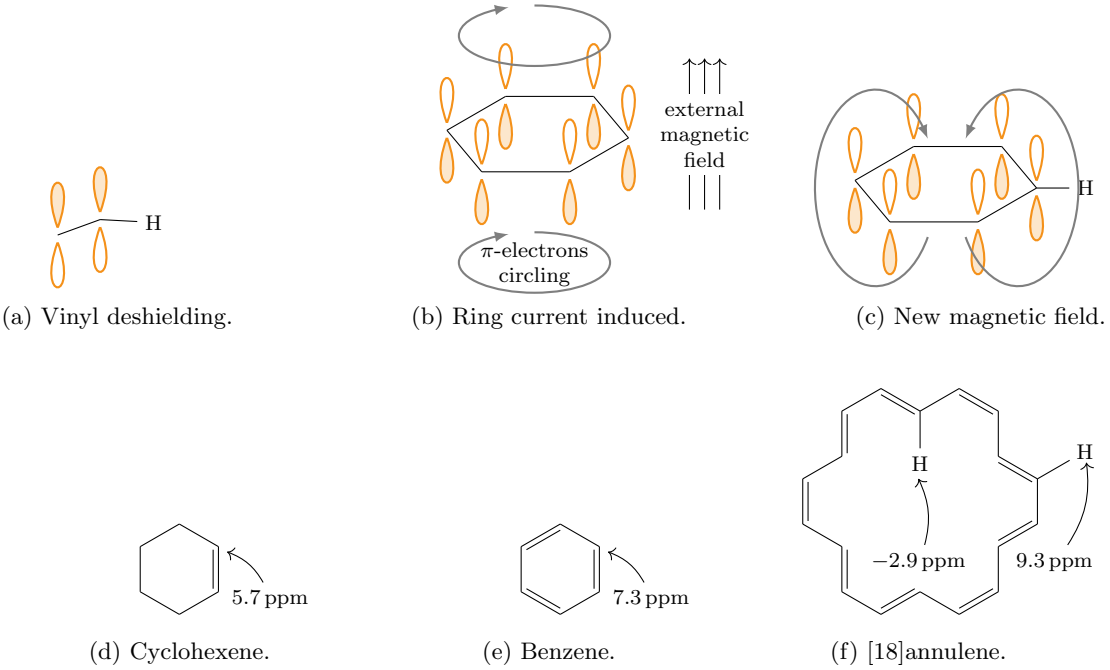
  - EA key signals? No.
    - The molecules have identical empirical formulas.
  - MS key signals? Tough.
    - We'd get $\alpha$-cleavage with both ketones, leading to similar fragments.
  - IR key signals? Tough.
    - The C=O stretch would be the main IR-active signal, and both carbonyls are fairly 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 $\pi$-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 $\pi$-system, coplanar with the so-called "$\sigma$-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 $\pi$-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 $\pi$-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 $\lambda$. *Denoted by* $[\boldsymbol{\alpha}]_{\boldsymbol{\lambda}}^{\boldsymbol{T}}$.
  - 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.

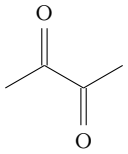



Figure 1.36: Diacetyl.

  - 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.

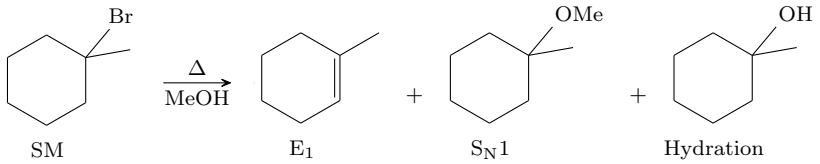



Figure 1.37: Characterizing the products of a chemical reaction.

  - 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 $\beta$ to the alkene.
    - ➢ We form an oxygen-stabilized carbocation from $S_N1$ by performing $\alpha$-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.