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.

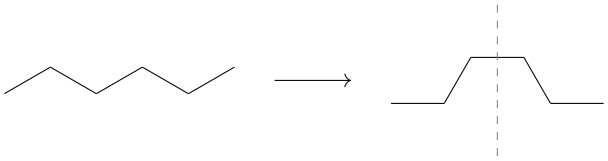


Figure 1.1: Mirror plane in hexane.

  - 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.

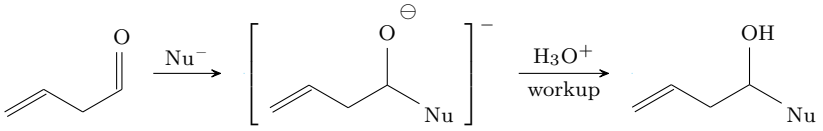


Figure 1.2: H_3O^+ workup.

  - 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).

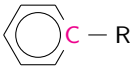
Type of Carbon	**Chemical Shift (δ, ppm)**
1° Alkyl, RCH_3	0-40
2° Alkyl, RCH_2R	10-50
3° Alkyl, $RCHR_2$	15-50
Alkyl halide or amine, R_3CX ($X = Cl, Br, NR'_2$)	10-65
Alcohol or ether, R_3COR'	50-90
Alkyne, $RC{\equiv}R'$	60-90
Alkene, $R_2C{=}R'$	100-170
Aryl, 	100-170
Nitrile, $RC{\equiv}N$	120-130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

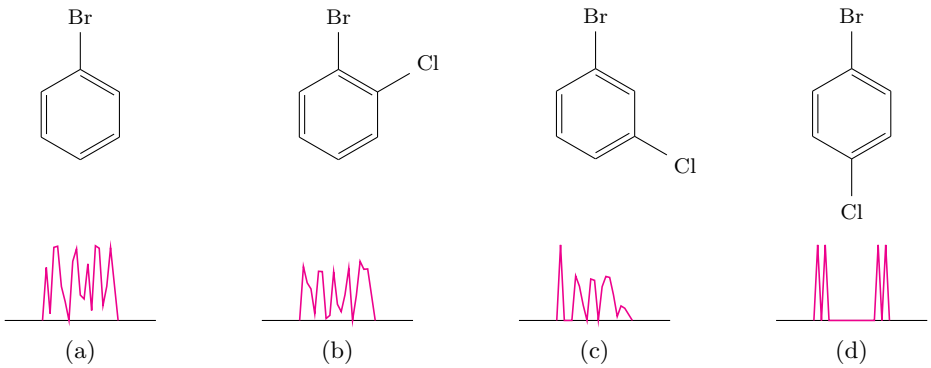
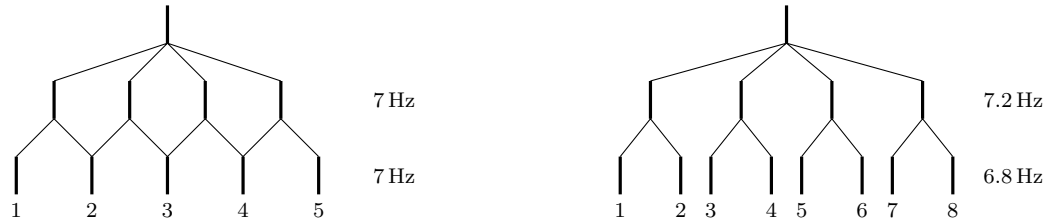


Figure 2.1: Benzenes in ^{1}H NMR spectroscopy.

  - 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.

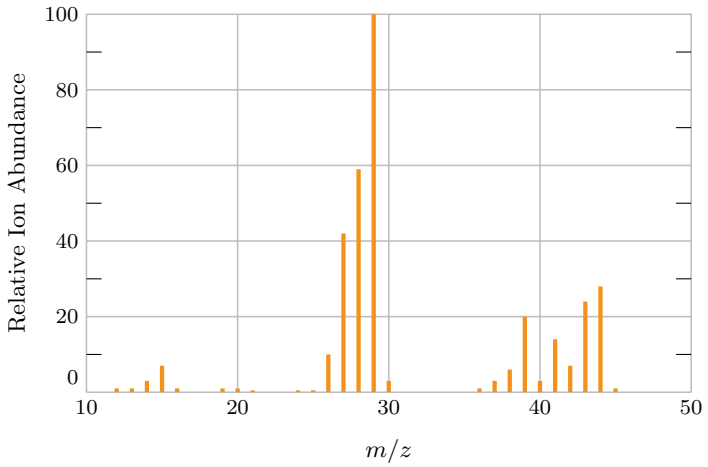


Figure 2.3: The mass spectrum of propane.

  - 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.

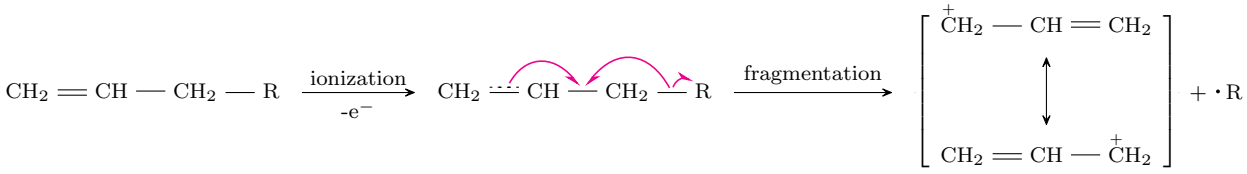


Figure 2.5: Resonance fragmentation: Alkenes.

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

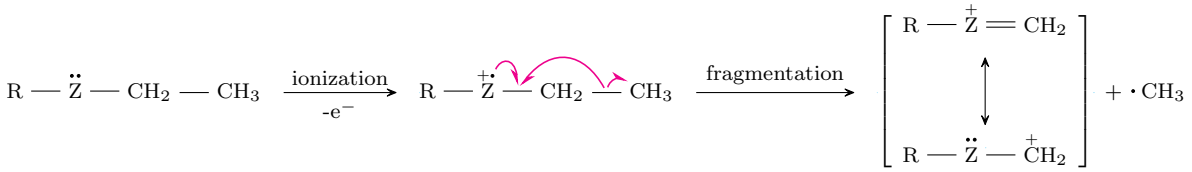


Figure 2.6: Resonance fragmentation: Lone pairs.

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.

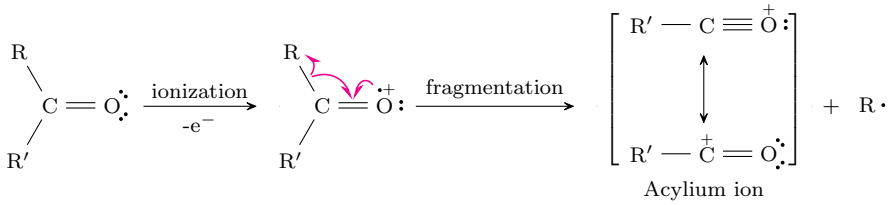
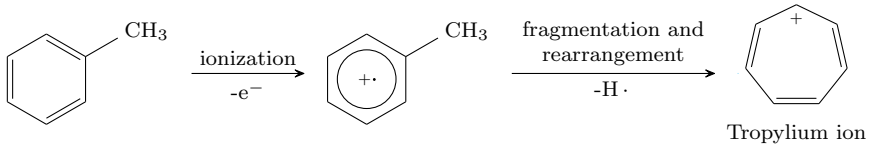


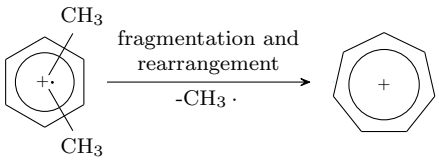
Figure 2.7: Resonance fragmentation: Carbonyls.

   – 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 $m/z = 77$.

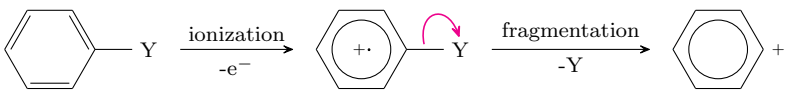


Figure 2.9: Resonance fragmentation: Monosubstituted benzene rings with nonalkyl groups.

   – 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.

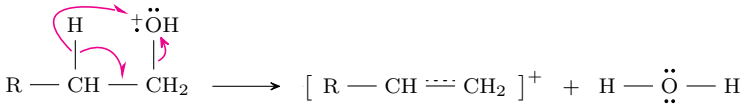


Figure 2.10: Fragmentation: Loss of H_2O.

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

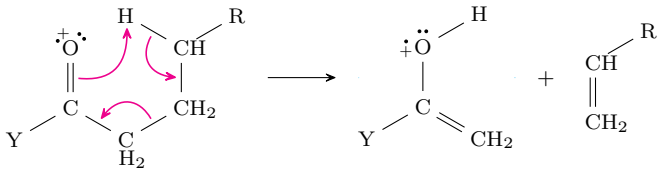


Figure 2.11: Fragmentation: McLafferty rearrangement.

     – 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.

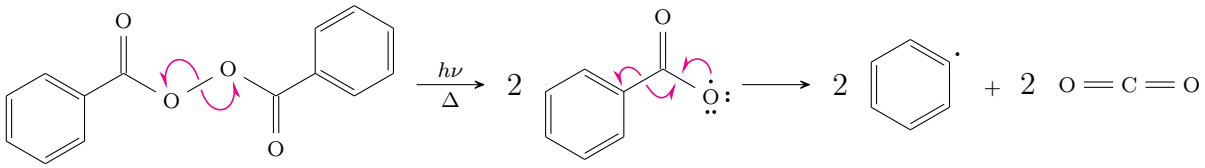
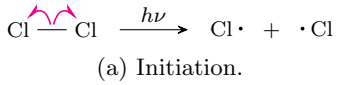
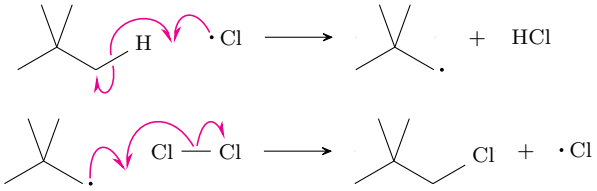


Figure 3.1: Losing CO_2 in a radical mechanism.

  - 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.

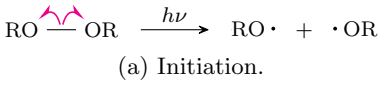
Figure 3.2: Chlorination of alkanes mechanism.

  - 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.

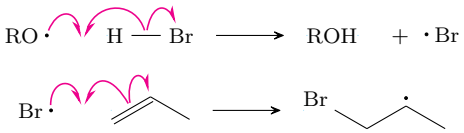
- Bromination of alkanes is basically the same.
  - One difference is that bromination is incredibly sensitive to radical stability, so whatever is the most stable radical will be the brominated one.
- Multistep synthesis example.
  - Propane to propane-1,2-diol.
  - Use radical bromination to put a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

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

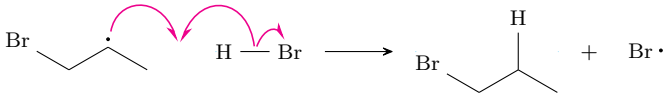
  - A possible side reaction is bromination of the alkene, but this requires a high temperature and low concentration.
  - The mechanism is entirely analogous to that of chlorination.
- HBr addition to alkenes.
  - The hydrohalogenation mechanism produces the Markovnikov product.
  - Morris Kharasch at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

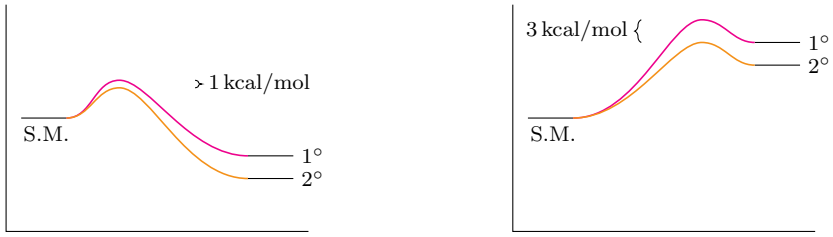
- Discusses exam.
- Reviews radical chemistry from last time.
- Radicals are different species, but they behave much like carbocations.
- Initiation: Breaking a bond between two atoms that are exactly the same.
- Propagation: Using a radical to make a new radical.
  - Two half arrows make a new bond;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

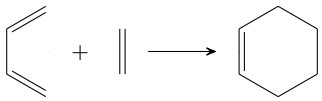


Figure 3.5: Diels-Alder general form.

  - 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.

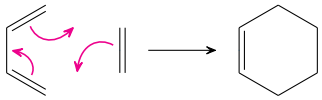


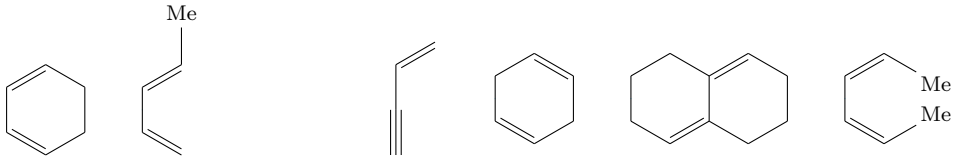
Figure 3.6: Diels-Alder mechanism.

  - 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).

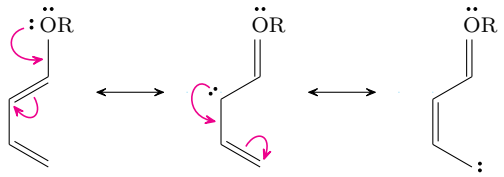


Figure 3.8: Diels-Alder EDGs.

    - 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.

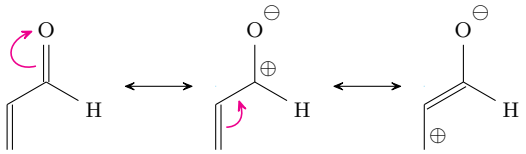
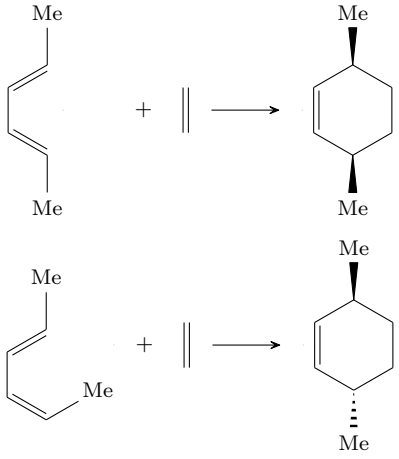


Figure 3.9: Diels-Alder EWGs.

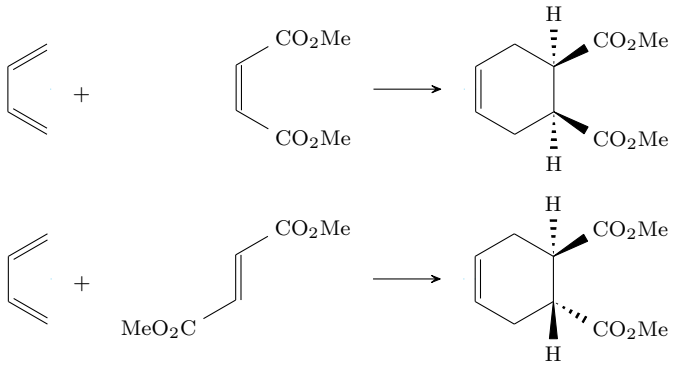
    - These all have a π-system directly attached to your double bond, and electronegativity pulls electrons out towards these π-systems.

- **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**.

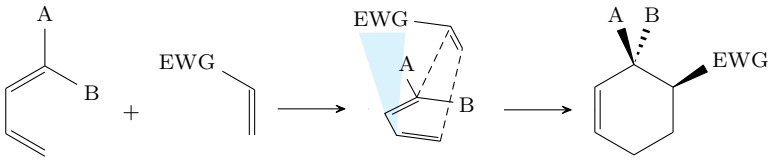


Figure 3.11: Diels-Alder diastereoselectivity.

  - 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.

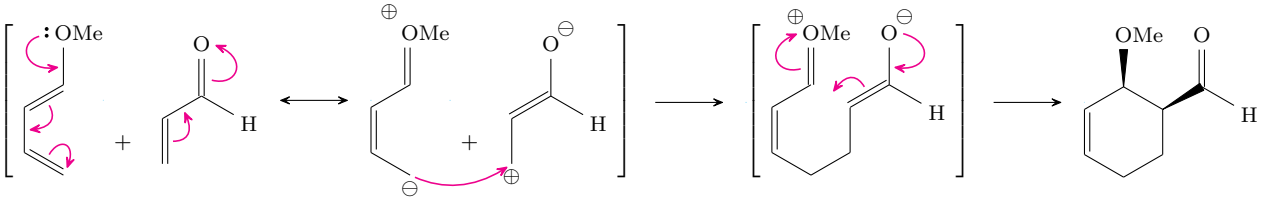


Figure 3.12: Diels-Alder regioselectivity.

  - 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 meta 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.

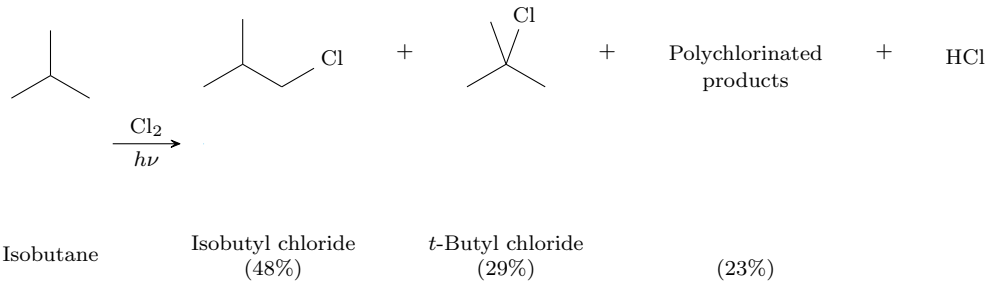


Figure 3.13: Unselectivity of chlorination of alkanes.

  - 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].

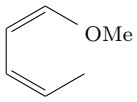
Week 4

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:

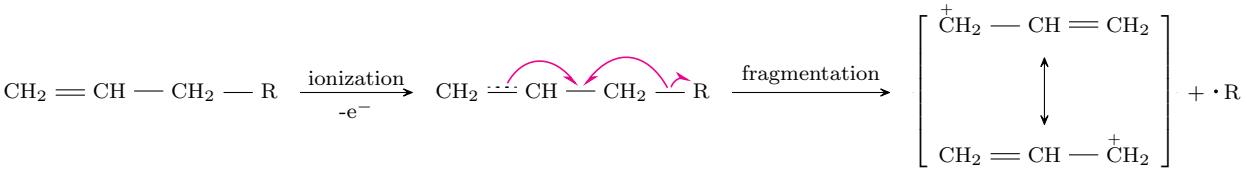
COMMON ABSORPTIONS	
Aromatic C–C	Two peaks usually in the range of $1500 - 1600\,cm^{-1}$
C=C	$\sim 1650\,cm^{-1}$
C=O	$\sim 1710\,cm^{-1}$ (shifts to $\sim 1735\,cm^{-1}$ for esters)
C≡C	$2100 - 2300\,cm^{-1}$
C≡N	$2100 - 2300\,cm^{-1}$
C–H (aldehyde)	Two peaks at $2170\,cm^{-1}$ and $2810\,cm^{-1}$
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*

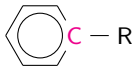
*The chemical shifts of these protons vary in different solvents and with temperature and concentration.

Approximate proton chemical shifts.

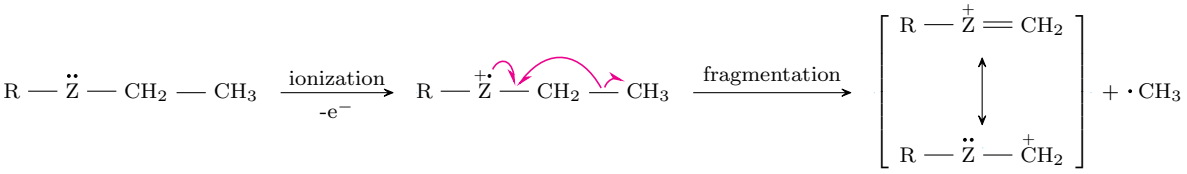


Resonance fragmentation: Alkenes.

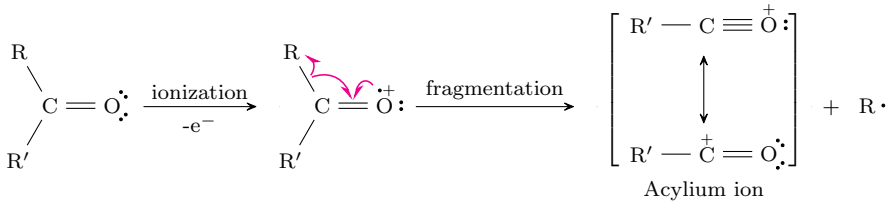
- Alkene reactions to know: hydrogenation (H_2 Pd/C), dihydroxylation (OsO_4), ozonolysis (O_3 Me_2S), hydrobromination (HBr), and bromination (Br_2).

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

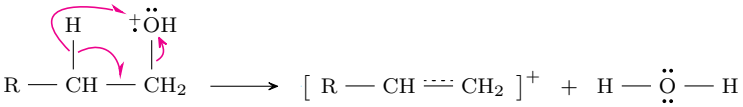
Approximate carbon-13 chemical shifts.



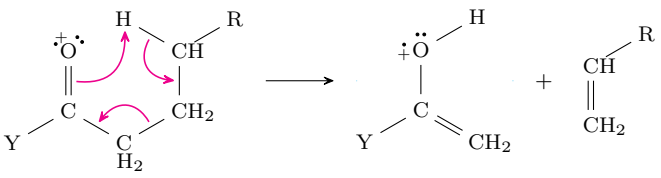
Resonance fragmentation: Lone pairs.



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.

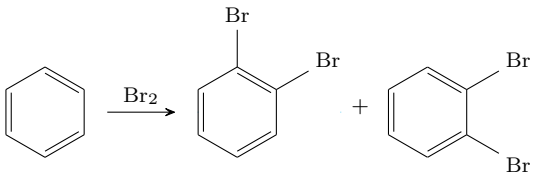


Figure 5.1: Bromination of cyclohexatriene.

    - 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.

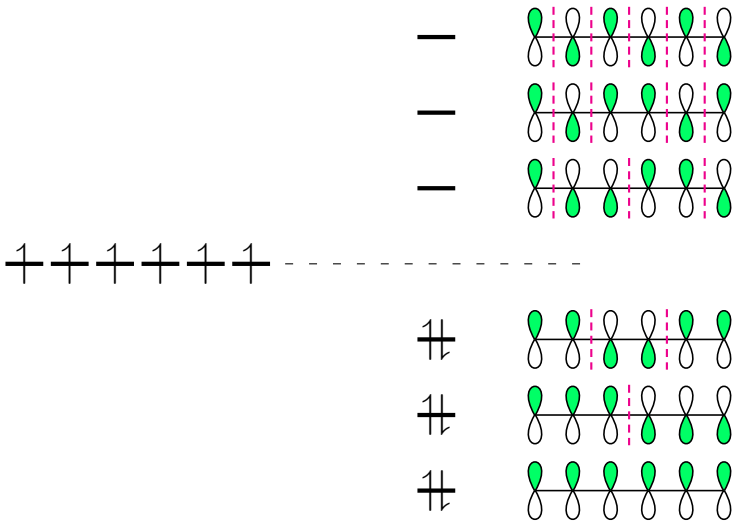


Figure 5.2: Hexa-1,3,5-triene MO diagram.

  - 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.

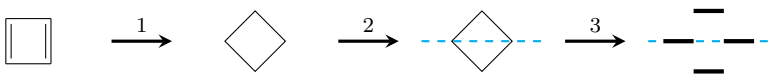


Figure 5.3: Frost method: Butadiene.

- We can even apply this to cyclotetradecaheptaene.

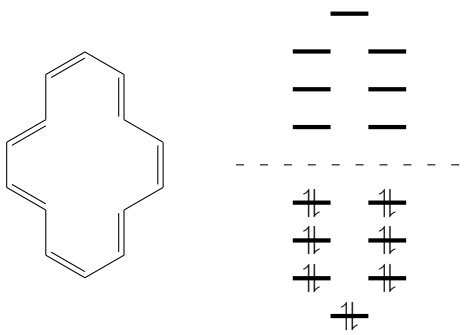


Figure 5.4: Frost method: Cyclotetradecaheptaene.

- **$(4n+2)$ 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.

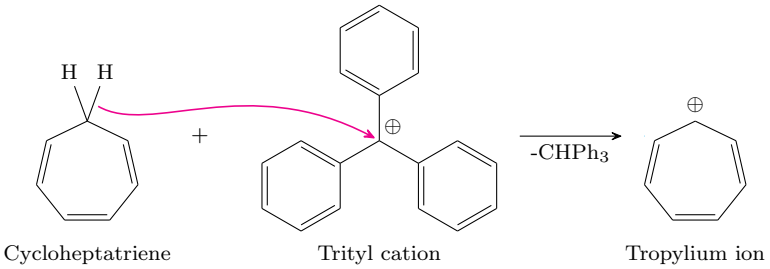


Figure 5.5: Aromaticity in the tropylium ion.

- 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.

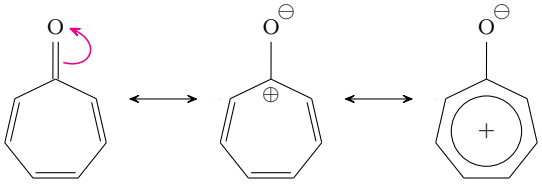


Figure 5.6: Aromaticity in tropone.

- 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].

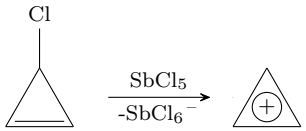


Figure 5.7: Aromaticity in the cyclopropenyl ion.

  - 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.

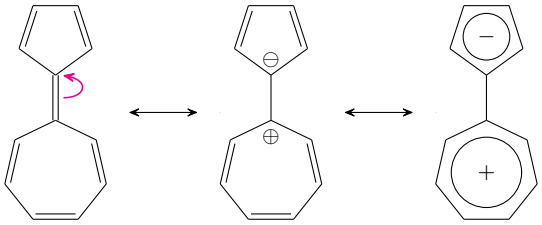


Figure 5.8: Aromaticity in sesquifulvalene.

  - 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.

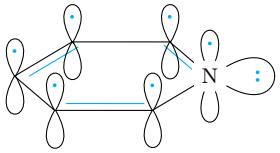


Figure 5.10: The structure of pyridine.

  - 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 decrease 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.

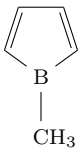
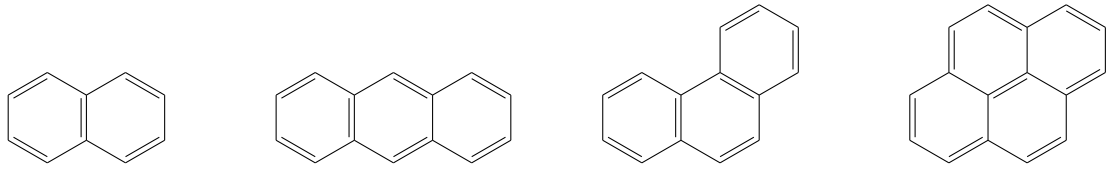


Figure 5.11: An anti-aromatic heterocycle.

  - 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.

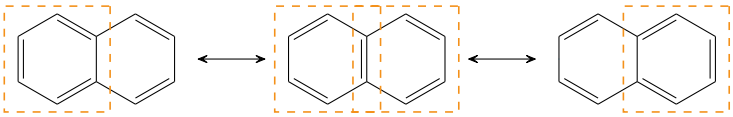


Figure 5.13: The structure of naphthalene.

  - 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 $1.36\,\text{Å}$ and $1.42\,\text{Å}$, a $0.03\,\text{Å}$ 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.

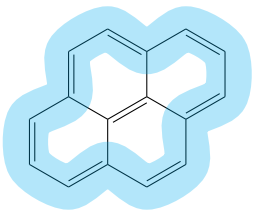


Figure 5.14: The structure of pyrene.

  - 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.

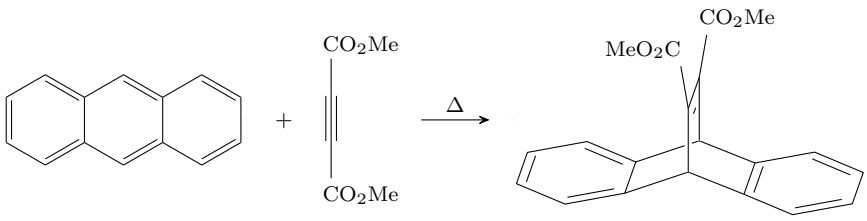


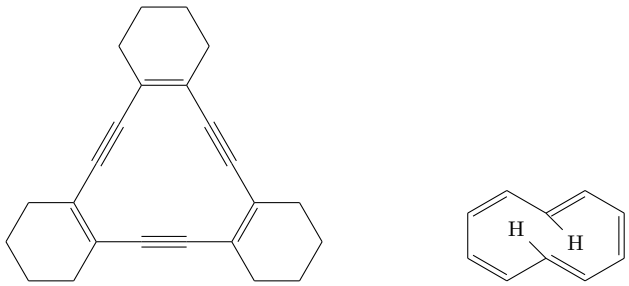
Figure 5.15: Diels-Alder reactivity of anthracene.

  - 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: Fluorobenzene, 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:

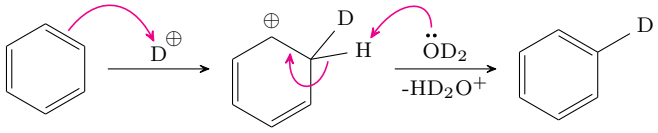


Figure 6.1: Electrophilic aromatic substitution mechanism.

  - 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 E1-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.

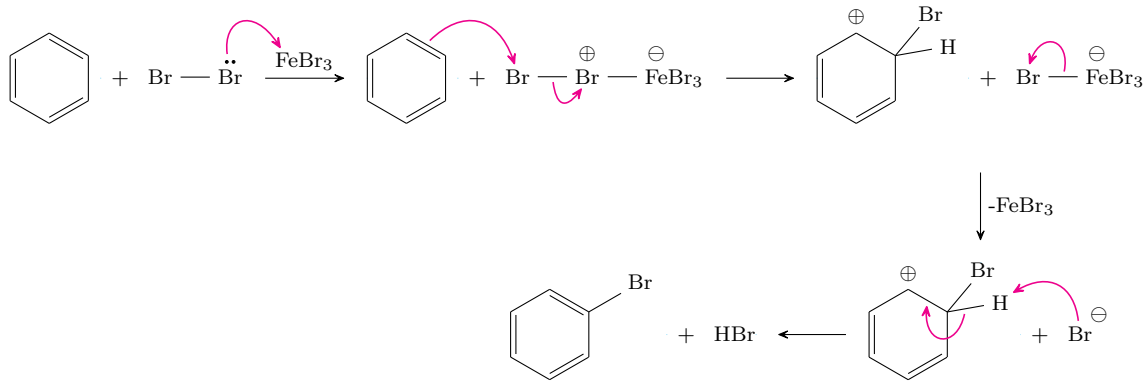


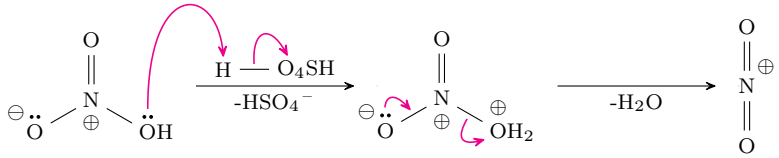
Figure 6.2: EAS halogenation mechanism.

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

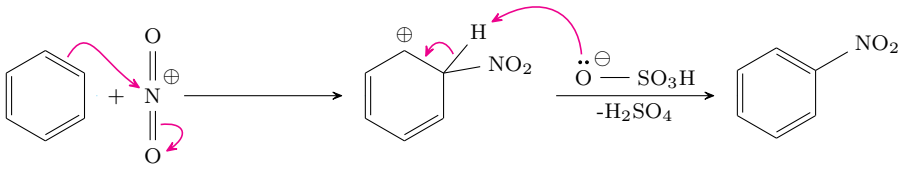
$$\mathrm{PhH} + \mathrm{HNO_3} \xrightarrow{\text{cat. } \mathrm{H_2SO_4}} \mathrm{PhNO_2} + \mathrm{H_2O}$$

  - 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.
- Sulfonation.
- 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.

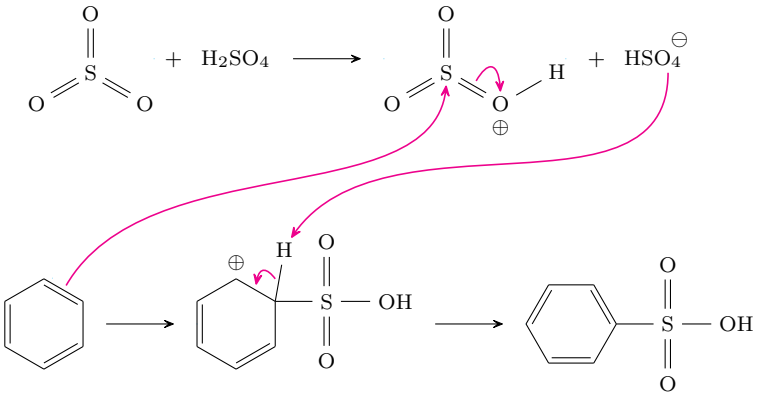


Figure 6.4: EAS sulfonation mechanism.

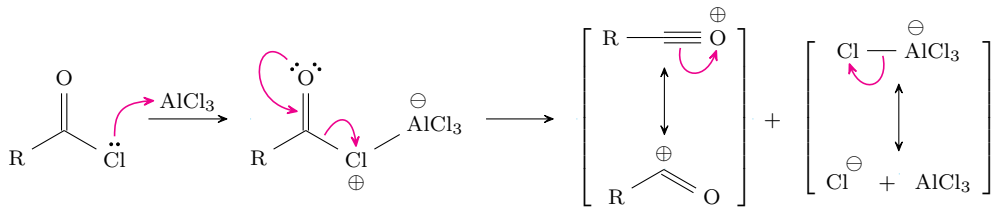
  - As with nitration (Figure 6.3), we use sulfuric acid to protonate a species that will then interact with benzene.
- Friedel-Crafts acylation.
- General form.

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

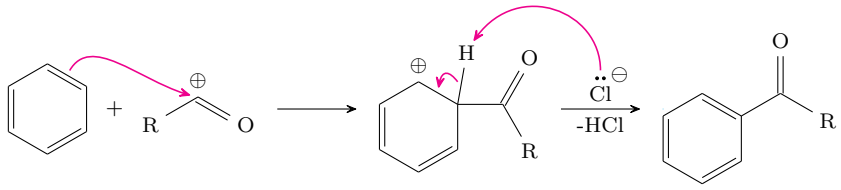
  - The acid chloride is a very strong electrophile, but it needs to be even stronger. We can make it stronger with the $\mathrm{AlCl_3}$ catalyst.

- 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.

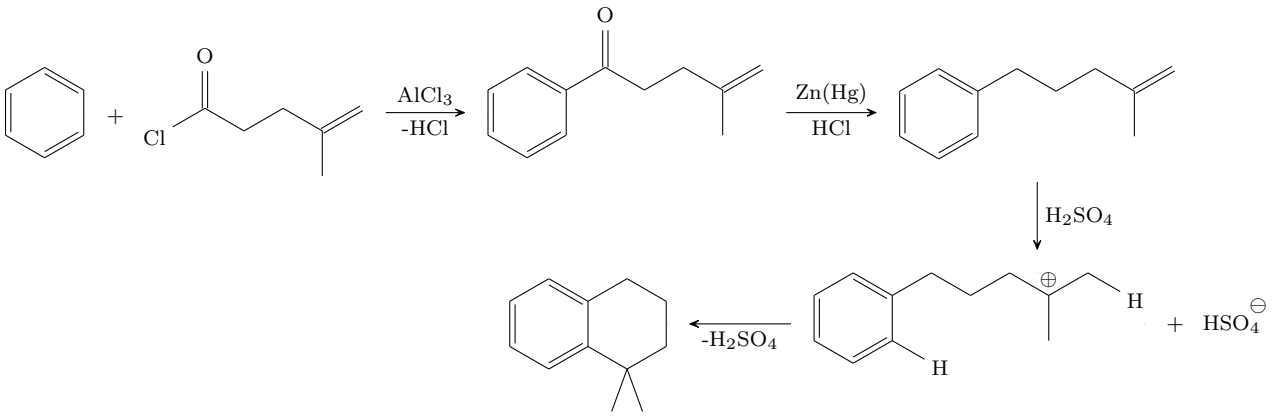


Figure 6.6: Ring-closing Friedel-Crafts mechanism.

  - 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).

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

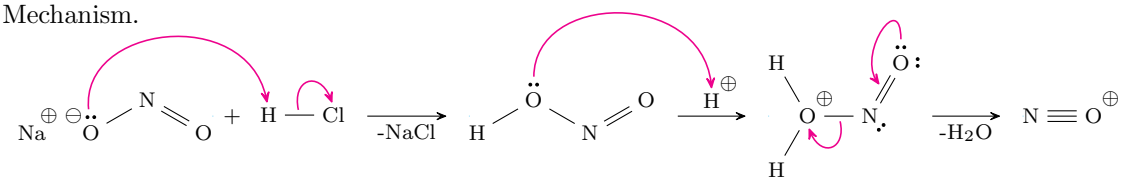
  - A number of reductive reagents can work here. Explicitly, we may use $H_2 + Pd/C$, H^+ (acid), or $SnCl_2 + H_2O$.
  - This reaction takes a strong EWG and turns it into an EDG.
  - The amine is also a gateway to a number of other functional groups, so being able to get one is very helpful.

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

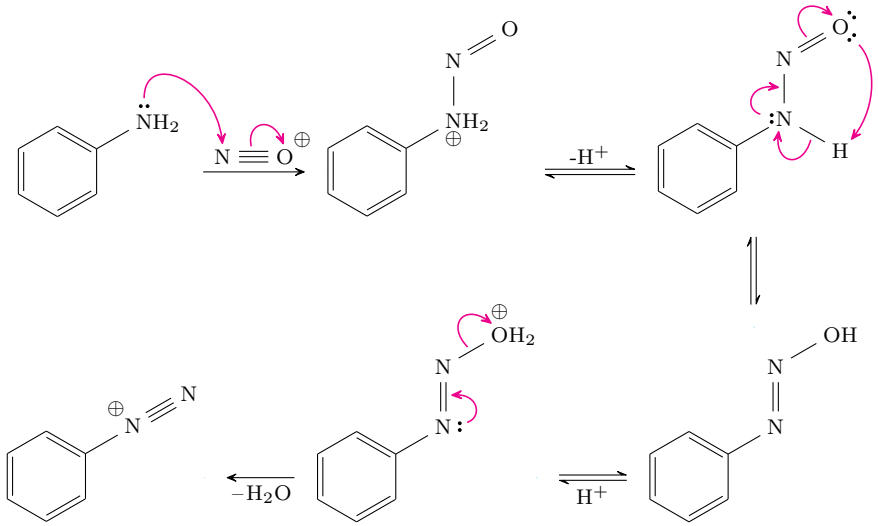
- Diazotization.
- General form.

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

  - 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.

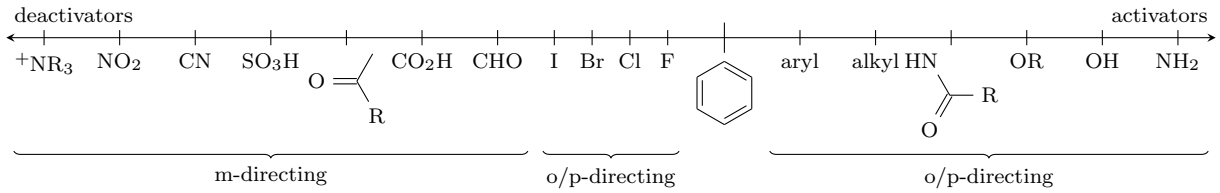


Figure 6.8: Activators and deactivators.

  - 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.
  - Halogens will be discussed next week.

6.3 Chapter 15: Reactions of Aromatic Compounds

From Solomons et al. [1].

2/23:

- "Kekulé structures are more appropriate for writing mechanisms such as electrophilic aromatic substitution because they permit the use of resonance theory, which, as we shall soon see, is invaluable as an aid to our understanding" [1, p 663].
- Halogenation.
- Bromination and chlorination of benzene are analogous (see Figure 6.2).
  - Flourination of benzene occurs so rapidly that it is hard to limit it to monofluorination. There are indirect methods of producing fluorobenzene, though.
  - Iodination of benzene requires incredibly forcing conditions, and is thus carried out in the presence of a strong oxidizing agent such as nitric acid. Biochemically, iodination of benzene is enzymatically catalyzed.
- Sulfonation.
- **Fuming sulfuric acid**: Sulfuric acid that contains added sulfur trioxide.
- It is the reaction of benzene with fuming sulfuric acid that produces benzenesulfonic acid.
  - Note that since H_2SO_4 partially decomposes into SO_3 over time, the reaction will take place in the presence of concentrated sulfuric acid alone, but much more slowly.
  - The presence of SO_3 is essential to the mechanism.
- Sulfonation is reversible; the equilibrium depends on the conditions.
  - Fuming sulfuric acid promotes sulfonation.
  - Dilute sulfuric acid with steam bubbled through (high $[H_2O]$) promotes desulfonation.
- **Protecting group**: A functional group used to temporarily block a position from electrophilic aromatic substitution.
- Since sulfonation is reversible, sulfonate is often used as a protecting group.
- Friedel-Crafts alkylation.
- For primary halides, an aluminum chloride-alkyl halide complex forms instead of a carbocation. In this case, the C–Cl bond is all but broken, making the carbon atom positive to the point that it acts as if it were a carbocation, but there is still some connecting electron density.
- Any process that creates a carbocation may be used as a precursor to F-C alkylation.
  - A mixture of an alcohol and an acid (e.g., BF_3) can also be used.
- Friedel-Crafts acylation.
- **Acetyl group**: The MeCO group. *Also known as* **ethanoyl group**.
- **Benzoyl group**: The PhCO group.
- **Acyl halide**. *Also known as* **acid halide**.
- Friedel-Crafts acylations can also be carried out using carboxylic acid anhydrides.
- Additional limitation: "Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily" [1, p 672].

- Side reaction with the Clemmensen reduction: Zinc and HCl can also reduce nitro groups to amino groups.
- **Wolf-Kishner reduction**: The basic complement of the Clemmensen reduction, which hydrogenates a ketone with hydrazine (H_2NNH_2), KOH, and heat.
- **Arene**: A hydrocarbon that consists of both aliphatic and aromatic groups.
- Covers side-chain reactions, stability, and transmutations.

Week 7

Nucleophilic Aromatic Substitution

7.1 Office Hours (Salinas)

2/21:

- Setup drawings points for Eucalyptus Oil and Bromination of Vanillin notebook pages? No new glassware setups so no drawings needed, right?
  - Nope, not needed — we can just refer back.
- Go over Eucalyptus Oil reagent table column entries; make sure I have everything I need.
  - Any hydrocarbon component.
- Crude yield and percent recovery calculations?
  - I did them correctly.
- Do we not need an entry for one of the substances this week? Perhaps EtOH in H_2O? Since there are only 15 points on Canvas, that leads me to think you're only looking for 5 entries.
  - Do all six reagents.
  - Just treat 50% EtOH in H_2O as EtOH (though there might be slight safety differences; check to make sure there isn't a separate MSDS for EtOH in H_2O).

7.2 Nucleophilic Aromatic Substitution

2/22:

- Office hours Wednesday/Thursday at 4:00 PM.
- 1 page notes sheet for the exam next week.
- Alkyl groups activate aromatic rings via induction.
- Halogens.
  - Electron-withdrawing due to induction.
  - Unlike alkyl groups, however, they have lone pairs that can contribute to resonance once the electrophile is added (i.e., in the carbocation intermediate).
  - Halogens with greater electronegativity are more strongly electron-withdrawing and thus more deactivating.
- Two major problems:
  1. Predicting the products based off of the substituents present on a ring.
  2. Synthesizing a ring with multiple substituents on it (the order you add them matters!).

- Practice problem takeaways.
  - When you have an ortho/para-directing substituent, you don't have to indicate major/minor products.
  - However, when doing a synthesis, try and make the reaction more selective by precluding one of the sites with another functional group. You could synthesize ortho/para products and then purify (throw away half of your yield), and while this is an acceptable answer, it is not the best answer when there are other options.
  - *t*-butyl groups generate significant steric hindrance, so groups will avoid adding ortho to them (even though *t*-butyl is an ortho/para-director by induction).
  - We will not see trick questions where something is so deactivating that we don't have a reaction; in these cases in reality, raising the temperature would suffice to force the reaction.
  - Resonance donation outcompetes induction donation.
- Rules.
  1. If all substituents direct to the same place, EAS happens there.
  2. If not, the strongest *activator* wins.
     - This is because deactivators slow everything down (but just the meta site less) whereas activators specifically accelerate particular sites.
  3. If one site is significantly more crowded than a second (out of two choices), sterics can play a role.
     - You do need a really big *t*-butyl group (or something larger) though to see this effect.
- Synthesis practice problem.
  - Benzene to 3-bromoaniline.
  - Preferentially use $H_2 + Pd/C$ to form an amine from a nitro group. The others are less common.
- **Nucleophilic aromatic substitution**. *Also known as* **NAS**, **S_NAr**.
- Reacting various aromatic compounds with methoxide and methanol.
  - Chlorobenzene: No reaction.
  - para-chloronitrobenzene: The methoxide substitutes the chloride (at high temperatures).
  - 1-chloro-2,4-dinitrobenzene: The methoxide substitutes the chloride (much faster at lower temperatures).
  - meta-chloronitrobenzene: No reaction.
- Mechanism.

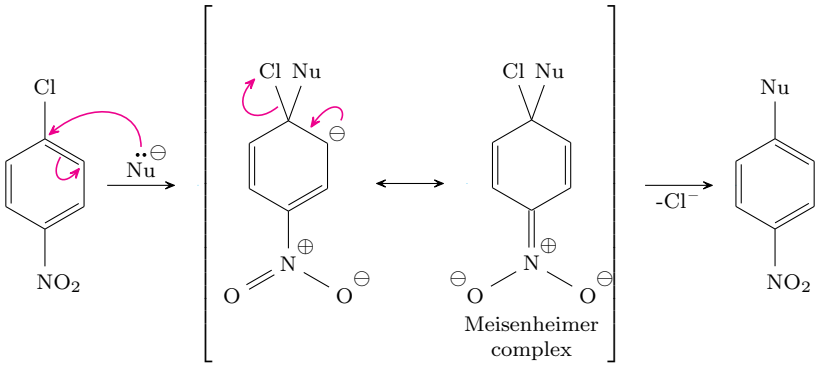
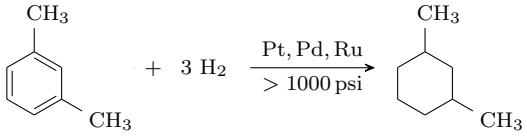


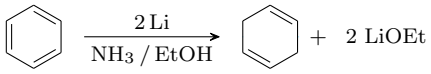
Figure 7.1: Nucleophilic aromatic substitution mechanism.

  - The driving force for the reaction is having the better leaving group leave.
    - Between methoxide and chloride, for example, chloride is the better LG.
  - To form the Meisenheimer complex, you need a strongly electron-withdrawing group (such as a nitro group) or an intramolecular kinetic driving force.
    - You also need the EWG in the right position to be able to accept electron density through resonance.

- **Meisenheimer complex**: The intermediate with a double-bonded nitrogen in a nitrobenzene derivative undergoing S_NAr.
  - Can be isolated at very low temperatures.
- 1,2-dichloro-4-nitrobenzene becomes 2-chloro-1-methoxy-4-nitrobenzene due to the para-activation of the nitro group.
- Reduction of aromatic compounds.
  - Useful when you want to create a cyclohexane derivative — you can put on functional groups with EAS and NAS, and then reduce at the end.
- High pressure catalyzed.
- General form.



  - Only one of the listed transition metals is needed.
  - This is not practical because you don't want such high pressure bombs in the lab.
- Birch reduction.
- General form.



  - Creates a singly-reduced, dearomatized system.
  - Sodium and potassium metals can also be used (in place of lithium).
  - This is similar to alkyne reduction.
- Mechanism.

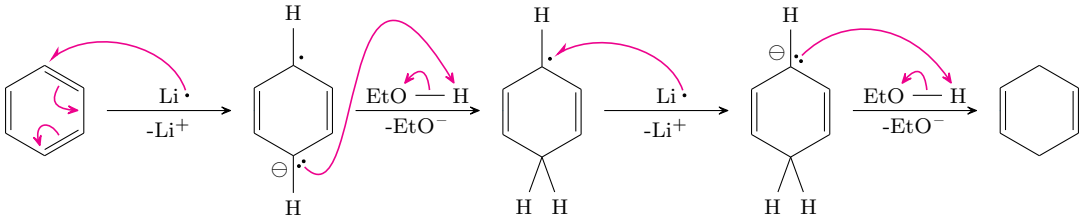


Figure 7.2: Birch reduction mechanism.

  - Although we draw the lithium radical directly attacking benzene, in reality, lithium gives up one of its electrons to become a cation, and this electron is solvated by NH_3.

- One more reaction.
- General form.

$$\mathrm{PhBr} \xrightarrow[\mathrm{NH_3}]{\mathrm{NaNH_2}} \mathrm{PhNH_2}$$

  - Also works with other alkali metals.

- A radiolabeling study.

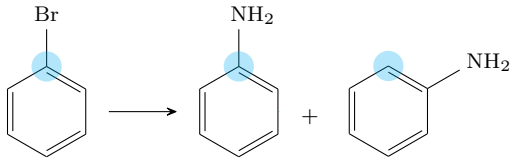


Figure 7.3: Radiolabeling bromobenzene and transforming it into aniline.

  - When we radiolabel the carbon to which bromine is initially bonded, we see that two products are formed in equimolar ratios.
  - This means that something other than S_NAr is occurring, and that whatever is happening is proceeding through some sort of symmetric intermediate.

- Mechanism.

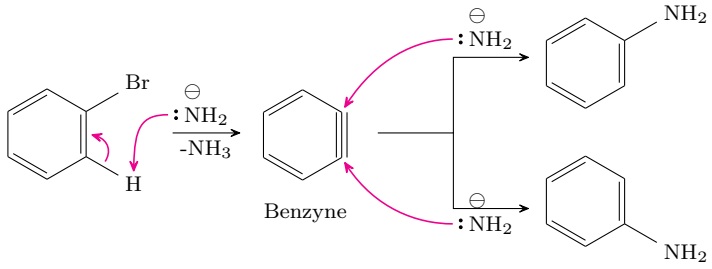


Figure 7.4: Bromobenzene to aniline mechanism.

  - With a strong enough base, we can formally abstract a hydrogen from benzene to create an alkyne-like species.
  - Orbitally, we can picture the triple bond in benzyne as a weak interaction (weak because of the nonlinearity/intense angle strain) between adjacent p orbitals in the molecular plane.

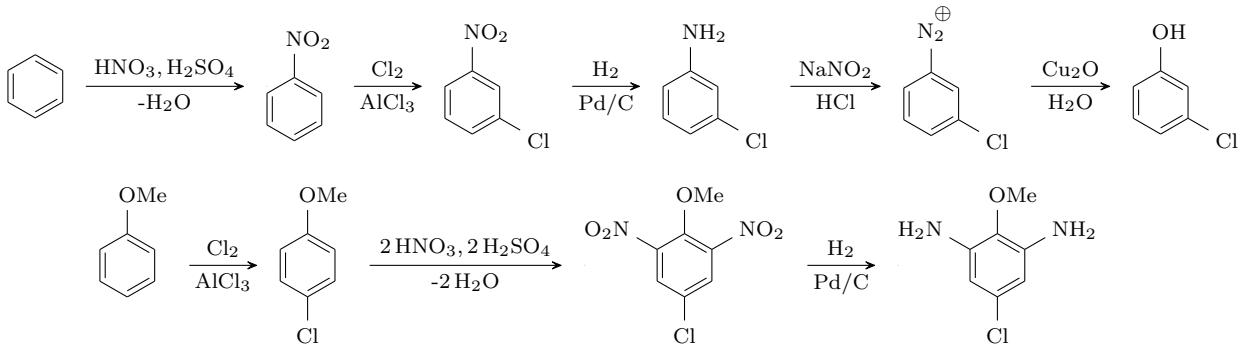
- Applications of this reaction and further mechanistic evidence.

  1. Using the strong base KNH_2, we can generate the benzyne intermediate and then trap it with other nucleophiles, leading to an equimolar mixture of products.
  2. We can also trap benzyne by using it as the dieneophile in a Diels-Alder reaction.
  3. Lastly, we note that 2-bromo-1,3-dimethylbenzene does not react under these conditions, confirming the need for an α-proton to make the benzyne intermediate.

7.3 Review / Alcohols

2/24:

- Practice synthesis problems.



- Takeaways.
  - Don't be afraid to get another isomer than what you need and chuck it out if you have to.
  - It's always better to activate first and deactivate later if possible.
- One new reaction.

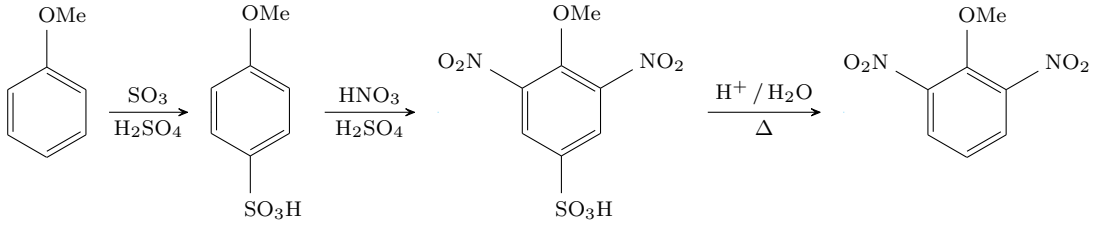


Figure 7.5: Protecting groups.

  - Make use of a protecting group.
  - Note that the sulfate group adds para due to sterics.
  - To finish the synthesis, just chlorinate para (Cl_2 / $AlCl_3$) and reduce the nitro groups ($H_2 + Pd/C$).
- If they want us to draw all of the resonance structures, they'll ask. Most likely yes in a mechanism but no in a synthesis.
- Answer to PSet 4, Q6 given.
- For PSet 4, Q7a, recall that you can't run F-C alkylation when you have EWGs on the ring.
- PSet 4, Q7b's issue is not the reactivity. Guessing the actual product is p-bromoisopropylbenzene.
- Hint for PSet 4, Q8: You can create an aromatic ring by brominating one of the alkenes in cyclohexa-1,4-diene and then doing E2 twice.
  - Looks like Dickinson may be asking us to invent new stuff on PSets and the exam.
- Synthesis and reactivity of alcohols.
- Alcohols have unique properties.
  - Boiling points: Alcohols significantly raise the boiling points of the compounds to which they're attached (because of hydrogen bonding).
- General reactivity of alcohols.
  - Adding acid to an alcohol makes water a leaving group, yielding an alkyl carbocation that can then react with nucleophiles.

  - Adding a very strong base/good nucleophile (a Grignard reagent) leads to the creation of an alkoxide (and the fully protonated Grignard species as a side product).

- Relative strengths of nucleophiles.

$$^{-}\mathrm{NRH} > \mathrm{RO}^{-} \,/\, \mathrm{HO}^{-} > \mathrm{Br}^{-} > \mathrm{NR}_3 > \mathrm{Cl}^{-} > \mathrm{F}^{-} > \mathrm{H_2O} \,/\, \mathrm{ROH} > \text{alkene} > \text{benzene}$$

- Acidity effects.
  - $1^\circ > 2^\circ > 3^\circ$.
  - More inductive donating effects (e.g., from alkyl groups) means more destabilization of the conjugate base.
  - On the other hand, $\mathrm{CF_3CH_2OH}$ has a much lower $\mathrm{p}K_\mathrm{a}$ because of the strong inductive withdrawing effects and resultant delocalization.
  - Similarly, phenoxide is stabilized via resonance.
  - At the extreme, $(\mathrm{CF_3})_3\mathrm{COH}$ is a true acid (will be predominantly deprotonated in water).
  - Inductive and resonance effects can be mixed, too: 2,4,6-trinitrophenol[1] is a very strong acid ($\mathrm{p}K_\mathrm{a} = 0.6$).

- Alkoxide generation.
  1. $\mathrm{EtOH} + \mathrm{NaOH} \rightleftharpoons \mathrm{NaOEt} + \mathrm{H_2O}$.
  2. $\mathrm{EtOH} + \mathrm{Na}^\circ \longrightarrow \mathrm{NaOEt} + \frac{1}{2}\mathrm{H_2}$.
     - Na° is sodium metal.
     - This is a strongly exothermic reaction and a dangerous one (since $\mathrm{H_2}$ is explosive).
     - It is common in laboratory use, though.
  3. $\mathrm{CyOH} + \mathrm{NaNH_2} \rightleftharpoons \mathrm{NaOCy} + \mathrm{NH_3}$.
     - A more common form of this reaction uses LDA (lithium diisopropylamine), a sterically hindered strong base, instead of $\mathrm{NaNH_2}$.
  4. $i\text{-BuOH} + \mathrm{NaH} \rightleftharpoons \mathrm{NaOBu}^i + \mathrm{H_2}$.
  5. $\mathrm{CH_3OH} + \mathrm{LiMe} \rightleftharpoons \mathrm{LiOMe} + \mathrm{CH_4}$.
     - We can also use LiBu, MeMgBr, etc. as other sources of carbanions.
  6. $\mathrm{PhOH} + \mathrm{NaOH} \rightleftharpoons \mathrm{NaOPh} + \mathrm{H_2O}$.

7.4 Office Hours (Dickinson)

- Is the order of the deactivating halogens reversed?
  - Yes — fluorine should be the most deactivating. The way I have it drawn in Figure 6.8 is correct.
- Why would the Clemmensen reduction work for reducing a nitro group to an amine — isn't it for carbonyls?
  - Don't get caught up on the name. The same reagents do the same thing in a few contexts; it's just using them to reduce ketones in particular that is termed the "Clemmensen reduction."
- Electron flow in Figure 7.4?
- Sulfonation vs. sulfation?
  - Would have to ask the IUPAC, but he could have it backwards. There probably isn't any issue though.

[1] Also known as picric acid.

Week 8

Alcohols, Ethers, and Epoxides

8.1 Office Hours (Salinas)

2/28:

- Does $H_2 + Pd/C$ hydrogenate ketones or not? Conflict between Lecture 11 and 2020 Exam 2A Q1e.
  - Either way.
  - $H_2 + Pd/C$ hydrogenates *benzylic* ketones only; it will leave ketones that are farther away from the benzene ring alone.
  - $Zn(Hg) + HCl$ hydrogenates all ketones, but nothing else.
- When do alkenes in PAHs get hydrogenated?
  - Ones that are added onto the Rocks of Gibraltar molecules.
- Do we have to know that aryl amines present a problem in F-C alkyl/arylations? It seems like there's a lot of content on this exam that BCD never went over.
  - Things like this probably won't show up on the exam.
- Can we use $HCN + NaCN$ to substitute CN?
  - This would work, but Sandmeyer is the go-to.
- How do you indicate you want to do something twice (e.g., bromination on 2020 Exam 2A Q3a)?
  - Write (2x): For example, "Br_2 / $FeBr_3$ (2x)".
- Is it $KMnO_4$ (2020 Exam 2A answer key), $KMnO_4$ / H_2O (class), $KMnO_4$ / $NaOH + \Delta$ (PSet 4 key), or $KMnO_4$ / $NaOH + \Delta$ followed by H_3O^+ (PSet 4 key) for benzoic acid formation?
  - $KMnO_4 + H_2O$ is pretty solid.
- 2020 Exam 2A Q3c: Is it preferable to use S_NAr or a novel Sandmeyer reaction? What are the limits of the Sandmeyer reaction?
  - Note that we can achieve meta addition of an amine when an o/p-director is present by brominating para and then using the benzyne intermediate.
- 2020 Exam 2A Q3d: Is $SnCl_2$ / H_2O selective reduction of nitro groups?
  - Perhaps, Omar will get back to me on whether to use $SnCl_2$ / H_2O or $H_2 + Pd/C$.
- When adding an alkane via F-C alkylation to later be transformed into a benzoic acid, is it preferable to use 2-chloropropane for some reason?

– Anything's fine.

- PSet 4 2021 1f/h:

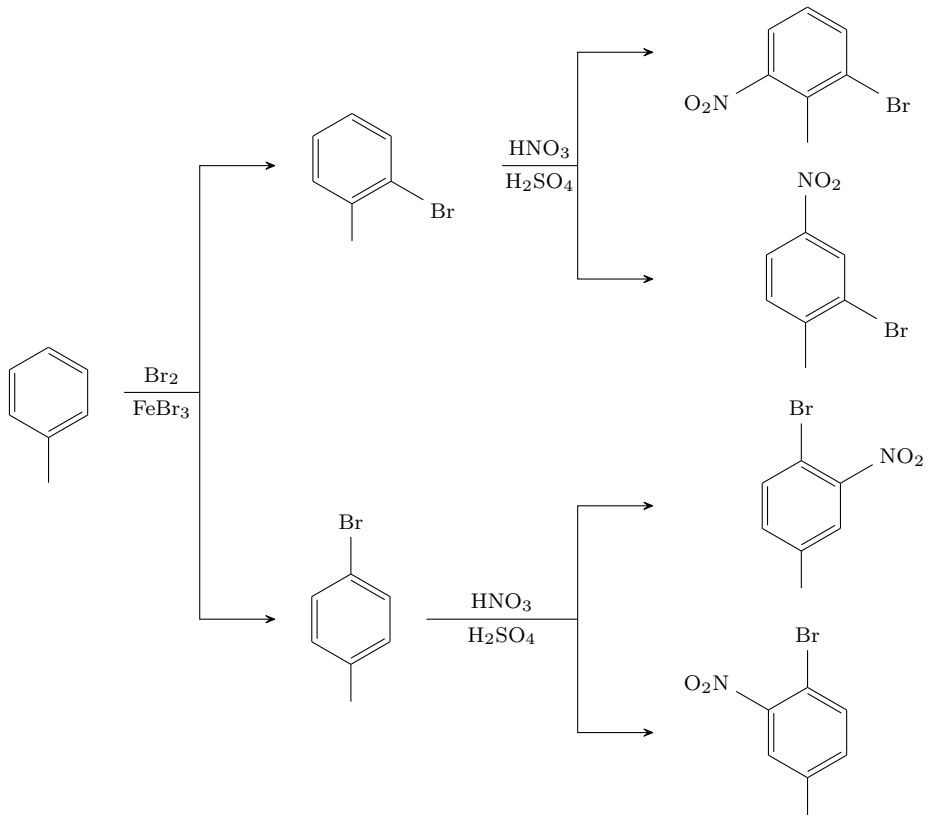


Figure 8.1: Major and minor synthesis products.

– When asked to determine major/minor when it could be kind of ambiguous, assume equimolar concentrations of reactants after the step before the last step.

– In the example above, notice how the two products on the bottom are identical, so they constitute the major product.

8.2 Exam 2 Cheat Sheet

Reactions:

- $C_6H_6 \xrightarrow{D_3O^+} C_6D_6$
- $PhH \xrightarrow[FeBr_3]{Br_2} PhBr$
  - $AlCl_3$, CuI_2.
- $PhH \xrightarrow[H_2SO_4]{HNO_3} PhNO_2$
- $PhH \xrightarrow[H_2SO_4]{SO_3} PhSO_3H$
- $PhH \xrightarrow[AlCl_3]{RCOCl} PhCOR$
- $PhH \xrightarrow[AlCl_3]{RCl} PhR$
- benzylic carbonyl $\xrightarrow[HCl]{Zn(Hg)}$ reduced carbon
- $PhR \xrightarrow[H_2O]{KMnO_4} PhCOOH$
  - Needs benzylic hydrogen.
- $PhNO_2 \xrightarrow{\text{reagents}} PhNH_2$
  - $H_2 + Pd/C$ or $SnCl_2 + H_2O$ (selective).
- $PhNH_2 \xrightarrow[HCl]{NaNO_2} PhN_2^+ + X^-$
  - Mechanism has many equilibrium steps (only first and last are not).
- $PhN_2^+ \xrightarrow[H_2O]{Cu_2O} PhOH$
  - $PhN_2^+ \xrightarrow{CuCl} PhCl$
  - $PhN_2^+ \xrightarrow{CuBr} PhBr$
  - $PhN_2^+ \xrightarrow{CuI} PhI$
  - $PhN_2^+ \xrightarrow{CuCN} PhCN$
- $PhN_2^+ \xrightarrow{D_3PO_2} PhD$
- $PhBr \xrightarrow[NH_3]{NaNH_2} PhNH_2$
- $PhCl \xrightarrow[NuH]{NaNu} PhNu$
- $PhH \xrightarrow[> 1000\,\text{psi}]{Pd} CyH$
- benzene $\xrightarrow[NH_3\,/\,EtOH]{2\,Li}$ cyclohexa-1,4-diene $+ 2\,LiOEt$

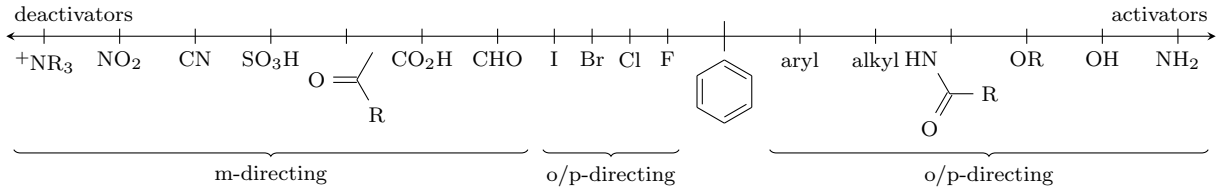
Reminders:

- Aromatic stabilization of benzene: -36.5 kcal/mol.

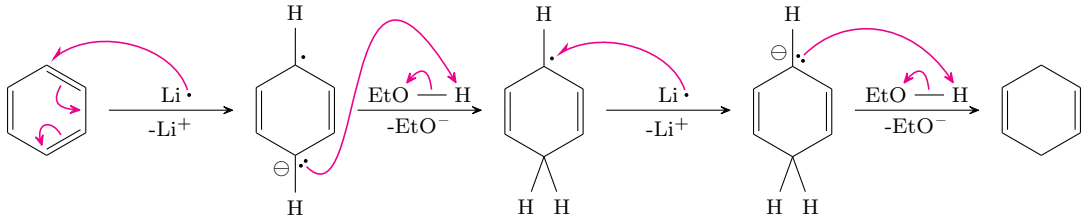
- Frost method: Point down, MOs at the carbons.
  - 5-membered rings: 3 bonding / 2 antibonding. 7-membered: 3 bonding / 4 antibonding.
- Aromaticity checklist: Flat, cyclic, conjugated, uninterrupted flow of p-orbitals, $(4n+2)$-rule.
- $(+/-)$ for Diels-Alder reactions!
- F-C reactions happen ONLY IF there is not an EWG on the ring.
- Add stronger EWGs later.
- Nucleophile strengths.

$$^{-}\text{NRH} > \text{RO}^{-} \,/\, \text{HO}^{-} > \text{Br}^{-} > \text{NR}_3 > \text{Cl}^{-} > \text{F}^{-} > \text{H}_2\text{O} \,/\, \text{ROH} > \text{alkene} > \text{benzene}$$

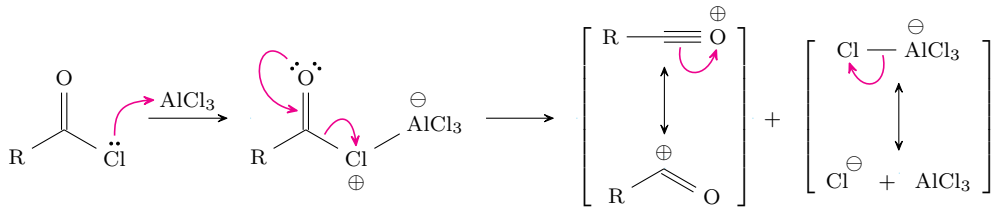
- Breslow (1967), Faraday (1825), Kekulé (1865), Jack Roberts (benzyne).



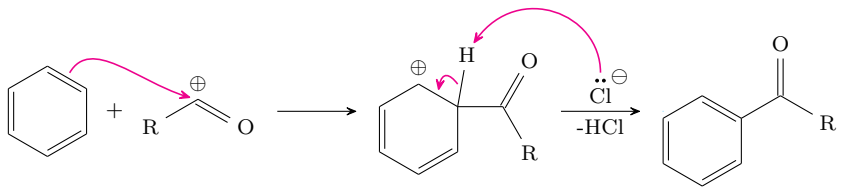
Activators and deactivators.



Birch reduction mechanism.



(a) Acylium ion formation.



(b) Acylation of benzene.

Friedel-Crafts acylation mechanism.

8.3 Alcohols, Ethers, and Epoxides 1

3/3:

- Alcohol chemistry today.
- A fifth optional problem set will be posted today.
- Review of ways to add C–O bonds into molecules.
- **Dihydroxylation**: The treatment of an alkene with OsO_4 followed by $NaHSO_3$, yielding a cis-1,2-diol.
- **Oxidative cleavage**: The treatment of an alkene with $KMnO_4, OH^-, \Delta$ followed by H_3O^+, yielding a ketone.
- Alcohol formation.
  1. Acid-catalyzed hydration.
     - Generally not so useful due to the possibility of rearrangements (CC+ intermediate).
  2. Hydroboration/oxidation.
     - Syn-addition and anti-Markovnikov.
  3. Oxymercuration/demercuration.
     - Markovnikov addition with no rearrangements.
- Now that we know how to make alcohols, we look into what we can do with them.
- Conversion of alcohols into alkyl halides.
- General form.

$$ROH \xrightarrow{HBr} RBr$$

- Mechanism.
  - For a primary alcohol, we use an S_N2 mechanism.
    - Before the main step, however, we need to make the alcohol into a better leaving group. To do so, we protonate the alcohol, converting it into an H_2O^+ group.
  - Secondary, tertiary, benzylic, and allylic alcohols can perform an S_N1 reaction.
    - Hydride shifts are important! They will happen if a 2° CC+ is created next to a 3° carbon, and will make the tertiary product the major one.
    - Additionally, the S_N1 mechanism erases stereochemical information in the reactant.
    - As such, we should avoid reactions in which this mechanism would take place if at all possible.
- Because of the limitations of the above mechanism, we introduce an alternate way to transform alcohols into good leaving groups without passing through a CC+ intermediate.
- Use $SOCl_2$ as a chlorinating reagent.
- General form.

$$ROH + SOCl_2 \xrightarrow{Py} RCl + SO_2 + Cl^- + PyH^+$$

  - There is an inversion of stereochemistry from the alcohol to the alkyl halide.
- Mechanism.
  - The structure of $SOCl_2$.
    - The polar S=O bond makes sulfur electrophilic, which is why the lone pair on the alcohol attacks it in the first step.
    - Chlorine, in addition to being the halogen we are trying to add to our reactant, is a good leaving group, which is necessary for this mechanism to proceed.

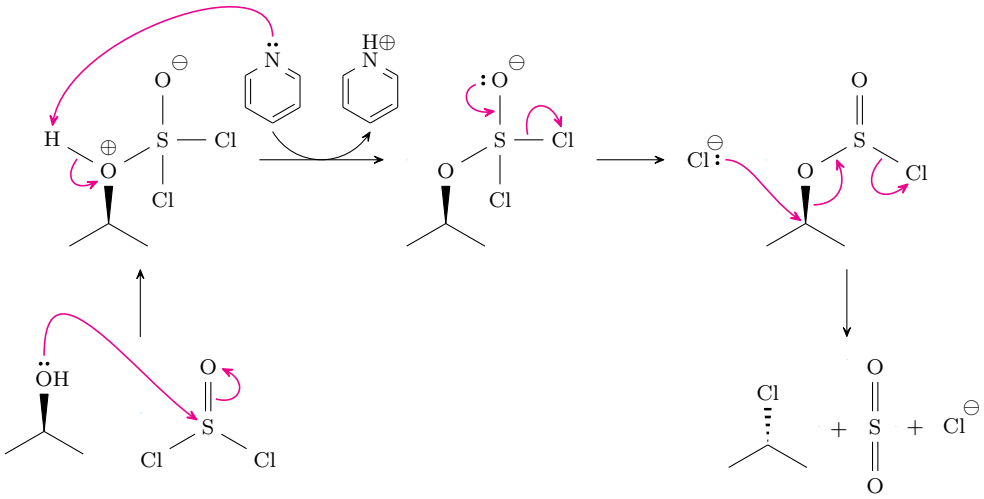


Figure 8.2: Chlorination of an alcohol via the mechanism.

  - The general idea of the reaction is to convert the alcohol into a good leaving group and then perform an S_N2 reaction, thereby avoiding a CC+ intermediate.
  - Indeed, the second-to-last intermediate contains a very good leaving group (SO_2Cl), which is easily pushed out in an S_N2 fashion by Cl^-.

- Use PBr_3 for bromination and PI_3 for iodination.
- The intermediate with the SO_2Cl leaving group is far too reactive to ever be isolated. However, there are mechanisms that can convert an alcohol into a good leaving group without sacrificing stability (i.e., so that the compound can be transformed further at a later date).
- We utilize a 2-step mechanism with tosylate.

$$\mathrm{ROH + Nu} \xrightarrow[\mathrm{NEt_3}]{\mathrm{TsCl}} \mathrm{RNu + HCl}$$

  - This reaction also has an inversion of stereochemistry.

- Mechanism.

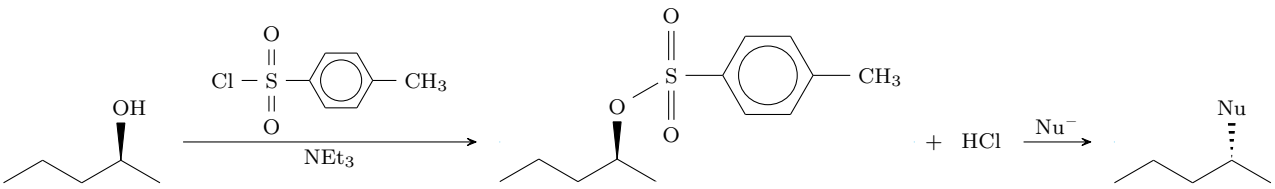
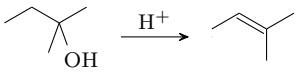


Figure 8.3: Nucleophilation of an alcohol via tosylate mechanism.

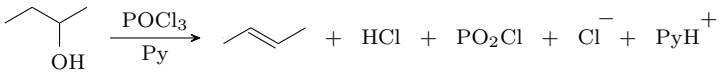
  - As before, we begin by using a chlorocompound and a weak base to convert the alcohol into a leaving group. This first step yields an isolable compound.
  - In the second step, which does not need to be performed immediately, we just add the desired nucleophile and S_N2 proceeds.
  - Br^-, I^-, CN^- are all good nucleophiles. Cl^- is not.
  - Note that we can fine tune the aromatic system in tosylate to suit the conditions of a specific reaction better as needed.

- Creating alkenes from alcohols.
- Old way.
- General form.



  - Works only with 3° alcohols.
  - You get a mixture of products.

- These issues are solved the same way as halogenation, i.e., by activating the alcohol, hence avoiding CC+ intermediates and allowing the elimination to proceed in a controlled process.
- New way.
- General form.



  - Uses phosphoryl chloride ($POCl_3$).
  - We use pyridine as our base because it is weak and not very nucleophilic (you want to avoid competition from S_N2).

- The mechanism is analogous to Figure 8.2, except that it ends with E2.
- Having discussed the reactivity of alcohols with respect to substitution and elimination, we now discuss the reactivity of alcohols as nucleophiles.
- Williamson Ether Synthesis.
- General form.

$$\mathrm{ROH} \xrightarrow[\mathrm{MeI}]{\mathrm{NaH}} \mathrm{ROMe} + \mathrm{H_2} + \mathrm{NaI}$$

  - NaH is a very strong base (H does not like to be negative).

- Mechanism.

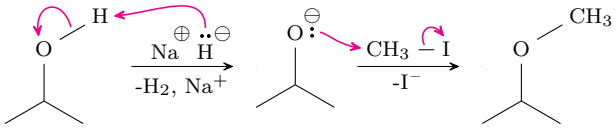


Figure 8.4: Williamson ether synthesis mechanism.

  - S_N2, so use 1° or 2° if needed.
    - For example, t-BuOH + MeI proceeds but t-BuI + MeOH will not proceed.

- The Williamson Ether Synthesis is a reversible process, however.
- Reversal of ethers: Acid-catalyzed cleavage.
- General form.

$$\mathrm{ROR'} \xrightarrow{\mathrm{HBr}} \mathrm{RBr} + \mathrm{R'OH}$$

- Mechanism.

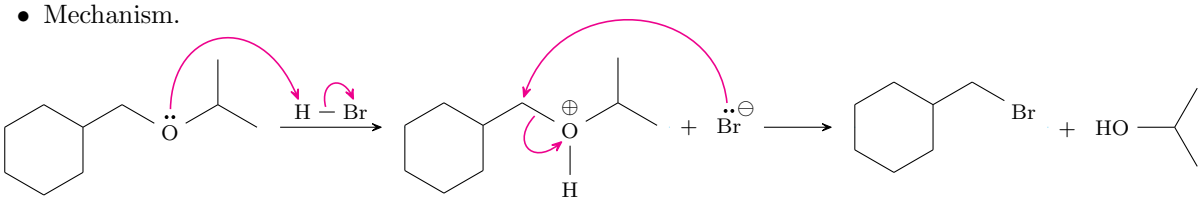


Figure 8.5: Acid-catalyzed cleavage of ethers mechanism.

  - Must have Br^- or I^- to proceed; Cl^- is not nucleophilic enough.

- Protecting groups.
  - Can be added to inactivate reactive sites.
  - For example, you can turn an alcohol ROH into ROPg where Pg is a protecting group. This will inactivate the alcohol so that the rest of the molecule can react under conditions that would usually make the alcohol react. When you are finished tuning the rest of the molecule, you can then remove the protecting group and react the alcohol, if desired.
  - Different protecting groups suit different reactions.
- **Protection**: Adding a protecting group.
- **Deprotection**: Removing a protecting group.
- **Epoxide**: A cyclic ether with a three-atom ring.
- **mCPBA**: meta-Chloroperoxybenzoic acid, the peroxy acid most commonly used to create epoxides from alkenes. *Structure*

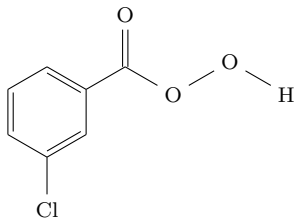
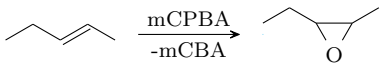


Figure 8.6: meta-Chloroperoxybenzoic acid (mCPBA).

- Creating epoxides from alkenes.
- General form.



  - Epoxides are formed from a reactive carbon-carbon system, e.g., an alkene that interacts with an oxygen donor group.
  - Their formation is formally an oxidation.
  - To add into the carbon-carbon system, the oxygen must be both nucleophilic and electrophilic.
  - A peroxy acid fits the bill because oxygen-oxygen single bonds are good oxidants. In particular, the oxygen further away from the carbonyl is electrophilic, and the ester to which it's bonded is a good leaving group.
  - Relative to peroxy acids, alkenes are nucleophilic.

- Mechanism.

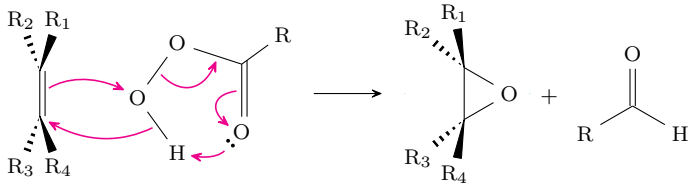
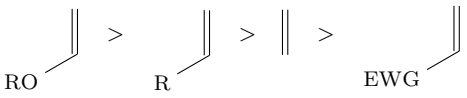
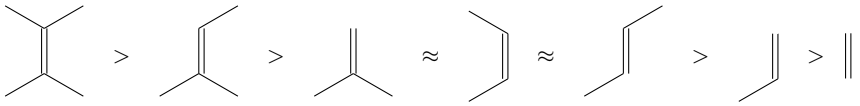


Figure 8.7: Creating epoxides from alkenes mechanism.

  - A concerted mechanism.
  - Stereospecific (chirality is maintained).
  - Note that the most nucleophilic alkenes will react the fastest.



(a) Substituent types.

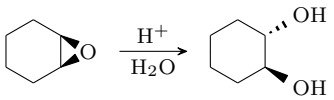


(b) Substitutions.

Figure 8.8: Alkene nucleophilicity.

  - Note that all of the alkenes in Figure 8.8b would rank behind the resonance EDG and ahead of the EWG in Figure 8.8a.
  - Knowing the relative reactivity of alkenes allows us to predict the major/minor products in polyenes. In particular, the more nucleophilic, reactive alkene will be converted into an epoxide more often.

- Creating diols from epoxides.
- General form.



  - Creates a cis-diol.

- Mechanism.

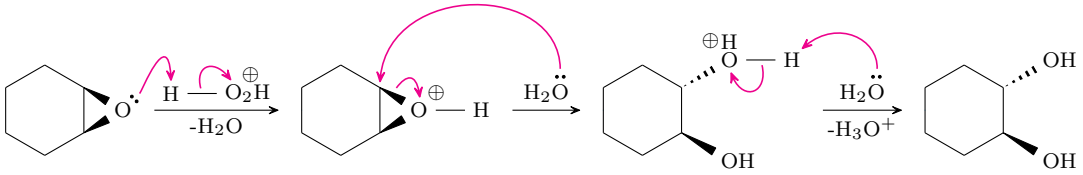


Figure 8.9: Creating diols from epoxides mechanism.

  - 1° or 2° epoxides.
    - The mechanism will primarily be S_N2.
    - Given the choice, the nucleophile will attack the less substituted carbon.
  - Epoxides with at least one 3° carbon.
    - The S_N1 mechanism will be active.
    - Even in this case, though, we will form a cis-product due to the steric bulk of the alcohol group hindering attacks on its face of the molecule.

- We can use the same mechanism with HCl or HBr instead of H_2O to yield a halohydrin with cis stereochemistry.
- Acid- and base-catalyzed ring openings.

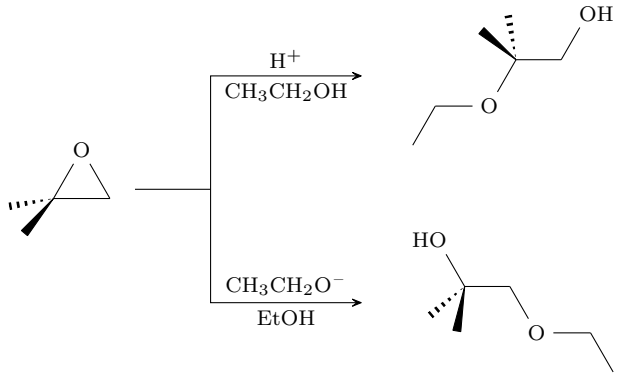


Figure 8.10: Acid- and base-catalyzed epoxide ring openings.

  - Under acidic conditions, carbocation stability drives the reaction.
    - In the acidic reaction in Figure 8.10, we form a formal 3° CC+. This intermediate is subsequently attacked by ethanol, which is then deprotonated.
  - Under basic conditions, the alkoxide ion attacks less hindered carbon via S_N2.
    - In the basic reaction in Figure 8.10, the ethoxide engages in an S_N2 reaction with the 1° epoxide position.
  - If there aren't strong driving forces, though, we can get a mixture of products.

- Epoxide ring openings can be triggered by nucleophiles other than alkoxides, too.
- For example, we can add alkenes into the epoxide with Grignard reagents.

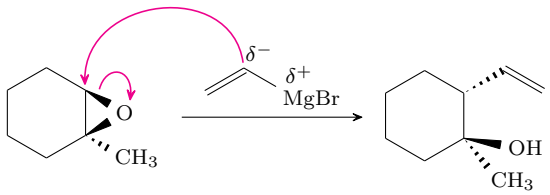
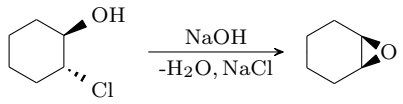


Figure 8.11: Epoxide ring-opening via a Grignard reagent mechanism.

  - This is important as another C–C bond-forming reaction.
  - It is stereoselective, as with the related preceding reactions.
  - It yields a quite complex molecule that can react further in a number of ways.

- Creating epoxides from halohydrins.
- General form.



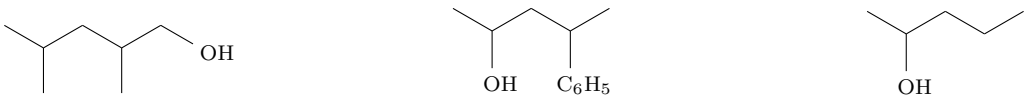
  - This reaction is not reversible under basic conditions because Cl^- is not nucleophilic enough to attack one of the epoxide carbons without the epoxide oxygen first having been protonated (by an acid).
  - The reactant *must* be a cis-halohydrin because after the alcohol is deprotonated, it reacts with the α-carbon through a backside attack (i.e., in an S_N2 fashion).

8.4 Chapter 11: Alcohols and Ethers

From Solomons et al. [1].

3/7:

- **Alcohol**: A hydroxyl group bonded to a saturated carbon atom.
- Alcohol nomenclature.



(a) 2,4-Dimethyl-1-pentanol (2,4-dimethylpentan-1-ol)

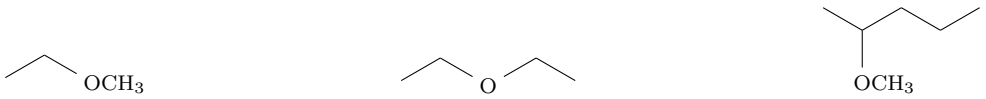
(b) 4-Phenyl-2-pentanol (4-phenylpentan-2-ol)

(c) 4-Penten-2-ol (pent-4-en-2-ol

Figure 8.12: Alcohol nomenclature.

  - The parent chain is the longest chain to which the hydroxyl group is attached.
  - Number it so as to give the carbon bearing the hydroxyl group the lowest number.
  - The hydroxyl group has precedence over double bonds and triple bonds in deciding which functional group to name as the suffix.

- Ether nomenclature.



(a) Ethyl methyl ether.

(b) Diethyl ether.

(c) 2-Methoxypentane.

Figure 8.13: Ether nomenclature.

  - List (in alphabetical order) both groups that are attached to the oxygen and append the word "ether."
  - For more complicated ones, name the ether as an alkoxy substituent.

- **Replacement nomenclature**: A method of naming cyclic ethers via relating the compound in question to the correspondign hydrocarbon ring system and using the prefix oxa- to indicate that an oxygen atom replaces a CH_2 group.

- Cyclic ether nomenclature.

(a) Oxacyclopropane (oxirane / ethylene oxide)

(b) Oxacyclobutane (oxetane)

(c) Oxacyclopentane (tetrahydrofuran)

(d) 1,4-Dioxacyclohexane (1,4-dioxane)

Figure 8.14: Cyclic ether nomenclature.

  - The above lists several examples of replacement nomenclature, as well as the common names.

- Methanol was originally synthesized by burning wood in the absence of air, hence why it is known as wood alcohol.
  - It is now synthesized industrially by hydrogenating CO at high temperatures and pressures.
  - Methanol is highly toxic, even in small quantities.

- Ethanol was originally synthesized by fermenting sugars from grains, hence why it is known as grain alcohol.
  - It is now synthesized industrially via the acid-catalyzed hydration of ethene.
  - Ethanol is **hypnotic**.

- **Hypnotic** (compound): A compound that depresses brain activity even as it give the illusion of being a stimulant.

- Ethylene glycol is a good antifreeze, since it has a low molecular weight, high boiling point, and is readily miscible with water.
  - However, it is highly toxic and has thus been largely phased out in favor of the less toxic, more environmentally friendly propylene glycol.

- Diethyl ether is a low boiling, highly flammable liquid.

- **Autoxidation**: A radical process in which an ether reacts slowly with oxygen to form hydroperoxides and peroxides.
  - Most ethers participate in autoxidation.
  - Hydroperoxides and peroxides accumulate when ethers are stored with air (even just the air at the top of a bottle), and are dangerously explosive.
  - Solomons et al. [1] gives the mechanism.

- Basic reactivity of alcohols.
  1. The oxygen atom of the hydroxyl group is nucleophilic and weakly basic.
  2. The hydrogen atom of the hydroxyl group is weakly acidic.
  3. The hydroxyl group can be converted to a leaving goup so as to allow substitution or elimination reactions.

- Alkoxide ions are used as bases when we need something stronger than hydroxide but not super strong, and when we have to carry out a reaction in alcohol solution instead of water for solubility reasons.

- For the conversion of alcohols to alkyl halides, $3^\circ > 2^\circ > 1^\circ$ and HI > HBr > HCl in terms of reactivity.

  - We can also use a mixture of a sodium or potassium halide and sulfuric acid.
  - When the S_N1 mechanism is active, the leaving of the H_2O group is the RDS.
- $ZnCl_2$, a weak Lewis acid, can accelerate the formation of primary alkyl chlorides.
- Tosylates, mesylates, and triflates are all leaving group derivatives of alcohols.
- Ethers can also be synthesized by alkoxymercuration/demercuration.

Week 9

Oxidation/Reduction and Organometallics

9.1 Reduction of Carbonyls

3/8:

- In general chemistry, oxidation and reduction referred to the loss and gain of electrons, respectively.
  - In organic chemistry, we think about it differently.
- **Organic oxidation**: Increasing the number of bonds to oxygen or decreasing the number of bonds to hydrogen.
- **Organic reduction**: Decreasing the bonds to oxygen or increasing the bonds to hydrogen.
- Example: Ethene to ethanol is neither an oxidation or reduction since the C−O bond formed is cancelled by the C−H bond formed.
- We now transition to carbonyl chemistry, which will also be really important next quarter.
- **Carbonyl**: Any carbon-oxygen double-bonded system.
  - Important derivatives include aldehydes, ketones, carboxylic acids, esters, and amides.
  - A defining character of carbonyls is their resonance, which we can formalize by representing them as an oxygen anion and a carbocation.
- General reactivity of carbonyls.
  1. Nucleophiles can add to the carbonyl carbon. A slightly acidic aqueous workup from here can form an alcohol.
  2. Oxidation/reduction. Alcohol to carbonyl and vice versa.
- Reduction of aldehydes and ketones.
- General form.

$$\mathrm{RCOR'} \xrightarrow{\text{reagents}} \mathrm{RC(OH)HR'}$$

  - This is a two-step process. We first need a source of H^-, and then an acidic workup.
    - Possible hydride sources are $NaBH_4$ (a weak source) and $LiAlH_4$ (a strong source).
    - The acidic workup reagents are always H_3O^+, H_2O.
- Mechanism.
  - We use the hydride as a nucleophile to attack the carbonyl carbon, and then the acid to protonate the alkoxide intermediate.

- Varying types of carbonyls.
  - Aldehydes and ketones go through the full reaction with both reagents.
  - Esters do not react with $NaBH_4$ (not powerful enough), but do react with $LiAlH_4$. However, they form a primary alcohol in this case.
- Reactivity of carbonyls.

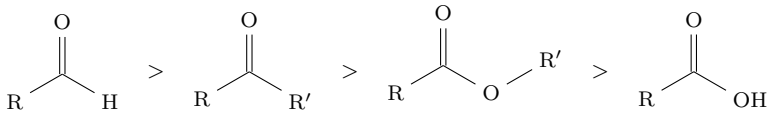
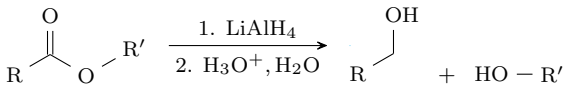


Figure 9.1: Reactivity of carbonyls.

  - $NaBH_4$ stops working after ketones.
- Reduction of esters.
- General form.



- Mechanism.

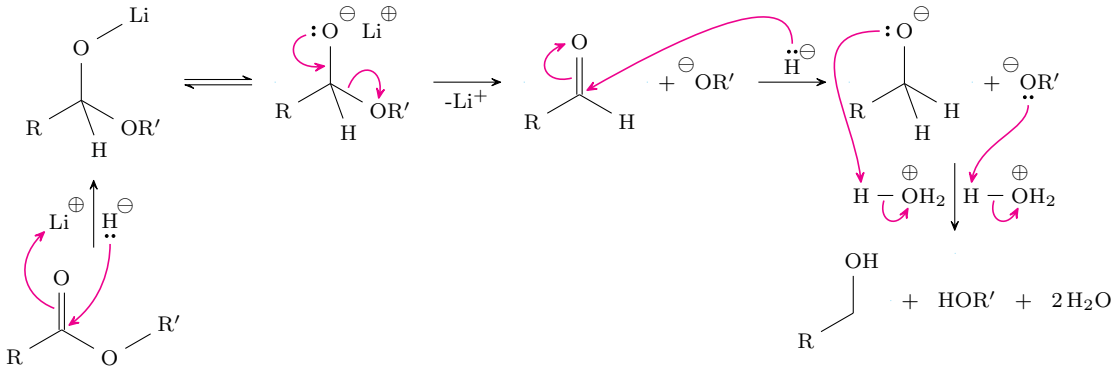
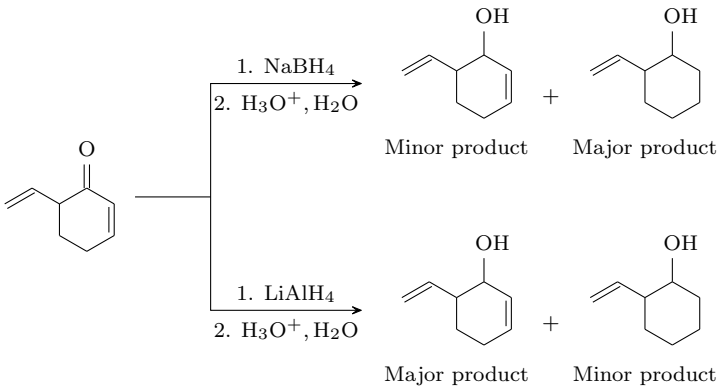


Figure 9.2: Reduction of esters mechanism.

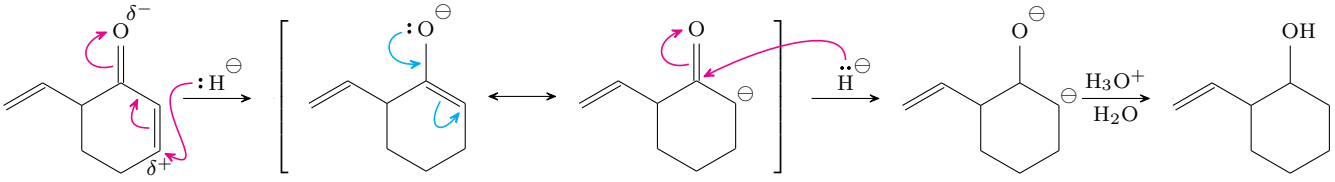
  - Positive lithium ions combine with the oxygen of the carbonyl in the first step. This activates the C=O bond, making the carbon more electrophilic.
    - Thus, by using $LiAlH_4$, we both make the electrophile stronger and introduce a stronger nucleophile.
- **Chemoselective** (reaction): React with one group in the presence of other "related" groups.
  - For example, if we have a ketone and ester in the same molecule, reacting with $NaBH_4$ / H_3O^+, H_2O will yield a chemoselective reduction of the ketone in the presence of an ester. (Reacting with $LiAlH_4$ / H_3O^+, H_2O will alter both groups in a non-chemoselective fashion.)
- Note that we can reduce alkyl halides to hydrocarbons with $LiAlH_4$ / H_3O^+, H_2O.
- Reactivity of an α-β unsaturated compound.

- General form.

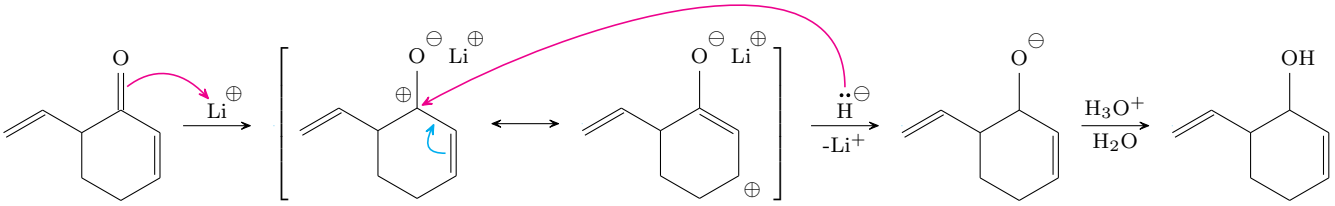


  - With $NaBH_4$, the major product has been reduced both at the ketone and the alkene.
  - With $LiAlH_4$, the major product has been reduced at the ketone only.
  - Note that the alkene that is not conjugated with the carbonyl is untouched.

- Mechanism.



(a) Reduction via $NaBH_4$.



(b) Reduction via $LiAlH_4$

Figure 9.3: Reduction of an α-β unsaturated compound mechanism.

  - On Figure 9.3a.
    - In the leftmost molecule, resonance draws charge toward the electronegative oxygen, making the carbon at the end of the conjugated chain the most electrophilic site in the molecule. Thus, hydride attacks there.
    - The resulting molecule has a ketone as one of its resonance structures, so since ketones are reactive to further hydride attacks, we take this to be the major contributor and react the molecule with hydride again.
    - The 2− product can how be reduced with acid and water.
  - On Figure 9.3b.
    - When Li^+ bonds to the oxygen, it creates a formal carbocation in the ring system that can be delocalized by resonance.
    - However, the carbocation will preferentially exist as a 3° carbocation, so the α-carbon is the most electrophilic site in the molecule in this case, making hydride attack there.

- Grignard reagents provide a new way to form C–C bonds.
- **Grignard reagent**: An alkyl magnesium halide compound.
  - Creates carbanions that are both strong bases and strong nucleophiles.
- Forming Grignard reagents.

$$\mathrm{RBr} \xrightarrow[\mathrm{Et_2O}]{\mathrm{Mg^\circ}} \mathrm{RMgBr}$$

  - We need an aprotic solvent such as diethyl ether to stabilize the positive Mg.
    - If there are acidic protons present, the Grignard will just deprotonate them.
- Common Grignard reagents.
  - To add phenyl groups to systems, use phenylmagnesium chloride.
  - To add alkenes to systems, use allylmagnesium bromide.
- Making a Grignard reagent basically inverts the reactivity of the precursor: While the precursor alkyl halide is electrophilic, Grignards are very nucleophilic.
- Grignards can be made out of iodides, bromides, and chlorides.
  - Iodides are more reactive than bromides, are more reactive than chlorides.
  - We commonly find them as bromides, though.
- We can use Grignards as nucleophiles in the reduction of formaldehyde.
  - Creates primary alcohols.
- Using an aldehyde makes a secondary alcohol.
- Using a ketone makes a tertiary alcohol.
- Using an ester adds the Grignard twice and kicks out an alcohol.
- Using a carboxylic acid protonates the alkyl part of the Grignard, releases a magnesium salt, and regenerates the carboxylic acid.
- Since Grignards deprotonate any acids present, we can't use them on molecules that contain alcohols, thiols, carboxylic acids, phenols, amines, and acetylenes.
- Organolithium reagents are conceptually identical to Grignards, but even more ionic/reactive.
- Forming organolithium reagents.

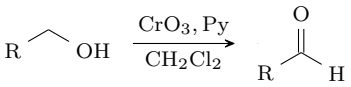
$$\mathrm{RBr} \xrightarrow[\mathrm{Et_2O}]{2\,\mathrm{Li^\circ}} \mathrm{RLi} + \mathrm{LiBr}$$

  - Organolithium reagents are more ionic than Grignards.
    - They are 40% ionic; Grignards are much less.
  - Very reactive (nucleophile and base), but very dangerous, too.

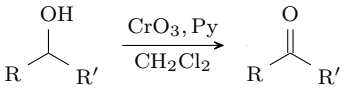
9.2 Oxidation of Alcohols

3/10:

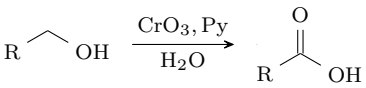
- Alcohol oxidation often occurs with the help of chromium (VI) reagents, of which there are three "flavors."
- **Collins reagent**: The compound CrO_3.
- General form.



(a) Anhydrous oxidation of a primary alcohol.

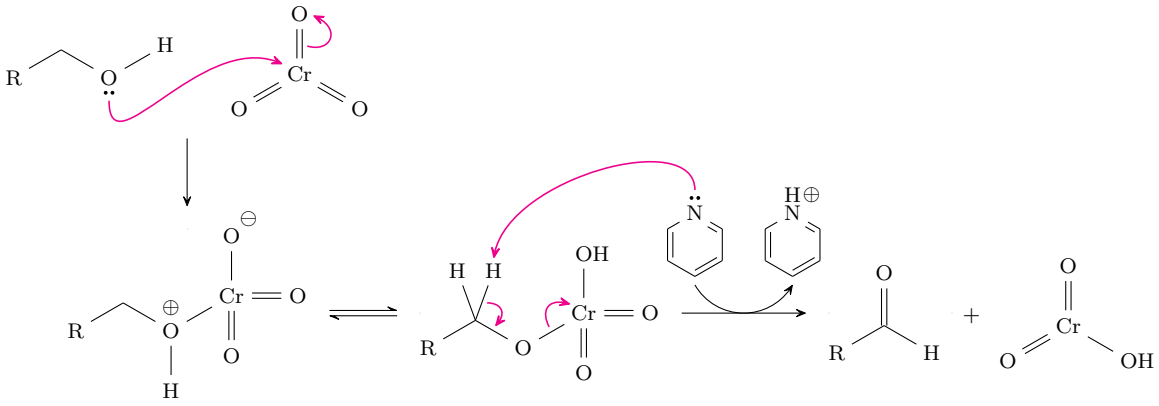


(b) Anhydrous oxidation of a secondary alcohol.

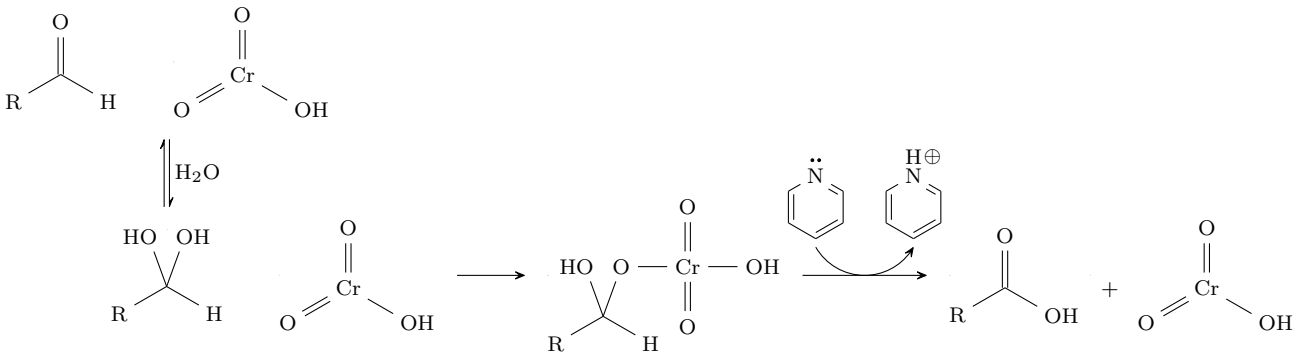


(c) Aqueous oxidation of a primary alcohol.

- Mechanism.



(a) Anhydrous oxidation of a primary alcohol.

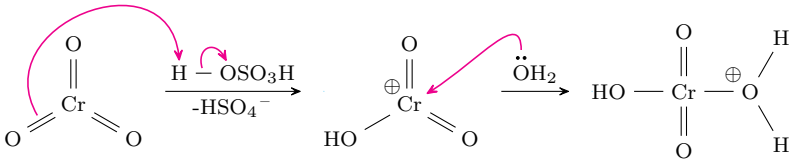


(b) Aqueous oxidation of a primary alcohol.

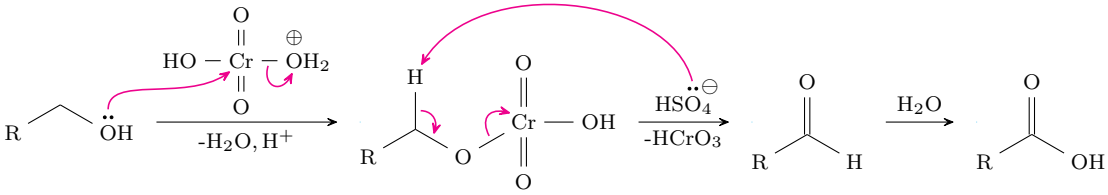
Figure 9.5: Alcohol oxidation via Collins reagent mechanism.

  - On Figure 9.5a.
    - The reversible proton shift may be a 1- or 2-step process.
    - Having a leaving group on the oxygen makes the protons on the α carbon weakly acidic, so pyridine can attack them.
  - On Figure 9.5b.
    - This reaction picks up directly where the other one left off. Essentially, if water is absent, the mechanism will stop after the sequence of steps in Figure 9.5a, and if water is present, the mechanism will continue through the sequence of steps in Figure 9.5a.
    - In the beginning, we note that aldehydes are one of the most electrophilic carbon compounds.
    - Thus, in the presence of water, aldehydes exist in equilibrium with **acetals**.
    - Any acetal that is generated can react with chromium again and another equivalent of pyridine as in the previous mechanism, but this time to generate a carboxylic acid.

- Since water has such an effect on the mechanism, we should be sure specify in the case of oxidation reactions whether the reaction is run under aqueous or anhydrous conditions.
- **Jones reagent**: The mixture $CrO_3 + H_2SO_{4(aq)}$.
- The general form is the same as with Collins reagent, except obviously for the reagents used. In particular...
  - 1° alcohols go to carboxylic acids (water is present).
  - 2° alcohols will go to ketones.
- Mechanism.



(a) Protonated chromic acid formation.



(b) Oxidation of a 1° alcohol.

Figure 9.6: Alcohol oxidation via Jones reagent mechanism.

- **Pyridinium chlorochromate**: The mixture Py, HCl, CrO_3. *Also known as* **PCC**.
  - Mixing these three compounds together yields PyH^+ and CrO_3Cl^-.
    - Note that the chloride is bonded to the chromium center and one of the oxygens adopts the negative charge.
  - We've essentially suped up chromium by adding chloride as a leaving group.
  - Running this in anhydrous conditions allows us to control reactivity (DCM is a good anhydrous solvent here).
- As before, we take 1° alcohols to carboxylic acids and 2° alcohols to ketones.

- **Oxalyl chloride**: The following compound. *Structure*

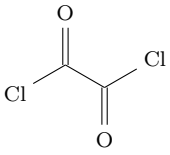
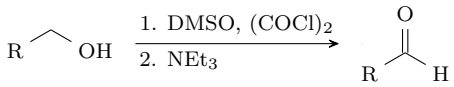
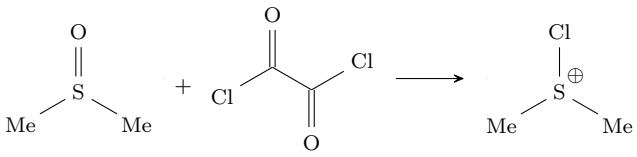


Figure 9.7: Oxalyl chloride.

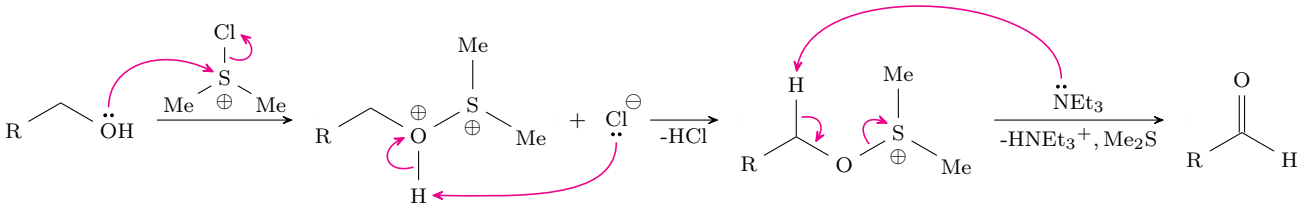
- **Swern oxidation**: An eco-friendly alcohol oxidation mechanism that does away with toxic metal chromium.
- General form.



- Mechanism.



(a) Chlorodimethylsulfonium ion formation.



(b) Oxidation of a 1° alcohol.

Figure 9.8: Swern oxidation mechanism.

  - We won't worry about how the first step proceeds because it's pretty complicated. However, know that it generates an electrophilic sulfur analogous to the chromium.

- A side note on biology.
  - Alcohol dehydrogenase (ADH1), an enzyme in our body, deals with EtOH and other harmful alcohols by transforming them into acetaldehyde.
  - Acetaldehyde is very toxic, though, but in the presence of ADH2 and H_2O, it will form acetic acid (vinegar, which is relatively nontoxic).
  - Being flushed when you drink is a result of having a deficiency of ADH2.
    - Many of the problems associated with drinking come from a buildup of acetaldehyde!
    - You can take ADH1 inhibitors to keep the ethanol around for longer because that's safer than letting acetaldehyde build up.

- Protecting groups.
  - Trimethylsilyl chloride (TMSCl) is a common one.

– Adding it and then a weak base such as NEt_3 with DCM as a solvent leads to the formation of a **silyl-protected alcohol** (see Figure 8.3).

- **Silyl-protected alcohol**: A very stable form of an alcohol which allows the addition of Grignards, etc. to react with the rest of the compound in question. *Given by*

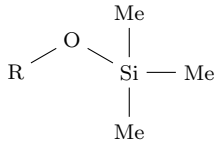
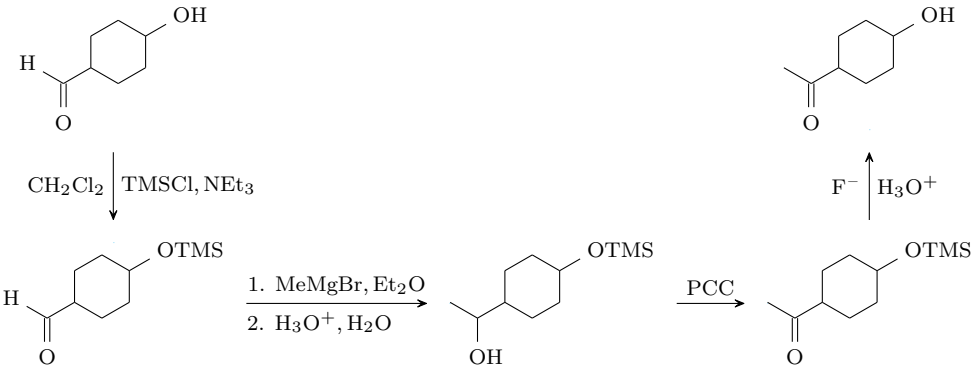


Figure 9.9: Silyl-protected alcohol.

– The silyl protecting group can be removed by acid (H_3O^+, H_2O). This kicks out TMSOH and the alcohol.

– It can also be removed by fluoride (F^-) followed by acid. This kicks out TMSF and RO^- which is protonated to become ROH.

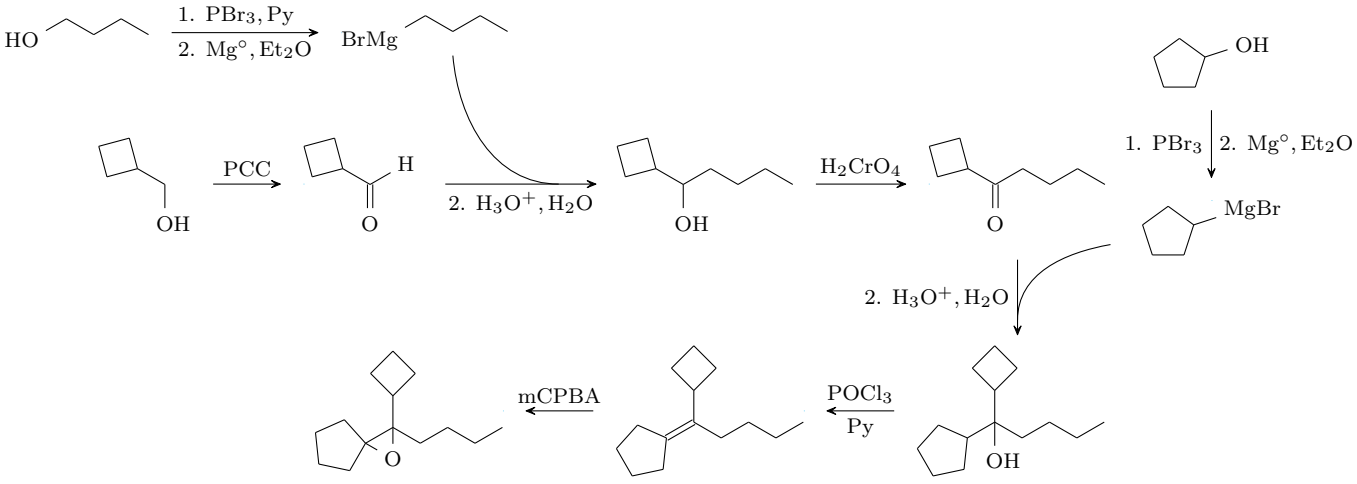
- Example of using protecting groups in a synthesis:



– Remember: Grignards are bases (look out for acidic protons), and make sure there are no other reactive sites on your molecule.

– You can get the products you want, though, via protection and deprotection.

- Practice problem: Synthesize the end product using only carbon atoms from alcohols with 5 or fewer carbons.



- Zaitsev's rule eliminates one alkene and ring strain eliminates the other. Thus, the alkene that's formed is the most stable one.

9.3 Exam 3 Cheat Sheet

3/15:

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.

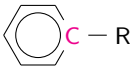
Type of Proton	Chemical Shift (δ, ppm)	Type of Proton	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0.8-1.2	Alkyl bromide, RCH_2Br	3.4-3.6
2° Alkyl, RCH_2R	1.2-1.5	Alkyl chloride, RCH_2Cl	3.6-3.8
3° Alkyl, R_3CH	1.4-1.8	Vinylic, $R_2C{=}CH_2$	4.6-5.0
Allylic, $R_2C{=}CR{-}CH_3$	1.6-1.9	Vinylic, $R_2C{=}CRH$	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.

Reminders:

- Alkene reactions to know: hydrogenation ($H_2 + Pd/C$), dihydroxylation (1. OsO_4, 2. $NaHSO_3$), ozonolysis ($O_3 + Me_2S$), hydrobromination (HBr), and bromination (Br_2).
  - Extra possibles: Acid-catalyzed hydration ($H_2SO_4 + H_2O$), oxymercuration/demercuration (1. $Hg(OAc)_2, H_2O$, 2. $NaBH_4$), hydroboration/oxidation (1. BH_3, 2. H_2O_2, NaOH), hydrogenation (H_2 + Lindlar's catalyst for alkynes to *cis*-alkenes, $2\,Na + 2\,NH_3$ for alkynes to *trans*-alkenes), alkyne synthesis (terminal alkyne + 1. $NaNH_2$, 2. RBr).
  - Make ketones/aldehydes with ozonolysis, acid-catalyzed hydration of alkynes, and hydroboration of alkynes (with $(sia)_2BH$ for terminal alkynes to aldehydes).
  - Alkene to diene: 1. Br_2, 2. NaOH.
    - Alkene to alkyne: 1. Br_2, 2. $3\,NaNH_2$.
- Frost method: Point down, MOs at the carbons.

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.

  - 5-membered rings: 3 bonding / 2 antibonding. 7-membered: 3 bonding / 4 antibonding.

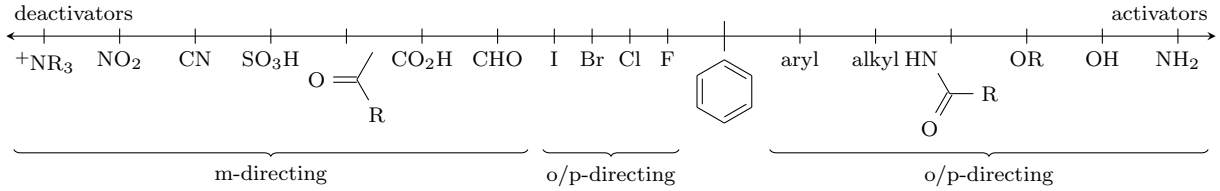
- Aromaticity checklist: Flat, cyclic, conjugated, uninterrupted flow of p-orbitals, $(4n+2)$-rule.
- $(+/-)$ for Diels-Alder reactions!
- F-C reactions happen ONLY IF there is not an EWG on the ring.
- Add stronger EWGs later.
- Nucleophile strengths.

$$^{-}\text{NRH} > \text{RO}^{-} \,/\, \text{HO}^{-} > \text{Br}^{-} > \text{NR}_3 > \text{Cl}^{-} > \text{F}^{-} > \text{H}_2\text{O} \,/\, \text{ROH} > \text{alkene} > \text{benzene}$$

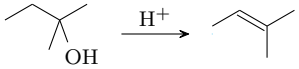
Reactions:

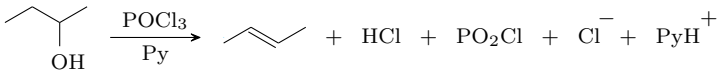
- $=- \xrightarrow[h\nu]{Br_2} =--Br$
  - Chlorination problems: Polychlorination, selectivity.
- $-= \xrightarrow[air]{HBr,\, h\nu} ---Br$
- $C_6H_6 \xrightarrow{D_3O^+} C_6D_6$
- $PhH \xrightarrow[FeBr_3]{Br_2} PhBr$
  - $AlCl_3$, CuI_2.
- $PhH \xrightarrow[H_2SO_4]{HNO_3} PhNO_2$
- $PhH \xrightarrow[H_2SO_4]{SO_3} PhSO_3H$
- $PhH \xrightarrow[AlCl_3]{RCOCl} PhCOR$

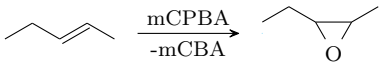
- $\mathrm{PhH} \xrightarrow[\mathrm{AlCl_3}]{\mathrm{RCl}} \mathrm{PhR}$
- benzylic carbonyl $\xrightarrow[\mathrm{HCl}]{\mathrm{Zn(Hg)}}$ reduced carbon
- $\mathrm{PhR} \xrightarrow[\mathrm{H_2O}]{\mathrm{KMnO_4}} \mathrm{PhCOOH}$
  - Needs benzylic hydrogen.
- $\mathrm{PhNO_2} \xrightarrow{\text{reagents}} \mathrm{PhNH_2}$
  - $\mathrm{H_2} + \mathrm{Pd/C}$ or $\mathrm{SnCl_2} + \mathrm{H_2O}$ (selective).
- $\mathrm{PhNH_2} \xrightarrow[\mathrm{HCl}]{\mathrm{NaNO_2}} \mathrm{PhN_2}^+ + \mathrm{X}^-$
  - Mechanism has many equilibrium steps (only first and last are not).
- $\mathrm{PhN_2}^+ \xrightarrow[\mathrm{H_2O}]{\mathrm{Cu_2O}} \mathrm{PhOH}$
  - $\mathrm{PhN_2}^+ \xrightarrow{\mathrm{CuCl}} \mathrm{PhCl}$
  - $\mathrm{PhN_2}^+ \xrightarrow{\mathrm{CuBr}} \mathrm{PhBr}$
  - $\mathrm{PhN_2}^+ \xrightarrow{\mathrm{CuI}} \mathrm{PhI}$
  - $\mathrm{PhN_2}^+ \xrightarrow{\mathrm{CuCN}} \mathrm{PhCN}$
- $\mathrm{PhN_2}^+ \xrightarrow{\mathrm{D_3PO_2}} \mathrm{PhD}$
- $\mathrm{PhBr} \xrightarrow[\mathrm{NH_3}]{\mathrm{NaNH_2}} \mathrm{PhNH_2}$
- $\mathrm{PhCl} \xrightarrow[\mathrm{NuH}]{\mathrm{NaNu}} \mathrm{PhNu}$
- $\mathrm{PhH} \xrightarrow[> 1000\,\mathrm{psi}]{\mathrm{Pd}} \mathrm{CyH}$
- benzene $\xrightarrow[\mathrm{NH_3\,/\,EtOH}]{2\,\mathrm{Li}}$ cyclohexa-1,4-diene $+ 2\,\mathrm{LiOEt}$

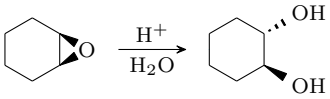


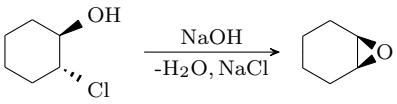
Activators and deactivators.

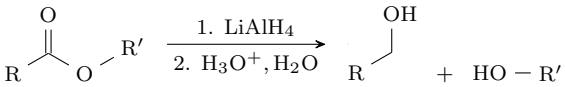
- $\mathrm{ROH} \xrightarrow{\mathrm{HBr}} \mathrm{RBr}$
- $\mathrm{ROH} + \mathrm{SOCl_2} \xrightarrow{\mathrm{Py}} \mathrm{RCl} + \mathrm{SO_2} + \mathrm{Cl}^- + \mathrm{PyH}^+$
  - $\mathrm{PBr_3}$, $\mathrm{PI_3}$.
- $\mathrm{ROH} + \mathrm{Nu} \xrightarrow[\mathrm{NEt_3}]{\mathrm{TsCl}} \mathrm{RNu} + \mathrm{HCl}$
- 

- 

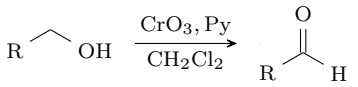
- $ROH \xrightarrow[MeI]{NaH} ROMe + H_2 + NaI$ — Williamson Ether Synthesis.
- $ROR' \xrightarrow{HBr} RBr + R'OH$
  - Must use HBr or HI, not HCl.
- 

- 

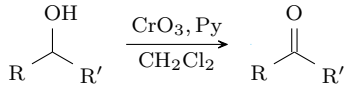
  - Can be trapped by HCl or HBr.
  - Acidic conditions → CC+ stability is important; basic → sterics.
- 

- $RCOR' \xrightarrow{reagents} RC(OH)HR'$
  - $NaBH_4$ or $LiAlH_4$.
- 

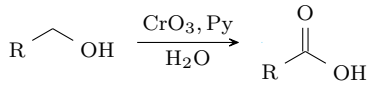
- $RBr \xrightarrow[Et_2O]{Mg^\circ} RMgBr$
- $RBr \xrightarrow[Et_2O]{2\,Li^\circ} RLi + LiBr$
- Collins reagent:



(a) Anhydrous oxidation of a primary alcohol.



(b) Anhydrous oxidation of a secondary alcohol.



(c) Aqueous oxidation of a primary alcohol.

  - Jones reagent: $CrO_3 + H_2SO_{4(aq)}$; PCC: Py, HCl, CrO_3; Swern oxidation: $1.\,DMSO, (COCl)_2$, $2.\,NEt_3$.

9.4 Chapter 12: Alcohols from Carbonyl Compounds

From Solomons et al. [1].

- Together, reduction of carbonyls and modification by Grignards and organolithium reagents fall under the category of **nucleophilic addition**.
- There exist lowest and highest oxidation states of an organic compound.

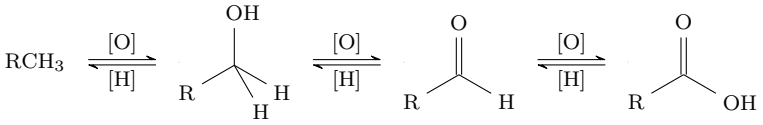


Figure 9.11: Oxidation state spectrum.

  - Note that we use [H] to indicate in a general way that a molecule has been reduced and vice versa for [O].
- "Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon" [1, p 537].
- $LiAlH_4$ is also denoted by the acronym LAH.
- Since LAH reacts violently with proton donors to release hydrogen gas, $NaBH_4$ is a much safer (and therefore preferable) reagent for reducing aldehydes and ketones.
  - Importantly, it can be used along with protic solvents.
  - LAH is typically used in Et_2O. After the reaction is complete, EtAc is added cautiously to decompose remaining LAH and then water to decompose the alumina complex, rendering it inert.
- Aldehydes and ketones can also be reduced via $H_2 + Pd/C$ (hydrogen and a metal catalyst) and $Na^\circ +$ ROH (sodium metal in an alcohol solvent).
- Almost all types of alkyl halides can be reduced by $LiAlH_4$ in ether followed by sulfuric acid in water.
  - Note that the proton comes from $LiAlH_4$, so we may use $LiAlD_4$ to replace the halide with deuterium.
- Primary and secondary alcohols can be reduced to carbonyl compounds, but tertiary ones cannot.
  - This is because we need a hydrogen on the α-carbon to lose along with the hydrogen from the alcohol group.
- Oxidation of alcohols.

3/11:
  - "Primary alcohols can be oxidized to aldehydes, and aldehydes can be oxidized to carboxylic acids" [1, p 542].
  - "Secondary alcohols can be oxidized to ketones" [1, p 542].
  - "Tertiary alcohols cannot be oxidized to carbonyl compounds" [1, p 542].
- The common mechanistic theme of alcohol oxidation by elimination.
  - We attach a leaving group to the hydroxyl oxygen and deprotonate.
  - Attacking an α-hydrogen subsequently causes elimination of that hydrogen and the leaving group; the hydrogen's electrons become the double bond.
- The Swern oxidation is usually carried out at low temperatures.

- Chromic acid (H_2CrO_4) oxidation is discussed, but in a mechanistically different manner to that presented in class.
- Chromic acid is orange-red, but Cr(III) (in the product mixture) is greenish blue. Thus, reagents like Jones reagent can serve as a color-based test for the presence of functional groups including primary and secondary alcohols and aldehydes.
  - This color change was the basis of the original brethalyzer test.
- Since PCC is soluble in solvents other than water (e.g., CH_2Cl_2), it can be used for the necessarily anhydrous monooxidations of alcohols.

3/10:
- **Organometallic compound**: A compound that contains a carbon-metal bond.
- C–M bonds are largely ionic when $M = Na, K$, are largely covalent when $M = Pb, Sn, Hg, Ti$, and are in between when $M = Mg, Li$.
- Reactivity of organometallics increases with increasing ionic character.
  - Alkylsodium an alkylpotassium compounds are among the most powerful of bases, but also react explosively with water and burst into flame when exposed to air.
  - The more stable ones may only be volatile in air, but are still highly poisonous (e.g., Et_4Pb, the infamous antiknock compound formerly used in leaded gasoline).
- Most Grignards exist in equilibrium between an alkylmagnesium halide and a dialkyl magnesium.

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

- Grignards in their alkylmagnesium halide state also form a complex with their aprotic solvent, attracting electron pairs in two partial bonds to their positive magnesium.
- A Grignard reagent behaves like a strong base and reacts to form a weak conjugate acid (such as its protonated or otherwise alkylated form).
- Grignard reagents can even deprotonate terminal alkynes.
  - This serves as a method of production of alkynylmagnesium halides and alkynyllithiums, though.

References

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