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

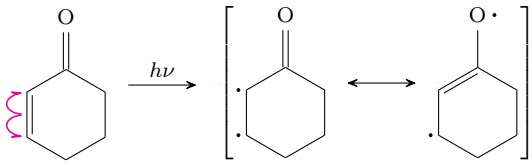


Figure 2.44: Systems with more stable excited states preferentially absorb light.

  - 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!!

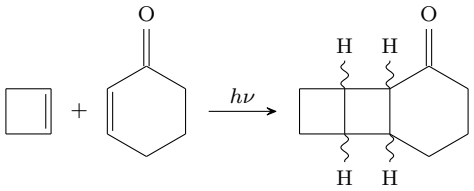
- Looking ahead (Friday).
  - We will begin with a bit more content on cycloadditions that we could not get to today.
  - After that, we will cover electrocyclizations.
  - It's going to be a long lecture, but you'll have the weekend to digest it.

2.16 Electrocyclizations

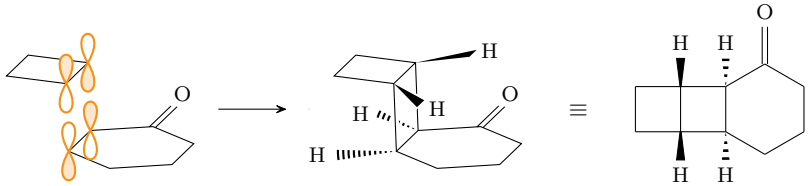
10/11:

- 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.

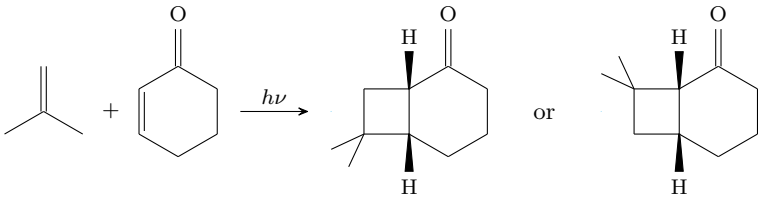


(b) *exo* pathway.

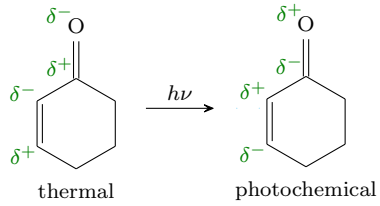
Figure 2.45: [2 + 2] cycloaddition stereochemistry.

  - 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![10]

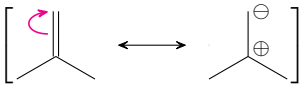
- Regiochemistry of the [2 + 2] cycloaddition.



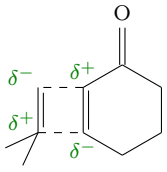
(a) Possible products of an asymmetric [2 + 2] cycloaddition.



(b) Partial charges (enone).



(c) Resonance (alkene).



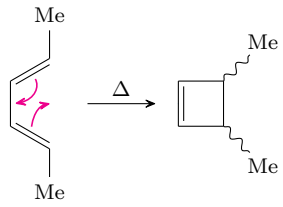
(d) Matching partial charges.

Figure 2.46: [2 + 2] cycloaddition regiochemistry.

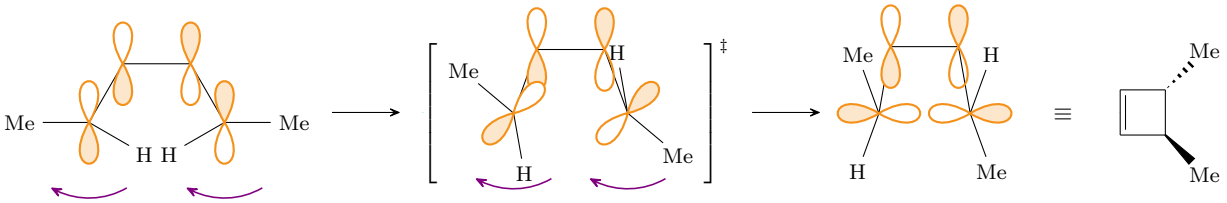
[10]Note that we did not talk about the stereochemistry of dipolar cycloadditions because they are *not* stereoselective: A fairly even balance of secondary orbital interactions with sterics makes the stereochemistry of dipolar cycloadditions very hard to predict.

  - 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.

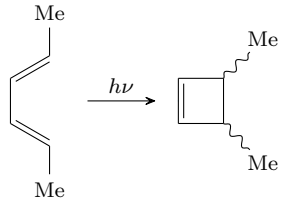


(b) Conrotatory pathway.

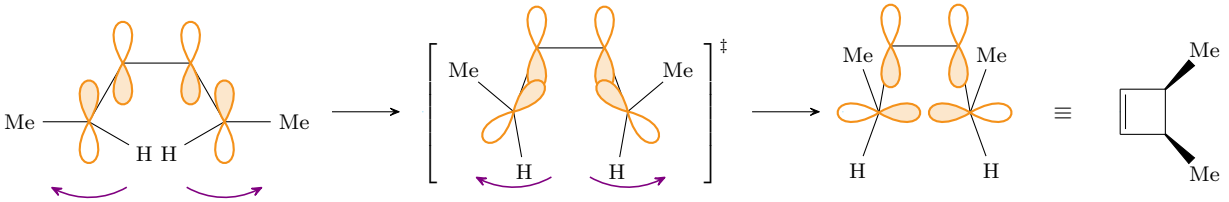
Figure 2.47: Thermal 4π electrocyclization.

- 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.[11]
    - ➢ 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.

[11] 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.

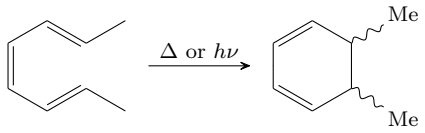
$\#\,\mathbf{e^-}$	$\boldsymbol{\Delta}$	$\boldsymbol{h\nu}$
$4n$	con	dis
$4n+2$	dis	con

Table 2.1: Woodward-Hoffmann rules.

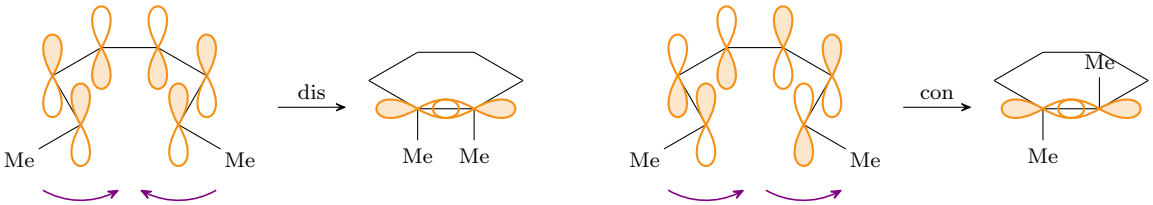
- Aside (chemis-tea): Who was R. B. Woodward?
  - R. B. Woodward was an MIT alum, even though he failed out after his freshman year.
  - He was readmitted though, and after graduating, he went on to become our most famous synthetic organic chemist.
  - He won a Nobel Prize and would have won a second, 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.



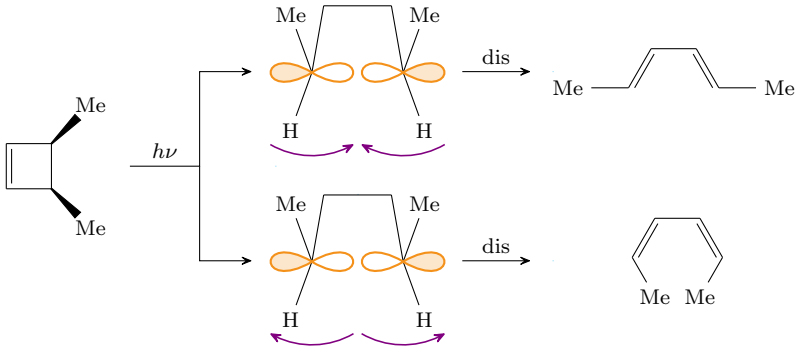
(b) Thermal product (disrotatory).

(c) Photochemical product (conrotatory).

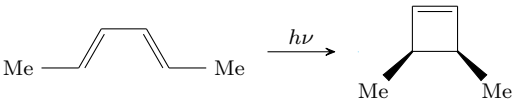
Figure 2.49: Thermal and photochemical 6π electrocyclizations.

  - 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!

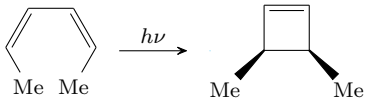
- Example: Retro-4π electrocyclization.



(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.

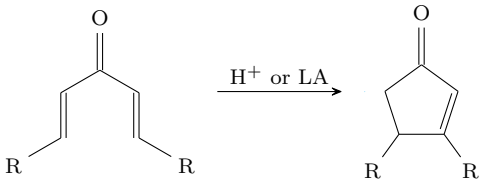


Figure 2.51: Nazarov cyclization.

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

- Mechanism.

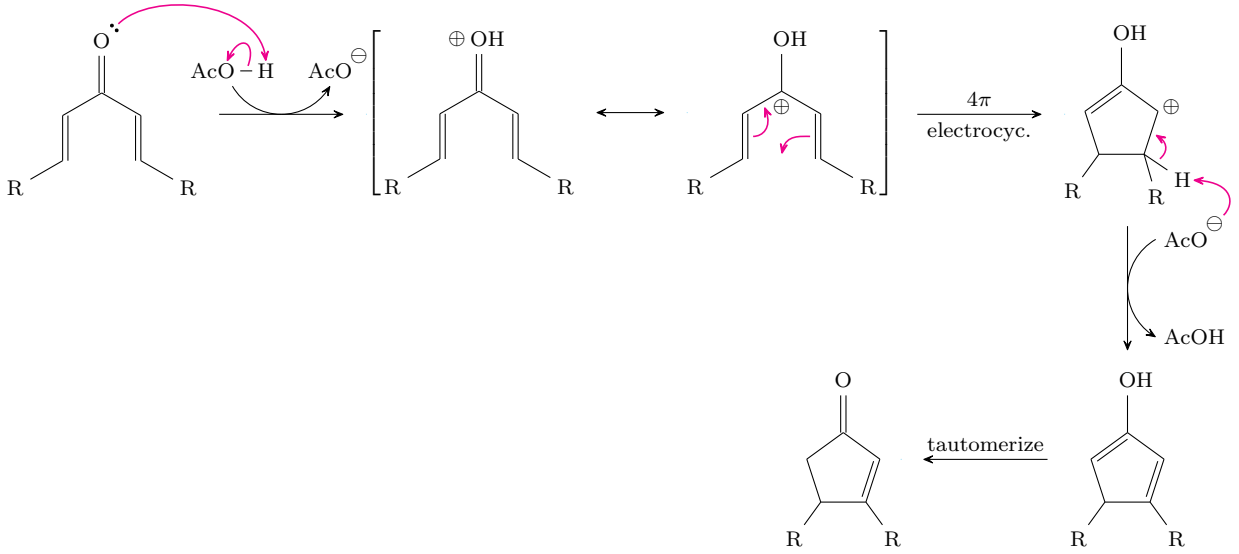


Figure 2.52: Nazarov cyclization mechanism.

  - 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.

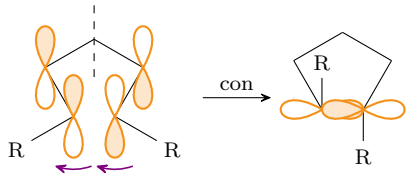


Figure 2.53: Nazarov cyclization stereochemistry.

  - 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.

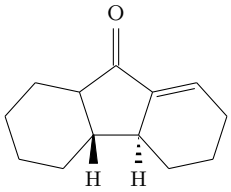


Figure 2.54: Alternate deprotonation sites in Nazarov cyclizations.

  - 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.