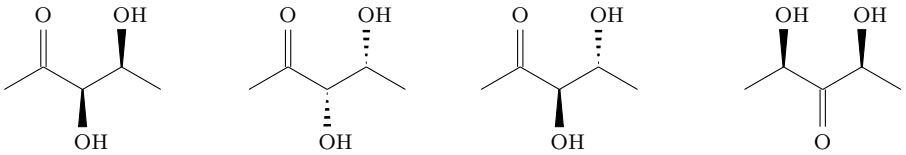
1.6 Structure Determination - 1

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.

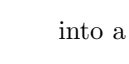
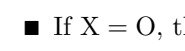
- If we try to distinguish the original structure (Figure 1.31a) from any of the others using the structure determination techniques, we'll find that the results are...

	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.