5.13 (Organic Chemistry II) Notes

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Unit 1

Structure Determination

1.1 Intro + Elemental Analysis

9/4:

- Teaching team.
  - Prof. Masha Elkin.
  - Prof. Steve Buchwald.
  - 8 Teaching Fellows (TFs).
- Masha Elkin begins. Steve Buchwald and all TFs introduce themselves. Special roles:
  - Head TF: Minh Le.
  - Electronic TF (contact with questions on Canvas, Piazza, BACON): Angel Garcia-Ramirez.
- In this class, you will learn...
  - New things in organic chemistry;
  - Old things at a deeper level;
  - Real-world applications of chemistry.
- Why study organic chemistry?
  - Chemists manipulate matter, and that's awesome!
  - By "manipulate matter," we mean making molecules, breaking molecules, making polymers, making detergents, and making sure that all of these things break down in the environment :)
- Core questions.
  - *How* do we make molecules?
  - What molecules *should* we make?
- Course logistics.
  - Seven (7) units total (2 big units before the halfway mark & 5 smaller units after).
  - The units.
    - Unit 1: How do we know what molecule(s) we have?
    - Unit 2: How do electrons move?
    - Units 3-7: How do we make molecules? How do reactions work?
  - Exams after units 1, 2, 4, and 6; final exam after unit 7.
  - Questions? Ask your TF first, then the Head TF, then the profs (Masha & Steve).

- Prerequisites.
  - Official prerequisites: 5.12 (equivalent to Orgo I, in case you took it elsewhere) & Gen Chem.
  - Recommended reading for review: Chapters 1-2 of the main textbook, referred to in these notes as Clayden et al. (2012).
- Grading.
  - Your grade will (hopefully) be a reflection of your learning.
  - There are no curves in this class or at MIT, so *everyone can get an A!!!*
  - How to improve your grade: Do problems!
    - Problem sets (PSets) and recitation worksheets will be provided.
    - You may also do as many textbook problems as you want. Feel free to buy the solutions manual, or borrow a copy from the ChemEd office[1] to check your answers.
- How to learn organic chemistry.
  - Analogy: Learning Orgo is like learning a language.
    - Basic vocab and grammar that must be memorized. Examples: Drawing structures, curved arrow formalism, etc.
    - Recognizing patterns and trends. Examples: Nucleophiles tend to have lone pairs (or be other regions of high electron density).
    - Developing intuition.
    - Practice, practice, practice! (Focus on drawing structures.)
  - Tips for success.
    - Be active and participate in lecture, recitation, etc. Take notes while you're here!
    - Practice **metacognition**, i.e., learn how you learn.
      - ➢ Do you learn best in a crowded coffee shop, or in your own room? Would you rather recopy your notes, or read the textbook?
      - ➢ Note that what works for somebody else may not work for you, and vice versa!
      - ➢ Invest the time and effort that *you* need to succeed. This may be more (or less) than other students, and that's ok!
    - Communicate with *the whole* teaching team. They're here to help!!!
      - ➢ Seek out accommodations as needed: It's the student's responsibility to ask.
- **Metacognition**: Being aware of your own understanding.
- We now begin the content for Unit 1.
- Goal: Learn how to determine the chemical structure of a given organic compound.
- Why do we need to determine structures?

Figure 1.1: Why we study structure determination.

  - With the naked eye, organic chemists see a flask with a colorless liquid. But we draw the skeletal diagram for benzene (which is a colorless liquid). What tools enable us to convert from the flask to the structure?

[1] Located in 6-203.

  - Here's another reason: Suppose we run a brand new chemical reaction. Organic chemists do this all the time in research! How do we now what the product is? How do we know which atoms it contains, and in what arrangement?

- Structure determination workflow.

  1. Identify the atoms present.
     - Questions to answer: What is the molecular formula?
     - Relevant tools: Elemental analysis (EA) and mass spectrometry ("mass spec" or MS).
  2. Identify the functional groups and substructures present.
     - Questions to answer: Do we have ketones? Esters? Alcohols? Rings?
     - Relevant tools: MS, infrared spectroscopy (IR), and nuclear magnetic resonance (NMR).[2]
  3. Identify how all the functional groups fit together.
     - Questions to answer: Are they close? Far apart? Ortho/meta/para? What stereochemistry?
     - Relevant tools: NMR and X-ray diffraction.

- We now begin talking about EA.
  - History: Began development in the 1820s.
  - Purpose: Determine which elements are present, and in what quantities (in a given sample).

- In this course, we will apply EA to compounds containing carbon, hydrogen, and oxygen *exclusively*.
  - To reiterate, in an EA problem for this course, we will *not* have to worry about any other elements.
  - The typical EA technique for such compounds is **combustion analysis**.

- **Combustion analysis**: Burn the sample and measure the products.
  - All C in the sample becomes CO_2.
  - All H in the sample becomes H_2O.
  - O is then determined via process of elimination, explained as follows.

- Advanced techniques (beyond the scope of this class): Nitrogen to NO or NO_2, sulfur to SO_2, etc.

- A schematic of combustion analysis.

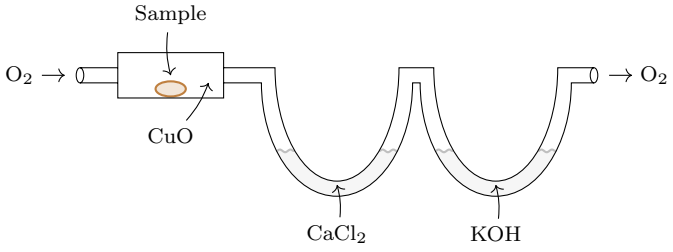


Figure 1.2: Combustion analysis schematic.

  - Burn the sample in the presence of an oxidant such as cupric oxide (CuO).
  - Flow O_2 into the combustion chamber to facilitate burning as well.
  - The combusted gas then flows through a series of reaction containers.
    - The first one contains a desiccant (like $CaCl_2$) that absorbs the water.

[2] NMR is an organic chemist's best friend!

    - The second one contains a base (like KOH) that absorbs the CO_2.
  - The remaining oxygen flows out the end.

- The *analysis* part of combustion analysis.
  - The amount of H is equal to the change in mass of the $CaCl_2$.

$$\Delta\text{mass}(CaCl_2) = \text{mass}(H_2O) \rightarrow \text{ratio(H)}$$

  - The amount of C is equal to the change in mass of the KOH.

$$\Delta\text{mass(KOH)} = \text{mass}(CO_2) \rightarrow \text{ratio(C)}$$

  - The amount of O is equal to the change in mass of the sample.

$$\text{mass(sample)} - \text{mass(H)} - \text{mass(C)} = \text{mass(O)} \rightarrow \text{ratio(O)}$$

  - Result: We get an **empirical formula** of the form $C_xH_yO_z$. Remember that this is *not* (necessarily) the **molecular formula**; it is *only* a ratio of elements.

- EA example: Let's burn 0.5 g of propanol (C_3H_8O).
  - Suppose we obtain 0.600 g H_2O and 1.09 g CO_2.
  - This means that there was 0.067 g (H) and 0.300 g (C) in the sample. The remaining 0.133 g must then be due to O.
  - Therefore, the elements exist in a 3:8:1 (C:H:O) ratio.
  - Bonus: Convert the masses to a ratio via stoichiometry.
    - $0.600\,\text{g } H_2O \times \dfrac{1\,\text{mol } H_2O}{18.02\,\text{g } H_2O} \times \dfrac{2\,\text{mol H}}{1\,\text{mol } H_2O} \times \dfrac{1.01\,\text{g H}}{1\,\text{mol H}} = 0.067\,\text{g (H)}$
    - $1.09\,\text{g } CO_2 \times \dfrac{1\,\text{mol } CO_2}{44.01\,\text{g } CO_2} \times \dfrac{1\,\text{mol C}}{1\,\text{mol } CO_2} \times \dfrac{12.01\,\text{g C}}{1\,\text{mol C}} = 0.300\,\text{g (C)}$
    - $0.5\,\text{g propanol} - 0.067\,\text{g (H)} - 0.300\,\text{g (C)} = 0.133\,\text{g (O)}$

- A note on the previous example.

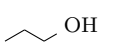
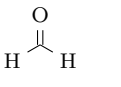
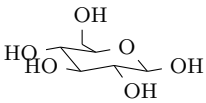
Name	Propanol	Methyl ethyl ether	Formaldehyde	Acetic acid	Glucose
Structure					
Emp. formula	C_3H_8O	C_3H_8O	CH_2O	CH_2O	CH_2O
Mol. formula	C_3H_8O	C_3H_8O	CH_2O	$C_2H_4O_2$	$C_6H_{12}O_6$

Table 1.1: Questions that EA can't answer.

  - EA has given us the empirical formula, but it has *not* confirmed that the sample is propanol. For example, methyl ethyl ether has the same empirical formula!
  - Additionally, we don't yet have the molecular formula. Consider, for instance, the breadth of compounds with empirical formula CH_2O!
  - Takeaway: EA gives you the empirical formula; we need MS to get the molecular formula (we'll see this on Friday), and we may need even more to get the atomic connectivity.

- Application of EA to real-world chemistry.
  - A home furnace burns natural gas — which is mostly methane (CH_4) — for heat.

  - **Ideal combustion**[3] corresponds to the reaction

$$CH_4 + O_2 \longrightarrow CO_2 + H_2O$$

  - Real-world combustion is incomplete; you make

$$CH_4 + \text{air} \longrightarrow CO_2 + H_2O + NO_2 + CO$$

  - When a technician comes to your home, they analyze the flue gas (i.e., your furnace exhaust).
    - Their analysis could determine that our combustion has too much O_2, which is called "air rich." This is inefficient and doesn't yield enough heat.
    - They could also determine that you have too much CO_2 and CO, which is called "fuel rich." This yields too much soot and CO. CO can be dangerous and lead to carbon monoxide poisoning, which makes you sleepy before it kills you.
  - To measure this flue gas, though, they have a little handheld elemental analysis device!

- Note that there is a relation between ideal/real-world combustion and the CuO oxidant in Figure 1.2: The CuO ensures that when we combust our EA sample, all the carbon is fully oxidized to CO_2! Without it, some CO would be formed, and our stoichiometry would be thrown off.

1.2 Mass Spectrometry

9/6:

- Lecture 1 recap.
  - Elemental analysis (EA).

$$SM + O_2 \xrightarrow{\Delta} CO_2 + H_2O$$

    - SM means "starting material."
    - SM's we will focus on: Compounds of the form $C_xH_yO_z$.
  - Empirical formula vs. molecular formula (see Table 1.1).
- Today: Mass spectrometry (MS).
  - Purpose: Convert empirical formulas to molecular formulas (and more!).
  - Reading: Clayden et al. (2012), Chapter 3.
- Lecture outline.
  - Mass spectrometer schematic.
  - Mass spectrum elements.
  - Fragmentation, and common types.
  - Isotope effects in MS.
  - Ionization methods.
- **Mass spectrometry**: A structure determination technique that tells us the exact mass of molecules and their "fragments." *Also known as* **MS**, "**mass spec**."
- Overview.

$$[M] \xrightarrow{e^- \quad 2e^-} [M]^{+\cdot} \longrightarrow \begin{cases} [M-a]^+ + [a]^\cdot \\ [M-b]^+ + [b]^\cdot \\ [M-c]^+ + [c]^\cdot \end{cases}$$

[3] You can learn more about in a chemical engineering/ChemE course.

  - You have a sample — denoted by [M] — that you bombard with electrons (e^-). When an electron hits a molecule of your sample, it knocks off one of the molecule's electrons (and flies off itself). This ionizes your molecule to a **radical cation**, denoted by $[M]^{+\cdot}$ and called the **molecular ion**.
  - This radical cation is unstable and fragments into a proper cation and a proper radical. The radical is usually not detected, but any cationic fragment produced — the $[M-a]^+$, $[M-b]^+$, and $[M-c]^+$ above — usually *is* detected.

- A (stepwise) schematic of a mass spectrometer.

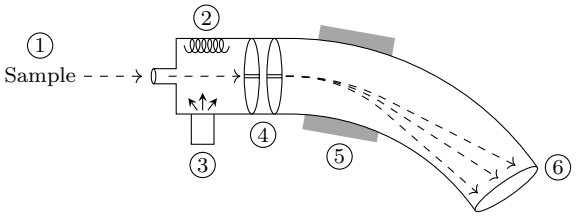


Figure 1.3: Mass spectrometer schematic.

1. The sample is injected into a curved tube.
2. A heater vaporizes the sample.
3. An electron source (also known as an electron gun) shoots electrons at the vaporized sample, ionizing it. The ionized sample starts fragmenting.
4. The fragments encounter a series of negatively charged plates with slits in the middle. These negatively charged plates accelerate the positively charged cations.
5. A magnet deflects the accelerated, positively charged ions. The magnet deflects them based on their **mass-to-charge ratio**. Because of physics, the lightest ions are deflected the most, and the heaviest ions are deflected the least.
6. A detector records where the ions hit. This data is converted into a mass-to-charge ratio for each ion. This yields a spectrum of all the fragments' masses.

- **Mass-to-charge ratio** (of a cation): The cation's mass divided by its net charge. *Denoted by* $\boldsymbol{m/z}$.
  - For the purposes of this class, $z = 1$.
- Example mass spectrum: Acetone ().

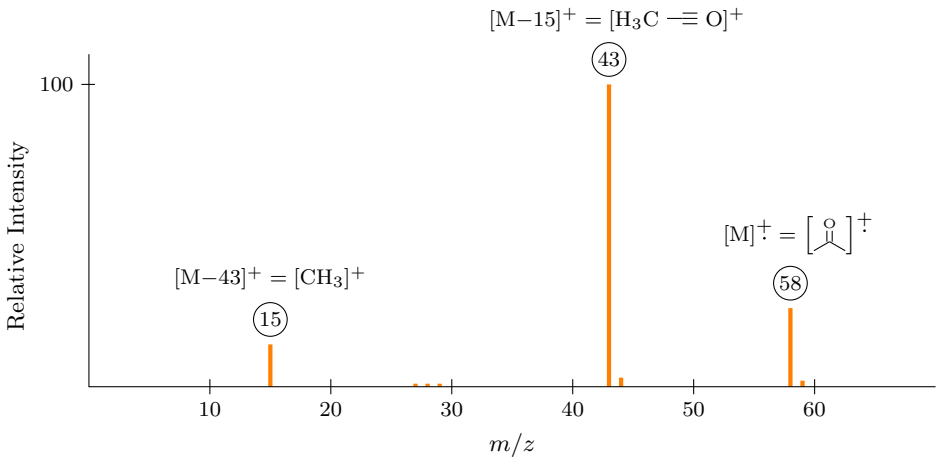


Figure 1.4: Mass spectrum of acetone.

  - The x-axis is the mass-to-charge ratio, and the y-axis is the "relative intensity" of each peak.
    - If a certain fragment gets produced more than another (and hence recorded more than it), we say it has a "higher relative intensity."
  - We identify two special types of peaks in a mass spectrum: The **parent peak** and the **base peak**. In the case of acetone...
    - The parent peak lies at 58;
    - The base peak lies at 43.
  - The peak at 15 also has a relatively large magnitude, and from the fact that the mass of a methyl cation is approximately 15, we can infer that this peak corresponds to the methyl cation fragment.
    - Notice that its intensity is significantly lower than the intensity of the base peak because we may recall from Orgo I that the methyl cation is a far less stable cation than the resonance-stabilized, secondary acylium ion at 43.
  - There are a number of smaller peaks, too, but they give less information.
  - Note that the major peaks may be appropriately referred to by *any* of the three nomenclature methods in Figure 1.4: By exact mass, by $[\mathrm{M}-a]^+$, and/or by structure.

- **Parent peak**: The peak in a mass spectrum corresponding to the molecular ion.
  - The parent peak is always the rightmost peak in the spectrum.[4] This is because it is created by the heaviest ion, and you can't have more mass than your initial molecule!
  - It is typically *not* the tallest peak in the spectrum.
  - Useful information: It gives the molecular weight of the molecule.
- **Base peak**: The tallest peak in a mass spectrum.
  - The base peak corresponds to the fragment that the molecule forms most preferentially, which is usually also the most stable fragment.
- **Fragmentation peak**: Any peak to the left of the parent peak.
- Maxim: Molecules fragment in predictable ways to form stable cations.
- At this point, let's formally define **fragmentation**.
- **Fragmentation**: The formation of stable(-ish) cations.
  - Recall from Orgo I (review your notes on cation stability!!) that stable cations tend to be more substituted, delocalized, atom-stabilized (e.g., close to a heteroatom), etc.
- Let's now discuss some common species that we analyze via MS — and how they fragment.
- Alkane fragmentation: Preferentially break bonds to get more substituted (e.g., 2° & 3°) carbocations.
- Example: Isopentane ( ).

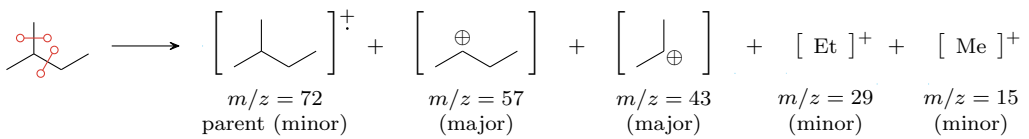


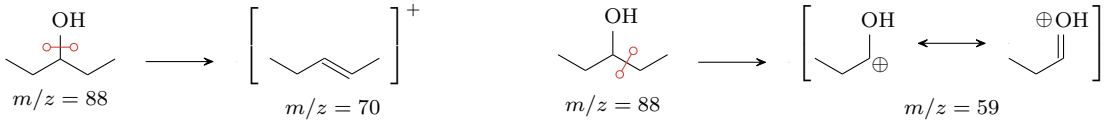
Figure 1.5: Fragmentation of alkanes.

  - All these peaks will appear, but the tallest will correspond to the species labeled "major" above.

[4] Excepting isotope effects; discussed later in this lecture.

- Alcohol fragmentation.
  - Dehydration: Yields an $[M-18]^+$ peak, corresponding to the loss of water.
  - α-cleavage: Leads to a resonance-stabilized product.
- Example: Pentan-3-ol (

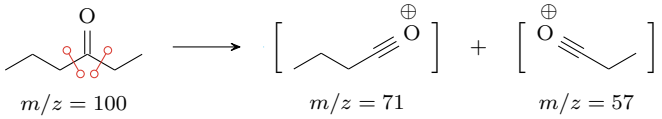
).



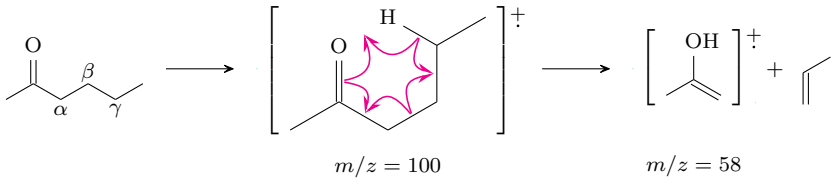
(a) Dehydration. (b) α-cleavage.

Figure 1.6: Fragmentation of alcohols.

- Ketone fragmentation.
  - α-cleavage: Leads to a resonance-stabilized product, once again.
  - McLafferty rearrangement: Only happens for ketones with a γ-proton.
    - We select for this type of ketone because in this case, we can form a six-membered transition state. Recall that six-membered transition states are super stable in organic chemistry!
    - This fragmentation leads to a charged enol (that we see in the spectrum) and an uncharged olefin (that we don't see in the spectrum).
- Example: Hexanones.



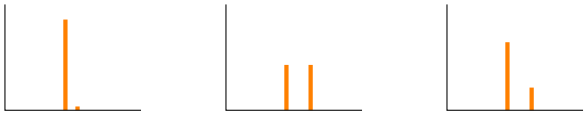
(a) α-cleavage.



(b) McLafferty rearrangement.

Figure 1.7: Fragmentation of ketones.

- Isotope effects.
- Principle: Mass spectrometry weighs individual molecules, so molecules containing a heavier (or lighter) isotope will appear separate from other molecules in the mass spectrum.
- Atoms with notable isotope effects.



(a) Carbon. (b) Bromine. (c) Chlorine.

Figure 1.8: Isotope effects in MS.

- Carbon: The $^{12}C : {}^{13}C$ ratio is 99 : 1.
  - Implication: For every $[M]^{+\cdot}$, we see 1% $[M+1]^{+\cdot}$.
  - This is why we see tiny "shadow" peaks to the right of the parent peak and base peak in Figure 1.4!
    - ➢ Note that the "shadow" of the parent peak is 3% its height (not 1%) because there are *three* carbons in the acetone molecular ion.
    - ➢ Similarly, the "shadow" of the base peak is 2% its height because there are *two* carbons in the acylium ion.
- Bromine: The $^{79}Br : {}^{81}Br$ ratio is 1 : 1.
  - Implication: The $[M]^{+\cdot}$ and $[M+2]^{+\cdot}$ peaks exist in a 1 : 1 ratio, i.e., have the same height/relative intensity.
  - The splitting of the molecular ion peak into two such peaks is a super recognizable, distinct, and useful fingerprint of bromine-containing compounds!
- Chlorine: The $^{35}Cl : {}^{37}Cl$ ratio is 3 : 1.
  - Implication: The $[M]^{+\cdot}$ and $[M+2]^{+\cdot}$ peaks exist in a 3 : 1 ratio.
  - Similar to bromine, this peak splitting is a fingerprint of chlorine-containing compounds.

- Combining everything we've learned up to this point, let's do another example.
- Example: Benzyl chloride ().

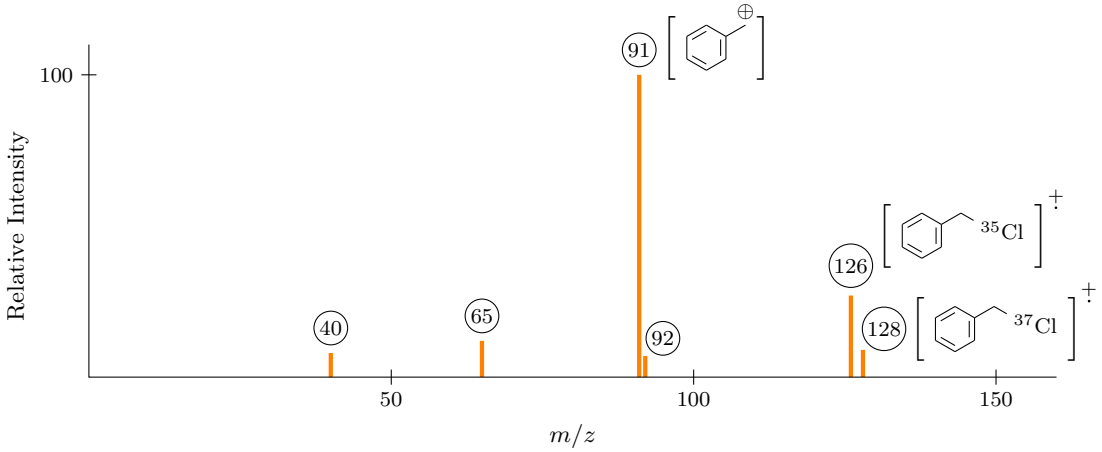


Figure 1.9: Mass spectrum of benzyl chloride.

- The parent peak will lie at 126, and the corresponding chlorine isotope peak will lie at 128 and be one-third the height.
- The base peak will lie at 91, and the corresponding carbon isotope peak will lie at 92 and be 7% the height (to account for the 7 carbons in the benzylic cation that may be heavy).
  - It will correspond to the most stable fragment, which in this case is the benzylic cation.
  - The benzylic cation is super stable because its positive charge can be resonance delocalized to four different atoms!
  - A large peak at $m/z = 91$ strongly suggests the presence of an aromatic system.
- This example focused on predicting the peaks in a mass spectrum based on reasonable fragmentation patterns. But what if we are given the mass spectrum? What data can we pull out then?

- To answer this question, here are some guidelines for the interpretation of mass spectra.

- Guidelines for interpretation.
  - The parent peak provides the molecular weight of the molecule.
    - This allows you to convert an empirical formula obtained from EA to the molecular formula.
  - The parent peak also reveals key atoms via distinct isotopic fingerprints.
    - Examples include bromine and chlorine.
    - An additional one is the **nitrogen rule**.
  - Fragmentation patterns can identify substructures.
    - Recall from Lecture 1 (9/4) that identifying substructures is part of the second step of the structure determination workflow!
    - Common fragments:
      - Loss of a methyl group is -15.
      - Loss of an OH group is -17.
      - Loss of H_2O is -18.
      - Loss of CO_2 is -44.
      - Loss of a ^{t}Bu group is -57.
    - Look at the m/z of the fragments *and* the difference in m/z between certain fragments.
      - Example: Maybe a certain fragment is formed by losing both a methyl group *and* water.
  - Important note: These guidelines are just a guide; we will need multiple forms of evidence to support an assignment.
- **Nitrogen rule**: If you have an odd number of nitrogen in a molecule, you will get an odd molecular weight.
  - The basis for this rule lies in the fact that nitrogen is trivalent but has an even mass.
    - This means that nitrogen tends to bond an odd number of groups (specifically, 3), making the overall mass odd.
  - Examples: Ammonia has an odd mass of $17 = 14 + 1 + 1 + 1$ and methylamine has an odd mass of $31 = (14 + 1 + 1) + (12 + 1 + 1 + 1)$, while methane has an even mass of $16 = 12 + 1 + 1 + 1 + 1$ and ethane has an even mass of $30 = (12 + 1 + 1 + 1) + (12 + 1 + 1 + 1)$.
  - You can read more about the nitrogen rule here.
  - Implication: If you see an odd molecular weight, you *might* have a nitrogen present!
- Types of ionization.
- **Electron ionization**: A beam of electrons. *Denoted by* **EI**. *Also known as* **hard ionization**.
  - This is the method we are using in this class.
- **Electrospray ionization**: Forms charged droplets. *Denoted by* **ESI**. *Also known as* **soft ionization**.
  - ESI causes less fragmentation.
  - One implication of this is that you observe a larger parent peak.
  - Another consequence is that ESI can analyze a broader range of compounds via mass spectrometry than EI can, since some sensitive compounds (like proteins) would never survive an electron beam.
    - Nobel Prize in Chemistry (2002) for this application of MS to biology!
- **High resolution mass spectrometry**. *Denoted by* **HRMS**.
  - In "normal" low-resolution mass spectrometry (LRMS), both N_2 and C_2H_4 have $m/z = 28$.
  - In HRMS, N_2 has $m/z = 28.0061$ and C_2H_4 has $m/z = 28.0314$.

- HRMS leads nicely into our application for today!
- Application of MS to real-world chemistry: Isotopic signatures.
  - Today, you learned that the $^{12}C : {}^{13}C$ ratio is 99 : 1.
    - In reality, this is an *average* value.
    - The actual ratio of isotopes is globally uneven, and we as humans have mapped it.
  - Indeed, isotope abundances vary by time and location due to air patterns, etc.
  - For example, Montana is home to 2% more ^{13}C than Florida!
  - Implication: We can tell if a narcotic is made in the US (and where) or another country based on the isotopic abundance in it.
  - We can also track where a person, drug, or uranium sample is from.
    - Naturally, the government is very interested in this technology :)
  - You can also tell if a person eats corn or rice because this leads to different ratios of nitrogen isotopes in our bodies.

1.3 Infrared Spectroscopy

9/9:
- Lecture 2 recap.
  - In mass spectrometry, you ionize your sample [M] to the molecular ion $[M]^{+\cdot}$.
  - $[M]^{+\cdot}$ is detected as the parent peak.
    - The parent peak provides the molecular weight (MW) of the molecule.
    - The parent peak also reveals any isotopic signatures.
  - Many molecular ions — once formed — will fragment into cations $[M-a]^+$, $[M-b]^+$, $[M-c]^+$, etc.
    - More stable cations are formed more often, resulting in higher relative intensities.
    - The *most* stable fragment gives rise to the base peak.
  - Common fragments include those resulting from...
    - The loss of a methyl group;
    - The loss of a water molecule;
    - α-cleavage;
    - The McLafferty rearrangement (for ketones).
- Today: Infrared Spectroscopy (IR).
  - Reading: Clayden et al. (2012), Chapter 3.
  - Prof. Elkin highly recommends the section on IR; be sure to read this!!
- Lecture outline.
  - Spectrometer schematic.
  - Theory.
  - Spectrum elements.
  - Key regions of a spectrum.
- Principle: Irradiate a sample with infrared waves and detect where the sample absorbs these waves.
  - This technique is useful for identifying certain functional groups, namely those that absorb IR waves well.

- A schematic of an infrared spectrometer.

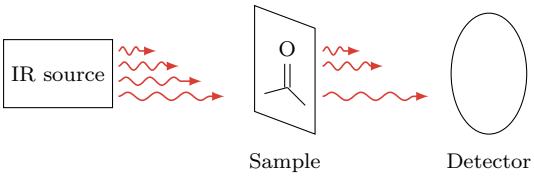
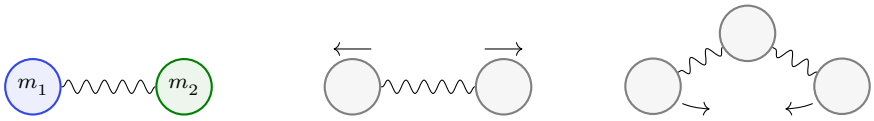


Figure 1.10: Infrared spectrometer schematic.

  - We begin with a source of infrared radiation. This source shoots waves at our sample, which could be a molecule like acetone. The IR waves that the source emits have a range of frequencies.
  - The sample will absorb certain frequencies, and the frequencies that are not absorbed are detected by a detector. In other words, the director detects the **transmittance** of the sample.

- **Transmittance**: How much of each frequency of radiation passes through the sample.

- IR theory.



(a) Springy bonds. (b) Stretch. (c) Bend.

Figure 1.11: Infrared spectroscopy theory.

  - Fundamental assumption: A chemical bond is like a spring between atoms.
    - Recall from Gen Chem that in science, we often call a spring a **harmonic oscillator**. If you don't quite remember this term, review your Gen Chem notes or Google it!!
  - Let's dive a bit deeper into this analogy: Imagine we have two different atoms of masses m_1, m_2 joined by a "spring," as in Figure 1.11a.
    - Just like a real spring, chemical bonds can vibrate in different ways: They can stretch and contract (as in Figure 1.11b), bend (as in Figure 1.11c), etc.
    - All of these different motions are called the **vibrational modes** of the chemical bonds.
  - Bonds absorb energy from IR waves when the frequency (ν) of the IR wave matches the frequency of the stretching/bending motion.
    - In other words, when you hit the resonance frequency, you absorb energy.
    - This absorption of energy is detected as the loss of transmittance.
  - The change in energy between vibrational modes is related to characteristics of the bond as follows.

$$\Delta E \approx \sqrt{\frac{k(m_1 + m_2)}{m_1 m_2}}$$

    - k is the force constant (proportional to the bond strength).
    - m is the mass of atom 1 or 2.
    - Implication: Stronger bonds (i.e., those with larger values of k) require more energy (i.e., higher ν IR waves) to absorb.
    - Implication: Lighter atoms (i.e., those with lower values of m) require more energy (i.e., higher ν IR waves) to absorb.
  - One additional requirement: The chemical bond must have a dipole in order to absorb IR waves.
    - Example: C≡O absorbs because O is more electronegative than C, but N≡N does not.

- Questions on IR theory.
  - Why do bonds absorb energy *only* when the frequency of the IR waves matches the frequency of the bond's vibration?
    - The answer to this question is beyond the scope of the class, but Prof. Elkin gives the quantum mechanical explanation.
    - Essentially, when a chemical bond absorbs energy, it gets excited to a higher-energy vibrational mode, which we may think of as a more intense vibration.
    - However, because vibrational modes are separated by a set amount of energy, lower energy photons won't have enough energy to make it to the next vibrational mode while higher energy photons will provide too much energy to reach anything stable.
  - Why don't bonds without dipoles absorb IR waves?
    - The explanation is also quantum mechanical, and hence also beyond the scope of this class.
    - Essentially, symmetric bonds and molecules lack something called a dipole moment, and zero dipole moment zeroes out the absorption in the math of quantum mechanics.
    - Note that there is some really cool math and physics underlying the answer to this question, and Prof. Elkin recommends you look it up if you're interested!!
    - In organic chemistry, however, we're more interested in what we can do with IR spectroscopy than in *exactly* how it works. Essentially, for this class, you should learn how it works well enough to make sense of the trends in spectrum interpretation presented in this lecture, but you don't need to go deeper than that for now.
  - Why do lighter atoms require more energy? It seems like it would take more energy to push around a heavier atom.
    - Check out the explanation in Clayden et al. (2012); it's pretty comprehensive and understandable.
- Example IR spectrum: Propionic acid ().

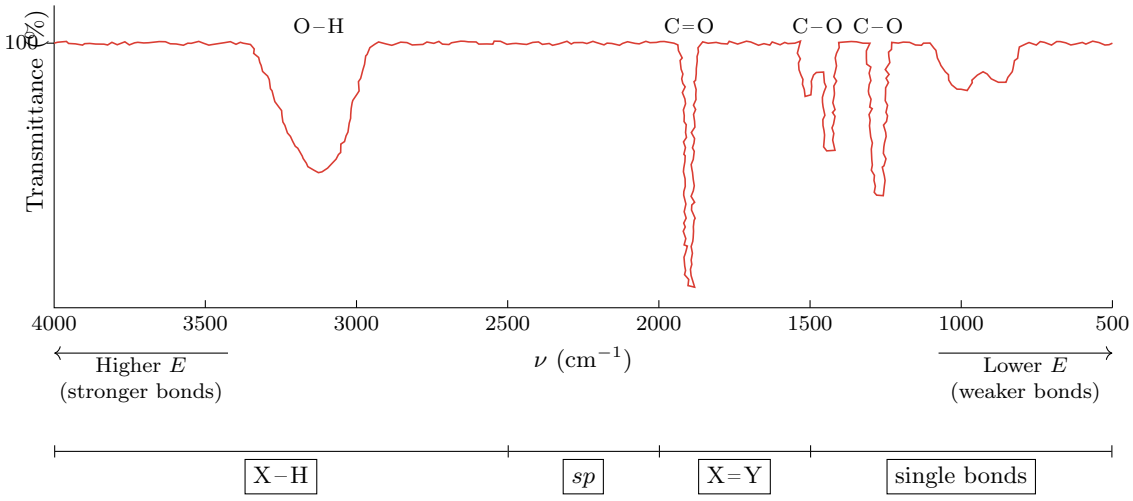


Figure 1.12: Infrared spectrum of propionic acid.

  - The x-axis is the frequency of the IR waves, measured in wavenumbers (cm^{-1}).
    - We typically are interested in the region from $4000 - 1500\,\mathrm{cm}^{-1}$.
  - The y-axis is the percent transmittance.
  - The **baseline** is 100%, which means pure transmittance (aka, no **absorption**).

        - Then we have **absorbance peaks**, each of which corresponds to a different chemical bond.
    - We can further break the spectrum down into regions.
        - X–H bonds occur in the $4000 - 2500\,\mathrm{cm}^{-1}$ region.
            - Peaks in this region are often broad. Specifically, a peak will be broad if the corresponding protons are **exchangeable**.
            - Hydrogen bonding can also lead to broadening.
            - We see this effect in both IR and NMR, so we'll talk about it more later this week!
            - For example, the O–H peak is broad because this acidic proton is exchangeable.
        - *sp*-hybridized atoms occur in the $2500 - 2000\,\mathrm{cm}^{-1}$ region.
            - In other words, polar triple bonds show up here.
            - Examples: C≡N and C≡C′.
        - X=Y bonds occur in the $2000 - 1500\,\mathrm{cm}^{-1}$ region.
            - This is for polar double bonds.
            - Examples: C=O, C=C′,[5] and C=N.
        - Single bonds occur in the $1500 - 500\,\mathrm{cm}^{-1}$ region.
            - Examples: C–C′, C–O, and C–F.
        - Some of these regions are useful, and some less so.
    - As you can infer from Figure 1.12, IR spectra look a bit like icicles.
    - Note that C–O has two peaks because there are multiple bonding modes per bond.

- **Absorption**: The loss of tranmittance.
    - We typically plot transmittance in a spectrum, but the two measures are inversely proportional.
- **Exchangeable** (proton): A hydrogen atom that is liable to break off of the rest of the molecule and be replaced by another hydrogen atom in solution.
    - This is very much related to acidic protons! Recall that a Brønsted acid will donate its proton and then the conjugate base will pick up a new (possibly new) proton all the time.
- **Diagnostic regions**: $4000 - 1500\,\mathrm{cm}^{-1}$ (useful) and $1500 - 500\,\mathrm{cm}^{-1}$ (useless).
- **Fingerprint region**: The region of an IR spectrum from $1500 - 500\,\mathrm{cm}^{-1}$.
    - Within the fingerprint region, we have so many overlapping peaks that the spectrum becomes difficult to interpret.
    - However, its shape is characteristic of a molecule, even if it doesn't tell you anything specifically. This is just like a real fingerprint! Your fingerprint doesn't tell anyone else your name, age, date of birth, etc. — but it does tell people that you're you!
- Key regions.

X–H		***sp***		**X=Y**	
FG	**ν (cm^{-1})**	**FG**	**ν (cm^{-1})**	**FG**	**ν (cm^{-1})**
O–H	3600-3200	C≡N	2200	C=O	1840-1630
N–H	3100-2700	C≡C′	2100	C=N	1700-1600
C–H	3000-2850	C=C=C′	1950	C=C′	1670-1600

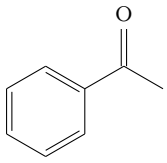
Table 1.2: Key regions of an infrared spectrum.

[5] The prime on the second carbon indicates that the carbons have different substituents. This is necessary if we are to have a dipole (symmetric C=C bonds are nonpolar).

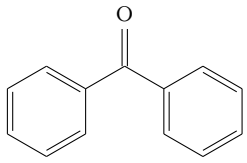
  - Note that functional groups listed higher up in each column of Table 1.2 have stronger bonds, and thus absorb higher energy/higher ν photons.
  - Both O–H and N–H peaks are broad *if* the proton is exchangeable.
    - There is an example in Clayden et al. (2012) of an O–H that is so sterically encumbered that you don't get proton exchange!!
  - Note also that C–H peaks are often weak, and may not show up at all in some spectra.
  - Should this information be memorized, or will it be provided in a reference chart?
    - Memorize the general regions and trends (as presented in the discussion following Figure 1.12), but not the explicit data in Table 1.2.

- **Broad** (peak): An absorbance peak that stretches over a wide range of wavenumbers.
- **Sharp** (peak): An absorbance peak that is restricted to a narrow range of wavenumbers.
- What determines the *exact* absorption frequency of a chemical bond?

(a) Acetone.



(b) Acetophenone.



(c) Benzophenone.

Figure 1.13: Related molecules with slightly different infrared absorption peaks.

  - The exact frequency is determined by the atoms and functional groups surrounding the bond.
  - For example, consider acetone, acetophenone, and benzophenone.
    - These three molecules all have C=O bonds, but their C=O bonds absorb IR waves at 1715, 1692, and 1664 cm^{-1}, respectively.
    - This effect can be attributed to increasing conjugation with the π-systems of the aromatic rings.
  - Indeed, the more conjugated the C=O bond, the weaker it is. Conjugation takes off $20 - 30\,\mathrm{cm}^{-1}$ per conjugation!
  - Conjugation is just one example, however; many other group of atoms can affect the absorption frequency.

- Guidelines for interpretation.
  - Look for the presence or absence of key functional groups.
    - This is really good for O–H, N–H, C≡N, C=O, C=N, C=C′, etc.
  - We'll also rationalize trends.
    - Stronger bonds have higher frequencies, and hence get shifted to the left.
    - Weaker bonds have lower frequencies, and hence get shifted to the right.
    - Etc.

- Why do we use wavenumbers instead of per second for frequency?
  - Historical reasons; this is just the way chemists have always done it.

- Example spectrum: But-3-yn-2-one ().

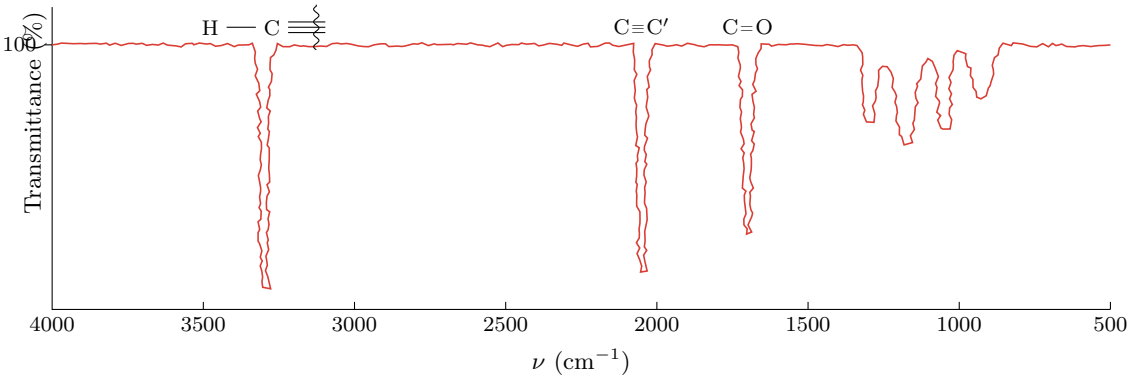


Figure 1.14: Infrared spectrum of but-3-yn-2-one.

  - This spectrum is composed of four major elements: A sharp peak at 3300 cm^{-1}, a sharp peak just to the left of 2000 cm^{-1}, a sharp peak at 1700 cm^{-1}, and the fingerprint region.
  - The sharp peak at 3300 cm^{-1} can be attributed to the propionic C–H bond.
  - But wait: We said in Table 1.2 that C–H bonds lay between $3000 - 2850\,\mathrm{cm}^{-1}$. What gives?
    - The leftward shift is due to the unique chemical environment of this specific C–H.
    - In particular, the carbon in this bond is *sp*-hybridized. It follows that this C–H bond is more polarized. Thus, the bond is stronger than usual, and we need higher frequency IR waves.
  - Evidence that propionic C–H bonds are stronger: Bond dissociation energies (BDEs).[6]
    - The BDE for a propionic C–H is about 125 kcal/mol, while the BDE for an alkane C–H is about 98 kcal/mol.
    - This difference is also reflected in the relative pK_a's of the two hydrogens: Alkane C–H's have pK_a's in the 50s, while propionic C–H's have pK_a's in the 20s.
  - Note that in this molecule, the sp^3 C–H stretch only absorbs weakly, hence why we don't see a peak around 3000 cm^{-1}.

- There is some theory on how much a certain vibration will absorb, but for our purposes, we'll assume that all stretches absorb a good healthy amount of radiation.

- Application: IR is nondestructive.

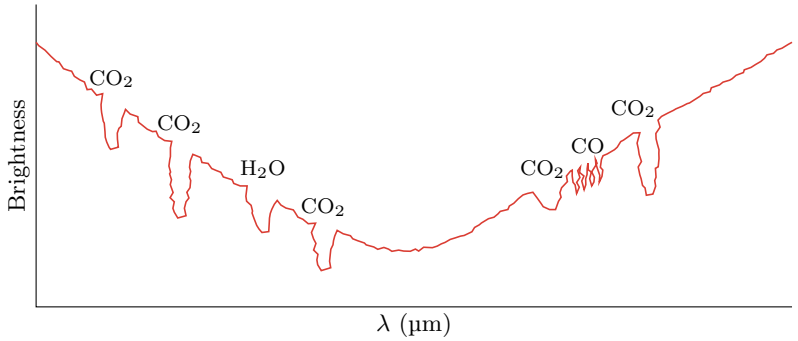


Figure 1.15: Infrared spectrum of the atmosphere of Mars.

[6] Look up BDEs in your Orgo I and Gen Chem notes if you don't remember them. These are important to know!!

  - EA and MS are destructive analytical techniques, meaning that the sample gets destroyed (e.g., by burning or fragmentation) in the process. This requires sample in hand, some of which we can destroy.
  - IR is nondestructive. This means that we can recover our sample after the experiment! In other words, IR spectroscopy can be run from afar.
  - For example, consider the spectrum in Figure 1.15.
    - This is still an IR spectrum, even though the x-axis is in wavelength (λ) — measured in µm — and y-axis is in brightness.
    - The spectrum has a bad baseline, but we'll just forgive this.
    - A number of vibrational modes of CO_2, H_2O, and CO are recorded.
  - What is this spectrum?
    - It is an IR spectrum of the atmosphere of Mars!
    - It was taken by the James Webb Telescope two years ago, in 2022.
    - We've had an IR spectrum of the moon since the 1940s, but this is new and cool!
  - To generalize, here are some major applications of IR spectroscopy.
    - Space.
      - Just like the example in Figure 1.15, IR spectroscopy can be used to find new molecules in celestial bodies.
      - If you ever see a news story along the lines of "Amino acids found on an asteroid," the amino acids in question were probably detected using IR spectroscopy.
    - Climate science.
      - Example: Measuring the concentrations of methane (a potent greenhouse gas) over the arctic.
    - Art.
      - Example: Authenticating old paintings.
      - Indeed, we can use IR to look for diagnostic pigments.
      - A nondestructive method like IR is better in this context than a destructive method like EA or MS because you obviously don't want to chip off a bit of the paint just for an analysis!

- Why is CO_2 (a nonpolar molecule) IR active?
  - The stretching modes are IR silent.
  - However, some of the bending modes induce a dipole, and these are the IR active modes.
- Could we use IR to detect the presence of oxygen on Mars?
  - Oxygen is probably not IR active, so we could not use IR to detect its presence on Mars. There is probably another way, though!

1.4 Nuclear Magnetic Resonance - 1

9/11:

- Lecture 3 Recap.
  - Key regions of an IR spectrum from Figure 1.12.
  - A follow-up on C–H peaks.
    - See Steven's announcement on Canvas.

  - Essentially, C–H peaks are typically (1) small and (2) not diagnostic.
    1. The reason why C–H peaks may be small is outside the scope of this class, but it has to do with the polarizability of the C–H bond.
    2. By not diagnostic, we mean that their presence or absence in an IR spectrum doesn't tell us very much since C–H bonds exist in almost every organic molecule. Indeed, the real power of IR spectroscopy is in identifying heteroatoms and their stretches.
  - Takeaway / expectation for this course: If you are given a spectrum displaying a peak in the C–H region and there's nothing else to which you can assign this peak, you are expected to know that it's a C–H peak.

- A preview of what's to come in this course.
  - The remainder of this week: Rich in content, because there's a lot to talk about in NMR.
  - Next week: We'll begin putting all of the structure determination techniques together.

- Today: Nuclear magnetic resonance (NMR).
  - Reading: Clayden et al. (2012), Chapters 3 & 13.
  - Be sure to read this!!

- Lecture outline.
  - Theory.
  - Spectrometer schematic.
  - Spectrum elements.
  - Trends in identifying peaks.
  - Integration.
  - Coupling.

- **Nuclear magnetic resonance**: A method in which we measure the magnetic environment of the nucleus to learn about the chemical environment around atoms.
  - This is one of the most powerful and widely used techniques in modern, real-life Orgo research.

- NMR theory.

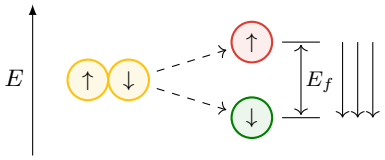


Figure 1.16: Nuclear magnetic resonance theory.

  - Postulate: The nuclear spin has a small magnetic moment.
    - We won't be diving too deeply into the physics, but recall from Gen Chem that *spin* is one of the main quantum numbers of a nucleus.[7]
  - Normally (i.e., in the absence of an external magnetic field), nuclei can be either spin up (↑) or spin down (↓) and have the same energy.
    - However, in an external magnetic field (↓↓↓), the nuclei split into different energy levels.
    - The level that is **parallel** to the magnetic field is stabilized, and the level that is **antiparallel** to the magnetic field is destabilized.

[7] n, ℓ, m_ℓ, m_s.

  - If we irradiate a nucleus in the spin down state, we can flip it to the spin up state.
    - However, we must irradiate it using a photon with the **resonance frequency** (E_f).
  - A plot of the frequency required to flip each nucleus is called an NMR spectrum.
    - Example: If we only had one kind of nucleus in our sample, we would only see one peak in the spectrum. In particular, this peak would correspond to the frequency at which all of the (identical) nuclei present would flip.
  - Another consideration is that for a nucleus to spin flip, its nuclear spin must not equal zero.
    - For example, the nuclei in ^{1}H and ^{13}C atoms have nonzero spin.
      - ➢ We'll look at NMR spectra of these nuclei extensively in this course.
    - However — and this is beyond the scope of this class — chemists can also look at spin-active nuclei like ^{11}B, ^{19}F, and ^{31}P.
  - Lastly, note that the resonance frequency is not the same for all nuclei due to a phenomenon called **shielding**.

- **Resonance frequency** (of an atomic nucleus in a certain magnetic field): The frequency of radiation needed to flip the spin of the nucleus from spin down to spin up. *Denoted by* $\boldsymbol{E_f}$.
- **Shielding**: The chemical environment affects the frequency at which a nucleus flips.

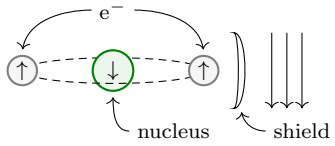


Figure 1.17: Shielding in NMR.

  - Essentially, electrons have their own magnetic moments, which "shield" the nucleus they surround from the external field.
  - More electron density — such as that from electron-donating groups (EDGs) — leads to more shielding.

- A schematic of an NMR spectrometer.

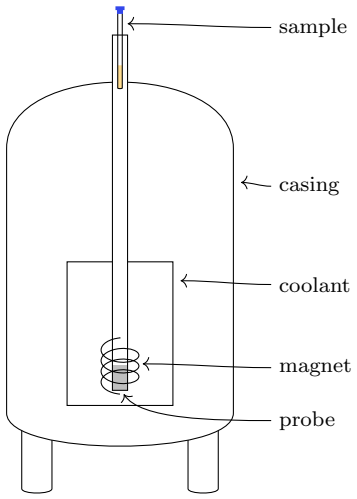


Figure 1.18: NMR spectrometer schematic.

  - We have NMR spectrometers all over campus at MIT!
  - Basically, an NMR machine looks like a box with legs.
  - The "box" is a casing containing coolant.
  - The coolant keeps everything at the right temperature.
    - Typically, the coolant is either liquid helium or liquid nitrogen.
    - We use coolant because the magnet in an NMR spectrometer works more efficiently at lower temperatures.
  - The sample we are analyzing gets lowered into the magnet.
    - The "sample" consists of a glass tube filled with the chemical we seek to analyze.
    - Note that before we put the chemical in the tube, we usually dissolve it in a liquid solvent.
  - In the center of the magnet, there is a probe. The probe detects the frequencies that the nuclei absorb.
  - For scale, a typical NMR machines are about the size of a person, though some are smaller and some are as big as a shed!

- Example ^{1}H NMR spectrum: Methyl acetate ().

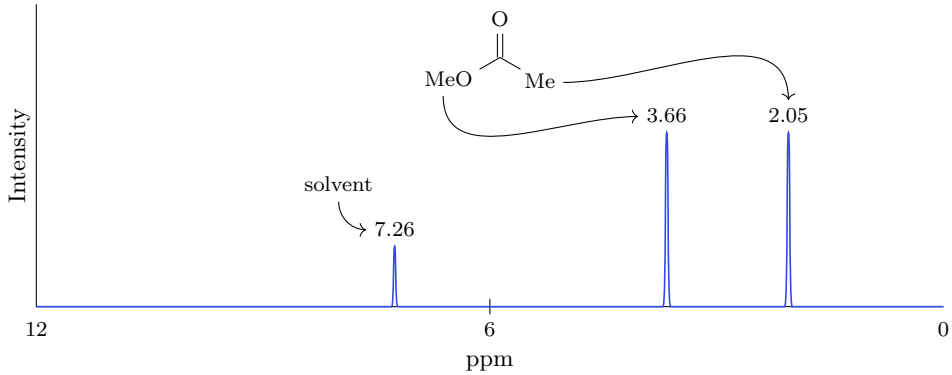


Figure 1.19: ^{1}H NMR spectrum of methyl acetate.

  - The y-axis is the intensity of the NMR peaks.
  - The x-axis is in parts per million (ppm).
    - Raw NMR peaks are reported in hertz, but then we can divide by the magnet strength to get ppm (a uniform scale).[8]
  - We get two peaks at 3.66 and 2.05, corresponding to the two types of protons in the molecule.
  - We also get a third peak at 7.26, corresponding to the solvent in which the methyl acetate is dissolved.
    - However, you can ignore this peak.
    - We are discussing solvent peaks now so that if you ever look up an NMR spectrum online (or something) and see an extra peak, you know it probably corresponds to the solvent.

- We now discuss some common resonance frequencies, i.e., the resonance frequencies for protons in common functional groups. We call such resonance frequencies the **chemical shift**.

[8] To elaborate: It is a fact of physics that the stronger the external magnetic field, the larger the energy level splitting E_f (see Figure 1.16). If the E_f of a nucleus increases, then we will need a higher frequency photon to flip it than we would have needed in the previous, weaker external magnetic field. Thus, to cancel out the influence of the external magnetic field strength on our raw data, we divide by the magnetic field strength. This division ensures that whether a specific NMR spectrometer's magnet is stronger or weaker, we can identify identical nuclei with an identical ppm value in our spectrum.

- **Chemical shift** (of a nucleus): The resonance frequency of the nucleus. *Denoted by* $\boldsymbol{\delta}$. *Units* **ppm**.

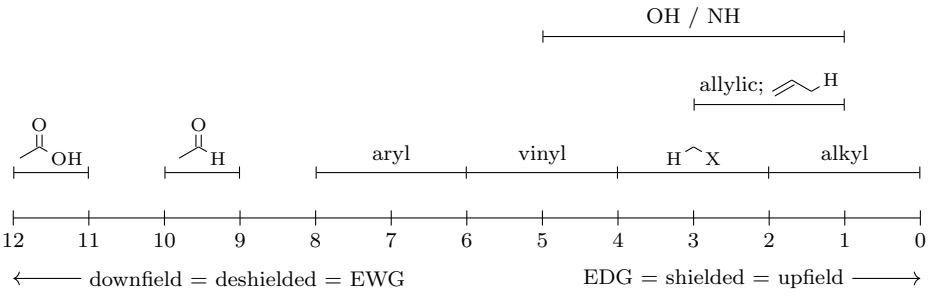


Figure 1.20: Chemical shifts of common proton types.

  - Tetramethylsilane (TMS / $SiMe_4$) has a chemical shift of 0 *by definition*.
    - In other words, TMS is used as an NMR reference compound, and we express the chemical shift of all other nuclei as the distance from TMS in ppm.
  - There are two directions: **Upfield** and **downfield**.
  - Peaks corresponding to carboxylic acid protons, alcohol protons, and amine protons are often broad due to chemical exchange.
    - This is exactly the same as exchangeable protons from IR spectroscopy!
  - OH and NH peaks are *often* broad, although they can appear as sharp peaks, including with coupling to neighboring protons.
- **Upfield** (chemical shift): A chemical shift that is more to the right side of an NMR spectrum. *Also known as* **shielded**.
  - Protons with upfield chemical shifts are often near electron donating groups (EDGs).
- **Downfield** (chemical shift): A chemical shift that is more to the left side of an NMR spectrum. *Also known as* **deshielded**.
  - Protons with downfield chemical shifts are often near electron withdrawing groups (EWGs).
- Important trend: More and stronger EWGs leads to a higher chemical shift.
- Example: $H_3C{-}F > H_3C{-}Cl > H_3C{-}Br$.
  - Sorted by electronegativity, fluorine is more electronegative than chlorine, which is more electronegative than bromine.
  - As such, the chemical shift of the protons in fluoromethane (4.10) is greater than the chemical shift of the protons in chloromethane (3.05), which is greater than the chemical shift of the protons in bromomethane (2.68).
- Example: Isopentane ( ).
  - The sole tertiary proton is surrounded by three EWGs (2 methyl and 1 ethyl), so it has the highest chemical shift at 1.46.
  - The secondary protons are surrounded by two EWGs (1 methyl and 1 isopropyl), so it has the second highest chemical shift at 1.20.
  - The primary protons then have the lowest chemical shifts. For example, the three protons at the right end of the molecule have a chemical shift of 0.86.
- Why are tertiary carbons more deshielded when adjacent methyl groups donate to a carbocation?
  - Prof. Elkin will not answer this question in full now because the answer comes from MO theory.
  - Simply, carbon is more electronegative than hydrogen, so carbon is a better EWG than hydrogen.

- Why does more electron density lead to a greater shielding effect and hence a lower resonance frequency?
  - Because they feel more of the external magnetic field, so it takes more energy to flip them to the higher spin state.
- **Integration** (of an NMR peak): The area under the peak.
  - The integration of a peak is equal to the number of nuclei in that chemical environment.
    - In other words, nuclei that are **chemically equivalent** help form the same peak in an NMR spectrum.
  - Only *relative* integrations matter; there is no use for *absolute* integration values.
- **Chemically equivalent** (protons): A set of protons within a molecule that are in the same chemical environment.
- Example ^{1}H NMR spectrum: Methanol (MeOH).

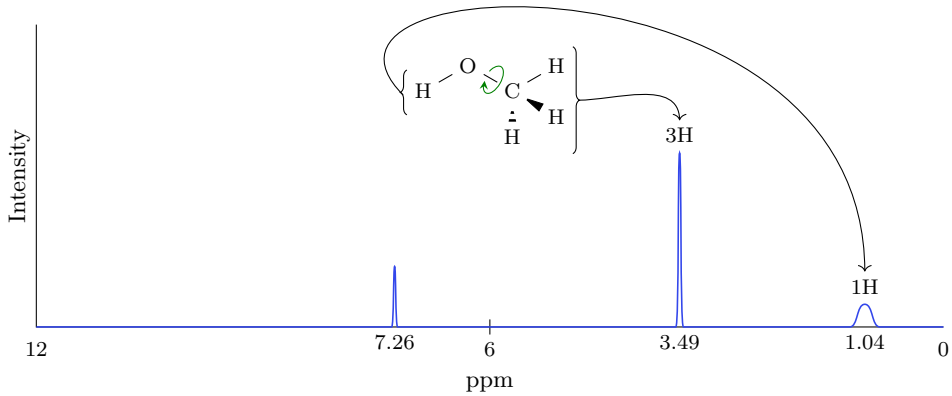


Figure 1.21: ^{1}H NMR spectrum of methanol.

  - In this example, there is free rotation around the C–O single bond. This rotation puts all of the methyl protons in the chemical environment, i.e., they are chemically equivalent. Thus, because they are chemically equivalent they all have the identical resonance frequency of 3.49 and all contribute to that peak.
    - Indeed, *any* single bond with unrestricted rotation makes protons chemically equivalent, leading to them resonating at the same frequency.
  - However, the alcohol proton is in a different chemical environment from the other protons, leading to a second peak.
    - Notice that this peak is broad because the alcohol proton is exchangeable!
  - Key takeaway: Chemical equivalence is why we see two peaks in Figure 1.21 (one for each *chemically nonequivalent* type of proton) instead of four (one for *every* proton).
    - It is also why one peak integrates to three times the area of the other peak.
    - These integrations are often denoted 1H and 3H.
  - Notice that once again, we have an extra peak at 7.26 due to our solvent.
- In our next example, we will see another way in which integration ratios can manifest themselves.
  - However, there will also be another feature (as of yet unmentioned).
  - We will discuss this feature subsequently.

- Example ^{1}H NMR spectrum: Propane ( ).

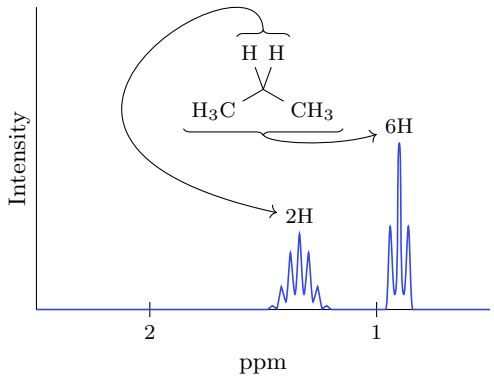


Figure 1.22: ^{1}H NMR spectrum of propane.

  - This NMR spectrum consists of two "funny-shaped" peaks.
  - The ratio of their integrations is 1 : 3. However, note that a 1 : 3 ratio is equivalent to a 2 : 6 ratio! (And a 3 : 9 ratio, a 4 : 12 ratio, etc.)
  - Thus, based on the NMR spectrum alone, we do not have enough information to decide what exact ratio the peaks are showing.
    - Rather, we will need to know something else about the structure (such as the molecular formula!) in order to decide if it is 1 : 3 or 2 : 6!
    - Supposing we knew from EA and MS that the molecular formula was C_3H_8, we could then confirm that this is a 2 : 6 ratio because $2 + 6 = 8$ total protons.

- Peaks have "funny shapes" due to an effect called **coupling**.
- **Coupling**: When nuclei are adjacent to each other, they alter one another's resonance frequency by inducing a ½ increase or ½ decrease. *Also known as* **proton coupling**, **peak splitting**, **multiplicity**.
  - Coupling is based on the same physical idea as shielding.
    - Indeed, just like electrons have magnetic moments that can interfere with their host nucleus, adjacent nuclei have magnetic moments that can interfere with their host nucleus.
  - When peaks split, they do so symmetrically about the original resonance frequency, and the new peaks have the same integration as the old peak.
- There are more kinds of coupling besides proton-proton coupling, but proton-proton is all we'll talk about today (and probably in this whole class).
- More on proton-proton splitting.

Adjacent Protons (n)	**Peak Pattern ($n+1$)**	**Ratio of Peaks**	**Image**
0	singlet (s)	1	
1	doublet (d)	1 : 1	
2	triplet (t)	1 : 2 : 1	
3	quartet (q)	1 : 3 : 3 : 1	

Table 1.3: Proton-proton coupling.

  - Thus, in Figure 1.22, our peaks are a 2H septet and a 6H triplet.
  - The ratio of peaks forms **Pascal's Triangle**! You can Google why, if you're interested!!
  - Sometimes, these peak patterns are called **multiplets**.
    - We tend to use the term "multiplet" when the splitting is either very complicated or low resolution, that is, when we cannot tell if the splitting is a triplet, quartet, septet, or something even more exotic (like what we'll discuss next class!).

- Note that identical protons do not couple themselves.[9]
  - This is why (for example) the septet in Figure 1.22 is not an octet: The two secondary protons do not couple to each other.
- **Coupling constant**: A measure of coupling. *Denoted by* ***J***. *Units* **Hz**.
  - Protons that couple each other have identical J values.
- Coupled protons split via **roofing**.
- **Roofing**: A phenomenon in which coupled peaks slant towards each other.

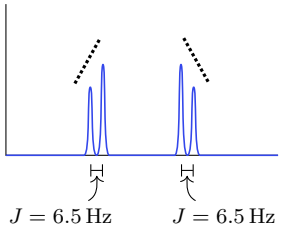


Figure 1.23: Roofing in NMR.

  - When you couple two doublets, they have this extra fun shape that helps hint toward coupling.
- Next time: Where J comes from, compounds coupling, carbon NMR, and more!

1.5 Nuclear Magnetic Resonance - 2

9/13:

- Lecture 4 recap: A summary of the features in an NMR spectrum.
  1. Chemical shift (δ).
     - This tells us the ppm of the peak, specifically whether the proton is more downfield or upfield.
     - It indicates which functional group a proton is in or near, e.g., EWG/EDG (see Figure 1.20).
  2. Integration.
     - The integration is the area under the peak.
     - It tells us how many unique protons make up a peak.
  3. Coupling.
     - The coupling determines the shape of the peak.
     - It tells us how many protons are adjacent to the peak.
  4. Coupling constant (J).
     - The coupling constant gives an exact, quantitative measure of the shape of the peak.
     - It tells us where (geometrically) the adjacent protons are.

[9] For a (heavily mathematical, quantum mechanical) explanation of why, see this resource.

- Today: More NMR.
  - Reading: Clayden et al. (2012), Chapter 13.
- Lecture outline.
  - More on the coupling constant.
  - ^{13}C NMR.
  - Guidelines for interpreting a ^{1}H NMR spectrum.
- To begin, we will pick up where we left off in discussing J.
- What determines the magnitude of J?
  - J is determined by the geometry between protons, especially the **dihedral angle**.
  - The typical range of J values is $6 - 8$ Hz.
- **Dihedral angle**: The angle between two coupled protons in a Newman projection sighted along the C–C bond connecting the coupled protons' carbons. *Denoted by* ϕ.
- **Karplus equation**: An expression of the magnitude of J for two coupled protons as a function of their dihedral angle.

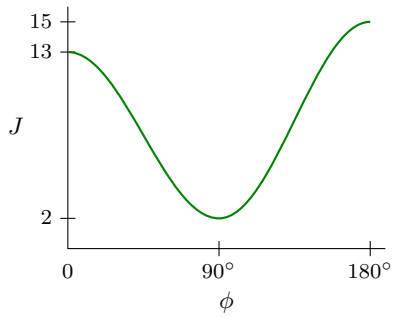


Figure 1.24: Karplus equation.

  - Coupling is greatest when the protons are either directly aligned, or directly antiperiplanar (180°).
- Example coupling constants: In a vinyl group.

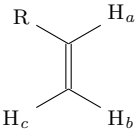


Figure 1.25: Coupling constants in a vinyl group.

  - Since there is no free rotation around the double bond, the three proton pairs in this functional group all have distinct and recognizable couplings.
  - In this functional group...
    - The *cis* protons couple at $J_{H_{a,b}} \approx 6 - 12$ Hz;
    - The *trans* protons couple at $J_{H_{a,c}} \approx 12 - 18$ Hz.
    - The **geminal** protons couple at $J_{H_{b,c}} \approx 1 - 3$ Hz.
  - Implication: Geminal protons *can* couple (provided that they are not chemically equivalent).
    - In other words, protons do not *need* to be **viscinal** in order to couple.

- **Geminal** (atoms or groups): Two atoms or groups in a molecule that are both bonded to the same "parent" carbon atom.
- **Viscinal** (atoms or groups): Two atoms or groups in a molecule that are bonded to adjacent, viscinal carbon atoms (i.e., in a 1,2-relationship).
- Example coupling constants: In benzene.

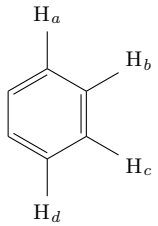
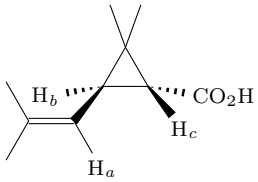
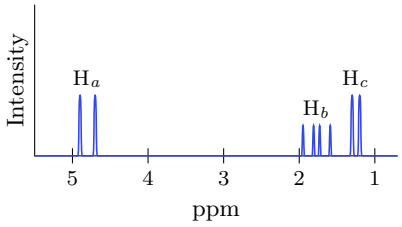


Figure 1.26: Coupling constants in benzene.

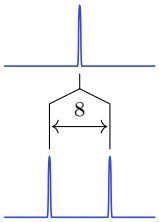
  - **Long-range coupling** is possible with π-systems.
    - Thus, protons *meta* and *para* to each other can couple even though they're not viscinal.
  - $J_{\text{ortho}} \approx 7 - 10\,\text{Hz}$.
  - $J_{\text{meta}} \approx 2 - 3\,\text{Hz}$.
  - $J_{\text{para}} \approx 0 - 14\,\text{Hz}$.
- Coupling to nonequivalent protons.



(a) An example molecule.

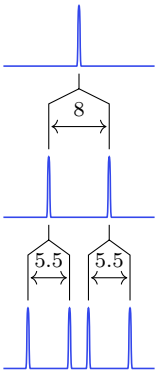


(b) The molecule's ^{1}H NMR spectrum.



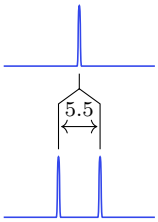
doublet

(c) Splitting diagram: H_a.



doublet of doublets

(d) Splitting diagram: H_b.



doublet

(e) Splitting diagram: H_c.

Figure 1.27: Nonequivalent proton coupling.

- Before covering this example in class, Prof. Elkin flags a typo from where this example is covered in Clayden et al. (2012).
  - Specifically, the molecule in Figure 1.27a is called chrysanthemic acid, and its ^{1}H NMR spectrum is also covered on Clayden et al. (2012, p. 292).
  - However, when the authors of the textbook drew the molecule, they forgot to include the two methyl groups on the "top" carbon in Figure 1.27a: This is their mistake, not ours.
- We now return to analyzing the example.
- Maxim: If a proton is adjacent to multiple unique protons, it couples to each.
  - Indeed, the molecule in Figure 1.27a is interesting to us because H_b is viscinal to both H_a and H_c (so it will couple to both of them), but H_a and H_c are not chemically equivalent, i.e., are unique.
  - The resultant splitting is captured in Figure 1.27b.
  - Note, however, that some of chrysanthemic acid's proton NMR peaks have been edited out of Figure 1.27b for the sake of clarity, e.g., those from the four methyl groups at the top and left of the molecule, as drawn in Figure 1.27a.
- To explain the splittings observed in Figure 1.27b, we draw **splitting diagrams**.
  - Figures 1.27c, 1.27d, and 1.27e constitute three such diagrams. Let's go through them one by one.
- Figure 1.27c.
  - H_a is viscinal to a single proton, namely H_b.
  - Thus, H_b will split H_a into a doublet.
  - Experimentally, we observe that the coupling constant is 8 Hz.
- Figure 1.27e.
  - Similarly to H_a, H_c gets split by H_b.
  - However, H_c is distinct from H_a, and thus it interacts differently with H_b. This may be observed since H_b only splits H_c by 5.5 Hz.
- Figure 1.27d.
  - H_b will get split by both H_a and H_c, however.
  - In particular, H_a will split it by 8 Hz, and H_c will split it by 5.5 Hz. But how does this splitting manifest itself?
  - To answer this question, we may think of H_a as splitting H_b "first," and then H_c as splitting the resultant doublet "second."
  - As an exercise, draw out this splitting diagram again, but switch the order of the splitting (i.e., let H_c do the splitting "first" and H_a do the splitting "second"). You will see that you get the exact same peak pattern!![10]
- The peak pattern derived in Figure 1.27d is known as a **doublet of doublets** (dd).
- Note: Doublet of doublets *must* be symmetric.
  - For example, we couldn't have 1 peak on the left more separated from the other 3.
- Doublets aren't the only peak patterns that are susceptible to this kind of twofold splitting: Indeed, we can mix and match others!
  - For example, we can have a **triplet of doublets** or a **doublet of doublets of doublets**. (These are for you to dig into on your own, if you're curious :)
- Note that a doublet of doublets is *not* a quartet; in a quartet, you have equal spacing between every peak and a 1 : 3 : 3 : 1 ratio of peak heights.

[10] An additional exercise you can try is figuring out why we can draw splitting diagrams for the splitting caused by equivalent protons, too. If you draw out a splitting diagram for the splitting caused by two (or more!) equivalent protons, you will see that the process is needlessly redundant since our rule in Table 1.3 summarizes everything well enough.

- Why do we use Hz for J but ppm for δ?
  - Chemical shifts and coupling are slightly different phenomena. In particular, they differ in the way they interact with the applied external magnetic field.
  - We use ppm for the chemical shift because ppm is a uniform scale for the chemical shift, even when we change the magnetic field strength of our NMR spectrometer.
  - We use Hz for coupling because Hz is a uniform scale for the coupling, even when we change the magnetic field strength of our NMR spectrometer!
- We now switch our focus from ^{1}H NMR to ^{13}C NMR for a bit.
- ^{13}C NMR vs. ^{1}H NMR.
  - Recall from the lecture on mass spec that the ^{13}C isotope makes up approximately 1% of carbon. (Most naturally occurring carbon is the NMR-silent isotope ^{12}C.)
    - The fact that most carbon nuclei are NMR silent means that we get less signal from ^{13}C NMR than ^{1}H NMR.
  - Spectral window: $0 - 200$ ppm for organics.
    - Note that this is much larger than the $0 - 12$ ppm window for ^{1}H NMR.
  - Coupling is rare; you almost always get singlets.
  - No integration; the peak height changes, but exactly why is complicated.
    - Google it if you're curious!!
  - Sometimes "cleaner" than ^{1}H NMR, by which we mean that you get better resolution in the absence of splitting.
    - In other words, it's easier to interpret how many peaks you have in ^{13}C NMR.
  - We can now see carbons without protons!
    - Examples: Carbonyl, tetrasubstituted, and quaternary carbons.
- Example ^{13}C NMR spectrum: Cyclohexanol ().

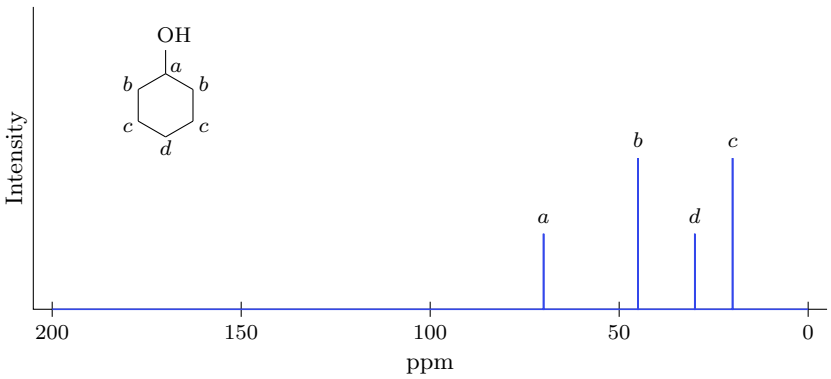


Figure 1.28: ^{13}C NMR spectrum of cyclohexanol.

  - When analyzing a ^{13}C NMR spectrum, we label the carbons in our molecule with letters.
  - Specifically, one letter is used for each *unique* carbon.
  - This is why cyclohexanol (a symmetric molecule) only needs 4 letters instead of 6: It has 4 *unique* carbons and 6 total carbons.

- The example in Figure 1.28 illustrates one of the things for which ^{13}C NMR is most useful: Telling us how many unique carbons we have!

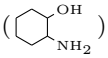
Molecule	Cyclohexanol ()	2-Aminocyclohexanol ()	Cyclohexane ()
# carbons	6	6	6
# unique carbons	4	6	1

Table 1.4: ^{13}C NMR identifies the number of unique carbons.

  - Indeed, for almost identical molecules, we observe big differences in the ^{13}C NMR spectrum.
  - For example, the asymmetric molecule 2-aminocyclohexanol has 6 unique carbons while the highly symmetric cyclohexane has only 1 unique carbon, despite the fact that all of these molecules only differ by a couple of functional groups!

- ^{13}C NMR — like ^{1}H NMR — helps us identify key functional groups.

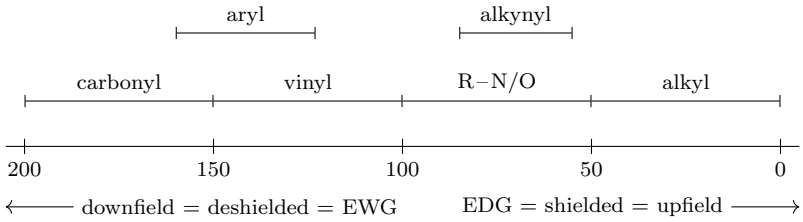


Figure 1.29: Chemical shifts of common carbon types.

  - Note that we have a carbonyl region here that we did not have in Figure 1.20!

- If ^{13}C NMR can be used for functional group identification, why would we ever want to use IR?
  - There are some functional groups between which ^{13}C NMR can't distinguish.
    - Example: ^{13}C NMR can't distinguish C=N from C=O, but IR can.
  - As a general rule, though, a chemist would collect data from both sources (as well as all the others) and make sure that the data is consistent.
    - For example, if ^{13}C NMR suggests that a molecule has an alkynyl carbon but IR doesn't show a stretch at $3300\,\mathrm{cm}^{-1}$, we might have a problem!
    - One potential solution to this problem could be that we mistakenly identified a R–N/O peak in the ^{13}C NMR spectrum as an alkynyl peak.

- We now return to ^{1}H NMR for some guidelines on interpreting these spectra.
  - NMR can tell you how many distinct ^{1}H/^{13}C groups you have, what kind of functional group they are, and how they're connected.
  - Example step-by-step workflow for ^{1}H NMR.
    1. Identify the number of unique peaks, and watch out for overlap!
    2. Note the chemical shifts and propose likely functional groups.
    3. Calculate or consider integrations.
    4. Observe the peak shape and start hypothesizing about connectivity.
    5. Calculate J to confirm or support connectivity.
    6. Make sure that all the data is consistent.

- Let's now look at an example of how we could identify a compound from its ^{1}H NMR spectrum using the above workflow.
- Example ^{1}H NMR spectrum: 4,4-Dimethylcyclohex-2-en-1-one ().

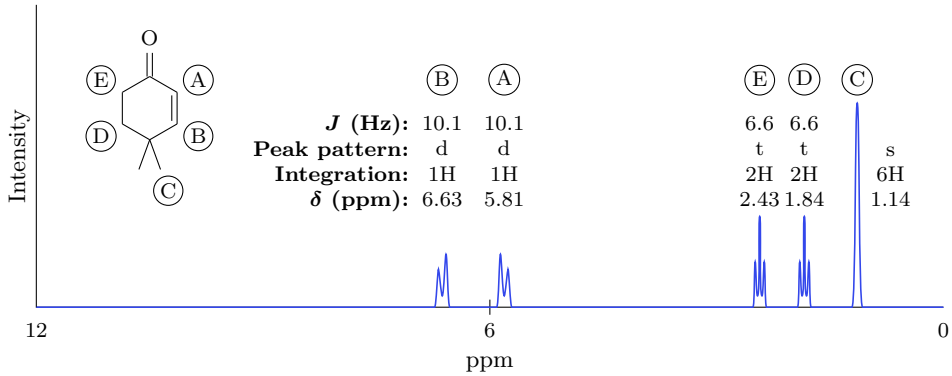


Figure 1.30: ^{1}H NMR spectrum of 4,4-dimethylcyclohex-2-en-1-one.

1. There are 5 unique peaks.
   - This means that there are 5 unique proton positions.
2. There are 2 peaks in the vinyl region,[11] and 3 peaks in the alkyl region.
3. The ratio of integrations is 1 : 1 : 2 : 2 : 6.
   - The 6H integration must be 2 identical groups of 3 protons (i.e., methyl groups)!
   - Similarly, if we saw 9H, it would probably be 3 identical methyl groups.
4. There are 2 roofing doublets, 2 triplets, and 1 singlet.
   - The 2 roofing doublets correspond to the vinyl protons.
     - This implies that our vinyl protons are adjacent to each other.
     - Thus, part of our molecule looks like this: 
     - Note that we will not know that the vinyl protons are *cis* until Step 5; they could still be *trans* or geminal until the coupling constant tells us otherwise.
   - The 2 triplets correspond to some of the alkyl protons.
     - This splitting pattern implies the presence of two protons next to two protons.
     - Thus, part of our molecule looks like this: 
     - Note that this splitting pattern analysis lines up with the integrations as well!
   - The 1 singlet corresponds to the remaining alkyl protons.
     - Six chemically identical protons that are not split by anything implies geminal methyl groups on a tetrasubstituted carbon.
     - Thus, part of our molecule looks like this: 
5. The J's agree with all the motifs we've proposed so far.
   - The 6.6 Hz splitting of the triplets doesn't get us much new information.
   - However, per Figure 1.25 and the associated discussion, a coupling constant of 10.1 Hz for the vinyl protons confirms that they are in a *cis* orientation, as drawn above.
6. All of the data is, indeed, consistent with the proposed molecule's structure.

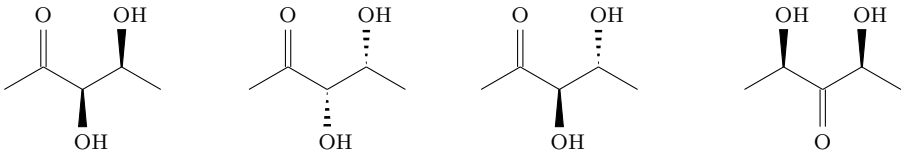
[11] Note that we include the peak at 6.63 ppm in the vinyl region even though it would normally fall in the aryl region (per Figure 1.20) due to the nearby carbonyl EWG.

1.6 Structure Determination - 1

9/16:

- Lecture 5 recap: A review of the suggested ^{1}H NMR interpretation workflow.
  1. Identify unique peaks: Tells you if the molecule has symmetry.
     - Example: 6 protons but 4 peaks.
  2. Chemical shifts: Tells you which functional groups may be present.
  3. Integrations: Tells you how many protons there are at each position in the molecule.
  4. Peak shape: Tells you which protons neighbor which other protons.
  5. J values: Tells you which protons *really* neighbor which other protons.
     - Example: If two peaks share a coupling constant, they correspond to neighboring protons.
  6. Sanity check: Ensures that all your hypotheses derived from the previous steps are consistent.
- Today: Structure determination.
  - Reading: Clayden et al. (2012), Chapter 18.
  - This reading covers several examples of when NMR is really useful. In some of these examples, NMR is the technique *needed* to solve a problem.
  - There's a good bit of stuff that's beyond the scope of the class, but it's really short (only 20 pages) and will be very helpful for you, so please read it!!
- Lecture outline.
  - Overview and recap of the 5 structure determination methods we've discussed to date.
  - Key signals across the 5 methods.
  - Examples of when certain techniques are more useful.
- Methods overview.
  - EA: Get the empirical formula.
  - MS: Get the molecular formula, isotope identities, stable fragments, and fragmentation patterns.
    - Fragmentation patterns tell us a lot about connectivity.
  - IR: Get key functional groups.
  - ^{13}C NMR: Get the number of unique carbons, key functional groups.
    - The number of unique carbons gives info on molecular symmetry.
  - ^{1}H NMR: Get the number of unique protons, key functional groups, and data about connectivity.
    - The relevant connectivity data here comes from J values.
- Why do we need multiple analytical techniques for key functional groups?
  - A single spectrum rarely contains the full picture. Rather, each technique gives a hint, and we — as chemists — are like detectives following the different lines of inquiry.
  - Different spectra can help in a *confirmational* manner or an *orthogonal* manner.
    - Confirmational: Both IR and ^{13}C NMR show a ketone, so I'm pretty sure there's a ketone!
    - Orthogonal: Here's a new piece of information that none of the other techniques have given me yet.
  - Critical point: The final proposed molecular structure must be consistent with *all* data.
    - If you're matching the IR and the ^{1}H NMR but not the ^{13}C NMR, it can't be right!
- We now look into some common signals and what they tell us.

- Shortcuts: "Give away" signals.
  - Bromine and chlorine in MS.
  - C=O in IR and ^{13}C NMR.
  - OH stretch in IR and the (typically) broad peak in ^{1}H NMR.
  - CH_3 peaks in ^{1}H NMR (i.e., upfield peaks that integrate to 3H) and MS (i.e., $[M-15]^+$ peaks).
  - Aldehyde protons in the $10-11$ ppm region of ^{1}H NMR.
  - Roofing doublets in the aromatic region of ^{1}H NMR.
    - Tends to indicate a *para*-substituted benzene ring with different substituents on both sides.
  - And more! Practice, and notice trends!!
- Let's do some practice now on some particularly hard examples.
- Consider the following isomers.



(a) Original structure. (b) Enantiomer. (c) Diastereomer. (d) Constitutional isomer.

Figure 1.31: Isomer identification with structure determination.

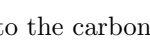
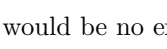
- If we try to distinguish the original structure (Figure 1.31a) from any of the others using the structure determination techniques, we'll find that the results are...

	Enantiomer	**Diastereomer**	**Constitutional isomer**
EA:	identical	identical	identical
MS:	identical	similar	different
IR:	identical	similar	different
^{13}C NMR:	identical	different	different
^{1}H NMR:	identical	different	different

Table 1.5: Isomer identification with structure determination.

  - Distinguishing the enantiomer.
    - In order to distinguish chiral materials, you have to have a chiral technique.
    - Specificaly, you would need a chiral light source to distinguish chiral molecules.
      - ➢ We'll talk on Wednesday about IR with plane polarized light (Circular Dichroism), which would work, but we don't have that technique yet.
    - The only time the enantiomers could be distinguished using any of the techniques we've learned so far is with a weird edge case like a chiral solvent.
  - Distinguishing the diastereomer.
    - Diastereomers can look different on MS and IR, but it's subtle. This is why we say *similar*.
    - With ^{13}C NMR, the peaks are technically different, but practically similar.
    - With ^{1}H NMR, the Karplus equation makes certain J values larger or smaller depending on the diastereomer.
      - ➢ This can help us differentiate gauche, syn, and anti conformations.
    - Chapter 13 of Clayden et al. (2012) has more on distinguishing diastereomers; read it!!

  - Distinguishing the constitutional isomer.
    - This molecule has a plane of symmetry, and thus only 3 unique carbons; this makes this molecule much easier to pick out using the techniques we know (e.g., ^{13}C NMR).

- Example: Determine the structure of the molecule described by the following data.
  - ^{13}C NMR: δ 171.4, 60.5, 21.0, 14.2.
    - Per Figure 1.29, these peaks respectively correspond to a carbonyl, C–X,[12] and two alkyl carbons.
  - ^{1}H NMR: δ 4.12 (q, 2H), 2.05 (s, 3H), 1.26 (t, 3H).
    - The middle peak corresponds to a methyl group: 
    - The left peak corresponds to a C–X, with 2H bonded to the C and 3H adjacent (it's split into a quartet): 
    - The right peak probably corresponds to the adjacent 3H introduced above. This is because we'd predict that the adjacent 3H introduced above would be an alkyl 3H that gets split into a triplet, just like the right peak.
  - After this initial analysis, redraw the biggest fragment and start combining fragments.
    - We could try bonding the ethyl-X group into the other methyl group (), but this would leave no space for the carbonyl.
    - Thus, we can bond into the carbonyl and then the methyl group: 
  - The last thing we have to determine now is the identity of the heteroatom X.
    - If X is a halogen, then the above structure implies that it's divalent. Since halogens don't like to form more than 1 bond, X is probably not a halogen.
    - If X = NH, then this proton would have a ^{1}H NMR signal as well and should have shown up in the data.
      - ➢ The proton could be ^{1}H NMR silent due to exchange, but we should probably **Occam's razor** that possibility out.
    - If X = O, then there would be no extra ^{1}H NMR signals: 
      - ➢ This structure is consistent with all the data we have, so we can be confident that we have determined the structure.
  - This molecule is called ethyl acetate, and every organic chemist knows it because it's a common laboratory solvent and traces of it often appear in our NMR experiments.

- **Occam's razor**: The simplest explanation is usually the best explanation.
- Maxim: Occam's razor is king with structure determination.
- Example: Describe how you would use the key signal(s) in the structure determination data of the following two compounds to tell them apart.

(a) *p*-Toluoyl chloride. (b) Phenylacetyl chloride.

Figure 1.32: Two compounds to differentiate using structure determination.

[12] Recall that "X" is a placeholder for some as-of-yet-undetermined electronegative heteroatom, such as oxygen, nitrogen, or a halogen.

  - EA key signals? No.
    - The molecules have identical empirical formulas.
  - MS key signals? Tough.
    - We'd get α-cleavage with both ketones, leading to similar fragments.
  - IR key signals? Tough.
    - The C=O stretch would be the main IR-active signal, and both carbonyls are fairly similar.
  - ^{13}C NMR key signals? Tough.
    - The molecules have roughly the same symmetry (8 carbons, 6 unique ones).
  - ^{1}H NMR key signals? Yes: Multiple key signals!
    - Let's start in the alkyl region.
      - ➢ Both molecules would have one alkyl peak: Figure 1.32a has a methyl group at the bottom-left of the aromatic ring, and Figure 1.32b has a methylene group connecting the aromatic ring to the acid chloride.
      - ➢ The methyl group will appear as a 3H singlet between $1-2$ ppm.
      - ➢ The methylene group will appear as a 2H singlet between $2-4$ ppm (it is more downfield due to the nearby EWGs).
    - The peaks in the aryl region will also be different.
      - ➢ For Figure 1.32a, the protons will split into two roofing doublets, both of which integrate to 2H.
      - ➢ For Figure 1.32b, the protons will split into a 2H doublet, a 2H doublet of doublets, and a 1H triplet.
      - ➢ However, note that for Figure 1.32b, the actual aromatic peaks of this molecule show up as what we call a "multiplet (m)," meaning that it is a messy mound of peaks that we can't assign a clean pattern to because they overlap too much. You can still integrate the multiplet and see that it contains 5H, and that's how you could differentiate this molecule from the other in practice.

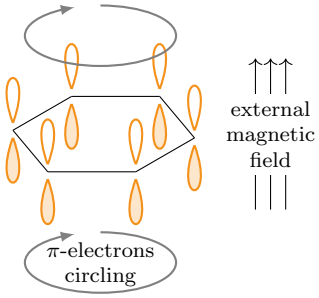
1.7 Structure Determination - 2

9/18:

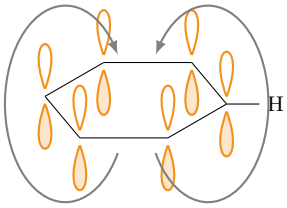
- Lecture 6 recap: The journey from having a liquid to having the liquid's molecular structure.
  1. EA: Get the empirical formula.
  2. MS (parent peak): Transform the empirical formula to the molecular formula.
  3. IR: Get key functional groups.
  4. ^{13}C NMR: Get the number of unique carbons, and confirm key functional groups.
  5. ^{1}H NMR: Get data about connecting fragments, and confirm key functional groups.
  6. MS (fragments): Confirm connectivity data.
  7. Double check: Does the proposed structure align with *all* information?
- Autumn-themed aside: Eugenol (cloves) and cinnamaldehyde (cinnamon) make up pumpkin spice!
- Today: More structure determination.
- Lecture outline.
  - Ring currents.
  - X-ray crystallography.
  - Circular dichroism.
  - Structure determination practice.
- Note that X-ray and CD won't be on Exam 1, but they will be useful for any lab work we do.

- Ring currents and related effects.

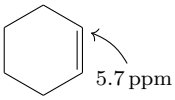
(a) Vinyl deshielding.



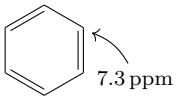
(b) Ring current induced.



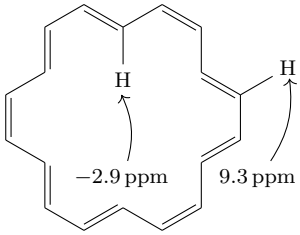
(c) New magnetic field.



(d) Cyclohexene.



(e) Benzene.



(f) [18]annulene.

Figure 1.33: Ring currents and related effects.

  - Protons next to π-systems are deshielded.
    - Example: Cyclohexene's vinyl protons are downfield at 5.7 ppm (see Figure 1.33d).
    - Alkene protons are deshielded because they lie in the nodal plane of the π-system, coplanar with the so-called "σ-bond network." This means that much of the electron density is above or below these protons in the p-lobes. Thus, the protons have less electron density near them, which we observe as deshielding (see Figure 1.33a).
  - While cyclohexene's vinyl protons are certainly deshielded compared to normal alkyl protons, benzene's six protons are even more deshielded, lying at 7.3 ppm.
  - What makes aromatic protons so much more deshielded?
    - When benzene is placed in an external magnetic field, it orients itself perpendicular to the magnetic field because the p-orbitals all want to align with the magnetic field (see Figure 1.33b).
      - ➢ Once benzene is oriented, the magnetic field causes the π-electrons to circle around the ring system.
    - These rotating electrons create a new magnetic field (see Figure 1.33c).
      - ➢ This small, local magnetic field reinforces the external magnetic field, deshielding the external protons.
    - Prediction: In an aromatic ring big enough to have *internal* protons (see Figure 1.33f), such protons will be extra shielded.
      - ➢ Indeed, this prediction is experimentally confirmed: The internal protons of [18]annulene have a whopping −2.9 ppm chemical shift.
    - More π-electrons increases the ring current and ups the external protons' chemical shift, too.
    - There's much more physics here, if you're curious!! But it's beyond the scope of the course.
  - Ring currents of aromatic compounds have tons of applications to organic semiconductors, etc.

- X-ray crystallography.

(a) 2-bromopentan-3-one. (b) X-ray structure.

Figure 1.34: X-ray crystallography.

  - To begin, you grow a **crystal** of your sample.
  - We then shoot X-rays at the crystal.
    - We choose *X-rays*, in particular, from among all types of light because their wavelength is approximately 1 Å. This is on the same order of magnitudeas most bond lengths, so we get nice interactions, described as follows.
  - Specifically, these X-rays **diffract** when they hit a nucleus, and then we measure the location to which they bounce back.
    - X-rays don't interact with electrons so much; they more interact with hard, heavy, localized nuclei.
    - We have detectors all around the sample, and this allows us to back-calculate the positions of the nuclei.
  - The result of this data collection is that we know the exact position of every nucleus in every atom of our crystal.
    - Once we have these positions, we can connect the dots to identify bonds.
    - So to clarify, X-rays do not "see" the bonds directly, but if two nuclei are 1.4 Å apart (for example), then we can reasonably assume that 1.4 Å is the bond length.
  - Result: We get a 3D structure of our molecule with exact connectivity.
  - Example: How a molecule looks to X-ray crystallography (see Figure 1.34).
    - To reiterate, every atom looks like a ball with size proportional to how much it weighs.
      - ➢ For example, bromine is really heavy, so it shows up as a really big ball.
    - Once we have the atoms' positions, we — as analysts — draw in the bonds ourselves.
      - ➢ For example, we know that C=O bonds (as double bonds) tend to be shorter than single bonds, so it should not be surprising that the oxygen and C3 atoms appear closer together than any others.

- **Crystal**: A regular lattice of repeating **unit cells**.
- **Unit cell**: The simplest thing that repeats.
- Pros and cons of X-ray diffraction.
  - Pros:
    - It's super awesome: gives you an exact 3D picture of the molecule.
    - Can show you atoms that don't have NMR signals (like bromine).
    - Often considered the "smoking gun" in structure determination. That is to say, X-ray crystallography is the spectroscopic technique that produces results you can't really argue with.
  - Cons.
    - It's expensive (∼$1000/run).
    - You can't just push a button, like you can with NMR.

➢ Rather, you need a technician to set the sample and an analyst to interpret the data (there's an art to it).

- It's hard to grow crystals of certain compounds.
- You can't see the hydrogens because they're very small, but that's usually not an issue because we can infer where they are from all the other data.
- This *crystal* structure naturally represents the molecule is the solid phase.
  - ➢ This means that we don't get much information on the molecule's dynamics in solution (for example).

- Circular dichroism (CD).

(a) Absorption of L light. (b) Absorption of R light.

Figure 1.35: Circular dichroism spectrophotometer schematic.

  - CD can be used to differentiate enantiomers!
  - Uses circularly polarized light, that is, light that rotates either left or right.
    - Circularly polarized light is created with a **polarimeter**.
  - Once the light is created, you shoot it at your sample and see what gets absorbed.
    - Some molecules — e.g., (*R*)-2-bromobutane — will not absorb the L light, but will absorb some of the R light.
    - Note the similarities between Figure 1.35 and Figure 1.10.
  - One enantiomer will absorb one handedness of light, and the other enantiomer will absorb the other handedness of light.
    - I.e., one enantiomer absorbs L and the other enantiomer absorbs R.
    - You don't know which enantiomer will absorb which light before you test it!
    - Implication: It's not always that (*R*)-enantiomers absorb R-light. It's just that one will absorb one, and the other will absorb the other.
  - CD allows us to calculate the **specific rotation** of a molecule.
  - Example measurement of $[\alpha]$: 2-bromobutane.
    - The (*R*)-enantomier has $[\alpha] = -23.1°$,[13] and the (*S*)-enantiomer has $[\alpha] = +23.1°$.
    - For a racemic mixture, $[\alpha] = 0°$.
    - If you have an 80 : 20 mixture $R : S$, then this mixture has 60% ee. This is because in an 80 : 20 ratio, the 20% of the sample that's (*S*) cancels out 20% of the sample that's (*R*). Thus, the ee is $80\% - 20\% = 60\%$. It follows that $[\alpha] = -13.9°$.
  - It follows from the last line above that CD can be used to measure the ee of your system!

- **Specific rotation** (of a molecule): A measure of the degree to which a molecule at temperature T rotates plane-polarized light of wavelength λ. *Denoted by* $[\boldsymbol{\alpha}]^{\boldsymbol{T}}_{\boldsymbol{\lambda}}$.
  - We calculate this using both the sign (+/−) and the amplitude of the light after passing through the sample.
  - The typical temperature is 25 °C, and the typical wavelength is 589 nm.

[13] Verbally, we say, "the R enantiomer rotates plane-polarized light by 23 degrees in the negative direction."

- How do you obtain a pure sample of your enantiomer for an initial CD experiment, i.e., how do you know what 100% ee looks like?
  - There are methods that can purify enantiomers, like chiral column chromatography.
  - Thus, even if your reaction doesn't yield 100% ee, you can separate the products into two samples that are 100% ee and 0% ee, and analyze those first.
- What if you have multiple chiral centers?
  - Enantiomer pairs have opposite-signed specific rotations.
  - Diastereomers look like completely different molecules to CD, but (to reiterate) each enantiomeric pair of diastereomers will have opposite-signed specific rotations.
- Example structure determination: Diacetyl.

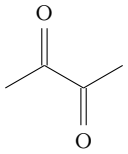


Figure 1.36: Diacetyl.

  - EA: C_2H_3O (MW = 43).
  - MS: 86, 43.
    - Larger mass is the parent peak!
    - With EA, this tells us that the molecular formula is $C_4H_6O_2$.
  - ^{13}C NMR: 200, 20.
    - 4 carbons but only 2 signals implies symmetry.
    - One alkyl peak and one carbonyl peak.
  - ^{1}H NMR: 1 singlet (6H).
    - This means you have 2 CH_3's, 3 CH_2's, or 6 CH's.
    - 6 CH's is impossible because that's too many carbons!
    - 3 CH_2's is also not possible.
    - Diacetyl is possible; in fact, diacetyl's ability to cleave symmetrically into acylium ions explains the MS peaks!
- Example structure determination: Determine the product.

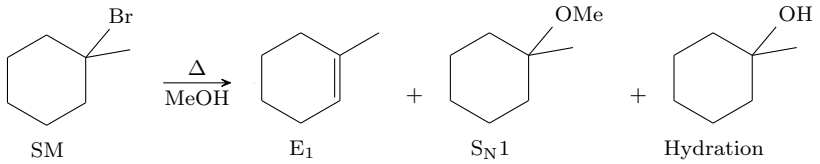


Figure 1.37: Characterizing the products of a chemical reaction.

  - We begin by predicting the products that will result upon heating the 1-bromo-1-methylcyclohexane starting material (SM) in methanol.
    - E_1 elimination is one thing that could happen.
    - S_N1 substitution of the methanol solvent is another thing that could happen.
    - And if your methanol is somehow contaminated with water, hydration could also happen (S_N1 mechanism as well, just with a different nucleophile).

- What key signals can we look for to differentiate these 3 structures in our product mixture?
- MS.
  - $[M]^+$ and $[M+2]^+$ peaks of equal height is characteristic of bromine, and hence unreacted SM.
  - The most stable fragment for the SM is the tertiary carbocation formed by cleaving the C–Br bond.
  - The most stable fragments for both E_1 and S_N1 have the same mass as the parent peak.
    - ➢ We form an allylic carbocation from E_1 by cleaving the ring β to the alkene.
    - ➢ We form an oxygen-stabilized carbocation from S_N1 by performing α-cleavage adjacent to the ether and then stabiliing the primary carbocation with one of the oxygen's lone pairs.
  - Thus, the bromine-containing SM is the only compound that can truly be distinguished from the other four using MS alone.
- IR.
  - E_1's C=C bond is unique among the four compounds.
  - The hydration product's O–H stretch will likewise be unique.
- ^{13}C NMR.
  - S_N1's ether methyl peak is unique among the four compounds.
  - We can also pick up on E_1's C=C bond here.
- ^{1}H NMR.
  - E_1's proton off the vinyl group is unique.
  - We can also pick up on S_N1's ether methyl peak here.
  - We can also pick up on the hydration product's O–H stretch here.

1.8 Review for Exam 1

9/23:

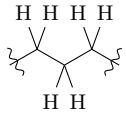
- Lecture 7 recap: Determining the products in Figure 1.37.
  - When you run a reaction (as in Figure 1.37), how do you know what your products are?
    - To answer such questions, chemists use a suite of structure determination techniques!
    - Examples include EA, MS, IR, ^{13}C NMR, and ^{1}H NMR.
  - EA: Can give us the empirical formulae of the compounds.
    - EA takes a while to run, so it might not be our first tool, but it can be useful.
  - MS: Can identify the ^{79}Br and ^{81}Br peaks in the SM.
  - IR: Can identify the O–H and C=C peaks where present.
  - ^{13}C NMR: Can identify the C=C bonds, and some symmetry differences (by number of peaks).
  - ^{1}H NMR: Can identify the C=C and O–Me fragments where present.
    - Recall that this is sometimes our most powerful method.
- Today: Review for Exam 1.
- Lecture outline.
  - Exam logistics and tips.
  - Review (EA → MS → IR → ^{1}H NMR → ^{13}C NMR).
  - Practice problems.

- Exam logistics.
  - Wednesday, 12-1pm in 50-340 (the third floor of the Walker Memorial).
  - Exam starts a 12:05pm on the dot!!
- Study techniques.
  - Study by practicing.
    - This unit is not about reciting information, but about applying techniques.
    - Try timing yourself on the practice exams to get a feel for what it's like to do structure determination problems under a time crunch.
  - Familiarize yourself with the reference material.
    - Know how to look stuff up!
    - Don't waste seconds or minutes searching for information because the first time you're seeing the reference sheets is when you take the exam.
  - Prof. Elkin's test-taking strategy: Go through the exam quickly first, answering what you can right away. Then go back a second time to ensure your answers are consistent with *all* the data.
- Will ^{1}H NMR peaks be labeled, e.g., with their splitting, coupling constant, and integration?
  - There will be some problems where more data is given, and some where less data is given.
- EA review.
  - Combust organic compounds into CO_2 and H_2O.
  - This provides the empirical formula.
- MS review.
  - Identify key atoms (use the parent peak): Cl, Br, and N.
  - Identify key fragments: Stable-ish cations.
  - Watch for common mass differences ($-$Me, $-H_2O$, etc.)
    - Don't do too much math on your calculator! Just look for *common* differences.
- IR review.
  - Key regions: X$-$H, *sp*, and X$=$Y.
  - Stronger bonds have a higher ν (cm^{-1}).
- ^{1}H NMR review.
  - Key regions of chemical shift.
    - A general rule is that more EWGs yields a more downfield/deshielded/to the left peak.
  - Consider integration and symmetry.
  - Coupling (shape and J value) tell us about connectivity.
- ^{13}C NMR review.
  - Key regions of chemical shift.
  - The number of peaks tells us about symmetry.
- Are we responsible for book information or just what was presented in class?
  - Yes and no.
  - You do need to read the textbook, because it explains class concepts in greater depth (specifically, the depth we're expecting you to know).
  - However, we're not going to try to ask "gotcha" questions on specific things in the textbook.

- Example structure determination: 1,1-dichlorocyclobutane.

Figure 1.38: 1,1-dichlorocyclobutane.

  - Given data.
    - EA: C_2H_3Cl.
    - ^{13}C NMR: 84.1, 46.6, 15.4.
    - ^{1}H NMR: 2.94 (t, $J = 7.6\,\text{Hz}$, 4H), 2.15 (pentet, $J = 7.6\,\text{Hz}$, 2H).[14]
  - Let's start by deducing the molecular formula.
    - How can we do this if we don't have MS data?
    - Instead, sum the ^{1}H NMR integrations to learn that the molecule has 6H total. Thus, since the empirical formula has only 3H, we must double the empirical formula to get $C_4H_6Cl_2$.
  - Let's now look for the presence of symmetry in the molecule.
    - Even though the molecule has 4 carbons, there are only 2 proton peaks — and their matching J values indicate that the protons in the peaks couple to each other.
    - Additionally, since the 2.94 triplet integrates to *four* protons, this peak probably corresponds to 2 sets containing 2 chemically equivalent protons each. Indeed, the only time when four protons are located on the same carbon is in methane!
  - This analysis of the ^{1}H NMR data can be used to draw the following molecular fragment.



    - The bottom two protons correspond to the pentet, since they are split by the other four (chemically equivalent) protons.
    - The other four protons are, in turn, split into a triplet by the two pentet protons.
  - Having constructed the above fragment, we only have one carbon left in our molecular formula.
    - We must maintain symmetry, so we can't just add it to one side or the other of the above fragment.
    - If we can't add it to one side or the other, we must add it to both! That is, let's close this fragment into a cyclobutane ring.
    - Then the last two atoms we have are the two chlorines, and we can bond these to the new carbon to fill its octet, include them in the molecule, and eliminate the possibility of any hydrogens on this last carbon interfering with the splitting of the other two sets of hydrogens.
  - Sanity check: Does this molecule match the ^{13}C NMR peaks?
    - It is a symmetric molecule with only three chemically unique carbon positions, so we expect three peaks (which we see).
    - We expect one of these peaks to be in the R–X region ($50 - 100\,\text{ppm}$), which we see.
    - We expect the other two peaks to be in the alkyl region ($0 - 50\,\text{ppm}$), with one significantly more downfield than the other due to the nearby chlorine EWGs. We see this, too.
  - Therefore, since 1,1-dichlorocyclobutane was deduced from our data and matches it all, we can be fairly confident that it is the right structure.

[14] Pentets are also sometimes referred to as quintets.

- Example structure determination: Dimethoxyethane.

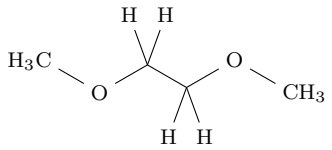


Figure 1.39: Dimethoxyethane.

  - Given data.
    - EA: C_2H_5O.
    - MS: 90, 45.
    - ^{13}C NMR: 71.3, 59.3.
    - ^{1}H NMR: 3.55 (s, 4H), 3.40 (s, 6H).
  - As before, let's start by deducing the molecular formula.
    - Via ^{1}H NMR: 10H total, so double the empirical to $C_4H_{10}O_2$.
    - Via MS: C_2H_5O has a mass of 45, so double the empirical to $C_4H_{10}O_2$ (mass 90).
  - Key signals.
    - The ^{1}H NMR peak at 3.40 ppm has an integration of 6H, so it likely corresponds to two chemically equivalent methyl groups. Additionally, the relatively downfield chemical shift (and lack of splitting) indicates that the methyl groups are coordinated to a heteroatom.
      - ➢ From the molecular formula, the heteroatom would have to be oxygen!
      - ➢ This means that our molecule contains two methoxy () groups.
    - The ^{1}H NMR peak at 3.55 ppm has an integration of 4H, so it likely corresponds to two chemically equivalent CH_2 groups. As before, its relatively downfield chemical shift (and lack of splitting) also indicates coordination to oxygen.
      - ➢ This means that our molecule also contains two groups that look like this: 
  - Now how do we couple the fragments?
    - The methoxy groups must go at either end of the molecule, and this forces coordination to an additional CH_2 past the oxygen. Now we have two fragments that look like this: 
    - Since this consists of all atoms, the only thing left to do is combine these two fragments to make the molecule in Figure 1.39 — in spite of the fact that this appears to bring protons that we *know* don't couple right next to each other.
    - However, looking at the full molecule, we can observe that it has rotational symmetry! (In other words, if you rotate the molecule 180° in the plane of the page, you get the same molecule.) This explains the lack of coupling: All four protons in the center of the molecule are actually chemically equivalent, and adjacent but chemically equivalent protons don't couple each other!
  - Sanity check: Could this molecule fragment to give the right MS peaks?
    - Yes!
    - The molecular ion would give rise to the parent peak at 90.
    - Cleavage of the central C–C bond would break the molecule in half, yielding a resonance-stabilized fragment half the weight of the molecule (i.e., $m/z = 45$).

- When do we need to take long-range coupling into account?
  - It is oftentimes very small, and we can't really see it on low-resolution NMR machines.
  - Mainly, you should know that it exists, but you should not expect too many examples of it on the exam.

- Example structure determination: Isobutyl acetate.

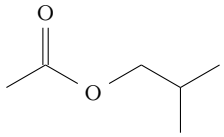


Figure 1.40: Isobutyl acetate.

  - Given data.
    - Molecular formula: $C_6H_{12}O_2$.
    - IR: 1746.
    - ^{13}C NMR: 170.2, 70.4, 27.6, 20.7, 19.4.
    - ^{1}H NMR: 3.76 (d, $J = 7.0\,\text{Hz}$, 2H), 2.04 (s, 3H), 1.97 (triplet of septets, $J = 7.0, 6.8\,\text{Hz}$, 1H), 0.95 (d, $J = 6.8\,\text{Hz}$, 6H).
  - Key signals.
    - The sole IR stretch and most downfield ^{13}C NMR peak both suggest a carbonyl: 
    - The second most downfield ^{13}C NMR peak and 3.76 ppm ^{1}H NMR peak combine to suggest a carbon adjacent to a heteroatom and bearing 2 hydrogens: 
      - ➢ Again, the molecular formula implies that the heteroatom would have to be oxygen: 
    - The two most upfield ^{1}H NMR peaks combine to suggest an isopropyl group: 
      - ➢ Indeed, in this isopropyl group, the drawn proton will split all 6 methyl protons into a doublet, and the six chemically equivalent methyl protons will split the drawn proton into a septet (the triplet part must then come from additional protons vicinal to the fragment).
    - The last remaining ^{1}H NMR peak (2.04 ppm) suggests a methyl group:
  - We can now hijack the J values to find out exactly how to assemble these fragments.
    - The two methyl groups in the isopropyl group have $J = 6.8\,\text{Hz}$.
    - Thus, they are coupled to the other proton(s) with $J = 6.8\,\text{Hz}$. We can see that this is the sole proton in the triplet of septets, which corresponds to the hydrogen in the isopropyl group, as we would expect. This hydrogen also couples to some other group with $J = 7.0\,\text{Hz}$.
    - The other group with $J = 7.0\,\text{Hz}$ is the peak at 3.76 ppm, and which corresponds to the fragment. Therefore, we can join these two fragments to create: 
    - At this point, we've used everything except the methyl group and the carbonyl. But the only way to include both of these is to bond the carbonyl to the above fragment and then the methyl to the carbonyl. This bonding will yield the final structure in Figure 1.40.
  - Sanity check: Do the protons and carbons in isobutyl acetate have the chemical shifts we'd expect based on their position in the molecule?

^{1}H NMR	Region
3.76	α-heteroatom
2.04	alkyl
1.97	alkyl
0.95	alkyl

(a) ^{1}H NMR.

^{13}C NMR	Region
170.2	carbonyl
70.4	α-heteroatom
27.6	alkyl
20.7	alkyl
19.4	alkyl

(b) ^{13}C NMR.

Table 1.6: Correlating isobutyl acetate's NMR peaks and functional groups.

        - Per Table 1.6, yes!
        - Note: The 2.04 ppm peak corresponds to the methyl group α to the carbonyl.
        - Note: The 1.97 ppm peak corresponds to the substituted proton β to the oxygen.
            - ➢ Recall from Lecture 4 that this hydrogen is relatively downfield because it's surrounded by "electronegative" carbon atoms!

- When does a peak display complex splitting, versus a "simple" doublet, triplet, quartet, etc.?
    - You're a "something of somethings" if you couple chemically distinct protons, and you're just a "something" if you only couple one type of chemically equivalent protons.

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

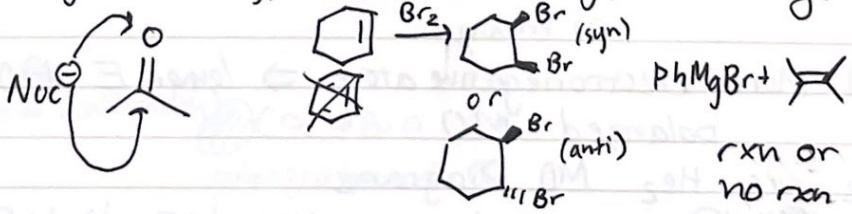
- You all did great
- "How did I do?"
  - 90-100 excellent
  - 80-90 good
  - <80 adequate, reach out
- exams hand back in recitations
- these guidelines are exam specific
  - ↳ first exam typically best
- You learned structure determination!

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

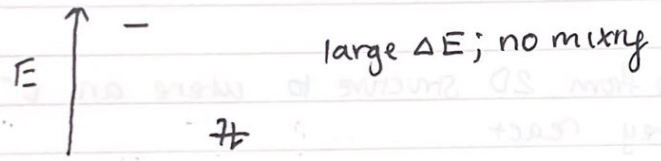
- review gen chem (5.11/5.12) & Orgo I (5.12)
- Clayden: ch. 4, 5, 6

27 Sept Lecture 10 : Cont

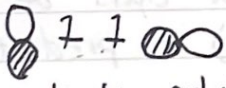
- orbitals are wavefunctions that describe the ability to find an electron in space
  ↳ they interact constructively & destructively

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



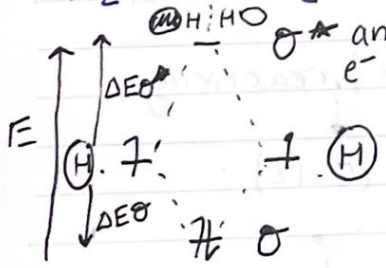
3. interacting orbitals must overlap efficiently and have similar ~~energy~~ symmetry



perpindicular orbitals
- poor overlap
- no mixing

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

H_2 vs He_2 MO Diagrams

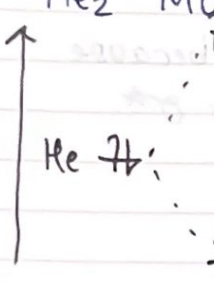


HOH
bonding; e⁻ in middle

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

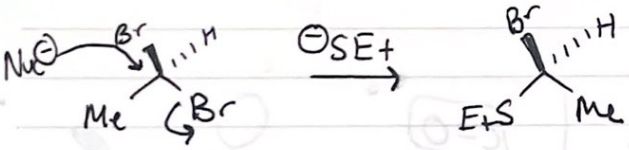
He_2 MO Diagram



- 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

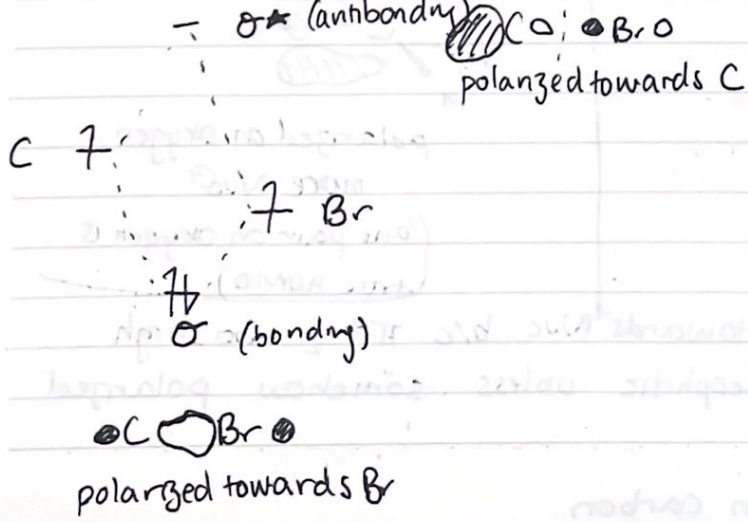


Why backside attack?
- identify HOMO & LUMO

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

DATE 27 Sept

Lecture 10: Cont

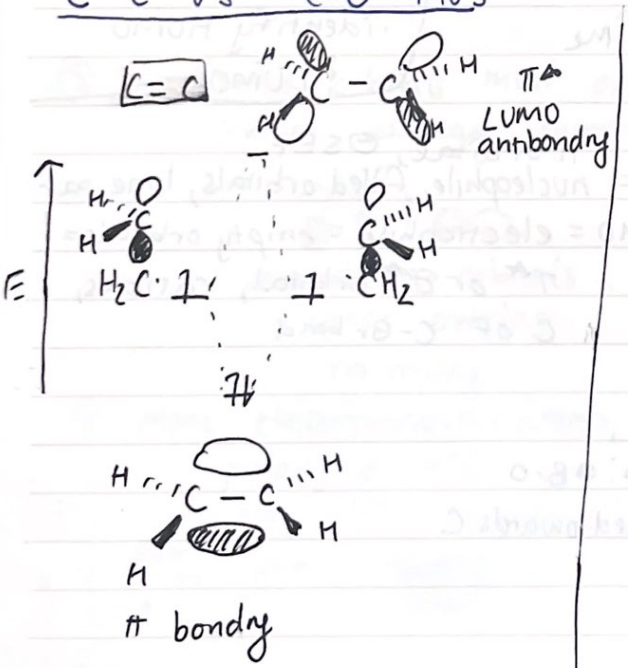
backside attack because there is a larger σ^* lobe there

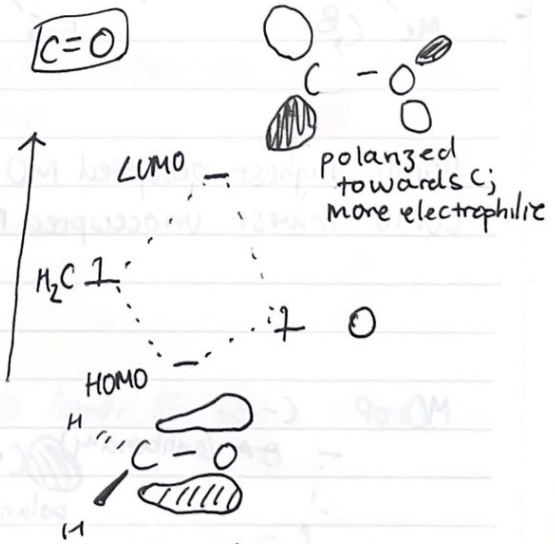
Meanwhile

σ bond breaks because σ^* populated

Our mechanistic arrows show this

C=C vs C=O MOs





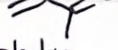
polarized on oxygen, more Nuc⊖

(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

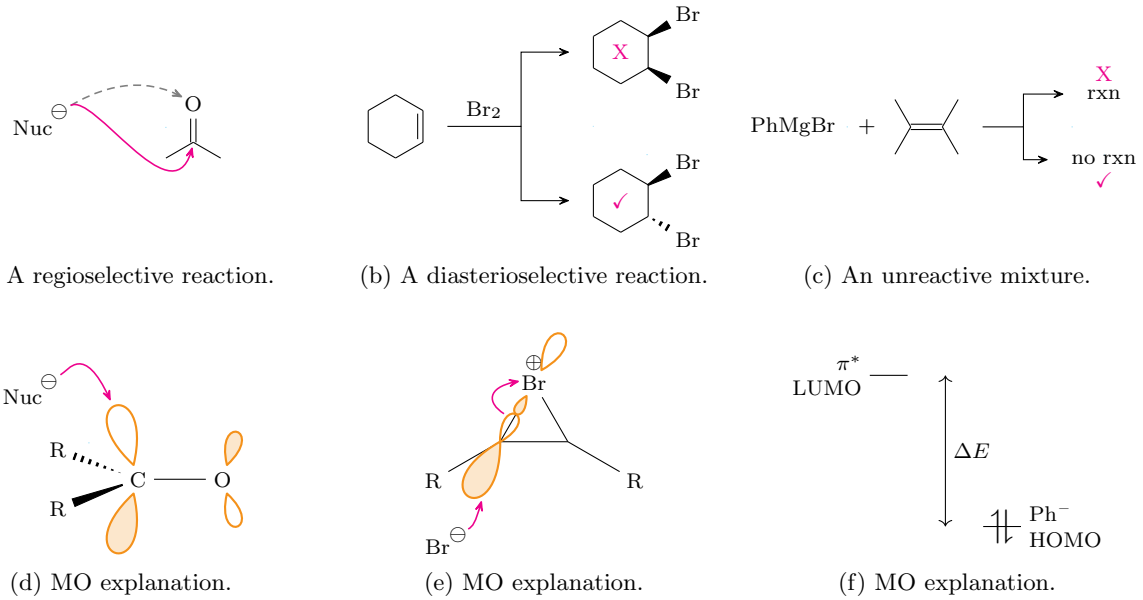
ex: 

C=O electrophilic on carbon

2.11 Molecular Orbital Theory - 2

9/30:

- Lecture 10 recap: What MO theory can explain.



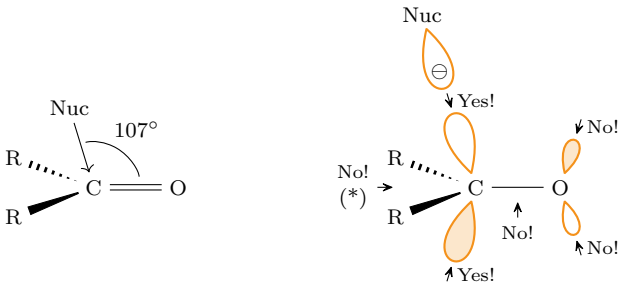
(a) A regioselective reaction. (b) A diasterioselective reaction. (c) An unreactive mixture.

(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.

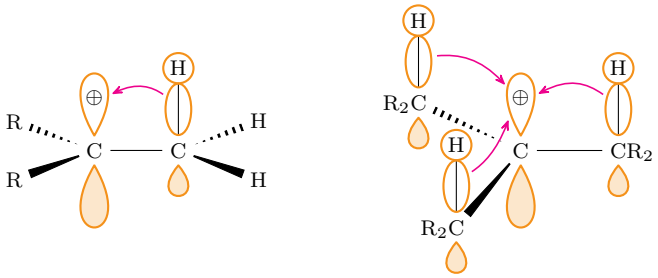
- Today: More MO theory.
- Lecture outline.
  - The Bürgi-Dunitz angle.
  - Hyperconjugation.
  - The anomeric effect.
  - Stereoelectronic effects and the rate of reaction.
- **Bürgi-Dunitz angle**: The angle at which nucleophiles typically add to carbonyls. *Given by* 107°.



(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.

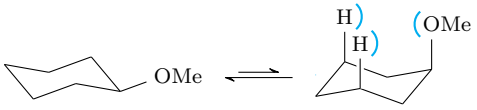
- **Hyperconjugation notation**: The concise method for denoting a certain hyperconjugative orbital interaction. *Given by*

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

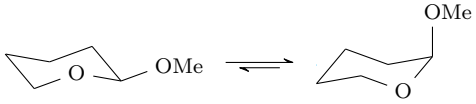
  - The arrow means "donates into."
    - Indeed, we always write the filled orbital first (before the arrow) and the empty orbital second (after the arrow).
  - Possible orbitals: $\sigma, \sigma^*, \pi, \pi^*, p, n$.
    - Note that n denotes a nonbonding lone pair.

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

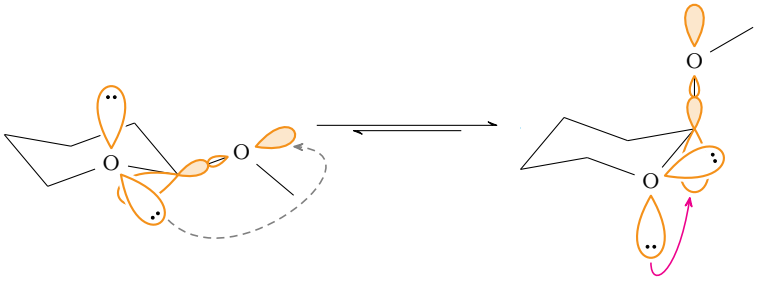
- Let's break this rather complicated definition down through an example.



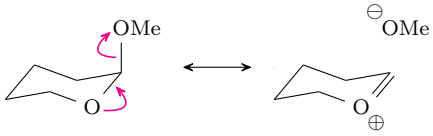
(a) Sterics win in methoxycyclohexane.



(b) Anomeric wins in 2-methoxytetrahydropyran.



(c) MOs explain the anomeric effect.



(d) Resonance explains the anomeric effect.

Figure 2.4: Anomeric effect.

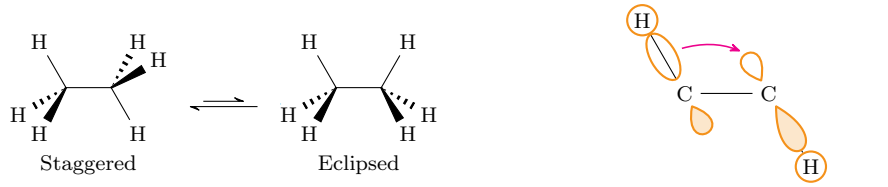
[1] This is pronounced "sigma C–H to p C donation" or (very explicitly) "sigma see aech to pee see donation."

- 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.



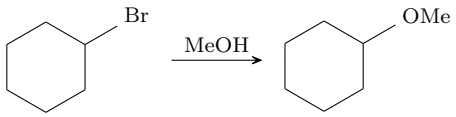
(a) Ethane's conformers.

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

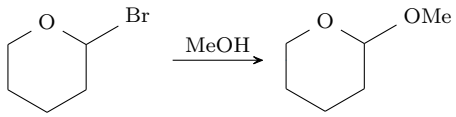
Figure 2.5: Hyperconjugation stabilizes staggered ethane.

  - 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.

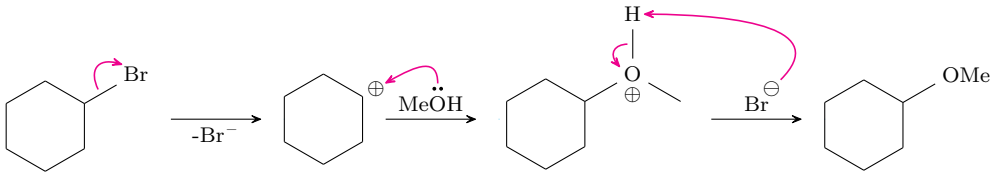
- Example: Stereoelectronic stabilization can accelerate reactions.



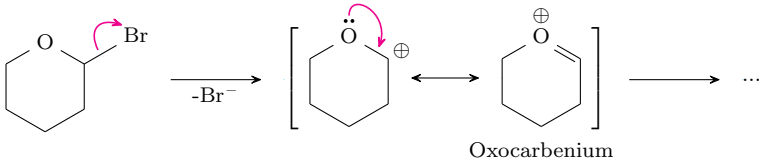
(a) S_N1 without an adjacent heteroatom.



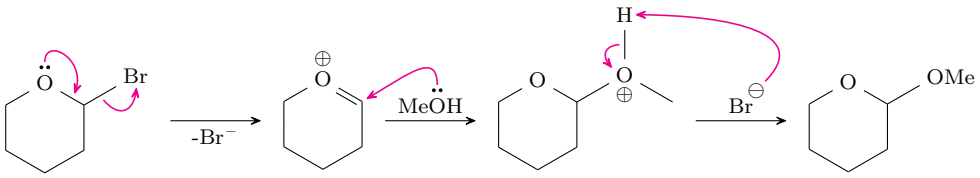
(b) S_N1 with an adjacent heteroatom.



(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.

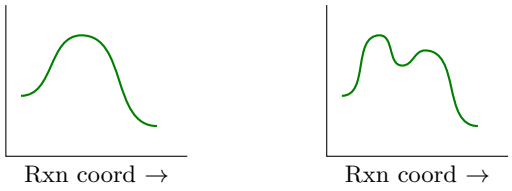
2.12 Pericyclics

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.

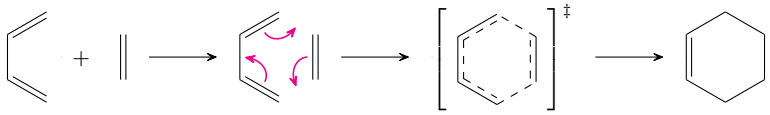


Figure 2.8: Diels-Alder reaction.

  - 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.

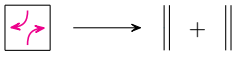
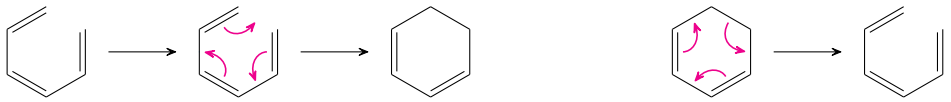


Figure 2.9: A cycloreversion.

  - 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.

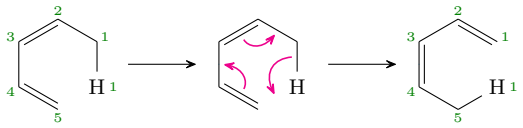


Figure 2.11: A $[1, 5]$ sigmatropic rearrangement.

  - 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.

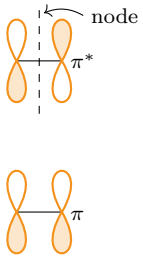


Figure 2.13: Nodes in π and π^* molecular orbitals.

  - 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.

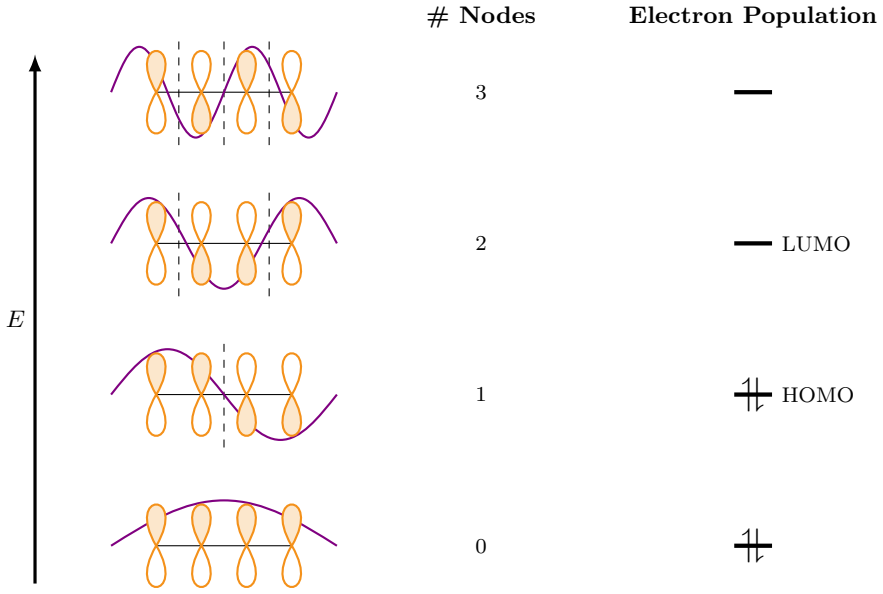


Figure 2.14: Reactive molecular orbitals of a diene.

- 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 ($h\nu$)!

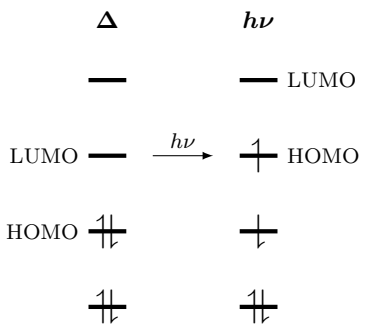


Figure 2.15: A diene's reactive orbitals in thermal vs. photochemical pericyclic reactions.

- 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.

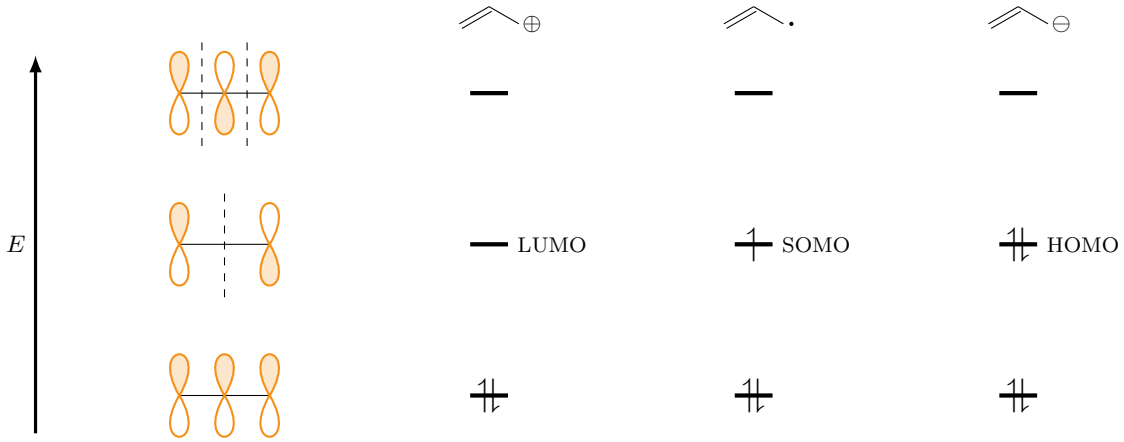


Figure 2.16: Reactive molecular orbitals of an allyl group.

- 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.

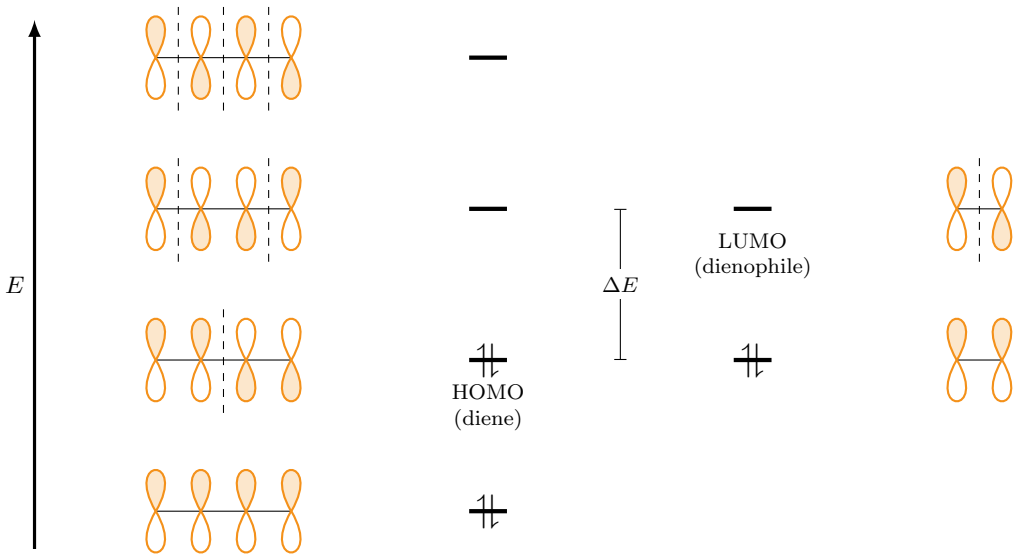
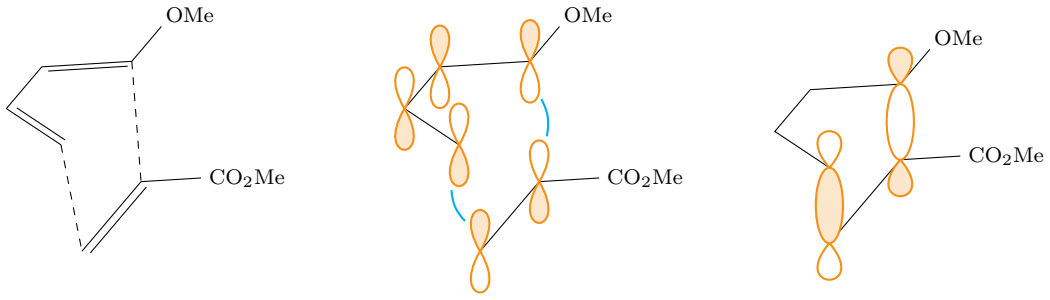


Figure 2.17: Reactive molecular orbitals in a Diels-Alder.

  - 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.



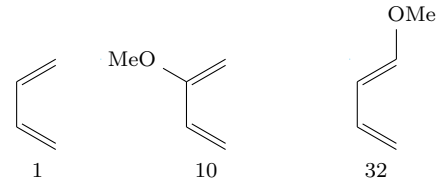
(a) Reactants. (b) Reactant orbitals. (c) Product orbitals.

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

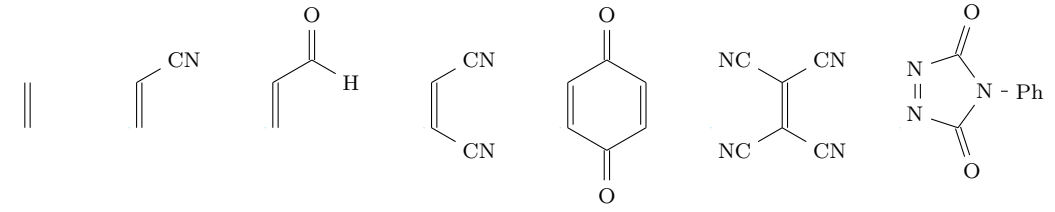
[5] Prof. Elkin reviews the three rules for drawing the MOs of conjugated systems; remember these!!

- 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.

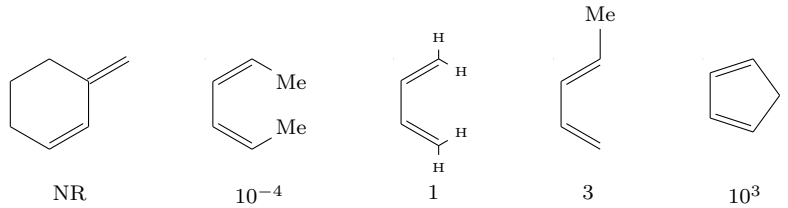
- Accelerating Diels-Alder reactions.



(a) Various dienes (electronic effects).



(b) Various dienophiles.

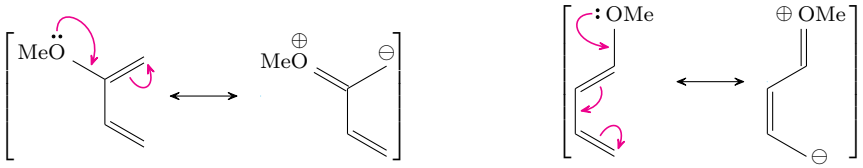


(c) Various dienes (steric effects).

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.

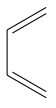


Figure 2.21: s-*cis* diene.

[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.

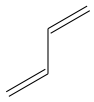
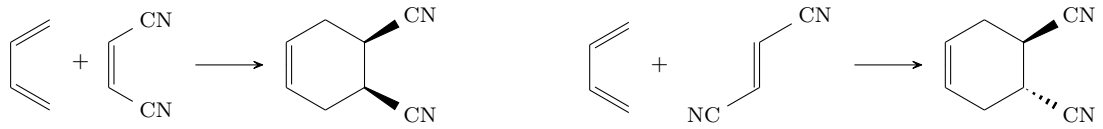


Figure 2.22: s-*trans* diene.

- 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*.

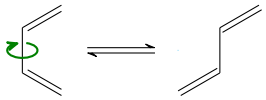


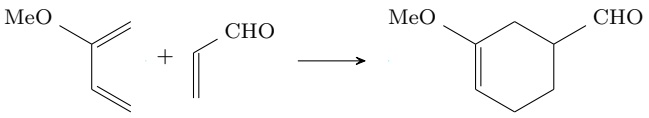
Figure 2.24: s-*cis* and s-*trans* conformers rapidly interconvert.

  - 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.

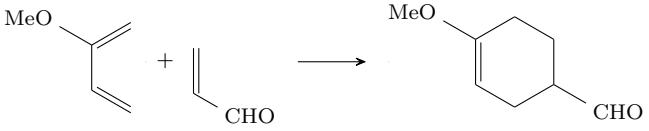
- **Stereospecific** (reaction): A reaction in which the stereochemistry of the reactants translates directly into a single stereochemical product.
- **Stereoselective** (reaction): A reaction in which when a certain stereochemical product is favored, but a mixture is still produced and the stereochemistry 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**.

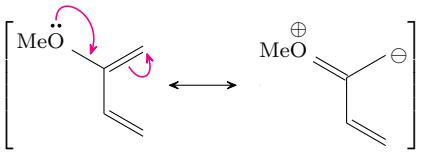
- Regioselectivity.



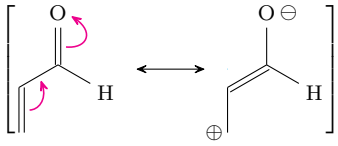
(a) *meta*-product.



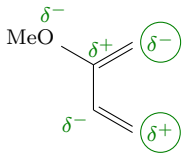
(b) *para*-product.



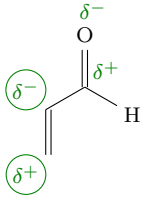
(c) Diene (resonance).



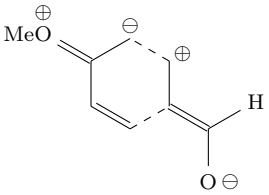
(d) Dienophile (resonance).



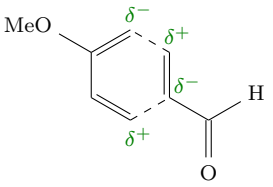
(e) Diene (hyperconjugation).



(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

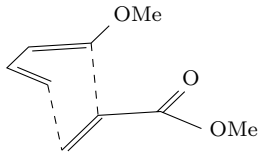
10/7:
- Lecture 13 recap.
  - Corrections to Lecture 13.
    - The word "Diels-Alder" usually has a hyphen; it is *not* written "Diels Alder" with a space.
    - The methyl-activated diene in Figure 2.19c is faster because of *electronics*, not sterics.
      - ➢ Indeed, this diene has the same steric 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 :)

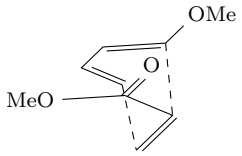
        - Definitions of **stereoretentive**, **stereospecific**, and **stereoselective** reactions.
    - Recap of regioselectivity.
        - Prof. Elkin redraws Figure 2.25h as a method of predicting the *para*-product (Figure 2.25b).

- **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.

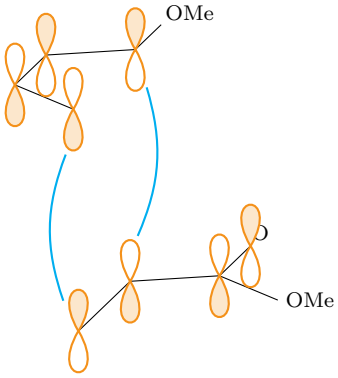
- *exo* vs. *endo* transition states.



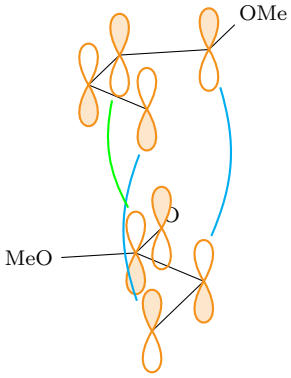
(a) *exo* transition state.



(b) *endo* transition state.



(c) *exo* orbitals.

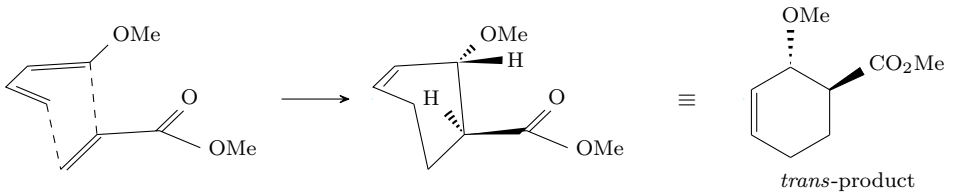


(d) *endo* orbitals.

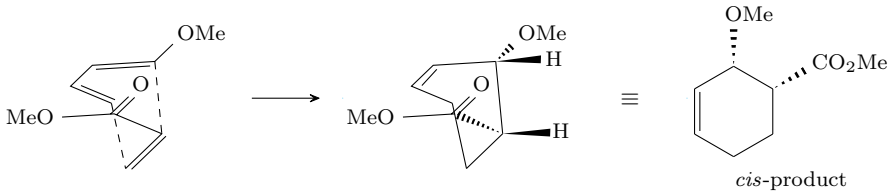
Figure 2.26: *exo* vs. *endo* transition states in the Diels-Alder.

  - 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.

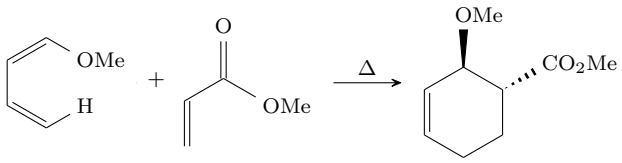


Figure 2.28: Diels-Alder reaction of (*Z*)-1-methoxybuta-1,3-diene and methyl acrylate.

  - 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?

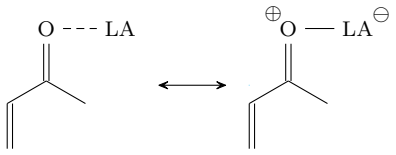


Figure 2.29: Lewis acid catalysis of Diels-Alder reactions.

  - 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.

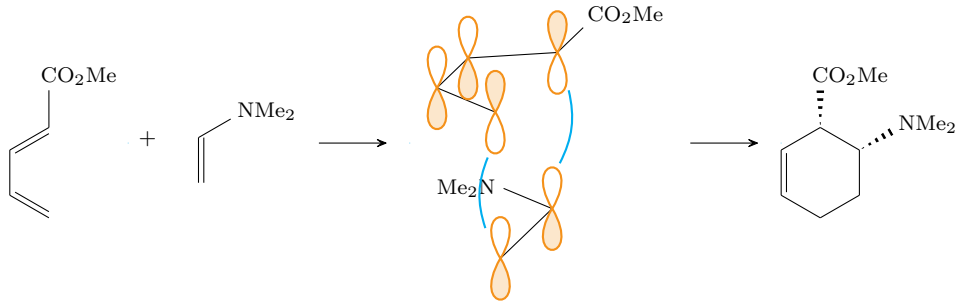
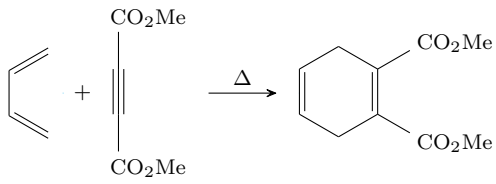


Figure 2.30: Diels-Alder reaction with inverse electron-demand.

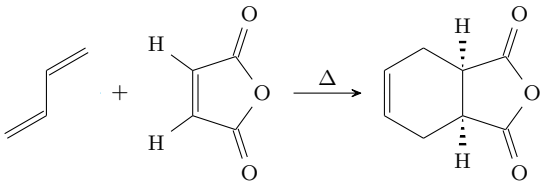
  - Because of the methyl ester EWG, the diene in Figure 2.30 is now electron-poor.
    - As such, it will react with its LUMO (the third energy level in Figure 2.14).
  - Because of the amine EDG, the dienophile in Figure 2.30 is now electron-rich.
    - As such, it will react with its HOMO (the first/lowest 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!

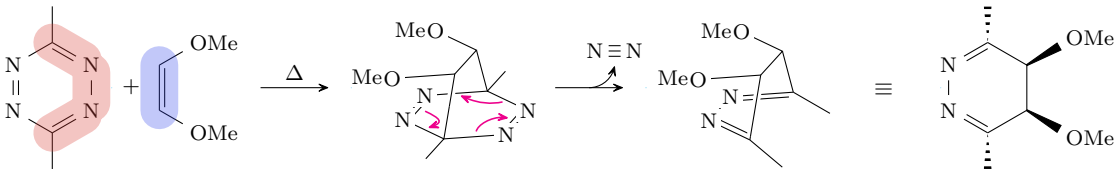
- More example Diels-Alder reactions.



(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**.

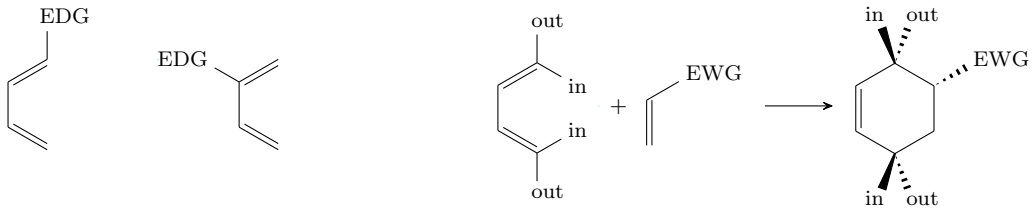
- **Tetrazine**: A molecule with a central six-membered aromatic ring containing four nitrogen atoms.
- **Diazine**: A molecule with a central six-membered aromatic ring containing two nitrogen atoms.

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*

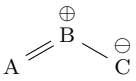


Figure 2.33: Dipole.

  - 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.

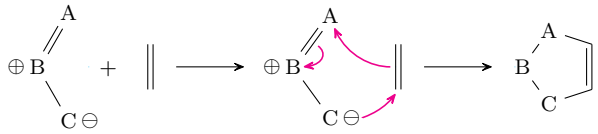
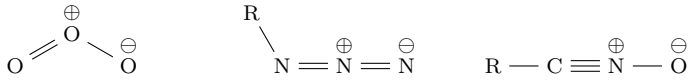


Figure 2.34: Dipolar cycloaddition.

  - 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.



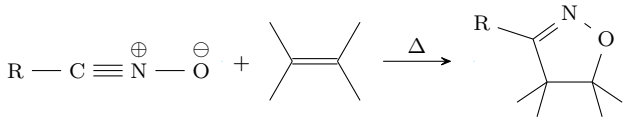
(a) Ozone. (b) Azide. (c) Nitrile oxide.

Figure 2.35: Examples of dipoles.

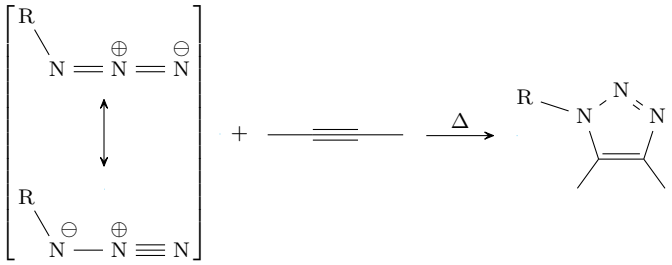
1. **Ozone**.
2. **Azide**.
3. **Nitrile oxide**.

- **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.

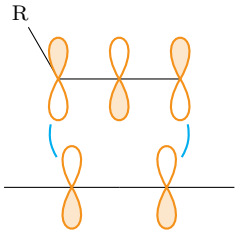


Figure 2.37: Dipolar cycloaddition orbitals in 3D space.

  - 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.

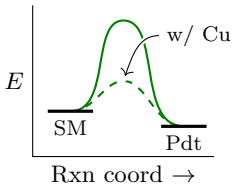
  - So, without loss of generality, let's suppose our dipole reacts with its LUMO.
    - Per Figure 2.35b, the Lewis structure for the azide has two π-bonds (which naturally contain four total electrons) along the three-atom-long dipole.
    - Thus, when we're making molecular orbitals, we should consider 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.

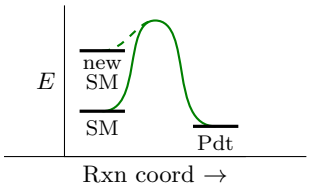
- **Chemoselective** (reaction): A reaction between molecules that only react with each other, even in the presence of related functional groups.
  - Chemoselective reactions are essential for certain biological applications.
    - Imagine you have two molecules in a cell that you want to join together, 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.

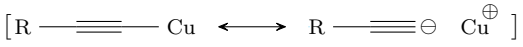
- For the reaction to be able to be run at room temperature, we needed to make the reaction even more highly reactive. There are two approaches that met this goal.



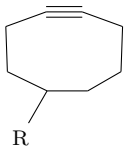
(a) Copper-catalyzed energy diagram.



(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.

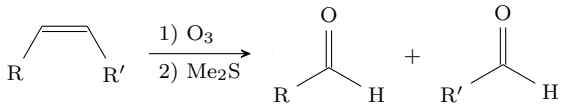
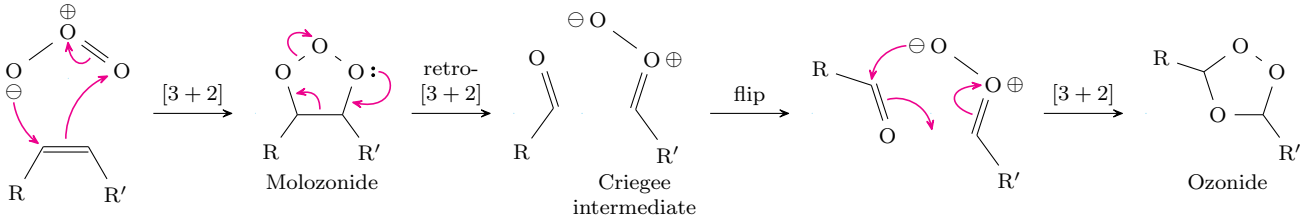
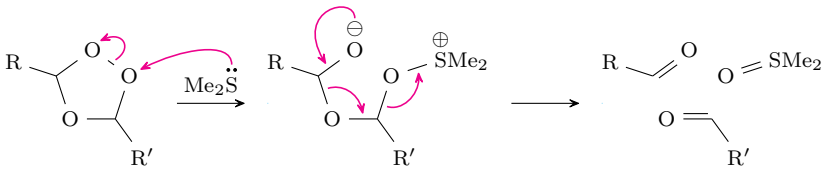


Figure 2.39: Ozonolysis.

  - 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.

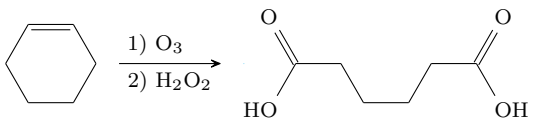


Figure 2.41: An alternate ozonide reaction.

  - 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.

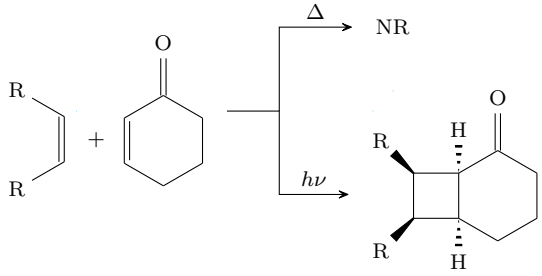
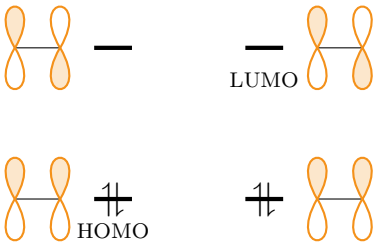
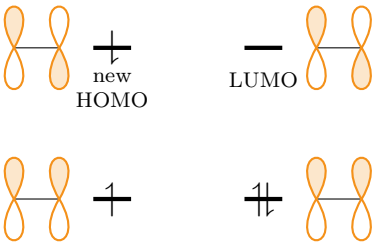


Figure 2.42: $[2+2]$ cycloaddition.

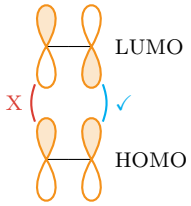
- Why $[2+2]$ cycloadditions *must* be photochemical instead of thermal: MO theory!



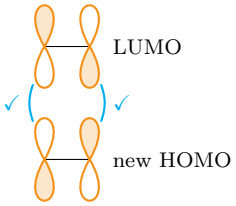
(a) Thermal $[2+2]$ MOs.



(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.

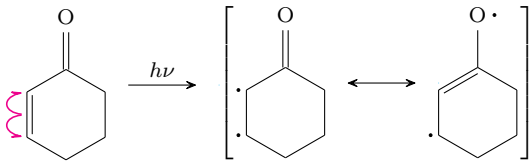


Figure 2.44: Systems with more stable excited states preferentially absorb light.

  - 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!!

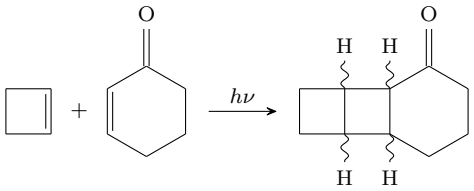
- Looking ahead (Friday).
  - We will begin with a bit more content on cycloadditions that we could not get to today.
  - After that, we will cover electrocyclizations.
  - It's going to be a long lecture, but you'll have the weekend to digest it.

2.16 Electrocyclizations

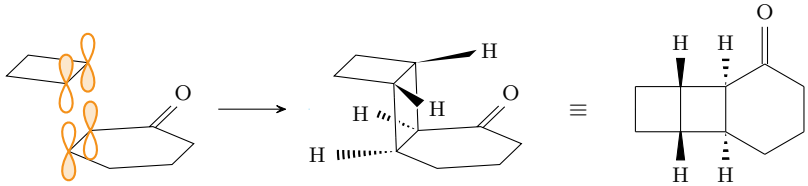
10/11:

- 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.



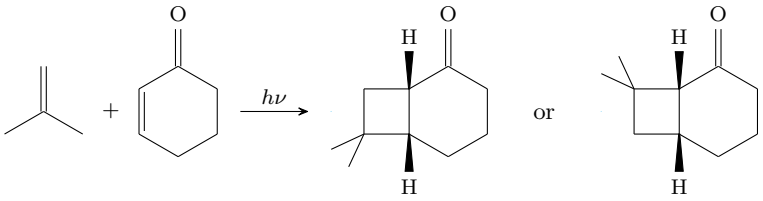
(a) A [2 + 2] cycloaddition.



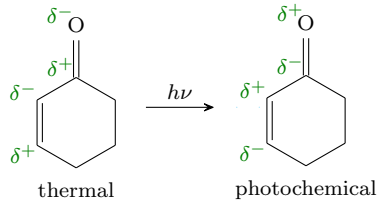
(b) *exo* pathway.

Figure 2.45: [2 + 2] cycloaddition stereochemistry.

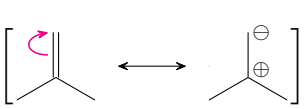
  - Consider the [2 + 2] cycloaddition in Figure 2.45a.
    - Last time, we learned that such a reaction yields the product shown, but we haven't yet discussed the relative stereochemistry of the four hydrogens.
    - Note that wavy lines mean "undefined stereochemistry."
  - Unlike [4+2] (Diels-Alder) 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.



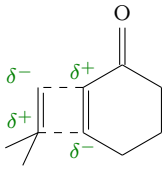
(a) Possible products of an asymmetric [2 + 2] cycloaddition.



(b) Partial charges (enone).



(c) Resonance (alkene).



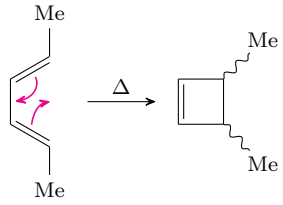
(d) Matching partial charges.

Figure 2.46: [2 + 2] cycloaddition regiochemistry.

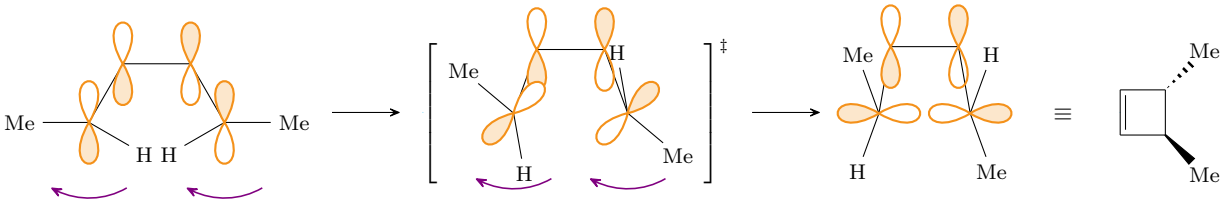
[11] Note that we did not talk about the stereochemistry of dipolar cycloadditions because they are *not* stereoselective: A fairly even balance of secondary orbital interactions with sterics makes the stereochemistry of dipolar cycloadditions very hard to predict.

  - 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.

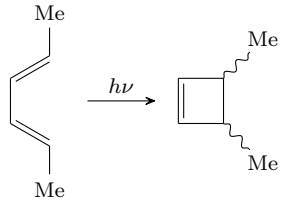


(b) Conrotatory pathway.

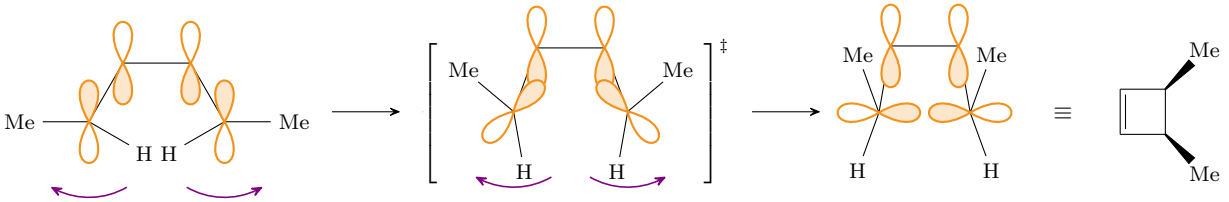
Figure 2.47: Thermal 4π electrocyclization.

- 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.

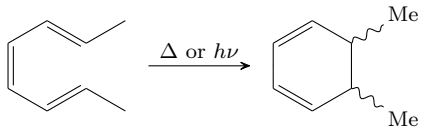
$\#\,\mathbf{e^-}$	$\boldsymbol{\Delta}$	$\boldsymbol{h\nu}$
$4n$	con	dis
$4n+2$	dis	con

Table 2.1: Woodward-Hoffmann rules.

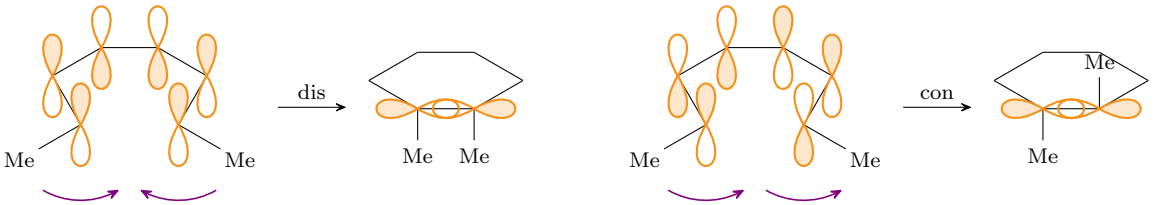
  - Aside (chemis-tea): Who was R. B. Woodward?
    - R. B. Woodward was an MIT alum, even though he failed out after his freshman year.
    - He was readmitted though, and after graduating, he went on to become our most famous synthetic organic chemist.
    - He won a Nobel Prize and would have won a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

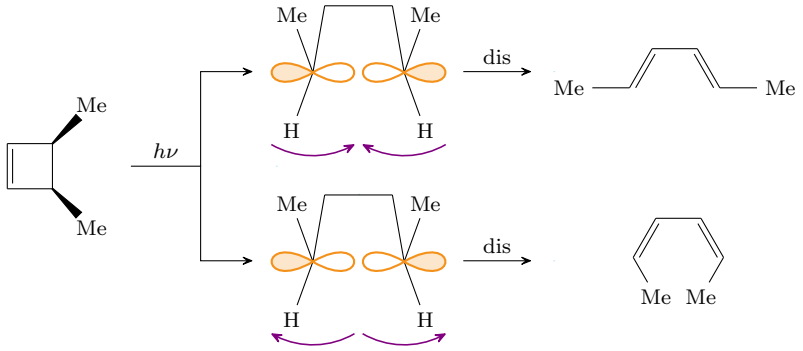


(b) Thermal product (disrotatory). (c) Photochemical product (conrotatory).

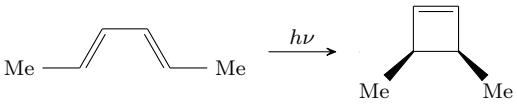
Figure 2.49: Thermal and photochemical 6π electrocyclizations.

  - 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!

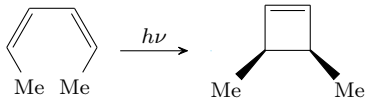
- Example: Retro-4π electrocyclization.



(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.

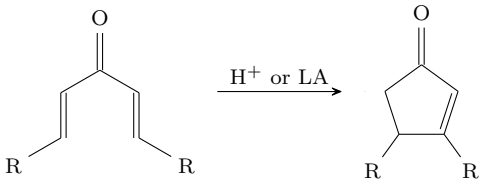


Figure 2.51: Nazarov cyclization.

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

- Mechanism.

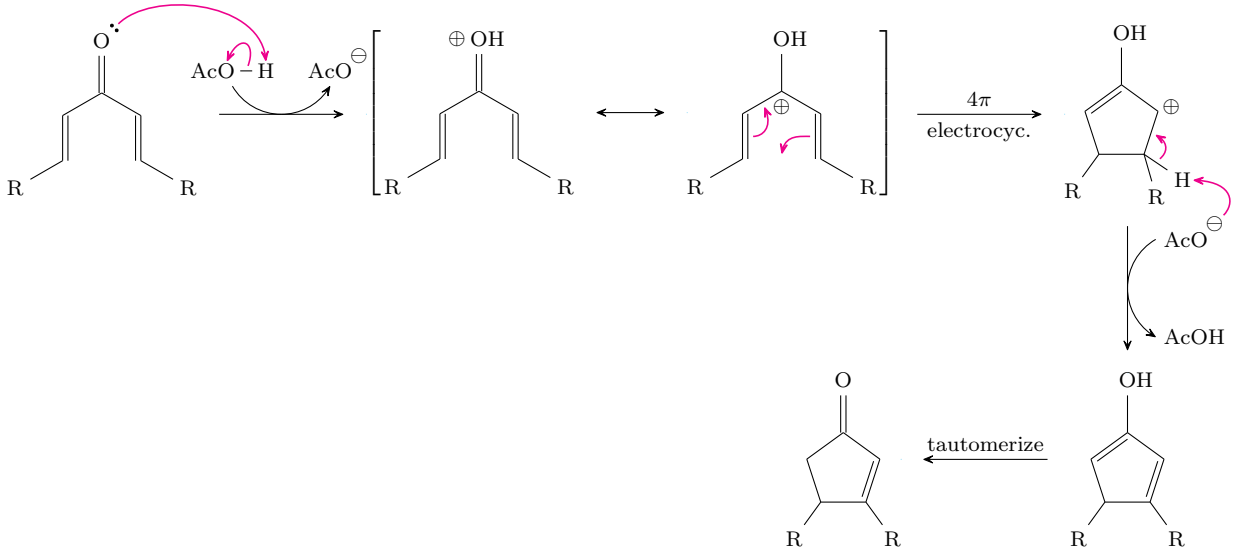


Figure 2.52: Nazarov cyclization mechanism.

  - 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.

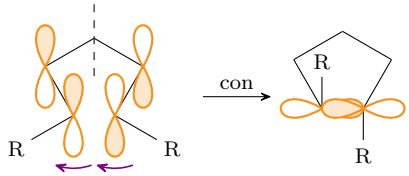


Figure 2.53: Nazarov cyclization stereochemistry.

  - 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.

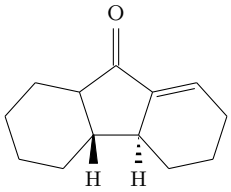


Figure 2.54: Alternate deprotonation sites in Nazarov cyclizations.

  - 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.

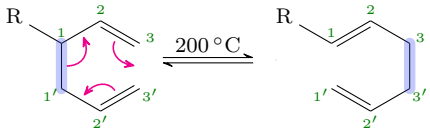
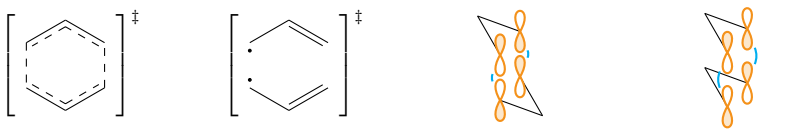


Figure 2.55: Cope rearrangement.

  - 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.

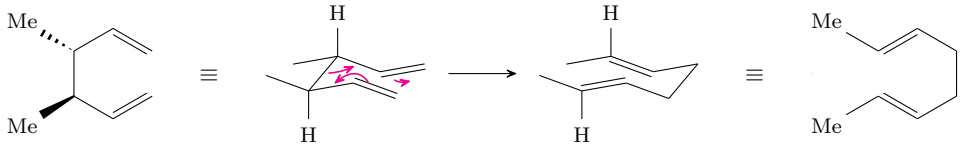
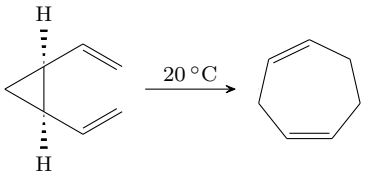


Figure 2.57: Cope rearrangement stereochemistry.

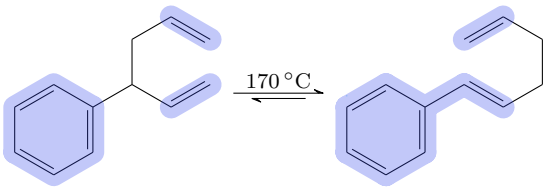
- The Cope rearrangement is stereospecific.
  - Indeed, just like the Diels-Alder (see Figure 2.23), the stereochemistry of the reactant translates directly into whether the product has *cis*- or *trans*-olefins.
- To determine the (major[14]) product, draw the starting material in the most stable chair 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!

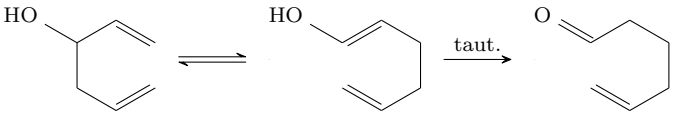
- As mentioned in Figure 2.55, the Cope rearrangement is an equilibrium reaction. But for it to be synthetically useful, we need to be able to drive the equilibrium toward starting materials or products. How can we do this?



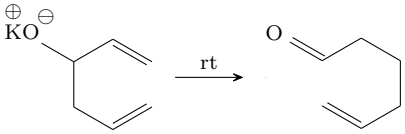
(a) Release of ring strain.



(b) Conjugate a product olefin.



(c) Oxy-Cope rearrangement.

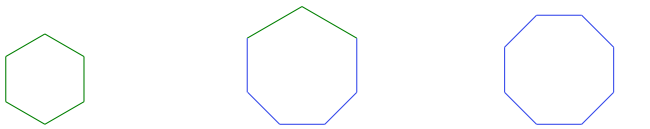


(d) Anionic oxy-Cope rearrangement.

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.

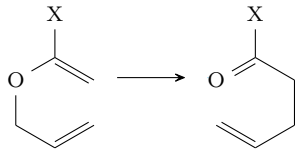


Figure 2.60: Claisen rearrangement.

  - 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.

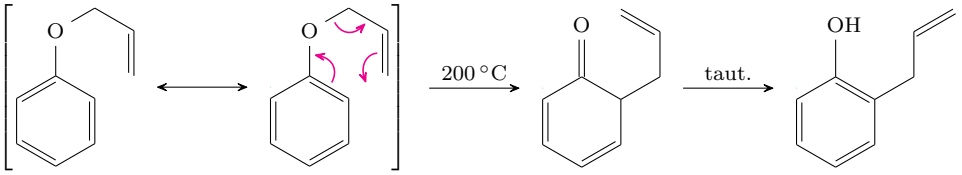


Figure 2.61: Claisen rearrangement of allyl phenyl ether.

  - 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.

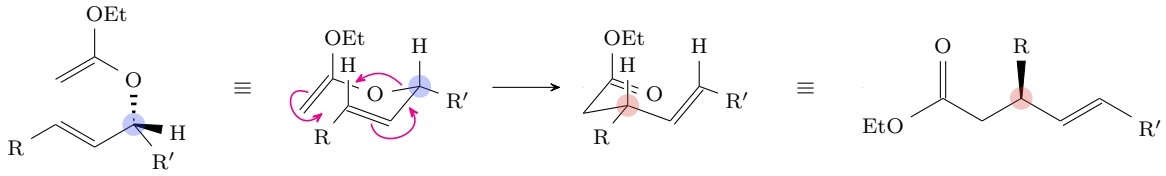


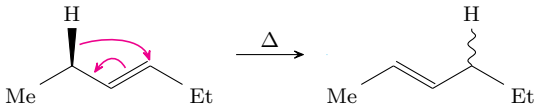
Figure 2.62: Claisen rearrangement stereochemistry.

  - 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.

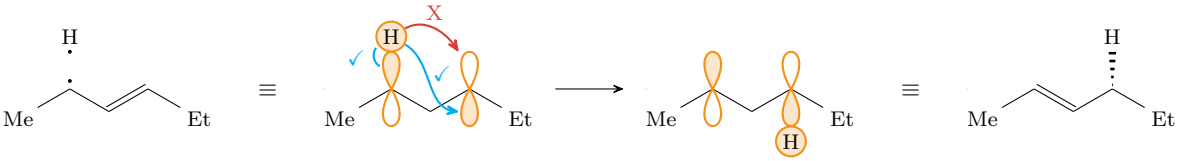
- This concludes our discussion of the Claisen rearrangement.

[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.



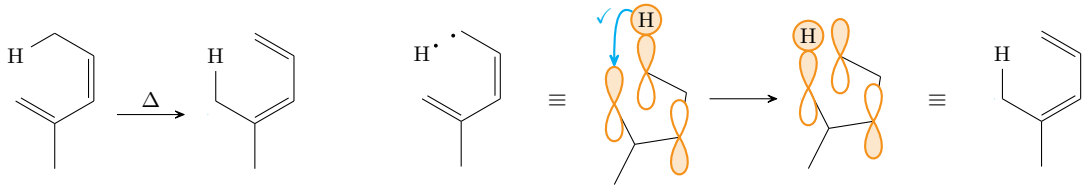
(a) A $[1,3]$ H-shift.



(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!!

Unit 3

Amines

3.20 Special Topics

10/23:

- Grade cutoffs on Exam 2.
  - A-B cutoff: 80.
  - B-C cutoff: 60.
  - C-D cutoff: 45
  - Only F's were people who did not take the exam.
  - This was a significantly harder exam; y'all have been crushing it so far.
  - Remember that these grades are meant to give you a perspective for what you're on track for; they are *not* binding!
- Notes on Steve Buchwald.
  - He's a real big-name chemist: Has his name on a ton of reactions, can make a ton of pharmaceutical drugs, does a lot of consulting for chemical companies, etc.
  - But also super kind, humble, and nice.
  - Knows a ton, but is very down-to-earth and approachable.
- The rest of this course will be much more synthesis-heavy.
  - Feel free to continue to reach out to Prof. Elkin even though she's no longer at the blackboards!
- Today: We'll have fun and talk about machine learning.
  - Prof. Elkin will go through Beker et al. (2018), a paper about using machine learning to predict the outcome of Diels-Alder reactions.
- The basic idea of what the authors are saying is that if you encode the substituents, you get good prediction of the outputs!
  - Your computer doesn't know what a molecule is, so you have to encode your molecule in a way that is meaningful to a computer.
  - For example: You should not encode benzene with alternating single- and double bonds; benzene has six equivalent bonds due to resonance!
- Nowadays, computers can predict biological activities (doesn't work perfectly yet, though great progress), solubility and crystal structures (works fine), NMR spectra (works awesome), etc.
  - Predicting optimal reaction conditions works awesome.

- Predicting reaction outcomes or yields can be hit or miss.
- There have been maybe 1 000 000 chemical reactions ever catalogued, but most of them are not that useful.
- The low-data regime of predictive modeling is the final frontier, and the especially important one for chemistry.
- Taking high-level expertise and making it algorithmically applicable can be really difficult.
- "High accuracies are achieved only if the machine is provided some chemical 'insight' about the reaction (in particular, information about the reaction's core and key substituents)."
- While ML models cannot provide the generality of quantum mechanics, they work much faster.
- They trained the model with inverse electron-demand Diels-Alder reactions, Diels-Alder reactions that need to be site-selective, etc.
- The website to help you predict Diels-Alders is historical at this point, so don't worry if you can't access it in the paper.
- There are several classes on computational chemistry in both Course 5 and Course 10 if you're interested!
- A problem with Reaxys: All of the reactions in the database are data-scraped from old papers, so a significant number of them are wrong or incomplete (20-30%, and worse in other databases).
- Predictive modeling really reveals how difficult it is to predict reaction outcomes: Prof. Elkin has published papers where their model can predict yield far better than even chemistry experts.
- Conclusion: ML can be useful in predicting outcomes and can generalize to unseen reactions when descriptors carrying physically relevant information are used, and the machine gets appropriately formatted information.
- Note: None of this is testable material!

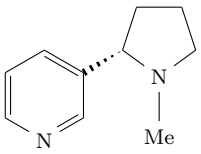
3.21 Amines - 1

10/25:

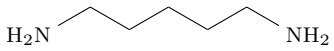
- New lecturer for the second half of the course: Prof. Steve Buchwald.
  - Born in Bloomington, Indiana.
  - Undergrad at Brown, PhD at Harvard, Postdoc at Caltech (with Bob Grubbs, a Nobel laureate).
  - At MIT for 40 years (since 1984).
  - Has two cats :)
  - Researches **organometallic chemistry**, with a focus on the synthesis of fine chemicals like pharmaceuticals.
    - Most organometallic chemistry is predicated on the development of ligands.
    - Many of Prof. Buchwald's ligands are named after his former cats!
    - Example: The RuPhos ligand is named after Prof. Buchwald's since-passed cat, Rufus.
- **Organometallic** (chemistry): A hybrid of organic and inorganic chemistry.
- Prof. Elkin is in Washington, D.C. today advising the federal government!

- Announcements.
  - The first half of this semester covered analytical techniques and physical chemistry; this half is more synthesis-focused.
  - Review your 5.12 reactions!! A list of what you need to know for PSet 5 will be posted on Canvas.
    - The teaching team will also keep a running list of reactions from this half of the course.
    - This will tell you what to know for the exams and PSets.
  - Prof. Buchwald will post "study guides" for each unit, containing all the unit's content.
    - Clayden et al. (2012) doesn't have a specific section on amines. Thus, the study guide lists all the pages spread throughout Clayden et al. (2012) where the different reactions can be found.
    - If you still have Smith (2023) — your 5.12 textbook — it's Chapter 23.
  - Plan: This lecture and the following one will cover amines.
    - Amines have a special place in Prof. Buchwald's heart because they're connected to a lot of his research!
  - Like Prof. Elkin, Prof. Buchwald will continue giving fun facts that relate these topics to the real world.
- Outline for the next two lectures.
  A. Intro.
  B. Chirality (or "handedness;" recall from 5.12).
  C. Brønsted basicity.
  D. Synthesis and reactivity (we'll spend the majority of our time on this topic).
     1. Alkylation of ammonia and alternatives.
     2. Reductive amination.
     3. Acylation and reduction.
     4. Reduction of nitriles (i.e., R–C≡N functional groups).
     5. Other miscellaneous methods.
- Today: We'll cover Topic A through most of Topic C.
- We now begin with Topic A: Introduction.
- **Amine**: An R_3N compound, where each R may be distinct and R is an H, alkyl, or aryl group.
- The simplest amine is ammonia (NH_3).
  - Notice that ammonia *is* an amine by the definition: All of its R groups are identically equal to H!
  - Fun fact: Ammonia is a necessary ingredient in fertilizer.
    - It is prepared industrially from N_2 using the Haber-Bosch process.
    - One could make a reasonable argument that the industrial production of ammonia is the most important technological advance in the history of the world.
      - ➢ This is because it enabled us to produce far more fertilizer, so that we could produce more food, so that we can feed a population of seven billion people.
    - Before Haber-Bosch, fertilizer came from an island covered in bird feces.
    - Two Nobel prizes were awarded in connection with the development of this process.
      - ➢ Haber won the Nobel Prize for his work on this process in 1918 (for the process).
      - ➢ Bosch won the Nobel Prize for his work on this process in 1931 (for high-pressure chemistry).

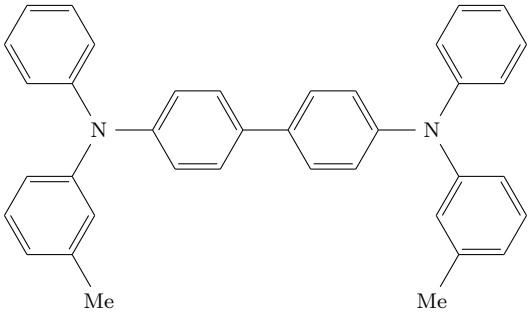
- Examples of amines.



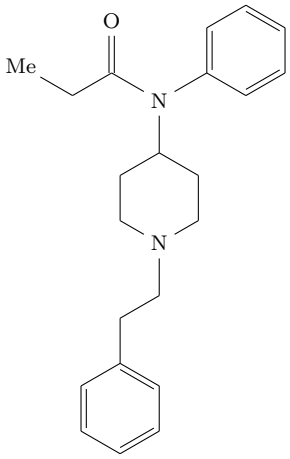
(a) Nicotine.



(b) Cadaverine.



(c) TPD.



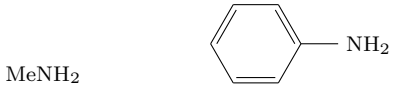
(d) Fentanyl.

Figure 3.1: Amine examples.

  - The top-selling pharmaceuticals in the world are all amines, at least in part.
    - Not all of these "pharmaceuticals" are fun, though! Some are illicit drugs.
  - Example: Nicotine (Figure 3.1a).
    - It's one of the most difficult habits to break.
    - There are drugs that mimic the structure of nicotine but bind to the receptor better and block nicotine from doing its job.
  - Example: Cadaverine (Figure 3.1b).
    - Does not smell good.
    - When animals die, their flesh putrifies/rots and this is what causes the smell.
  - Example: TPD (Figure 3.1c).
    - This is a hole transport agent commonly found in the toner cartriges of laser printers.
  - Example: Fentanyl (Figure 3.1d).
    - A synthetic opioid that has caused unbelievable amounts of societal problems.

- Classes of amines.
  - Ammonia (NH_3).
    - Good because it helps feed the world.
    - Bad because it's a toxic gas and smells horrible.
  - **Primary amines**.
  - **Secondary amines**.
  - **Tertiary amines**.
  - **Quaternary ammonium salts**: A related family of comounds.

- **Primary** (amine): An amine in which we've replaced one of the H's in ammonia with an (alkyl or aryl) R group. *Denoted by* **1°**. *General form* RNH_2.

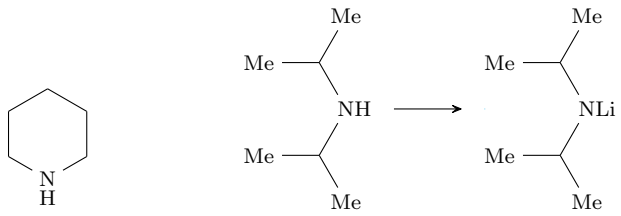


(a) Methylamine. (b) Aniline.

Figure 3.2: Primary amine examples.

  - Example: Methylamine (Figure 3.2a).
    - A gas like ammonia, but a liquid under pressure.
    - It's a controlled substance.
      - ➢ In *Breaking Bad*, this is what Walt, Jessie, and Todd heisted from the train!
  - Example: Aniline (Figure 3.2b).
    - Very important historically: Modern chemistry began in the 1800's with aniline-based dyes.
      - ➢ These companies are the precursor to modern-day pharmaceutical companies!

- **Secondary** (amine): An amine in which we've replaced two of the H's in ammonia with (alkyl or aryl) R groups. *Denoted by* **2°**. *General form* RR′NH.



(a) Piperidine. (b) Diisopropylamine and LDA.

Figure 3.3: Secondary amine examples.

  - The R groups can be separate, or they can be linked together.
  - Example of a cyclic secondary amine: Piperidine (Figure 3.3a).
    - Piperidine is important in a number of applications, including sequencing DNA.
  - Example of an acyclic secondary amine: Diisopropylamine (Figure 3.3b).
    - If you replace the amine hydrogen with lithium, you get lithium diisopropylamide (LDA).
      - ➢ This is a very strong base that we'll talk more about later in this course.

- **Tertiary** (amine): An amine in which we've replaced all three of the H's in ammonia with (alkyl or aryl) R groups. *Denoted by* **3°**. *General form* RR′R″N.

- **Quaternary ammonium salt**: A nitrogen covalently bonded to four R groups (and hence having a positive formal charge), coordinated to a negative counterion. *General form* $R_4N^+ X^-$.

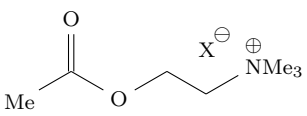


Figure 3.4: Quaternary ammonium salt example.

  - Example: Acetylcholine, an important neurotransmitter (Figure 3.4).

- This concludes our introduction to amines.
- Aside: Prof. Buchwald *strongly* recommends you show up for lecture the day before Halloween :)
- We now move onto Topic B: Chirality.
- Recall from 5.12 that some compounds are *chiral*, i.e., they can have enantiomers.

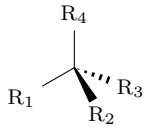


Figure 3.5: A chiral compound.

  - These enantiomers can often be separated.
  - They can also have different biological activities.
    - Fun fact: The FDA now requires all chiral molecules to be prepared in both enantiomers and independently tested, in part because of the thalidomide scandal.
- The structure of amines.

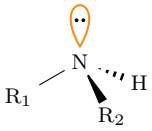


Figure 3.6: Amine structure.

  - Amines are sp^3-hybridized with a tetrahedral electron pair arrangement.
    - 3 bonding orbitals and 1 lone pair (lp).
  - The lp is responsible for the Brønsted basicity of amines.
  - If one of the R groups is hydrogen, then the amine can participate in hydrogen bonding (a very important interaction you should recall from Gen Chem).
- Is pyridine a tertiary amine?
  - Technically, yes; we'll discuss pyridine next lecture.
- Amines have two enantiomers as well.

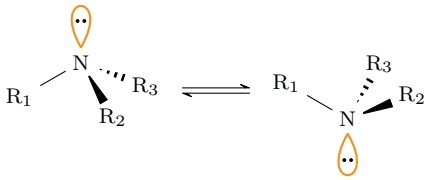


Figure 3.7: Amine enantiomer interconversion.

  - The energy barrier ($\Delta G^{\ddagger}$) between the two enantiomers is 5-6 kcal/mol.
  - Additionally, note that if $\Delta G^{\ddagger} \leq 20$ kcal/mol, the process is fast at room temperature.
  - Thus, amine enantiomers rapidly interconvert at room temperature, so we (usually) cannot resolve amines into individual enantiomers.
    - One time we can resolve amines into enantiomers is in the case of **aziridines**.

- **Aziridine**: A three-membered ring containing one nitrogen and two carbons. *Structure*

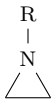


Figure 3.8: Aziridine.

  - These are the amine equivalent of an epoxide.
  - Like in any other amine, R can still be H, alkyl, or aryl.
  - The sp^3-hybridized atoms all want to have 109° bond angles but are strained to 60°.

- In order for aziridines to undergo **racemization**, the molecules must go through a transition state with an sp^2-nitrogen.

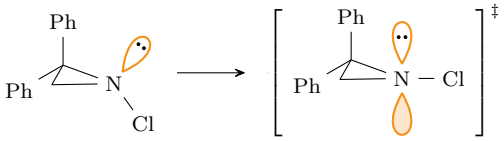


Figure 3.9: Aziridine enantiomer interconversion.

  - This sp^2-nitrogen wants to have 120° bond angles but is still strained down to 60°.
    - This is even worse than the strain in an sp^3-nitrogen!
  - Thus, the energy barrier to aziridine enantionmer interconversion is $\Delta G^{\ddagger} \approx 24\,\text{kcal/mol}$.
  - Therefore, (many) aziridines *do not* interconvert at room temperature because $24 > 20$.

- **Racemization**: The interconversion of enantiomers.
- This concludes our discussion of chirality.
- We now move onto Topic C: Brønsted basicity.
- Consider the following two protonation reactions.

(a) Methanol. (b) Methylamine.

Figure 3.10: Basicity of methanol vs. methylamine.

  - For $MeOH_2^+$, $pK_a \approx -2$.
    - This means that $MeOH_2^+$ is very acidic.
    - It follows that MeOH is only weakly basic.
  - For $MeNH_3^+$, $pK_a \approx 9 - 11$.
    - Thus, $MeNH_2$ is *much* more basic than MeOH.

- Something critical to everyday life: Why do fish smell so bad after they die?

Figure 3.11: Amines explain why fish smell, and how to season them!

  - Not all fish smell to the same degree.
    - Ocean fish (like cod) smell worse than river fish (like catfish) after they die.
  - Ocean fish smell worse because of trimethylamine oxide.
    - There's a lot of salt in the ocean, so ocean fish use trimethylamine oxide to balance the salt levels in their cells.
    - This compound does not smell very much, but after they die, enzymes from the fish (and from bacteria in the fish) reduce trimethylamine oxide to trimethylamine (which smells horrible).
  - Second important thing: We put lemon juice on fish because the acidity of the lemon juice (coming from citric acid) protonates the trimethylamine, decreasing the smell (and the taste since smell is connected to taste) so that the fish tastes better.

- Resonance decreases the basicity of amines.

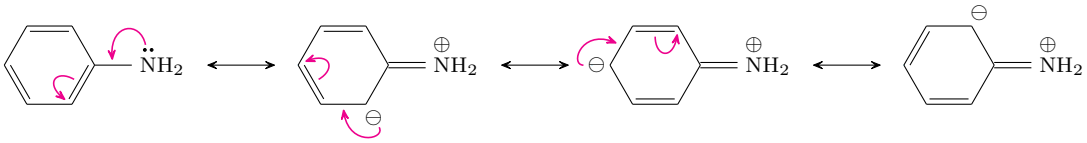


Figure 3.12: Basicity of aniline.

  - The conjugate base of aniline ($PhNH_3^+$) has $pK_a \approx 5$, indicating that aniline is much less basic than methylamine ($pK_a \approx 9 - 11$).
  - Why? Two reasons:
    1. The sp^2-carbon adjacent to the nitrogen in aniline is more electoron-donating than the sp^3-carbon adjacent to the nitrogen in methylamine.
    2. Resonance.
       - Just like in a phenol, we can push the heteroatom electrons into the benzene ring to get three other resonance forms (Figure 3.12).
       - Resonance decreases basicity, so aniline is much less basic than the any alkylamine.

3.22 Amines - 2

10/28:

- Lecture 21 recap.

  A. Amines are basic, nitrogen-containing compounds.
     - Their general form is R_3N, where $R = H, alkyl, aryl$.
     - Some other types will be discussed at the end of the semester.

  B. Types of amines: Ammonia (NH_3), 1°, 2°, or 3° depending on the number of hydrogens.

  C. Amines are often chiral, but rarely resolvable.

  D. Amines are Brønsted bases.
     - Substituents affect the acidities of the conjugate acids.
     - You can compare the basicity of methylamine and aniline by comparing the pK_a's of the conjugate acids.
     - Resonance makes amines less basic.

- Today: We'll cover Topic D.
  - The reading — Clayden et al. (2012, pp. 700–702) — covers snippets of amine synthesis.
- We'll begin with Subtopic D.1: Alkylation of amines.

- Specifically, let's look at how we might synthesize a primary amine.

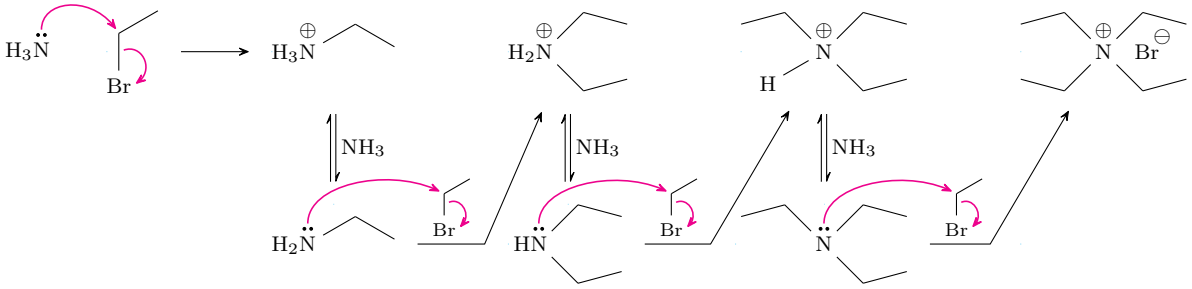


Figure 3.13: Alkylation of amines from ammonia and an alkyl halide.

  - If we wanted to synthesize ethylamine ($EtNH_2$), we might first think to react ammonia with bromoethane via an S_N2 mechanism.
  - Would this work? Sort of.
    - When we carry out this reaction, we obtain a primary ammonium cation that is easily (and reversibly) deprotonated to ethylamine by other basic ammonia molecules floating around.
    - This frees up the ethylamine product to react again! In fact, even though ethylamine is sterically more hindered, it is electronically more activated.
    - It follows that the ethylamine we've created will react *even faster* than ammonia, forming a secondary ammonium cation.
  - After a few more successive cycles of S_N2's and deprotonations — creating iteratively more substituted and hence more electronically activated amines — we obtain a quaternary ammonium salt[1] as our major product.
  - Therefore, the major product is tetraethylammonium, a quaternary ammonium salt.

- Aside: When we do synthesis, we do *not* want to form a mixture of products.
  - Mixtures decrease our efficiency and require separation.
  - We have all sorts ways to separate things, but separation techniques are inelegant, time consuming, and expensive.

- As such, if we do want to use ammonia and an alkyl halide, we must use a *large excess* of ammonia. However, this is not a great fix because...
  - Ammonia is toxic and smells horrible;
  - Ammonia is also a gas, and hence harder to control in the lab than a liquid.

- So we need an alternate method to synthesize primary amines. In fact, we'll discuss two!

- Alternative #1: Gabriel synthesis.

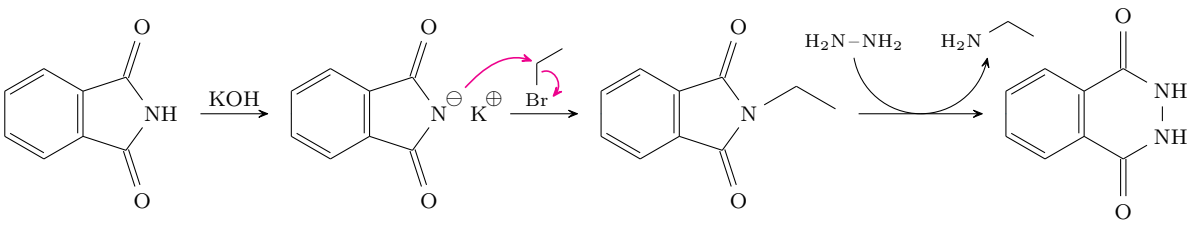


Figure 3.14: Gabriel synthesis.

[1] Note that at the board, Prof. Buchwald uses parentheses and numerical subscripts to indicate groups that are repeated multiple times.

  - This method can be used to synthesize primary amines.
  - The molecule we begin with is called phthalimide.
    - Phthalimide has $pK_a \approx 8$.
    - For comparison, NH_3 has $pK_a \approx 33 - 35$.
  - First step: Put phthalimide in the presence of KOH to yield the potassium salt.
  - Second step: The potassium salt can do an S_N2 reaction to monoalkylate.
    - Importantly, this monoalkylated intermediate cannot react further! This is because its nitrogen lone pair is tied up in conjugation with the carbonyls.
  - Third step: We need to release the product, which we can do by adding hydrazine.
    - This releases our desired ethylamine product and forms a byproduct.
    - Aside: Hydrazine is also used as rocket fuel! It's an extremely high energy molecule.

- Alternative #2: Reduction of azides.

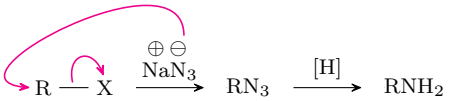


Figure 3.15: Reduction of azides.

  - This method can be used to synthesize primary *or* secondary amines.
  - We begin with an alkyl halide (RX), where R is primary or secondary.
    - Importantly, R *cannot* be tertiary because the first step proceeds through an S_N2 mechanism, and S_N2 cannot happen with tertiary alkyl halides.
  - First step: We react RX with sodium azide (NaN_3).
    - Sodium azide is a source of azide (N_3^-), a fantastic nucleophile.
    - This will give us an RN_3 intermediate.
  - Second step: We reduce the azide to the amine. There are two different ways to do this.[2]
    - Use lithium aluminum hydride ($LiAlH_4$ *or* LAH) followed by a water workup.
      - ➢ Note: Whenever we use LAH, we need a water workup.
    - Use hydrogen gas (H_2) and palladium on carbon (Pd/C).
      - ➢ Downside of these reagents: H_2 is explosive, and it's a gas (recall from our discussion of ammonia earlier today that gases are harder to control).
  - Downside of this method: RN_3 is explosive, so it is too dangerous to run this process industrially.
    - However, it's fine in small, controlled research settings when you know what you're doing.
  - Relevant reading: Clayden et al. (2012, p. 354).

- We now move onto Subtopic D.2: Reductive amination.
  - Reductive amination is super useful!
    - It is always in the *Journal of Medicinal Chemistry*'s decadal list of the top 5 most common reactions used in their papers.
    - Aside: Amide-bond formation is always (by far) the number 1 reaction, and a subject of Prof. Buchwald's research! It's not a perfectly solved problem, but we've gotten much better.
  - Relevant reading: Clayden et al. (2012, pp. 234–235).

[2] "[H]" is a general way of denoting a reduction. It is useful in Figure 3.15 because there are two possible reducing agents we can use, discussed next.

- Using reductive amination to convert secondary amines into tertiary amines.

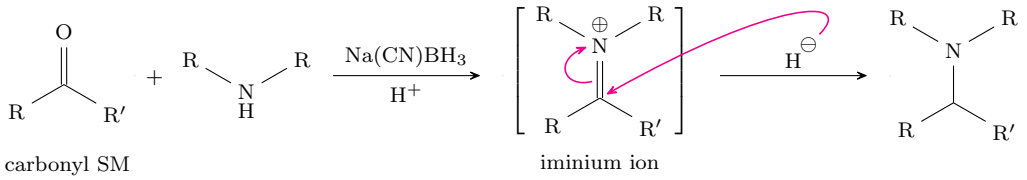
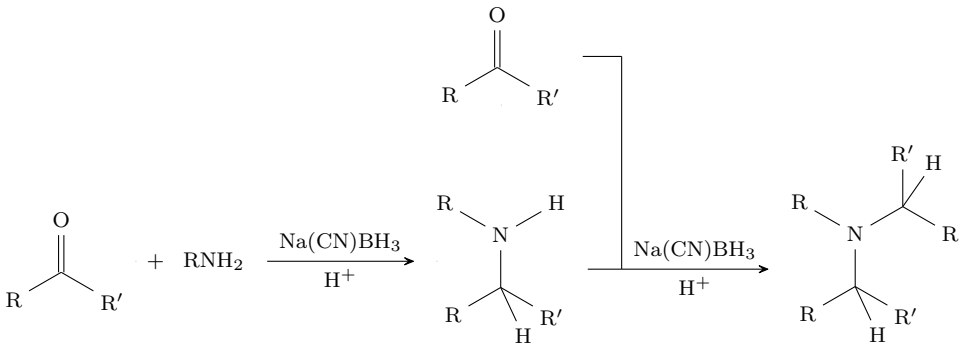


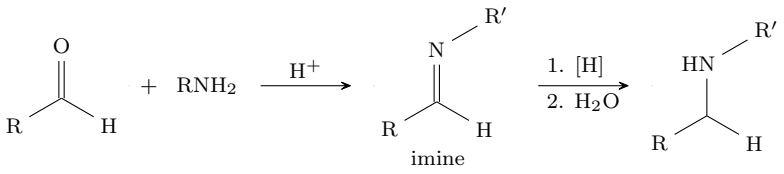
Figure 3.16: Reductive amination: $2^\circ \rightarrow 3^\circ$.

  - We begin with an aldehyde or a ketone (i.e., $R' = H, alkyl, aryl$).
  - Single step: Use sodium cyanoborohydride ($Na(CN)BH_3$) in acidic medium.
  - $Na(CN)BH_3$ is a much milder, nicer reducing agent than sodium borohydride ($NaBH_4$).
    - It selectively reduces **iminium ions** instead of the carbonyl starting material.
      - ➢ This is important because if the carbonyl gets reduced to an alkane, it can no longer react with the secondary amine!
    - It is also stable under moderately acidic conditions.
      - ➢ This is important because we don't want the acid to just neutralize our reducing agent.
  - After the iminium ion is formed, hydride from $Na(CN)BH_3$ attacks it. This yields the product.
  - To reiterate: This is an incredibly powerful transformation.

- Using reductive amination to convert primary amines into secondary amines.



(a) Concurrent iminium formation and reduction.



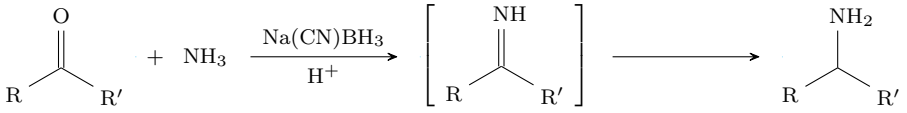
(b) Separate imine formation and reduction.

Figure 3.17: Reductive amination: $1^\circ \rightarrow 2^\circ$.

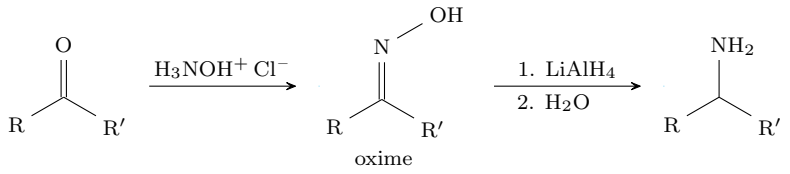
  - Let's first try using the same conditions as in Figure 3.16.
    - If we do this, we run into the same problem as in Figure 3.13.
    - In particular, the product of the first reductive amination in Figure 3.17a is a secondary amine and hence can react again to yield the rightmost product in Figure 3.17a.
    - Thus, if we did this, we'd have a mixture of products, and *we do not like mixtures*!

- Solution: Back off and run the reaction in two steps (Figure 3.17b).
  - First step: React an aldehyde with an amine to form an **imine**.
  - Second step: Reduce the imine with either $NaBH_4$ or $LiAlH_4$, followed by a water workup.
- Aside: $NaBH_4$ vs. $LiAlH_4$.
  - Since $NaBH_4$ is milder, we almost always prefer to use it over $LiAlH_4$ when we can.
- Aside: Why can't we use $Na(CN)BH_3$?
  - Worse at reducing imines.
  - More expensive than $NaBH_4$.
  - Toxic (cyanide exposure).

- Using reductive amination to make a branched primary amine.



(a) Concurrent imine formation and reduction.



(b) Oxime formation and reduction.

Figure 3.18: Reductive amination: Forming 1°.

- Let's first try using the same conditions as in Figures 3.16 & 3.17a.
  - If we do this, the bracketed imine intermediate proposed in Figure 3.18a would be unstable.
  - As such, we would need to resort to using a large excess of ammonia if we really want to make this work, even though such volumes are not ideal.
- But what if you work in a place that doesn't allow you to handle gases?
- Solution: The two-step reaction in Figure 3.18b.
  - First step: Take your ketone or aldehyde and treat it with hydroxylamine hydrochloride ($H_3NOH^+\ Cl^-$) to form an **oxime**.
    - ➢ Unlike the proposed imine intermediate in Figure 3.18a, oximes are *really, really, really* stable.
  - Second step: Take the oxime and treat it with $LiAlH_4$ followed by a water workup.
    - ➢ Because oximes are so stable, we *need* a really strong reducing agent like $LiAlH_4$ to get the job done.
    - ➢ More ways to reduce oximes are listed on Clayden et al. (2012, pp. 702, 762, 902).
- Thus, we obtain a gas-free synthetic route to branched primary amines.

- We now move onto Subtopic D.3: Acylation and reduction.
- Acylation/reduction does monoalkylation, that is, the addition of one alkyl group to an amine.
  - This may be $NH_3 \to 1°$, $1° \to 2°$, or $2° \to 3°$!
- Reading on the acylation of amines, including the mechanism: Clayden et al. (2012, pp. 202–203).
- Reading on the reduction of amides: Clayden et al. (2012, p. 531).

- Example: Using acylation/reduction to convert primary amines to secondary amines.

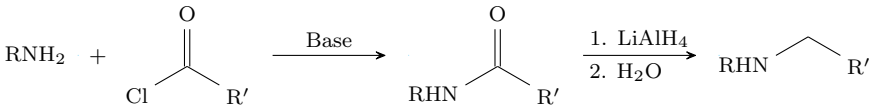


Figure 3.19: Monoalkylation by acylation and reduction.

  - We begin with an acid chloride and a primary amine.
  - First step: Mix the starting materials with a base (such as Et_3N).
    - This will form an amide.
    - As in the Gabriel synthesis (see Figure 3.14), this secondary amide does not react further because its nitrogen lone pair is tied up in conjugation with the carbonyl.
  - Second step: Reduce the amide with $LiAlH_4$, followed by a water workup.
    - This affords the secondary amine product.

- Aside: Why do we need so many methods of making amines?
  - Textbook chemistry (what we're doing) always works.
  - In the lab, molecules have many properties that might get in the way of one method working, so we need alternatives to try.
    - Example: Methods 1-26 might not work, but perhaps method 27 does.
  - This is the really exciting thing about Prof. Elkin's research: Prof. Elkin is using data science to avoid doing the first 26 bad reactions and make it so that the first time we try to do the reaction, it has a better chance of working.

- We now move onto Subtopic D.4: Reduction of nitriles.

- The general form of this reaction is as follows.

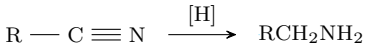


Figure 3.20: Reduction of nitriles.

  - The reducing agent can be $LiAlH_4$, or hydrogen and a nickel catalyst (H_2/Ni cat).

- This reaction is pretty straightforward, but where did we get the nitrile from?

Figure 3.21: Reduction of nitriles: Alkyl halide starting material.

  - Nitriles are often synthesized from (primary or secondary) alkyl halides through an S_N2 reaction in which CN^- is the nucleophile.
    - Once we have the nitrile, we can reduce it as in Figure 3.20.
  - Therefore, the overall reaction in Figure 3.21 takes an alkyl halide to an amine with one additional **methylene** (CH_2) interspersed.
    - This is called a **homologation** reaction, though you don't have to know that.

- Using the reduction of nitriles to synthesize 1,2-aminoalcohols.

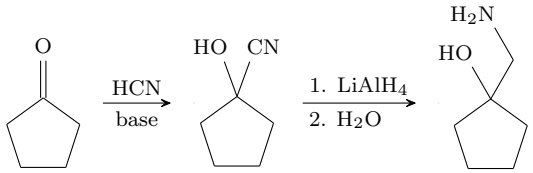
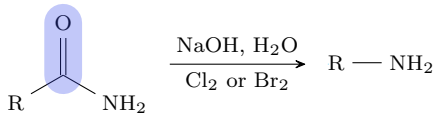


Figure 3.22: Reduction of nitriles: 1,2-aminoalcohol formation.

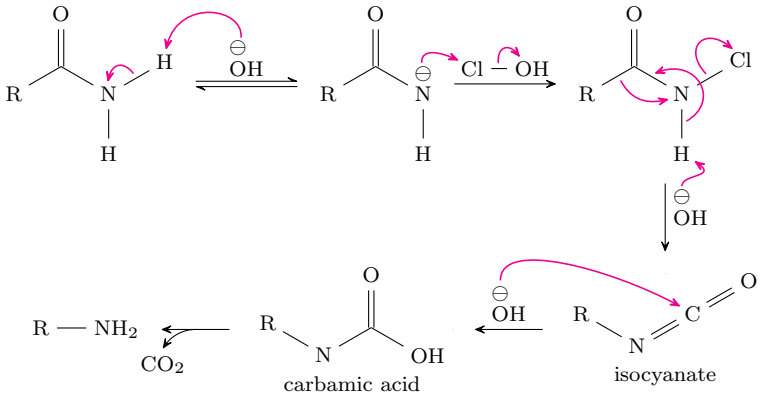
  - We begin with a ketone.
  - First step: Add HCN and a base catalyst to form a **cyanohydrin**, a quasi-stable intermediate.
  - Second step: Reduce the nitrile to afford the 1,2-aminoalcohol product.
  - Why do we care about 1,2-aminoalcohols?
    - Aside: Always ask why we care! Is it fundamentally interesting? Is there a practical application?
    - In this case, 1,2-aminoalcohols are critical to a number of pharmaceuticals, so that's why we care about being able to synthesize them.
  - Reading on cyanohydrin formation: Clayden et al. (2012, pp. 127–29).

- We now move onto Subtopic D.5: Miscellaneous reactions.

- The Hofmann rearrangement.



(a) General form.



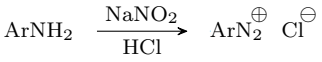
(b) Mechanism.

Figure 3.23: Hofmann rearrangement.

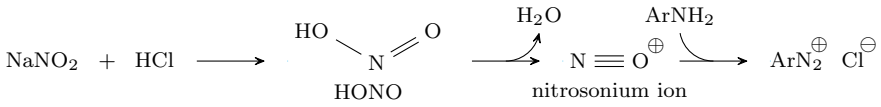
  - Figure 3.23a shows a very different kind of reaction from what we've seen.
    - This reaction starts with a primary amide and involves reduction to a primary amine, excising the CO highlighted in blue.
    - *Hint*: This reaction is related to the polymer problem on PSet 5!!
  - Reading: Clayden et al. (2012, p. 1022).

  - Let's now discuss the partial mechanism (Figure 3.23b).
  - First step: The base attacks an amide proton.
  - Second step: The amide anion grabs a halogen from a hypohalous acid.
    - Note that either hypochlorous acid (HOCl) or hypobromous acid (HOBr) will be formed *in situ* from the reaction of the hydroxide base with Cl_2 or Br_2, respectively.
    - The acid function as an X^+ equivalent, attracting the amide anion and leading to the formation of an *N*-chloroamide intermediate.
    - The amide halogen functions as an EWG, making the amide's remaining proton even more acidic than in the starting compound!
  - Third step: The extra-acidified *N*-chloroamide proton get attacked by an equivalent of base, leading to a significant rearrangement step.
    - This rearrangement produces an **isocyanate** intermediate.
  - Fourth step: The *sp*-hybridized carbon in the isocyanate reacts very rapidly to form a **carbamic acid** intermediate.
    - As with "homologation" reactions, we won't ask you to name "carbamic acids" on an exam!!
  - Fifth step: The carbamic acid spontaneously loses CO_2 to afford the amine.

- Forming an aryl diazonium salt ($ArN_2^+\ Cl^-$).



(a) General form.



(b) Mechanism.

Figure 3.24: Aryl diazonium salt formation.

  - Reading: Clayden et al. (2012, pp. 520–23).
  - First step: Sodium nitrite ($NaNO_2$) and HCl form **HONO** *in situ*.
  - Second step: HONO loses water and forms the **nitrosonium ion** *in situ*.
  - Third step: The nitrosonium ion then reacts with aniline to do the nitration.

- Next time (preview): A key reaction with aryl diazonium salts, related to the formation of an aryl diazonium salt from benzene.

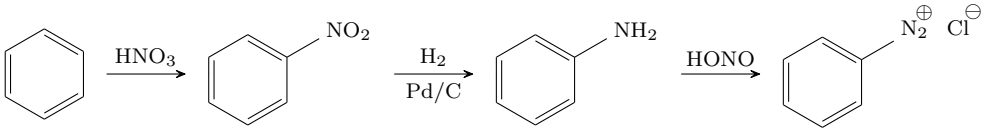


Figure 3.25: Synthesizing an aryl diazonium salt from benzene.

Unit 4

Carboxylic Acids and Derivatives

4.23 Carboxylic Acids Intro

10/30:

- Lecture 22 recap.
  - A. Amine synthesis by direct S_N2 (of, for example, NH_3) leads to mixtures unless you use a very large excess of ammonia (Figure 3.13).
    - Alternative: Gabriel synthesis (Figure 3.14).
    - Alternative: Conversion of a primary or secondary alkyl halide to an azide and subsequent reduction (Figure 3.15).
  - B. Reductive amination is an incredibly powerful technique (Figures 3.16, 3.17, & 3.18).
    - It can build primary, secondary, and tertiary amines.
    - Be intimately familiar with this process for Exam 3!!
  - C. Acylation/reduction is also a great method (Figure 3.19).
    - Acylate the amine to give an amide intermediate, reduce with LAH, and quench with water.
  - D. Primary and secondary alkyl bromides, iodides, and tosylates can be substituted to the nitrile and reduced to an amine (Figure 3.21).
    - This is a 1-carbon homologation.
  - E. HONO (generated from $NaNO_2 + HCl$) converts aniline to an aryl diazonium salt (Figure 3.24).
- Announcement: The notes taken by the TFs are posted on Canvas (that's these!).
  - Consider referring to these even over the ones that Prof. Buchwald provides.
- Lecture 22 continued.
- Using the sequence of reaction in Figure 3.25, you can form an aryl diazonium salt.
  - Treating it with KI yields an aryl iodide.
  - Treating it with H_2O yields a phenol.
  - Treating it with hypophosphorus acid (H_3PO_2) yields benzene again.
    - Once again, you are not responsible for the name "hypophosphorus acid."
  - Treating it with CuX (where $X = Cl, Br, CN$) yields PhX.
- This is a great example of what we do with synthesis!
  - Synthesis is all about connecting compounds with transformations.
  - Breaking down the example in such a way is called **retrosynthetic analysis**.

- Recall from last time that azides are reduced to amines by $LiAlH_4$ and a subsequent water workup (Figure 3.15). Here's a further note on this.

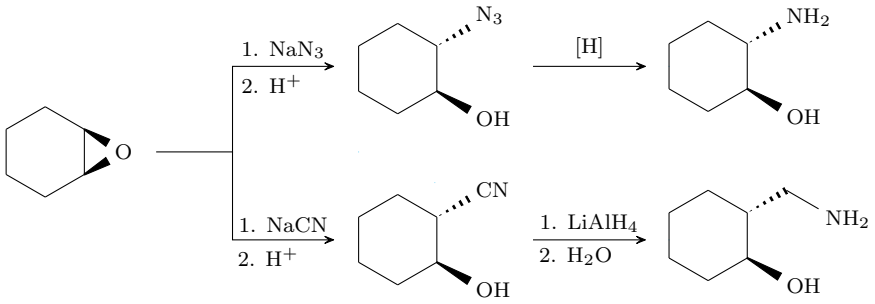


Figure 4.1: Aminoalcohol synthesis from epoxides.

  - Recall from 5.12 that **epoxides** are essentialy just reactive ethers, due to their ring strain.
  - Therefore, if we treat an epoxide with NaN_3, we'll get a backside attack that yields a certain intermediate.
  - Then upon reduction, we get a *trans*-1,2-aminoalcohol.
    - This is an important functional group for β-blockers in biology!
  - Alternatively, we can treat epoxides with CN^-, yielding the cyanoalcohol.
    - We can then reduce this to the 1,3-aminoalcohol.

- This concludes our discussion of amines.
- Today: Introduction to carboxylic acids and their derivatives.
  - Reading: Chapter 10 of Clayden et al. (2012).
- Lecture outline.
  1. Introduction.
  2. Synthesis of carboxylic acids.
     a. Oxidation of alcohols and aldehydes.
     b. Carboxylation of Grignard reagents.
     c. Hydrolysis of nitriles.
     d. Types of carboxylic acid derivatives.
  3. Acyl transfer reactions.
     a. Background.
- We'll begin with Topic 1: Introduction.
- **Carboxylic acid derivative**: A compound of the following form, where $X \neq H, R$. *Structure*

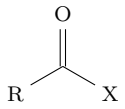


Figure 4.2: Carboxylic acid derivative.

  - Since X is *not* equal to H or R, we're not considering aldehydes or ketones.

- **Carboxylic acid**: A carboxylic acid derivative for which X = OH. *Structure*

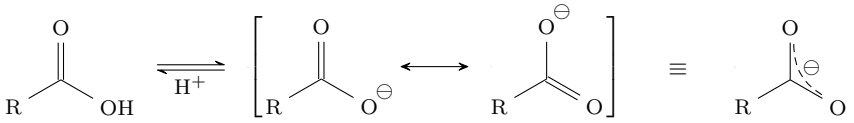


Figure 4.3: Carboxylic acid.

  - $pK_a \approx 5$.
    - By comparison, $pK_a \approx 16$ for an alcohol.
    - Therefore, carboylic acids are *eleven orders of magnitude* more acidic than alcohols.
  - Deprotonation gives us a resonance-stabilized **carboxylate**, which can be drawn either as resonance forms or as a delocalized anion.

- One of the simplest carboxylic acids is **acetic acid**.

- **Acetic acid**: The carboxylic acid for which R = Me. *Structure*

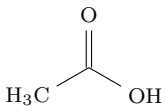


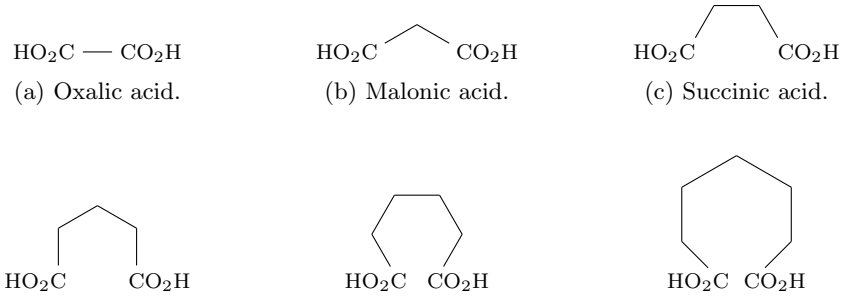
Figure 4.4: Acetic acid.

  - Acetic acid is in vinegar! In fact, vinegar is about 4-5% acetic acid in water.
  - Acetic acid is also used as an industrial solvent (in the 100% pure form, which is quite caustic).
  - How is acetic acid made?

$$\mathrm{MeOH} \xrightarrow[\text{cat}]{\mathrm{CO}} \mathrm{CH_3COOH}$$

    - Acetic acid is produced industrially via the Monsanto acetic acid process, which carries out the carbonylation of methanol using a rhodium catalyst.

- The first several biscarboxylic acids.



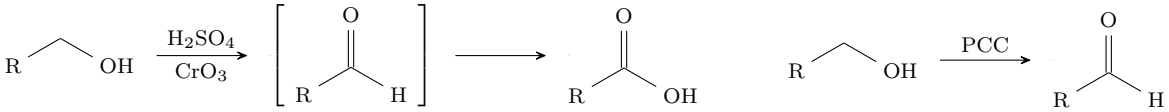
(a) Oxalic acid. (b) Malonic acid. (c) Succinic acid.

(d) Glutaric acid. (e) Adipic acid. (f) Pimelic acid.

Figure 4.5: Biscarboxylic acids.

  - **Oxalic**, **malonic**, **succinic**, **glutaric**, **adipic**, and **pimelic** acids.
  - Aside: Adipic acid is really important because it's involved in the manufacture of nylon.
  - How do you remember all these names? There's a neumonic: OMSGAP or "Oh My, Such Good Apple Pie."

- We now move onto Topic 2: Synthesis of carboxylic acids.
- Aside: A new definition of **oxidation** and **reduction**.
  - Notice that in a carboxylic acid (e.g., see Figure 4.4), the central carbon has 3 bonds to oxygen.
  - In contrast, a primary alcohol's central carbon has 1 bond to oxygen.
    - Thus, we need to do a 4-electron oxidation to turn an alcohol into a carboxylic acid.
  - An aldehyde's central carbon has 2 bonds to oxygen.
    - Thus, we need to do a 2-electron oxidation to turn an aldehyde into a carboxylic acid.
  - CO_2's central carbon has 4 bonds to oxygen.
    - Thus, we need to do a 2-electron reduction to turn CO_2 into a carboxylic acid.
  - This array of related compounds motivates the following two definitions.
- **Oxidation**: A chemical reaction that increases the number of carbon-oxygen bonds.
- **Reduction**: A chemical reaction that decreases the number of carbon-oxygen bonds.
- We now discuss Subtopic 2.a: Oxidation of alcohols and aldehydes.



(a) Primary alcohol or aldehyde to carboxylic acid. (b) Primary alcohol to aldehyde.

Figure 4.6: Oxidation of alcohols and aldehydes.

  - Suppose you have a primary alcohol.
    - To convert it into a carboxylic acid, treat it with **Jones reagent**.
      - ➢ The mechanism proceeds through the aldehyde.
      - ➢ However, it can't stop, so it goes all the way to carboylic acid.
    - To stop the oxidation at the aldehyde, use PCC!
  - Now suppose you're starting at the aldehyde.
    - To convert it to the carboxylic acid, just subject it to Jones reagent conditions! This is like picking up in the middle of the Figure 4.6a mechanism.
  - Relevant reading: Clayden et al. (2012, pp. 194–196).
- **Jones reagent**: The combination of excess H_2SO_4 and CrO_3.
- We now discuss Subtopic 2.b: Carboxylation of Grignard[1] reagents.

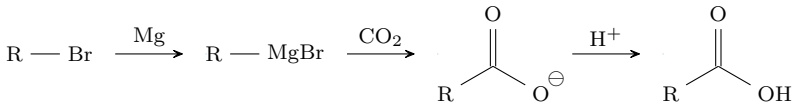


Figure 4.7: Carboxylation of Grignard reagents.

[1] "GRIN-yurd"

  - To make a Grignard reagent, react an alkyl bromide with magnesium.
    - Aside (chemis-tea): Victor Grignard won the Nobel Prize for Grignard reagents, even though his mentor invented them!
    - Note that Grignard reagents are very reactive! They are strong bases and strong nucleophiles, so if there's an acidic hydrogen in solution, it will get deprotonated.
      - ➢ Essentially, we have to consider the functional group tolerance of a method.
    - These reactions are fun to do in the lab!
  - Once you make the Grignard reagent, just throw dry ice (a source of CO_2) into the flask. There will be a bunch of bubbling, and we'll get our carboxylic acid.

- We now discuss Subtopic 2.c: Hydrolysis of nitriles.

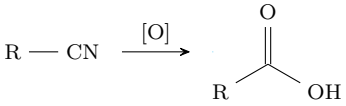


Figure 4.8: Nitrile hydrolysis.

  - Two ways to do this.
    - Acid (H_3O^+) and heat (Δ).
    - Base (HO^-), water (H_2O), and heat (Δ) followed by quenching with acid and heat.
  - Nitriles are *really, really, really* good intermediates (hint for Exam 3!!).

- We'll now look at how nitriles may come up in a typical test question.
- Typical test question (TTQ): Provide two ways to convert benzyl bromide into phenylacetic acid.

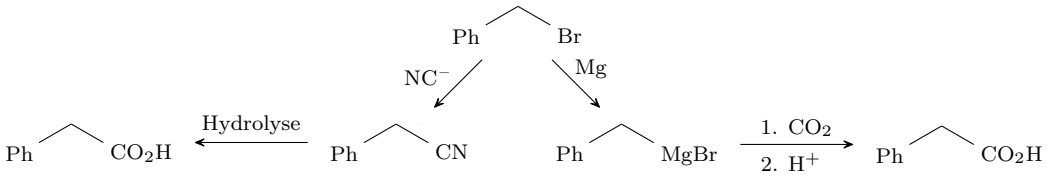


Figure 4.9: Typical test question: Multiple synthetic paths.

  - First way: Make the Grignard and add CO_2.
  - Second way: Do an S_N2 with CN^-, and then hydrolyze the nitrile.
  - Note that Prof. Buchwald uses checkmarks to denote the product on the board.[2]

- If we're answering a test question like this, will you want two separate arrows, or is one arrow with "1. *reagent*" above and "2. *reagent*" below?
  - Either is good.

- We now discuss Subtopic 2.d: Types of carboxylic acid derivatives.
- **Acid chloride**: A carboxylic acid derivative for which X = Cl. *Structure*

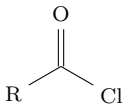


Figure 4.10: Acid chloride.

[2]For an example of how this might look, see Figure 4.58b.

  - These are far more common than acid bromides or acid iodides.[3]
  - To convert a carboxylic acid into an acid chloride, use $SOCl_2$ and pyridine.[4]
  - Mechanism: Clayden et al. (2012, pp. 214–215).

- **Acid anhydride**: A carboxylic acid derivative for which $X = RCO_2$. *Structure*

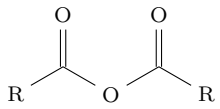


Figure 4.11: Acid anhydride.

  - Synthesize these from two carboylic acids that combine and release water.

- Example of an acid anhydride: Phthalic anhydride.

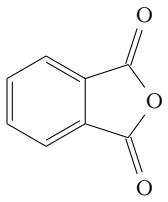


Figure 4.12: Phthalic anhydride.

- **Ester**: A carboxylic acid derivative for which $X = OR'$. *Structure*

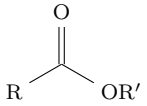


Figure 4.13: Ester.

  - Esters are common in scents and smells.

- Example of an ester: Isoamyl acetate.

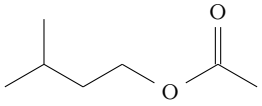


Figure 4.14: Isoamyl acetate.

  - This is the odor of banana oil! The infinite corridor smells like this because of the Banana Lounge.
  - There are easy ways to make this chemical that can legally be described as natural, even if it did not come from a banana.

[3] Coincidentally, acid iodides are used in the Monsanto acetic acid process!
[4] See the 5.12 equation review sheet!!

- **Lactone**: A cyclic ester. *Example*

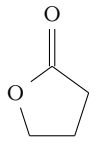


Figure 4.15: γ-butyrolactone.

- **Amide**: A carboxylic acid derivative for which X = NR′R″. *Structure*

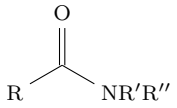


Figure 4.16: Amide.

- Example of a (poly)amide: Nylon.

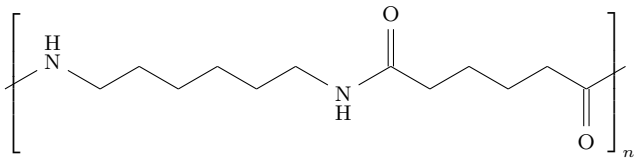


Figure 4.17: Nylon.

- **Lactam**: A cyclic amide. *Example*

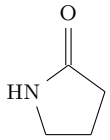


Figure 4.18: 2-Pyrrolidone.

  - Lactams are incredibly imporant; many of us are only alive because of lactams.

- Examples of lactams: The penicillins, a class of molecules that changed the world.

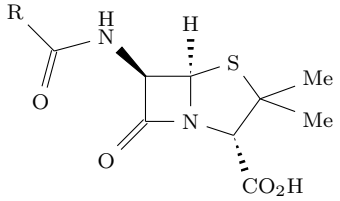


Figure 4.19: Penicillin core structure.

  - Varying R yields different penicillins; all penicillins share the core motif above, though.
  - Penicillins were discovered by Alexander Flemming and changed the course of the world wars.
  - Penicillin and amoxycillin are both β-lactam antibiotics.

- We now move onto Topic 3: Acyl transfer reactions.
- Subtopic 3.a: Background.
- For each X group in a carboxylic acid derivatives, let's see how good of a leaving group it is.

X	Cl	RCO_2	OR	NR_2	O^-
pK_a (HX)	-7	5	16	≈ 35	VERY HIGH

Table 4.1: Leaving groups in carboxylic acid derivatives.

  - To be clear, we're measuring the pK_a's of the following reactions.

$$HX + H_2O \rightleftharpoons X^- + H_3O^+ \qquad K_a = ?$$

    - Example: $HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$.
    - Example: $HO^- + H_2O \rightleftharpoons O^{2-} + H_3O^+$.
  - pK_a — a theromodynamic parameter — is a good measure of how good of a leaving group something is.
    - Important because acyl transfer reactions involve an X group from Table 4.1 departing.
    - Thus, knowing how stable the X group is after leaving as a conjugate base in an acid reaction can help us predict how stable it will be as a departed nucleophile in an acyl transfer reaction, and hence how likely a proposed acyl transfer reaction is to proceed.
- Let's now investigate the resonance stabilization of each of our carboxylic acid derivatives.

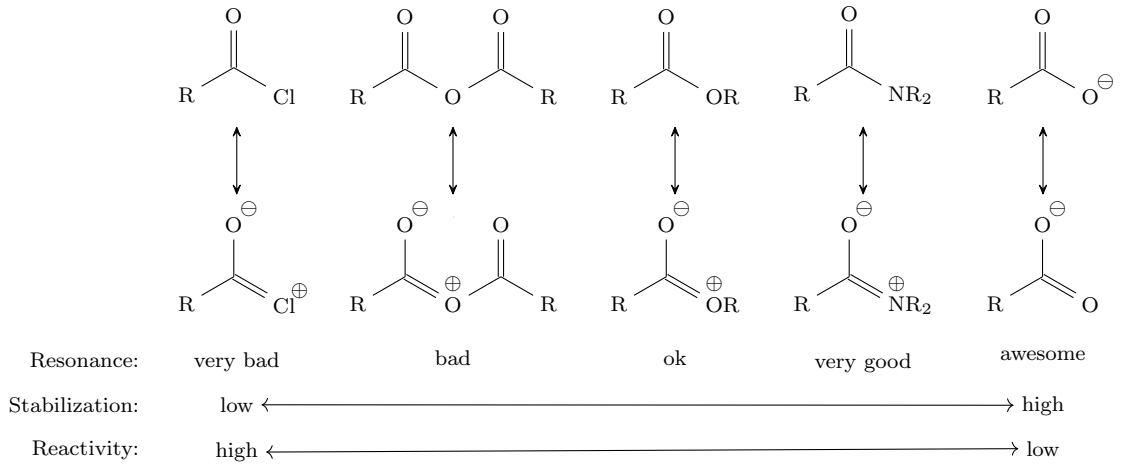


Figure 4.20: Resonance stabilization of carboxylic acid derivatives.

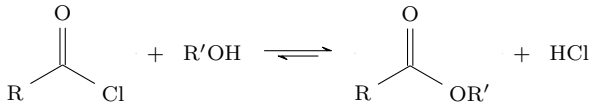
  - The lone pairs on chlorine are high energy, so we can get some degree of resonance, but the resonance structure is very bad.[5]
  - Keep in mind that we have "awesome" resonance *only* for the deprotonated, carboxylate form of a carboxylic acid; carboxylic acids, themselves, aren't nearly as stabilized.
  - Stability and reactivity are clearly inversely related; it should make sense that the less stable something is, the more reactive it is!
- From Table 4.1 and Figure 4.20, we can see that the better leaving groups tend to form more reactive carboxylic acid derivatives, and vice versa!

[5] Think about MOs! Big energy difference means bad mixing and hence poor conjugation

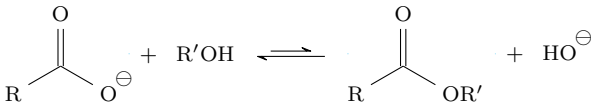
4.24 Acyl Transfer Reactions - 1

11/1:

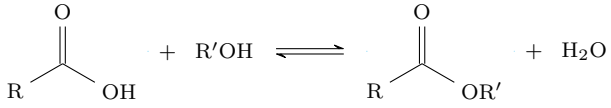
- Lecture 23 recap.
  1. Carboxyic acid derivatives.
     - Substances of the form in Figure 4.2, where $X \neq H, R$.
  2. Synthesis of RCO_2H.
     - Carboxylic acids (Figure 4.3): $pK_a \approx 5$.
     - Oxidation of (primary) alcohols and aldehydes (Figure 4.6).
     - Carboxylation of Grignard reagents (Figure 4.7).
     - Hydrolysis of nitriles (Figure 4.8).
  3. Acyl transfer reaction.
     - Reactivity decreases from acid chlorides > acid anhydrides > esters > amides > carboxylates.
       - Remember that carboxylates are anions.
       - See Table 4.1 and Figure 4.20.
- Before we begin in earnest, let's build a bit more off of this idea of reactivity differences in carboxylic acid derivatives.



(a) Reactivity of an acid chloride.



(b) Reactivity of a carboxylate.



(c) Reactivity of a carboxylic acid.

Figure 4.21: Reactivity of carboxylic acid derivatives toward esterification.

- Measures of reactivity tell us if a given acyl transfer reactions will be thermodynamically favorable, thermodynamically unfavorable, or thermoneutral.
  - Like any thermodynamically favorable reaction, thermodynamically favorable acyl transfer reactions are characterized by high energy reactants becoming low energy products and vice versa for a thermodynamically unfavorable reaction.
  - In a thermoneutral reaction ($K_{eq} \approx 1$), the reactants and products have similar energies.
- Examples.
  - Figure 4.21a: Very favorable because acid chlorides are much more reactive than esters.
  - Figure 4.21b: Very unfavorable because carboxylates are much more stable.
  - Figure 4.21c: Thermoneutral because carboxylic acids and esters have similar reactivity.
- Today: Types of acyl transfer reactions.

- Lecture outline.
  3. Acyl transfer reactions.
     a. Background.
     b. Reactions of acid chlorides.
     c. Reactions of esters.
        i. Hydrolysis.
        ii. Transesterification.
        iii. Amide formation.
     d. Reactions of carboxylic acids.
        i. Fischer esterification.
        ii. Basic esterification (not possible).
        iii. Formation of acid chlorides.
     e. Reactions of amides.
        i. Acid-catalyzed hydrolysis.
        ii. Base-catalyzed hydrolysis.
- We begin by resuming Subtopic 3.a: Background.
- The mechanism of an acyl transfer reaction.

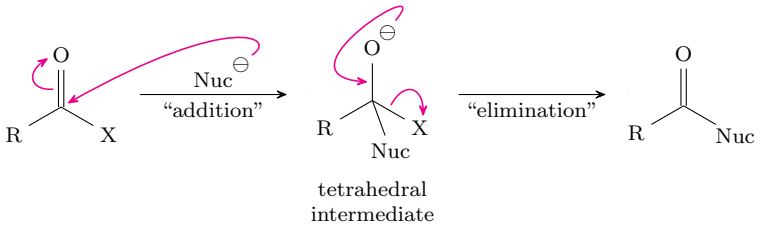


Figure 4.22: Mechanism of a (neutral) acyl transfer reaction.

  - Almost always addition-elimination, not direct displacement.[6]
  - First step: Addition.
    - The nucleophile adds in to the electrophylic site.
    - This gives us a **tetrahedral intermediate**, so named because of its tetrahedral carbon.
  - Second step: Elimination.
    - The best leaving group leaves.
    - There can be equilibriums between which group leaves, but we won't consider those details right now.
- We now move onto subtopic 3.b: Reactions of acid chlorides.

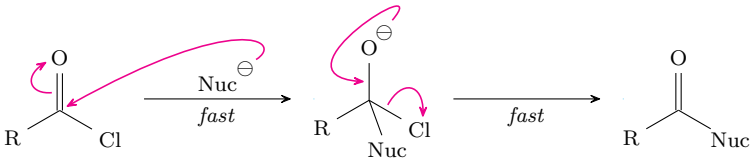


Figure 4.23: Mechanism of an acyl transfer reaction with an acid chloride.

[6]Think about the molecular orbital reasons for why! Nucleophile donation into the C=O π^*-orbital (at the Bürgi-Dunitz angle) *forces* the C=O π-bond to break as the new C−Nuc σ-bond is formed, with the former C=O π-electrons migrating to become a lone pair on the more electronegative atom (oxygen).

- The addition step is fast in this case because the acid chloride is the least resonance stabilized of the carboxylic acid derivatives we've considered.
  - This is because the chlorine atom is a really bad π-donor; there is a large energy mismatch between the n_{Cl} and π^*_{CO} MOs.
- The elimination step is also fast because Cl^- is a great leaving group.
  - We know that Cl^- is a great leaving group because $\mathrm{p}K_{\mathrm{a}}(\mathrm{HCl}) = -7$ (see Table 4.1), meaning that the conjugate base (Cl^-) is weak.
  - When the conjugate base is weaker, it's a better leaving group.
- Thus, overall, acid chlorides are very reactive and no catalyst is needed for their acyl transfer reactions.

- Aside: Like acid chlorides, acid anhydrides are very reactive and also don't need a catalyst to participate in an acyl transfer reaction.

- Example acyl transfer reaction of an acid chloride: Forming an ester.

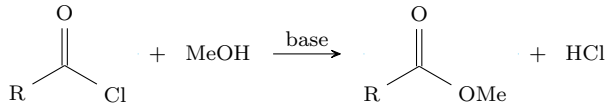


Figure 4.24: Acyl transfer: Acid chloride to ester.

- This is a very vigorous reaction: Lots of bubbling, flask gets really hot, releases a white cloud of caustic gas (HCl).
- As such, you usually add a base to solution.
  - The base is not necessary for the reaction to work, but rather for us to be alive.
  - Indeed, the base neutralizes the acid as it's formed, making a salt: $\mathrm{B} + \mathrm{HCl} \longrightarrow \mathrm{HB}^+\,\mathrm{Cl}^-$.
- Typical bases: $\mathrm{Et_3N}$ or pyridine.

- Example acyl transfer reaction of an acid chloride: Forming an amide.

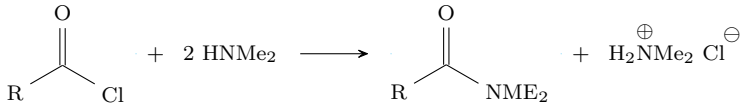


Figure 4.25: Acyl transfer: Acid chloride to amide.

- This reaction forms an amide.
  - Recall from Figure 4.20 that amides are very stable.
- We do not need an additional base this time because the amine already acts as one!
  - Indeed, a *second* equivalent of the amine forms a salt at the end of the reaction, again preventing us from dying.

- Do we need two equivalents of $\mathrm{HNMe_2}$?
  - If you have a valuable amine, maybe add in $\mathrm{Et_3N}$ as a second base because it will do basically the same thing.

- We now move onto Subtopic 3.c: Reactions of esters.
  - Three ester reactions to consider: **Hydrolysis**, **transesterification**, and **amide formation**.

- We now discuss Subtopic 3.c.i: Hydrolysis of esters.
- Let's first consider the energetics of the overall reaction.

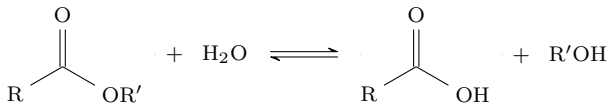


Figure 4.26: Acyl transfer: Ester hydrolysis.

  - Esters are not great electrophiles, and water is not a great nucleophile.
    - Thus, the general addition-elimination mechanism (Figure 4.22) will proceed very slowly here.
  - Additionally, the reaction is thermoneutral overall ($K_{eq} \approx 1$), so we'll get a 50 : 50 mixture of reactants and products under many experimental setups.
- So how do we get the reaction to proceed? Two ways:
  - Use an acid to make the ester a better electrophile.
  - Use a base to make water a better nucleophile.
- Acid-catalyzed mechanism.

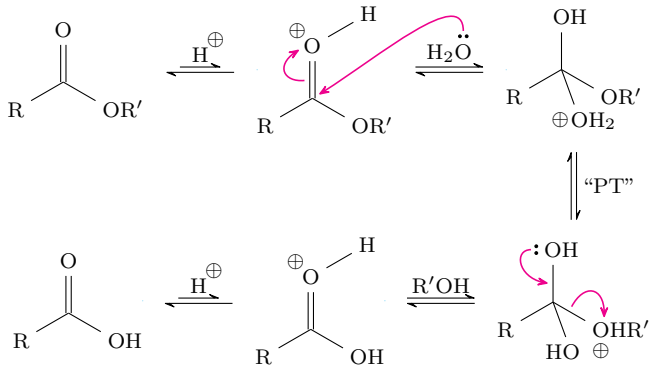


Figure 4.27: Ester hydrolysis mechanism (acid-catalyzed).

  - First step: We get a small quantity of protonated, activated ester that is a much better electrophile.
  - Second step: Now that we have a much better electrophile, water can add in.
  - Third step: Proton transfer (PT), likely intermolecular and possibly stepwise.
  - Fourth step: Elimination.
  - Fifth step: Deprotonation.
  - Observe that we have only drawn positively charged intermediates.
    - If we're in acidic solution, we should not draw any anionic intermediates!
    - This is because anions will immediately be protonated, stopping the reaction there.
  - Since acid adds in at the beginning and leaves at the end, this mechanism is *catalytic* in acid.
- Basic mechanism.

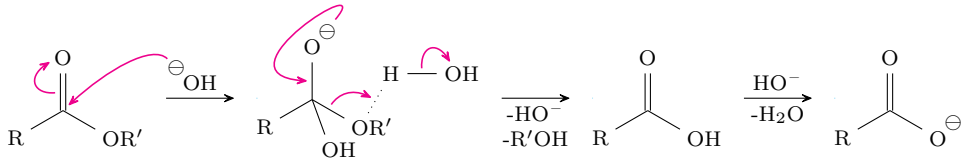


Figure 4.28: Ester hydrolysis mechanism (basic).

- This is much more similar to the general mechanism (Figure 4.22): The starting material undergoes addition by hydroxide, followed by subsequent elimination.[7]
  - However, a final deprotonation step will make the *carboxylate* the major product, not the carboxylic acid.
  - If we want the carboxylic acid, we can recover that with a water workup.
- Problem: RO^- is a bad leaving group (see Table 4.1).
  - Solution: In aqueous media, RO^- will be a slightly better leaving group due to hydrogen bonding with water.
  - This spreads out and stabilizes its negative charge, and also provides a nearby proton donor.
- Since carboxylates are the most stable carboxylic acid derivative we've considered (see Figure 4.20), this *is* a thermodynamically favorable pathway.
- Observe that analogously to Figure 4.27, we have only drawn *negatively* charged intermediates.
  - This is again because cations should not be formed in basic solution.
- Since one equivalent of base is used in this mechanism, it is *not* catalytic in base.
  - We may think of this pathway as base-*accelerated* if we prefer.

- We now discuss Subtopic 3.c.ii: Transesterification.
- Let's first consider the energetics of the overall reaction.

Figure 4.29: Acyl transfer: Transesterification.

- This reaction involves taking one ester and going to another ester.
- Usually, $K_{eq} \approx 1$ and the reaction is not very fast, so we use catalysis again.

- Acid-catalyzed mechanism.

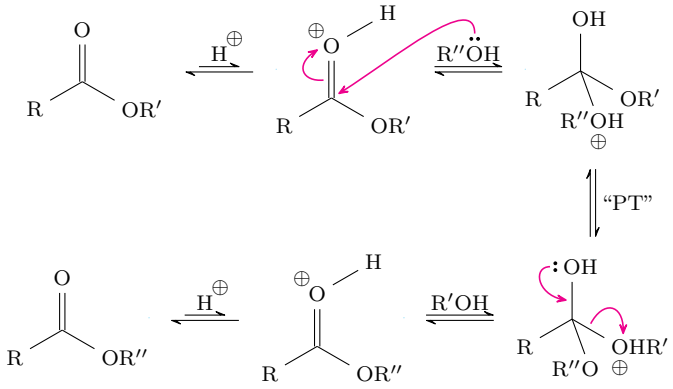
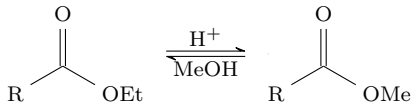


Figure 4.30: Transesterification mechanism (acid-catalyzed).

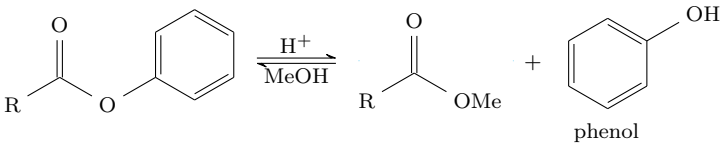
- Mostly the same as Figure 4.27.
- Proton transfer is thermoneutral, so we'll get a mixture of the final product and the pre-PT intermediate.

[7] A good way of introducting hydroxide base is with NaOH.

- Two methods to drive the acid-catalyzed mechanism in the forward direction.



(a) Excess nucleophile.



(b) Ground state destabilization and product stabilization.

Figure 4.31: Driving the transesterification equilibrium.

  - Use R″OH as the solvent.
    - Example: If we want to change an ethyl ester into a methyl ester, use methanol (MeOH) as the solvent instead of just as the nucleophile (Figure 4.31a).
  - Destabilize the reactants and stabilize the products.
    - Example: Use a phenyl ester (Figure 4.31b).
      - ➢ The phenyl ester is more electrophilic than, for example, a methyl ester. This is because the n_O lone pair can now donate into the aromatic ring as well, lowering its electron density near the carbonyl carbon.
      - ➢ Additionally, phenol is a very stable byproduct (again, due to resonance delocalization of its lone pair).
    - Phenol was the horrible smell of paste used in nursery schools.

- Base-accelerated conditions.

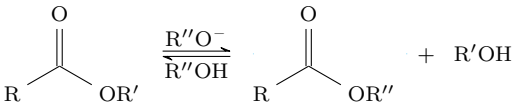


Figure 4.32: Transesterification (basic).

  - The mechanism is analogous to Figure 4.28.[8]

- We now discuss Subtopic 3.c.iii: Amide formation from esters.

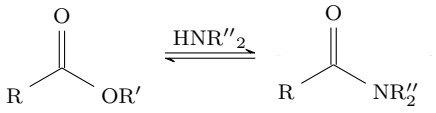


Figure 4.33: Acyl transfer: Ester to amide.

  - The mechanism is also analogous to Figure 4.28, and we don't need base because HNR_2 is one!
  - This reaction is driven forward by the greater resonance stabilization of amides relative to esters (see Figure 4.20).

[8] A good way of introducing alkoxide base is with NaOR.

- We now move onto Subtopic 3.d: Reactions of carboxylic acids.
- We'll begin with Subtopic 3.d.i: The Fischer esterification.

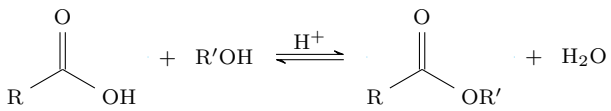


Figure 4.34: Fischer esterification.

  - Combine a carboxylic acid and an alcohol under acidic conditions.
  - Again, $K_{eq} \approx 1$.
  - However, we can drive the reaction forward by removal of water (either by distillation or drying agents).
- We now discuss Subtopic 3.d.ii: Why basic esterification isn't possible.
- Under basic conditions, the first thing that happens will be an acid-base reaction between the carboxylic acid and whatever base we've added to solution.

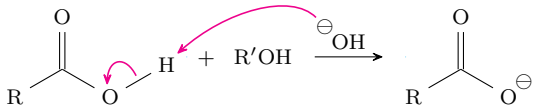


Figure 4.35: Side reaction under "basic esterification" conditions.

  - This will produce a carboxylate, which (recall from Figure 4.20) is a *terrible* electrophile with a *terrible* leaving group.
- As such, we *cannot* do basic esterification of carboxlic acids!
- So what do we do if we want to convert a carboxylic acid into an ester but can't use acidic conditions, perhaps because there are other functional groups in our molecule that would react with acid?
- The answer lies in Subtopic 3.d.iii: Formation of acid chlorides.

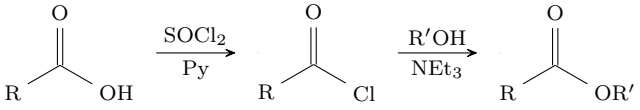


Figure 4.36: Acyl transfer: Carboxylic acid to ester.

  - Essentially, we back off and run the reaction in two steps: A review reaction from 5.12 followed by Figure 4.24.
  - Note that Py stands for pyridine.
- We now move onto Subtopic 3.e: Reactions of amides.
- Recall that amide-bond formation is an incredibly useful driving force in other reactions (e.g., see Figures 4.25 & 4.33).
  - As such, amides are very stable, and we might not expect them to do much.
  - Regardless, however, they hydrolyse to the carboxylic acid under acidic conditions.

- Let's first consider the energetics of the overall reaction.

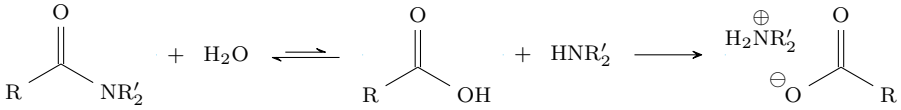


Figure 4.37: Acyl transfer: Amide hydrolysis.

  - As stated above, it seems unlikely that a stable SM would become a less stable product.
    - Indeed, the first step has $K_{eq} < 1$.
  - However, we get a subsequent acid-base reaction between the carboxylic acid and amine base.
    - This forms $H_2NR_2{}^+ \, RCOO^-$ (a salt), taking the reaction to near completion.
  - This process is called **linking** steps!

- **Linked** (steps): A phenomena in which a disfavored reaction step is coupled to an irreversible reaction step to drive product formation.

- We now discuss Subtopic 3.e.i: Acid-catalyzed hydrolysis.

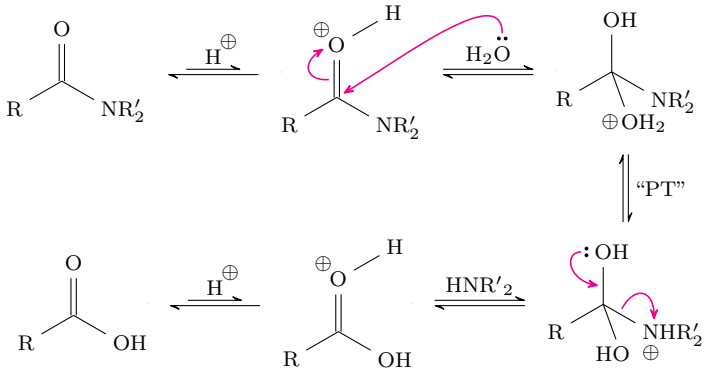


Figure 4.38: Amide hydrolysis mechanism (acid-catalyzed).

  - Acid catalyis is needed because, per Figure 4.20, amides are very poor electrophiles.
    - Indeed, there is excellent $n_N \rightarrow \pi^*_{CO}$ resonance.
  - We protonate the carbonyl instead of the amide because the carbonyl has lone pairs not currently in resonance; if we protonate the amide nitrogen, the result no longer has resonance stabilization.
  - Once we protonate/activate the carbonyl, the rest of the mechanism is analogous to Figure 4.27.

- We now discuss Subtopic 3.e.ii: Basic hydrolysis.

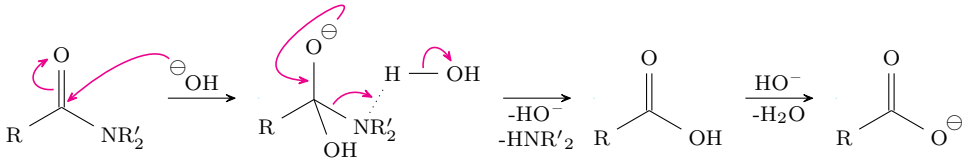
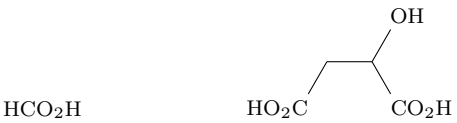


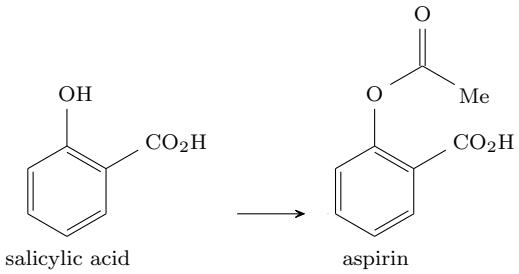
Figure 4.39: Amide hydrolysis mechanism (basic).

  - Conundrum: Like with basic ester hydrolysis (see Figure 4.28), $NR_2{}^-$ is a poor leaving group.
    - However, we can once again solve this issue with a hydrogen bond to water
  - Under basic conditions, we can't form the salt in Figure 4.37, but we are still thermodynamically driven toward the more stable carboxylate (see Figure 4.20).

- Application to real-world cheimstry: Wine.
- Carboxylic acids in wine.



(a) Formic acid. (b) Malic acid. (c) Butyric acid. (d) Tartaric acid.



(e) Salicyclic acid can be made into aspirin.

Figure 4.40: Wine contains carboxylic acids.

  - Formic acid (Figure 4.40a): Used in the leather tanning industry.
  - Malic acid (Figure 4.40b): An ingredient in dermatology products; a skin exfoliating agent.
  - Butyric acid (Figure 4.40c): The smell in dirty gym socks.
  - Salicylic acid (Figure 4.40e): No real connection to taste or smell, but it's a precursor in the synthesis of the pain medication, aspirin.
  - You ever notice the crystalline material at the bottom of a wine glass?
    - It's just (2*R*,3*R*)-(+)-tartaric acid (Figure 4.40d)!
    - The potassium salt of tartaric acid (which contains the carboxylate, tartarate!) is more commonly known as cream of tartar and used in many baking recipes.
- Bonus: What does it mean to say that a bad-tasting wine is "corked?"

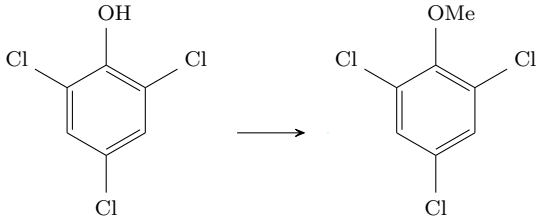


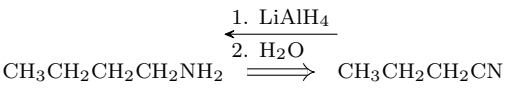
Figure 4.41: Wine can be "corked."

  - It means that the wine has too much trichloroanisole, a compound that smells and tastes bad.
  - Trichloroanisole can be transferred to the wine from the cork.
    - Cork comes from a cork tree.
    - Humans spraying synthetic trichlorophenol insecticides onto trees led funghi to evolve and detoxify it by adding a methyl group.
    - Trichloroanisole is then good for the funghi, but tastes bad to us.

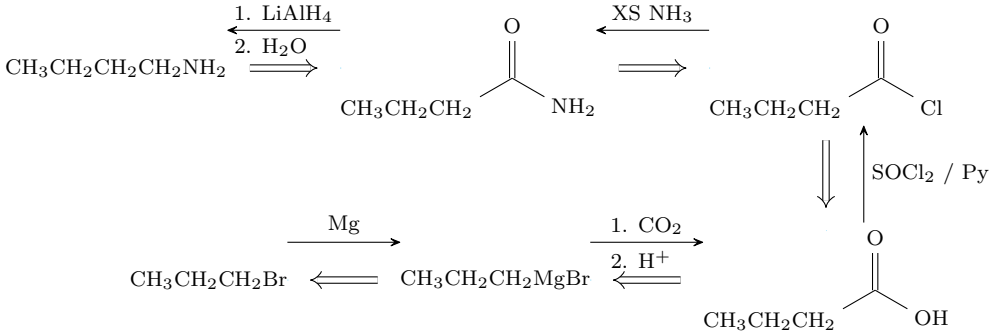
4.25 Acyl Transfer Reactions - 2

11/4:

- Lecture 24 recap.
  1. Mechanism of acyl transfer (Figure 4.22).
     - Proceeds via a two-step addition-elimination process and a tetrahedral intermediate.
  2. Acid chlorides (Figure 4.10) and acid anhydrides (Figure 4.11) are very reactive, so no catalyst is needed for their acyl transfer reactions.
  3. Esters have three important reactions: Hydrolysis (Figure 4.26), transesterification (Figure 4.29), and amide formation (Figure 4.33).
     - Esters are *not* great electrophiles, so we need an acid or base catalyst to promote their reactions.
     - We can make an amide from an ester by heating the amine and ester. The amine acts as both the nucleophile and the base in this case.
  4. Acid catalyzed esterification: Fischer esterification (Figure 4.34).
     - Driven by excess alcohol or removal of water.
     - Under basic conditions, we form an unreactive carboxylate (Figure 4.35).
  5. Amide hydrolysis (Figure 4.37).
     - Driving force under acidic conditions: The formation of a (very stable) salt.
     - Driving force under basic conditions (Figure 4.39): The formation of a (very stable) carboxylate.
- Feedback: Prof. Buchwald has heard that there's a lot of anxiety about synthesis questions, so he'll go over one example problem today, another on Wednesday, and many on Friday!
  - Source of anxiety around synthesis: There's no one right answer.
  - Positive outlook: There is more than one thing you can write down for 100% credit!
- TTQ: How can we make *n*-butyl amine (^{n}BuNH$_2$) from *n*-propyl bromide (^{n}PrBr) and any 1-carbon compound?



(a) Pathway through the nitrile.



(b) Pathway through the amide.

Figure 4.42: TTQ: Synthesis of *n*-butyl amine from *n*-propyl bromide.

  - This is a medium-difficulty question.
  - We'll start with a retrosynthetic analysis.[9]
    - You may want to start by identifying the number of carbons in the starting material and product.
    - This tells us that we need to attach a CH_2NH_2 to the starting material. How can we do this?
  - We don't know too many reactions yet, but here are two possibilities.
    - Transform ^{n}BuNH$_2$ to butyronitrile (^{n}PrCN).[10]
      - ➢ In the forward direction, we'd use $LiAlH_4$ and then H_2O (a water workup).
    - Transform ^{n}BuNH$_2$ to butyramide (^{n}PrCONH$_2$).
      - ➢ In the forward direction, we'd use $LiAlH_4$ and then H_2O, as well.
      - ➢ Next step: Transform butyramide to the acid chloride via excess (XS) ammonia.
      - ➢ Next step: Transform the acid chloride to the carboxylic acid via $SOCl_2$ / Py.
      - ➢ Next step: The carboxylic acid could have come from the primary alcohol via Jones reagent. However, this route would require a 4-carbon primary alcohol starting material, which would be difficult to access from *n*-propyl bromide. More simply, transform the carboxylic acid to a Grignard reagent via carboxylation with CO_2.
      - ➢ Final step: Transform the Grignard reagent to the original *n*-propyl bromide via magnesium metal.

- Aside (connection to real-world chemistry): In real-life synthesis problems, chemists work to make compounds as inexpensively as possible.
  - However, cost is not a consideration in 5.13.
- Prof. Buchwald's advice on 5.13-level synthesis problems: The more practice problems you do, the more you'll see how things work retrosynthetically.
- This concludes today's synthesis example; we now return to acyl transfer reactions.
- Lecture outline.

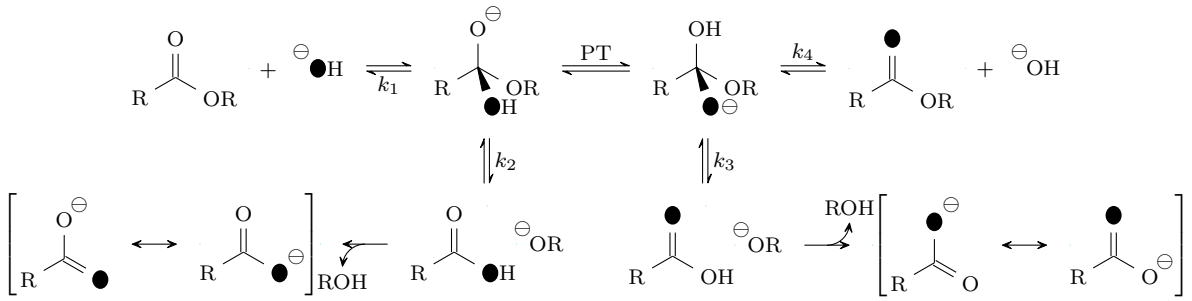
4. Evidence for a tetrahedral intermediate.
   a. Ester hydrolysis.
   b. Amide hydrolysis (basic).
   c. Amide hydrolysis (acidic) — deferred to recitation.
5. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.

- We'll begin with Topic 4: Evidence for a tetrahedral intermediate.
- According to Prof. Buchwald, every acyl transfer reaction goes through a tetrahedral intermediate.
  - But Prof. Buchwald just told us this; why should we believe it's true?
  - Here's some evidence that this happens.
- Recall the general addition-elimination mechanism from last lecture (Figure 4.22).
  - Why couldn't we have the S_N2-like mechanism instead?

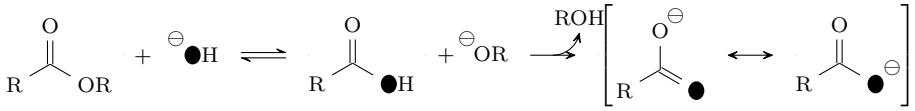
[9] Note that the backwards double-lined arrows are called "retrosynthetic arrows." It is common nomenclature to see retrosynthetic arrows in the reverse direction, overset by forward arrows and conditions.

[10] Although it was not covered in class, we could then transform butyronitrile to *n*-propyl bromide with CN^- (see Figure 3.21). This would be a highly efficient synthesis!

- We can differentiate these two mechanisms via an isotopic labeling study.
  - Most naturally occurring oxygen is ^{16}O.[11] However, we can also use molecules containing heavy oxygen, which is interchangeably denoted as ^{18}O, ^{18}●, or just ●.[12]
  - In particular, we could run an ester hydrolysis reaction using H●$^-$ as the nucleophile and H$_2$^{18}● as the solvent!
    - Such a reaction would yield RCO●H as the product instead of RCOOH.
    - We can then use mass spec to measure how much ^{18}O has been incorporated, for example by looking at the ratio of the heights of the parent peak (RCOOH) and the $[M+2]^+$ peak (RCO●H).
  - In this particular experimental setup, we will stop the ester hydrolysis process at partial conversion for reasons that will become clear shortly.
    - We can then look for ^{18}● in the acid *and* in the starting material.
- We now discuss Subtopic 4.a: Evidence for a tetrahedral intermediate in the ester hydrolysis reaction.



(a) The kinetic network for the addition-elimination mechanism.



(b) The kinetic network for the S_N2 mechanism.

Figure 4.43: Isotopic labeling to prove a tetrahedral intermediate: Ester hydrolysis.

  - Figure 4.43a displays the full kinetic network of the addition-elimination mechanism.
    - All of the little k's indicate kinetic rate constants.
    - This is the ugliness of reality: It's a very complicated kinetic network.
  - Here's a rough explanation of the network.
    - We begin in the upper-left corner, with our ester and isotopically labeled H●$^-$ nucleophile.
    - H●$^-$ can add into the ester, yielding the tetrahedral intermediate.
    - Now we have three options: Go backwards and eliminate H●$^-$, go down and eliminate RO$^-$, go right and do proton transfer followed by eliminating HO$^-$.
      - ➢ Going backwards occurs with rate constant k_1 from the tetrahedral intermediate.
      - ➢ Going down occurs with rate constant k_2 from the tetrahedral intermediate.
      - ➢ Going right occurs with rate constant k_4 from the tetrahedral intermediate.

[11] "oh sixteen."

[12] All pronounced "oh eighteen;" these notes will use these symbols interchangeably, as well, so that you get practice looking at all of the forms.

- The last option is that we could do proton transfer, and then eliminate RO^-. This process occurs with rate constant k_3.
- Note that any time we eliminate RO^- (k_2 or k_3), the resultant carboxylic acid will be irreversibly deprotonated under the present basic conditions.

– HO^- and RO^- are comparable leaving groups (i.e., comparably good at leaving).
- Thus, we should have $k_1 \approx k_2 \approx k_3 \approx k_4$.
- So if this scheme is correct, we expect to get some ^{18}O in the recovered ester, via the k_4 pathway!

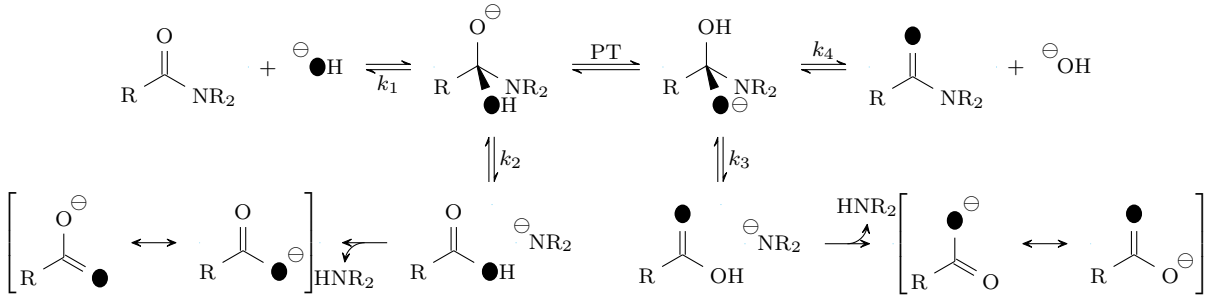
– Now let's consider the other possibility: Figure 4.43b displays the full kinetic network for the S_N2 mechanism.

– If we do an S_N2 reaction, we should get a stable carboxylate that does not participate in a back reaction.
- Therefore, we should see no ^{18}O in the recovered ester SM at 50% conversion.

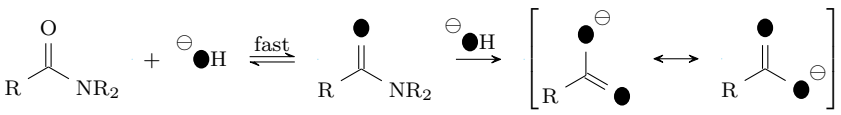
– Experimentally, what we find is that there *is* ^{18}O in the recovered ester.
- Therefore, the tetrahedral intermediate does exist!

– If this experimental setup isn't making sense right now, go home, meditate, relax, and then look at this again under calmer circumstances.

- This concludes our discussion of how an isotopic labeling study provides evidence for the existence of the tetrahedral intermediate over an S_N2 pathway.
- We now move onto an isotopic labeling study of amide hydrolysis, with the goal of showing how a mechanism that proceeds through a tetrahedral intermediate can explain the following two experimental results.
  – Under basic amide hydrolysis conditions (which we stop at 50% conversion), we get lots of ^{18}O in the recovered amide.
  – Under acidic amide hydrolysis conditions (which we stop at 50% conversion), we get much less ^{18}O in the recovered amide.
- We now dive more deeply into the mechanism under basic conditions, which is Subtopic 4.b.



(a) The kinetic network for the addition-elimination mechanism.



(b) The overall reaction.

Figure 4.44: Isotopic labeling to prove a tetrahedral intermediate: Amide hydrolysis.

  - The overall scheme (Figure 4.44a) bears a great resemblence to Figure 4.43a. However, there is one key difference.
    - H_2O has a much lower pK_a than HNR_2 (see Table 4.1), which means that HO^- (the conjugate base of H_2O) is a *much* better leaving group than R_2N^- (the conjugate base of HNR_2).
    - This means that while $k_1 \approx k_4$ and $k_2 \approx k_3$, we have that $k_1 \gg k_2$.
  - This implies that under basic conditions, the initial amide equilibrates fast with the isotopically labeled amide (Figure 4.44b).
    - It follows that we'll often observe a carboxylate product with two ^{18}O's!
    - To reiterate, this is because the first gets incorporated fast, and the second happens more slowly. So by the time we do amide hydrolysis, some ^{18}O will have already been incorporated!

- A deep dive into the mechanism under acidic conditions will be covered in recitation by the TFs.
- We now move onto Topic 5: Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
- Per a conversation this morning between Prof. Buchwald and Dr. Wendlandt — the chemistry professor currently teaching 5.12 — this should be review.
- Let's consider how our carboxylic acid derivatives react with the above four reagents.

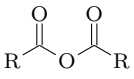
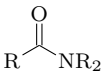
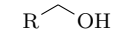
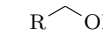
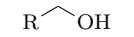
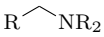
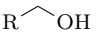
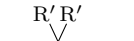
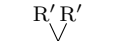
					
$NaBH_4$			NR	NR	NR
$LiAlH_4$					
R′MgBr					NR
R′Li					

Table 4.2: Reactions of carboxylic acid derivatives with $NaBH_4$, $LiAlH_4$, RMgBr, RLi.

  - Recall from Figure 4.20 that our carboxylic acid derivatives can be partitioned into...
    - More reactive compounds (acid chlorides and acid anhydrides);
    - Mid-range compounds (esters);
    - More stable compounds (amides);
    - By the far least reactive compounds (carboxylates).
  - Our reagents also vary in strength.
    - $NaBH_4$ is weaker. This can be good because it's more selective!
    - $LiAlH_4$, in contrast, is stronger and less selective.
  - It follows that $NaBH_4$ will reduce acid chlorides, acid anhydrides, and ketones to primary alcohols, but it will *not* reduce esters, amides, or carboxylates.
    - Aside: This fact is useful in **chemoselective** syntheses!
    - For example, you could put an ester and acid anhydride in the same molecule and know that only the acid anhydride will react with $NaBH_4$!
    - Chemoselectivity is one of the big trends in modern synthesis.
  - $LiAlH_4$ reduces everything to alcohols.

  - The Grignard reagent adds twice to carboxylic acid derivatives, yielding a tertiary alcohol.
    - This happens to acid chlorides, acid anhydrides, and esters.
    - Amides turn into the ketone (this is a special case!).
    - Carboxylates do not react.
  - Organolithium reagents (more potent than Grignards) react exactly the same as Grignards, except that they will *also* turn carboxylates into ketones!
    - This is a very surprising result, since we've talked about how unreactive carboxylates are.

- Where do ketones and aldehydes fit into the picture?
  - Ketones and aldehydes are between anhyrides and esters, and aldehydes are more reactive than ketones.
  - $NaBH_4$ will reduce ketones and aldehydes to the primary alcohol.
  - We'll talk about this more later.

- Next time: A mechanistic explanation for Table 4.2.

4.26 Acyl Transfer Reactions - 3 / Nitriles

11/6:

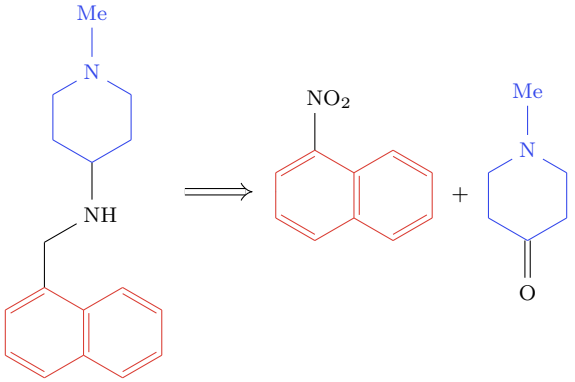
- Announcements.
  - Exam 3 is one week from today!
  - Lots of time today and Friday doing practice synthesis problems.
    - Friday's review will *not* involve a summary of the Unit 3-4 material; instead, Prof. Buchwald will send a synopsis in advance.
  - The more problems you work, the easier synthesis will become!!
  - Take advantage of the fact that we don't know *too* many reactions yet!

- Lecture 25 recap.
  - Evidence for a tetrahedral intermediate in acyl transfer reactions: Isotopic labeling studies.
  - Recall Table 4.2.
    - This gets back to what is key for synthesis: **Chemoselectivity**.
      - ➢ Example: Consider a molecule with an aldehyde and an amide. We can selectively reduce the aldehyde to the alcohol and not touch the amide if we reduce with $NaBH_4$.
      - ➢ This can be important in fancy molecules if we want to play with the **pharmacokinetics**.
    - Acid chlorides and anhydrides are *super* reactive.
    - Aldehydes and ketones get reduced by $NaBH_4$, too!
    - $NaBH_4$ is mild, while $LiAlH_4$ is *violent*. If you throw LAH into water, you'll get a *violent* reaction.
    - Similarly, Grignards are more mild than alkyllithium reagents.
      - ➢ Amides and carboxylates can become asymmetric ketones!

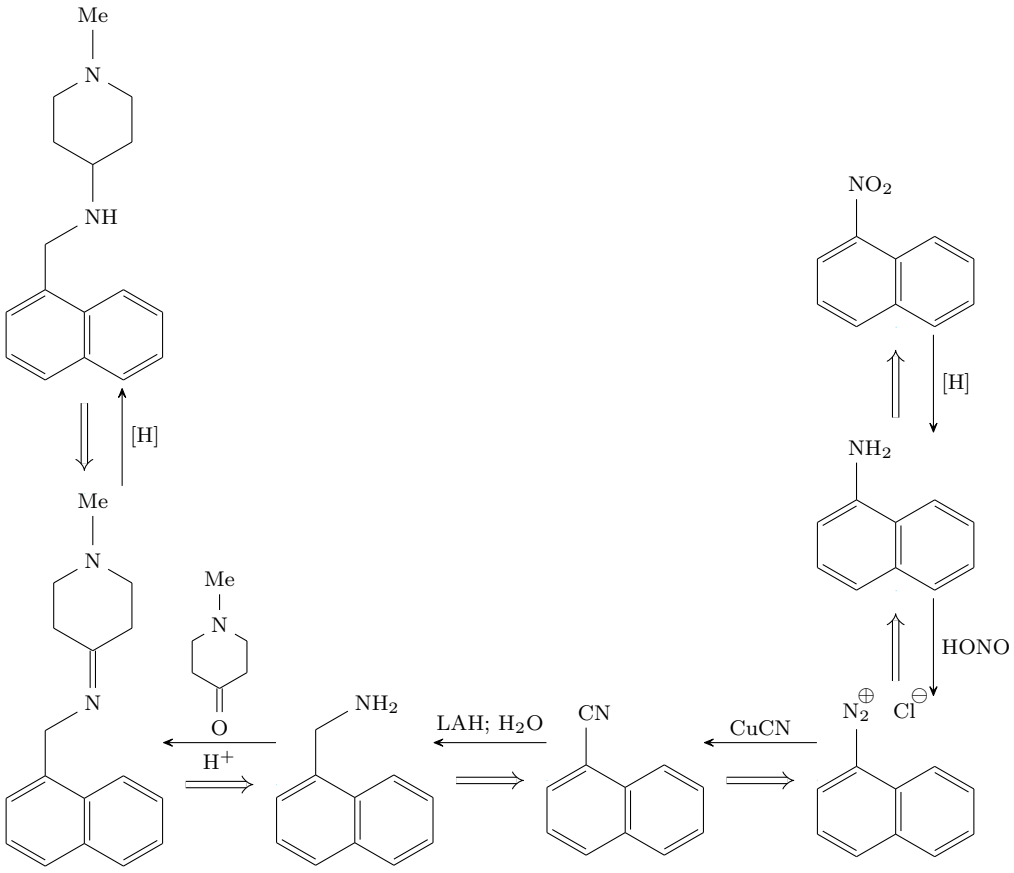
- **Chemoselectivity**: Selectivity for certain functional groups in the presence of other functional groups.

- **Pharmacokinetics**: The speed with which a drug moves into, through, and out of the body.
  - We don't want drugs to go straight through our bodies; we want them to hang around for a bit and do their thing (e.g., reduce our headache, soothe our cough, etc.).
  - We don't want to have to take it 5 times per day, so we modify functional groups with chemoselective reactions to slow the pharmacokinetics.

- TTQ: Synthesize the molecule at left in Figure 4.45a — a simplified version of a recently proposed candidate for treating epilepsy — from the provided starting materials.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 4.45: TTQ: Synthesis of a drug molecule.

– Like last time (see Figure 4.42), let's start by mapping out the carbons.

  ■ Using color coding, we can identify which carbons in the starting materials become carbons in the products (Figure 4.45a).

  - It then becomes clear that what we need to add is a carbon-nitrogen linkage.
    - This could come from a cyano group!
    - Carbon-nitrogen doesn't *always* mean we need a cyano group, but it often does.
  - So thinking backwards, the desired molecule could have come from an imine.
    - In the forward direction, we'd use a reducing agent ($NaBH_4$ or $LiAlH_4$ and a water workup) to reduce the imine to the amine.
    - Next step: Transform the imine to an amine via reducitve amination.
    - Next step: Transform the amine to the nitrile via LAH and a water workup.
    - Next step: Transform the cyano group to an aryl diazonium salt via a **Sandmeyer reaction** (i.e., with CuCN).
    - Next step: Transform the aryl diazonium salt to the amine via HONO.
    - Final step: Transform the amine to the nitro group via reduction with H_2 / Pt, H_2 / Pd/C, or H_2 / Ni. LAH and H_2O are not ideal here.

- **Sandmeyer reaction**: Any method of displacing an aryl diazonium salt with a nucleophile in the presence of catalytic copper (I) salts.
- Takeaway: A general strategy for synthesis problems.
  1. Identify matching fragments (mostly carbon fragments).
  2. Look for functional groups and disconnections.
- This concludes today's synthesis example; we now return to the chemistry of carboxylic acid derivatives.
- Lecture outline.

  5. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
  6. Chemistry of nitriles.
     a. Formation.
     b. Reactions.

- We begin by resuming Topic 5: Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
  - Specifically, we'll give the mechanistic explanation for Table 4.2 promised at the end of last lecture.
- Let's first consider why an acid chloride would react with hydride so quickly.

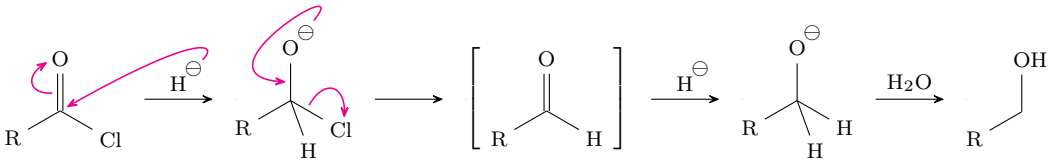


Figure 4.46: Reduction of acid chlorides mechanism.

  - For the same reasons as with Figure 4.23, both addition to and elimination from an acid chloride is fast — it makes no difference that our nucleophile is a hydride!
  - The first equivalent of hydride yields the aldehyde.
    - But we can't stop here!
    - Aldehydes are still reactive, so another equivalent of hydride will add in.
    - Then after a workup, we'll get the alcohol.
  - Aside: Reagents exist that *can* convert an acid chloride to an aldehyde and stop there.

- Let's now look at the addition of a Grignard to an acid anhydride.

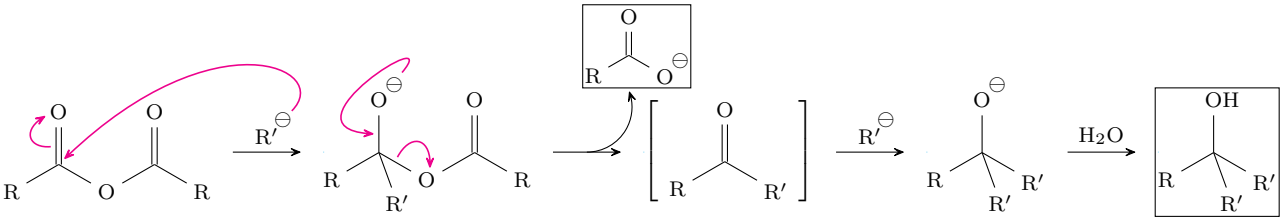


Figure 4.47: Grignard addition to acid anhydrides mechanism.

  - The Grignard (R′–MgBr) adds fast because acid anhydrides are not very resonance-stabilized either.
    - Then a good leaving group leaves to give a ketone.
    - Then the ketone reacts again to give us the tertiary alcohol.
  - But the carboxylate is still hanging around.
    - It will *not* react with a Grignard.
    - Thus, we get 50% of 3° alcohol and 50% carboxylate, so this is *not* an elegant reaction.

- If we use R′Li instead of R′MgBr, this gives us 100% of the 3° alcohol, so this *is* a good reaction.

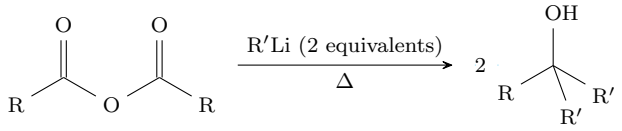


Figure 4.48: Alkyllithium addition to acid anhydrides.

  - R′Li is necessary because alkyllithium reagents are strong enough to reduce carboxylates, too (see Table 4.2).
  - Note that this reaction only proceeds with heating.
  - This reaction will *not* be tested!!

- With alkyllithium reagents, we can stop the reaction at the dianion and then quench.

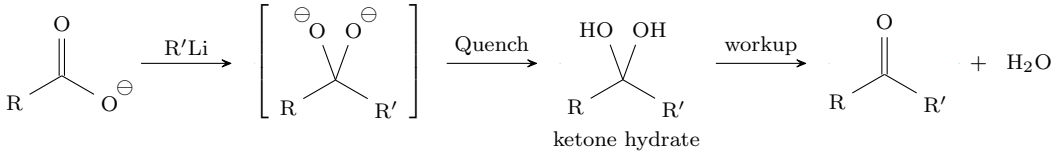


Figure 4.49: Alkyllithium addition to carboxylates.

  - To quench, use either water or H_3O^+.
    - You should write one of these two reagents above the arrow on a test, not "quench."
  - This gives us the ketone hydrate.
    - But ketone hydrates are not stable, so under workup, we'll lose H_2O and obtain the ketone.
  - This is the money reaction, and very much could be tested!!

- TTQ: How would you make a ketone from RLi and R′Li?

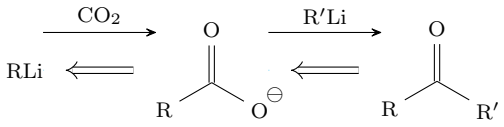


Figure 4.50: TTQ: Applying the addition of alkyllithium reagents to carboxylates.

  - First step: Transform the ketone into the carboxylate and R′Li via the reaction in Figure 4.49.
  - Second step: Transform the carboxylate into RLi via CO_2 carboxylation.

- Both LAH and R′M (M = MgBr, Li) can do add twice to esters.

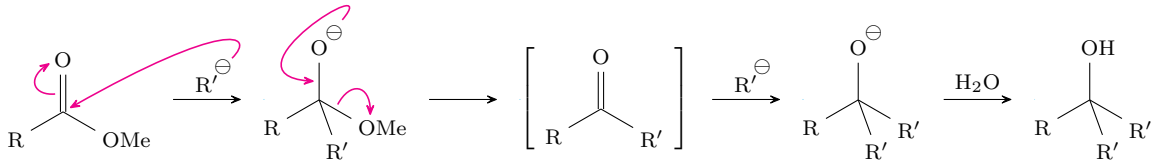


Figure 4.51: Organometallic addition to esters mechanism.

  - As we've seen before, the first step is addition to an electrophilic carbon center.
    - The resultant alkoxide anion is so powerful it can even push out a methoxide.
    - Then you get another addition to form the tertiary alcohol, after workup.
  - Takeaway: If you see a tertiary alcohol with two like substituents, get used to thinking that it might come from the reaction of two equivalents of a Grignard (or alkyllithium reagent) with an ester!

- We now discuss two other reactions to make ketones.
  - These take acyl derivatives — "acyl X" — to ketones.

- Reaction #1: Beginning with an acid chloride.

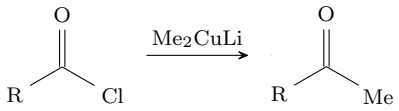


Figure 4.52: Monoaddition to acid chlorides with dimethylcopper lithium.

  - If we introduce a Grignard or alkyllithium reagent, the reaction will proceed all the way to the tertiary alcohol.
    - Thus, we need a gentler, more selective version of a Grignard or alkyllithium.
    - An example of such a reagent is **dimethylcopper lithium**.
  - TTQ: Given the reaction above (except for the starting material, reagent, or product), fill in the missing compound.

- **Dimethylcopper lithium**: A reagent composed of an anionic copper atom covalently bonded to two methyl groups and ionically bonded to a lithium cation. *Also known as* **Gilman reagent**, **organocuprate**. *Structure*

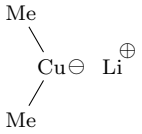


Figure 4.53: Dimethylcopper lithium.

  - History: Invented by Henry Gilman, an organic chemist at Iowa State University.
  - Aside: This compound is really good at 1,4-addition, also known as conjugate addition. We'll cover such this class of reactions in Unit 5.
  - Synthesis (not testable material): $2\,\mathrm{MeLi} + \mathrm{CuX} \longrightarrow \mathrm{Me_2CuLi}$

- Reaction #2: Beginning with a **Weinreb amide**.

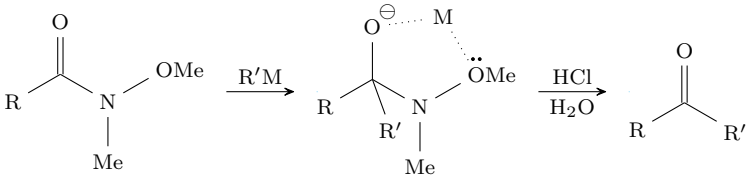


Figure 4.54: Weinreb ketone synthesis.

  - This reaction works with either Grignards or alkyllithium reagents.
  - After addition to the carbonyl, the metal coordinates to both the *N*-oxygen's lone pair and the alkoxy anion.
    - This is a quasi-stable species.
  - Water-workup then gets you the ketone.

- **Weinreb amide**: An amide with an *N*-methyl and *N*-methoxy group. *Structure*

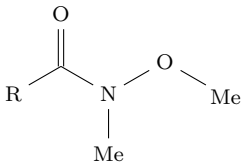
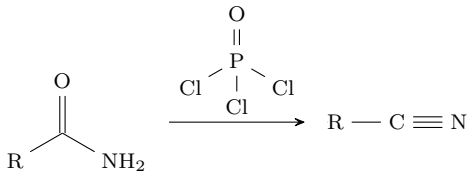


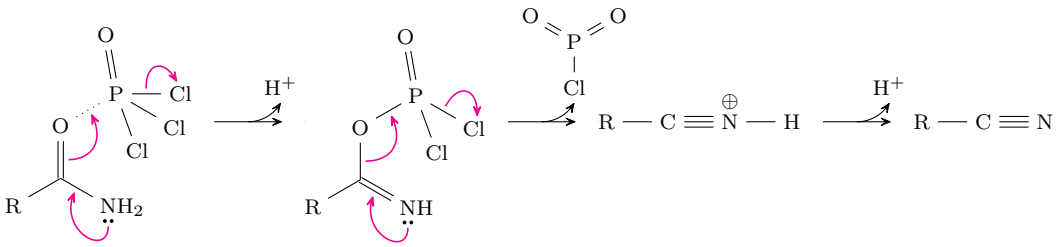
Figure 4.55: Weinreb amide.

- We now move onto Topic 6: The chemistry of nitriles.
- We'll begin with Subtopic 6.a: Formation of nitriles.
  - We'll start with three reactions you already know: S_N2 displacement, cyanohydrin formation, and the Sandmeyer reaction.
  - Then we'll cover one new method.
- S_N2 displacement (see Figure 3.21).
  - The X group can be Br, I, or OTs.

- Cyanohydrin formation (see Figure 3.22).
  - This reaction should be familiar from 5.12.
  - Note that the base catalyst usually has $pK_a \approx 9.5$.
- Sandmeyer reaction (see Figure 4.45b).
- One new method: Dehydration of amides.



(a) The reaction.



(b) A partial mechanism.

Figure 4.56: Nitrile synthesis: Dehydration of amides.

  - We add $POCl_3$ (the triacid chloride of phosphorous acid) to our amide (Figure 4.56).
    - $POCl_3$ is a very strong Lewis acid.
    - It rips out an equivalent of H_2O from our amide in a process known as dehydration.
  - Approximate mechanism (Figure 4.56b).
    - $POCl_3$ is a strong Lewis acid, so it will head straight for one of the carbonyl lone pairs. The amide lone pair can then kick up to allow proper O–P bond formation, and kick out a Cl^-.
    - Following deprotonation of the amide, we obtain an intermediate with a great leaving group. The new nitrogen lone pair can then kick out this leaving group, which will also lose another Cl^- to enable O=P bond formation.
    - A final deprotonation gives us our nitrile.
- We now move onto Subtopic 6.b: Reactions of nitriles.
- Nitrile hydrolysis (see Figure 4.8).
  - Adding a harsh acid or base gets you all the way to the carboxylic acid.
  - Adding a mild acid or base gets you the amide.
  - We will not ask you either set of conditions on an exam!!
- Converting nitriles to ketones.

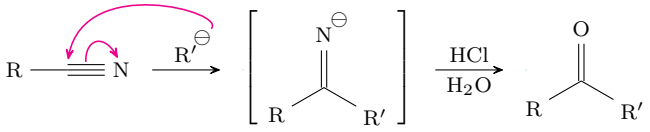
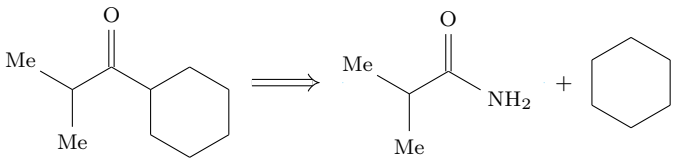


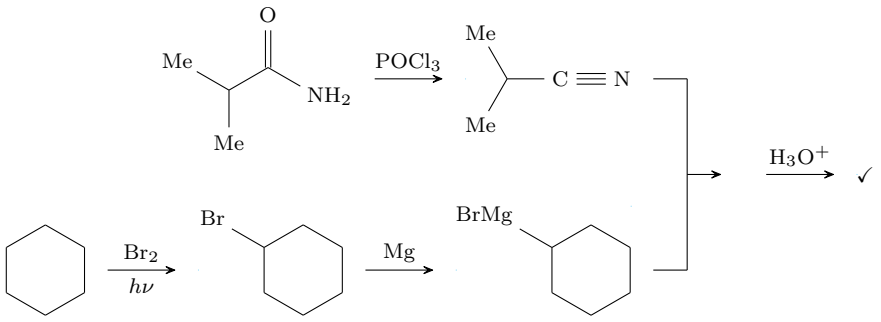
Figure 4.57: Organometallic addition to nitriles mechanism.

- Use an alkyllithium reagent or Grignard followed by an acidic workup.
- Implication: When you see a ketone in a molecule you're trying to synthesize, you can now think about whether it would be helpful if this retrosynthetically came from a nitrile and organometallic reagent, too!

- TTQ: Synthesize the molecule at left in Figure 4.58a from the provided starting materials.



(a) The desired molecule and starting materials.



(b) Solution.

Figure 4.58: TTQ: Applying nitrile addition chemistry.

- The cyclohexane to cyclohexyl bromide to Grignard reaction sequence in Figure 4.58b should be familiar from 5.12.
- Amide goes to nitrile with dehydration conditions ($POCl_3$).
- Then the nitrile plus the Grignard makes the product.

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