

# 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<sup>[1]</sup> 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?

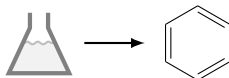


Figure 1.1: Why we study structure determination.

- 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?

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<sup>1</sup>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).<sup>[2]</sup>
  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  $\text{CO}_2$ .
  - All H in the sample becomes  $\text{H}_2\text{O}$ .
  - O is then determined via process of elimination, explained as follows.
- Advanced techniques (beyond the scope of this class): Nitrogen to NO or  $\text{NO}_2$ , sulfur to  $\text{SO}_2$ , etc.
- A schematic of combustion analysis.

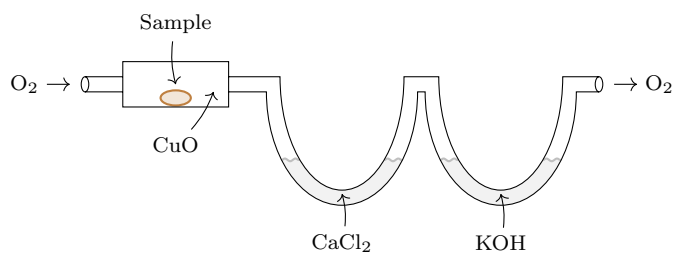


Figure 1.2: Combustion analysis schematic.

- Burn the sample in the presence of an oxidant such as cupric oxide ( $\text{CuO}$ ).
- Flow  $\text{O}_2$  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  $\text{CaCl}_2$ ) that absorbs the water.

<sup>2</sup>NMR is an organic chemist's best friend!

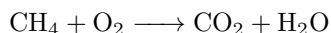
- The second one contains a base (like KOH) that absorbs the CO<sub>2</sub>.
  - The remaining oxygen flows out the end.
- The *analysis* part of combustion analysis.
  - The amount of H is equal to the change in mass of the CaCl<sub>2</sub>.
 
$$\Delta\text{mass}(\text{CaCl}_2) = \text{mass}(\text{H}_2\text{O}) \rightarrow \text{ratio}(\text{H})$$
  - The amount of C is equal to the change in mass of the KOH.
 
$$\Delta\text{mass}(\text{KOH}) = \text{mass}(\text{CO}_2) \rightarrow \text{ratio}(\text{C})$$
  - The amount of O is equal to the change in mass of the sample.
 
$$\text{mass}(\text{sample}) - \text{mass}(\text{H}) - \text{mass}(\text{C}) = \text{mass}(\text{O}) \rightarrow \text{ratio}(\text{O})$$
  - Result: We get an **empirical formula** of the form C<sub>x</sub>H<sub>y</sub>O<sub>z</sub>. 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<sub>3</sub>H<sub>8</sub>O).
  - Suppose we obtain 0.600 g H<sub>2</sub>O and 1.09 g CO<sub>2</sub>.
  - 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.
    - $0.600 \text{ g H}_2\text{O} \times \frac{1 \text{ mol H}_2\text{O}}{18.02 \text{ g H}_2\text{O}} \times \frac{2 \text{ mol H}}{1 \text{ mol H}_2\text{O}} \times \frac{1.01 \text{ g H}}{1 \text{ mol H}} = 0.067 \text{ g (H)}$
    - $1.09 \text{ g CO}_2 \times \frac{1 \text{ mol CO}_2}{44.01 \text{ g CO}_2} \times \frac{1 \text{ mol C}}{1 \text{ mol CO}_2} \times \frac{12.01 \text{ g C}}{1 \text{ mol C}} = 0.300 \text{ g (C)}$
    - $0.5 \text{ g propanol} - 0.067 \text{ g (H)} - 0.300 \text{ g (C)} = 0.133 \text{ g (O)}$
- A note on the previous example.

Name	Propanol	Methyl ethyl ether	Formaldehyde	Acetic acid	Glucose
Structure					
Emp. formula	C <sub>3</sub> H <sub>8</sub> O	C <sub>3</sub> H <sub>8</sub> O	CH <sub>2</sub> O	CH <sub>2</sub> O	CH <sub>2</sub> O
Mol. formula	C <sub>3</sub> H <sub>8</sub> O	C <sub>3</sub> H <sub>8</sub> O	CH <sub>2</sub> O	C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>	C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>

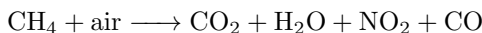
Table 1.1: Questions that EA can't answer.

- 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<sub>2</sub>O!
- 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<sub>4</sub>) — for heat.

- **Ideal combustion**<sup>[3]</sup> corresponds to the reaction



- Real-world combustion is incomplete; you make

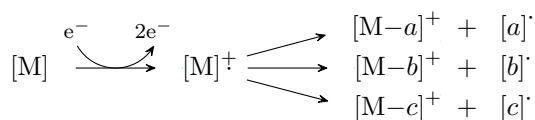


- When a technician comes to your home, they analyze the flue gas (i.e., your furnace exhaust).
  - Their analysis could determine that our combustion has too much O<sub>2</sub>, which is called “air rich.” This is inefficient and doesn’t yield enough heat.
  - They could also determine that you have too much CO<sub>2</sub> 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<sub>2</sub>! 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).
 
$$\text{SM} + \text{O}_2 \xrightarrow{\Delta} \text{CO}_2 + \text{H}_2\text{O}$$
    - SM means “starting material.”
    - SM’s we will focus on: Compounds of the form C<sub>x</sub>H<sub>y</sub>O<sub>z</sub>.
  - 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.



<sup>3</sup>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  $[M]^+$  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.

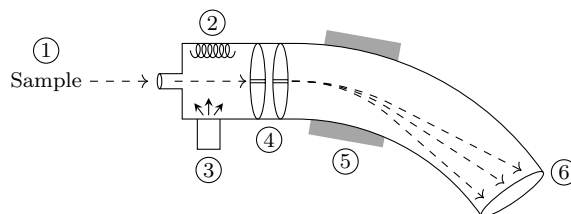


Figure 1.3: Mass spectrometer schematic.

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  $m/z$ .*
    - For the purposes of this class,  $z = 1$ .
  - Example mass spectrum: Acetone (CC(=O)C).

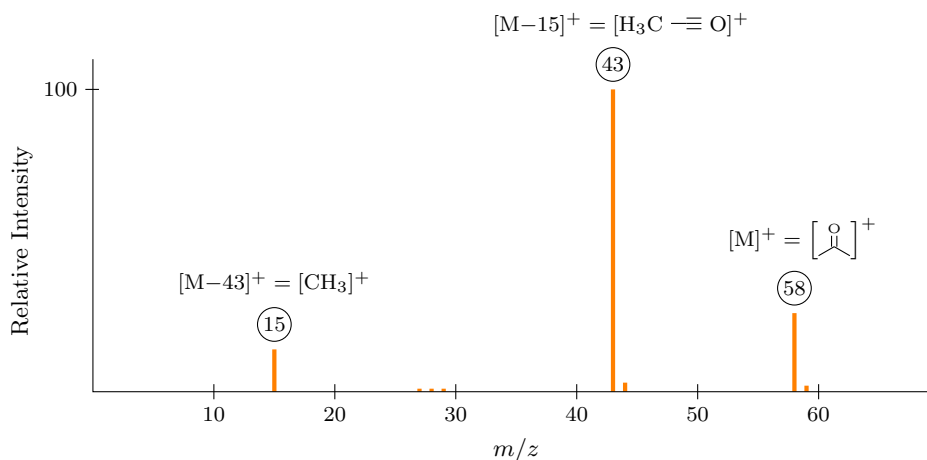



Figure 1.4: Mass spectrum of acetone.

- 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  $[M-a]^+$ , 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.<sup>[4]</sup> 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: 2-methylbutane ().

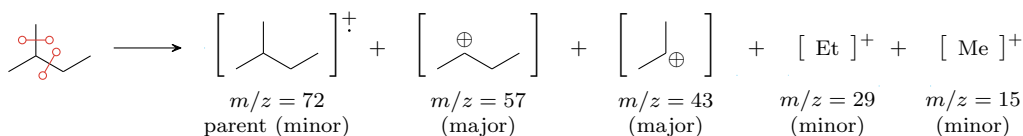


Figure 1.5: Fragmentation of alkanes.

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

<sup>4</sup>Excepting isotope effects; discussed later in this lecture.

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

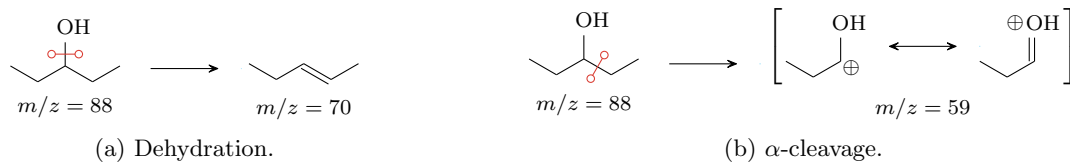


Figure 1.6: Fragmentation of alcohols.

- Ketone fragmentation.
  - $\alpha$ -cleavage: Leads to a resonance-stabilized product, once again.
  - McLafferty rearrangement: Only happens for ketones with a  $\gamma$ -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.

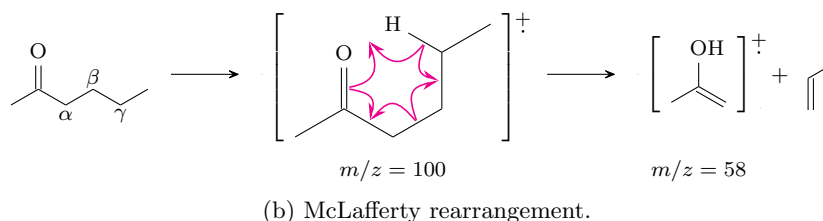
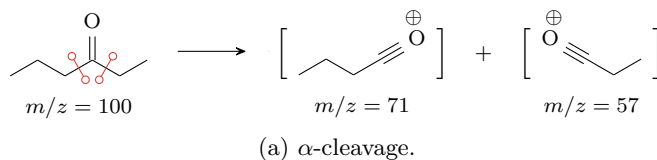


Figure 1.7: Fragmentation of ketones.

- 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.

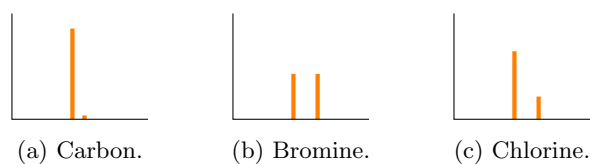


Figure 1.8: Isotope effects in MS.



- Carbon: The  $^{12}\text{C} : ^{13}\text{C}$  ratio is 99 : 1.
  - Implication: For every  $[\text{M}]^+$ , we see 1%  $[\text{M}+1]^+$ .
  - 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  $^{79}\text{Br} : ^{81}\text{Br}$  ratio is 1 : 1.
  - Implication: The  $[\text{M}]^+$  and  $[\text{M}+2]^+$  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  $^{35}\text{Cl} : ^{37}\text{Cl}$  ratio is 3 : 1.
  - Implication: The  $[\text{M}]^+$  and  $[\text{M}+2]^+$  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 (c1ccccc1CCl).

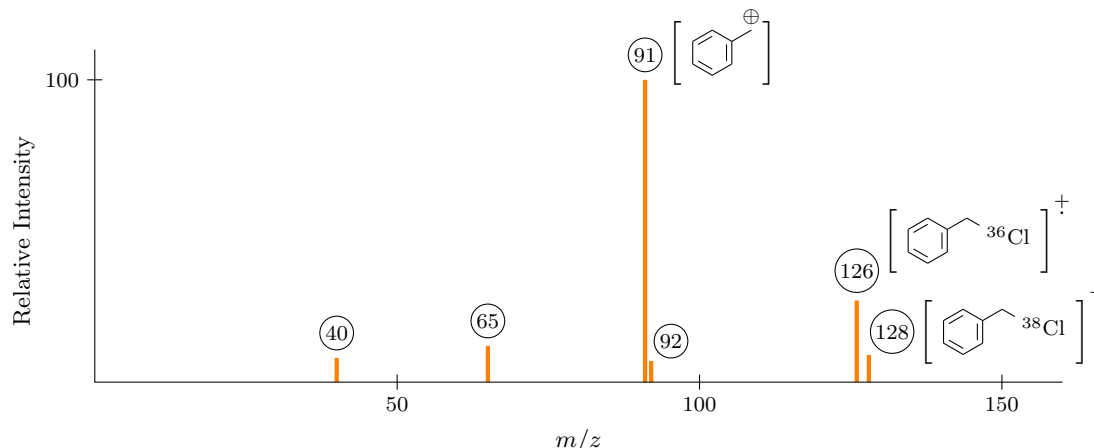


Figure 1.9: Mass spectrum of benzyl chloride.

- 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  $\text{H}_2\text{O}$  is  $-18$ .
      - Loss of  $\text{CO}_2$  is  $-44$ .
      - Loss of a  $^t\text{Bu}$  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  $\text{N}_2$  and  $\text{C}_2\text{H}_4$  have  $m/z = 28$ .
  - In HRMS,  $\text{N}_2$  has  $m/z = 28.0061$  and  $\text{C}_2\text{H}_4$  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  $^{12}\text{C} : ^{13}\text{C}$  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  $^{13}\text{C}$  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.