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.

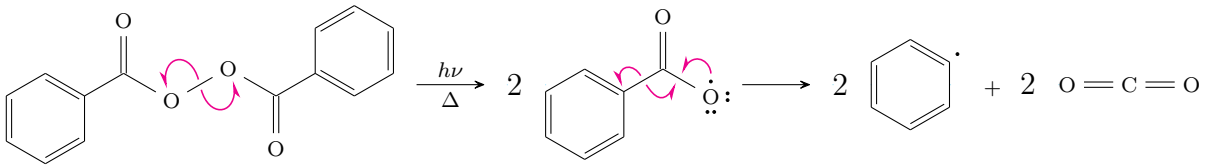
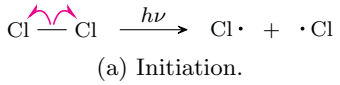
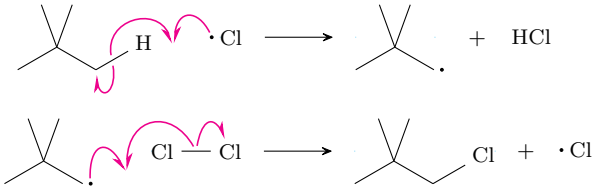


Figure 3.1: Losing CO_2 in a radical mechanism.

  - 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.

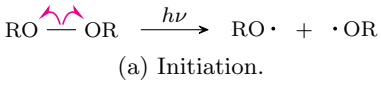
- General form.

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

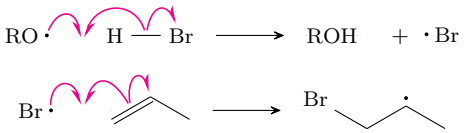
  - A possible side reaction is bromination of the alkene, but this requires a high temperature and low concentration.
  - The mechanism is entirely analogous to that of chlorination.

- 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.

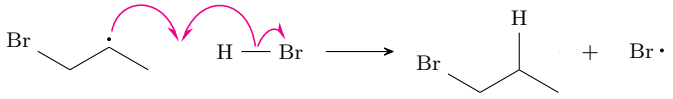
- Mechanism.



(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).
- $\mathrm{Br}\cdot$ 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.

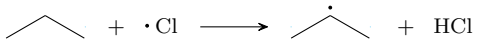
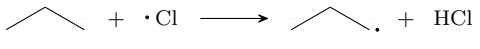
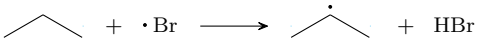
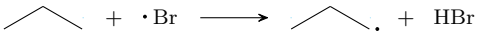
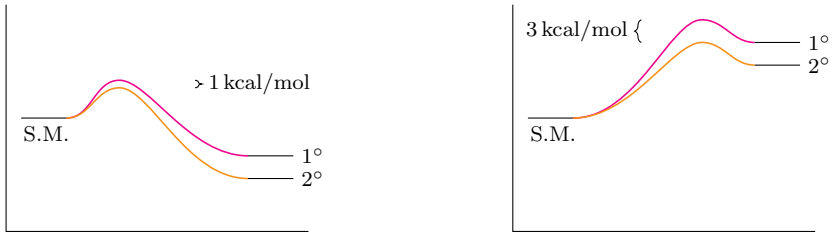
Reaction	E_A (kcal/mol)
	3
	4
	13
	16

Table 3.1: Analyzing the RDS of halogenation of alkanes.

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



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

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

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

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

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

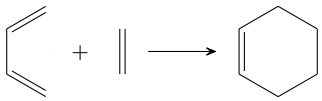


Figure 3.5: Diels-Alder general form.

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

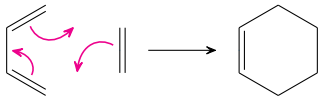
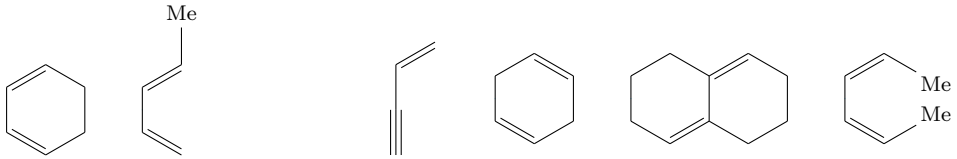


Figure 3.6: Diels-Alder mechanism.

  - This is a **pericyclic** reaction.
- **Pericyclic** (reaction): A reaction that proceeds via a concerted mechanism involving a single, cyclic transition state.
- The basics.
  1. The diene must be composed of two alkenes in conjugation, and those alkenes must be capable of achieving an **s-cis** orientation.
     - How much of the time the diene is in the s-cis orientation affects the reaction rate.
     - For example, the diene on the left in Figure 3.7a is in the s-cis orientation 100% of the time, but the diene on the right in Figure 3.7a is in the s-cis orientation only 50% of the time.



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

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

  - The dienes in Figure 3.7b, for one reason or another, are never capable of achieving the s-cis orientation.

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

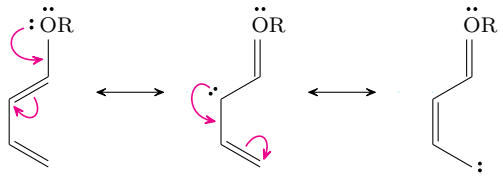


Figure 3.8: Diels-Alder EDGs.

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

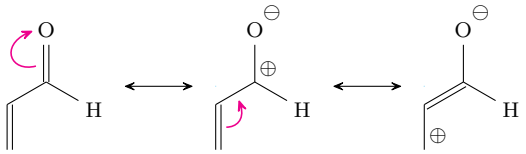
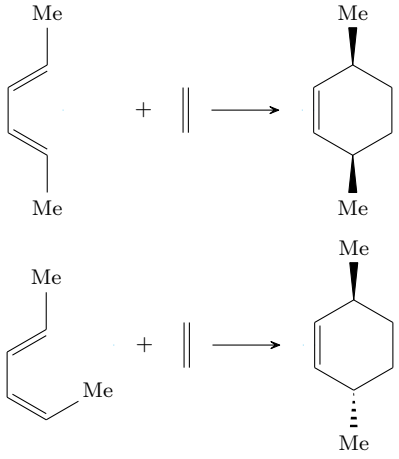


Figure 3.9: Diels-Alder EWGs.

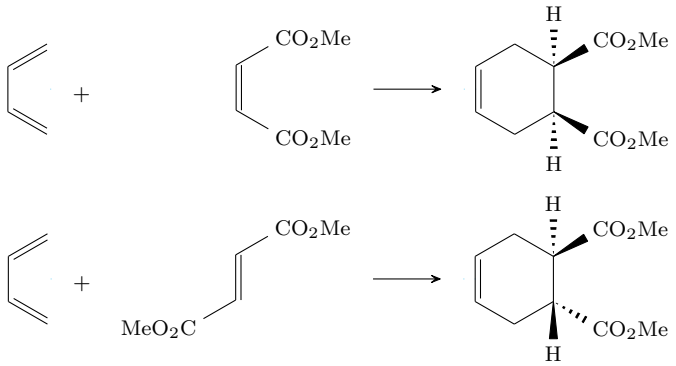
    - These all have a π-system directly attached to your double bond, and electronegativity pulls electrons out towards these π-systems.

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

- The Diels-Alder reaction is **stereospecific**.



(a) Stereoselectivity of the diene.



(b) Stereoselectivity of the dienophile.

Figure 3.10: Diels-Alder stereoselectivity.

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

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

- The Diels-Alder reaction is **diastereoselective**.

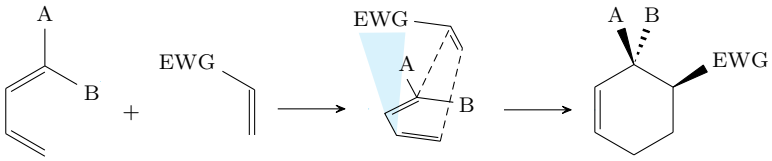


Figure 3.11: Diels-Alder diastereoselectivity.

  - When we add a substituted diene to a substituted dienophile, we might intuitively think that we will form the less sterically encumbered product (via an **exo** transition state).

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

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

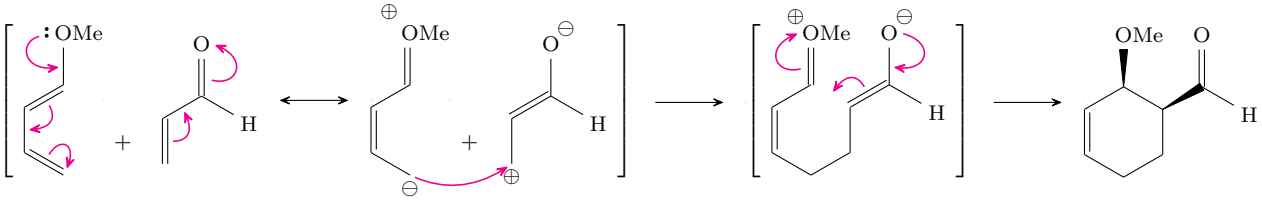


Figure 3.12: Diels-Alder regioselectivity.

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

3.4 Office Hours (Keller)

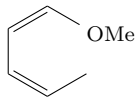
1/28:

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

3.5 Office Hours (Snyder)

1/31:

- Sterics vs. an EDG on the diene?



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

3.6 Office Hours (Salinas)

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

3.7 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^tBu and ^tBuOH 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.

3.8 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.

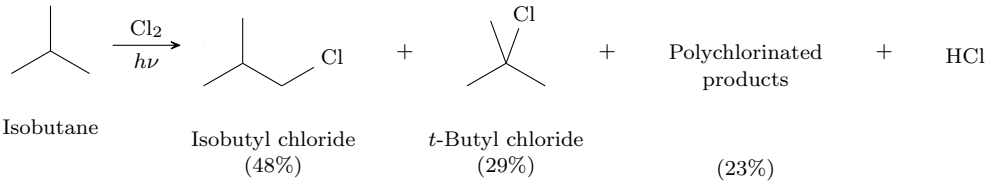


Figure 3.13: Unselectivity of chlorination of alkanes.

  - 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.

3.9 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].

3.10 Exam 1 Cheat Sheet

2/3:

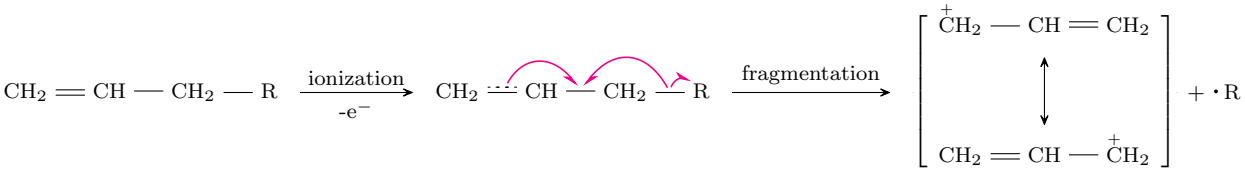
COMMON ABSORPTIONS	
Aromatic C–C	Two peaks usually in the range of $1500 - 1600\,cm^{-1}$
C=C	$\sim 1650\,cm^{-1}$
C=O	$\sim 1710\,cm^{-1}$ (shifts to $\sim 1735\,cm^{-1}$ for esters)
C≡C	$2100 - 2300\,cm^{-1}$
C≡N	$2100 - 2300\,cm^{-1}$
C–H (aldehyde)	Two peaks at $2170\,cm^{-1}$ and $2810\,cm^{-1}$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

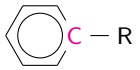
*The chemical shifts of these protons vary in different solvents and with temperature and concentration.

Approximate proton chemical shifts.

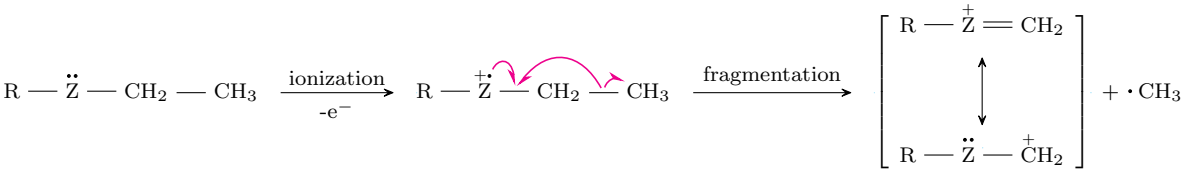


Resonance fragmentation: Alkenes.

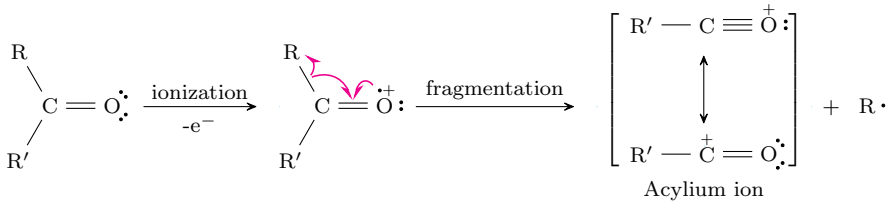
- Alkene reactions to know: hydrogenation (H_2 Pd/C), dihydroxylation (OsO_4), ozonolysis (O_3 Me_2S), hydrobromination (HBr), and bromination (Br_2).

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

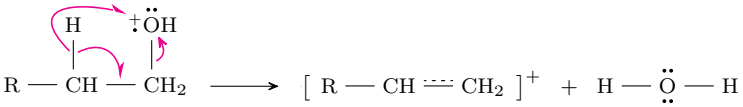
Approximate carbon-13 chemical shifts.



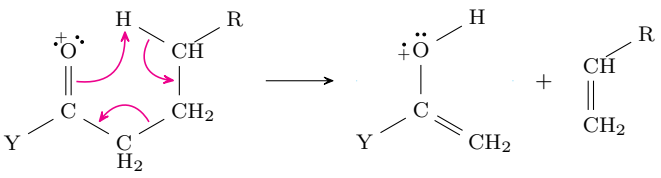
Resonance fragmentation: Lone pairs.



Resonance fragmentation: Carbonyls.



Fragmentation: Loss of H_2O.



Fragmentation: McLafferty rearrangement.