CHEM 22100 (Organic Chemistry II) Notes

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Week 1

Review and Intro to NMR

1.1 Introduction and Review

1/11:

- We're skipping alcohols and ethers and coming back later because that's what third quarter really focuses on.
- What you need to worry about is class content — if he doesn't mention it, even if it's in the book, we won't be responsible for it on exams.
- Natural products inspire new drugs.
  - Salicylic acid mediates pain, but it will erode the lining of your stomach.
  - Hoffmann functionalizes the alcohol to an ester, removing the negative effects and creating aspirin.
- Sucrose (table sugar) is glucose plus fructose. Glucose tastes slightly less sweet, and fructose tastes a whole lot sweeter.
- We now consume 120 pounds of sugar per person per year, different from 20 pounds per person per year in 1976 and 1 pound per person per year in older times.
  - So we have developed artificial sweeteners that cut calories, such as saccharin, aspartame, and sucralose.
  - Sucralose is thermally stable (you can bake with it), has no chloric content, and is made from sugar by protecting some alcohols and replacing others with chlorines.
- Capsaicin (spiciness) evolved to prevent bugs from biting their host plants.
  - Both capsaicin and resiniferatoxin have the same vanillin group; thus, this group is probably important for reacting with pain receptors.
- Compactin from mushrooms lowers cholesterol.
  - Zocor and lipitol are derived from it!
- Taxol (breast cancer treatment) accumulates slowly in rare trees.
  - We can derive from the needles (a renewable resource), however, a compound that is easily functionalized to taxol.
- It is essential to understand the mechanisms in this course!
  - We won't have to worry much about competing reactivity, but we do need to know how reactivity can change in different situations.
- Quinine treats malaria.

  - Quinine is what makes fizzy water taste bitter.
  - In trying to fabricate Quinine, Perkin discovers a compound that dyes fabric purple. Never gets his PhD but makes millions off of this invention. Before, only royals could wear purple (the sole source was mediterranean sea slugs).

- Identify S_N1 by the fact that all chiral information in the reactant will be lost.
- Identify S_N2 by the inversion of stereochemistry.
- We won't worry much about E1 this quarter.
- We'll see a lot of E2 this quarter.
- We'll look into radical and pericyclic (Diels-Alder) reactions this quarter.
- Molecules that may look similar can actually be quite different.
- Color is related to the number of double bonds in a molecule.
- Blue lobsters are blue because they have enough of an enzyme to sequester all of the colorant in the shells of the lobsters.
  - Would you pay more for it because of its rare color? Probably shouldn't because cooking it will still make it red. It won't taste any better.
- Fleming and penicillin.
  - Initially we have no idea what its structure is.
  - It's hard to synthesize something if we have no idea what it is.
  - During WWII, American and Britain embark on a campaign to synthesize penicillin equal in scope to the Manhatten project, but it wasn't successful.
  - Eventually, Dorthy Crowfoot Hodgkin gets its structure with x-ray crystallography, after wrong attempts from R. B. Woodward and Sir Robert Robinson (future Nobel laureates who hated each other).
  - The moldy cantaloupe.
  - In 1955, John Sheehan at MIT comes up with the first chemical reagent capable of synthesizing penicillin's 4-membered ring.
  - But we made too many antibiotics and antibiotic resistance developed.
  - MRSA is only killed by vancomycin, but they're even developing resistance to that.
  - Thinking chemically to get off the pesticide treadmill.
  - We need the sophistication of nature to build molecules more complex than we can build en masse pharmaceutically.
  - As species go extinct, though, we are losing potential weapons.
- X-ray crystallography pinpoints the location of all atoms other than hydrogen in a molecule.
- Line-angle is gonna be big this quarter.
- We will not be tested on IUPAC nomenclature, but we should know it just to be able to communicate.
- Talks about resonance and induction.
- The IR spectroscopic signal of a carbonyl is $1700\,\mathrm{cm}^{-1}$.
- Resonance affects acidity and IR spectroscopy — bonds that resonate (have less double bond character) will have lower IR frequencies.
- A lot of reactions are quenched by an H_3O^+ workup — just enough to quench, not enough to react.

1.2 Office Hours (Snyder)

- Reviews degrees of unsaturation.
- Talks about resonance, too.
- Make sure you know your functional groups!
- Alkene-based reactions are the most important to review.
- Glucose and mannose are diastereomers.
- Global vs. local symmetry.
  - Helps you determine how many signals you will see in a ^{13}C NMR spectrum.
  - Acetone only has 2 ^{13}C NMR signals (the methyl and the carbonyl one).
  - The ability to draw a mirror plane tells you that certain signals are equivalent.
  - You can rotate hexane into a conformation in which it will have a mirror plane.

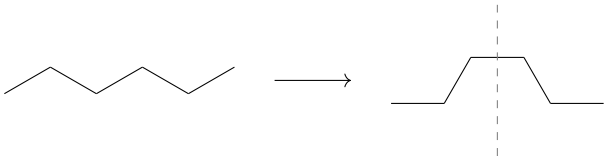


Figure 1.1: Mirror plane in hexane.

  - No symmetry, such as in 1-bromo-2,5-dichloro-3,4,6-trimethylbenzene, means all (nine) distinct signals.
  - Local symmetry (think an isopropyl group).
    - Look for branch points.
    - You must have consistency of structure for the entirety of branches.
  - para-dibromobenzene has only 2 signals since it has *two* mirror planes.

1.3 NMR

1/13:

- He is going to try and present a different perspective from the book because otherwise, why take the class.
- There is no preset curve for this class — everyone can get an A.
- The right and left boards will be there for the whole class, every class.
- H_3O^+ workup.

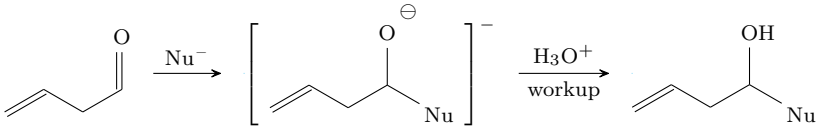


Figure 1.2: H_3O^+ workup.

  - Don't think acid-catalyzed hydration. Acid-catalyzed hydration is a very specific reaction. Organic chemists don't really use it because those conditions are so acidic that no other functional groups survive it.

  - An H_3O^+ workup is adding H_3O^+ at the end of a reaction to neutralize the structure and excess nucleophile in solution without affecting other groups.

- Next three lectures: Tools for characterizing molecules, e.g., determining what we have in solution.
- It could take decades or even centuries to determine the structure of molecules in the early days of chemistry.
  - It would also take large quantites for experiments.
  - Now we can determine the structures of quantities we can only isolate milligrams of.
- IR can only identify the presence of some functional groups and maybe the identity of a compound that's already been determined (i.e., from the fingerprint region and an online database).
- NMR.
  - Such machines exist in hospitals as MRI.
  - We have dropped the "N" in NMRI because of nuclear's negative connotation, even though MRI machines have nothing to do with radioactivity.
- Any nucleus that has an odd atomic number will have a dipole moment.
  - The four most significant ones for organic chemistry are ^{1}H, ^{13}C, ^{15}N, and ^{17}O.
  - The last three are all not commonly occurring isotopes. Oxygen, especially, can barely be measured. Hydrogen will be the most useful because ^{1}H is the most commonly occurring isotope.
  - For ^{13}C, we will need a longer experiment since only 1/1000 carbon atoms is ^{13}C.
- Theory-lite for NMR.
  - Parallel spins are lower energy, but the difference in energy from anti-parallel is very small (approximately 5×10^{-6} kcal/mol).
  - $1 - 20$ mg of compound is needed in 0.75 mL of solvent.
  - This is a non-destructive process — we can recover our compound after running the experiment.
  - We typically use $CDCl_3$ as our solvent.
  - A part per million (ppm) is a Hz/MHz.
- George Van Dyke Tiers, a grad student at UChicago, determined in 1958 that TMS might be the best standard (low chemical shift, chemically inert, easily removed, etc.).
- Goes over examples from office hours.
- DEPT: Changes the angle of the magnetic field to distinguish CH, CH_2, and CH_3 groups.
  - DEPT 90 changes the angle by 90°; DEPT 135 by 135°.
  - In DEPT 90, we'll only see CH carbons.
  - In DEPT 135, CH and CH_3 groups will peak in the positive direction, and CH_2 groups will peak in the negative direction.
  - Neither experiment will show carbons that aren't bonded to any hydrogens.
  - Note that DEPT works for any type of carbon of any hybridization; it only discriminates based on the number of ^{1}H's attached.

1.4 Chapter 9: Nuclear Magnetic Resonance and Mass Spectroscopy

From Solomons et al. [1].

1/11:

- **Nuclear magnetic resonance spectrum**: A graph that shows the characteristic energy absorption frequencies and intensities for a sample in a magnetic field. *Also known as* **NMR spectrum**.
- The chemical shift of a signal gives important clues about molecular structure (see Table 1.1).

Type of Proton	Chemical Shift (δ, ppm)	Type of Proton	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0.8-1.2	Alkyl bromide, RCH_2Br	3.4-3.6
2° Alkyl, RCH_2R	1.2-1.5	Alkyl chloride, RCH_2Cl	3.6-3.8
3° Alkyl, R_3CH	1.4-1.8	Vinylic, $R_2C{=}CH_2$	4.6-5.0
Allylic, $R_2C{=}CR{-}CH_3$	1.6-1.9	Vinylic, $R_2C{=}CRH$	5.2-5.7
Ketone, $RCOCH_3$	2.1-2.6	Aromatic, ArH	6.0-8.5
Benzylic, $ArCH_3$	2.2-2.5	Aldehyde, $RCOH$	9.5-10.5
Acetylenic, $RC{\equiv}CH$	2.5-3.1	Alcohol hydroxyl, ROH	0.5-6.0*
Alkyl iodide, RCH_2I	3.1-3.3	Amino, $R{-}NH_2$	1.0-5.0*
Ether, $ROCH_2R$	3.3-3.9	Phenolic, $ArOH$	4.5-7.7*
Alcohol, $HOCH_2R$	3.3-4.0	Carboxylic, $RCOOH$	10-13*

*The chemical shifts of these protons vary in different solvents and with temperature and concentration.

Table 1.1: Approximate proton chemical shifts.

- "In ^{13}C NMR spectroscopy, signal area is not relevant in routine analyses" [1, p 396].
- **Coupling**: The magnetic effect of nonequivalent hydrogen atoms that are within 2 or 3 bonds of the hydrogens producing the signal that splits individual **signals** into multiple **peaks**. *Also known as* **signal splitting**, **signal multiplicity**.
- **Vicinal** (hydrogens): Hydrogens on adjacent carbons.
- **Geminal** (hydrogens): Hydrogens bonded to the same carbon.
  - Coupling occurs between geminal hydrogens in chiral/conformationally restricted molecules, specifically diastereotopic hydrogens.
- Interpreting NMR spectra:
  1. Count the number of signals in the spectrum to determine how many distinct proton environments there are in the molecule.
  2. Use chemical shift tables (such as Table 1.1) to correlate the chemical shifts of the signals with possible structural environments.
  3. Determine the relative area of each signal, as compared with the area of other signals, as an indication of the relative number of protons producing the signal.
  4. Interpret the splitting pattern for each signal to determine how many hydrogen atoms are present on carbon atoms adjacent to those producing the signal and sketch possible molecular fragments.
  5. Join the fragments to make a molecule in a fashion that is consistent with the data.

- The external magnetic field causes the σ (and π, if applicable) electrons in the viscinity of each proton to circulate, producing a small local magnetic field that can serve to either increase or decrease the external magnetic field experienced by the proton.
  - Increasing the effective field causes a larger chemical shift (it takes a higher energy photon/less magnetic field to induce a spin flip).
  - Decreasing the effective field causes a smaller chemical shift (it takes less energy/more magnetic field to induce a spin flip).
- **Shielded** (proton): A proton for which the induced local magnetic field opposes the external magnetic field to a relatively large degree.
- **Deshielded** (proton): A proton for which the induced local magnetic field opposes the external magnetic field to a relatively small degree (or even reinforces the external magnetic field).
  - For example, the π electrons of benzene circulate in such a way that the external magnetic field at the aromatic hydrogens is *augmented*.
- "Chemically equivalent protons are chemical shift equivalent in ^{1}H NMR spectra" [1, p 403].
- **Homotopic** (atoms): A set of atoms on some molecule such that replacing different ones with the same group gives the same compound.
  - For example, the six hydrogens of ethane are homotopic since replacing any of them with chlorine (for instance) gives the same compound: chloroethane.
  - Homotopic hydrogens are chemical shift equivalent.
- **Heterotopic** (atoms): A set of atoms on some molecule such that replacing different ones with the same group gives different compounds.
  - For example, in chloroethane, the CH_2 hydrogens are heterotopic to the CH_3 hydrogens since replacing the former yields 1,1-dichloroethane and replacing the latter yields 1,2-dichloroethane.
  - Heterotopic atoms are *not* chemical shift equivalent.
- **Enantiotopic** (atoms): Two atoms on some molecule such that replacing different atoms with the same group gives enantiomers.
  - Example: The CH_2 hydrogens of bromoethane.
  - Enantiotopic atoms are chemical shift equivalent, except possibly when the compound in question is dissolved in a chiral solvent.
- **Diastereotopic** (atoms): Two atoms on some molecule such that replacing different atoms with the same group gives diastereomers.
  - Example: The CH_2 hydrogens of 2-butanol.
  - Diastereotopic atoms are *not* chemical shift equivalent (the asymmetry of the chirality center ensures this), except possibly by coincidence.
- **Coupling constant**: The separation in hertz between each peak of a signal. *Denoted by* $\boldsymbol{J}$.
  - On the order of $6 - 8\,\text{Hz}$.
- The reciprocity of coupling constants: The coupling constants of coupled atoms are the same.
  - In more complicated molecules, noting that two signals have the same coupling constant means the protons to which they correspond are likely coupled.
- **Dihedral angle** (between vicinal groups): The angle between viscinal groups as seen on the Newman projection through the bond connecting their parent atoms. *Denoted by* $\boldsymbol{\phi}$.

- **Karplus correlation**: The dependence of the coupling constant on dihedral angles.
  - Discovered by Martin Karplus of Harvard.
  - Useful for identifying cyclohexane conformations, and thus for determining which conformation is lower energy.
- An NMR spectrometer is a camera with a relatively slow shutter speed, in that it blurs pictures of rapidly occurring molecular processes.
- Examples of rapid processes that occur in organic molecules.
  - Chemical exchanges cause spin decoupling.
    - Consider ethanol.
    - Based on its structure, we'd predict that the signal corresponding to the hydroxyl proton would be a triplet.
    - However, it only appears as a triplet in very pure ethanol, where **chemical exchange** is slower due to the reduction in impurity-assisted chemical exchange catalysis common in normal ethanol.
    - Rapid chemical exchange means that neighboring protons don't have enough time to couple; thus, the hydroxyl proton appears as a singlet in relatively impure ethanol.
    - Occurs in the ^{1}H NMR spectra of alcohols, amines, and carboxylic acids; the signals of OH and NH protons are normally unsplit and broad.
    - "Protons that undergo rapid chemical exchange... can be easily detected by placing the compound in D_2O. The protons are rapidly replaced by deuterons, and the proton signal disappears from the spectrum" [1, p 413].
  - Conformational changes.
    - If, for example, we could isolate staggered bromoethane, the CH_3 hydrogens would be split into two signals, as the one anti-periplanar hydrogen is in a different chemical environment from its two geminal neighbors.
    - But we can't, so all three CH_3 hydrogens contribute to one peak.
- **Chemical exchange**: The swapping of identical atoms between molecules.
- **Exchangeable proton**: A proton that can engage in rapid chemical exchange.
- We now switch gears to ^{13}C NMR spectroscopy.
- Although ^{13}C does not occur naturally with nearly the same frequency as ^{12}C, it is important for its application to NMR spectroscopy.
- Simplifications from ^{1}H NMR spectroscopy.
  - Each distinct carbon produces one signal in a ^{13}C NMR spectrum.
  - Splitting of ^{13}C signals into multiple peaks is not observed in routine ^{13}C NMR spectra.
- No (technically just very little) carbon-carbon coupling since coupling only occurs for adjacent carbons and only 1 in 100 carbon atoms is ^{13}C (1.1 % natural abundance).
- Carbon-proton coupling can occur, however, splitting ^{13}C signals into multiplets.
- **Broadband proton decoupled** (spectrum): A ^{13}C NMR spectrum in which ^{1}H-^{13}C coupling is eliminated by choosing instrumental parameters to decouple the proton-carbon interactions. *Also known as* **BB proton decoupled**.

- Shielding and deshielding works the same way (see Table 1.2).

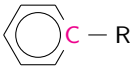
Type of Carbon	**Chemical Shift (δ, ppm)**
1° Alkyl, RCH_3	0-40
2° Alkyl, RCH_2R	10-50
3° Alkyl, $RCHR_2$	15-50
Alkyl halide or amine, R_3CX ($X = Cl, Br, NR'_2$)	10-65
Alcohol or ether, R_3COR'	50-90
Alkyne, $RC{\equiv}R'$	60-90
Alkene, $R_2C{=}R'$	100-170
Aryl, 	100-170
Nitrile, $RC{\equiv}N$	120-130
Amide, $RCONR'_2$	150-180
Carboxylic acid or ester, $RCOOR'$	160-185
Aldehyde or ketone, $RCOR'$	182-215

Table 1.2: Approximate carbon-13 chemical shifts.

- In addition to the TMS peak, ^{13}C spectra have a $CDCl_3$ solvent peak at δ 77.
- **DEPT ^{13}C NMR spectrum**: A ^{13}C NMR spectrum that indicates how many hydrogen atoms are bonded to each carbon, while also providing the chemical shift information contained in a broadband proton-decoupled ^{13}C NMR spectrum. *Also known as* **distortionless enhancement by polarization transfer**.

Week 2

Spectrometry

2.1 Office Hours (Snyder)

1/17:

- Does cyclohexane only have one ^{13}C NMR signal, and only one ^{1}H NMR signal?
  - 1 singlet for ^{13}C.
  - 1 singlet for ^{1}H.
  - We don't integrate carbon.
  - We only integrate to compare things.
  - We won't have to deal with cyclohexane conformations wrt. NMR on any test.
- What do we need to know about the Karplus correlation?
  - We won't need it for problems.
  - It's useful, but we've got other things to worry about.
- Do chemists/when do chemists run ^{13}C NMR experiments with all carbons isotopically carbon-13?
- Is the reason we don't integrate carbon because the placing of the carbon-13s is random? Would the proportions not still be representative?
- For ^{1}H NMR, feel free to draw in the hydrogen atoms on the line-angle structure.
- Multiplying $n+1$ of different types of neighbors (e.g., if a hydrogen has 3 neighboring hydrogens to one side and 2 neighboring hydrogens to the other side, it has a maximum of $(3+1)(2+1) = 12$ peaks in its signal).
  - The multiplication analysis applies only to chains that are completely different.

2.2 NMR

1/18:

- With a 1400 MHz NMR spectrometer, we can see 3D structure.
- Goes over an example of sketching a ^{13}C spectrum, DEPT 90, and DEPT 135 spectrum for a given molecule.
- You can flip groups in a problem, but you have to be consistent.
  - If you have closely spaced peaks in a sketch, be consistent with identifying a certain peak as CH, CH_2, or CH_3. But it doesn't matter which of the peaks you identify which way.
- There can be variation in signal height, but we won't discuss this.

- Transition to ^{1}H NMR spectroscopy.
- A typical ^{13}C NMR experiment takes 1-2 hours (for about 5 mg of material) to build appropriate peaks since there are so few ^{13}C atoms interspersed.
  - On a strong field machine, though, a ^{1}H spectrum can be done in seconds.
- ^{1}H NMR offers better resolution with respect to some functional groups than ^{13}C NMR.
  - Aldehydes and carboxylic acids will be clearly resolved.
  - Benzenes and alkenes will be better separated, too.
- Goes over typical chemical shifts (see Table 1.1).
- Goes over an example of sketching a ^{1}H spectrum.
- Neighboring spins parallel to the magnetic field increase ppm (deshielding).
- Introduces the coupling constant J.
- Splitting can happen in ^{13}C spectra, but it can't be observed on the time scale on which we measure.
- Terminology: Singlet, doublet, triplet, quartet, pentet, and sextet.
- Multiple neighbors? Multiply!
  - If you have 3 neighbors on one side and 2 on the other, for instance, you will have $(3+1)(2+1) = 12$ peaks.
  - Note that this is our predicted value — due to overlap, we may see fewer, but we will always go with the predicted value in this class.
- Count neighbors even on non-carbon atoms.
- Hybridization.
  - Don't get bothered by the hybridization of parent carbons if it doesn't restrict conformations. For example, the sp^2 carbon in an aldehyde behaves the same as any other parent carbon.
  - Do worry about hybridization if it makes hydrogens nonequivalent. In 1-butene for example, the two terminal hydrogens on the alkene are nonequivalent.
    - We will not worry about multiplicity due to this effect, though the rules are similar to what we've seen.
- Benzenes.

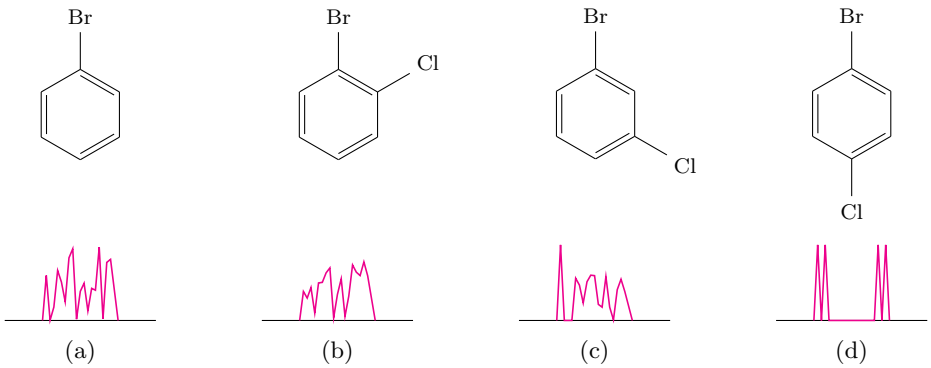
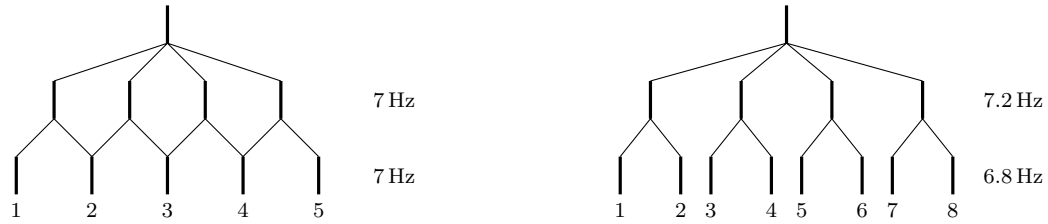


Figure 2.1: Benzenes in ^{1}H NMR spectroscopy.

  - We can predict a bunch of splitting and peaks, but often there is so much overlap that we more just get a jagged blob (see Figures 2.1a and 2.1b).
  - If you can find a clear singlet, perhaps separated a bit from the rest, integration can tell you how many substituents you have (see Figure 2.1c).
  - The pattern in Figure 2.1d is a dead giveaway for para substituents.
- Alkene coupling constants.
  - *cis*-alkenes typically have $J = 6 - 10\,\text{Hz}$.
  - *trans*-alkenes typically have $J = 12 - 18\,\text{Hz}$.
  - These are identifiable, diagnostic signals.
- Enantiomers are identical in NMR experiments.
  - Remember that all of their physical properties are the same (including the various forms of spectroscopy) except optical rotation.

2.3 Mass / IR Spectrometry

1/20:
- Solomons et al. [1] says to add (not multiply) in the $n + 1$ rule for multiple types of neighboring hydrogens.
  - What accounts for this inconsistency is the **Pascal approach**.
  - Solomons et al. [1] assumes that the coupling constants in the NMR instruments we use will be equal for both neighboring groups. This leads to overlap in the second splitting.
    - This is often a good assumption, but not always.
  - The multiplicative approach gives you the maximum number of signals you might see.
    - You will often see more signals on better machines, i.e., ones that can distinguish coupling constants to decimal places instead of just whole numbers.
- **Pascal approach**: A mode of analysis in which we explicitly draw splitting of NMR peaks.



(a) Additive rule. (b) Multiplicative rule.

Figure 2.2: Pascal approach.

  - The analyses in Figure 2.2 refer to a hydrogen with three neighbors to one side and one to the other (thus we split into $3 + 1 = 4$ peaks and then again into $1 + 1 = 2$ subpeaks per peak).
  - Notice how in Figure 2.2a, a less sensitive instrument displays peak overlapping and thus an additive rule works, while in Figure 2.2b, a more sensitive instrument resolves individual peaks.
  - Dr. Snyder always wants us to use the multiplicative rule on homeworks and tests.
- Reconstructs meta-bromomethylbenzene from its NMR spectrum.
- How spectroscopy is used in modern research.

  - X-ray crystallography was the first type of spectroscopy on the scene, being able to identify the position of every atom save hydrogen. Yet it was restricted to crystalline solids.
  - NMR is kind of the holy grail of today.
  - How we extract chemicals from natural materials: We look for things that are stationary (because they have to be able to repel things through chemical means). Then we dry them, grind them down, and add an organic solvent.
  - We then rotavap and use column chromatography.
- Mass spectrometry is a destructive process, but you only need a very tiny amount.
- Goes over theory of EI and hexane as an example.
  - Note that after EI, ions are accelerated around a corner where they bend in proportion to their mass to charge ratio (heavier ions bend less; ions with more charge bend more).
- We want to train our eyes to pick out the most dominant signals in a mass spectrum.
- A pattern of $-14, -14, -14$ is indicative of a linear alkane that's losing a CH_2 group each time.
- Alcohols will either have α-cleavage or dehydration.
- We should be able to detect bromine and chlorine.
- $m/z = 77$ is a dead giveaway for a phenyl cation.
- Now IR spectroscopy.
- Misc. IR notes.
  - Tighter bonds vibrate faster (e.g., C≡C > C=C > C−C).
  - Bonds that are more polar also have higher wave numbers.
  - Esters usually have higher carbonyl stretches than ketones.
  - Putting a double bond next to a ketone lowers it's stretching frequency due to resonance detracting from the double bond character of the C=O bond.
  - Sometimes you can tell benzene because it has a smaller C−H peak.
  - Hydroxyl groups in alcohols, carboxylic acids, and phenols have different peaks, properties, and reactivity.
- IR summary.
  - A great tool to determine functional groups on small molecules.
  - Non-destructive.
  - You should be able to understand why each bond is positioned at a specific wavenumber range, learn that range, and then be able to identify all of the following functional groups from an individual IR spectrum.
    - Carbonyls (aldehydes, ketones, esters, carboxylic acids).
    - Alkynes.
    - Nitriles/cyanides.
    - Alcohols.
    - Primary and secondary amines.

2.4 Chapter 9: Nuclear Magnetic Resonance and Mass Spectroscopy

From Solomons et al. [1].

1/18:

- **Mass spectrometry**: The formation of ions in a mass spectrometer followed by separation and detection of the ions according to mass and charge.
- **Mass spectrum**: A graph that on the x-axis represents the formula weights of the detected ions, and on the y-axis represents the abundance of each detected ion.

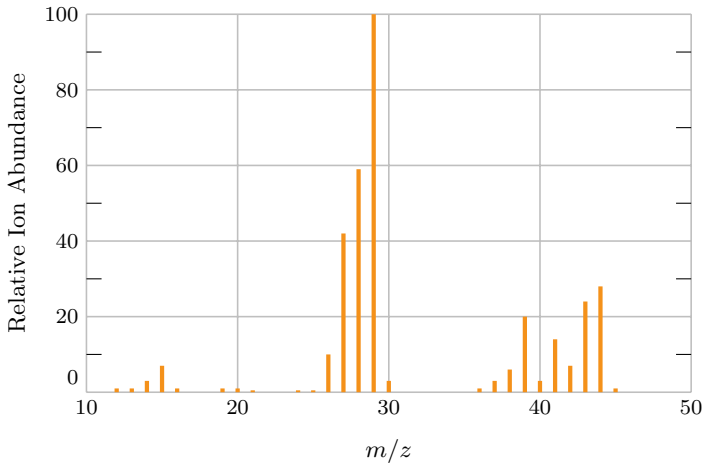


Figure 2.3: The mass spectrum of propane.

  - The x-axis is labeled m/z where m is mass and z is charge.
  - The examples Solomons et al. [1] consider all have $z = +1$, so the x-axis in them effectively represents the formula weight of each detected ion.
- **Base peak**: The tallest peak in a mass spectrum.
  - Usually caused by an easily formed fragment of the original compound.
  - Relative ion abundance on the y-axis is either expressed as a percentage of the base peak or directly as the number of detected ions.
  - The base peak in Figure 2.3 corresponds to the $C_2H_5{}^+$ ion, $m/z = 29 = 2 \cdot 12 + 5 \cdot 1$.
- **Molecular ion**: The ion with the formula weight of the original compound.
  - One of the higher value m/z peaks.
  - Usually not the base peak.
- Small peaks having m/z values 1 or 2 higher than the formula weight of the compound are due to ^{13}C and other isotopes.
- **Electron impact**: A method for ionizing molecules in a mass spectrometer by placing the sample under high vacuum and bombarding it with a beam of high-energy electrons. *Also known as* **EI**.
  - The energy of the electrons is in the range of 70 eV or 6.7×10^3 kJ/mol.
  - The incoming electrons ionize the molecules to molecular ions, which are radical cations since they have a +1 charge and an unshared electron.
- Note that there are ionization methods other than EI, but it is the most common.

- Localizing the radical and charge along the structure.

(a) Propane. (b) Methanol. (c) Trimethylamine. (d) 1-Butene.

Figure 2.4: Molecular ions.

  - The choice of where we localize the radical/charge is often arbitrary (esp. with hydrocarbons).
  - However, "as we might expect, ionization potentials indicate that in [the] formation of radical cations, the nonbonding electrons of nitrogen, oxygen, and halogen atoms, and the π electrons of alkenes and aromatic molecules, are held more loosely than the electrons of carbon-carbon and carbon-hydrogen σ bonds" [1, p 425].
  - Thus, "when a molecule contains oxygen, nitrogen, or a π bond, we place the odd electron and charge at a nitrogen, oxygen, halogen, or π bond. If resonance is possible, the radical cation may be delocalized" [1, p 425].

- Three important principles.

  1. The reactions that take place are all unimolecular since the pressure is kept so low.
  2. Single-barbed arrows denote the movement of single electrons.
  3. The relative ion abundances give key information about the structures of the fragments produced and their original locations in the molecule.

- Fragmentation by cleavage at a single bond.

  - When such a process happens in a molecular ion, a cation and a radical are produced, although only the cation will be detected by the positive ion mass spectrometers we're considering.
  - Each cleavage can happen in two ways (since one fragment will take the radical and the other will take the positive charge).
  - The path that produces the more stable carbocation will occur more rapidly.
    - Notice the difference in relative ion abundance between the secondary $CH_3CH_2^+$ ($m/z = 29$) and the primary CH_3^+ ($m/z = 15$) in Figure 2.3.

- When drawing cleavage reactions, use brackets and delocalization; when drawing cleavage mechanisms, use localization.

- Chain branching increases the likelihood of cleavage at a branch point because a more stable carbocation can result.

- Examples of fragmentation to form resonance-stabilized cations.

  1. Alkenes ionize and frequently undergo fragmentations that yield resonance-stabilized allylic cations.

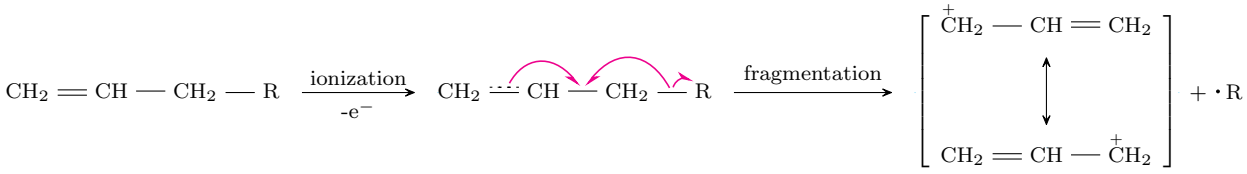


Figure 2.5: Resonance fragmentation: Alkenes.

2. Carbon-carbon bonds next to an atom with a lone pair usually break readily because the resulting carbocation is resonance stabilized.

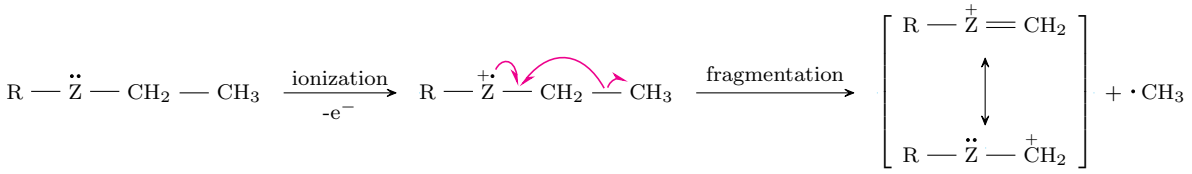


Figure 2.6: Resonance fragmentation: Lone pairs.

3. Carbon-carbon bonds next to the carbonyl group of an aldehyde or ketone break readily because resonance-stabilized ions called **acylium ions** are produced.

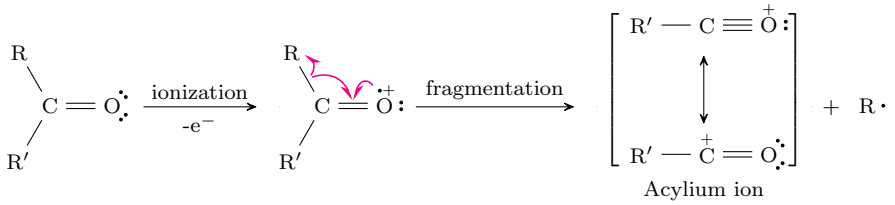
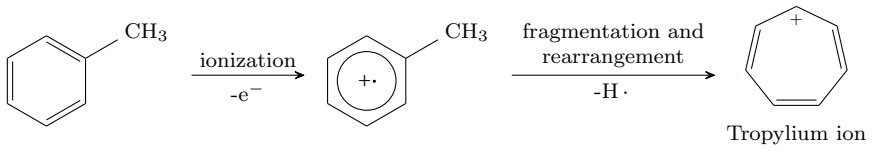


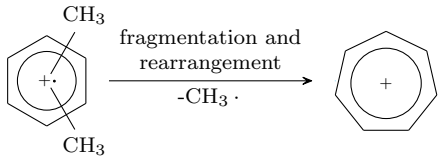
Figure 2.7: Resonance fragmentation: Carbonyls.

   – Note that either the C–R or the C–R′ bond could break.

4. Alkyl substituted benzenes ionize by loss of a π electron and undergo loss of a hydrogen atom or methyl group to yield the relatively stable **tropylium ion**. This fragmentation gives a prominent peak (sometimes the base peak) at $m/z = 91$.



(a) Losing a hydrogen radical.



(b) Losing a methyl radical.

Figure 2.8: Resonance fragmentation: Alkyl-substituted benzene rings.

5. Monosubstituted benzenes with other than alkyl groups also ionize by loss of a π electron and then lose their substituent to yield a phenyl cation with $m/z = 77$.

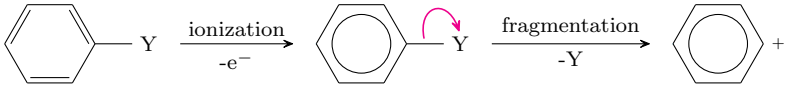


Figure 2.9: Resonance fragmentation: Monosubstituted benzene rings with nonalkyl groups.

   – Y is a halogen, nitro group, acyl group, nitrile group, etc.

- Fragmentation by cleavage of two bonds leads to a new radical cation and a neutral molecule.
  1. Alcohols frequently show a peak at $M^{+\cdot} - 18$. This corresponds to the loss of a molecule of water.

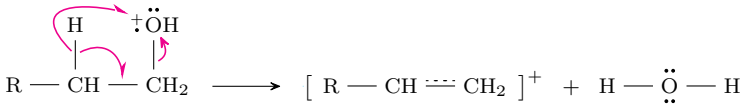


Figure 2.10: Fragmentation: Loss of H_2O.

  2. Carbonyl compounds with a hydrogen on their γ carbon undergo a fragmentation called the McLafferty rearrangement.

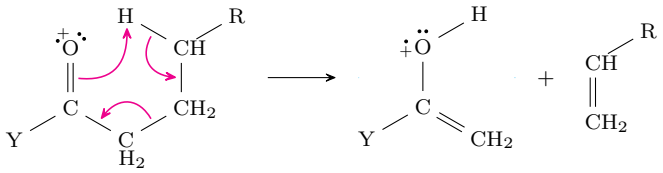


Figure 2.11: Fragmentation: McLafferty rearrangement.

     – Y may be an alkyl, hydride, ether, hydroxyl, etc.
  3. There are also often peaks corresponding to the elimination of other small molecules.

- Isotope effects:
  – The presence of ^{13}C will provide a small peak at $M^{+\cdot} + 1$.
  – "In the mass spectrum for a sample containing chlorine, we would expect to find peaks separated by two mass units, in an approximately 3 : 1 (75.5% : 24.5%) ratio for the molecular ion or any fragments that contain chlorine" [1, p 432].
  – "In the mass spectrum for a sample containing bromine, we would expect to find peaks separated by two mass units in an approximately 1 : 1 ratio (50.5% : 49.5% ^{79}Br to ^{81}Br)" [1, p 433].
  – In a molecule containing two bromine atoms, for example, we'll see peaks at $M^{+\cdot}$, $M^{+\cdot} + 2$, and $M^{+\cdot} + 4$ in a 1 : 2 : 1 ratio.

Week 3

More Types of Reactions

3.1 Radical Chemistry

1/25:

- Reviews mass spectroscopy.
- Radical chemistry allows us to do some reactions that we cannot do in a two-electron manifold.
  - If we want to attach a nucleophile to the C2 position of propane, heat alone will not make the hydrogen on that position leave (hydrides are terrible leaving groups).
- Presents how easy (in terms of ΔH) it is to homolytically cleave various C–H bonds in alkanes.
- Radical stability is the same as carbocation stability.
  - In terms of decreasing stability,

$$\text{benzylic} \approx \text{allylic} > \text{tertiary} > \text{secondary} > \text{primary} > \text{methyl}$$

  - Note that a benzylic or allylic *primary* radical is still more stable than a tertiary radical with no resonance stabilization.
- Three steps (initiation, propagation, and termination).
  - Initiation is either started by light ($h\nu$) or heat (Δ).
- You can lose CO_2 in a radical mechanism.

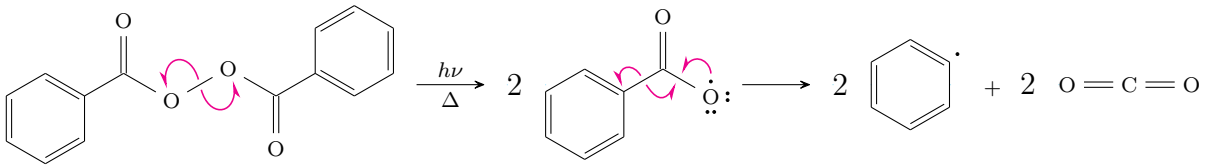
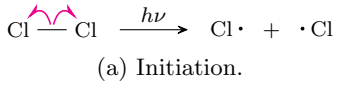
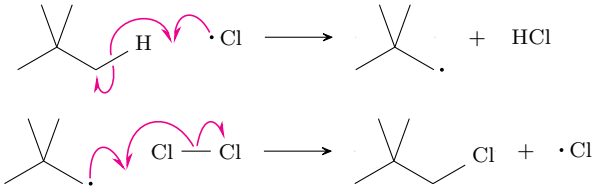


Figure 3.1: Losing CO_2 in a radical mechanism.

  - The second step is strongly favored by entropy (ΔS).
  - Note that this two-step reaction is a two-step initiation step. The radical produced could then react with ethene to form a primary ethylbenzene radical. Two of these species could then couple in a termination step.
- Chlorination of alkanes.
  - If multiple types of C–H bonds are present, they will all be functionalized but in differing amounts.



(a) Initiation.



(b) Propagation.

(c) Termination.

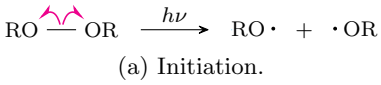
Figure 3.2: Chlorination of alkanes mechanism.

  - The mechanism is sensitive both to the number of available hydrogens of each type, how sterically accessible hydrogens are, and (most importantly) radical stability.
- You can also get polychlorinated products.
- Take-home message: If we use this, we only do so when all hydrogens are symmetric and we use excess starting material.

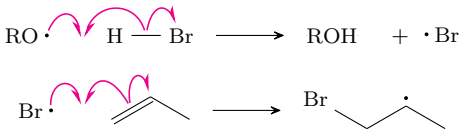
- Bromination of alkanes is basically the same.
  - One difference is that bromination is incredibly sensitive to radical stability, so whatever is the most stable radical will be the brominated one.
- Multistep synthesis example.
  - Propane to propane-1,2-diol.
  - Use radical bromination to put a bromine on C2, then β-elimination, then dihydroxylation.
- Allylic/benzylic halogenation.
- General form.

$$=- \xrightarrow[h\nu]{Br_2} =--Br$$

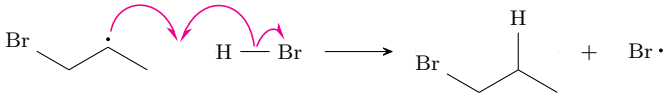
  - A possible side reaction is bromination of the alkene, but this requires a high temperature and low concentration.
  - The mechanism is entirely analogous to that of chlorination.
- HBr addition to alkenes.
  - The hydrohalogenation mechanism produces the Markovnikov product.
  - Morris Kharasch at UChicago in 1933 proposed that a radical mechanism produced the anti-Markovnikov product.
    - In particular, when run in the presence of air at low temperatures, organic peroxides are formed; these molecules allow the reaction to proceed.
  - Note that it is only HBr, not HCl or HI, that does this chemistry.
- Mechanism.



(a) Initiation.



(b) Propagation.



(c) Termination/propagation.

Figure 3.3: Non-Markovnokov addition of HBr to an alkene mechanism.

- In hydrohalogenation, the hydrogen adds into the double bond to form the most stable carbocation.
- In this mechanism, the bromine adds into the double bond to form the most stable radical.

3.2 Office Hours (Snyder)

1/26:

- We use excess (like 1000 : 1 ratio) substrate in radical chlorination reactions to avoid polychlorination — kinetically, we make it more likely for a chloride radical to collide with the reactant than the product.
- Problem set 1, Question 6.
  - Six is greater than exam strength.
  - 4 peaks in the aromatic region of ^{13}C means gives you a benzene ring.
  - From the ^{13}C NMR, we have 4 peaks in the aromatic region, so it is not a disubstituted asymmetric aryl ring. It's at least symmetric.
  - Once we get reasonably close, draw all possible structures and then analyze.
  - For isomer A, the two easiest lost groups are CH_3 and Cl, which both form benzylic carbocations. We also have that lower down primary methyl peak in the ^{13}C NMR.

3.3 Diels-Alder Reaction

1/27:

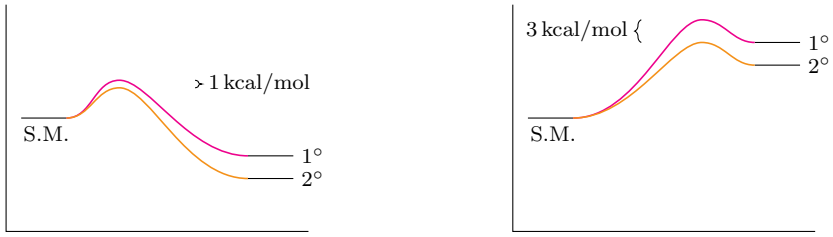
- Discusses exam.
- Reviews radical chemistry from last time.
- Radicals are different species, but they behave much like carbocations.
- Initiation: Breaking a bond between two atoms that are exactly the same.
- Propagation: Using a radical to make a new radical.
  - Two half arrows make a new bond; one half arrow becomes the new radical.
  - You can make the product during the propagation step.
- Termination: Bringing two radicals together, eliminating radicals from solution.
- Bromination and allylic/benzylic halogenation have broad synthetic utility.

- Chlorination, less so.
  - Polychlorination happens because the product is even more reactive than the starting material — a radical at the α carbon gains extra stability from the nearby EWG (chlorine).
- Br· reacts with a hydrogen in propene in allylic halogenation, but adds into the alkene in non-Markovnokov addition of HBr to an alkene.
  - The reason for this difference comes down to reaction conditions. Radical mechanisms are very sensitive to conditions, and having the strongly acidic HBr present in solution for the latter mechanism makes the former mechanism much less likely.
- Why bromination of alkanes is more selective than chlorination.
  - Consider the Maxwell-Boltzmann distribution.
    - To run a reaction, we need sufficient energy, and raising the temperature gives us more molecules with higher energy.
    - Having more molecules with sufficient energy means the reaction runs faster.
  - Chemists have determined that propagation (specifically C–H activation) is the RDS of halogenation of alkanes, so let's analyze that step.

Reaction	E_A (kcal/mol)
+ ·Cl → + HCl	3
+ ·Cl → + HCl	4
+ ·Br → + HBr	13
+ ·Br → + HBr	16

Table 3.1: Analyzing the RDS of halogenation of alkanes.

    - As we can see from Table 3.1, the formation of different kinds of radicals for different reactions has different energies of activation.
    - The 1 kcal difference between the chlorination types leads to a 3.7 : 1 ratio of products.
    - The 3 kcal difference between the bromination types leads to a 97 : 1 ratio.
    - Thus, bromination depends much more heavily on forming stable radicals.
  - Additionally, we know that in these mechanisms, HCl and HBr are formed as byproducts, and the heats of formation for these substances differ.



(a) Chlorination of alkanes. (b) Bromination of alkanes.

Figure 3.4: Reaction diagrams for the RDS of halogenation of alkanes.

    - Forming HCl *releases* 103 kcal/mol, and thus is exothermic.
    - Forming HBr *requires* 87 kcal/mol, and thus is endothermic.

    - By Hammond's postulate, the transition state in bromination of alkanes (Figure 3.4b) more closely resembles the products, while the transition state in chlorination of alkanes (Figure 3.4a) more closely resembles the reactants.
    - Thus, the transition states in the two bromination reactions, already more energetically separated than their chlorination cousins, are more sensitive to which type of radical is formed than the transition states in the two chlorination reactions.

- History of the Diels-Alder reaction.
  - Discovered in 1928 by Otto Diels and his grad student Kurt Alder.
  - Nobel prize (1952).
  - Diels and Alder tried to reserve the right to run the reaction to themselves, but they were not successful because it was so powerful.
  - This is the last time a grad student won the Nobel prize in chemistry along with their professor.
  - They were not the first people to run the reaction, but they were the first to correctly identify the products. Von Euler ran it and even correctly identified them, but said in his paper he wasn't sure he was correct.

- General form.

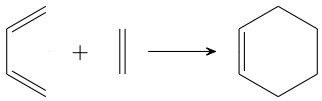


Figure 3.5: Diels-Alder general form.

  - Combines a diene (a 4π-electron component) and a dienophile (a 2π-electron component).
  - The real power of this reaction is not the synthesis of the ring, but the ability to synthesize chiral centers and put subsituents where you want in a way that is predictable and controllable.
  - Can build a second double bond into the product.
  - Can run this intermolecularly or intramolecularly.
  - Can synthesize bicyclic compounds.

- Mechanism.

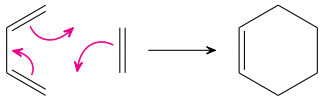


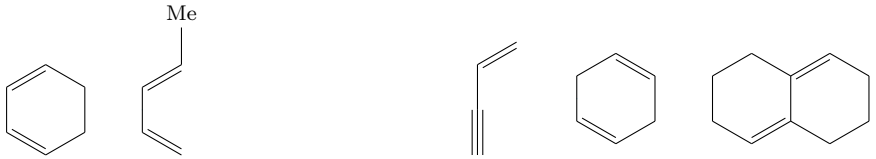
Figure 3.6: Diels-Alder mechanism.

  - This is a **pericyclic** reaction.

- **Pericyclic** (reaction): A reaction that proceeds via a concerted mechanism involving a single, cyclic transition state.

- The basics.

1. The diene must be composed of two alkenes in conjugation, and those alkenes must be capable of achieving an **s-cis** orientation.
   - How much of the time the diene is in the s-cis orientation affects the reaction rate.
   - For example, the diene on the left in Figure 3.7a is in the s-cis orientation 100% of the time, but the diene on the right in Figure 3.7a is in the s-cis orientation only 50% of the time.



(a) Viable dienes. (b) Non-viable dienes.

Figure 3.7: Constraints on the diene in a Diels-Alder reaction.

- The dienes in Figure 3.7b, for one reason or another, are never capable of achieving the s-cis orientation.
- Note that sterics can also prevent or hinder a molecule from achieving the s-cis orientation.

2. The diene and dienophile must be properly activated electronically.
   - Placing activating substituents on the diene and dienophile can lower the necessary reaction temperature from 200 °C all the way to 0 °C.
     - Moreover, it is preferable to do so because organic molecules are "happier" (less likely to denature) at lower temperatures.
   - This reaction is between the HOMO of the diene and the LUMO of the dienophile.
     - If you add an EWG to the dienophile, it lowers the LUMO.
     - If you add an EDG to the diene, it raises the HOMO.
     - Both of these changes lower the ΔE between the HOMO and LUMO, lowering the necessary temperature of reaction.
     - If you have the groups mixed, the reaction will not proceed; you can't go much higher than 200 °C, with the Diels-Alder. Note, however, that alkyl and aryl groups do not deactivate dienophiles enough to prevent reaction; it is the heteroatoms with donatable electron pairs that cause problems.
   - Typical electron-donating substituents are OR, SR, and NR_2 (all via resonance).

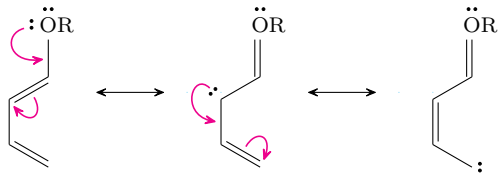


Figure 3.8: Diels-Alder EDGs.

     - Other donor groups include Me and Ph (both via induction). These are much less effective, though.
   - Typical electron-withdrawing substituents are aldehydes, ketones, esters, amides, nitriles, sulfones, maleic anhydride, and making the alkene an alkyne and adding an EWG.

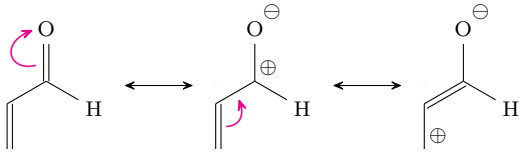
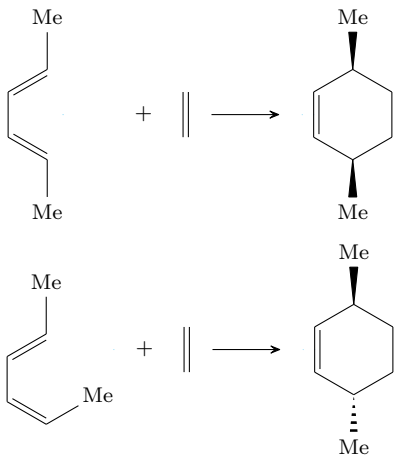


Figure 3.9: Diels-Alder EWGs.

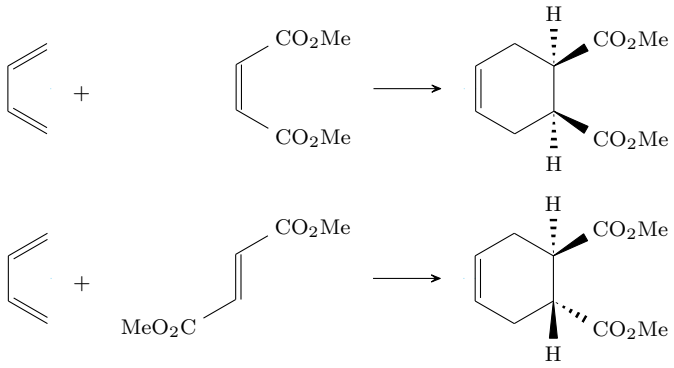
     - These all have a π-system directly attached to your double bond, and electronegativity pulls electrons out towards these π-systems.

- **S-cis**: Alkenes are cis relative to the sigma bond.

- **S-trans**: Alkenes are trans relative to the sigma bond.
- The Diels-Alder reaction is **stereospecific**.



(a) Stereoselectivity of the diene.



(b) Stereoselectivity of the dienophile.

Figure 3.10: Diels-Alder stereoselectivity.

  - The reactants are not chiral, but they do have information encoded in their double bonds (e.g., (E)- vs. (Z)-substituents). This information gets translated into whether those substituents are cis or trans in the product.

- **Stereospecific** (reaction): A reaction in which the geometry present in the starting material translates directly into the stereochemistry of the product.
- The Diels-Alder reaction is **diastereoselective**.

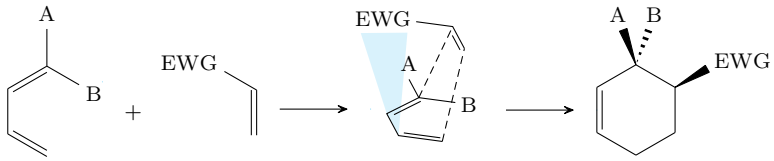


Figure 3.11: Diels-Alder diastereoselectivity.

  - When we add a substituted diene to a substituted dienophile, we might intuitively think that we will form the less sterically encumbered product (via an **exo** transition state).
  - However, we find that in spite of the steric penalty, we form the **endo** product. This is because there is an additional stabilizing interaction present in the endo transition state that is not present in the exo transition state, namely the one between the π-orbitals of the EWG and the bond that will be an alkene in the product (this interaction is shown in light blue in Figure 3.11).
  - Note that since it is equally likely that the dienophile will attack the diene from the top (as in Figure 3.11) and from the bottom, both enantiomers of the endo product will be formed.
    - To indicate this on a test question, write $(+/-)$ next to your answer!

- **Diastereoselective** (reaction): A reaction in which only one of two possible diastereomers is formed in those cases where two or more stereogenic centers are created.
- **Endo** (transition state): A transition state in which bulky groups EWGs on the dienophile lie below the dienophile.
- **Exo** (transition state): A transition state in which bulky groups EWGs on the dienophile lie away from the dienophile.
- Reviews kinetic vs. thermodynamic product.
  - The endo product is more easily formed (it's the kinetic product), and the exo product is usually more stable (it's the thermodynamic product).
  - However, since it's hard to walk the Diels-Alder reaction backwards (especially at low temperatures), this reaction is under kinetic control, and hence the kinetic, endo product is formed.
- The reaction is regioselective.

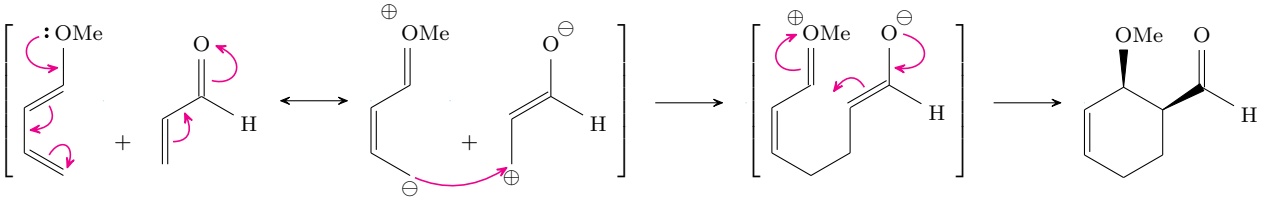


Figure 3.12: Diels-Alder regioselectivity.

  - If both reactants are substituted and we draw their resonance states (see Figures 3.8 and 3.9), we'd like to unite the carbon that is negative and the carbon that is positive.
  - This resonance analysis is not really what happens (all electrons move at once as in Figure 3.6), but it is quite predictive.
  - Note that we can have a diene with an EDG at one end, a diene with an EDG in the interior, or a diene with para EDGs (a so-called **synergistic eiene** because both EDGs push electrons toward the carbon at the end adjacent to the interior EDG).
- Does a number of examples.
- When facing a Diels-Alder question on a PSet or test, your first question to ask is "are my reactants appropriate for the Diels-Alder reaction?"
  - If not, just write "N.R." for "no reaction."
- We may have to analyze potential products to see if they could be formed by Diels-Alder means.
  - Sometimes, even if there are multiple potential dienes/dienophiles, only one pathway will work (such as with cyclohex-1,4-diene-1-carbonitrile).

3.4 Office Hours (Keller)

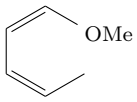
1/28:

- How do we read the chart below the IR spectrum?
  - The big numbers are wavenumbers, and the little numbers are the percent transmittance (smaller percent transmittance means bigger peak).

3.5 Office Hours (Snyder)

1/31:

- Sterics vs. an EDG on the diene?



  - Even if you have a strong EDG, if sterics prevents your diene from achieving the s-cis conformation, the reaction will be very slow and/or not proceed.
- PSet 2, 1f: Why is *t*-BuOH listed?
  - We need the Zaitsev product here; we ignore the bulky base — it's just used to favor E2 over S_N2.
- PSet 2, 5b: ?
  - Think Diels-Alder here with the given SM as the dienophile and then ozonolysis.

3.6 Office Hours (Salinas)

- E1 2020, 3b: Distinction between carbons 3 and 6?
  - 3 is shifted higher because it's next to two functional groups, whereas 6 is only next to one functional group.
- E1 2020, 4: Ordering of the last 2/3 steps? Shouldn't we take advantage of the allylic stability to make the process even more selective before hydrogenating?
  - Both are right.
- PSet 2, 1e: Is there reactivity with the alkene that's not next to the EWG in the dienophile?
  - Not enough reactivity to care about.
- PSet 2, 4(i): Is the diene too unreactive?
  - Yes
- PSet 2, 6: Are we using benzoyl peroxide to pull the bromine off the starting material and leave a radical behind at that site? A radical which we can either quench with $H\cdot$ or wind back around to form a ring and then quench?
  - Yes.

3.7 Chapter 10: Radical Reactions

From Solomons et al. [1].

1/29:

- Homolytically breaking the O – O bond in a dialkyl peroxide (ROOR) leads to the formation of two **alkoxyl radicals**.
- **Homolytic bond dissociation energy**: The energy required to break a covalent bond homolytically. *Denoted by* $\boldsymbol{DH°}$.
  - Breaking C – H bonds with lower $DH°$'s leads to more stable radicals.
- Unselectivity of chlorination of alkanes.

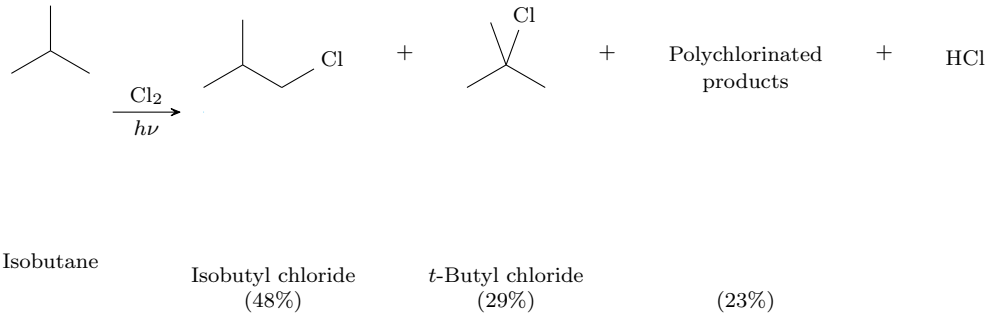


Figure 3.13: Unselectivity of chlorination of alkanes.

  - You want homotopic hydrogens to run chlorination of alkanes.
- All termination steps from Honors Organic Chemistry (including dimerizing the alkyl reactants) are discussed here.
- Note that you can run fluorination of alkanes, but it is even less selective than chlorination.
  - In other words, the distribution of products very closely mirrors the ratio of types of homotopic hydrogens (i.e., radical stability is essentially irrelevant to predicting products).
- Vinylic radicals are even less stable than primary radicals.

3.8 Chapter 13: Conjugated Unsaturated Systems

From Solomons et al. [1].

- Covers 1,4-addition (esp. of hydrobromination).
- Covers kinetic/thermodynamic control.
- **Pericyclic** (reaction): A concerted reaction that proceeds through a cyclic transition state in which symmetry characteristics of molecular orbitals control the course of the reaction.
- There are also $[2 + 2]$ cycloadditions that require light energy.
- "Cyclopentadiene is so reactive, in fact, that on standing at room temperature it slowly undergoes a Diels-Alder reaction with itself" [1, p 602].

References

(1) Solomons, T. W. G.; Fryhle, C. B.; Snyder, S. A., *Organic Chemistry*, 12th; John Wiley & Sons.