CHEM 22100 (Organic Chemistry II) Notes

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Weeks

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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.

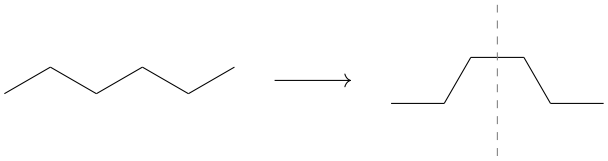


Figure 1.1: Mirror plane in hexane.

  - 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.

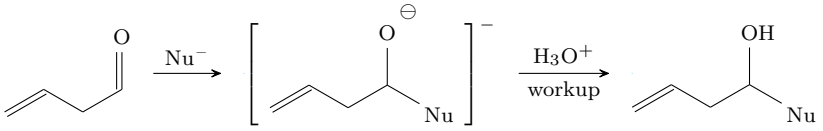


Figure 1.2: H_3O^+ workup.

  - 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).

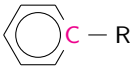
Type of Carbon	**Chemical Shift (δ, ppm)**
1° Alkyl, RCH_3	0-40
2° Alkyl, RCH_2R	10-50
3° Alkyl, $RCHR_2$	15-50
Alkyl halide or amine, R_3CX ($X = Cl, Br, NR'_2$)	10-65
Alcohol or ether, R_3COR'	50-90
Alkyne, $RC{\equiv}R'$	60-90
Alkene, $R_2C{=}R'$	100-170
Aryl, 	100-170
Nitrile, $RC{\equiv}N$	120-130
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.

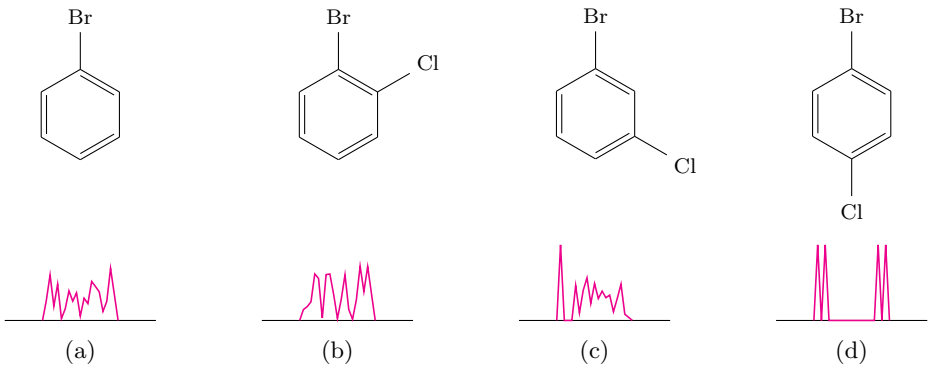
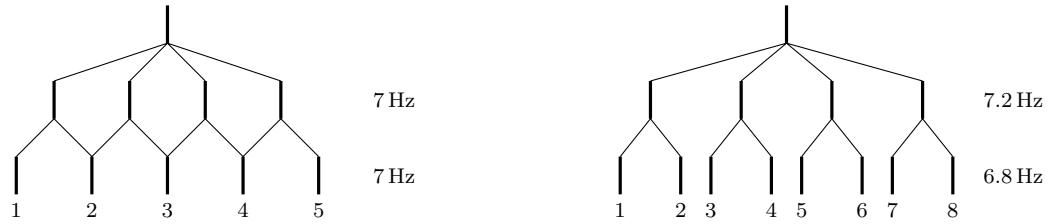


Figure 2.1: Benzenes in ^{1}H NMR spectroscopy.

  - 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.

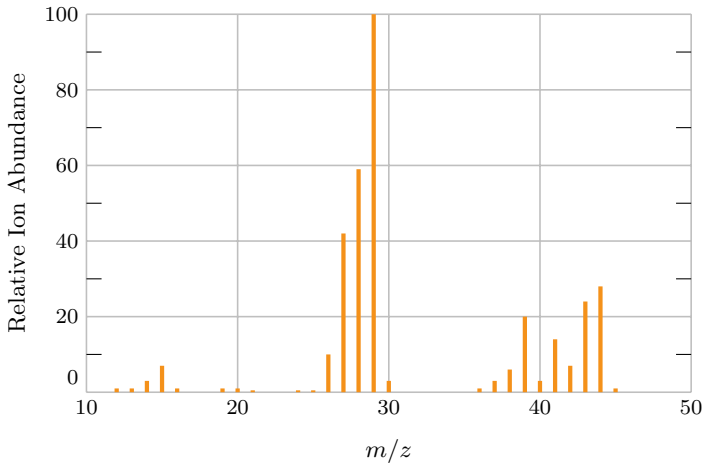


Figure 2.3: The mass spectrum of propane.

  - 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.

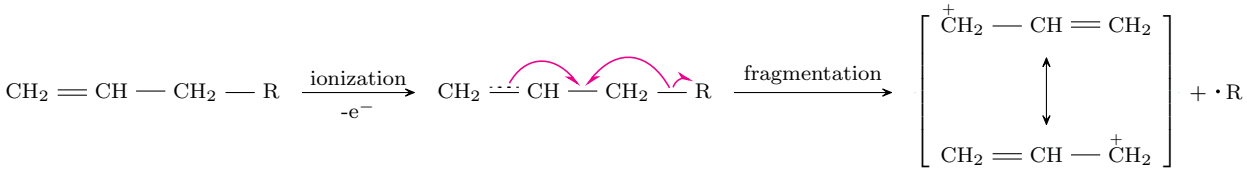


Figure 2.5: Resonance fragmentation: Alkenes.

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

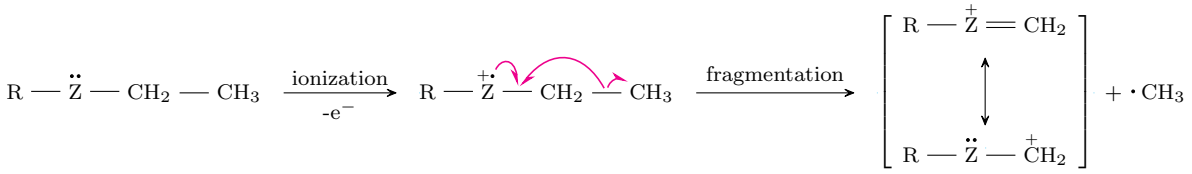


Figure 2.6: Resonance fragmentation: Lone pairs.

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.

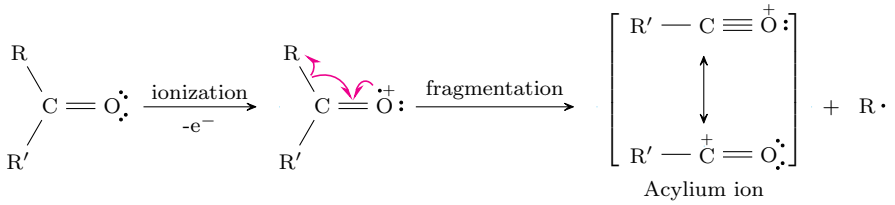
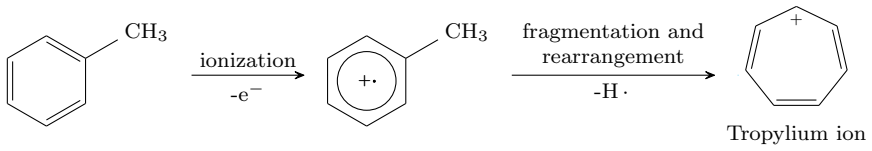


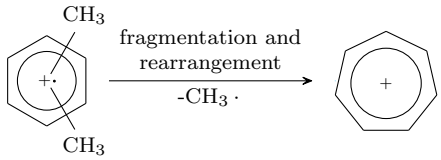
Figure 2.7: Resonance fragmentation: Carbonyls.

   – 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 $m/z = 77$.

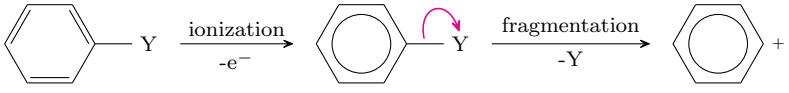


Figure 2.9: Resonance fragmentation: Monosubstituted benzene rings with nonalkyl groups.

   – 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.

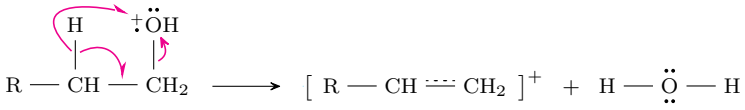


Figure 2.10: Fragmentation: Loss of H_2O.

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

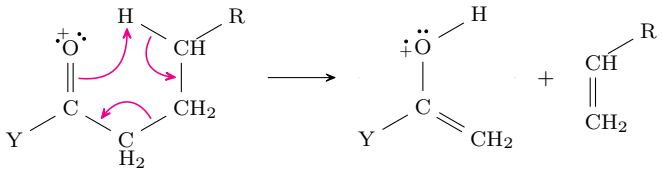


Figure 2.11: Fragmentation: McLafferty rearrangement.

     – 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.

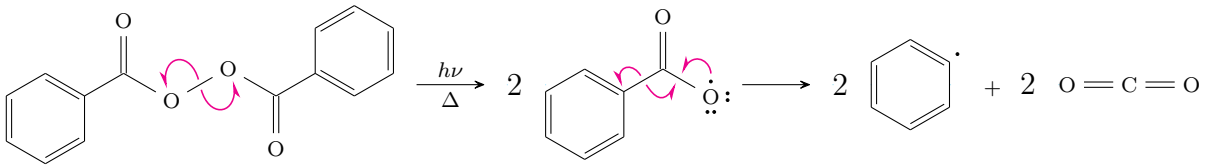
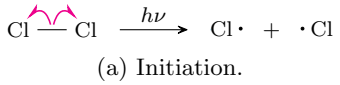
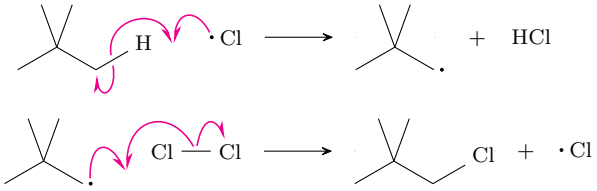


Figure 3.1: Losing CO_2 in a radical mechanism.

  - 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.

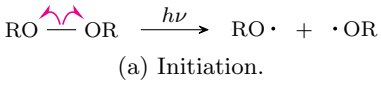
Figure 3.2: Chlorination of alkanes mechanism.

  - 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.

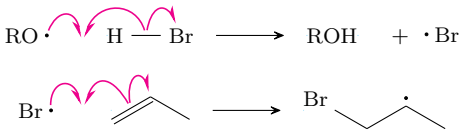
- Bromination of alkanes is basically the same.
  - One difference is that bromination is incredibly sensitive to radical stability, so whatever is the most stable radical will be the brominated one.
- Multistep synthesis example.
  - Propane to propane-1,2-diol.
  - Use radical bromination to put a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

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

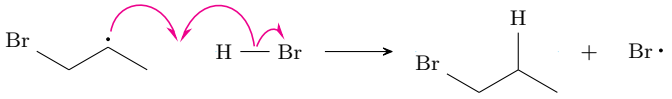
  - A possible side reaction is bromination of the alkene, but this requires a high temperature and low concentration.
  - The mechanism is entirely analogous to that of chlorination.
- HBr addition to alkenes.
  - The hydrohalogenation mechanism produces the Markovnikov product.
  - Morris Kharasch at 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:

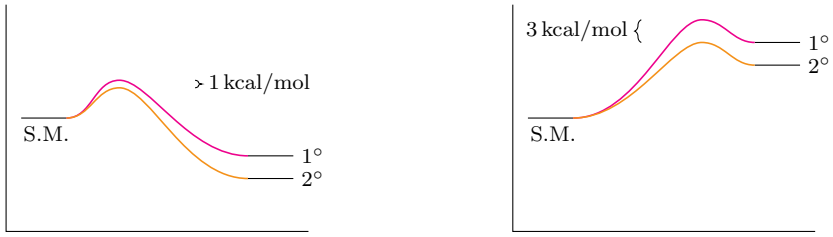
- Discusses exam.
- Reviews radical chemistry from last time.
- Radicals are different species, but they behave much like carbocations.
- Initiation: Breaking a bond between two atoms that are exactly the same.
- Propagation: Using a radical to make a new radical.
  - Two half arrows make a new bond; 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.

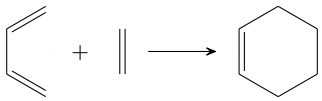


Figure 3.5: Diels-Alder general form.

  - 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.

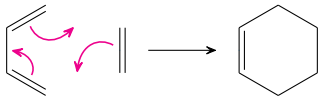


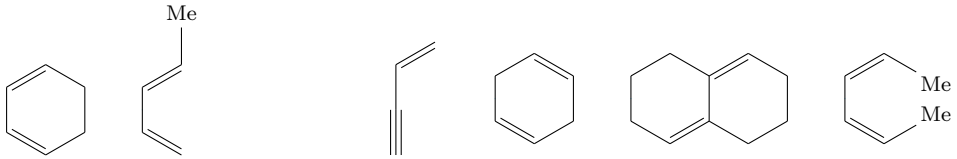
Figure 3.6: Diels-Alder mechanism.

  - 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.

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).

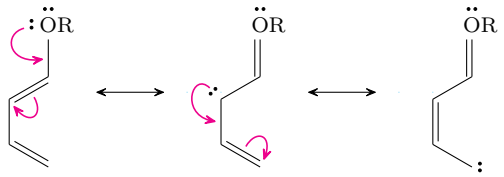


Figure 3.8: Diels-Alder EDGs.

    - 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.

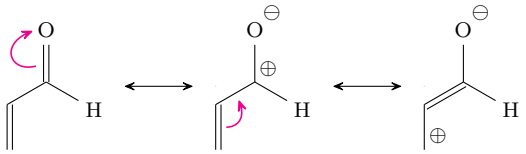
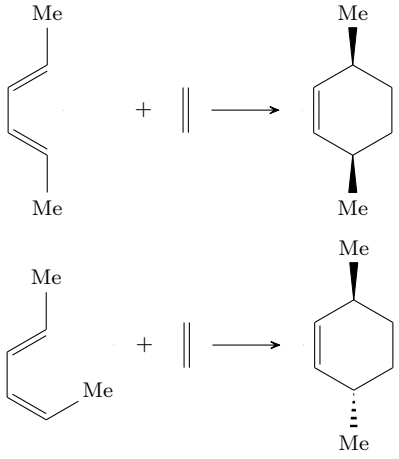


Figure 3.9: Diels-Alder EWGs.

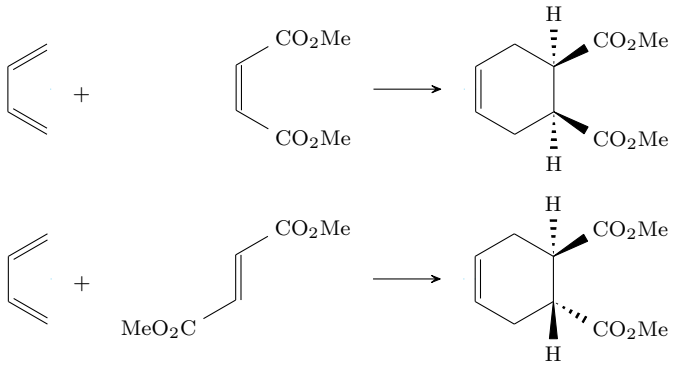
    - These all have a π-system directly attached to your double bond, and electronegativity pulls electrons out towards these π-systems.

- **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**.

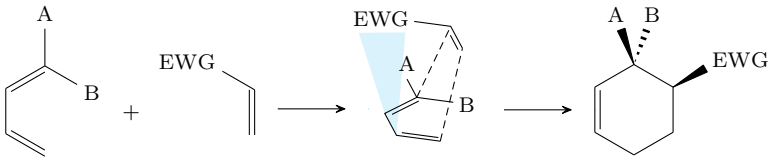


Figure 3.11: Diels-Alder diastereoselectivity.

  - 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.

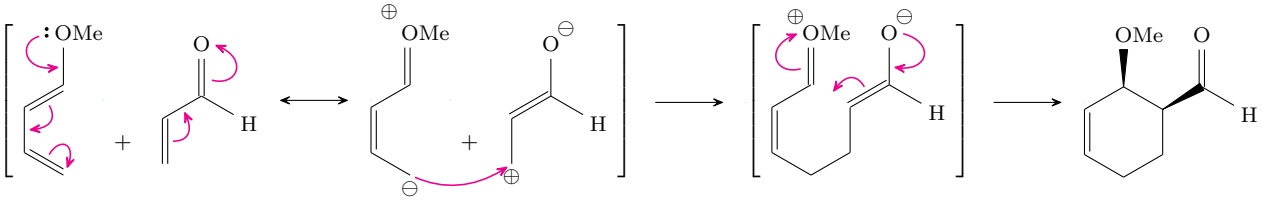


Figure 3.12: Diels-Alder regioselectivity.

  - 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:

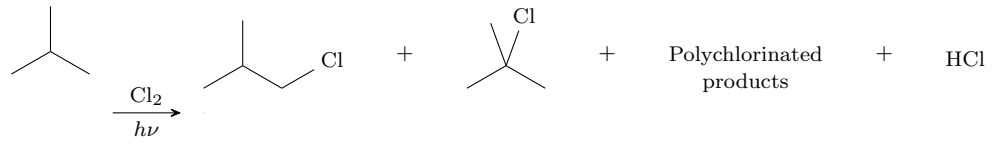
- How do we read the chart below the IR spectrum?
  - The big numbers are wavenumbers, and the little numbers are the percent transmittance (smaller percent transmittance means bigger peak).

3.5 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.



Isobutane

Isobutyl chloride (48%)

t-Butyl chloride (29%)

(23%)

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.

3.6 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].

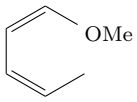
Week 4

Exam 1 Materials

4.1 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.

4.2 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.

4.3 Review

2/1:

- Esters bonded to the diene/dienophile through their single oxygen will be donor groups, but worse than groups like OMe.
  - This is because they *can* push electrons toward the diene/dienophile, but they also have the option to withdraw electrons through resonance.
  - This effect is enough to strongly deactivate a dienophile.
- Substituents that aren't on the double bond count as alkyl groups. Their inductive effect will vary based on other groups further down the chain, but they will have no resonance effects.
- When you have two groups on the diene in the "B" position, the diene will *never* be viable.
- He is going to ask us to use the reactions from last quarter, but not know the mechanisms.
  - Write "magic powder" over your arrow if you forget the reagents.
  - Alkene reactions to know: hydrogenation (H_2 Pd/C), dihydroxylation (OsO_4), ozonolysis (O_3 Me_2S), hydrobromination (HBr), and bromination (Br_2).
- We use both KO^{t}Bu and ^{t}BuOH to establish a buffer, an equilibrium that will allow us to both grab and release a proton.
  - This is not so important for E2 chemistry, but is important for other chemistry.
- MS: para-dimethylbenzene vs. ethylbenzene.
  - For para-dimethylbenzene, we can only lose one methyl group (losing the other would lead to a 2+ ion, which we will not observe). This gives a $m/z = 91$ peak.
  - For ethylbenzene, we can lose just a methyl radical *or* the entire ethyl chain. This gives a $m/z = 91$ *and* a $m/z = 77$ peak.
  - Rule: If you have ortho/meta/para substituents, you can lose *at most one* substituent at a time.
- For ^{13}C NMR, he's not above giving us cyclobutane with a ketone attached.
- If you need to form C–C bonds, that's probably going to be Diels-Alder for this exam.

2/2:

- PSet 1/2 review takeaways.
  - 4°/allylic ^{13}C peaks are higher than 3° peaks.
  - When asked how you can distinguish two molecules based on NMR spectra, answer in terms of the number of peaks/shapes of peaks, not the shift of peaks (that's not generally intuitively characteristic of a molecule).
  - Beware Diels-Alder products drawn with stereochemistry opposite to the way we've practiced.
  - Show the H–$SnBu_3$ bond homolytically cleaving if necessary.

4.4 Exam 1 Cheat Sheet

2/3:

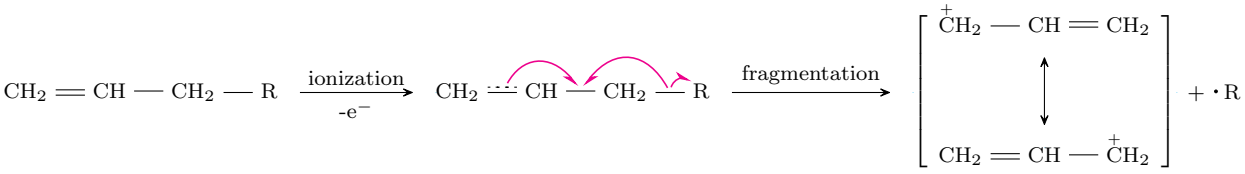
COMMON ABSORPTIONS	
Aromatic C–C	Two peaks usually in the range of $1500 - 1600\,cm^{-1}$
C=C	$\sim 1650\,cm^{-1}$
C=O	$\sim 1710\,cm^{-1}$ (shifts to $\sim 1735\,cm^{-1}$ for esters)
C≡C	$2100 - 2300\,cm^{-1}$
C≡N	$2100 - 2300\,cm^{-1}$
C–H (aldehyde)	Two peaks at $2170\,cm^{-1}$ and $2810\,cm^{-1}$
sp^3 C–H	Just to the right of $3000\,cm^{-1}$
sp^2 C–H	Just to the left of $3000\,cm^{-1}$
sp C–H	$\sim 3300\,cm^{-1}$
N–H	$\sim 3300\,cm^{-1}$ (one peak for –NH–, two peaks for $-NH_2$)
O–H (alcohol)	$\sim 3400\,cm^{-1}$ (a broad, smooth peak)
O–H (acid)	$\sim 2500 - 3500\,cm^{-1}$ (a very broad, ugly [not smooth] peak)

Common IR spectroscopy absorptions.

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*

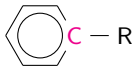
*The chemical shifts of these protons vary in different solvents and with temperature and concentration.

Approximate proton chemical shifts.

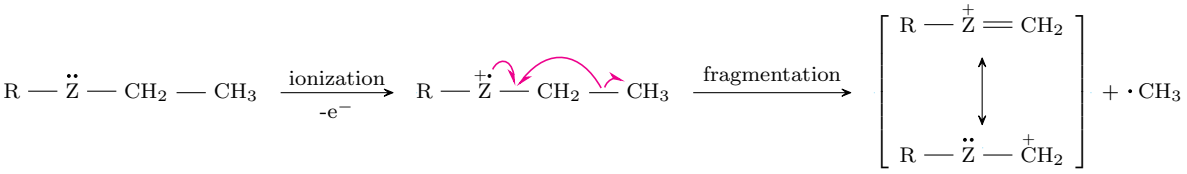


Resonance fragmentation: Alkenes.

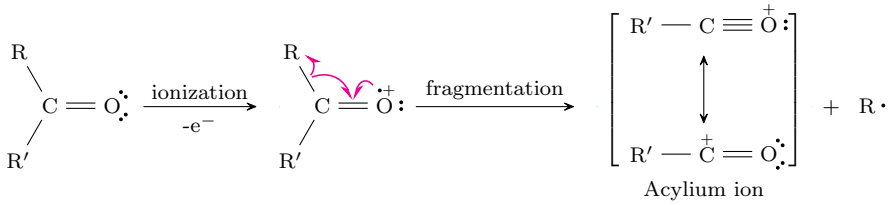
- Alkene reactions to know: hydrogenation (H_2 Pd/C), dihydroxylation (OsO_4), ozonolysis (O_3 Me_2S), hydrobromination (HBr), and bromination (Br_2).

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

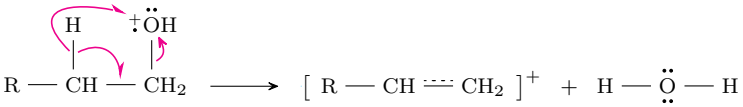
Approximate carbon-13 chemical shifts.



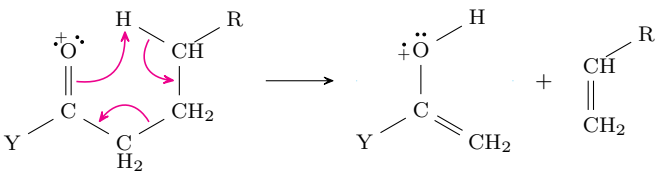
Resonance fragmentation: Lone pairs.



Resonance fragmentation: Carbonyls.



Fragmentation: Loss of H_2O.



Fragmentation: McLafferty rearrangement.

Week 5

Aromaticity

5.1 Aromaticity 1

2/8:

- Office hours: Tuesday and Friday at 4:00 PM.
- PSet 3 is due 2/17.
- Aromatic compounds are called such because they're often fragrant. They're heavily associated with biological systems.
- History of aromatic comounds.
  - 1825: Michael Faraday isolated a compound from his oil lamp having a C : H ratio of 1 : 1.
  - 1834: Benzoic acid plus heat makes $(CH)_n + CO_2$.
    - Even hex-1,3,5-triene still has more hydrogens than carbons.
  - Benzene.
    - There are about 60 possible structures for C_6H_6.
    - **Dewer benzene** is two fused 4-member rings with alkenes on opposing sides.
    - But benzene is highly unreactive in alkene reactions...
  - 1865: Kekulé proposed a "cyclohexatriene" structure.

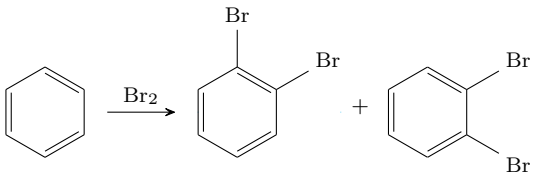


Figure 5.1: Bromination of cyclohexatriene.

    - Evidence: You would expect bromination of cyclohexatriene to produce two products, but it only produces one (the two molecules must be rapidly interconverting, i.e., via resonance).
  - Chemists began looking for more similar compounds.
  - 1911: Cyclooctatriene was made.
    - It can be hydrogenated, so not consistent with the low reactivity of benzene.
  - Cyclobutadiene was impossible to isolate due to a self-Diels-Alder reaction at any temperature greater than $-260\,^\circ\text{C}$.
- Enthalpies of hydrogenation.

  - Hydrogenation of cyclohexene has $\Delta H = -28.6\,\text{kcal/mol}$.
  - Hydrogenation of cyclohex-1,4-diene has $\Delta H = -57.2\,\text{kcal/mol}$.
  - Hydrogenation of cyclohex-1,3-diene has $\Delta H = -55.4\,\text{kcal/mol}$.
    - The 1.8 kcal/mol difference between the previous two comes from conjugation as predicted by resonance.
  - Hydrogenation of benzene has $\Delta H = -49.3\,\text{kcal/mol}$.
    - That is a huge stabilization effect.
- The bond lengths in benzene are all equally 1.39 Å.
- MO theory: We need a method to draw the MOs for flat, cyclic conjugated compounds. We will use the **Frost method**.
- For hexa-1,3,5-triene, six p-orbitals combine to make six MOs.

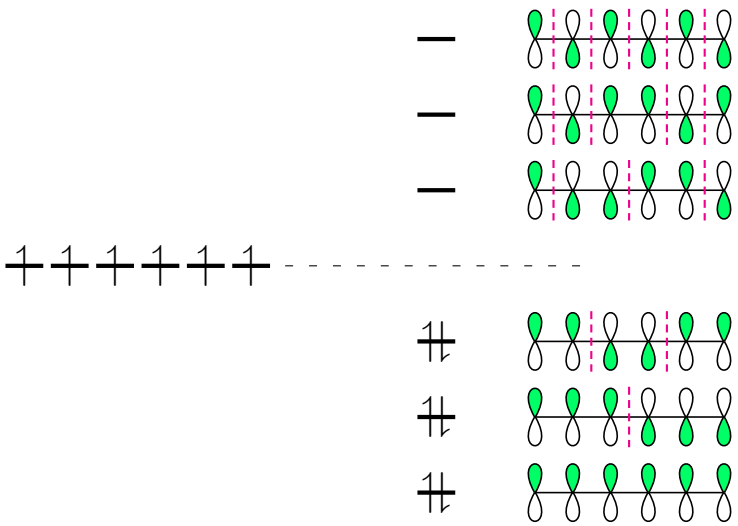


Figure 5.2: Hexa-1,3,5-triene MO diagram.

  - Three are bonding; three are antibonding. We can guess at what the SALCs look like with a nodal analysis.
- For benzene, six p-orbitals combine to make six different MOs.
  - See Figures III.1 and III.2 in Labalme [2].
  - For conjugated cyclic systems with an even number of atoms, there will always be a single high and single low MO energy level.
- **Frost method**: The following procedure for drawing MOs for flat cyclic conjugated compounds.
  1. Draw a polygon of the molecule without double bonds and with a vertex at the bottom.
  2. Draw a line halfway through the structure.
  3. Put an MO at each vertex.
- For example, if we want to find the MOs of butadiene, we do the following.

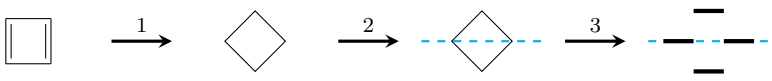


Figure 5.3: Frost method: Butadiene.

- We can even apply this to cyclotetradecaheptaene.

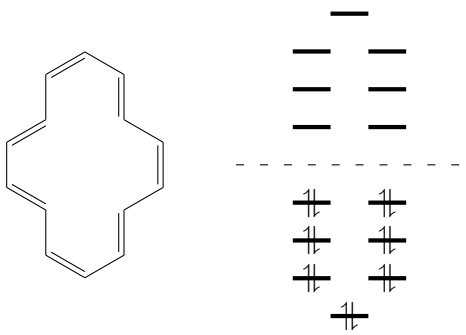


Figure 5.4: Frost method: Cyclotetradecaheptaene.

- **$(4n+2)$ rule**: If a system has $4n+2$ π-electrons for $n \in \mathbb{N}_0$, then it is aromatic.
  - Alternatively, if all bonding orbitals are filled and there are no electrons in non-bonding or anti-bonding orbitals, then the compound is aromatic.
- **Anti-aromatic** (molecule): A flat cyclic conjugated molecule with an uninterrupted flow of p-orbitals that does not satisfy the $(4n+2)$ rule.
  - Alternatively, the molecule must have electrons in non-bonding or antibonding orbitals and six or fewer atoms in the cycle.
- **Non-aromatic** (molecule): A molecule with electrons in non-bonding or antibonding orbitals and seven or more atoms in the cycle.
- Unpaired electrons in nonbonding orbitals can be very destabilizing.
  - But since cyclooctatetraene is not flat (it's tub-shaped), it avoids the MO overlap that leads to anti-aromaticity.

5.2 Aromaticity 2

2/10:

- Note that the bond lengths of benzene are equal because the two resonance structures each contribute equally, and we can measure the bond length via x-ray crystallography.
- A magnetic field induces the π-electrons of aromatic compounds to circulate. This motion reinforces the magnetic field, leading to a substantial deshielding effect in NMR experiments.
  - Indeed, NMR is one of our key tools for identifying aromatic compounds.
- People in the 1820s thought that a compound had to smell to be aromatic. Of course, we now know that smell has nothing to do with chemical aromaticity.
- **Hückel's rules**: A set of rules that determines whether or not a compound is aromatic; a shortcut to the Frost diagram method.
  - To apply Hückel's rule, the molecule in question must be flat, cyclic, and have a p-orbital on each atom.
  - If one of these conditions does not apply, the molecule is simply non-aromatic.
  - If the conditions do apply, $4n+2$ π electrons implies aromaticity and $4n$ ($n \in \mathbb{N}$) electrons implies anti-aromaticity (the number of atoms is less than 6) or non-aromaticity (the number of atoms is greater than 6).

- Note that if we chose the bottom vertex of cyclotetradecaheptaene to be any other vertex than the one shown in Figure 5.4 (or the one directly opposite it), we would end up with multiple lowest energy MOs (which would be incorrect).
- Anti-aromatic molecules react in any way they can to avoid existing in such a state.
  - Think of cyclobutadiene doing a self-Diels-Alder reaction to avoid being anti-aromatic.
  - Cyclooctatetraene is sufficiently big such that it need not react; it can just bend.
- Tougher Frost diagrams:
  - 5-membered ring: 3 bonding orbitals and 2 anti-bonding orbitals.
  - 7-membered ring: 3 bonding orbitals and 4 anti-bonding orbitals.
- Based on first principles, a structure with a ring system and a number of electrons that makes reasonable sense for aromaticity is aromatic.
  - However, in nature, 18 π-electrons tends to be the upper limit for aromaticity.
  - Chemists have gone up to 34 π-electrons and you can go even higher.
  - As long as the molecule is still flat, if everything else works, it is aromatic.
- Today, we will discuss three new classes of molecules that have aromaticity.
- Class 1: Anions/cations.
  - Treating cyclopentadiene with an appropriate base yields the cyclopentadienyl anion, which is aromatic.
    - The cyclopentadienyl anion has five equivalent resonance structures.
    - The Frost diagram analysis supports this claim, since the three bonding orbitals are completely filled and the two antibonding orbitals are empty.
  - Treating cycloheptatriene with the trityl cation abstracts a hydride leaving the tropylium ion, which is aromatic.

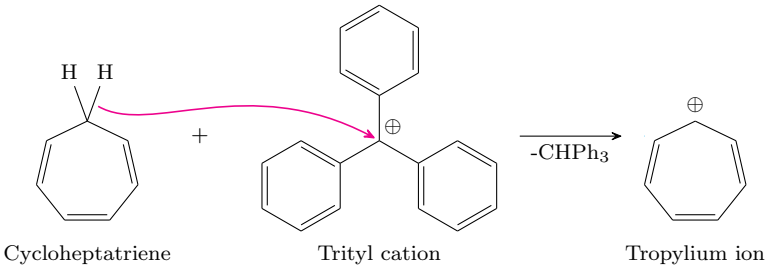


Figure 5.5: Aromaticity in the tropylium ion.

- When we have substituted compounds, we only care about the π-electrons in the ring system.
  - For example, in tropone, we only count seven π-electrons.

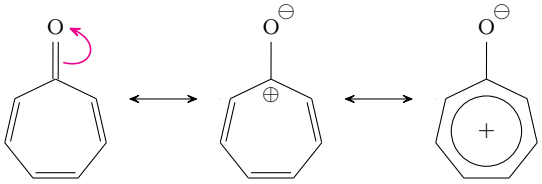


Figure 5.6: Aromaticity in tropone.

- However, if a molecule can become aromatic, it will. Thus, the actual structure of tropone is the right resonance structures above.

- We can indeed have 2π-electron aromatic systems [3].

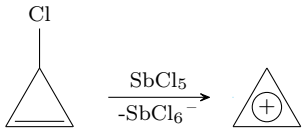


Figure 5.7: Aromaticity in the cyclopropenyl ion.

  - This was the crowning achievement of a push in the 1950s-60s by organic chemists to push the bounds of aromatic compounds. It was done by Ron Breslow of Columbia in 1967.

- Joined rings can also rearrange à la tropone (Figure 5.6) into an aromatic system.

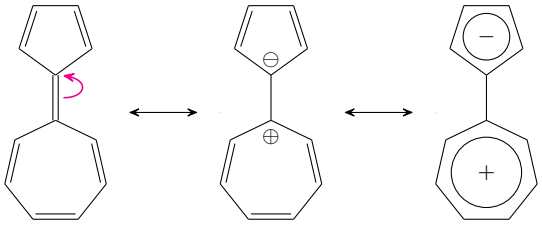


Figure 5.8: Aromaticity in sesquifulvalene.

  - Although we can call this molecule aromatic overall, it would be better to say each ring is separately aromatic.
  - In problems like this, get an initial electron count first (five for the top ring and seven for the bottom ring). This will then provide information about where you need to push electrons to create aromaticity. For example, seven is one too high and five is one too low, so we give one electron from the seven ring to the five ring to create two rings with six electrons.
  - Not all such systems do, however: Fulvalene[1], for instance would have to rearrange into an aromatic ring *and* an anti-aromatic ring, so it foregoes any rearrangement and is actually non-aromatic.
  - Take-away: If one ring becomes aromatic and one remains non-aromatic, that's fine. If both rings become aromatic, that's great. If one ring would have to become anti-aromatic for the other to become aromatic, that will not happen.

- **Heterocyclic compound**: A cyclic compound containing atoms other than carbon and hydrogen. *Also known as* **heterocycle**.

- **Heteroatom**: Any atom that is not carbon or hydrogen.
  - Commonly oxygen, sulfur, or nitrogen.

- Class 2: Heterocyclic compounds.

(a) Pyridine. (b) Furan. (c) Pyrrole. (d) Imidazole.

Figure 5.9: Common heterocyclic compounds.

[1] Fulvalene looks exactly like sesquifulvalene, except that both rings have only five carbons.

- An analysis of pyridine.

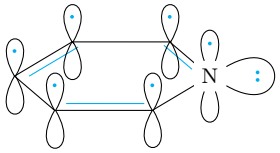


Figure 5.10: The structure of pyridine.

  - The three double bonds in pyridine contribute the six π-electrons necessary for it to be aromatic.
  - Importantly, this means that the lone pair of nitrogen is *not* needed for aromaticity, so it sits outside the compound in an sp^2 orbital.
  - The fact that this lone pair is free implies that pyridine is an excellent base.

- An analysis of pyrrole.

  - The two double bonds *plus* the lone pair of the nitrogen constitute the six π-electrons necessary for it to be aromatic.
    - Although VSEPR theory suggests that the nitrogen would be sp^3 hybridized so as to get all electron pairs as far away as possible, the increase in energy by rehybridizing to sp^2 is more than compensated for by the aromatic stabilization energy.
  - For this reason, pyrrole is *not* a good base.
  - Indeed, if the nitrogen picks up another hydrogen, you lose aromaticity and introduce a +1 formal charge on the nitrogen. Thus, since the hydrogen adduct is so unstable, it is a strong acid on the order of HCl ($\mathrm{p}K_\mathrm{a} = 0.9$).

- An analysis of furan.

  - The two double bonds plus one of the lone pairs of the oxygen constitute the six π-electrons necessary for it to be aromatic.
  - However, there is still a lone pair left over on the oxygen, so furan can still act like a base.

- Adenine is a heterocyclic aromatic compound with 10 π-electrons. Some of its nitrogens contribute their lone pair electrons to the π-system, and others have them free to act as bases.

- Heterocycles can be anti-aromatic as well.

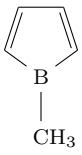


Figure 5.11: An anti-aromatic heterocycle.

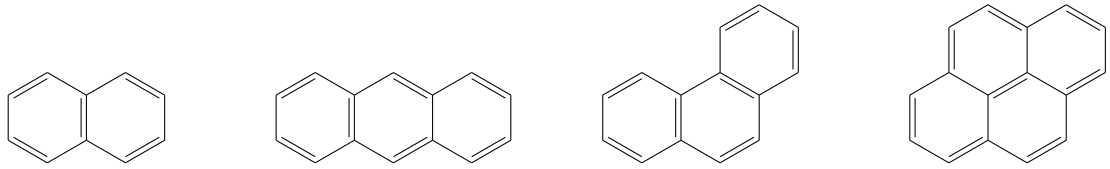
  - Boron is happy with three bonds, so it has an empty p-orbital.
  - Thus, this is a flat cyclic molecule with an uninterrupted chain of p orbitals and $4n$ ($n = 1$) π-electrons. But this implies that it is anti-aromatic.

- Degrees of aromaticity.

  - Benzene is "the most" aromatic compound.

  - All molecules with heteroatoms will have slightly different bond lengths and thus a lesser stabilization energy.
  - Indeed, under forcing enough conditions, we can make some of the heteroaromatics actually do reactions.
    - For example, we can make furan do a Diels-Alder reaction at very high temperatures; this is never something we would see with benzene.

- Class 3: Polycyclic aromatic hydrocarbons (PAHs).



(a) Naphthalene. (b) Anthracene. (c) Phenanthrene. (d) Pyrene.

Figure 5.12: Common PAHs.

  - Naphthalene is used in mothballs.
  - These names won't be tested, but they're useful to know.

- An analysis of naphthalene.

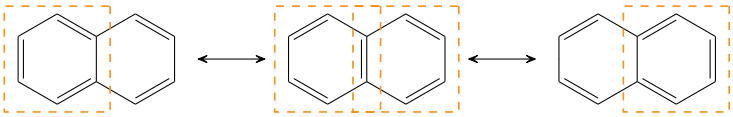


Figure 5.13: The structure of naphthalene.

  - Although Figure 5.12a shows that naphthalene is a 10 π-electron system, it can be useful to think of it as two separate benzene rings.
  - Doing so and drawing all resonance structures reveals that each ring only appears as benzene (as opposed to a diene) 2/3 of the time.
    - Every occurrence of a ring as benzene is boxed in Figure 5.13. Notice how each ring is boxed twice and not boxed once (across the three resonance structures).
  - Thus, the aromatic stabilization of naphthalene is not twice benzene's $-36.5\,\text{kcal/mol}$ but rather $\frac{2}{3} \cdot 2 \approx 1.33$ times benzene's $-36.5\,\text{kcal/mol}$.
    - If we assign benzene an aromaticity value of 1, we would assign naphthalene 1.33.
  - The bonds in naphthalene alternate between 1.36 Å and 1.42 Å, a 0.03 Å perturbation from the bond lengths in benzene.

- **Rocks of Gibraltar**: The molecules benzene, naphthalene, and pyrene, which in general will not undergo further chemical reactions due to the extent of their aromatic stabilization.

- An analysis of pyrene.

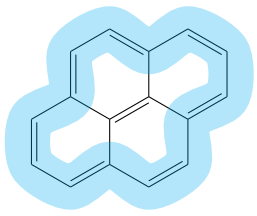


Figure 5.14: The structure of pyrene.

  - Pyrene is aromatic, but it appears to have $16 = 4n$ π-electrons.
  - However, since one of the criteria for aromaticity is a *cyclic* chain of π-orbitals, it is actually only the $14 = 4n + 2$ π-electrons around the periphery that constitute the aromatic system. The π-bond in the center of the molecule is just a lone alkene with no aromatic stabilization.
  - You can hydrogenate the central double bond at very high pressures, but essentially for all intents and purposes, pyrene is a nonreactive molecule.

- Diels-Alder reactivity of anthracene.

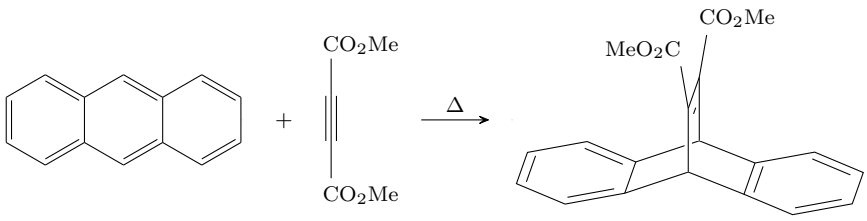


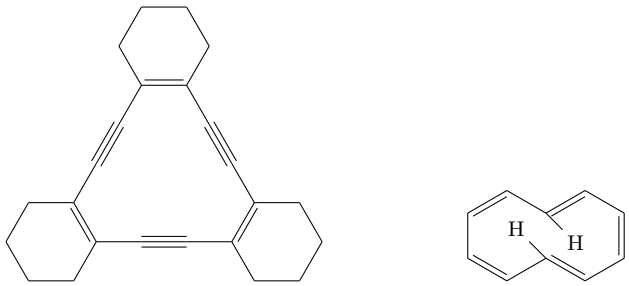
Figure 5.15: Diels-Alder reactivity of anthracene.

  - Anthracene is finally destabilized enough to react in a Diels-Alder reaction.
  - When we look to predict products, we want to maximize the amount of aromaticity left over after the reaction (because this will be the most stable product).
  - If we perform the Diels-Alder reaction with the central diene, the product will have two benzene rings.

- The char marks on grilled meat contain a number of PAHs, notably benzopyrene.
  - Benzopyrene is one ring too far to be stable.
  - Since it is flat, it can intercolate in our DNA and cause a lot of issues, notably with regulating the cell cycle.
  - Thus, our bodies want to get rid of it, so it sends enzymes to epoxidize the benzene hanging off the pyrene.
  - Now that the molecule is polar, it can be excreted, but this is a risky strategy because epoxides are highly reactive and can damage other things.

- Vioxx vs. Celebrex.
  - It is possible that the reason that Vioxx is harmful and Celebrex is not is that Vioxx has a ring that is not aromatic whereas all of Celebrex's rings are aromatic.

- Special considerations.



(a) (b)

Figure 5.16: Special considerations for determining aromaticity.

  - Triple bonds: A triple bond in the π-system still only contributes two electrons. This is because its other two π electrons are perpendicular to the π-system in question.
    - The compound in Figure 5.16a has 12 π-electrons but is still non-aromatic because the number of atoms is greater than six (it can bend).
  - Sterics: If sterics prevent a molecule from being flat, it cannot be aromatic.
    - The compound in Figure 5.16b cannot lie flat due to the steric clashing of the two indicated hydrogens. Note that this clashing is unavoidable due to the conformation and the lack of freedom of rotation about the double bonds.

- Next week is all about the reactions of benzene.

5.3 Chapter 14: Aromatic Compounds

From Solomons et al. [1].

2/16:

- Nomenclature.
  - "In many simple compounds, *benzene* is the parent name and the substituent is simply indicated by a prefix" [1, p 619].
    - Examples: Flurorbenzene, chlorobenzene, nitrobenzene.
  - Other simple compounds have commonly accepted parent names.
    - Examples: Methylbenzene $\rightarrow$ toluene, hydroxybenzene $\rightarrow$ phenol, aminobenzene $\rightarrow$ aniline.
    - Other compounds to be aware of: Benzenesulfonic acid ($C_6H_5SO_3H$), benzoic acid (C_6H_5COOH), acetophenone ($C_6H_5COCH_3$), and anisole ($C_6H_5OCH_3$).
  - Covers ortho, meta, para naming.
  - "When a substituent is one that together with the benzene ring gives a new base name, that substituent is assumed to be in position 1 and the new parent name is used" [1, p 620].
    - This means that molecules such as m-nitrobenzoic acid are named 3-nitrobenzoic acid.
  - Dimethylbenzenes are often known as xylenes.
  - Phenylmethyl becomes benzyl.
- The only alkene chemistry in which benzene participates is hydrogenation (in the presence of finely divided nickel, under high temperatures and pressures).
- **Benzene substitution**: The substitution of one of the hydrogens of benzene for a bromine, as initiated by the presence of a Lewis acid catalyst such as ferric bromide ($FeBr_3$).
  - Explanation: All hydrogens are equivalent and replacing any one of them with bromine results in the same product.
  - Possible explanation: Only one of benzene's hydrogens is reactive.
    - Wrong, though — ruled out by the structure of benzene but plausible when we didn't know its structure.
- The Kekulé structure for benzene (cyclohexatriene) satisfied the requirements but failed for the reason of Figure 5.1.
  - Kekulé proposed a rapid equilibrium between the structures (resonance), but today we prefer the explanation of delocalization.
- A new meaning of aromaticity: Aromatic compounds are highly unsaturated compounds that prefer substitution chemistry to addition chemistry.
- Richard Willstätter first synthesized cyclooctatetraene in 1911.

- **Resonance energy**: The difference between the amount of heat actually released and that calculated on the basis of the Kekulé structure.
- "Resonance contributors, we emphasize again, are not in equilibrium. They are not structures of real molecules. They are the closest we can get if we are bound by simple rules of valence, but they are very useful in helping us visualize the actual molecule as a hybrid" [1, p 625].
- It was recently discovered that "crystalline benzene involves perpendicular interactions between benzene rings, so that the relatively positive periphery of one molecule associates with the relatively negative faces of the benzene molecules aligned above and below it" [1, p 627].
- In 1931, Erich Hückel carried out a series of quantum mechanical calculations that concluded that planar monocyclic rings containing $4n + 2$ π-electrons have **closed shells** of delocalized electrons (like benzene) and therefore have substantial resonance energies.
- **Closed shell**: A set of molecular orbitals that are all either completely occupied or completely empty (i.e., no MO in the set contains only one electron).
  - Molecules that lack closed shells have unpaired electrons (radicals) and are usually not stable.
- The **polygon-and-circle method** was developed by C. A. Coulson of Oxford university as a simple method of deriving the same energy levels that the quantum mechanical calculations of Hückel would furnish.
- **Polygon-and-circle method**: The following procedure.
  1. We start by drawing a polygon corresponding to the number of carbons in the ring, placing a corner of the polygon at the bottom.
  2. Next, we surround the polygon with a circle that touches each corner of the polygon (the circumcircle).
  3. At the points where the polygon touches the circle, we draw short horizontal lines outside the circle. The height of each line represents the relative energy of each π molecular orbital.
  4. Next, we draw a dashed horizontal line across and halfway up the circle. The energies of bonding π molecular orbitals are below this line. The energies of antibonding π molecular orbitals are above, and those for nonbonding orbitals are at the level of the dashed line.
  5. Based on the number of π electrons in the ring, we then place electron arrows on the lines corresponding to the respective orbitals, beginning at the lowest energy level and working upward. In doing so, we fill degenerate orbitals each with one electron first, then add to each unpaired electron another with opposite spin if it is available.
- **Annulene**: A monocyclic compound that can be represented by a structure having alternating single and double bonds.
  - The ring size of an annulene is indicated by a number in brackets.
  - For example, benzene is [6]annulene and cyclooctatetraene is [8]annulene.
- Hückel's rule predicts that annulenes are aromatic iff they have $4n + 2$ π-electrons.
  - This prediction was verified in the 1960s (largely by F. Sondheimer) as numerous new annulenes became available for testing.
  - Annulenes 14-24 satisfy Hückel's prediction.
  - Annulenes 10-12 are too strained to be planar, regardless of double bond placement (see Figure 5.16b).
- The ^{1}H NMR spectrum of benzene supports both equivalent hydrogens (only a singlet appears) and the cyclic nature of the π-system (the high chemical shift is indicative of a ring current).

  - [18]annulene has six hydrogens within its ring and twelve hydrogens at the periphery. Because of the shape of the ring current, the internal hydrogens are highly shielded (δ -3.0) and the external hydrogens are highly deshielded (δ 9.3).
  - NMR spectroscopy provides direct physical evidence of whether or not the π-electrons are delocalized.

- Cycloheptatriene is also commonly known as tropylidene.
- To evaluate the stabilization (or lack thereof) of a cyclic compound with delocalized π electrons, we compare it to a conjugated linear model and consider what would happen (theoretically or experimentally) if we removed a hydrogen from each end of the linear compound to form a ring.
  - Such calculations/experiments are beyond the scope of Solomons et al. [1].
- **Benzenoid polycyclic aromatic hydrocarbon**: A molecule having two or more benzene rings fused together.
- **Nonbenzenoid aromatic compound**: A compound that is either the cyclopentadienyl anion, the cycloheptatrienyl cation, *trans*-15,16-dimethyldihydropyrene, or an aromatic annulene (except [6]annulene).
- Solomons et al. [1] briefly discusses fullerenes, such as buckyballs.
- Solomons et al. [1] discusses applications of aromatic compounds to biochemistry. In particular, it discusses NADH and NAD^+.
- Discusses the infrared absorptions of aromatic compounds (not covered in class, but potentially relevant?).

Week 6

Electrophilic Aromatic Substitution

6.1 Electrophilic Aromatic Substitution 1

2/15:

- Discusses the aromaticity of fluorescein as an example to review from last class.
- Reactions of aromatic compounds are divided into two classes: Electrophilic and nucleophilic aromatic substitutions.
- Example:
  - $C_6H_6 \xrightarrow{H_3O^+} C_6H_6$ means no reaction?
  - $C_6H_6 \xrightarrow{D_3O^+} C_6D_6$; thus, a substitution is occurring.
- Mechanism:

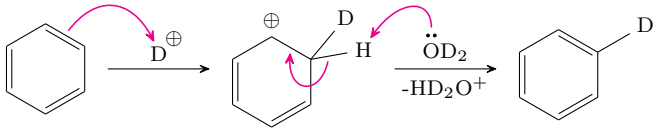


Figure 6.1: Electrophilic aromatic substitution mechanism.

  - To begin, one of the π-bonds of benzene attacks D^+. This causes the loss of aromaticity, but the carbocation is highly resonance delocalized.
  - Although we *could* make an alcohol at this point, this would lead to the loss of aromaticity in the product, so we won't do that.
  - Instead, we do an E_1-type reaction.
  - The first step is the RDS.
  - The intermediate in this mechanism is called the **arenium ion**, the **Wheland intermediate**, or the **sigma complex**.
  - Note that the electrophile used in this reaction has to be a very special, very reactive, very strong electrophile in order to make up the energy gap.
- We know that the sigma complex exists because we can trap the intermediate.
- Whether or not we see the product react again depends on whether the product or starting material is more nucleophilic.
- Adding an EDG to the benzene makes the reaction proceed faster.

  - A good EDG will stabilize the arenium ion, lowering the activation barrier of the first step (the RDS).

- Halogenation.
- General form.

$$\mathrm{PhH} + \mathrm{Br_2} \xrightarrow{\text{cat. } \mathrm{FeBr_3}} \mathrm{PhBr} + \mathrm{HBr}$$

  - Br_2 is too unreactive to have chemistry with benzene on its own.
  - In particular, when we say that Br_2 is too unreactive, we mean that there is not enough Br^+ character, i.e., it is not a good enough electrophile.
  - To overcome the problem, we add Br_2 to $FeBr_3$, a good Lewis acid with an open valence site. It follows that $Br{-}Br^+{-}Fe^-Br_3$ is a super awesome electrophile!

- Mechanism.

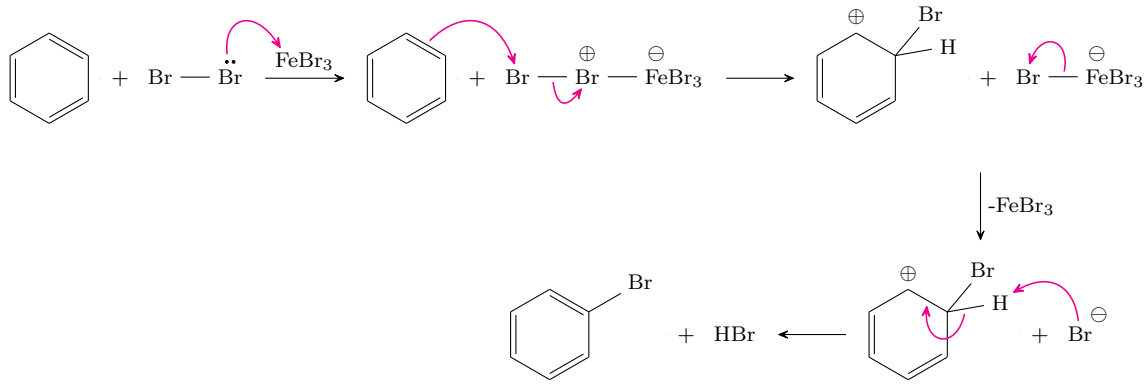


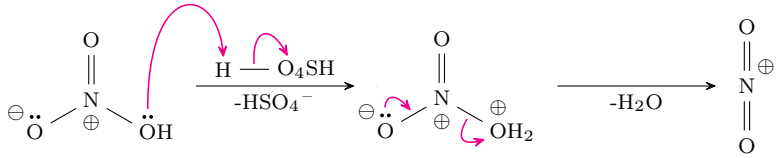
Figure 6.2: EAS halogenation mechanism.

- For chlorination, we use catalytic $AlCl_3$.
- For iodination, we use catalytic CuI_2.
- Nitration.
- General form.

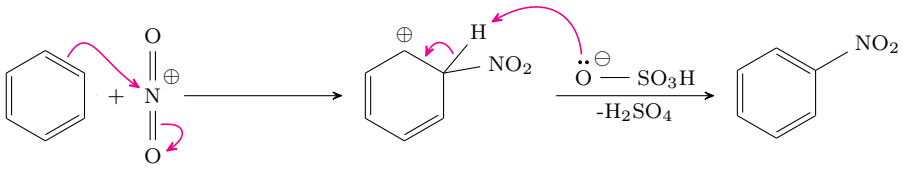
$$\mathrm{PhH} + \mathrm{HNO_3} \xrightarrow{\text{cat. } \mathrm{H_2SO_4}} \mathrm{PhNO_2} + \mathrm{H_2O}$$

  - We start with nitric acid, but as before, the nitrogen is not electrophilic enough.
  - Thus, we add catalytic sulfuric acid. Since H_2SO_4 is stronger than HNO_3, it protonates nitric acid to $H_2NO_3{}^+$, which quickly splits into $H_2O + NO_2{}^+$, where $NO_2{}^+$ is the nitronium ion (a super electrophile!).

- Mechanism.



(a) Nitronium ion formation.



(b) Nitration of benzene.

Figure 6.3: EAS nitration mechanism.

6.2 Electrophilic Aromatic Substitution 2

2/17:

- Problem set 4 posted today.
  - We will have all the material for it by the end of Tuesday.
- Today:
  - We run through a bunch of use cases of EAS (putting different functional groups on an aromatic ring).
  - Regioselectivity, reaction rates, etc. at the end of class.
- Sulfation.
- General form.

$$\mathrm{PhH} + \mathrm{SO_3} \xrightarrow{\text{cat. } \mathrm{H_2SO_4}} \mathrm{PhSO_3H}$$

  - Important for making detergents — sulfates are highly soluble, so we use them to solvate the constituent lipids.
- Mechanism.

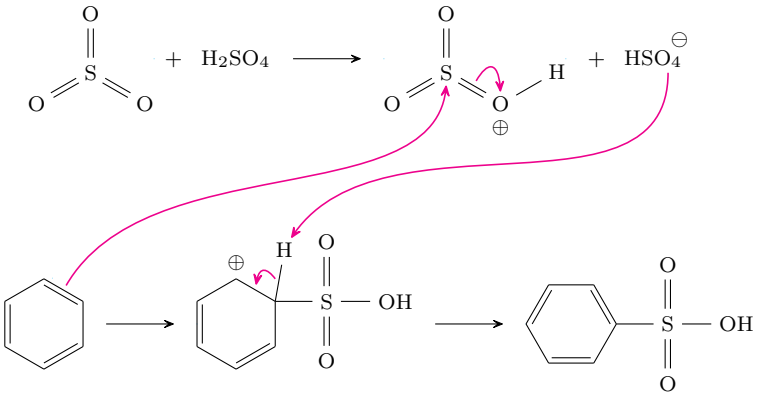


Figure 6.4: EAS sulfation mechanism.

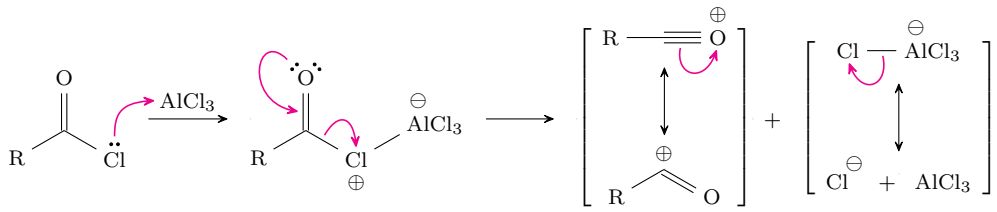
  - As with nitration (Figure 6.3), we use sulfuric acid to protonate a species that will then interact with benzene.
- Friedel-Crafts acylation.
- General form.

$$\mathrm{PhH} + \mathrm{RCOCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{PhCOR} + \mathrm{HCl}$$

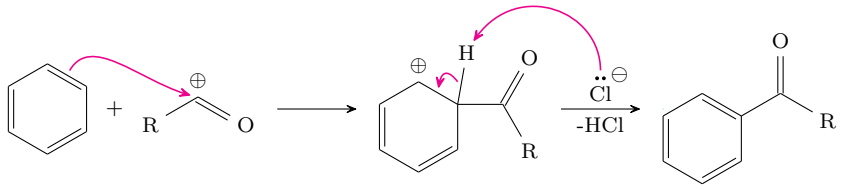
  - The acid chloride is a very strong electrophile, but it needs to be even stronger. We can make it stronger with the $\mathrm{AlCl_3}$ catalyst.

- This reaction is incredibly useful because it forms a new C–C bond.
- Limitation: You cannot have an EWG on the ring (the ring needs to be nucleophilic).

- Mechanism.



(a) Acylium ion formation.



(b) Acylation of benzene.

Figure 6.5: Friedel-Crafts acylation mechanism.

- The reaction with the catalyst makes the carbon center in $O{=}C^{+}{-}R$ extremely electrophilic.

- Friedel-Crafts alkylation.

- General form.

$$PhH + RCl \xrightarrow{AlCl_3} PhR + HCl$$

- Again, F-C alkylation is useful because it forms a C–C bond.

- Mechanism.
  - Mostly analogous to Figure 6.5.
  - Problems:
    - EWGs (you need a nucleophilic aromatic ring as with F-C acylation).
    - Selectivity (you get a mixture of products due to hydride/methyl shifts since the mechanism proceeds through a carbocation intermediate).
  - Additional issue: Over-alkylation. The products are more reactive because the electron-donating alkyl groups increase the nucleophilicity of the aromatic ring. Thus, we get ortho- and para-dialkyl compounds in addition to the monosubstituted products.
    - Note that this is not a problem with the other reactions we've learned so far (everything else added EWGs).
  - Note that since all we need to run the reaction is a carbocation, the other carbocation generation methods we've learned can also lead to F-C alkylation (if an aromatic compound is present in solution).
    - For example, mixing 2-methylpropene and acid generates a tertiary CC+ that can react with benzene to yield *t*-butylbenzene.
    - Intramolecular reactions can also occur this way — if a CC+ is formed on a substituent in an aromatic molecule, it can react with the aromatic ring in a ring-closing mechanism.

- More on the selectivity issue with F-C alkylation.

  - For example, reacting benzene with 1-chloropropane under F-C alkylation conditions will yield isopropylbenzene as the major product and propylbenzene as the minor product.
  - Thus, don't use F-C alkylation for linear *n*-alkyl compounds. It should be reserved for if you want to add a *t*-butyl group or another alkyl group with symmetric hydrogens.
  - If you *do* want to create propylbenzene, make use of the much more controllable F-C acylation reaction. Indeed, react benzene with propionyl chloride under F-C acylation conditions, and then either hydrogenate (H_2/Pd) or perform a **Clemmensen reduction**.

- **Clemmensen reduction**: The selective hydrogenation of a ketone using $Zn(Hg) + HCl$[1].
  - If there is an alkene in the acid chloride added to the benzene that you don't want to hydrogenate, you will have to use the Clemmensen reduction (as it will only hydrogenate the unwanted ketone).

- Example: Ring-closing acylation/alkylation reaction.

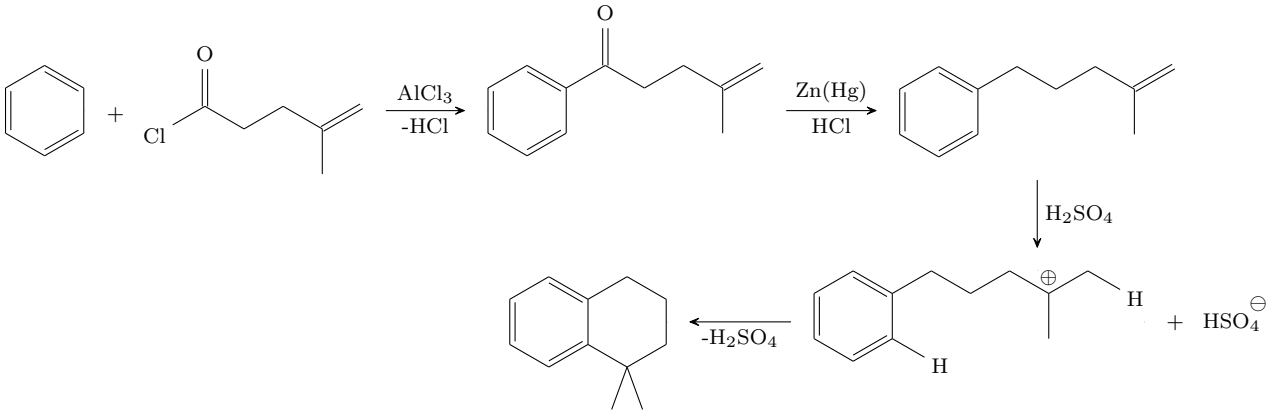


Figure 6.6: Ring-closing Friedel-Crafts mechanism.

  - The acylation product is formed. It can be hydrogenated with the Clemmensen reduction. Then we can turn the alkene into a carbocation with sulfuric acid and subject it to F-C alkylation conditions to yield a ring-closing reaction.

- Forming a benzoic acid.

$$\mathrm{PhR} \xrightarrow[\mathrm{H_2O}]{\mathrm{KMnO_4}} \mathrm{PhCOOH}$$

  - It is necessary to have a benzylic hydrogen for the mechanism to proceed (for example, $PhBu^t$ wouldn't react).
  - It is possible to convert multiple alkyl groups at the same time (for example, $C_6H_4MePr \longrightarrow C_6H_4(COOH)_2$ where the carboxylic acids wind up where the methyl and propyl groups originally were).

- Forming an amine (from a nitro group).

$$\mathrm{PhNO_2} \xrightarrow{\text{reagents}} \mathrm{PhNH_2}$$

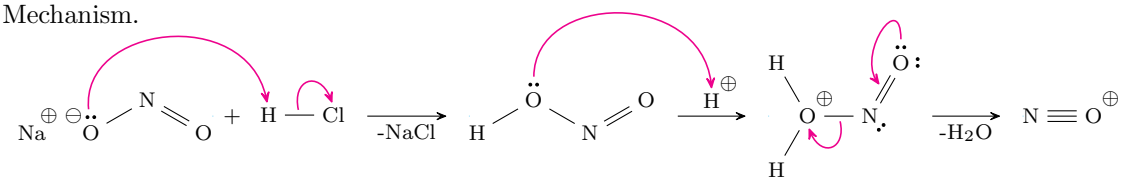
  - A number of reductive reagents can work here. Explicitly, we may use $H_2 + Pd/C$, H^+ (acid), or $SnCl_2 + H_2O$.
  - This reaction takes a strong EWG and turns it into an EDG.
  - The amine is also a gateway to a number of other functional groups, so being able to get one is very helpful.

[1] Note that Zn(Hg) is zinc amalgam.

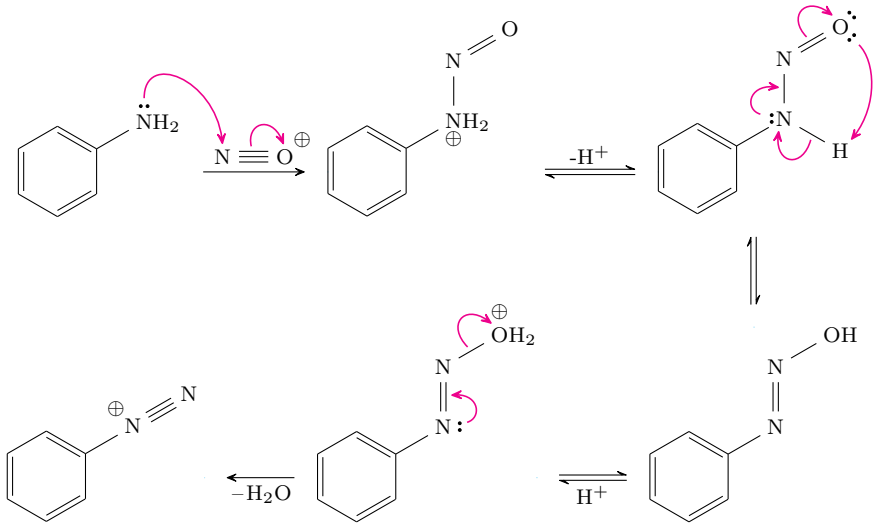
- Diazotization.
- General form.

$$\mathrm{PhNH_2} \xrightarrow{\text{reagents}} \mathrm{PhN_2^+} + \mathrm{X^-}$$

  - We use either $\mathrm{NaNO_2/HCl}$ or $\mathrm{HNO_2}$ as the reagent(s).
  - Note that the product is a diazonium salt.
- Mechanism.



(a) Nitrosonium ion formation.



(b) Diazotization of aniline.

Figure 6.7: EAS diazotization mechanism.

  - Note that the HONO intermediate in Figure 6.7a is called "HONO"[2].
  - Excess strong acid is used here (we need two equivalents of acid at least to form the nitrosonium ion).
  - The nitrosonium ion is very unstable and reacts quickly with the relatively nucleophilic amine.
  - The last step being irreversible serves as the driving force for this reaction.
- **Sandmeyer reaction**: Reacting an aryl diazonium salt with electrophiles in the presence of a copper catalyst substitutes those electrophiles for the diazonium group.
- In particular, mixing $\mathrm{PhN_2^+}$ with...
  - $\mathrm{Cu_2O}, \mathrm{H_2O}$ makes PhOH.
  - CuCl makes PhCl.
  - CuBr makes PhBr.

[2] "HOE-NOE"

  - CuI makes PhI.

- Mechanism.
  - Complex; sort-of S_N1-like.
  - The diazonium is a great leaving group, so it leaves, making a phenyl cation and N_2. At this point, a nucleophile can just swoop in and attack the phenyl cation.
  - Note that the phenyl cation intermediate is still aromatic — the electron removed was taken from an sp^2 orbital, not a p orbital.

- We can hydrogenate our diazonium phenyl compound with H_3PO_2.

$$PhN_2{}^+ \xrightarrow{H_3PO_2} PhH$$

- Why F-C alkylations lead to over-alkylation but others do not.
  - Consider nitration.
  - Nitro groups are strongly electron withdrawing. Thus, they deactivate their host aromatic ring.
    - Over a long time, however, we will see the formation of some meta-dinitrobenzene (not ortho or para).
    - This is because resonance gives us carbocations at the ortho and para positions. Thus, the molecule is 100 000 times less reactive then benzene toward EAS overall, but the molecule is even less reactive (less nucleophilic) at the ortho and para positions.
    - Additionally, if we substitute ortho or para, we will have a resonance structure in the transition state with a carbocation directly adjacent to the positive nitrogen of the nitro group. This is no good, and another reason why EWGs are meta-directing.
  - Same for acyl groups and SO_3H groups.

- With respect to ortho/para selectivity, sterics *may* sometimes make ortho-substitution less likely.

- Activators and deactivators.

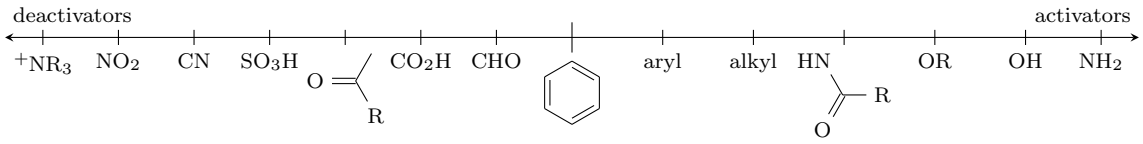


Figure 6.8: Activators and deactivators.

  - Deactivators are meta-directors (the meta position is the most nucleophilic position in a deactivator-substituted molecule).
  - Activators won't break aromaticity as in resonance structures, but said structures can indicate trends. They are ortho/para directors.
    - Convince yourself using resonance structures that ortho/para addition leads to 1 extra resonance structure.
  - Alkyl and aryl groups are ortho/para-directing activators.
    - Ortho/para addition allows us to access a resonance structure where the carbocation intermediate is tertiary.
    - For example, toluene is about 25 times more reactive than benzene, and it is even more reactive at the ortho/para positions.

References

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(2) Labalme, S. CHEM 20100 (Inorganic Chemistry I) Notes `https://github.com/shadypuck/CHEM20100Notes/blob/master/Notes/notes.pdf` (accessed 02/16/2022).

(3) Breslow, R.; Groves, J. T.; Ryan, G. *J. Am. Chem. Soc.* **1967**, *89*, 5048.