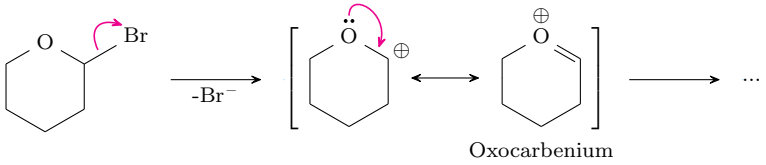
(a) S_N1 without an adjacent heteroatom.



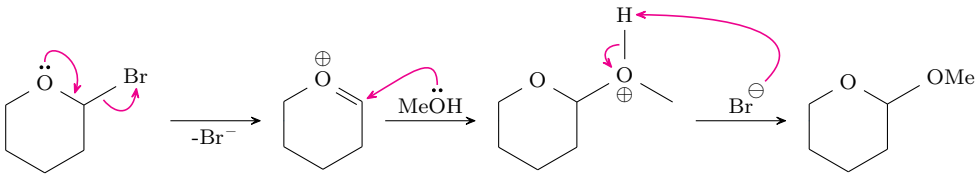
(b) S_N1 with an adjacent heteroatom.



(c) No heteroatom mechanism.



(d) Possible heteroatom-promoted mechanism.



(e) Better heteroatom-promoted mechanism.

Figure 2.6: Stereoelectronic effects accelerate reactions.

- Consider the S_N1 substitution of bromocyclohexane to methoxycyclohexane (Figure 2.6a), vs. the S_N1 substitution of 2-bromotetrahydropyran to 2-methoxytetrahydropyran (Figure 2.6b).
- Which of these substitutions occurs faster?
- To answer this question, let's look at the mechanism of each (Figures 2.6c-2.6d).
  - Note that in Figure 2.6c, either bromide or another equivalent of methanol can do the final deprotonation of the **oxonium** ion.[3]
  - Note that in Figure 2.6d, the fact that the **oxocarbenium** ion obeys the octet rule implies that it is the more stable resonance structure.
- In fact, the oxocarbenium ion is an example of oxygen stabilizing a carbocation through $n_O \to p_C$ hyperconjugation.
- This is one example of hyperconjugation in this reaction scheme, but there is another effect as well.
  - In the original 2-bromotetrahydropyran molecule, the oxygen lone pair will also hyperconjugate into the C–Br σ^*-orbital per the anomeric effect.
  - In other words, O mediates the departure of the leaving group through $n_O \to \sigma^*_{CBr}$ hyperconjugation.
- Thus, since both hyperconjugative stabilizing effects can (and do!) happen, it is better to say mechanistically that the arrow pushing in the first step happens simultaneously (Figure 2.6e).
  - Indeed, the rule in arrow pushing is "make a bond, break a bond," so that's what we do.
- We can now complete the mechanism for the heteroatom-promoted reaction (Figure 2.6e).
  - MeOH adds into the π^*-orbital of the oxocarbenium (at the Bürgi-Dunitz angle!), also kicking electrons up to the oxygen in a concerted step.
  - Then we get deprotonation again.
- Now that we've got both mechanisms, let's consider the energy surface in order to compare the rates of reaction.
  - Both reactions will have two-humped energy surfaces, befitting a mechanism with only one true catinoic intermediate.
  - However, in the energy surface for the heteroatom-promoted reaction, $n_O \to p_C$ hyperconjugation will stabilize the intermediate and $n_O \to \sigma^*_{CBr}$ will stabilize the transition state of the first step, lowering its activation energy!
  - Thus, the heteroatom-promoted S_N1 is faster!
- Takeaway: The overall reaction specifics depend on geometry and orbital overlap.

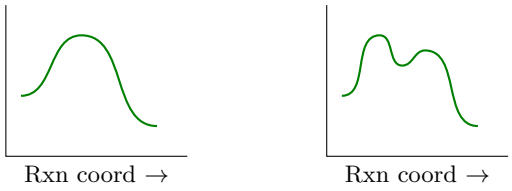
2.12 Pericyclics

10/2:

- Lecture 11 recap.
  - Hyperconjugation involves the delocalization of electrons, and hence is stabilizing.
    - This is a very common phenomenon, and it underlies most 5.12 reactions!
  - $\sigma_{CH} \to p_C$ hyperconjugation makes substituted cations more stable (see Figure 2.3).
  - $\sigma_{CH} \to \sigma^*_{CH}$ makes ethane more stable when staggered than eclipsed (see Figure 2.5b).
  - $n_O \to \sigma^*_{CX}$ stabilizes axially positioned heteroatom substituents with α-heteroatoms in cyclohexane derivatives, per the anomeric effect (see Figure 2.4c).

[3] Note that — comparing the pK_a of protonated methanol to HBr — methanol is actually almost a million times more basic than bromide. As such, for every one time bromide does the final deprotonation, methanol will do it to almost a million other oxonium intermediates. However, it can still be useful to think of bromide as *formally* doing the final deprotonation so as to balance the reaction $C_6H_{11}Br + CH_3OH \longrightarrow C_6H_{11}OCH_3 + HBr$.

- Today: Pericyclic reactions.
  - They are cool because they couple MO theory to reactivity.
  - This is a whole new class of reactions, and we will spend the rest of Unit 2 talking about them.
  - Essentially, the rest of this unit looks like: "Here's a new reaction, and here's the MO picture underlying it."
- **Pericyclic** (reaction): A reaction characterized by a **concerted** movement of electrons in a **cyclic** transition state.
- **Concerted** (reaction): A reaction in which all electron movements happen at the same time, i.e., all bonds break and form in the same step.
  - There are no intermediates, and hence only a single "hump" in the energy diagram (Figure 2.7a).
  - Concerted reactions contrast with **stepwise** reactions.
  - Concerted reactions can be **synchronous** or **asynchronous**.
    - Essentially, we ask, "Is the transition state symmetric? Are all bonds breaking and forming to the same extent at the same time, or are some bonds breaking/forming first with others breaking/forming later?"
    - We touch on this concept to illustrate that even *concerted* reactions can have subtle differences between them.
- **Stepwise** (reaction): A reaction that *has* intermediates in its energy landscape.
  - There *are* intermediates, and hence multiple "humps" in the energy diagram (Figure 2.7b).
- To reiterate, concerted and stepwise reactions can be differentiated using their energy diagrams.



(a) Concerted. (b) Stepwise.

Figure 2.7: Concerted vs. stepwise energy diagrams.

  - Example: S_N2 reactions are concerted, and S_N1 reactions are stepwise.
- **Synchronous** (concerted reaction): All bond-making and -breaking occurs to an equal extent in the transition state.
- **Asynchronous** (concerted reaction): All bond-making and -breaking does *not* occur to an equal extent in the transition state.
- **Cyclic** (transition state): A transition state in which all bonds that are being broken and made are connected in a ring.
  - Important implication: This is not as complicated as it sounds; rather, it just means that when you draw your electron arrows, you draw them in a ring.
  - See Figure 2.8 for an example.

- History of pericyclic reactions.
  - MO theory was developed *because* of pericyclic reactions.
    - Essentially, pericyclic reactions used to be called "no mechanism" reactions since everything happened in one step.
    - The extent to which organic chemists didn't understand how pericyclic reactions worked drove them to develop a theory that explained why they did.
  - Today, pericyclic reactions are credited with introducing quantum theory into organic chemistry.
    - Before pericyclic reactions, organic chemists thought that they could explain everything they needed to with Lewis structures and arrow pushing mechanisms.
    - However, after pericyclic reactions, it became clear to organic chemists that there *was* value in keeping track of where all the electrons are actually located in MOs and such.
- We'll now do an overview of the different classes of pericyclic reactions, i.e., what we have to look forward to over the next couple of weeks.
  - Types we'll discuss: **Cycloadditions**, **electrocyclizations**, and **sigmatropic rearrangements**.
  - Specifically, we've got one lecture on each of these topics coming up (and then a couple others).
  - As such, it's a good idea to get a general sense of these reactions now, but you don't need to think too much about them since you will get much more information in the coming days and weeks.
- **Cycloaddition**: A pericyclic reaction in which two separate π-systems react to convert two π-bonds into two σ-bonds.
  - Nomenclature: $[m+n]$, where m and n are the numbers of atoms in the two separate π-systems.
    - To reiterate: One of the π-systems has m atoms, and the other has n atoms.
  - Example: We may speak of a "$[4+2]$ cycloaddition." This specific pericyclic reaction is also called the **Diels-Alder reaction**.
  - The reverse reaction of a cycloaddition is called a **cycloreversion**.
- **Diels-Alder reaction**: A $[4+2]$ cycloaddition.

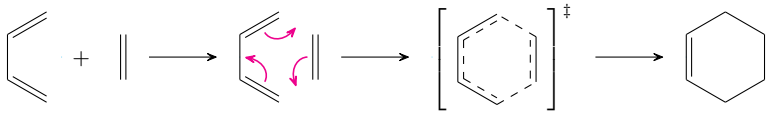


Figure 2.8: Diels-Alder reaction.

  - This is a really cool reaction — one of the most powerful in organic chemistry, in fact.
  - We'll spend the next two lectures talking about it!
  - Note that the magenta electron arrows in Figure 2.8 can go either counterclockwise *or* clockwise.
    - As long as they lead to the right product, you can draw either!
- **Cycloreversion**: A pericyclic reaction in which one system reacts to convert two σ-bonds back into two π-bonds in two separate π-systems.

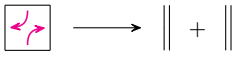
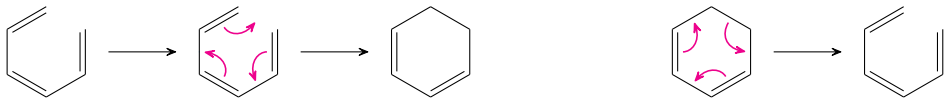


Figure 2.9: A cycloreversion.

  - Sometimes, we give cycloreversions special names.
  - Example: We can call the reaction in Figure 2.9 either a "4π cycloreversion" or a "retro-$[2+2]$."

- **Electrocyclization**: A pericyclic reaction in which one system reacts to convert one π-bond into one σ-bond, or vice versa.



(a) Converting $1\pi \rightarrow 1\sigma$ bond. (b) Converting $1\sigma \rightarrow 1\pi$ bond.

Figure 2.10: A forward and reverse 6π electrocyclization.

  - Nomenclature: $m\pi$, where m is the number of electrons involved.
  - Always ring-opening or ring-closing.
  - Example: We may speak of a "6π electrocyclization" (Figure 2.10a).
    - Notice how we go from 5 σ- and 3 π-bonds to 6 σ- and 2 π-bonds in Figure 2.10a.
  - We can also go in reverse (Figure 2.10b).

- **Sigmatropic rearrangement**: A pericyclic reaction in which a σ-bond moves to the end of the π-system.

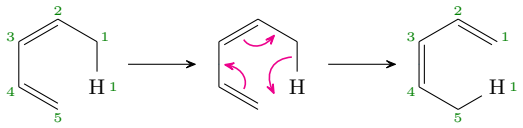


Figure 2.11: A $[1, 5]$ sigmatropic rearrangement.

  - Nomenclature: $[m, n]$, where m and n are the "numbers" of the atoms to which the two ends of the σ-bond moves.
    - We'll dive into this nomenclature more in the lecture on sigmatropic rearrangements.
    - In particular, we will discuss a very specific way of "numbering" the atoms in our starting material and product!
  - Example: We may speak of a "$[1, 5]$ sigmatropic rearrangement" (Figure 2.11).
    - You can push the electron arrows either way, but Prof. Elkin likes to start with the σ-bond and move that to the end of the π-system.
    - Observe that one end of the σ-bond (the side at the hydrogen) moved from atom 1 to atom 1, and the other end (the side at the carbon) moved from atom 1 to atom 5. This is related to the aforementioned "numbering."

- To reiterate from earlier, start familiarizing yourself with these types of reactions, but remember that we will go over these in more detail later in the course.

- Moving on, let's bring MOs back into the picture.

(a) Top view. (b) Side view.

Figure 2.12: Two views of buta-1,3-diene.

  - Observe that the reactants in Figures 2.8, 2.10, and 2.11 are all conjugated systems!
  - Thus, they have π-MOs. Let's consider the diene from Figure 2.8, in particular.
  - Looking at it from the side, we see that each π-bond is made up of two p-orbitals.

- We can mix the four p-AOs in Figure 2.12b to make MOs, but we have to do so according to the following rules.
  1. The number of MOs is equal to the number of atoms under consideration.
     - Example: A diene will have four MOs.
     - Example: An olefin will have two MOs.
  2. The lowest-energy MO has no **nodes**.
  3. For every increase in E, we add a node (in such a way that symmetry is maintained).
- **Node**: A change in sign of the orbital, at which there is no electron density.
- Example of nodes: Think of our π and π^* MOs.

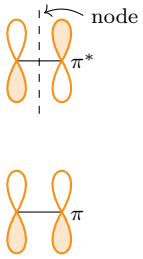


Figure 2.13: Nodes in π and π^* molecular orbitals.

  - The lower one has no nodes, because the phases are aligned left to right.
  - The upper one has 1 node, because the phases invert left to right.
- We are now ready to draw an MO diagram for the diene in Figure 2.12.
- Diene MOs.

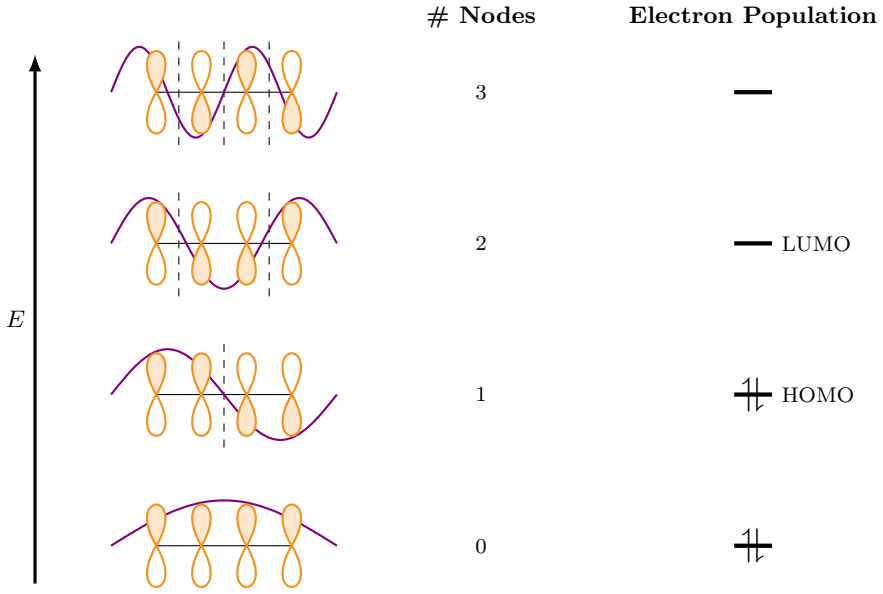


Figure 2.14: Reactive molecular orbitals of a diene.

- Let's start with a rule-by-rule analysis.
  1. We have 4 atoms, so we draw lines for 4 MOs.
  2. The lowest energy MO in Figure 2.14 does indeed have no nodes.
     - Observe that Prof. Elkin shades the top lobes first this time instead of the bottom lobes (as in Figure 2.13) because the shading is arbitrary. This comment is review, but the concept is important to remember!!
  3. For each increase in energy, we do indeed add one node.
     - For the second-lowest energy level, we draw our node symmetrically right in the middle.
       - ➢ We go along shading the top (or bottom) lobes until we hit our node, and then we switch to shading the other side.
     - For the third-lowest energy level, we draw our nodes symmetrically as well.
     - For the highest energy level, we draw a node between every orbital and alternate shading.
       - ➢ The highest energy level has the same alternating structure in the MOs of every conjugated π-system. For another example, see Figure 2.16.
- Note that we also draw (in purple) the **waveform** for every MO.
- Now let's populate our orbitals with electrons.
  - There are four π-electrons in a diene, so per Aufbau, Pauli, and Hund, we fill the bottom two energy levels of our diagram.
  - Filling electrons allows us to identify our HOMO and LUMO, which will be useful for justifying reactivity.
- Takeaway: You probably wouldn't just guess that the LUMO (or any other MO) of a diene looks the way it does, but you can derive it using the three rules and the method of Figure 2.14.
  - Then you can use the result of your derivation to make predictions about a diene's reactivity!
  - We'll cover such predictions next lecture.

- Why do the nodes have to be symmetric?
  - Because quantum mechanics.
  - Very simply, it has something to do with the waveform of each energy level, which you might notice mirrors the waveforms of the particle in a box.
  - See the end of my notes for this lecture for more detail.
    - Note: All extra detail on this topic is beyond the scope of this class, and will never be tested nor appear on problem sets; it is purely to satisfy your curiosity.

- An interesting finding about pericyclic reactions: They can be started by either heat (Δ) or light ($h\nu$)!

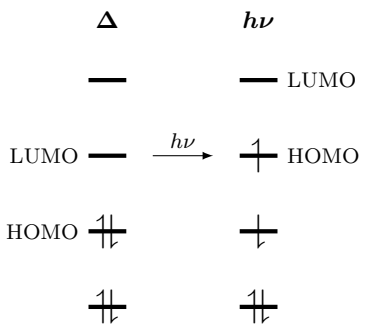


Figure 2.15: A diene's reactive orbitals in thermal vs. photochemical pericyclic reactions.

- When you think about it, heat and light are just different ways to add energy to our system so that the reaction goes.
- Indeed, pericyclic reactions are cool because you don't have to add a chemical reagent to make one go; rather, you just heat it up or shine light at it, and it reacts away!
- How do photochemical reactions work?
  - When light is absorbed, one electron is excited from the HOMO to the LUMO, and none of the spins of *any* of the electrons change (Figure 2.15).
    - ➢ There's a lot more photophysics here that you can go into, but that's beyond the scope of this course.
  - Such excitation is important because it gives us a new HOMO and a new LUMO.
    - ➢ These new reactive orbitals have important consequences that we'll discuss later, especially for the stereochemistry of the product.

- Let's now look at the MOs of one more conjugated system.
- Allyl MOs.

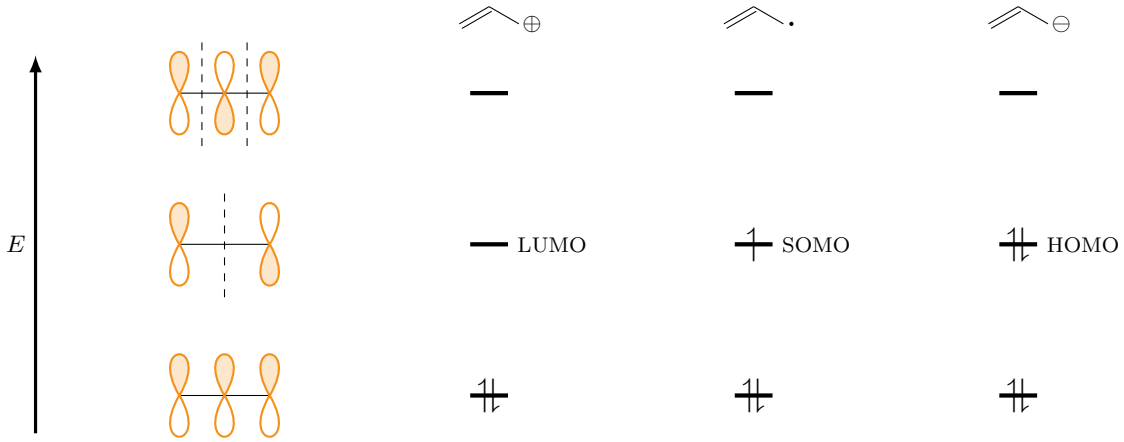


Figure 2.16: Reactive molecular orbitals of an allyl group.

- Let's do another rule-by-rule analysis.
  1. Three atoms going in means three MOs.
  2. Shade all the same phases in the bottom MO.
  3. Add nodes for the upper orbitals.
     - Put your node right in the middle for the middle MO.
       - ➢ It has to be symmetric!
       - ➢ Every time you have an odd number of atoms, some *p*-orbital will get deleted like this.
     - For the top MO, once again do everything alternating.
- Note that we have not yet specified whether this is an allyl cation, allyl radical, or allyl anion!
- We will have a different number of electrons for all three species (even though we have the same MOs), so let's fill electrons for each of these species.
  - Allyl cation: Two electrons, so fill just the bottom MO.
    - ➢ Like any carbocation, the allyl cation will react as an electrophile.
    - ➢ If it reacts as an electrophile, it must react with its LUMO (which is the middle orbital).
  - Allyl radical: Three electrons, so fill the bottom MO and start filling the middle MO.
    - ➢ Like any radical, the allyl radical reacts as a. . . well. . . radical.
    - ➢ If it reacts as a radical, it must react with its **SOMO** (also the middle orbital).

        - Allyl anion: Four electrons, so fill the bottom and middle MOs.
            - ➢ Like any carbanion, the allyl anion will react as a nucleophile.
            - ➢ If it reacts as a nucleophile, it must react with its HOMO (still the middle orbital!).
    - Interesting consequence of this filling: All three allyl species should only react with their middle-energy MO!
        - This would predict that all allyl reactivity occurs at the termini of the allyl group, not the middle carbon, since all of the density of the middle orbital is at the termini and none of it is at the middle carbon.
        - This prediction is experimentally confirmed!

- **Singly occupied molecular orbital**: The molecular orbital in which an unpaired radical electron exists. *Also known as* **SOMO**.

- An elaboration on why nodes must be placed symmetrically in the MOs of conjugated π-systems (see Figures 2.14 and 2.16 and the associated discussion).
    - Reminder: Everything from here, on, in these notes is beyond the scope of this class!
    - The long-short.
        - The waveforms in Figure 2.14 are *exactly* equal to their corresponding particle-in-a-box wave functions (according to some analyses of quantum mechanics).
            - ➢ This relationship can be rationalized intuitively because a conjugated π-system is like an extended, one-dimensional box in which a quantum particle (namely, an electron) lives.
        - The implication is that the molecular orbitals of a conjugated π-system look *exactly* like the particle-in-a-box orbitals, including having nodes in the same places.
        - This actually also means that the individual p-orbitals making up the MOs are different sizes!
            - ➢ For example, in the lowest energy MO in Figure 2.14, the two middle p-orbitals will be larger than the two terminal p-orbitals.
            - ➢ More relevantly, the HOMO and LUMO in Figure 2.14 will have larger terminal p-orbitals, which explains why dienes react at their ends and not in the middle; we have already seen an example of dienes reacting at their terminal carbons instead of their middle carbons in Figure 2.8.
    - More detail.
        - The exact sizes of each p-orbital in a given MO of a conjugated π-system can be calculated — by hand — using only linear algebra. This calculation is part of something called **Hückel theory**.
        - You can learn about Hückel theory by taking a course in quantum mechanics, inorganic chemistry, or graduate physical organic chemistry.
    - If you are interested in reading more about this now, look through the attached PDF. I'd recommend starting with the diagrams and sine/cosine functions on pages 6.6 and 6.7. Enjoy!

2.13 Diels-Alder - 1

10/4:
- Lecture 12 recap.
    - Periyclic reactions have concerted and cyclics transition states.
        - Essentially, what unites all of these reactions is that they have electron arrows moving in a ring!
    - All of these reactions are theoretically reversible.
    - Prof. Elkin redraws the prototypical pericyclic reactions from last class.

  - Three main classes.
    1. Cycloaddition.
       - Bond types changed: $2\pi \rightleftharpoons 2\sigma$.
       - Nomenclature: $[m+n]$.
       - General form: See Figure 2.8.
         - ➢ To reiterate: This reaction can also proceed in reverse, i.e., from right to left!
    2. Electrocyclization.
       - Bond types changed: $1\pi \rightleftharpoons 1\sigma$.
       - Nomenclature: $m\pi$.
       - General form: See Figure 2.10.
         - ➢ To reiterate: This reaction can also proceed in reverse, i.e., from right to left!
    3. Sigmatropic rearrangements.
       - Bonds moved: 1σ.
       - Nomenclature: $[m, n]$.
       - General form: See Figure 2.11.
         - ➢ To reiterate: This reaction can also proceed in reverse, i.e., from right to left!

- Announcements.
  - Please fill out the feedback survey in Canvas > Announcements.
  - PSet 3 is due today.
  - PSet 4 will be posted today.
    - It is the last PSet before Exam 2.
    - It only covers Diels-Alder content. However, the rest of this unit's content (cycloadditions, electrocyclizations, and sigmatropic rearrangements) *will* be on Exam 2 as well.
    - So to prepare for the exam, continue doing the Recitation Worksheets even after PSet 4!!
- Today: Diels-Alder (lecture 1 of 2).
- Recall from last lecture that a *Diels-Alder reaction* is a $[4+2]$ cycloaddition.
  - Specifically, a **diene** reacts with an olefin, which we call the **dienophile**.
  - The simplest Diels-Alder (DA) reaction is drawn in Figure 2.8.
    - This is actually a terrible Diels-Alder reaction because there's a poor HOMO-LUMO energy match (we'll talk more about what that means shortly).
  - The Diels-Alder is a powerful tool to make six-membered rings.
    - We see a lot of six-membered rings in organic chemistry, so the Diels-Alder is very useful.
  - This reaction is very predictible: It is **regioselective**, **stereospecific**, and **reliable**.[4]
- **Diene**: A compound that contains two conjugated double bonds.
  - The diene is (usually) the HOMO.
  - You can think of it as the nucleophile.
- **Dienophile**: An olefin. *Etymology* from Latin "lover of dienes."
  - The dienophile is (usually) the LUMO.
  - You can think of it as the electrophile.
- **Reliable** (reaction): A reaction that almost always works if you have the right energy matching.

[4] We'll discuss both regioselectivity and stereospecificity later this lecture, and stereospecificity even further on Monday.

- Let's look at the MO picture for a Diels-Alder reaction.

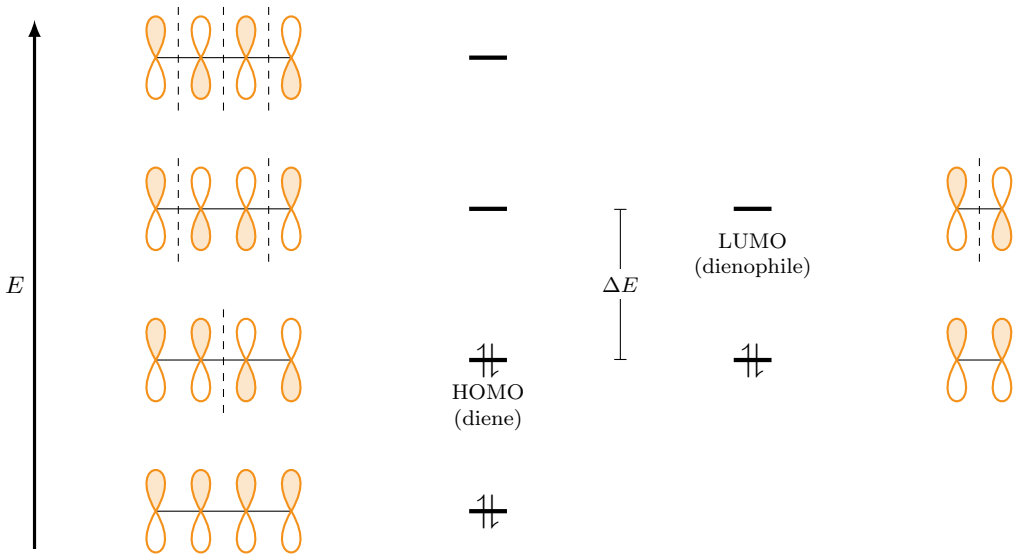
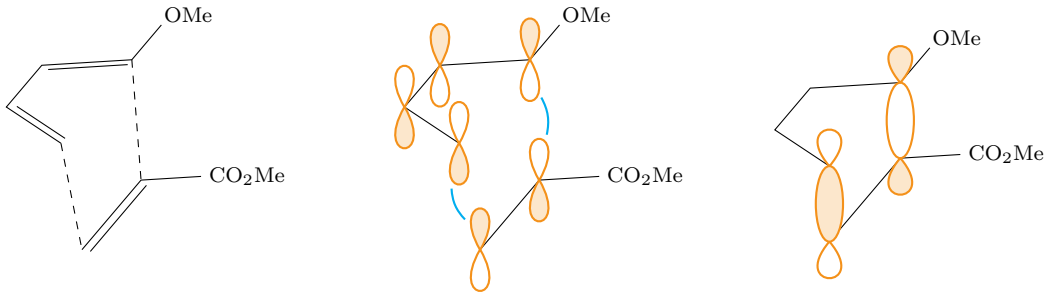


Figure 2.17: Reactive molecular orbitals in a Diels-Alder.

  - Recall our diene MOs from last lecture (Figure 2.14).[5]
    - Specifically, recall that our HOMO has the orbital picture of the second energy level. Since we have said that the diene reacts with its HOMO, this is the important orbital to watch.
  - Recall also our dienophile MOs from last lecture (Figure 2.13).
    - The olefin has two electrons, so its LUMO is the second energy level. Since we have said that the dienophile reacts with its LUMO, this is the important orbital to watch.
  - Initially, we have a poor energy match between HOMO and LUMO (ΔE is large). Therefore, if we want to improve the reaction, we should strive to bring their energies closer together.
  - Two main things to accomplish this goal of bringing HOMO and LUMO energies closer together.
    1. Raise the HOMO by adding EDGs to the diene.
    2. Lower the LUMO by adding EWGs to the dienophile.

- Example: A Diels-Alder reaction that does work well.



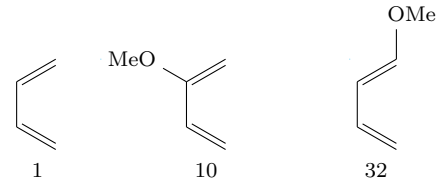
(a) Reactants. (b) Reactant orbitals. (c) Product orbitals.

Figure 2.18: Diels-Alder orbitals in 3D space.

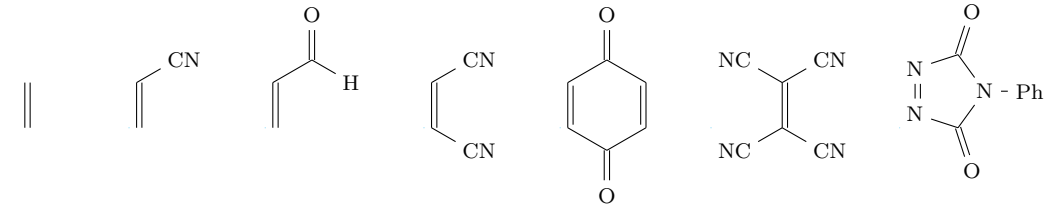
[5]Prof. Elkin reviews the three rules for drawing the MOs of conjugated systems; remember these!!

- Let's analyze the new reactants we've drawn (Figure 2.18a).
  - The methoxy-substituted diene is a better nucleophile than 1,3-butadiene because methoxy groups are electron-donating.
  - The ester-substituted dienophile is a better electrophile than ethylene because ester groups are electron-withdrawing.
  - Recall electrophilic aromatic substitution reactions, which tell you what substitutents are electron donating vs. withdrawing. Review this 5.12 content!!
- Now let's look at their orbitals (Figure 2.18b).
  - We draw a "perspective picture" of the HOMO and LUMO.
  - Observe that the phases of the HOMO and LUMO match!
    - ➢ Specifically, we mean that the lobes connected by the blue lines have the same shading.
  - A note on shading.
    - ➢ The *relative* shading between reacting molecules *does* matter because we've got to see overlap between pairs of shaded lobes and pairs of unshaded lobes when we're forming bonds.
    - ➢ Thus, while we could invert the shading of every p-orbital in Figure 2.18b and be fine, we *could not* invert the shading of just the diene and leave the dienophile unchanged (or vice versa).
- We now redraw the molecules, but after they've formed σ-bonds (Figure 2.18c).
  - As the π-orbitals come together, the middle lobes fuse and become σ-bonds.
  - Implication: You have to have a top-to-bottom approach so that the p-orbitals interact and mix. A side-to-side overlap would not form σ-bonds from p-orbitals.

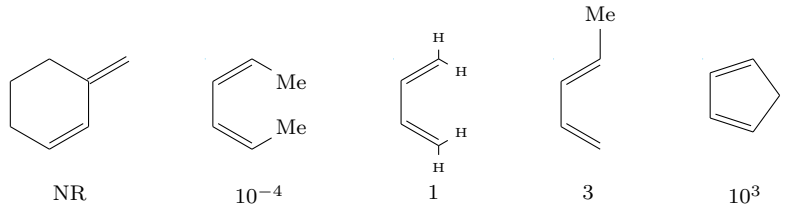
- Accelerating Diels-Alder reactions.



(a) Various dienes (electronic effects).



(b) Various dienophiles.

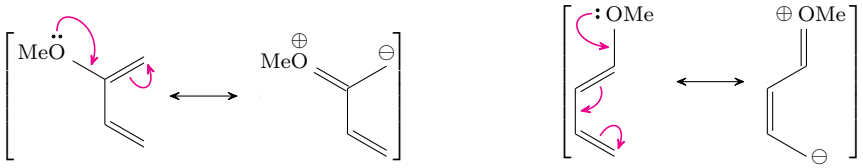


(c) Various dienes (steric effects).

Figure 2.19: The relative rate of reaction of different Diels-Alder substrates.

1. Raise the HOMO by putting EDGs on the diene (Figure 2.19a).
   - Adding a methoxy substituent (an EDG) will increase the rate regardless of the position to which you add it.
   - However, interestingly enough, it will increase the rate *more* when added to some positions over other positions.
   - This is because of the difference between **cross-conjugation** and regular conjugation.
2. Lower the LUMO by putting EWGs on the dienophile (Figure 2.19b).
   - From left to right, the names of these seven compounds are: ethylene, acrylonitrile, propenal, *cis*-1,2-dicyanoethene, *para*-quinone, tetracyanoethene, and 4-phenyl-1,2,4-triazole-3,5-dione (PTAD[6]).
3. Enforce the **s-*cis*** configuration (Figure 2.19c).
   - The leftmost compound is locked in the **s-*trans*** conformation.
   - The next one has a big steric clash between methyl groups, so it's much more stable in the s-*trans* configuration.
   - Buta-1,3-diene likes to be s-*trans* because it still has sterics from the hydrogens.
   - Penta-1,3-diene has the same mild steric preference for s-*trans* as buta-1,3-diene.
     - However, certain stereoelectronic effects (which you'll work out on PSet 4!) promote its reactivity.
     - Essentially, methyl groups are slightly electron-donating.
   - Cyclopentadiene is locked in an s-*cis* conformation.

- **Cross-conjugated** (molecule): A molecule containing multiple olefins that — despite being arranged in a row — do not delocalize efficiently.



(a) Cross-conjugation. (b) Regular conjugation.

Figure 2.20: Cross-conjugation vs. regular conjugation.

- Notice that for the molecule in Figure 2.20a, we cannot draw a resonance structure that engages the bottom π-bond.
- In contrast, regular conjugation (Figure 2.20b) disperses the oxygen's electron density across the entire π-system.

- **s-*cis*** (conformer): The rotational isomer of a diene in which the alkenes are *cis* relative to the σ-bond.

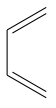


Figure 2.21: s-*cis* diene.

[6] According to Sauer and Schröder (1967), PTAD is approximately 10^5 times faster than tetracyanoethene. This means that it is approximately 4×10^{12} times faster than acrylonitrile!

- **s-*trans*** (conformer): The rotational isomer of a diene in which the alkenes are *trans* relative to the σ-bond.

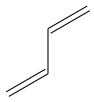
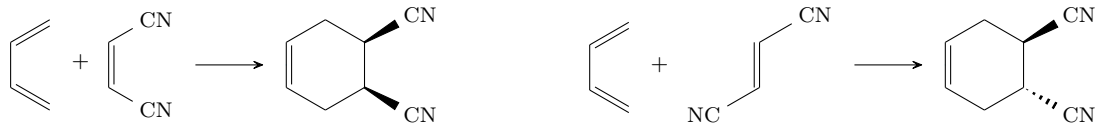


Figure 2.22: s-*trans* diene.

- Essentially, olefins can be *cis* or *trans*.



(a) *cis* olefins. (b) *trans* olefins.

Figure 2.23: Reacting *cis* and *trans* olefins in the Diels-Alder.

  - When you react the *cis*-olefin in a Diels-Alder, you get (exclusively) the *cis*-product.
  - When you react the *trans*-olefin in a Diels-Alder, you get (exclusively) the *trans*-product.
  - This means that the Diels-Alder is **stereospecific**.[7]

- On the other hand, dienes can be s-*cis* or s-*trans*.

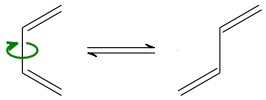


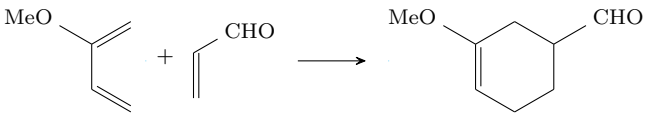
Figure 2.24: s-*cis* and s-*trans* conformers rapidly interconvert.

  - The "s" stands for "sigma bond."
  - These two diene conformers are not discrete species; rather, they interconvert like the gauche, anti, staggered, etc. conformers of ethane.
  - Only s-*cis* dienes react in Diels-Alders, so enforcing that geometry accelerates the reaction.

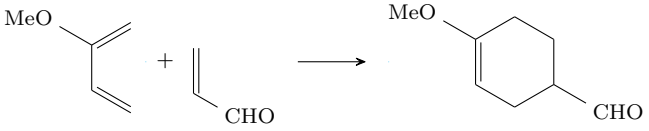
- **Stereospecific** (reaction): A reaction in which the stereochemistry of the reactants translates directly into a single stereochemical product.
- **Stereoselective** (reaction): A reaction in which when a certain stereochemical product is favored, but a mixture is still produced and the stereochemistry of the reactants doesn't exert excessive influence.
- **Stereoretentive** (reaction): A reaction in which the exact stereocenters present in the starting material are conserved in the product.
- Does the rightmost diene in Figure 2.19a have to be *trans* at the upper alkene?
  - Yes; we'll talk about that more next lecture.
- Can you lower the LUMO so much that the Diels-Alder reaction no longer proceeds?
  - Yes! This is related to **inverse electron-demand** Diels-Alder reactions, discussed next Monday.
- Can you have a photochemical Diels-Alder?
  - They're quite rare, but you can do similar things.
  - Note: Lewis acid acceleration of Diels-Alders will also be discussed next Monday.

[7] Next lecture, you will learn how the Diels-Alder is **stereoselective** but still not **stereoretentive**.

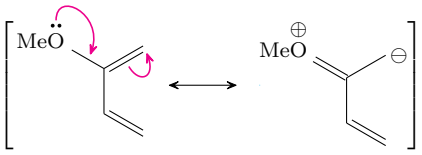
- Regioselectivity.



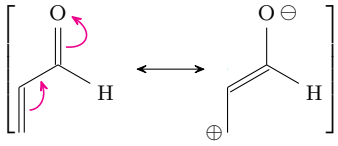
(a) *meta*-product.



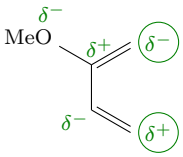
(b) *para*-product.



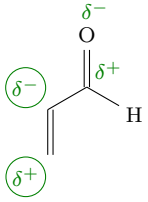
(c) Diene (resonance).



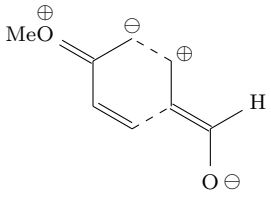
(d) Dienophile (resonance).



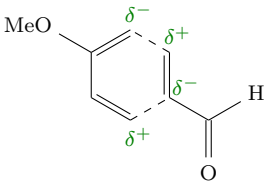
(e) Diene (hyperconjugation).



(f) Dienophile (hyperconjugation).



(g) Resonance matching.



(h) Hyperconjugation matching.

Figure 2.25: Diels-Alder regioselectivity.

- Observation: Depending on how the diene and dienophile are oriented when they react, we could conceivably form two different products (Figures 2.25a-2.25b).
  - These two products are called the ***meta*-product** and the ***para*-product**.

  - So which product do we actually get?
    - We will determine this by using either *resonance* or *hyperconjugation/partial negative charges* to identify and match the electron-rich and electron-poor sites on our diene and dienophile.[8]
    - Use whichever method your prefer since they give the same result, but you should learn both!!
  - The resonance analysis (Figures 2.25c-2.25d).
    - As in Figure 2.20, push arrows as far as we can to get the reactive resonance structure.
  - The hyperconjugation analysis (Figures 2.25e-2.25f).
    - Begin with an atom that we *know* will have a partial positive (δ^+) or partial negative (δ^-) charge.
      - ➢ For example, we know that oxygen will be δ^- because it is the most electronegative atom in both structures.
      - ➢ Thus, we can label it first in both Figures 2.25e and 2.25f.
    - Then expand out over the rest of the conjugated system, alternating δ^+ or δ^- atom-to-atom.
      - ➢ So since oxygen is δ^-, the carbon α to it should be δ^+, the carbon(s) β to it should be δ^-, the carbon(s) γ to it should be δ^+, etc.
    - Keep track of the partial charges on the termini of the diene and dienophile (i.e., the reactive sites). These are circled in Figures 2.25e-2.25f.
  - Notice the agreement/consistency between the two methods!
    - Indeed, the carbanion in Figure 2.25c corresponds to a δ^- carbon in Figure 2.25e, and the carbocation in Figure 2.25d corresponds to a δ^+ carbon in Figure 2.25f.
  - Once we have performed either analysis, matching up the negatives on the diene to the positives on the dienophile and vice versa predicts our product!
    - Thus, by both analyses, the *para*-product is favored!
    - This matching of positive and negative charges is indicative of the maxim that "organic chemistry is just magnets everywhere."
  - Exercise: Try drawing the meta-product, which will force you to put positive near positive and negative near negative.
    - "That's not fun, that's not how magnets work."

- ***meta*-product**: The product of a Diels-Alder reaction in which the substituents would be oriented *meta* to each other on the six-membered ring, if the six-membered ring were aromatic.
- ***para*-product**: The product of a Diels-Alder reaction in which the substituents would be oriented *para* to each other on the six-membered ring, if the six-membered ring were aromatic.
- Prof. Elkin has many more examples, but will go through them on Monday.

2.14 Diels-Alder - 2

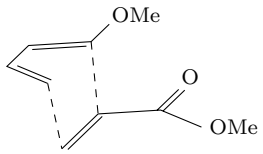
10/7:
- Lecture 13 recap.
  - Corrections to Lecture 13.
    - The word "Diels-Alder" usually has a hyphen; it is *not* written "Diels Alder" with a space.
    - The methyl-activated diene in Figure 2.19c is faster because of *electronics*, not sterics.
      - ➢ Indeed, this diene has the same steric preference for s-*trans* as buta-1,3-diene, but it is slightly faster because methyl groups are slightly electron-donating.

[8] Note that there is also a secret third method: MO theory! See Clayden et al. (2012, p. 890) for how to do this. As we would expect, the predictions we get by both resonance and hyperconjugation match the predictions of MO theory. (Note also that you are not required to learn the MO theory method because it was not covered in class; this comment is purely to point out an interesting connection :)

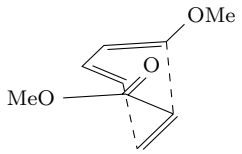
        - Definitions of **stereoretentive**, **stereospecific**, and **stereoselective** reactions.
    - Recap of regioselectivity.
        - Prof. Elkin redraws Figure 2.25h as a method of predicting the *para*-product (Figure 2.25b).

- **Stereoretentive** (reaction): A reaction in which the stereocenter(s) in the starting material are retained exactly.
    - Example: (*R*)-butan-2-ol reacts and is still an (*R*)-alcohol.
- **Stereospecific** (reaction): A reaction in which the stereocenter(s) of the starting material decide the stereocenter(s) of the product.
    - Example: Figure 2.23.
    - To reiterate: The phenomenon exemplified by Figure 2.23 is an example of stereospecificity, *not* stereoselectivity (as was incorrectly said last lecture).
- **Stereoselective** (reaction): A reaction in which a certain stereoisomer of the product is preferred.
    - Example: Butan-2-one is reduced to (*R*)-butan-2-ol, instead of racemic (±)-butan-2-ol.
    - Stereoselective is an "umbrella" term: Both stereoretentive and stereospecific reactions are stereoselective, but not all stereoselective reactions are stereoretentive or stereospecific.
- Today: More on the Diels-Alder reaction.
- Lecture outline.
    - More on regioselectivity.
    - *exo* vs. *endo* transition states.
    - *exo* vs. *endo* products.
    - Lewis acid catalysts for Diels-Alder reactions.
    - Inverse electron-demand Diels-Alder reactions.
    - Example Diels-Alder reactions; relevant to PSet 4!
- We'll begin today by continuing our discussion of regioselectivity.
    - Recap of Figure 2.25.
        - Note that like we have the *meta*-product and *para*-product, we can have the *ortho*-product.
    - General rules (timesavers).
        1. A single EDG on the diene and EWG on the dienophile (usually) leads to the *ortho*-product or the *para*-product, not (usually) the *meta*-product.
        2. If there isn't a clear preference (e.g., weak EDG or EWG only), you get a mixture of products.
            - Example: The methyl-actived diene, penta-1,3-diene (see Figure 2.19c), reacts with propenal to give both the *ortho*- and *meta*-products in an 8:1 ratio. On the other hand, the methoxy-activated diene, 1-methoxybuta-1,3-diene (see Figure 2.19a), reacts with propenal to give 100% of the *ortho*-product.
- Switching subjects, let's finally investigate what determines the full stereochemistry of the product.
    - We have previously discussed the stereo*specificity* implied by *cis* or *trans* starting materials, but we will now discuss a type of stereo*selectivity*.
    - Specifically, we will need to begin our investigation with a slight detour to define and analyze the ***endo*** and ***exo*** transition states.
- ***endo*** (transition state): The Diels-Alder TS in which the dienophile's EWG points *toward* the diene.
- ***exo*** (transition state): The Diels-Alder TS in which the dienophile's EWG points *away from* the diene.

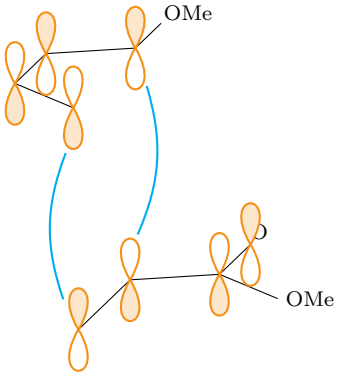
- *exo* vs. *endo* transition states.



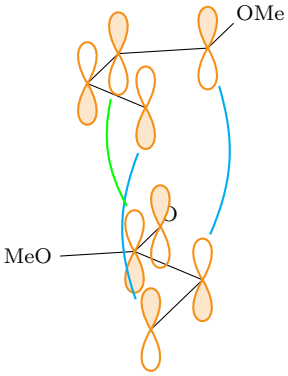
(a) *exo* transition state.



(b) *endo* transition state.



(c) *exo* orbitals.

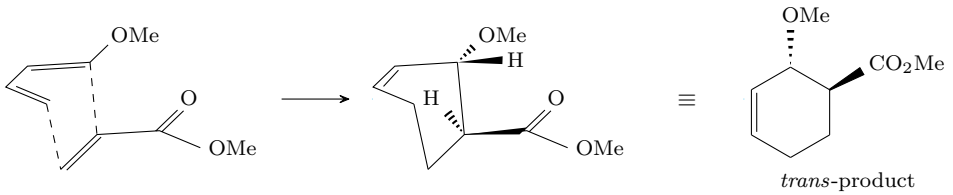


(d) *endo* orbitals.

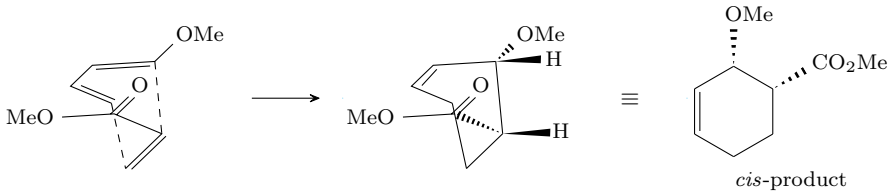
Figure 2.26: *exo* vs. *endo* transition states in the Diels-Alder.

  - Essentially, observe that when the starting materials in a Diels-Alder reaction encounter each other, the dienophile's substituent can either point "out" (Figure 2.26a) or "in" (Figure 2.26b).
    - Remember that per Figure 2.18, the substituents have to encounter each other top-to-bottom.
    - Remember that per regioselectivity, the reactants will encounter each other as drawn so as to form the *ortho*-product.
  - The lower energy transition state will lead to more product, so let's compare their relative energies.
  - To do this, we will have to consider the "full LUMO" of the dienophile.
    - While we've only considered the dienophile's alkene functional group so far, observe that methyl acrylate also has an adjacent carbonyl π-bond that can conjugate with the alkene functional group just like in a diene!
    - Thus, four p-orbitals will form the "full MOs" of the dienophile.
    - The four dienophile MOs resulting from these four p-orbitals can be drawn using the three rules from Lecture 12, resulting in a picture exactly like Figure 2.14.
    - Since the dienophile will still be reacting with its LUMO, the "full LUMO" of the dienophile will look like the third energy level in Figure 2.14. Indeed, that's what we draw on the dienophile in both Figures 2.26c-2.26d!
  - In both the *exo* and *endo* transition states, our "full LUMO" has **primary orbital interactions** with the diene HOMO analogous to Figure 2.18b. This enables the formation of σ-bonds as we'd expect, even (to reiterate) with the "full LUMO."
  - However, there are also some differences between the transition states.
    - *exo* transition state: There is *less steric clash* between the diene/dienophile substituents.
    - *endo* transition state: There is a new **secondary orbital interaction** that is stabilizing.
  - This secondary orbital interaction is (usually) more stabilizing than the lack of sterics, so the *endo* transition state is (usually) preferred!
    - This is technically a $\pi_{\text{HOMO}} \rightarrow \pi^*_{\text{full LUMO}}$ interaction.

- **Primary** (orbital interaction): An orbital interaction that leads to bonding.
- **Secondary** (orbital interaction): An orbital interaction that doesn't lead to bonding, but is stabilizing (or destabilizing).
- Let's now connect *endo* and *exo* transition states back to the stereochemistry of the product in a Diels-Alder reaction.



(a) *exo* pathway.



(b) *endo* pathway.

Figure 2.27: The transition state predicts Diels-Alder product stereochemistry.

  - In the course of a Diels-Alder reaction, once we form our (*endo* or *exo*) transition state, we will subsequently form bonds and then unfold the structure — like a book — into our product.
    - Consider drawing in the hydrogens to help see how we get from the second to the third picture.
  - For the particular Diels-Alder reaction we've considered in both Figures 2.26 and 2.27, the *exo* transition state yields the *trans*-product and the *endo* transition state yields the *cis*-product.
    - Because the *cis*-product arises from the *endo* transition state (which, to reiterate, is the preferred transition state), the *trans*-product will be preferred for this reaction!
    - I.e.: The *cis*-product is the major product, and the *trans*-product is the minor product.
  - Since the Diels-Alder is not **enantioselective**, we can draw either enantiomer of the product.
    - In other words: We could switch all wedges and dashes for dashes and wedges, respectively, in Figure 2.27a-2.27b and still have the right answer.
  - Help digesting this material: Look for some online visualizations, get a molecular model kit, etc.!!
- **Enantioselective** (reaction): A reaction that favors one enantiomer of the product over another.
- Example: Predicting the proper stereochemistry in the following Diels-Alder reaction.

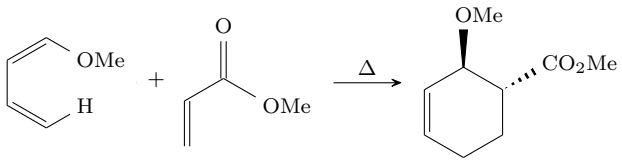


Figure 2.28: Diels-Alder reaction of (*Z*)-1-methoxybuta-1,3-diene and methyl acrylate.

  - The rate will be slower than if (*E*)-1-methoxybuta-1,3-diene were used because the diene in Figure 2.28 is s-*cis* destabilized.
    - The s-*cis* destabilization comes from steric clashing between the methoxy group and the hydrogen.
  - The regioselectivity will pair the bottom carbon on the diene in Figure 2.28 to the bottom carbon on the dienophile in Figure 2.28, yielding the *ortho*-product.
  - The stereoselectivity will favor the *endo* transition state because the dienophile's EWG has a π-system that can participate in secondary orbital interactions with the diene.
    - Thus, we will favor the drawn diastereomer (and its enantiomer!).
    - Note that in this reaction, the *endo* transition state yields the *trans*-product. This is the opposite of Figure 2.27b, in which the *endo* transition state yielded the *cis*-product.
    - This illustrates that it's not always the *cis*-product that's major! Rather, whether *cis* or *trans* is major depends on the transition state (*endo* or *exo*) from which each originates.
  - Tip for learning this content: Just practice, esp. drawing the product regio- and stereochemistry.

- This wraps up all we need to say about *endo* and *exo* transition states.
- So, switching topics, let's discuss accelerating Diels-Alder reactions with catalysis.
  - So far, every Diels-Alder reaction we've considered has been thermal.
  - We can accelerate these reactions with a Lewis acid catalyst (such as $SnCl_4$, $EtAlCl_2$, etc.).
  - This allows us to do our Diels-Alder reactions...
    1. At a lower temperature;
    2. With greater stereoselectivity.
       - Lower temperatures make the *endo* transition state even more preferred.
- Example: How does this Lewis acid catalysis work?

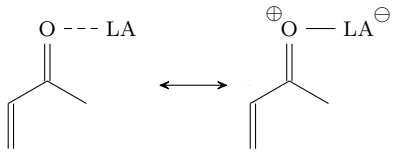


Figure 2.29: Lewis acid catalysis of Diels-Alder reactions.

  - Three-step process.
    1. The Lewis acid (LA) coordinates to the dienophile's EWG, making it more electron poor.
    2. This lowers the LUMO even further, which gives you better energy overlap.
    3. Better energy overlap stabilizes the transition state.
  - Essentially, Lewis acid catalysts work by making our EWG "better."
- Switching topics again, let's discuss something to which we've alluded a few times: What happens when the diene is super stabilized and the dienophile is super destabilized.
- **Inverse electron-demand** (Diels-Alder reaction): A Diels-Alder reaction in which the HOMO of the dienophile interacts with the LUMO of the dienophile.
  - Still ortho/para-directing.
  - Still *endo* TS preferred.
  - Often see this when we have a heteroatom in the ring.

- Example inverse electron-demand Diels-Alder reaction.

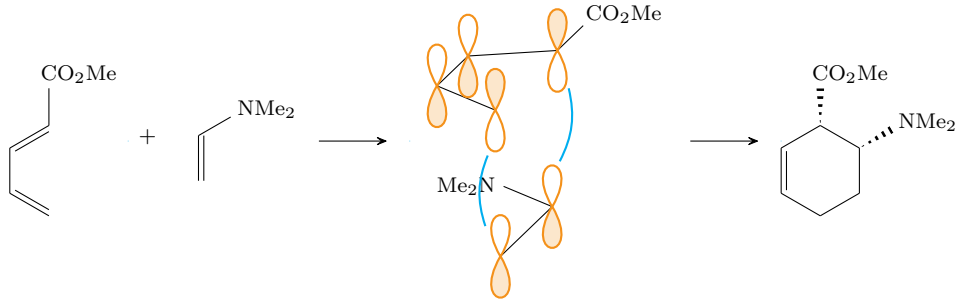
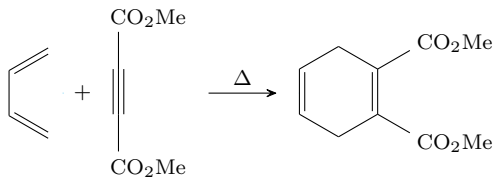


Figure 2.30: Diels-Alder reaction with inverse electron-demand.

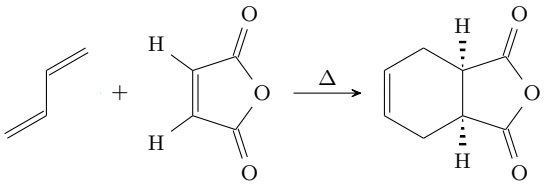
  - Because of the methyl ester EWG, the diene in Figure 2.30 is now electron-poor.
    - As such, it will react with its LUMO (the third energy level in Figure 2.14).
  - Because of the amine EDG, the dienophile in Figure 2.30 is now electron-rich.
    - As such, it will react with its HOMO (the first/lowest energy level in Figure 2.13).
  - However, when we draw the HOMO of the dienophile and LUMO of the diene, we still get good orbital overlap. Thus, this reaction can still proceed, forming the *ortho*-*cis*-product through the *endo* transition state.

- Why is the *endo* TS still preferred?
  - The exact orbital interactions here deal more with coefficients and differently sized orbital lobes, but that is beyond the scope of this class.
  - Take 5.43 and 5.53 if you want to learn more!

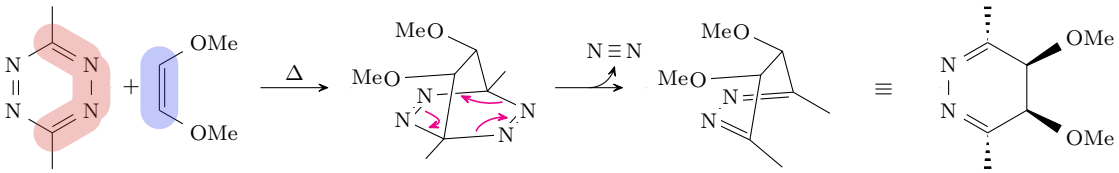
- More example Diels-Alder reactions.



(a) Alkynes can be dienophiles.



(b) *cis*/*trans* dienophiles and s-*cis*/s-*trans* dienes.



(c) Multistep one-pot inverse electron-demand Diels-Alder.

Figure 2.31: Exotic Diels-Alder reactions.

1. Figure 2.31a: Dienophiles can be triple-bonded as well!
   - If a given molecule has at least one double bond, it can (usually) react as a dienophile.
2. Figure 2.31b: Don't be fooled by s-*trans* drawing; the diene is still buta-1,3-diene!
   - We will form the *cis*-product because the alkene hydrogens in the dienophile reactant are locked in the *cis*-orientation. (See Figure 2.23 for more context.)

3. Figure 2.31c: A cool example of an inverse electron-demand Diels-Alder reaction.
   - The heteroatoms (nitrogens) in the ring of the diene should clue us into the fact that this might be an inverse electron-demand Diels-Alder reaction. (See the definition of inverse electron-demand Diels-Alder reaction.)
     - Indeed, this diene is called a **tetrazine**, and it can do inverse electron-demand reactions.
   - The diene within the tetrazine ring is highlighted in red, and the reactive alkene within the dienophile is highlighted in blue.
   - Drawing the product of the first Diels-Alder reaction can be a bit tricky, but Prof. Elkin has a good method for doing it.
     - Begin by stacking the starting materials in a perspective drawing.
     - Add dashed lines between the bonding atoms, yielding a drawing of your transition state.
     - Fill in the dashed lines and rearrange the double bonds to complete the transformation.
   - What's cool about this reaction is that there is an immediate follow-up reaction to the first Diels-Alder.
     - In particular, the product of the first step does a retro-Diels-Alder, releasing N_2 gas.
       - ➢ The release of an extremely stable gas molecule is a driving force for this second reaction.
     - Once N_2 is released, we can redraw the product (now the final product) as a **diazine**.

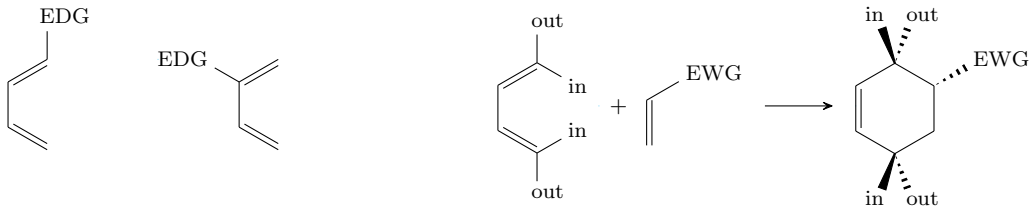
- **Tetrazine**: A molecule with a central six-membered aromatic ring containing four nitrogen atoms.
- **Diazine**: A molecule with a central six-membered aromatic ring containing two nitrogen atoms.

2.15 Cycloadditions

10/9:
- An update on who won this year's Nobel Prize in Chemistry!
  - Awarded for: The computational design and prediction of protein structures.
  - ½ share: David Baker (University of Washington-Seattle).
    - For artificial protein design and synthesis.
    - One of the things he did was design and synthesize a protein to catalyze Diels-Alder reactions, called Diels-Alderase! You can read more about it in Siegel et al. (2010).
      - ➢ Diels-Alderases were hypothesized to exist ever since the discovery of the Diels-Alder reaction, but they were not found in nature until 20 years ago when we isolated the first natural Diels-Alderase from a mango tree.
  - ¼ share, each: Dennis Hassabis and John Jumper (both from Google DeepMind).
    - For building a computer program called AlphaFold.
      - ➢ AlphaFold predicts protein structures from their amino acid sequences.
      - ➢ This largely solves the **protein folding problem**.
      - ➢ Hassabis and Jumper basically poured all of Google's computational resources into this endeavor and combined it with a lot of machine learning to create a true tour de force of engineering.
      - ➢ When the dust settled, AlphaFold worked pretty well, and it's now used all over the world.
      - ➢ AlphaFold still needs some future development, though.
    - Prof. Elkin is especially interested in this topic because she *researches* the intersection of machine learning and chemistry.
      - ➢ She will give a "special topics" lecture on it later this semester!
      - ➢ If you are curious about machine learning and chemistry, too, come talk to her!!

- **Protein folding problem**: Given a sequence of amino acids, predict the structure of the protein.

- Lecture 14 recap: A cheat sheet for Diels-Alder reactions.



(a) *o*- and *p*-selective dienes. (b) Stereochemistry.

Figure 2.32: Diels-Alder cheat sheet.

  - Reactivity.
    - Normal electron-demand Diels-Alder reactions are accelerated by...
      - EDGs on the diene;
      - EWGs on the dienophile;
      - Promoting the s-*cis* conformation of the diene;
      - Lewis acid catalysts.
    - Inverse electron-demand Diels-Alder reactions are also accelerated by all of these things, except you switch EDGs to the dienophile and EWGs to the diene.
  - Regiochemistry (Figure 2.32a).
    - *ortho*- and *para*-products are preferred.
    - A diene with an EDG on the 1-position (left diene in Figure 2.32a) favors the *ortho*-product.
    - A diene with an EDG on the 2-position (right diene in Figure 2.32a) favors the *para*-product.
  - Stereochemistry (Figure 2.32b).
    - The dienophile's stereochemistry matters.
      - A *cis*-dienophile implies a *cis*-product, and a *trans*-dienophile implies a *trans*-product.
      - See Figure 2.23.
    - The *endo* transition state is preferred.
      - This means that we usually form the sterochemistry shown in Figure 2.32b.
      - In particular, the EWG should be *cis* to the "out" substituents.
  - You *will* need to know the reasons behind all of these reaction characteristics, i.e., you may be asked to derive them with orbital pictures on the exam.
    - However, these shortcuts can help us on "predict the product"-type questions.

- Today: Cycloadditions.

- Lecture outline.
  - Dipolar cycloadditions.
    - Examples of dipoles.
    - Example reactions.
    - The molecular orbital picture.
    - Azide as a dipole: Click reactions.
    - Ozone as a dipole: Ozonolysis and ozonide trapping.
  - $[2 + 2]$ cycloadditions.

- **Dipolar** (cycloaddition): A (usually $[3+2]$) cycloaddition between a **dipole** and a **dipolarophile**.
  - These are nice because they make 5-membered rings the same way Diels-Alder reactions make 6-membered rings!
- **Dipole**: A molecule with the following general form. *Structure*

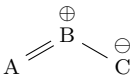


Figure 2.33: Dipole.

  - A, B, and C are atoms.
    - Depending on the specific atoms involved, the double bond above may be a triple bond or the single bond above may be a double bond.
    - The dipole can stand alone, or it may be bonded to an R group through one of its atoms.
    - The zwitterion (adjacent positive and negative formal charges) is always present, though; this is the actual dipole within the dipole molecule!
  - Tip from Prof. Elkin: Now is probably a good time to review how to draw Lewis structures, resonance forms, etc. from Gen Chem or 5.12; this content is relevant to how to draw dipoles!!
- **Dipolarophile**: The species that reacts with the dipole. *Etymology* from Latin "lover of dipoles."
  - This is usually an alkene or alkyne.
- Mechanism.

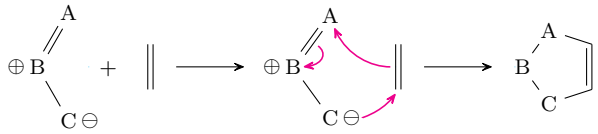
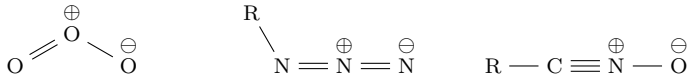


Figure 2.34: Dipolar cycloaddition.

  - Prof. Elkin likes to draw circle arrows starting from the region of highest electron density (i.e., the negative charge on atom C).
- Examples of dipoles.



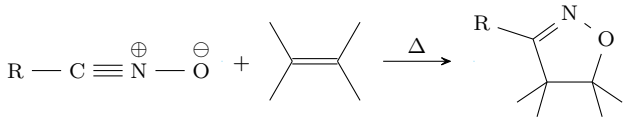
(a) Ozone. (b) Azide. (c) Nitrile oxide.

Figure 2.35: Examples of dipoles.

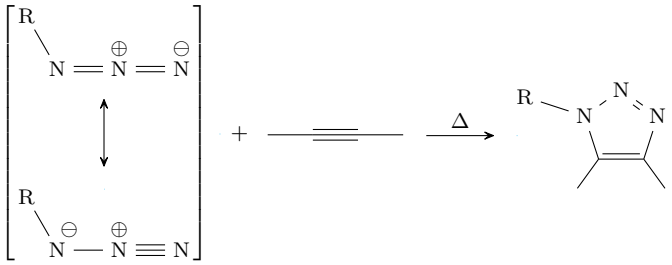
1. **Ozone**.
2. **Azide**.
3. **Nitrile oxide**.

- **Ozone**: The O_3 molecule. *Structure* (see Figure 2.35a.)
- **Azide**: The N_3^- functional group. *Structure* (see Figure 2.35b.)
- **Nitrile oxide**: The CNO^- functional group. *Structure* (see Figure 2.35c.)

- Examples of dipolar cycloadditions.



(a) Reacting a nitrile oxide.



(b) Reacting an azide.

Figure 2.36: Examples of dipolar cycloadditions.

  - Reacting a nitrile oxide with an alkene (Figure 2.36a).
    - Forms the 5-membered ring you'd expect by drawing arrows as in Figure 2.34.
  - Reacting an azide with an alkyne (Figure 2.36b).
    - Note that *both* resonance structures can react with the alkyne.
      - ➢ You will have to draw different arrows, but if you start from the negatively charged atom on the dipole (as Prof. Elkin likes to) both times, you'll get the same product.
      - ➢ Draw both mechanisms out as practice!!
    - Product is aromatic, so this is a very thermodynamically downhill (i.e., favorable) reaction.
    - This is our first example of a **click reaction**.

- Let's now look at the orbitals involved in a dipolar cycloaddition.

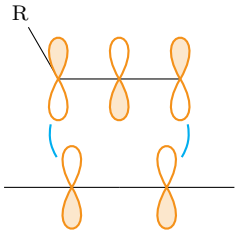


Figure 2.37: Dipolar cycloaddition orbitals in 3D space.

  - As a reference, we can think of the orbitals that would be involved in the azide reaction from Figure 2.36b, but it will be the same orbitals in any dipolar cycloaddition.
  - Something that's new with dipolar cycloadditions vs. the Diels-Alder reaction: It is hard to tell which reactant (dipole or dipolarophile) reacts with its HOMO, and which one reacts with its LUMO.
    - In fact, the choice to draw the HOMO for one and the LUMO for the other is arbitrary!
    - The shading will work out either way, as long as you're reacting a HOMO on one species and a LUMO on the other.

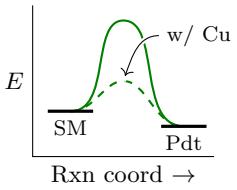
  - So, without loss of generality, let's suppose our dipole reacts with its LUMO.
    - Per Figure 2.35b, the Lewis structure for the azide has two π-bonds (which naturally contain four total electrons) along the three-atom-long dipole.
    - Thus, when we're making molecular orbitals, we should consider the case of 3 p-orbitals with 4 electrons. But this setup is isoelectronic to our allyl MOs (Figure 2.16) from a few lectures ago!
    - Therefore, the LUMO of the dipole will look like the third energy level of Figure 2.16. Indeed, that's what we've drawn in Figure 2.37!
  - If our dipole reacts with its LUMO, then our dipolarophile must react with its HOMO.
    - This time, we recognize a two-atom, two-electron system in each alkyne π-bond.
    - However, the alkyne will only react with one of its π-bonds. Thus, our MOs should align with the case of 2 p-orbitals with 2 electrons, which is analogous to Figure 2.13.
    - Therefore, the HOMO of the dipolarophile will look like the first energy level of Figure 2.13. Indeed, that's what we've drawn in Figure 2.37!
  - With our MOs drawn, we can see that the phases do indeed match between our LUMO and HOMO!
    - Thus, the reaction proceeds and new σ-bonds to begin to form.
  - To reiterate: We could alternatively draw the HOMO of the dipole and the LUMO of the dipolarophile, and the phasing would still work out!
    - Try this yourself for practice!!

- **Click** (reaction): A reaction that joins two molecules quickly and irreversibly.
  - History of click reactions.
    - Etymology: These reactions "click" molecules together like Legos.
    - It's fun that we're talking about them on Nobel Prize day of this year because these reactions won the 2022 Nobel Prize in Chemistry!
  - Defining characteristics.
    - Click reactions have to be very **chemoselective**.
    - Highly reactive (i.e., with a fast rate). We obtain this especially with some modifications.

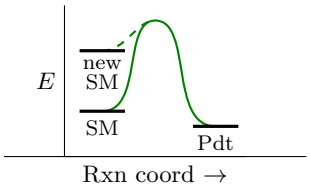
- **Chemoselective** (reaction): A reaction between molecules that only react with each other, even in the presence of related functional groups.
  - Chemoselective reactions are essential for certain biological applications.
    - Imagine you have two molecules in a cell that you want to join together, e.g., you've got a protein and you want to track where it goes by attaching a fluorescent dye to it.
    - To do this, you attach one reactant (e.g., an azide) to the protein and the other (e.g., an alkyne) to the fluorescent dye.
    - Then, once in the cell, the azide and alkyne will react with each other but nothing else in the cell because they're *chemoselective* for each other.
  - Azide-alkyne cycloadditions were great when they were developed because there's not a lot of azides or alkynes in cells, so once you put them in a cell, they'll click together very easily.

- The initial azide-alkyne cycloaddition was good, but it needed improvement in two main areas in order to be biocompatible.
  1. It needed to be able to be run at room temperature, so that it could work at body temperature inside a living cell.
  2. It needed to have nontoxic reactants, so that the reactants wouldn't damage anything else inside a living cell.

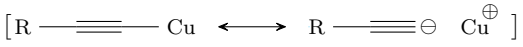
- For the reaction to be able to be run at room temperature, we needed to make the reaction even more highly reactive. There are two approaches that met this goal.



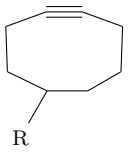
(a) Copper-catalyzed energy diagram.



(b) Cyclooctyne energy diagram.



(c) Copper catalysis.



(d) Cyclooctyne reactant.

Figure 2.38: Accelerating click reactions.

1. Copper catalysis.
   - Approach.
     - When you add copper into solution, it adds into the end of the alkyne (Figure 2.38c).
     - This pushes more electron density into the alkyne via resonance, raising our HOMO.
     - This is exactly the same phenomenon as putting an EDG on the diene in a Diels-Alder reaction!
   - Benefits.
     - This was great because now the reaction proceeds at room temperature!
     - Copper did this by lowering the activation energy/transition state barrier (Figure 2.38a).
   - Drawbacks.
     - Cu is toxic, so this accelerated reaction can't be run in cells.
     - Our second approach has to overcome the "copper kills everything in a cell" problem.
2. Strain release with cyclooctyne.
   - Approach.
     - Incorporate our alkyne into an 8-membered ring; this yields a very strained molecule (Figure 2.38d).
     - But when you go from an alkyne to an alkene in the course of the reaction (see Figure 2.36b), you release that strain because an alkene has appropriate bond angles to exist in an 8-membered ring.
     - Essentially, we've added an additional thermodynamic driving force: Strain is released when the reaction occurs, so it is more downhill.
     - This is an approach called **ground state destabilization**.
     - Here's how it looks on an energy diagram (Figure 2.38b): We've lowered the transition state energy *relative* to the starting materials by putting more energy into the reactants, specifically energy in the form of potential energy trapped in the strained ring.
   - Benefits.
     - Proceeds at room temperature, with no toxic copper.
   - Drawbacks: None!

- So to recap: Two strategies for accelerating a reaction are lowering the transition state barrier and raising the energy of the starting materials.

- Why not put an alkyne in a *six*-membered ring? Wouldn't that be more strained and hence better?
  - You can't have your reactant be so strained that it can't even be made; indeed, a six-membered ring with an alkyne is too strained to be synthesized.
  - 8 carbons is the "sweet spot," having room-temperature reactivity and a viable synthesis.[9]
- We now return to ozonolysis, a reaction with which you may be familiar from 5.12. The mechanism of ozonolysis actually involves a dipolar cycloaddition!
- General form.

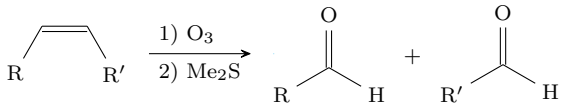
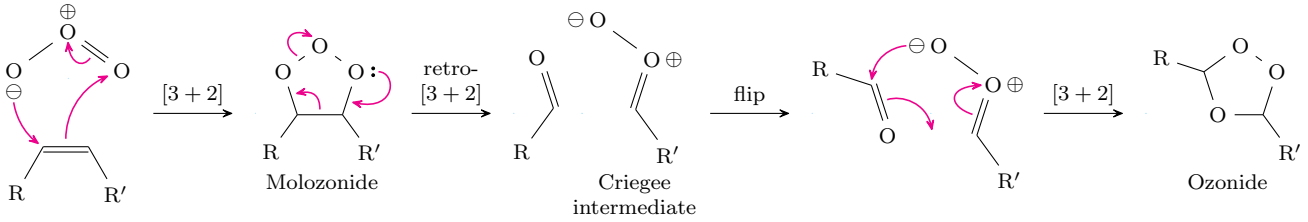
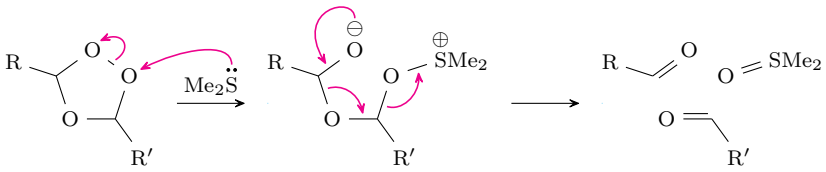


Figure 2.39: Ozonolysis.

  - Fun facts about ozone.
    - It's sky blue; there's a lot of it in the sky! It also absorbs UV rays: This protects us from the sun's radiation and is why the ozone layer is so important!
    - It's also very toxic and explosive; when we work with it in the lab, we do so very carefully.
    - Once upon a time: Chlorofluorocarbons (CFCs) were tearing a huge hole in the ozone layer (which would have let more UV rays through, causing skin cancer), the world banned CFCs, and the ozone layer healed! So we did once solve a climate change issue :)[10]
  - Fun facts about Me_2S.
    - It smells like farts; it's not fun when your labmate is running the reaction.
    - But if your reaction works, the fart smell goes away as the reaction proceeds!
- Mechanism.



(a) First step.



(b) Second step.

Figure 2.40: Ozonolysis mechanism.

[9] If you want to learn more about this type of chemistry, Georgia (one of the TFs) is happy to chat! She studied it in her undergrad research, except that her approach was photochemically synthesizing strained *trans*-cyclooctenes.

[10] The ban on CFCs was based on the work of Drs. Mario Molina and Sherry Rowland, who were both at UC-Irvine when they showed that CFCs were responsible for ozone depletion in the atmosphere. Following his time at Irvine, Molina became a chemistry professor at MIT! Notably, he was here in 1995, when he and Rowland received the Nobel Prize in Chemistry for their work; Molina was the first Mexican-born chemistry Nobel laureate. Until Schrock (chemistry Nobel 2005), Molina was the only faculty member in the MIT Department of Chemistry with a Nobel Prize. Current MIT chemist Dr. Susan Solomon also made significant contributions to this field; her work was pivotal in understanding the *mechanism* of CFCs' reaction with ozone, and she is still a professor here!

  - First step.
    - The alkene reactant does a dipolar $[3+2]$ cycloaddition with ozone to form a **molozonide**.
    - The molozonide does a retro-$[3+2]$, yielding an aldehyde and a **carbonyl oxide** (also known as a **Criegee intermediate**).
    - The aldehyde and Criegee intermediate then rearrange in space.
    - This rearrangement puts partial negative charges near partial positive charges, giving us the right regioselectivity for a *second* dipolar $[3+2]$ cycloaddition. This step yields an **ozonide**.
  - The ozonide is the product of the first step; if you don't add Me_2S, you'll isolate the ozonide.
  - Second step.
    - We introduce a mild reducing agent (Me_2S), which attacks the ozonide.
    - The last step is a final rearrangement splitting.
  - After the second step, we obtain three products: Two aldehydes, and **DMSO**.
  - Note that while we've drawn Figure 2.40 out with a reactant that gives us as aldehydes as products, we could equally well run this reaction with a geminal-, tri-, or tetra-substituted alkene to get some ketones as products!

- **Dimethylsulfoxide**: A common laboratory solvent, which essentially acts like "less polar water" and does not smell like farts. *Also known as* **DMSO**.
- Once we form the ozonide, we don't *have* to break it into ketones/aldehydes with Me_2S.
  - Something else we could do is react it with another reagent to get different products!
- Alternate second steps.
  1. Add H_2O_2.
     - This yields carboxylic acids instead of ketones/aldehydes.
  2. Add $NaBH_4$.
     - This yields secondary/primary alcohols instead of ketones/aldehydes.
- Example of an alternate second step: Cyclohexene to a ring-opened diacid.

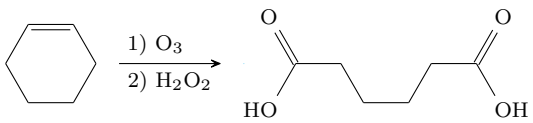


Figure 2.41: An alternate ozonide reaction.

  - Sanity check: Count the carbons in the starting material and product to confirm that there is the same number of carbons in each. Indeed, this chemical reaction only adds oxygens!
- Would adding hydrazone as a second reagent allow us to form the diamide?
  - If we wanted to synthesize an amide or ester, we'd typically form the acid and then do a separate, subsequent amidation.
  - That being said, there are other possible second steps that Prof. Elkin hasn't listed.
- $[2+2]$ cycloadditions.
  - Often photochemical.
  - If we react these with heat, we get no reaction.
  - Just like with dipolar cycloadditions, the stereochemistry of a $[2+2]$ mirrors the Diels-Alder: *cis*-alkenes give *cis*-products, and *trans*-alkenes give *trans*-products.

- General form.

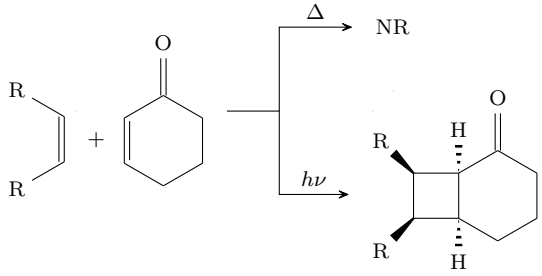
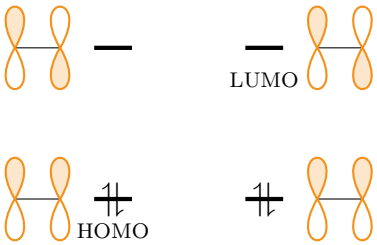
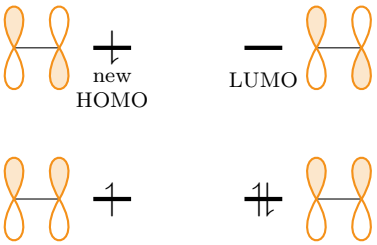


Figure 2.42: $[2+2]$ cycloaddition.

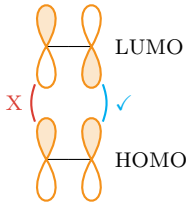
- Why $[2+2]$ cycloadditions *must* be photochemical instead of thermal: MO theory!



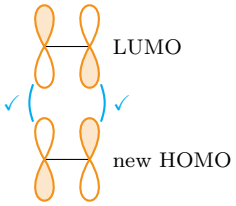
(a) Thermal $[2+2]$ MOs.



(b) Photochemical $[2+2]$ MOs.



(c) Thermal orbitals in 3D space.



(d) Photochemical orbitals in 3D space.

Figure 2.43: $[2+2]$ cycloaddition orbitals.

  - Let's consider a $[2+2]$ cycloaddition between ethylene and itself.
  - Since the reactants are identical, we may choose (arbitrarily and without loss of generality) which molecule reacts with its HOMO. It will then follow that the other molecule reacts with its LUMO.
    - Thus, let the left (Figures 2.43a-2.43b) and bottom (Figures 2.43c-2.43d) molecules react with their HOMO, and let the right/top molecules react with their LUMO.
  - In the thermal case, the HOMO and LUMO don't overlap well (Figure 2.43c).
    - The phasings match on one side, but not on the other.
  - However, in a *photochemical* reaction, we excite an electron up one energy level (Figure 2.43b).
    - Recall that we briefly discussed this phenomenon in Figure 2.15.
    - This excitation gives us a new HOMO.
  - The new HOMO can react with the LUMO (same as thermal) because the phasing now matches!
- In Figure 2.43, we could choose the HOMO and LUMO arbitrarily because the reactants were identical.
  - But in Figure 2.42, the reactants are *not* identical, and it turns out that there *is* a preference for which of these two species absorbs the photon!

- The species that can form the more stable diradical will absorb the light.

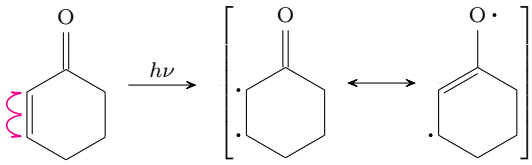


Figure 2.44: Systems with more stable excited states preferentially absorb light.

  - In the context of Figure 2.42, the enone will absorb the photon because its diradical is resonance-stabilized.
  - Thus, the enone will react with its (new) HOMO.
    - Note that this new HOMO is also a SOMO!
    - Per Figure 2.43b, the photoexcited species will actually have *two* SOMOs.
  - For more context, check out Clayden et al. (2012): The textbook actually does an excellent job covering this photochemistry stuff!!

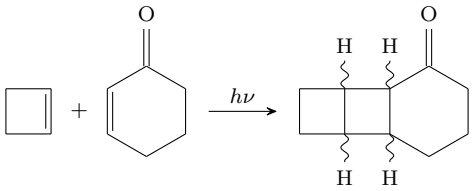
- Looking ahead (Friday).
  - We will begin with a bit more content on cycloadditions that we could not get to today.
  - After that, we will cover electrocyclizations.
  - It's going to be a long lecture, but you'll have the weekend to digest it.

2.16 Electrocyclizations

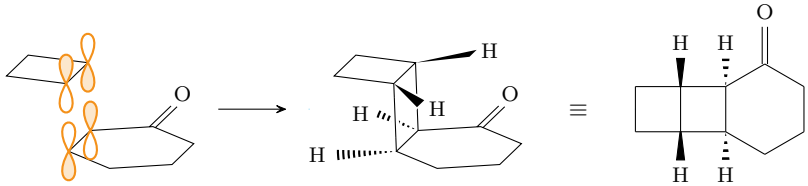
10/11:

- Lecture 15 recap.
  - Dipolar $[3+2]$ cycloadditions.
    - General form (Figure 2.34).
      - ➢ Recall that these are reactions between a dipole (Figure 2.33) and a dipolarophile.
    - Example: Ozonolysis (Figure 2.39).
      - ➢ Yields aldehydes or ketones with Me_2S as a second reagent.
      - ➢ Multiple products are accessible with alternate second reagents (e.g., H_2O_2 or $NaBH_4$).
    - Example: Azide-alkyne click reactions (Figure 2.36b).
    - Remember that there are more dipoles (e.g., Figure 2.35c) than the two we mainly talked about.
      - ➢ See Clayden et al. (2012) as well for more dipoles.
    - Reactions proceed when the HOMO and LUMO phases match (Figure 2.37).
  - $[2+2]$ cycloadditions.
    - General form (Figure 2.42).
    - Usually photochemical; this way, the HOMO and LUMO match (Figure 2.43)!
    - *exo* product preferred.
    - The regiochemistry for this photoactivated ($h\nu$) reaction is opposite of what we usually get with a thermally activated (Δ) reaction.
    - To learn more about the thermal $[2+2]$ cycloaddition, read Clayden et al. (2012, p. 898)!!
- Announcements.
  - This will be a long lecture.
  - As such, Prof. Elkin will ask most questions to be held to the end in case we have extra time.

- Lecture 15 (continued).
- Stereochemistry of the [2 + 2] cycloaddition.



(a) A [2 + 2] cycloaddition.

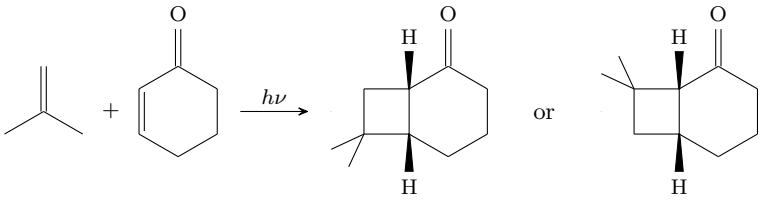


(b) *exo* pathway.

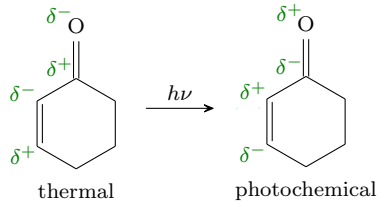
Figure 2.45: [2 + 2] cycloaddition stereochemistry.

  - Consider the [2 + 2] cycloaddition in Figure 2.45a.
    - Last time, we learned that such a reaction yields the product shown, but we haven't yet discussed the relative stereochemistry of the four hydrogens.
    - Note that wavy lines mean "undefined stereochemistry."
  - Unlike [4+2] (Diels-Alder) cycloadditions (in which the *endo* transition state is preferred), [2+2] cycloadditions prefer the *exo* transition state and product.
    - [2 + 2] cycloadditions prefer *exo* due to sterics, which prohibit secondary orbital interactions.
    - Essentially, the *endo* transition state is *only* for the Diels-Alder reaction![11]

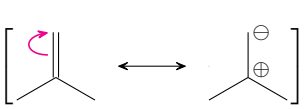
- Regiochemistry of the [2 + 2] cycloaddition.



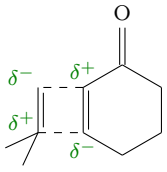
(a) Possible products of an asymmetric [2 + 2] cycloaddition.



(b) Partial charges (enone).



(c) Resonance (alkene).



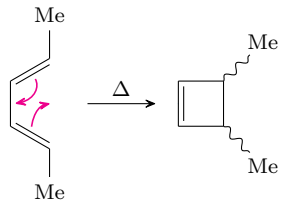
(d) Matching partial charges.

Figure 2.46: [2 + 2] cycloaddition regiochemistry.

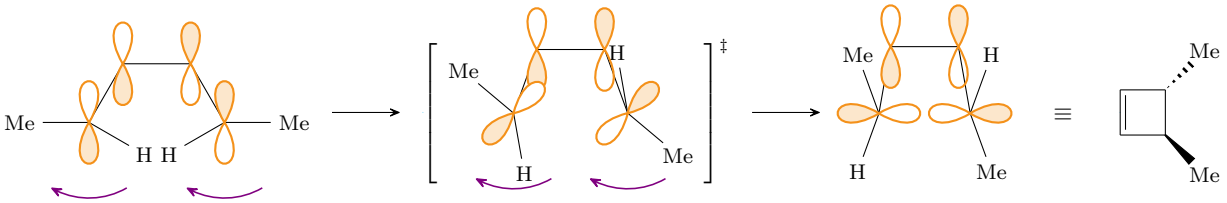
[11] Note that we did not talk about the stereochemistry of dipolar cycloadditions because they are *not* stereoselective: A fairly even balance of secondary orbital interactions with sterics makes the stereochemistry of dipolar cycloadditions very hard to predict.

  - Consider the reaction in Figure 2.46a, which is our first [2+2] cycloaddition in which *both* reactants are asymmetric. Which product will be observed?
    - In other words, what will be our regiochemistry?
    - Notice that in both possible cases, we obtain the *cis*-product per Figure 2.45.
  - Photochemical regiochemistry is the *opposite* of thermal regiochemistry.
  - To see how this change manifests, let's begin by looking at the enone. (Recall that Figure 2.44 tells us it is the enone, specifically, that gets photoexcited.)
    - In the thermal case, we draw partial charges starting with a negative on the oxygen, as in Figures 2.25e-2.25f.
    - However, when a molecule gets hit by light, we get an excited state with the *inverse* polarity (Figure 2.46b)!
      - ➢ This means that we will now start with a *positive* partial charge on the oxygen.
      - ➢ From here, we alternate the charges as before in Figures 2.25e-2.25f.
    - See Clayden et al. (2012) for why we get this inverse polarity.
  - The enone then reacts with an alkene (Figure 2.46c).
    - The alkene's partial charges can most easily be derived via resonance, wherein we push the negative charge *away* from the two methyl EDGs.
  - Having worked out the partial charges on both reactants, we can pair them up (Figure 2.46d).
    - This pairing then tells us that the *left* regioisomer in Figure 2.46a is observed.
    - Notice that we have paired our partial charges exactly as in Figure 2.25h.

- This concludes Lecture 15 content; we now begin Lecture 16.
- Today: Electrocyclizations.
- Lecture outline.
  - Conrotatory vs. disrotatory electrocyclizations.
  - Woodward-Hoffmann rules.
  - Retro-electrocyclizations and the principle of microscopic reversibility.
  - Nazarov cyclization.
  - Examples.
- We'll begin by determining the product in a thermal 4π electrocyclization.



(a) The reaction without stereochemistry.

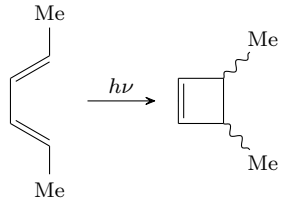


(b) Conrotatory pathway.

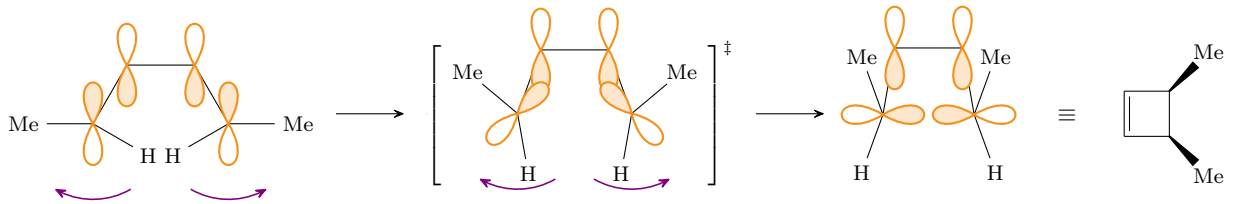
Figure 2.47: Thermal 4π electrocyclization.

- Recall that an electrocyclization proceeds with the general form of Figure 2.10.
  - Thus, in Figure 2.47a, we get a ring-closed product with one fewer π-bond.
  - But we still need to discuss the stereochemistry of the methyl groups.
- Just like in Diels-Alder reactions (Figure 2.27b) and [2+2] cycloaddition reactions (Figure 2.45b), the stereochemistry in an electrocyclization is set by the transition state.
- Thus, let's start by describing the transition state.
  - Begin by considering the HOMO, which is the reactive orbital in an electrocyclization.
    - ➢ The HOMO of the reactant in Figure 2.47a will be the second energy level of Figure 2.14, which we may draw on our reactant (left molecule in Figure 2.47b).
  - To form the new σ-bond, we must rotate the ends of the π-system so that the phases match.
    - ➢ Indeed, if we rotate both terminal p-orbitals clockwise, the unshaded lobes begin to come together (transition state in Figure 2.47b).
    - ➢ We could also rotate both terminal p-orbitals *counterclockwise* to pair the *shaded* lobes.[12]
    - ➢ However, we could *not* rotate them in different directions as this would pair a shaded lobe with an unshaded lobe.
  - Rotating the terminal p-orbitals enough forms the new σ-bond (right molecule in Figure 2.47b).
- Let's now discuss the implications of the transition state.
  - As we rotated the terminal p-orbitals, notice that we had to rotate the methyl and hydrogen substituents along with them!
  - Thus, in the course of the rotation, the left methyl group rotated upwards and the right methyl group rotated downwards.
  - Therefore, a thermal 4π electrocyclization (exclusively) yields the *trans*-product!
- This rotation of both π-bonds in the same direction (both clockwise or both counterclockwise) is called **conrotatory** rotation.

- **Conrotatory** (electrocyclization): An electrocyclization in which the termini of the π-systems rotate in the same direction.
- **Disrotatory** (electrocyclization): An electrocyclization in which the termini of the π-systems rotate in opposite directions.
- Let's now look at a *disrotatory* electrocyclization, which occurs under light instead of heat.



(a) The reaction without stereochemistry.



(b) Disrotatory pathway.

Figure 2.48: Photochemical 4π electrocyclization.

[12] In an asymmetric molecule, rotating one way or the other gives two different enantiomers! We will discuss an example later this lecture (a retro-electrocyclization) wherein there *is* a preference for one direction of rotation over another.

  - As with Figure 2.47, let's start by describing the transition state.
    - Once again, we'll begin by considering the HOMO.
    - However, since this is a *photochemical* reaction, the reactive orbital will be the "new HOMO" created by photoexcitation.
      - ➢ Per Figure 2.15, this new HOMO will be the third energy level of 2.14, which we may draw on our reactant (left molecule in Figure 2.48b).
    - Then as before, in order to form the new σ-bond, we must rotate the ends of the π-system so that the phases match.
      - ➢ If we want to bring the shaded lobes of the *new* HOMO together, we can still have the left terminal p-orbital rotate clockwise, but then we need the right terminal p-orbital to rotate counterclockwise!
    - Continuing this rotation to completion forms our new σ-bond again.
  - The implication of this "disrotatory" rotation is that — through rotating the methyl and hydrogen substituents along with our terminal p-orbitals — we produce (exclusively) the *cis*-product!
  - So to recap: The ends of the π-system rotated in different directions (disrotatory) to align like-shaded lobes and afford our product.

- A shortcut for remembering all this conrotatotory/disrotatory electrocyclization stuff: The Woodward-Hoffmann rules.

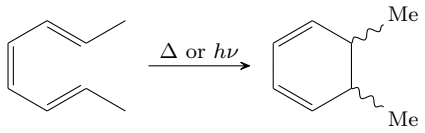
$\#\,\mathbf{e^-}$	$\boldsymbol{\Delta}$	$\boldsymbol{h\nu}$
$4n$	con	dis
$4n+2$	dis	con

Table 2.1: Woodward-Hoffmann rules.

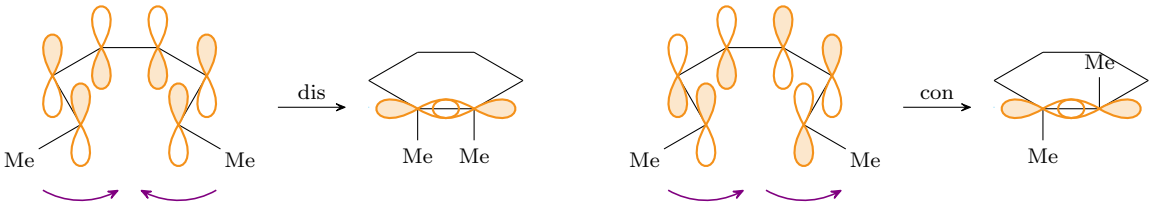
  - Aside (chemis-tea): Who was R. B. Woodward?
    - R. B. Woodward was an MIT alum, even though he failed out after his freshman year.
    - He was readmitted though, and after graduating, he went on to become our most famous synthetic organic chemist.
    - He won a Nobel Prize and would have won a second, but he died too soon.
    - You probably talked about him in 5.12; he's great.
  - The Woodward-Hoffmann rules were the original solution to the "no mechanism" debacle that we talked about in Lecture 12.

- How to derive the Woodward-Hoffmann rules.
  - On the exam, you will need to be able to both apply the shortcuts in Table 2.1 and derive these shortcuts with MOs as in Figures 2.47-2.48!!
  - To reiterate, the general workflow to derive a Woodward-Hoffman rule is as follows.
    1. Draw the π-system and all substituents at the ends of it.
    2. Identify the HOMO and shade in orbitals appropriately.
    3. Decide what kind of rotation will give you good overlap and hence a σ-bond.
    4. Use your hands/head/body to visualize this rotation (if you're a kinesthetic learner).
    5. Draw intermediates, and then draw the final product.
  - Practice doing this!!

- Example: Quickly solving two different 6π electrocyclizations with the Woodward-Hoffmann rules.



(a) The reaction without stereochemistry.



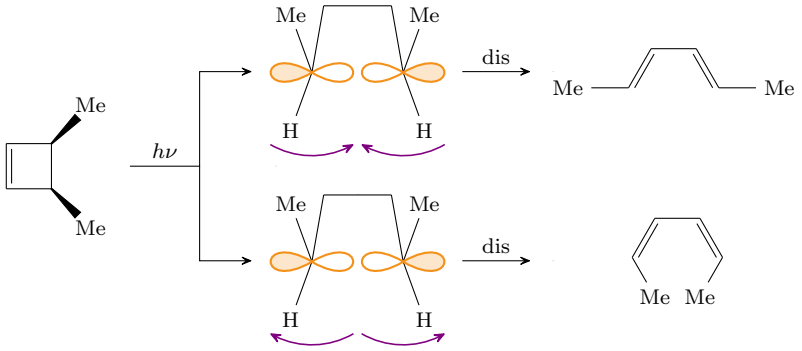
(b) Thermal product (disrotatory).

(c) Photochemical product (conrotatory).

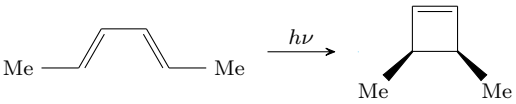
Figure 2.49: Thermal and photochemical 6π electrocyclizations.

  - Let's first address the thermal case (Figure 2.49b).
    1. As in Figures 2.47-2.48, our first step is *always* redrawing the starting material in a perspective from which we can see the rotation.
       - The perspective from which we view the left molecule in Figure 2.49b is indeed one in which we can see the substituents rotate.
    2. Then we need to figure out what the HOMO is.
       - There are 6 atoms and 6 electrons in the π-system, so per the three rules from Lecture 12, there will be six MOs and the lowest three will be filled.
         - ➢ For the exam, be sure to practice drawing molecular orbitals like this!! For reference, you can look back at the examples in Figures 2.14 and 2.16.
       - Thus, the HOMO is the 3rd energy level, so it will have 2 (symmetric) nodes.
       - This is why we draw 6 *p*-orbitals on the left molecule in Figure 2.49b and put nodes between the second and third *p*-orbitals and also between the fourth and fifth *p*-orbitals.
    3. As we have drawn our HOMO, a disrotatory pathway will unite lobes with like shadings.
    4. Thus, both methyl groups will rotate down (or up!).
    5. This yields the *cis*-product.
  - Now we'll address the photochemical case (Figure 2.49c).
    1. We redraw the starting material in the same perspective as in Figure 2.49b.
    2. Because we're photochemical this time around, we have to choose a "new HOMO."
       - There are still 6 atoms and 6 electrons in the π-system, so as before, there will be six MOs.
       - However, now the lowest *four* will be filled.
       - Thus, the HOMO is the 4th energy level, so it will have 3 (symmetric) nodes.
       - This is why we draw 6 *p*-orbitals on the left molecule in Figure 2.49c and put nodes between the first and second; third and fourth; and fifth and sixth *p*-orbitals.
    3. As we have drawn our HOMO, a conrotatory pathway will unite lobes with like shadings.
    4. Thus, one methyl group rotates both ways.
    5. This yields the *trans*-product.
  - To reiterate: Even though we only drew one enantiomer in Figures 2.49b-2.49c, both can form because it does not matter whether the unshaded or shaded lobes come together.
    - However, up next is an example of where the direction of rotation *does* matter!

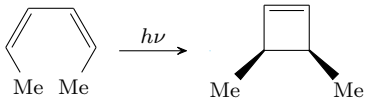
- Example: Retro-4π electrocyclization.



(a) Possible products of a retro-4π electrocyclization.



(b) Feasible "reverse" electrocyclization.



(c) Infeasible "reverse" electrocyclization.

Figure 2.50: Retro-4π electrocyclization.

  - Imagine you begin with the product of Figure 2.48b and expose it to light, inducing a retro-4π electrocyclization (Figure 2.50a)
    - Because this is a photochemical 4π-electrocyclization, the Woodward-Hoffmann rules (Table 2.1) tell us that we will follow a disrotatory pathway.
      - Note that the direction of reaction (forward or backward) doesn't matter for the Woodward-Hoffmann rules! All that matters is the number of electrons, and photochemical or thermal.
    - However, as the σ-bond breaks and the π-bonds reform, the σ-bond's orbitals can either both rotate "in" (top of Figure 2.50a) or both rotate "out" (bottom of Figure 2.50a).
    - This produces two geometric isomers as possible products. Which one will be observed?
  - To answer this question, we need the **principle of microscopic reversibility**.
    - This tells us that if the starting material in Figure 2.50a converts to the top (or bottom) product in Figure 2.50a via a retro-electrocyclization mechanism, that product had better convert back to the starting material via a forward electrocyclization mechanism.
  - So let's consider these two "reverse" reactions (Figures 2.50b-2.50c).
    - The reaction in Figure 2.50b looks like an electrocyclization that would happily proceed.
    - The reaction in Figure 2.50c does not: Just like in Figure 2.19c, steric clashing will significantly disfavor the s-*cis* conformation necessary for an electrocyclization. Thus, this reaction cannot easily proceed via an electrocyclization mechanism.
  - Therefore, by the principle of microscopic reversibility, the fact that Figure 2.50b's reverse reaction is so unfavorable means that the original retro-4π electrocyclization will *not* create this product.
    - It follows that the retro-4π electrocyclization will *exclusively* follow the top pathway in Figure 2.50a and *exclusively* produce the corresponding doubly *trans*-alkene.
    - In other words, the disrotatory motion only happens "in" — not "out" — in this case.

- **Principle of microscopic reversibility**: The reaction mechanism that gets you from starting material to product has to be the same (but in reverse) as the reaction mechanism that gets you from the product back to the starting material.

- **Nazarov cyclization**: A very neat reaction that goes by an electrocyclization mechanism.
- General form.

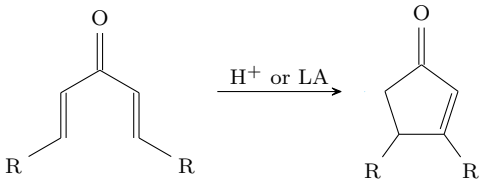


Figure 2.51: Nazarov cyclization.

  - Either Brønsted acid catalyzed (H^+) or Lewis acid catalyzed (LA).

- Mechanism.

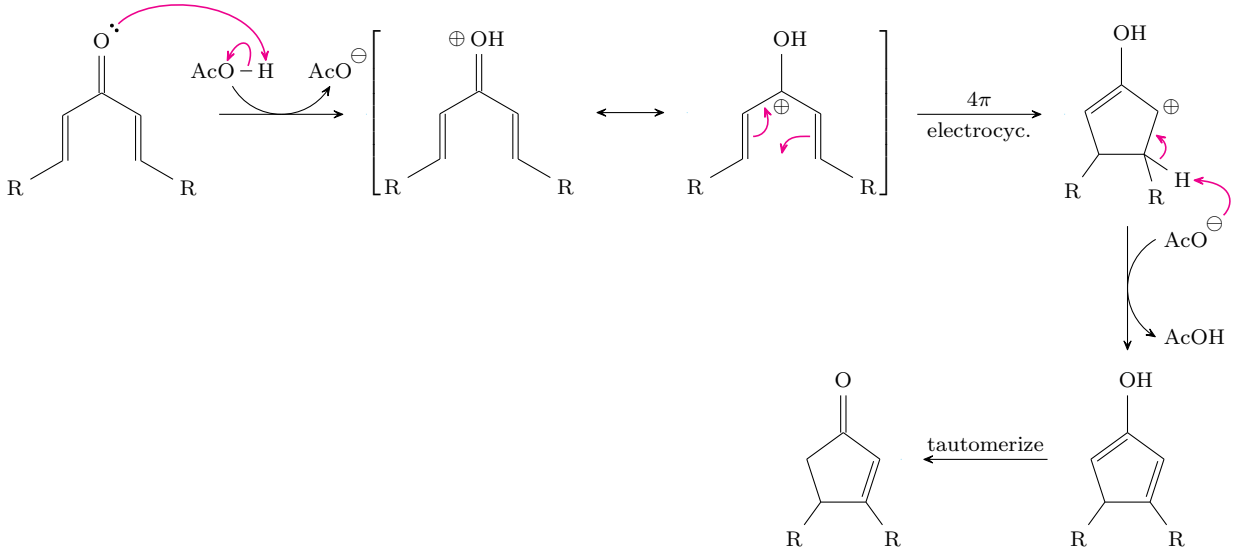


Figure 2.52: Nazarov cyclization mechanism.

  - To begin, the acid catalyst protonates the carbonyl.
  - The protonated intermediate has a resonance form with an empty *p*-orbital (i.e., a carbocation) in between the two π-systems.
    - This empty *p*-orbital in effect *bridges* the two π-systems, enabling a rearrangement of electrons that we call a "cationic 4π electrocyclization."
  - The cyclization step still leaves a carbocation behind, but we can quickly eliminate a nearby proton to form a double bond.
  - After the elimination, a final keto-enol tautomerization affords a more stable final product.

- Stereochemistry of the Nazarov cyclization.

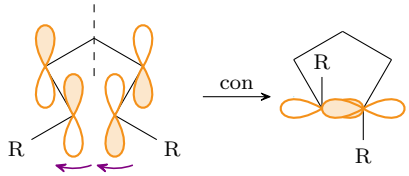


Figure 2.53: Nazarov cyclization stereochemistry.

  - We assume that this reaction is thermal (even though there is no Δ above the arrow) by default.
    - If we just see acid/reagents and no triangle, assume thermal.
    - If we see $h\nu$, *then* we consider the photochemical pathway.
  - There are 5 atoms and 4 electrons in the π-system, so per the three rules from Lecture 12, there will be five MOs and the lowest two will be filled.
    - Thus, the HOMO is the 2nd energy level, so it will have 1 (symmetric) node.
    - Because this is an odd number of atoms, the middle p-orbital gets deleted!
  - As we have drawn our HOMO, a conrotatory pathway will unite lobes with like shadings.
  - This yields the *trans*-product.

- Example: The product of a Nazarov cyclization after an alternate deprotonation.

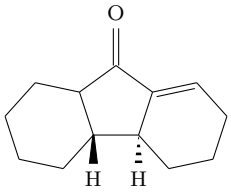


Figure 2.54: Alternate deprotonation sites in Nazarov cyclizations.

  - If we trace through the mechanism that would form this product, we can see that we just deprotonated the post-4π electrocyclization carbocation at a different β-H.
  - Under thermal conditions, we would get the *trans*-product (as drawn).
  - Under photochemical conditions, we would *not* get the molecule in Figure 2.54 but would get the *cis*-product instead.

- There are still a few examples that Prof. Elkin wanted to get through today, but we ran out of time, so they'll be shared in a Canvas announcement.

- Looking ahead.
  - Spend the weekend resting and catching up.
  - Next Wednesday: Sigmatropics.
  - Next Friday: Exam review.

2.17 Sigmatropic Rearrangements

10/16:

- Lecture 16 recap: Considerations for electrocyclizations.
  - Woodward-Hoffmann rules.
    - Prof. Elkin redraws Table 2.1.
  - Conrotatory and disrotatory.
    - To derive this, first draw the HOMO.
    - Then make σ-bonds by rotating the terminal p-orbitals so that the phases match.
  - Misc.
    - Nazarov cyclization (a 4π electrocyclization, not 5π as was accidentally written last lecture).
    - Principle of microscopic reversibility: This helps you understand which product you get in certain retro-electrocyclizations.

- Announcements.
  - Looking ahead: Friday.
    - A review of Unit 2 material.
    - Prof. Elkin will discuss what she believes you should focus on studying!
  - You will learn the most by taking the practice exams timed and closed-book!
- Today: Sigmatropic rearrangements.
  - This is the end of the material for Unit 2; sigmatropics are our last pericyclic reaction!
- Lecture outline.
  - Cope rearrangement: General form, orbital picture, stereochemistry, special types.
  - Claisen rearrangement: General form, examples, stereochemistry.
  - Hydrogen atom shifts: Antarafacial example, suprafacial example, photochemical.
- We'll start with a classic named reaction in the sigmatropic family: The Cope rearrangement.
  - Cope was an MIT alumnus!
- General form.

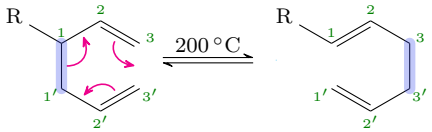
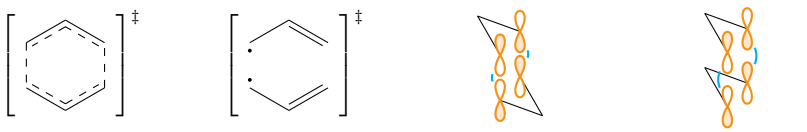


Figure 2.55: Cope rearrangement.

  - The Cope rearrangement proceeds circle arrows, as in any pericyclic reaction.
  - It is reversible.
  - It is thermal, typically occuring around 200 °C.
  - It is classified as a **[3, 3] sigmatropic rearrangement**.
- **[3, 3] sigmatropic rearrangement**: A sigmatropic rearrangement in which the σ-bond moves 3 atoms at one end and 3 atoms at the other end.
  - Numbering our atoms as in Figure 2.55, observe that the σ-bond moves from atoms 1 and $1'$ to atoms 3 and $3'$!
  - This nomenclature is defined another way in Clayden et al. (2012), and another way on Wikipedia and Google, so read a bunch of different definitions and see what sticks :)
  - We're not huge sticklers for nomenclature, but you should learn this!!
- An orbital picture for the Cope rearrangement.



(a) True TS. (b) Radical TS. (c) Chair TS. (d) Boat TS.

Figure 2.56: Cope rearrangement orbitals in 3D space.

- In a pericyclic transition state, all bonds are forming and breaking at the same time (Figure 2.56a).
  - Notice the similarity between Figure 2.56a and the transition state of Figure 2.8!
  - Observe that there is an unchanged "σ-backbone" on the top and bottom.
- Thus, the transition state is kind of like two allyl radicals interacting (Figure 2.56b).
  - Recall the MOs of an allyl radical from Figure 2.16.
  - These MOs tell us that both allyl radicals will interact with their SOMO.
- We can then draw out these SOMOs in 3D, interacting through either a *chair* (Figure 2.56c) or a *boat* (Figure 2.56d) transition state.
  - In each case, we get good overlap at both the bond-breaking and bond-forming positions.
  - However, since chair conformations are usually more stable than boat conformations (as you should recall from 5.12), the chair transition state will usually be more stable than the boat transition state.
  - Note that we mention the boat transition state at all because even though it's less favorable, it can still happen.[13]
- These transition states are super important because they're how we predict stereochemistry!
- Note that we can also split the system into a cation and an anion, and we'll still get good orbital overlap and all the same transition-state stereochemistry.
  - Indeed, splitting into two radicals is more of a convention.
  - You can (and should) try drawing this cation/anion scheme out!!
  - The fact that it works both ways is yet more evidence that MOs are a good, meaningful model.

- Stereochemistry of the Cope rearrangement.

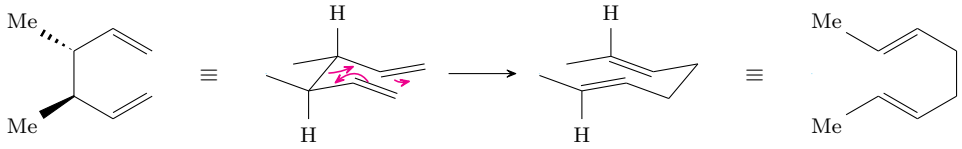
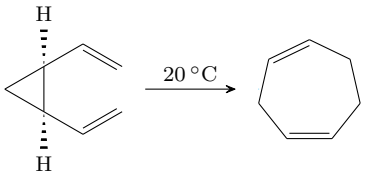


Figure 2.57: Cope rearrangement stereochemistry.

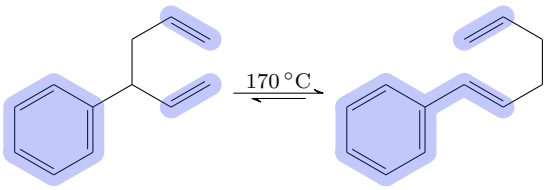
- The Cope rearrangement is stereospecific.
  - Indeed, just like the Diels-Alder (see Figure 2.23), the stereochemistry of the reactant translates directly into whether the product has *cis*- or *trans*-olefins.
- To determine the (major[14]) product, draw the starting material in the most stable chair conformer.
  - In this case, the most stable chair is the one in which both methyl groups are equatorial. This minimizes 1,3-diaxial interactions.
  - The double bonds also point down and up along the lines of the chair.
- Then we draw circle arrows to help us move the bonds.
  - These allow us to draw the product in the chair conformation.
  - Then we must "unfold" the chair into a 2D representation.
- To unfold this structure, first observe that both olefins are *trans*.
  - Then all we need to do is draw a 2D representation that also has two *trans*-olefins, and we're good to go!
- If it helps to draw in the hydrogens, you should feel free to.

[13] Specifically, it can lead to some alternate stereoisomers as minor side products; see Figure 2.57.
[14] We will also have some product formed from the boat transition state, but you are not responsible for this!

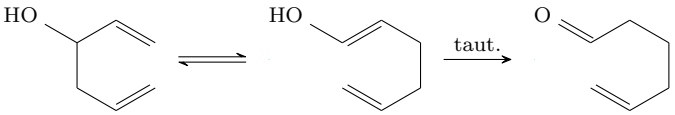
- As mentioned in Figure 2.55, the Cope rearrangement is an equilibrium reaction. But for it to be synthetically useful, we need to be able to drive the equilibrium toward starting materials or products. How can we do this?



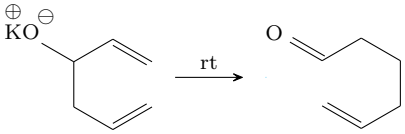
(a) Release of ring strain.



(b) Conjugate a product olefin.



(c) Oxy-Cope rearrangement.

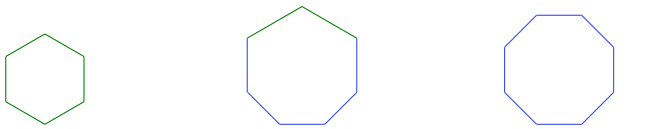


(d) Anionic oxy-Cope rearrangement.

Figure 2.58: Methods to drive the equilibrium in a Cope rearrangement.

1. Release ring strain (Figure 2.58a).
   - If we put a 3-membered ring in our reactant, we get a 7-membered ring in the product that is far more stable.
   - The temperature we need to run this reaction is only about 20 °C!
2. Create a conjugated product (Figure 2.58a).
   - If you can make your product significantly more stable, you'll drive the equilibrium that way.
   - One way to do this is to build a starting material such that one of the new double bonds formed will be conjugated to the *aryl* ring.
     - Note that the newly conjugated olefin will still *not* be conjugated with respect to the product olefin at the other terminal.
   - This is energetically favorable because it's a reduction of the number of independent alkene systems from 3 to 2.
   - The temperature we need to run this reaction is down from the initial 200 °C (Figure 2.55) to about 170 °C.
3. Make it an **oxy-Cope rearrangement** (Figure 2.58c).
   - To do so, add an alcohol to the 1 or 1′ carbon.
   - This way, the product tautomerizes to a ketone (which is far more stable than the starting material).
   - This method is very common and ubiquitous in the chemical literature, hence why it has it's own name.
4. Make it an **anionic oxy-Cope rearrangement** (Figure 2.58d).
   - To do so, start with an oxy-Cope substrate and add a base to solution so that we can form the deprotonated alkoxide.
   - Then the Cope rearrangement and subsequent keto-enol tautomerization will occur at room temperature (rt).
   - Why is this reaction so much faster than the oxy-Cope?
     - The anionic starting material is higher energy than the neutral starting material, so it takes less *additional* energy for the starting materials to reach the transition state.
     - Indeed, this is another example of ground state destabilization! See Figure 2.38b.

- Aside: Drawing 7-membered rings.



(a) 6-membered. (b) 7-membered. (c) 8-membered.

Figure 2.59: Drawing a 7-membered ring.

  - When drawing 7-membered rings on paper, draw an octagon with a hat!
  - This is much easier to draw freehand than the exact angles, as in Figure 2.58a.
  - Drawing 7-membered rings like this on your exam will make your graders' lives easier!
- Tip: If it's been a while since you've drawn chairs, practice this!!
- This concludes our discussion of the Cope; we now move onto another special sigmatropic.
- The Claisen rearrangement.
  - This reaction is like the Cope, but with an oxygen in the ring.
- General form.

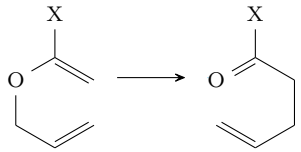


Figure 2.60: Claisen rearrangement.

  - The starting material in Figure 2.60 is called an **allyl vinyl ether**.
  - It does a rearrangement to form a carbonyl.
    - The driving force comes from the fact that carbonyls are more stable than ethers.
  - Like the Cope, this is *also* a $[3,3]$ sigmatropic rearrangement.
- The Claisen rearrangement can be accelerated by adding different substituents in the X position.

X	$\boldsymbol{\Delta H}$ **(kcal/mol)**
H	-16
OR	-28
NHR	-30

Table 2.2: Substituent effects on the Claisen rearrangement.

  - If X = H, the product is an aldehyde.
  - If X = OR, the product is an ester.
  - If X = NHR, the product is an amide.
    - This is the most stable product, so it's the most downhill reaction.
  - Why does stability decrease from amides to esters to aldehydes?
    - We'll cover this in another Unit later this semester!

- Example: Claisen rearrangements in aromatic systems.

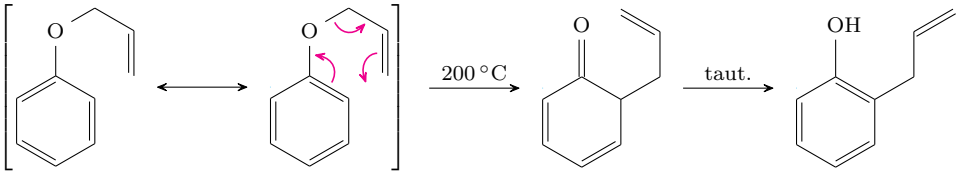


Figure 2.61: Claisen rearrangement of allyl phenyl ether.

  - Claisen rearrangements can occur even with substrates that might not immediately look like they could engage in such reactivity.
  - For example, consider the molecule at left in Figure 2.61.
    - This molecule is aromatic.
    - Indeed, the "vinyl" group is actually part of an aromatic system here!
  - To make it easier to see which aromatic double bond we should engage, we can redraw the starting material as its resonance structure.
    - Then we can push arrows in our Claisen rearrangement to yield a nonaromatic intermediate.
  - This intermediate then tautomerizes into an enol.
    - Enols are usually less stable than ketones, but this enol is aromatic.[15] Therefore, it's favored.
  - This Claisen rearrangement happens at 200 °C because it's not quite as thermodynamically downhill as some others.

- Stereochemistry of the Claisen rearrangement.

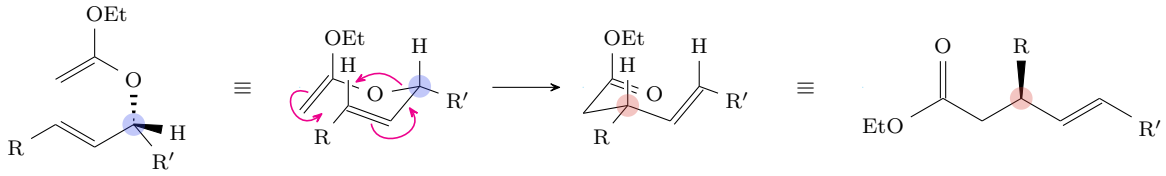


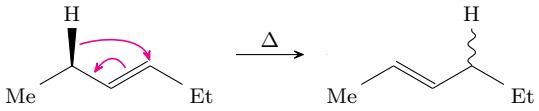
Figure 2.62: Claisen rearrangement stereochemistry.

  - Like the Cope, the Claisen rearrangement is stereospecific.
    - As such, the one stereocenter (blue) in the starting material will determine whether the product has a *cis*- or *trans*-olefin.
  - To determine the product stereochemistry, we once again draw a chair-like transition state.
    - This time, the way to make the most things equatorial is to put the two R groups equatorial and leave the ethoxy group axial.
    - Drawing in hydrogens can help you figure out the substituent positions at the stereocenter!
  - Then we draw circle arrows to help us move the bonds to the product chair.
  - We now unfold the product chair.
    - The new olefin is *trans*.
    - The new stereocenter (red) will be Cahn-Ingold-Prelog (R) if R = Me, for example.
    - Therefore, we can draw the product linearly with a *trans*-olefin and "(R)" stereocenter.

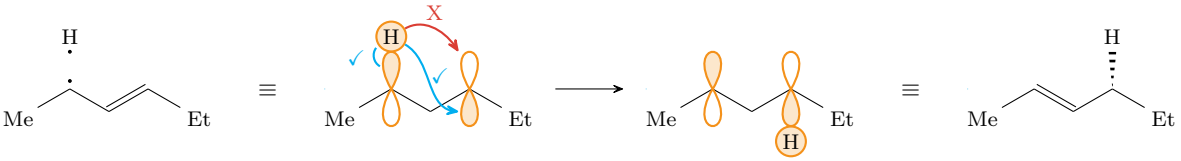
- This concludes our discussion of the Claisen rearrangement.

[15] Technically, we call aromatic enols, "phenols."

- We now move onto sigmatropic hydrogen atom shifts.
  - Note that chemists refer to these reactions interchangeably as "hydrogen atom shifts," "H-atom shifts," "H shifts," etc.
  - We can also have sigmatropic methyl shifts, though we won't discuss these explicitly this lecture.
- Example: A $[1,3]$ H-atom shift.



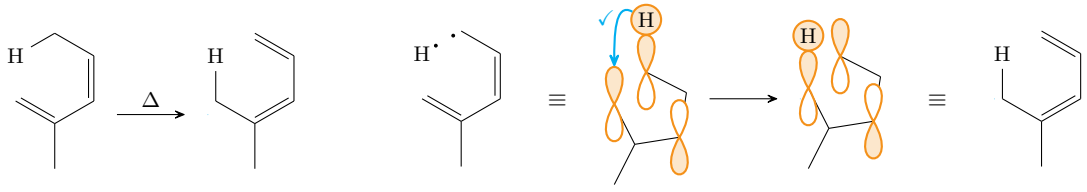
(a) A $[1,3]$ H-shift.



(b) Orbital pathway.

Figure 2.63: $[1,3]$ hydrogen atom shift.

  - This reaction is classified as a **[1, 3] sigmatropic rearrangement**.
  - The general form involves the migration of a hydrogen through a concerted, pericyclic transition state (Figure 2.63a).
  - However, we need orbitals to determine the stereochemistry at the new stereocenter (Figure 2.63b).
    - Treat the transition state as a diradical, like with the Cope (see Figure 2.56).
      - Breaking bonds, we get one allyl radical again (3 p-orbitals and 3 electrons), but we also get a hydrogen radical (1 s-orbital and 1 electron).
      - Draw the reactive MOs for these two radicals.
    - Now for the hydrogen to move, it has to find another lobe with the right shading.
      - In particular, the H can't just jump to the other top orbital because said top orbital has the wrong shading.
  - Takeaway: For H to move, it has to cross to the other face of the molecule.
    - This is called **antarafacial** movement.
      - This contrasts with **suprafacial** movement, which we'll discuss in the next example.
    - Practically speaking, antarafacial moves are rare. But they are possible!
      - See Clayden et al. (2012) for movement in larger systems!!
- **Antarafacial** (movement): Movement of an atom to a position on the *opposite* face of the molecule.
- **Suprafacial** (movement): Movement of an atom to another position on the *same* face of the molecule.
- Example: Consider a $[1,5]$ H-atom shift.



(a) A $[1,5]$ H-shift.

(b) Orbital pathway.

Figure 2.64: $[1,5]$ hydrogen atom shift.

  - This reaction is classified as a **[1, 5] sigmatropic rearrangement**.
    - In fact, it is the same reaction we discussed several lectures ago in Figure 2.11!
  - We predict the product stereochemistry by continuing to use the same method as before.
    - This time, we split into a pentadienyl radical (5 p-orbitals and 5 electrons) to complement our hydrogen radical (1 s-orbital and 1 electron).
    - The HOMO of the pentadienyl radical will be the 3rd energy level, so it will have 2 symmetric nodes.
      - ➢ It may be helpful to draw the HOMO on a straight line first (as in Figure 2.14) and then "wrap it around" onto the intermediate drawn in Figure 2.64b.
    - With the orbitals drawn, we must (once again) move the hydrogen to another lobe with the right shading.
      - ➢ This time, however, the H can just jump directly over from shaded to shaded.
      - ➢ This is suprafacial movement!
  - Practically speaking, suprafacial moves are common.
    - [1, 5] H-atom shifts happen frequently, whether we like it or not!
    - This is a real thing: When we try to make a product in the lab, we often access conditions in which the hydrogen will just dance back and forth.
    - Indeed, there are isotopic labeling studies in which a molecule with deuterium (D) on one position will engage in [1, 5] H/D-shifts to such an extent that the deuterium will become scrambled (i.e., equally distributed between the two possible positions) over time.
    - See Clayden et al. (2012) for more.

- We can do all of these rearrangements photochemically as well, instead of thermally.
  - This will lead to the opposite things from before, because we now have a new HOMO.
  - Implication: Photochemical [1, 3] shifts will be suprafacial and photochemical [1, 5] shifts will be antarafacial.
  - You should try drawing these new orbitals and arrangements out!!
- Note: Clayden et al. (2012) says that [1, 3] suprafacial is thermally forbidden, but practically, there is a small possibility that this will happen.

2.18 Review for Exam 2

10/18:

- Lecture 14 recap: Sigmatropics (our final pericyclic reaction).
  - Rate acceleration: Driving forces include...
    - Product conjugation (Figure 2.58b);
    - Strain release (Figure 2.58a);
    - A further downhill reaction, e.g., a keto-enol tautomerization (Figure 2.58c);
    - Ground state destabilization, e.g., the anionic oxy-Cope (Figure 2.58d).
  - Stereochemistry: Big for sigmatropics, just like every other pericyclic reaction!
    - For Claisen and Cope rearrangements, draw the chair (Figures 2.57 & 2.62).
    - We can think of the Claisen and Cope as suprafacial and antarafacial rearrangements, too, but that's harder.
      - ➢ This is why we use the shortcut of the chair.
      - ➢ If you want to learn more about this, see Clayden et al. (2012)!

  - Orbitals.
    - General procedure: Draw the system as two radicals, and then draw these radicals' orbitals (Figures 2.56, 2.63b, & 2.64b).
    - [1, 3] H-shifts: Antarafacial when thermal (Figure 2.63b), and suprafacial when photochemical.
      - ➢ Photochemical [1, 3] H-shifts are suprafacial because the allyl radical reacts with top MO in Figure 2.16, which has like-shaded orbitals at both ends!

- Study techniques.
  - For the exam, use your notecards and study hard!
  - The exam will be fair; the teaching team tried to write questions that legitimately probe your understanding of the material, not "gotcha" questions.
  - If you put in the practice and the time, you'll do great!

- Today: The key things you need to know or be able to do for the exam.
  - We'll go through each lecture of this unit with a focus on answering the question, "What is the skill from this lecture that you should be able to do?"

- Key takeaways: MO Theory - 1.
  - Bonding MOs are polarized toward electronegative atoms.
  - Correspondingly, antibonding MOs are polarized toward electropositive atoms.
  - Example: The C–I single bond.
    - There is a σ-orbital and a σ^*-orbital.
    - The σ-orbital is polarized toward I, and the σ^*-orbital is polarized toward C.
  - Example: The C=O double bond.
    - There is still a σ-bond here, but since the π-bond does all the reactivity, we'll narrow our focus to the π-bonding interactions.
    - The π-orbital is polarized toward O, and the π^*-orbital is polarized toward C.
    - The polarization of the π^*-orbital toward carbon explains why nucleophiles attack carbonyls at carbon!
  - Populating an antibonding (σ^* or π^*) orbital typically breaks a bond.
  - Word associations.
    - *HOMOs* act as *nucleophiles* because they are *electron-rich*, existing as a *filled orbital*.
    - *LUMOs* act as *electrophiles* because they are *electron-poor*, existing as an *empty orbital*.

- Key takeaways: MO Theory - 2.
  - Nucleophiles approach from certain angles to overlap with antibonding orbitals.
    - Example: The backside attack in an S_N2 reaction (Figure 2.1e).
    - Example: The Bürgi-Dunitz angle in a carbonyl attack (Figure 2.2b).
  - Hyperconjugation involves the interaction of a donor orbital with an acceptor orbital.
    - It is an overall stabilizing effect.
  - Example of how hyperconjugation manifests: The anomeric effect (Figure 2.4).
    - Substituents on a cyclohexane chair typically prefer to be equatorial because of sterics.
    - However, with a heteroatom in the 6-membered ring, *adjacent* substituents prefer to be axial.
    - MO explanation: The lone pair on the heteroatom in the ring donates into the σ^*-orbital of the axial substituent.
      - ➢ This is $n_O \rightarrow \sigma^*_{CO}$ donation; review your hyperconjugation notation!!

  - Example of how hyperconjugation manifests: Effects on structure.
    - Example: The staggered vs. eclipsed conformations of ethane (Figure 2.5).
  - Example of how hyperconjugation manifests: Stability of carbocations.
    - Example: Tertiary vs. primary (Figure 2.3).
  - Example of how hyperconjugation manifests: Reactivity.
    - Example: The rates of S_N1 reactions (Figure 2.6).
  - Takeaway: Key notions for hyperconjugation.
    - Know when it's there.
    - Be able to draw the donor and acceptor orbitals.
    - Understand the geometric factors, e.g., antiperiplanar donor-acceptor interactions.

- Key takeaways: Pericyclics.
  - Know your nomenclature; Prof. Elkin won't repeat it here, though.
  - Big takeaway from this lecture: The rules for drawing the MOs of conjugated systems.
    - We have used this technique in basically every lecture since it was introduced.
    - This is arguably the *key* concept in this unit.
  - Example: Butadiene (Figure 2.14).
    - The rules.
      - The number of nodes always starts with zero and goes up by 1 at every energy level.
      - Nodes are drawn symmetrically.
      - At the highest level, you always have one node between all adjacent orbitals.
      - The teaching team often gets questions about how to draw these; make sure to practice!!
    - Know how to populate orbitals as well.
      - We've got 4 π-electrons, which we populate starting from the bottom per the Aufbau principle, the Pauli exclusion principle, and Hund's rule.
  - Light excites one electron up one energy level (Figure 2.15).
  - The key to understanding most pericyclic reactions is to draw the HOMO, the LUMO, or both for conjugated system(s).

- Prof. Elkin pauses to ask for questions on MOs.

- For the anomeric effect, do we need to know anything besides the axial preference? For example, do we need to know about its effect on the rate of reaction, etc.?
  - By definition, the "anomeric effect" is the favoring of the axial substituent.
  - However, the anomeric effect has *consequences* (that you do need to know) for accelerating S_N1 reactivity. For example, axial leaving groups react/leave faster than equatorial leaving groups.

- For the anomeric effect, does the heteroatom have to be adjacent to the substituent?
  - Yes; you need the orbitals to overlap *efficiently*.
  - If you put the heteroatom one carbon away from the substituent, it doesn't work.

- Key takeaways: Diels-Alder.
  - Review the cheat sheet from the Lecture 14 recap at the beginning of Lecture 15 (Figure 2.32)!!.
  - You must be able to rationalize regiochemistry with resonance structures (Figure 2.25).
  - You must be able to rationalize stereochemsistry with the *endo* transition state (Figure 2.27b).
    - This involves your diene and dienophile substituents.
    - This involves knowing your HOMO-LUMO interactions.

  - You must be able to rationalize stereochemistry based on the incoming olefin (Figure 2.23).
  - Note: Relative stereochemistry is all that matters; the Diels-Alder is *not* enantioselective!
  - You can accelerate these reactions with EWGs and EDGs (Figure 2.17), by enforcing the s-*cis* conformation (Figure 2.19c), and with Lewis acid catalysts (Figure 2.29).
  - Remember the inverse electron-demand Diels-Alder reaction, in which the diene is the LUMO and the dienophile is the HOMO (Figure 2.30).
    - This is still *o*/*p*-directing and still *endo*.
    - Identify these by noting EWGs on the diene and EDGs on the dienophile.

- Do you need to show wedges and dashes in unfolded the 3D product, as in Figures 2.27 & 2.45b?
  - No; only in the final hexagonal product.
  - All we need to show in the 3D product is the groups pointing in the correct direction (e.g., correct regiochemistry and *endo* transition state), but lines are find to connect all atoms in 3D structures.

- Key takeaways: Cycloadditions.
  - For a dipolar cycloaddition, you choose the HOMO and LUMO arbitrarily.[16]
    - However, the phases still must match.
    - Example: See Figure 2.37 and the associated discussion.
  - We talked a lot about azide-alkyne cycloadditions (Figures 2.36b & 2.38).
  - Ozonolysis (Figures 2.39 & 2.40).
    - Multiple product options from Me_2S, H_2O_2, or $NaBH_4$ as second-step additives (Figure 2.41).
  - $[2 + 2]$ cycloadditions are often photochemical (Figure 2.42).
    - The photochemical requirement originates from the need to get the orbital phases to match (Figure 2.43).
    - These are *exo*-selective (Figure 2.45b).
    - The regiochemistry is the opposite of a thermal reaction because the photoexcited state has inverse polarity (Figure 2.46b).

- On PSet 4, there were some questions where additional chemical steps changed the final structure. For example, there was a TMS deprotection and an anhydride hydrolysis. Do we have to have such reactions memorized?
  - Prof. Elkin: "I love the idea that you know 5.12 material, so you should know this."
  - But this course is 5.13, so we'll be assessing 5.13 material.
  - Takeaway: Review 5.12 content, but if you have limited time, focus on reviewing 5.13 - Unit 2 content first.

- Key takeaways: Electrocyclizations.
  - Only consider the HOMO.
    - Identify the orbitals at the end of the π-system that form the σ-bond.
    - Decide if these should rotate in a conrotatory (Figure 2.47b) or disrotatory (Figure 2.48b) fashion.
    - Draw the resulting stereochemistry.
  - Woodward-Hoffmann rules: A shortcut to determining conrotatory or disrotatory without orbitals (Table 2.1).
    - Use these as a sanity check for your orbital derivation.
    - Example: If you draw orbitals and predict conrotatory but the Woodward-Hoffmann rules tell you that it is disrotatory, your orbital drawing must be wrong. Check it again!

[16] At least for the purposes of this class; further chemistry courses would teach you to differentiate.

  - Definitely practice taking a molecule, drawing it in perspective, putting your HOMO on it, identifying like lobes, etc. In effect, practice the whole procedure!!
  - For a retrocyclization, determine the product by using the principle of microscopic reversibility to consider the forward cyclization (Figure 2.50).
  - The Nazarov cyclization: Know the mechanism (Figure 2.52).
    - It involves protonation, deprotonation, keto-enol tautomerization, etc.
    - This is 5.12 content that you *have* to know!!
    - To clarify her earlier remarks, Prof. Elkin cares less about Friedel-Crafts, for instance.

- When do we use a HOMO vs. a SOMO?
  - In a photochemical reaction, we excite an electron, creating a SOMO.
  - But this SOMO is just a new HOMO!
  - So we always use the *highest*-occupied molecular orbital; it's just that sometimes, this orbital is singly occupied!

- Key takeaways: Sigmatropic rearrangements.
  - The Cope and Claisen rearrangements occur via a chair transition state (Figure 2.57 & 2.62).
    - The most stable chair predicts the product stereochemistry.
  - The MO picture (Figure 2.56).
    - Procedure to know: We divide the molecule into two SOMOs, and then consider whether the required shift or motion would be suprafacial or antarafacial.
  - We can accelerate the reaction with strain release, forming a more stable olefin, further reactions, ground state destabilization, etc. (Figure 2.58).

- Key tip: Study by practicing.
  - Draw the MOs for conjugated systems, draw chairs for *endo* and *exo* transition states, unfold a transition state into a 2D form! These are the hardest things from this unit.
  - Give yourself the time and energy to practice!!