

- 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  $\sigma$ -orbital and a  $\sigma^*$ -orbital.
    - The  $\sigma$ -orbital is polarized toward I, and the  $\sigma^*$ -orbital is polarized toward C.
  - Example: The C=O double bond.
    - There is still a  $\sigma$ -bond here, but since the  $\pi$ -bond does all the reactivity, we'll narrow our focus to the  $\pi$ -bonding interactions.
    - The  $\pi$ -orbital is polarized toward O, and the  $\pi^*$ -orbital is polarized toward C.
    - The polarization of the  $\pi^*$ -orbital toward carbon explains why nucleophiles attack carbonyls at carbon!
  - Populating an antibonding ( $\sigma^*$  or  $\pi^*$ ) 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  $\sigma^*$ -orbital of the axial substituent.
      - This is  $n_O \rightarrow \sigma^*_{C-O}$  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  $\pi$ -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 stereochemistry 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 fine to connect all atoms in 3D structures.
- Key takeaways: Cycloadditions.
  - For a dipolar cycloaddition, you choose the HOMO and LUMO arbitrarily.<sup>[16]</sup>
    - 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  $\text{Me}_2\text{S}$ ,  $\text{H}_2\text{O}_2$ , or  $\text{NaBH}_4$  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  $\pi$ -system that form the  $\sigma$ -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!

<sup>16</sup>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!!