Week 3

Applications of Bonding Theory

3.1 Computational Chemistry

9/17:
- Lecture 3 recap.
    - Huckel theory: A fast way to draw the MOs of conjugated π-systems.
        - If the conjugated π-system in question is cyclic, use a Frost circle.
    - Aromaticity.
        - Huckel's definition: $4n + 2$.
        - Möbius's definition: $4n$.
        - Leads to properties like stabilization, quadrupoles, and ring current.
    - Cyclopropane: sp^2-like banana bonds (the only thing we need to remember from that discussion).
    - Wavefunctions: Solutions to the Schrödinger equation.
- Today: Computational chemistry (an overview).
    - Computational chemistry is typically an entire class!
- Lecture outline.
    - Methods of computational chemistry.
    - Molecular mechanics.
    - Semi-empirical methods.
    - Ab initio methods.
    - Hartree-Fock.
    - Density functional theory (DFT).
    - Best practices for calculations.
    - Properties that are especially easy (or hard) to calculate.
- Why do we do computational chemistry?
    - If we could fully solve the Schrödinger equation, we could know the properties of all of our electrons!
    - However, the Schrödinger equation can only be fully solved (practically) for the simplest systems.
        - For now, at least: People are working on this.
    - As such, we *approximate* solutions instead.

- **Computational chemistry**: The science of approximating solutions to the Schrödinger equation.

  – Computational chemistry can be broken up into two general strategies (**ab initio** and **empirical** methods) and one in-between strategy called **semi-empirical** mehods.

- **Ab initio** (methods): Make well-defined approximations to the Schrödinger equation, and then solve the approximations mathematically. *Etymology* from Latin "from first principles."

  – Essentially, make your math simpler.

- **Semi-empirical** (methods): Replace complicated parts of the Schrödinger equation with experimentally derived parameters, such as bond lengths, vibrational frequencies, and more that we can get from spectroscopy.

  – Essentially, shortcut the hardest parts of solving with experimentally derived features.

- **Empirical** (methods): Approximate molecules with force fields that are experimentally derived, and adjust with further experimental parameters.

  – Essentially, start with reality and derive computational things from that.

- We now look at some commonly derived methods. The following list is sorted from methods with high **accuracy** and low **speed** to methods with low accuracy and high speed.

  – Methods at the high end of accuracy and the low end of speed (ab initio).
    - **Coupled cluster**.
    - **Perturbation theory**.
    - **Density functional theory**.
    - **Hartree-Fock**.
  – Methods in the middle (semi-empirical).
    - **Semi-empirical methods**.
  – Methods at the high end of speed and the low end of accuracy (empirical).
    - **Molecular mechanics**.

- **Speed**: Ease of calculations.

- **Accuracy**: Careful and diligent.

- **Coupled cluster**: Useful for approximately 10 **heavy atoms**. *Also known as* **CC**.

- **Density functional theory**: Useful for approximately 80 heavy atoms, though we can use more (it just gets slower). *Also known as* **DFT**.

- **Hartree-Fock**. *Also known as* **HF**.

- **Molecular mechanics**: Useful for hundreds of heavy atoms. *Also known as* **MM**.

- **Heavy atom**: Any atom that's not hydrogen.

- In this course, we'll discuss further the bottom four methods in the above list of six.

- Molecular mechanics (MM).

  – Atoms are treated as balls and springs (this is a classical analogy and thus much easier to simulate).
  – We use force fields to describe electrons.
    - These force fields are derived from experimental data, i.e., choose a force field that gives us the bonds we calculate from XRD or the vibrations we see in IR.
  – Very fast; often considered "quick and dirty."

- ■ Gives us a general picture of what we're thinking about.
  - – Common application: Very large and flexible systems.
    - ■ Think proteins, polymers, etc.
    - ■ Things that have a lot of degrees of freedom.
    - ■ Very useful for chembio, polymer chemistry, etc.
  - – Subset application: **Molecular dynamics** (MD).
    - ■ Simulating movement; uses MM as a basis.
  - – If you're going to use this method, know that it is (in general) only appropriate for approximating the ground states of molecules (not their transition states).
    - ■ However, MM can be a good starting point for higher-level calculations (i.e., more accurate methods).
    - ■ In Orgo, it's mainly used for first approximations to be refined later (and for heavier stuff).
    - ■ All the same, it is a super useful tool with tons of applications, and its simplicity should not lead us to discount it.
  - – Running MM.
    - ■ If we have a PC, try clicking the MM2 button in Chem3D (which is part of our ChemDraw package).
    - ■ This may not work on Macs; figure this out!!
    - ■ PerkinElmer (who developed ChemDraw) initially developed their stuff for Macs; Masha's not quite sure where they dropped the ball.

- Semi-empirical quantum mechanical (SQM) methods.

  - – Use empirical parameters to simplify *ab initio* calculations.
    - ■ Tries to deliver the best of both worlds (speed and accuracy).
  - – We can add corrections for missing phenomena and underestimated features.
  - – Theoreticians (developers) will draw the line on accuracy somewhere, and then organic chemists will say, "this model fails here."
    - ■ Once that feedback gets into the literature, theoreticians redefine their line.
    - ■ They might need to account for d-orbitals, London dispersion forces (LDFs), flexibility, solvent, or more.
      - ➢ Methods of accounting for solvent effects are continuously being optimized.
    - ■ It's important to be on top of the literature here, since things are always getting better!
  - – Modern implementations (these are getting fast enough to be usable and really good!).
    - ■ Density function based tight binding (DFTB): Approximate DFT.
    - ■ eXtended Tight Binding (xTB)
      - ➢ Developed primarily by the Grimme lab.
      - ➢ Basically just adding more parameters.
  - – LDFs are becoming increasingly important for selective catalysis, so there's a lot of work to approximate them.
    - ■ Catalysis is not about partial positive and negative charges so much as it is about electrons flopping around to achieve incredible selectivities in next-gen catalysts.
  - – Very fast (seconds) and pretty accurate. Increasingly used, especially for ML and data science.
    - ■ Nowadays, if you want to do ML, you need these hundreds of experimental data points.

- Ab initio methods.

  - – Background theories (neither is technically true, but it is helpful for speed).

■ **Born-Oppenheimer approximation**.
■ **Independent electron theory**.

- **Born-Oppenheimer approximation**: Nuclei are way bigger than electrons (have over 1000 times more mass), so they are basically fixed in space relative to the electrons.

  – This means that you can treat the nuclei separately; you can use one approach for the nuclei and an entirely different approach for the electrons.

- **Independent electron theory**: Electron movements are not correlated to each other; all electrons whiz around independently.

  – Making this approximation will cause some issues.

- Hartree-Fock (HF).

  – Treat electrons as a delocalized cloud with independent electron movement.

    ■ Remember the plum pudding model of the atom? This is not that dissimilar from that.

  – This approximation ignores Coulombic interactions (like LDFs).

    ■ This becomes very problematic for transition states.

  – HF methods are largely historical today.

    ■ There are applications where they're still used today, but not in Orgo and not without an understanding of their shortcomings.

- We can run any and all of these computations throughout grad school as MIT students, and we should! They're in our toolbelt now, and we should try them out!!

- Density functional theory (DFT).

  – Instead of calculating wavefunctions, we're going to calculate electron density.

    ■ We're going to do this using **functionals**.
    ■ We can include functionals for things like Coulombic interactions, etc.[1]

  – This is a good workhorse method in organic chemistry.

    ■ DFT is appropriate for reaction coordinate mapping, transition states, etc.
    ■ We'll often work with collaborators that can tailor a model to our needs.

  – There are many specific functionals and basis sets.

    ■ You have to choose the functional (choose what to include), and then choose the basis sets (how much detail do I need for this calculation, e.g., treating polarization, charge, unpaired electrons more accurately).
    ■ It is best to find a basis set and functional appropriate for our context.

  – Basis sets don't describe all types of elements.

    ■ Some describe elements 1-30, others do 1-86.
    ■ Don't be that person who has to redo their entire calculation because they forgot that tin is one of their reagents!
    ■ We often use **split basis sets** (esp. for transition metals), i.e., certain atoms (i.e., metals) get more functionals.
      ➢ Carbon, hydrogen, and oxygen (CHO) don't need the craziest level of theory to approximate, but that palladium center will!
    ■ Think about what level of theory you need for each atom.

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[1]Maybe what I can be known for in research is custom building computational tools for specific organic problems, and turning that into a workflow that people do. Maybe that's what ML already is.

- **Functional**: A function of functions.[2] *Also known as* **higher-order function**.

- Best practices for running calculations for our own things.

  - This part of the lecture is *critical*; it tells us what we need to know to use computational chemistry.
    - If we want to learn the theory for all of these things, we should read a textbook or take Heather Kulik's class.
  - Use the appropriate level of theory for your needs and capabilities.
  - Questions to ask yourself to assess your needs and capabilities.
    - Do you have a supercomputer? How much time on the supercomputer do you have?
    - When do you need this result by? Is your PI breathing down your neck?
    - What am I trying to model?
    - Is this a thought experiment or something serious?
  - Additional things to consider wrt your needs and capabilities.
    - Consider speed vs. accuracy.
      - ➢ You can always start at a lower level theory and then ramp it up if you need more accuracy. This is a great general approach.
    - Consider size and flexibility (no HF on proteins, or MM on methane).
    - Consider "weirdness": If you've got something that's all inverted and Möbius like, you're gonna need something more tailor-made.
    - Find a *reliable* literature precedent for a similar system.
      - ➢ If you want to model a cationic cyclization, use a precedent paper's level of theory.
      - ➢ How do I model an iridium catalyst? Find an iridium catalyst paper and go from that!
    - Know how your level of theory works.
      - ➢ Does it account for polarizability? Charge? Solvent? d-orbitals?
      - ➢ It is our responsibility as an experimentalist to know this if we're going to publish it; our PI probably won't be as deep into the nitty-gritty as us.
  - Don't blindly trust calculations.
    - Calculations always give you an answer (unless they fail or don't converge). However, just because you get a number doesn't means that that number is accurate!
    - Benchmark your calculation with experiments whenever we can. Examples: X-ray structure, ratio of products (we can back-calculate from temperature the activation energy barrier, and from the transition states what ratio of products we expect).
    - Redo a couple of calculations at a higher level of theory to see if you get the same answer.
    - Chris Cramer (a founding father of computational chemistry): "There is no particular virtue to the speed at which a wrong answer can be obtained."
  - Example of doing calculations wrong: Doing an S_N1 reaction without solvent. These reactions are so solvent-dependent, and there's no gas-phase cation that will replicate this solution-phase reaction.

- What's easy to calculate?

  - Spectra: IR, Raman, NMR.
    - Masha likes to predict the NMR spectra of wacky intermediates.
    - ChemDraw does this for free.
      - ➢ The default solvent is THF; make sure you change it to $CDCl_3$!
    - MNova's function is better; it's ML-based, but it also costs money to run?? I think Masha has this wrong for MIT students.

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[2]This is the computer science definition; it is largely unrelated to the mathematical definition that is equivalent to linear forms and duals.

- Geometries, conformers, and ground state structures.
    - ■ "Geometry optimization" or "energy minimization" is very common.
    - ■ Draw a 3D structure, give it to our program, move atoms, calculate E, repeat (let the program perturb the atom's positions a bit) until we reach a *local* minimum.
    - ■ This is what we'll do on the problem set.
    - ■ If we want to get the *global* minimum, we have to look for lower energy structures (manually, automatically, or a combination of both).
    - ■ We often start at a low level of theory and then refine. Start with a search of the chemical space to find some stable conformers, and then pop that into DFT.
- Frequencies, well-defined transition states, and **single point calculations**.
    - ■ Important because transition states are saddle points on the potential energy surface with 1 imaginary frequency corresponding to the bond-making or -breaking event.
    - ■ If you have a structure that you think is a ground state, you have to prove this.

- **Single point calculation**: Calculating the energy of a structure without any other atoms around.

- Note: Nucleophiles typically come in at a 120° angle (the **Bürgi-Dunitz angle**), because that's where it's easiest to donate into the π^*-lobe.

- What's "hard" to calculate?

    - Caveat: Do your research!!
        - ■ Many applications require specialized approaches.
        - ■ There's an army of computational chemists who are trying to develop niche methods for our little problem; find them, connect with them, collaborate with them, etc.
        - ■ It is our responsibility to know what part of a certain experiment is difficult.
            - ➢ Example: In photophysics, you need to know the limitations of certain parts of our model.
            - ➢ The system will not say, "I'm bad at predicting excited states;" you have to know that.
    - Things that require more finessing to study.
        - ■ Open-shell species, e.g., radicals.
        - ■ Transition metals: Heather researches how to model TMs with SQM, etc. This is really important and really hard.
        - ■ "Unusual structures," e.g., gas-phase plasma nonsense.
    - Thermochemistry.
        - ■ E.g., thermodynamical parameters, calorimetry, etc.
        - ■ There are specific packages that work for this, if we need to look into them.
        - ■ Masha doesn't know anything about any of this, but recommends that we can learn them!!
    - Solvent effects, LDFs, etc.
        - ■ For these topics, the methods are getting better all the time (which is code for, "the programs don't work great yet").
        - ■ **Implicit solvation** vs. **explicit solvation**.

- **Implicit solvation**: Treat the solvent as a continuous medium.

- **Explicit solvation**: Draw solvent molecules and add them to the calculation.

    - If you think the solvent is stabilizing the transition state in an S_N1, you need to draw a little THF donating its lone pair to the carbocation.
    - This gets complicated in proteins, where we need to identify how many waters we need to draw to accurately represent water; recent papers suggest that effects matter up to 44 H_2O molecules away!

3.2   Pericyclic Reactions

9/19:
- Lecture 4 recap.

  - Masha redraws the accuracy/speed list of computational techniques.
  - She also rewrites the Cramer quote.
  - Basically, Tuesday was the methods, theory, and applications of computational chemistry.

- Announcements.

  - PSet 1 posted.
  - Conference room booked this afternoon for collaboration on the PSet.

- Today: Pericyclic reactions.

  - Reading: Anslyn and Dougherty (2006), Chapters 15 (pericyclics in general) and 16 (photochemical pericyclics).
  - See Jonathan's reading list!!

- Lecture outline.

  - Pericyclic reaction types and vocabulary.
  - History of pericyclic reactions.
  - Woodward-Hoffmann rules.
  - Dewar-Zimmerman analysis.
  - Frontier molecular orbital theory.
  - Miscellaneous pericyclic reactions.

- **Pericyclic** (reaction): A **concerted** (as opposed to **stepwise**) reaction with a transition state (TS) consisting of a cyclic[3] array of atoms and orbitals. *Antiquated* **thermoreorganization**.

  - Informal definition: "If you can draw circle arrows, it's a pericylic reaction."
  - Can be **synchronous** or **asynchronous**.
    - Indeed, sometimes we see asynchronous concerted Diels-Alders! These make us ask, "is the TS truly symmetric, or are some bonds longer or shorter?"
  - There are 5 (main) types of pericyclic reactions. The first three are "the big three," and the latter two are less common.
    1. **Electrocyclizations**.
    2. **Cycloadditions**.
    3. **Sigmatropic rearrangements**.
    4. **Group transfers**.
    5. **Chelotropic reactions**.
    6. Etc.
  - This lecture assumes that we've seen all of these; if we haven't seen these reactions before in undergrad or if it's been a while. . .
    - Read the textbook;
    - Review your notes from undergrad;
    - Do some Googling (the Wikipedia pages are pretty helpful!!);
    - Ideally, do all of the above!

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[3]This stands in contrast to "normal" organic reactions, which prefer to proceed through a *linear* TS.

- **Concerted** (mechanism): A mechanism with no **intermediates**.

- **Stepwise** (mechanism): A mechanism *with* intermediates.

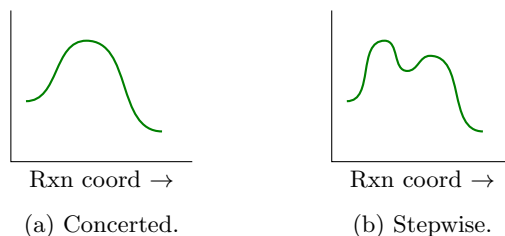- Concerted and stepwise mechanisms can be differentiated based on their respective energy diagrams.

Rxn coord →   Rxn coord →

(a) Concerted.   (b) Stepwise.

Figure 3.1: Concerted vs. stepwise energy diagrams.

- **Intermediate**: A local ground state structure.

- **Synchronous** (mechanism): All bond-making and -breaking occurs to an equal extent in the TS.

- **Asynchronous** (mechanism): The bond-making and -breaking does *not* occur to an equal extent in the TS.

- David: Would the fact that bond breaking/making happens more sequentially in an asynchronous mechanism imply that these reactions have energy diagrams that differ from the synchronous, concerted ideal of Figure 3.1a?

  - The energy diagram *is* different between synchronous and asynchronous.
  - Look into Dean Tantillo at UC-Davis for more!!

- **Electrocyclization**: A pericyclic reaction in which one π-bond gets converted into one σ-bond or vice versa. *Also known as* **electrocyclic reaction**. *Denoted by* $m\pi$.
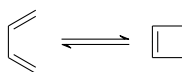
  - Example: We can refer to the above reaction as a "4π electrocyclization."

- **Cycloaddition**: A pericyclic reaction in which two or more unsaturated molecules (intermolecular) — or parts of the same molecule (intramolecular) — combine to form a cyclic adduct with a net reduction of bond multiplicity. *Denoted by* $[m+n]$.
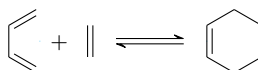
  - Example: We can refer to the above reaction as a "$[4+2]$ cycloaddition."
  - This specific cycloaddition is also known as a **Diels-Alder reaction**!

- **Sigmatropic rearrangement**: A pericyclic reaction in which a σ-bond migrates along with a corresponding reorganization of the π-electrons. *Also known as* **sigmatropic reaction**. *Denoted by* $[m, n]$.
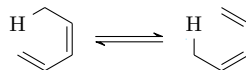
  - Example: We can refer to the above reaction as a "$[1, 5]$-sigmatropic hydride shift."

- **Group transfer** (reaction): A reaction that transfers atoms from one molecule to another, but in a concerted pericyclic transition state.

- **Chelotropic** (reaction): A cycloaddition in which two bonds are made to one atom.

- **Diels-Alder** (reaction): A $[4 + 2]$ cycloaddition.

- Aside (chemis-tea): One of Steve Buchwald's pet peeves.

  - Don't erase the chalkboard with your fingers; use the eraser.
  - If Steve is on your thesis committee, the first thing he'll tell you is to use the eraser.

- History of pericyclic reactions.
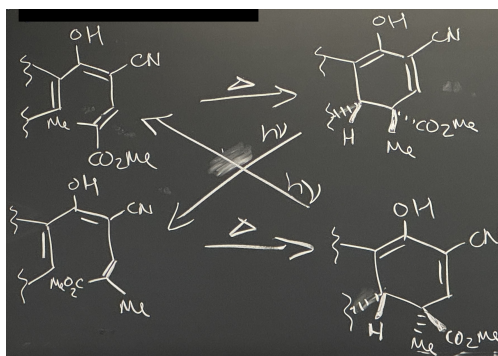
Figure 3.2: First observation of a pericyclic mechanism.

  - Long considered to have "no mechanism."
    - ■ This is because people saw a starting material and a product, with nothing in between.
    - ■ Quote from the '60s: "No-mechanism is the designation, given half in jest, half in desperation, to thermoreorganization reactions" – von Eggers Doering and Roth (1962).
  - In 1966, Woodward and his army of grad students were synthesizing Vitamin B_{12}. During one particular ring-closing 'thermoreorganization' reaction, they noticed that using different geometric isomers as starting materials formed different stereoisomers as products (see Figure 3.2).
    - ■ This gave a hint!
    - ■ Shortly after, Woodward and colleagues made a second (even weirder) observation: In the presence of light, the cyclized products would revert to their starting materials, but to the *opposite* geometric isomer (also see Figure 3.2)!
  - These observations kickstarted a series of studies into the mechanism of such reactions.

- In time, we came to classify the reaction in Figure 3.2 as a "6π electrocyclization," governed by the mechanism described as follows.
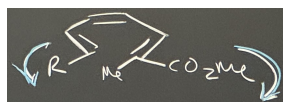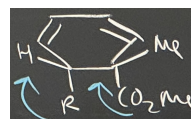
(a) Disrotatory.   (b) Conrotatory.

Figure 3.3: 6π electrocyclization mechanisms.

- During a **thermal** electrocyclization, the termini of the π-systems rotate in opposite directions.
  - ■ Notice how in Figure 3.3a, both *exo* groups rotate down, but the right one rotates clockwise and the left one rotates clockwise.
- During a **photochemical** electrocyclization, the termini of the π-system rotate in the same direction.
  - ■ Notice how in Figure 3.3b, both axial groups rotate clockwise.
- This "rotation" of the π-systems' termini is classified as **disrotatory** and **conrotatory**, respectively.
  - ■ The disrotatory/conrotatory phenomenon led us to the **Woodward-Hoffmann rules**.
- The fact that Woodward and colleagues' forward reaction is thermal but reverse reaction is photochemical is what yields the opposite starting material!

• **Thermal** (reaction): A reaction driven by high temperatures.

• **Photochemical** (reaction): A reaction driven by light.

• **Disrotatory** (electrocyclic reaction): An electrocyclic reaction in which the termini of the π-systems rotate in opposite directions.

• **Conrotatory** (electrocyclic reaction): An electrocyclic reaction in which the termini of the π-systems rotate in the same directions.

• **Woodward-Hoffmann rules**: Pericyclic reactions occur by the conservation of orbital symmetry from starting material to product.

| Activation	$\#\,e^-$	Rotation
Δ	$4n$	con
Δ	$4n+2$	dis
$h\nu$	$4n$	dis
$h\nu$	$4n+2$	con

Table 3.1: Woodward-Hoffmann rules.

- These rules are important because they allows us to predict the stereochemistry of our products.
- Nobel prize (1981) to Hoffmann and Fukui.
  - ■ Fukui was jointly awarded this prize for his work on frontier molecular orbital theory, which we'll talk about later in this lecture.
  - ■ Woodward didn't win because he had died. It was ok, though, because he had already won the Nobel once; this would have been his second.
  - ■ Aside (chemis-tea): A spat over who invented the Woodward-Hoffmann rules.
    - ➢ E. J. Corey claimed credit for giving Woodward the idea for the Woodward-Hoffmann rules in 2004 — see Corey (2004).
    - ➢ Then Hoffmann rebuts Corey with a show-me-the-receipts type article — see Hoffmann (2004).
    - ➢ Woodward and Corey were both titans in their field at Harvard, both Nobel laureates, but also both big personalities.
  - ■ Aside: Anyone who believes that science is somehow unbaised and empirical has never worked with a real scientist. Masha: "Scientists are some of the most human, emotional colleagues I've has ever worked with. . . and I love them, don't get me wrong."
- Historical impact: One of the first successful unions of theory and experiment in chemistry.
  - ■ Credited with leading organic chemists to finally accept MO theory.

- Let's now schematize the orbital machinations underlying the Woodward-Hoffmann rules.

- **Correlation diagram**: A method of tracking orbital symmetry from starting materials to products in an electrocyclization.

  - Workflow.
    1. Draw MOs.
    2. Assign symmetry (S = symmetric, A = antisymmetric).
    3. Populate with electrons.
    4. Correlate orbitals with the same symmetry.

  - We assign symmetry differently depending on whether we're investigating a disrotatory or conrotatory pathway.

    ■ Disrotatory pathway: Ask yourself, "are the orbitals symmetric with respect to the $\boldsymbol{\sigma}$-**plane**?"
    ■ Conrotatory pathway: Ask yourself, "are the orbitals symmetric with respect to the C_2 axis perpendicular to the σ-bond that forms in the electrocyclization and lying in the plane of the pericyclic TS?"

  - For clarification on what exactly this all means, we'll look at a few examples. In particular, we'll investigate the favorability of the thermal and photochemical, disrotatory and conrotatory pathways through which the 4π electrocyclization of butadiene could proceed.

- $\boldsymbol{\sigma}$-**plane**: The mirror plane lying perpendicular to the σ-bond that forms in an electrocyclization.

- Example: The possible thermally activated, 4π electrocyclizations of butadiene.

(a) Disrotatory.　　　　　(b) Conrotatory.
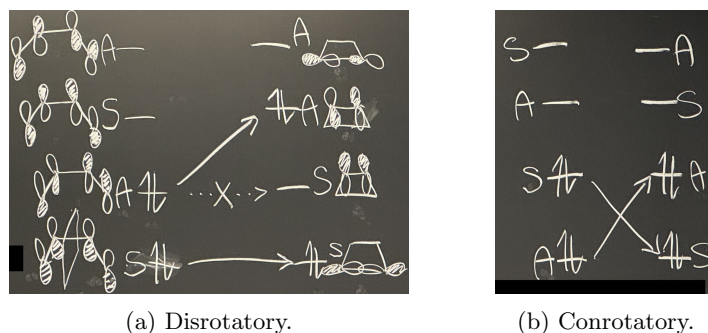
Figure 3.4: Correlation diagrams for butadiene's thermal 4π electrocyclizations.

  - We will first apply the correlation diagram workflow to the disrotatory case (Figure 3.4a).
    1. Draw MOs for both the starting material and product.
        ■ Let's begin by drawing the MOs for the starting material.
          ➢ We'll draw four p-orbitals and shade them in to create a conjugated π-system exactly as in Huckel theory.
          ➢ Specifically, notice the no nodes $\to$ 1 node $\to$ 2 nodes $\to$ 3 nodes pattern.
        ■ Then we draw the product's MOs adjacent.
          ➢ We know that the original four p-orbitals are transforming into a new σ-bond and a new π-bond, so we draw the bonding and antibonding phases of the new σ-bond as well as the bonding and antibonding phases of the new π-bond.
          ➢ Essentially, we are drawing a σ, π, π^*, and σ^* MO.
          ➢ Note that the π and π^* orbitals split less (energetically) than the σ and σ^* orbitals — just like in IChem — because they have less direct overlap; this is why we get the ordering $\sigma \to \pi \to \pi^* \to \sigma^*$ as opposed to $\pi \to \sigma \to \sigma^* \to \pi^*$ or something like that.

   2. Assign symmetry to each of our drawn MOs.
      ■ Since we are looking at the *disrotatory* case, we will look at symmetry with respect to the σ-plane.
      ■ As a guide, we draw in the σ-plane in the bottom-left MO.
      ■ This particular MO is clearly symmetric with respect to the σ-plane, so we label it "S".
      ■ We then perform this analysis for the remaining MOs, noting them as either symmetric or antisymmetric.
   3. Populate the starting MOs with electrons.
      ■ 4π electrocyclization, so 4 electrons to fill normally (i.e., per Aufbau, Pauli, and Hund).
   4. Correlate the filled starting MOs to the lowest energy product MOs with matching symmetry.
      ■ Maxim: An orbital cannot flip its symmetry during an electrocyclization.
      ■ As such, the lowest energy starting MO (being symmetric) has no problem becoming the lowest energy product MO (which is also symmetric).
      ■ However, the second-lowest energy starting MO (being antisymmetric) *cannot* become the second-lowest energy product MO because the latter is symmetric. (We say that this transition is formally **forbidden** because symmetry is not conserved.) As such, it must go up in energy to become the third-lowest energy product MO.
      ■ This population of a higher energy orbital means that the 4π electrocyclization of butadiene is *disfavored* to occur through a thermal, disrotatory pathway.
 – We now apply the correlation diagram workflow to the conrotatory case (Figure 3.4b).
   1. The MOs will be the same as in Figure 3.4a, so we don't need to redraw them.
   2. The symmetry must be evaluated with respect to that C_2 axis this time, though, so we have to reassign S or A to each MO.
      ■ For the MOs as drawn in Figure 3.4a, the C_2 axis we need goes into the plane of the page.
   3. We populate the starting MOs as before.
   4. When we correlate, this time we can fill the bottom two product MOs!
      ■ We didn't populate electrons directly across, but we *did* populate the lowest energy orbitals again, so the conrotatory pathway is *favored*.
      ■ Both arrows involve a conservation of orbital symmetry, so (to reiterate) this reaction is **allowed** (thermally).

• David: Why do we only draw some of the molecular orbitals?
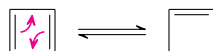
Figure 3.5: MOs relevant to butadiene's 4π electrocyclization.

 – We only consider the orbitals involved in the reaction; considering the whole σ-network would get more complicated without changing our results.
 – This is actually an example of why arrow-pushing is useful! Namely, because it shows that the p-MOs we consider in the starting material become the σ- and π-MOs we consider in the product.

• **Photochemical reaction**: A reaction driven by the absorption of a photon, leading to an excited state.

 – Later in this course, we'll go more into detail on photochemical reactions, but this is the only level of detail we need right now.
 – In the reactions we'll look at today, one electron is kicked up an energy level with no other changes to the structure.

- Example: The possible photochemically activated, 4π electrocyclizations of butadiene.

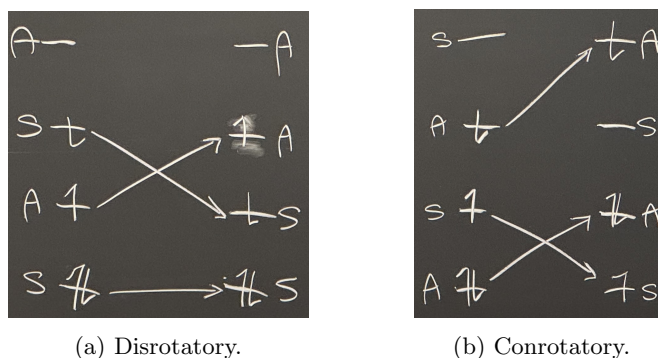(a) Disrotatory.   (b) Conrotatory.

Figure 3.6: Correlation diagrams for butadiene's photochemical 4π electrocyclizations.

   - We use the same MOs and symmetries as in the corresponding subfigures of Figure 3.4.
   - Differences only start to appear when we populate with electrons.
       - In particular, we excite one electron up a level (without altering its spin) in both sets of starting-material MOs.[4]
   - Disrotatory case (Figure 3.6a).
       - Orbital symmetries are such that we end up with the *same* populations as in the starting material.
       - Therefore, this pathway is allowed/favored.
   - Conrotatory case (Figure 3.6b).
       - Orbital symmetries are such that we end up with a *higher-energy* population than in the starting material.
       - Since electrons are in "much higher" energy levels, this pathway is forbidden/disfavored.

- Notice that the photochemical result that disrotatory is favored and conrotatory is disfavored is the opposite of thermal!

   - Thus, we just derived the Woodward-Hoffmann rules (Table 3.1) about what is favored and disfavored!
       - At least we derived the case for 4 electrons.
       - A more general mathematical proof can be done to rigorously verify Table 3.1, but the details are beyond the scope of this class.
   - If you ever forget the WH rules, just rederive them from first principles :)

- A note on the correlation arrows in Figures 3.4 and 3.6.

   - The uppermost correlation arrow in Figure 3.6b corresponds to an *allowed* but *disfavored* electronic transition.
   - The X'ed-out correlation arrow from A to S in Figure 3.4a corresponds to an explicitly *forbidden* electronic transition.

- The Woodward-Hoffmann rules are one way to look at pericyclic reactions, probably the most complex way.

   - We'll now look at two simpler ways.

---

[4]I.e., without intersystem crossing to a triplet state.

- Dewar-Zimmerman analysis: Aromatic TS theory.

  – Principle: Reactions that go through aromatic transition states are allowed.
  – We already like 6-membered TS's because they're geometrically stable; 6-membered *aromatic* TS's are even lower energy and more favored!

- Examples of aromatic and antiaromatic transition states.

(a) Aromatic TS in a $[4 + 2]$ cycloaddition.

(b) Anitaromatic TS in a $[2 + 2]$ cycloaddition.

Figure 3.7: Aromatic and antiaromatic transition states.

  – Figure 3.7a shows that the transition state in a Diels-Alder reaction is aromatic.
    - This is why the forward Diels-Alder reaction is favored (under thermal conditions).
  – Figure 3.7b shows that the transition state in a $[2 + 2]$ cycloaddition is antiaromatic.
    - This is why the forward reaction to cyclobutane is disfavored (under thermal conditions).

- Let's get a little more formal now.

- Rules.

  1. Draw orbitals with any phasing, and decide the reaction topology.
     – By "any phasing," we do mean that you can take *any* of the MOs you would draw and the Dewar-Zimmerman analysis will still work. So "go crazy," if you want!
       - Masha does not draw out any examples to inductively prove this to us, but it would probably be a good exercise to do this on my own!!
     – By "reaction topology," we mean how the two reactants approach each other. Is something coming from the top? The bottom?
  2. Connect orbitals through the reaction topology and count the number of phase inversions (PIs).
     – In other words, count how many lines connect lobes of opposite phases.
     – This will tell us whether we should evaluate the transition state for *Huckel* or *Möbius* aromaticity.
     – Essentially...
       - If there are an *even* number of PIs, having $4n + 2$ electrons will lend *Huckel* aromaticity to the transition state and favor its formation;
       - If there are an *odd* number of PIs, having $4n$ electrons will lend *Möbius* aromaticity to the transition state and favor its formation.
  3. Count the number of electrons.
     – As mentioned above, this number will tell us (depending on whether we're in Huckel-land or Möbius-land) whether the transition state is aromatic.

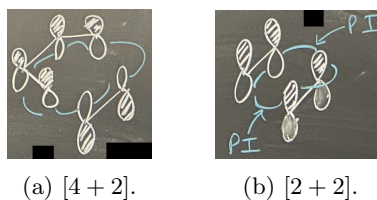- To practice using these rules, let's reevaluate the examples in Figure 3.7.

(a) $[4+2]$.   (b) $[2+2]$.

Figure 3.8: Dewar-Zimmerman connections for $[4+2]$ and $[2+2]$ cycloadditions.

- Example: $[4+2]$ cycloaddition (Figure 3.8a).
  1. Draw MOs, and decide the reaction topology.
     - MOs: Let's arbitrarily choose to use the MOs with no nodes for both butadiene and ethene.
     - Topology: Let ethene approach butadiene from the bottom.
  2. Connect orbitals, and count PIs.
     - Connections: We connect all the bottom lobes of butadiene, the two top lobes of ethene, and (since ethene is approaching from the bottom, per the reaction topology) the bottom terminal lobes of butadiene to the top terminal lobes of ethene.
       ➢ The connections are all drawn as blue lines in Figure 3.8.
     - PIs: All of the connected lobes are unshaded, so there are 0 PIs.
     - 0 is an even number, so we are in Huckel-land.
  3. Count the number of electrons.
     - There are $6 = 4(1) + 2$ π-electrons.
     - Therefore, our TS will be *stabilized* by *aromaticity* of the *Huckel* type.
- Example: $[2+2]$ cycloaddition (Figure 3.8b).
  1. Draw MOs, and decide the reaction topology.
     - MOs: We once again choose (arbitrarily) the MOs with no nodes for both ethenes.
     - Topology: The right ethene approaches the left ethene from the bottom.
  2. Connect orbitals, and count PIs.
     - Connections: We connect the bottom lobes of the left ethene to each other and to the top lobes of the right ethene (which are also connected to each other).
     - PIs: This time — because of the way we have drawn the right ethene — we have 2 PIs.
     - 2 is an even number, so we are in Huckel-land.
  3. Count the number of electrons.
     - There are $4 = 4(1)$ π-electrons.
     - Therefore, our TS will be *destabilized* by *antiaromaticity* of the *Huckel* type.

- The Dewar-Zimmerman analysis is useful for predicting the feasibility of sigmatropic rearrangements.

  - Recall from above that a *sigmatropic rearrangement* involves the migration of a σ-bond along with a corresponding reorganization of the π-electrons.
  - Specifically, in a sigmatropic rearrangement, the total number of π- and σ-bonds does not change.

- Example sigmatropic rearrangements.

  1. **Claisen rearrangement**.
  2. **Cope rearrangement**.

- **Claisen rearrangement**: A [3, 3]-sigmatropic rearrangement of allyl vinyl ethers to form correspond-
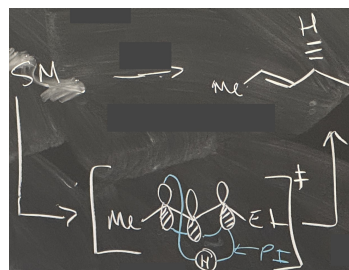 ing γ, δ-unsaturated carbonyls.
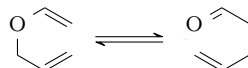
- **Cope rearrangement**: A [3, 3]-sigmatropic rearrangement of 1, 5-dienes to form other 1, 5-dienes.
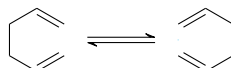
- We should be familiar with both the Claisen and Cope rearrangements; if we're not, Google them!!

- Example: Dewar-Zimmerman analysis of **suprafacial** and **antarafacial** [1,3]-sigmatropic H shifts.
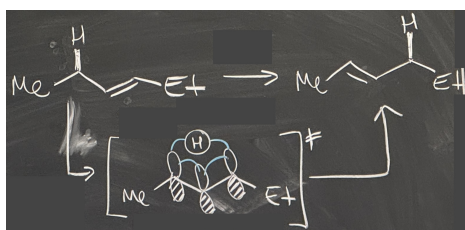
(a) Suprafacial.

(b) Antarafacial.

Figure 3.9: Dewar-Zimmerman analysis of [1, 3]-sigmatropic hydride shifts.

– We'll start with the suprafacial case (Figure 3.9a).
  1. Draw MOs, and decide the reaction topology.
     ■ MOs: We choose the MO with no nodes for the π bonds, and the hydrogen atom's $1s$
        orbital.
        ➢ Notice that we draw a p-orbital for all three carbons involved in the bond break-
           ing/making process in the transition state, not just the two carbons involved in the
           initial or final bond!
     ■ Topology: Draw the H atom in the process of migrating.
  2. Connect orbitals, and count PIs.
     ■ Connections: Connect all the top lobes together and to hydrogen.
     ■ PIs: 0.
     ■ Even PIs, hence Huckel.
  3. Count the number of electrons.
     ■ We have two electrons in the C=C π-bond, and two electrons in the C–H σ-bond.
        ➢ We also get a clue that there are 4 electrons present because we drew 4 orbitals!
     ■ Thus, there are $4 = 4(1)$ electrons present.
     ■ Therefore, our TS will be destabilized by Huckel antiaromaticity.
     ■ It follows that the suprafacial pathway is (thermally) forbidden.
        ➢ This is an interesting result because at first glance, it "looks" like a nice TS (with the
           H just bouncing over), but nope! It's not allowed.

– We now move onto the antarafacial case (Figure 3.9b).

1. Draw MOs, and decide the reaction topology.
   - MOs: Same as in Figure 3.9a.
   - Topology: The H atom is switching faces, so it will have to engage with the top lobe on one side and the bottom lobe on the other side.

2. Connect orbitals, and count PIs.
   - Connections: We connect the three p-orbitals as expected, but note the explicit connection of the top-left p-lobe and the bottom-right p-lobe to the hydrogen, in accordance with the reaction topology.
     - ➤ Note that it doesn't really matter which lobes of the p-orbitals we connect because we get the same result either way.
   - PIs: 1.
   - This is our first time having an *odd* number of PIs, so we are now in Möbius-land!

3. Count the number of electrons.
   - As above, there are $4 = 4(1)$ electrons.
   - However, because we are in Möbius-land, this nevertheless means that our TS will be *stabilized* by *aromaticity* of the *Möbius* type.
   - Thus, "ugly" antarafacial transition states are nevertheless totally allowed!

– Despite the fact that antarafacial $[1,3]$-sigmatropic hydride shifts are favored over their suprafacial counterparts, our intuition that the antarafacial transition state would be sterically strained is correct.
   - Indeed, there are examples of $[1,3]$-hydride shifts occurring with stereoinversion, but they are rare.
   - Nevertheless, this is a fun and nonintuitive finding!
   - If you are interested, you can look into work on antarafacial $[1,3]$-methyl shifts, which are also favored over their suprafacial counterparts!

– Aside: One place where we do see stereoinversions.
   - The keto-enol tautomerization could be thought of as a $[1,3]$-sigmatropic hydride shift!
   - Indeed, if it occurs intramolecularly, it would occur with stereoinversion.
   - However, the rate of this intramolecular rearrangement is naturally very slow due to strain, which is why we need a solvent, acid, or base catalyst to do the proton transfer intermolecularly with any appreciable rate.
   - Essentially, the reaction can't really happen intramoleuclarly because it'd be forbidden electronically with *cis* hydrogens or very disfavored sterically with *trans* hydrogens.

- **Suprafacial** (sigmatropic rearrangement): A sigmatropic rearrangement in which the bond-breaking and bond-making processes occur on the *same* face of the π-system.

- **Antarafacial** (sigmatropic rearrangement): A sigmatropic rearrangement in which the bond-breaking and bond-making processes occur on *opposite* faces of the π-system.

- Notice how. . .

   – In Figure 3.9a, the hydride is on the same side of the molecule in both starting material and product, i.e., coming out of the plane of the page;
      - That's why we call this suprafacial!

   – In Figure 3.9b, the hydride is on opposite sides of the molecule in the starting material vs. the product, i.e., coming out of the plane of the page vs. going into the plane of the page.
      - That's why we call this antarafacial!

- Frontier molecular orbital theory (FMO).

  - By Fukui, as mentioned above.
  - This is a simplification of some other models in which you only consider the HOMO/LUMO interactions (instead of all MOs).
  - Principle: If the HOMO of the electron-donating species and LUMO of the electron-accepting species mix favorably, then the reaction is allowed.
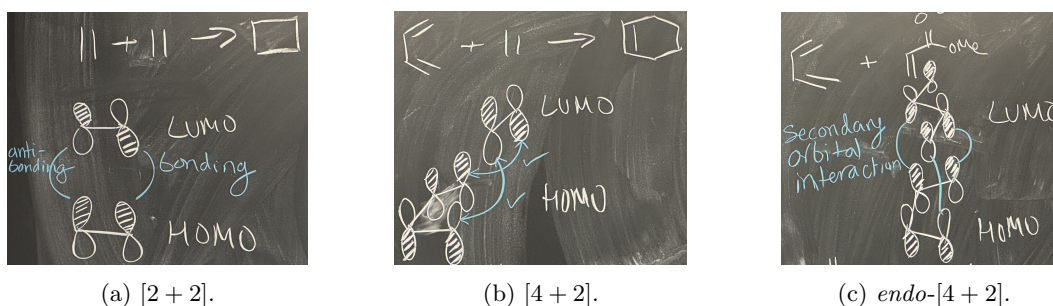
- Example: FMO analysis of cycloadditions.

(a) [2 + 2].   (b) [4 + 2].   (c) *endo*-[4 + 2].

Figure 3.10: Frontier molecular orbital analysis of cycloadditions.

  - A [2 + 2] cycloaddition (Figure 3.10a).
    - ■ As in a Dewar-Zimmerman analysis we begin by drawing the HOMO and LUMO of the reactants and deciding the reaction topology.
      - ➢ MOs: Recall that for ethene, the HOMO has 0 PIs and the LUMO has 1 PI.
      - ➢ Topology: We have decided to have the 'electron-donating' ethene attack from the bottom.
    - ■ Then (also as in a Dewar-Zimmerman analysis) we connect lobes and check for bonding and antibonding interactions.
      - ➢ Here, we have 1 bonding and 1 antibonding interaction.
    - ■ The presence of an antibonding interaction means that this reaction is forbidden/disfavored.
    - ■ Bonus content: Ketenes engage in [2 + 2] cycloadditions at ambient temperatures!
      - ➢ Masha encourages us to look more into this!!
  - A [4 + 2] cycloaddition (Figure 3.10b).
    - ■ Performing an analogous analysis to the above, we observe 2 bonding interactions. This means that this reaction is allowed.
  - A [4 + 2] cycloaddition with a more elaborate dienophile (Figure 3.10c).
    - ■ As in both previous cases, we begin by drawing the HOMO of the 'electron-donating' species and the LUMO of the 'electron-accepting' species.
      - ➢ MOs: Notice that it does not matter that the dienophile's π-system contains a heteroatom.
      - ➢ Topology: This time, we have the dienophile attack from the top.
    - ■ Connecting orbitals.
      - ➢ First, observe that we get the same favorable bonding interactions as in Figure 3.10b.
      - ➢ In addition, we get a new, secondary orbital interaction if we draw the *endo* transition state.
      - ➢ This additional, stabilizing interaction rationalizes why the *endo* transition state is favored in a Diels-Alder reaction!
    - ■ Therefore, this reaction is allowed, and the *endo* product is preferred due to secondary orbital interactions.

- Miscellaneous pericyclics: Group transfer and chelotropic reactions.

- Recall from above that a *group transfer* reaction transfers atoms from one molecule to another, but in a concerted pericyclic transition state.

- Example group transfer reactions.

    1. **Diimide reduction**.
    2. The **ene reaction**.

- **Diimide reduction**: A group transfer reaction that converts an unsaturated organic compound to a reduced alkane using diimide (N_2H_2).
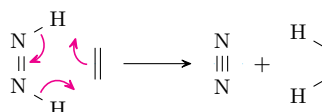

    – Remember to draw arrows to the place where you're making the bond, not to an atom unless the electrons are going on that atom!!

- **Ene reaction**: A group transfer reaction between an **ene** and an **enophile** that forms a new σ-bond with migration of the ene double bond and a $1, 5$-hydrogen shift. *Also known as* **Alder-ene reaction**.
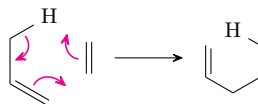

- **Ene**: An alkene with an allylic hydrogen.

- **Enophile**: A compound containing a multiple bond.

- Moving on, recall from above that a *chelotropic* reaction is a cycloaddition in which two bonds are made to one atom.

- Example chelotropic reactions.

    1. **Carbene addition**.
    2. Certain **cycloreversions**.

- **Carbene addition**: The addition of a singlet carbene to an alkene to make a cyclopropane.
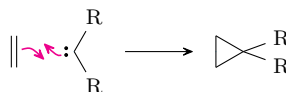
    – Observe how the two arrows form two σ-bonds to the carbene.

- **Cycloreversion**: The reverse of a cycloaddition reaction.
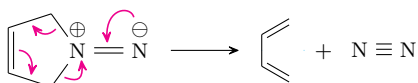
    – Since two of the left nitrogen's bonds are being *broken*, this is technically a *retro-chelotropic* reaction.

- Lecture summary: Three models to study pericyclic reactions.

    1. The Woodward-Hoffmann rules.
        - These are all about the conservation of orbital symmetry.
    2. The Dewar-Zimmerman analysis, also known as aromatic TS theory.
        - This is the "I can't believe it works!" one, where you can draw any phasing and the model still gives you the right answer.
    3. FMO theory.
        - This is where we only look at HOMO/LUMO interactions.

- Matthew: When would you use one model over the others?

    - All three models should always give the same result (otherwise, there's a problem with the model), but sometimes you care more about one aspect of a reaction or another.
    - For example, if you want to figure out whether you get the conrotatory or disrotatory product, it is easier to use the Woodward-Hoffmann rules.
        - This is because they're designed specifically for such questions.
    - If you need a quick-and-dirty "is this reaction going to happen," use FMO.
    - If you want to determine whether a reaction will be antarafacial or suprafacial, use Dewar-Zimmerman.