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.

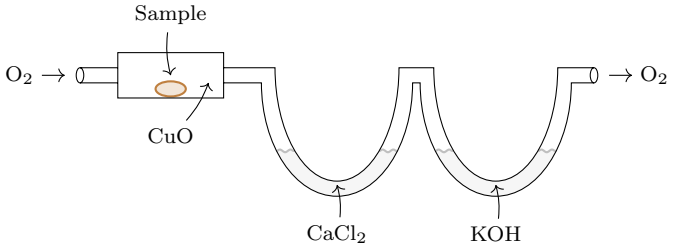


Figure 1.2: Combustion analysis schematic.

  - 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.

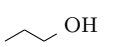
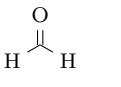
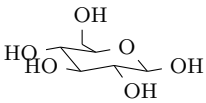
Name	Propanol	Methyl ethyl ether	Formaldehyde	Acetic acid	Glucose
Structure					
Emp. formula	C_3H_8O	C_3H_8O	CH_2O	CH_2O	CH_2O
Mol. formula	C_3H_8O	C_3H_8O	CH_2O	$C_2H_4O_2$	$C_6H_{12}O_6$

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.

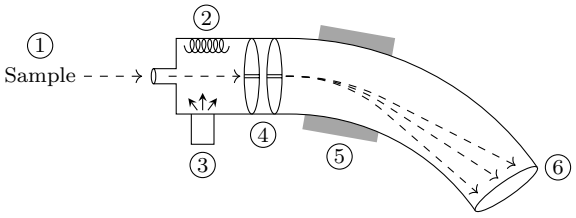


Figure 1.3: Mass spectrometer schematic.

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 ().

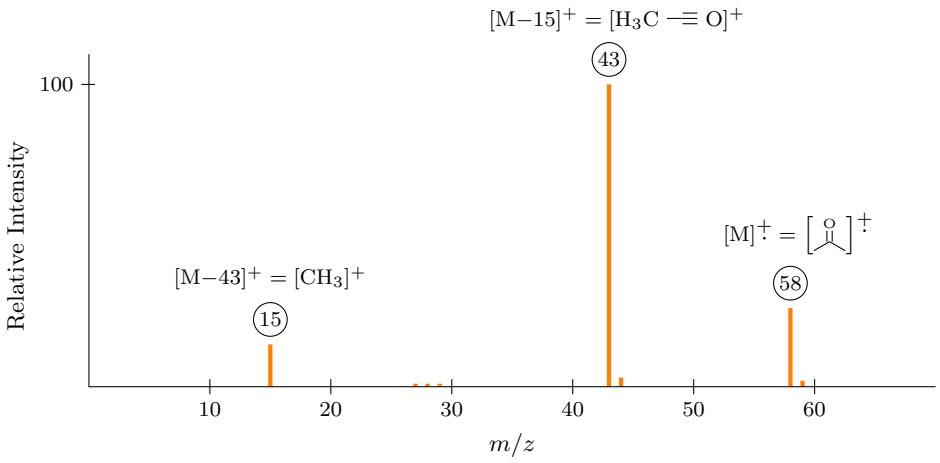


Figure 1.4: Mass spectrum of acetone.

  - 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 ( ).

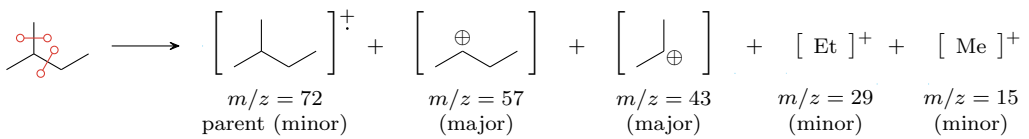


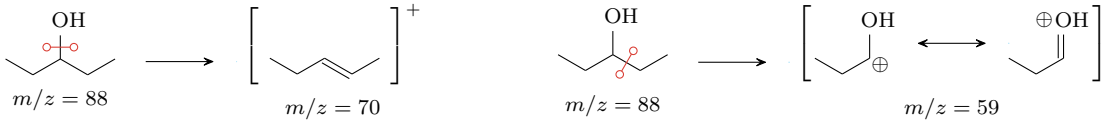
Figure 1.5: Fragmentation of alkanes.

  - 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 (

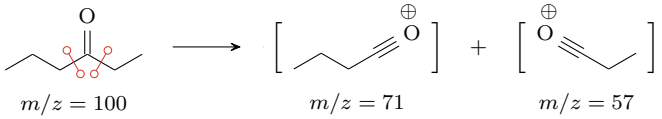
).



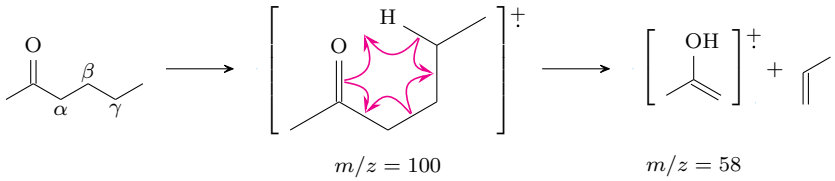
(a) Dehydration. (b) α-cleavage.

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.



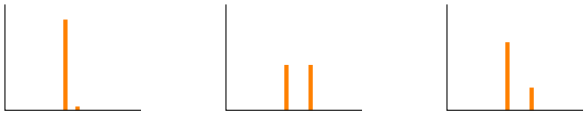
(a) α-cleavage.



(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 ().

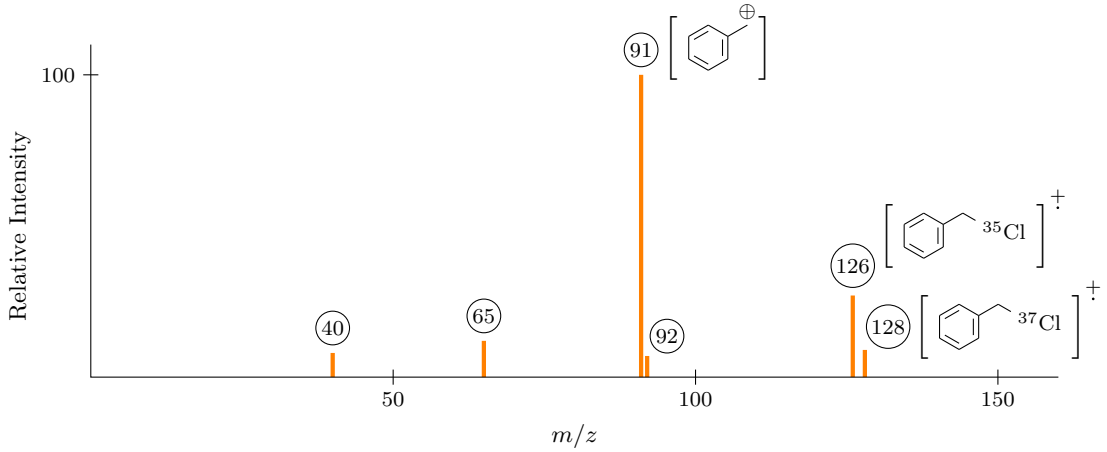


Figure 1.9: Mass spectrum of benzyl chloride.

  - 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.

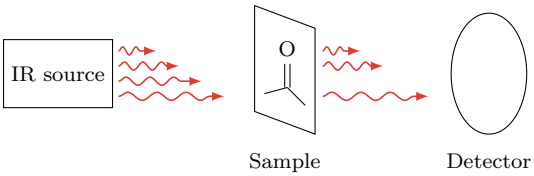
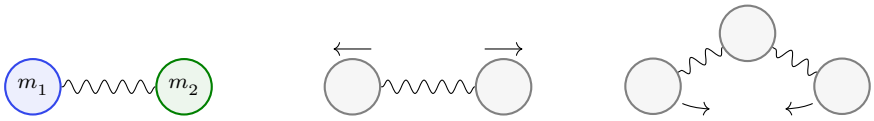


Figure 1.10: Infrared spectrometer schematic.

  - 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.



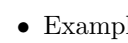
(a) Springy bonds. (b) Stretch. (c) Bend.

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 ().

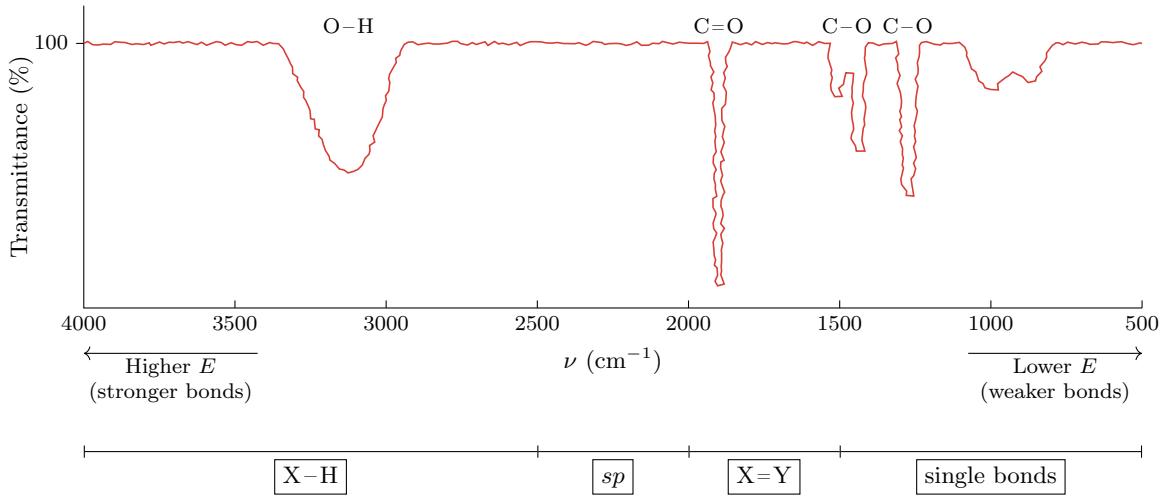


Figure 1.12: Infrared spectrum of propionic acid.

  - The x-axis is the frequency of the IR waves, measured in wavenumbers (cm^{-1}).
    - We typically are interested in the region from $4000 - 1500\,\text{cm}^{-1}$.
  - 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 $4000 - 2500\,\text{cm}^{-1}$ 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 $2500 - 2000\,\text{cm}^{-1}$ region.
      - In other words, polar triple bonds show up here.
      - Examples: C≡N and C≡C′.
    - X=Y bonds occur in the $2000 - 1500\,\text{cm}^{-1}$ region.
      - This is for polar double bonds.
      - Examples: C=O, C=C′,[5] and C=N.
    - Single bonds occur in the $1500 - 500\,\text{cm}^{-1}$ 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**: $4000 - 1500\,\text{cm}^{-1}$ (useful) and $1500 - 500\,\text{cm}^{-1}$ (useless).
- **Fingerprint region**: The region of an IR spectrum from $1500 - 500\,\text{cm}^{-1}$.
  - 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	$\boldsymbol{\nu}$ **(cm^{-1})**	**FG**	$\boldsymbol{\nu}$ **(cm^{-1})**	**FG**	$\boldsymbol{\nu}$ **(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

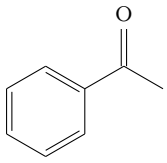
Table 1.2: Key regions of an infrared spectrum.

[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).

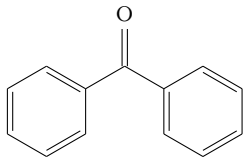
  - Note that functional groups listed higher up in each column of Table 1.2 have stronger bonds, and thus absorb higher energy/higher ν photons.
  - Both O–H and N–H peaks are broad *if* the proton is exchangeable.
    - There is an example in Clayden et al. (2012) of an O–H that is so sterically encumbered 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 ( ).

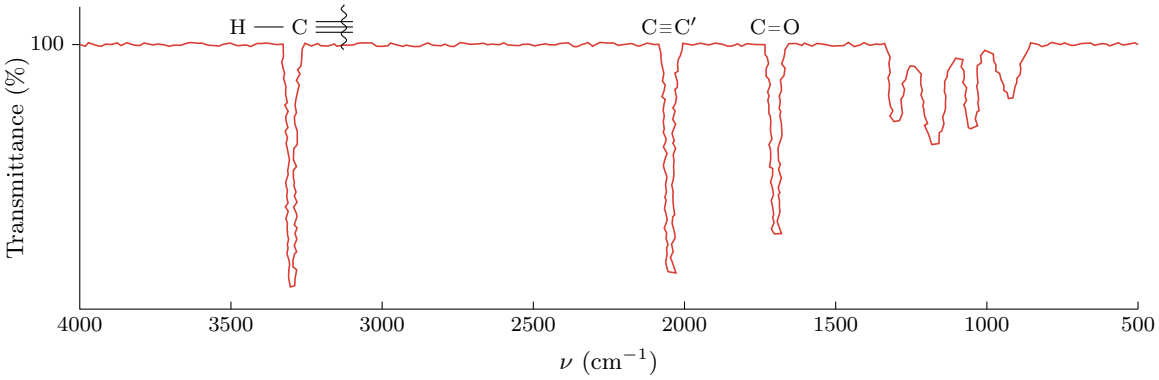


Figure 1.14: Infrared spectrum of but-3-yn-2-one.

  - 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.

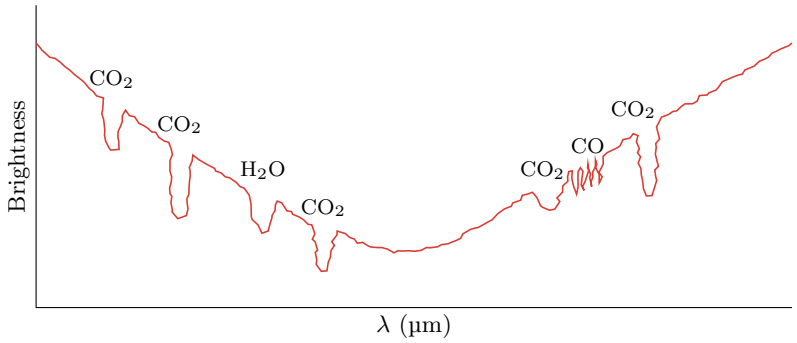


Figure 1.15: Infrared spectrum of the atmosphere of Mars.

[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.

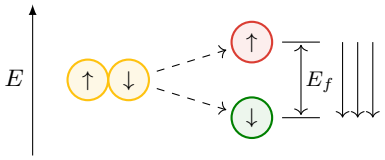


Figure 1.16: Nuclear magnetic resonance theory.

  - 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.

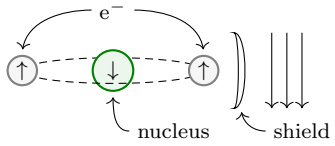


Figure 1.17: Shielding in NMR.

  - 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.

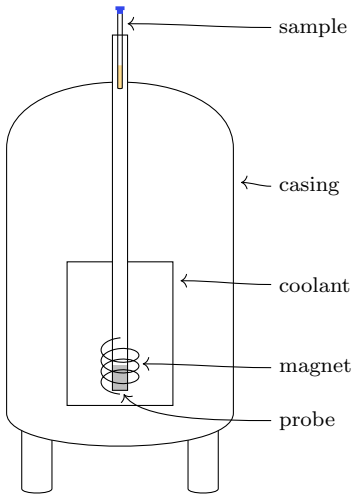


Figure 1.18: NMR spectrometer schematic.

  - 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 ().

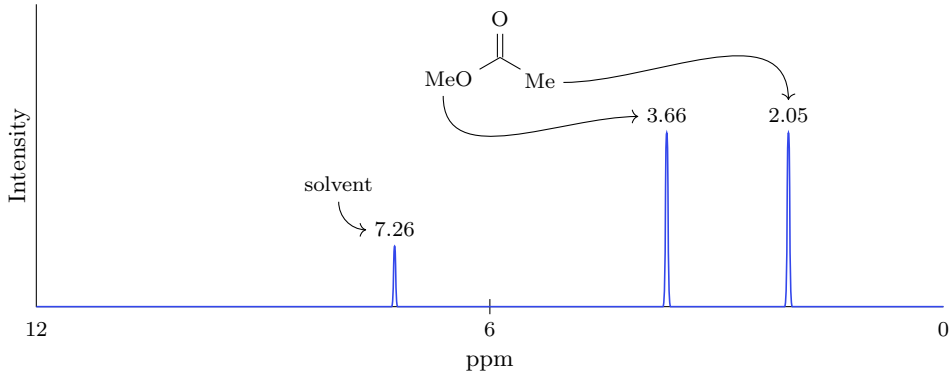


Figure 1.19: ^{1}H NMR spectrum of methyl acetate.

  - 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**.

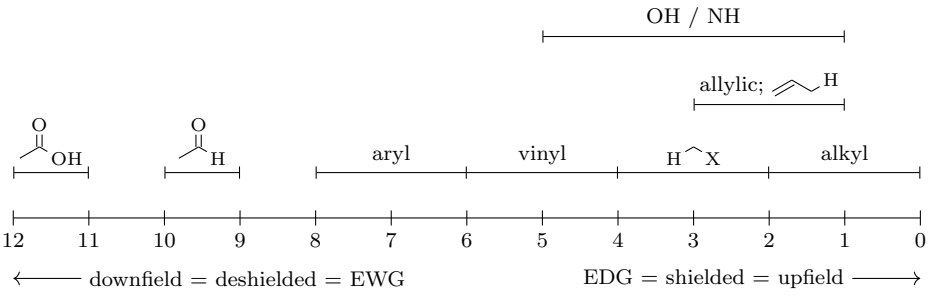


Figure 1.20: Chemical shifts of common proton types.

  - 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).

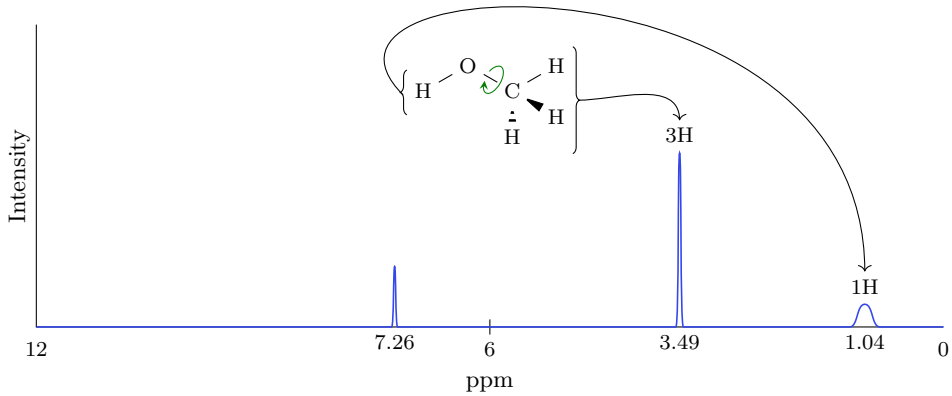


Figure 1.21: ^{1}H NMR spectrum of methanol.

  - 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 ( ).

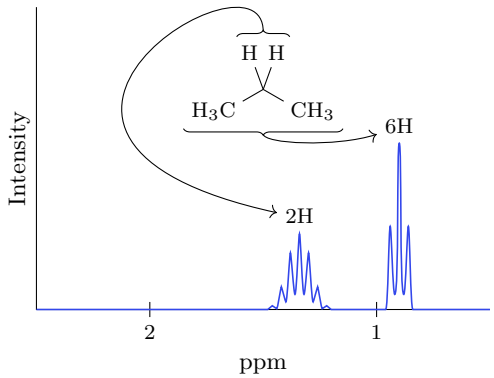


Figure 1.22: ^{1}H NMR spectrum of propane.

  - 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.

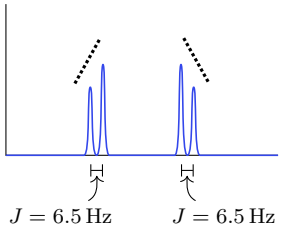


Figure 1.23: Roofing in NMR.

  - 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.

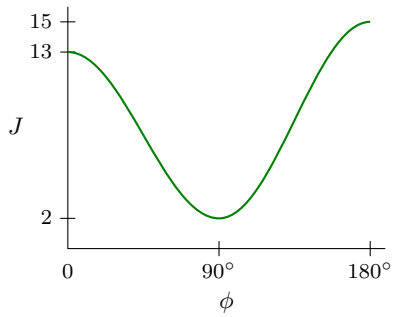


Figure 1.24: Karplus equation.

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

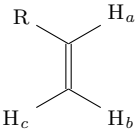


Figure 1.25: Coupling constants in a vinyl group.

  - 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.

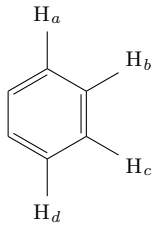
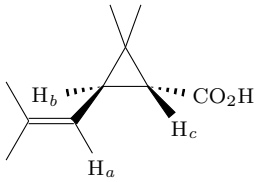
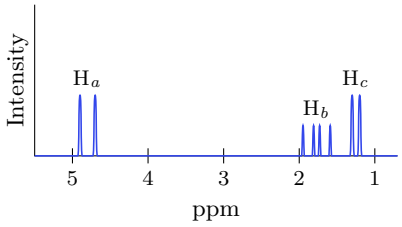


Figure 1.26: Coupling constants in benzene.

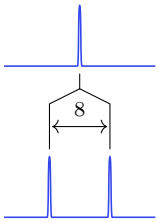
  - **Long-range coupling** is possible with π-systems.
    - Thus, protons *meta* and *para* to each other can couple even though they're not viscinal.
  - $J_{\text{ortho}} \approx 7 - 10\,\text{Hz}$.
  - $J_{\text{meta}} \approx 2 - 3\,\text{Hz}$.
  - $J_{\text{para}} \approx 0 - 14\,\text{Hz}$.
- Coupling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



(a) An example molecule.

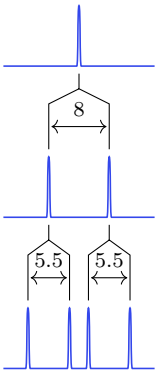


(b) The molecule's ^{1}H NMR spectrum.



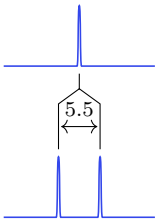
doublet

(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 ().

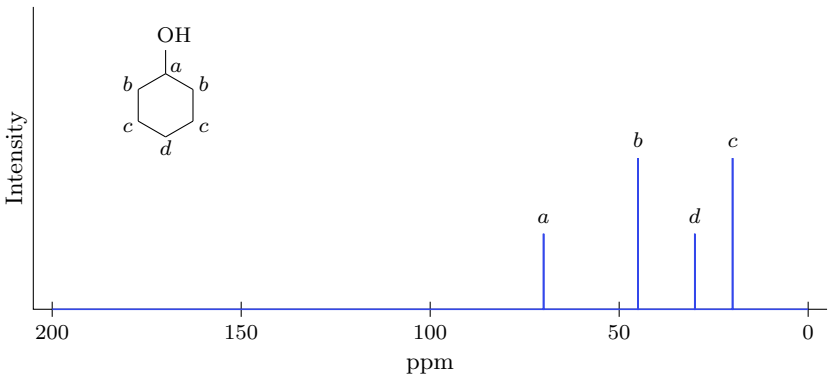


Figure 1.28: ^{13}C NMR spectrum of cyclohexanol.

  - 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!

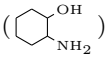
Molecule	Cyclohexanol ()	2-Aminocyclohexanol ()	Cyclohexane ()
# carbons	6	6	6
# unique carbons	4	6	1

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.

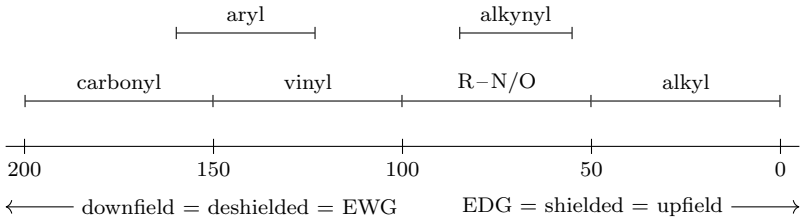


Figure 1.29: Chemical shifts of common carbon types.

  - 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 ().

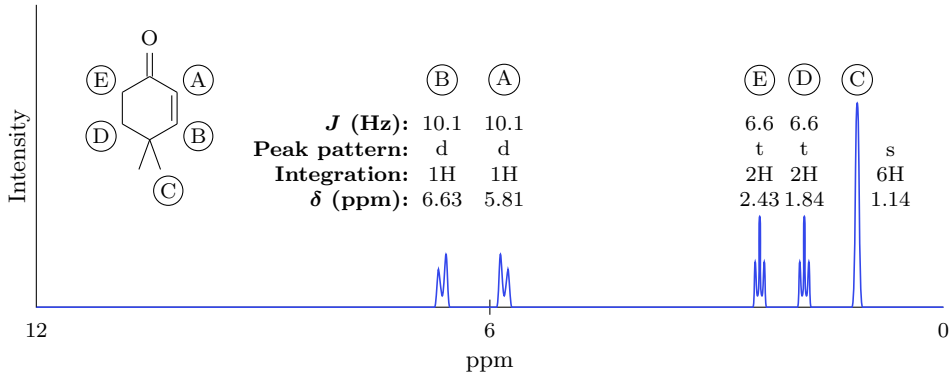


Figure 1.30: ^{1}H NMR spectrum of 4,4-dimethylcyclohex-2-en-1-one.

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.

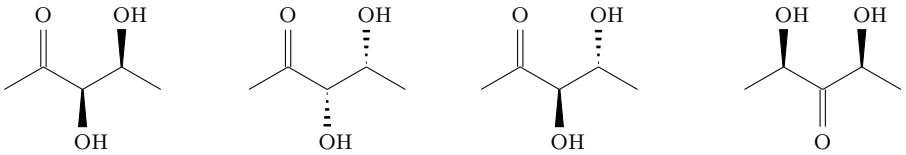
[11] Note that we include the peak at 6.63 ppm in the vinyl region even though it would normally fall in the aryl region (per Figure 1.20) due to the nearby carbonyl EWG.

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.

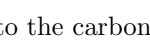
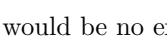
- If we try to distinguish the original structure (Figure 1.31a) from any of the others using the structure determination techniques, we'll find that the results are...

	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.

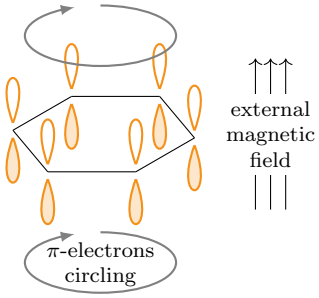
1.7 Structure Determination - 2

9/18:

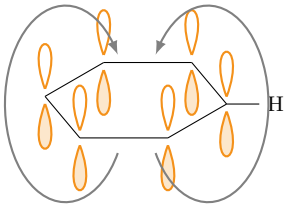
- Lecture 6 recap: The journey from having a liquid to having the liquid's molecular structure.
  1. EA: Get the empirical formula.
  2. MS (parent peak): Transform the empirical formula to the molecular formula.
  3. IR: Get key functional groups.
  4. ^{13}C NMR: Get the number of unique carbons, and 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.

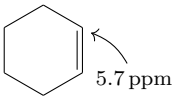
(a) Vinyl deshielding.



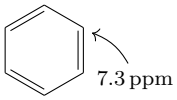
(b) Ring current induced.



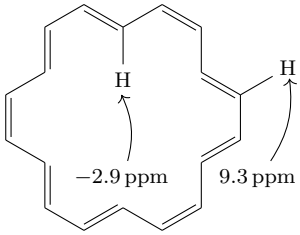
(c) New magnetic field.



(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.

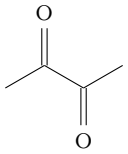


Figure 1.36: Diacetyl.

  - 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.

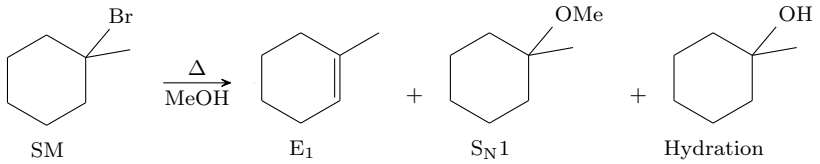


Figure 1.37: Characterizing the products of a chemical reaction.

  - 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.
  - $[M]^{+\cdot}$ and $[M+2]^{+\cdot}$ 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.

References

Clayden, J., Greeves, N., & Warren, S. (2012). *Organic chemistry* (Second). Oxford University Press.