

MIT 5.12 Organic chemistry I

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I god fucking hate this subject. Hopefully quantum mech gives me more insight

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1 Polar covalent bonds; acids and bases

Fact 1

Bond polarity is due to differences in electronegativity. The greater the difference in electronegativity the greater the tendency exchange electrons rather than share that is

covalent bond → polar covalent bond → ionic bond

Fact 2

Rules for resonance forms

1. individual resonance forms are imaginary not real. The real structure is a composite or resonance hybrid of different forms
2. resonance forms differ only in the placement of their π or nonbonding electrons. A curved arrow indicates the movement of electrons not the movement of atoms
3. different resonance forms of a substance don't have to be equivalent
4. resonance forms obey normal rules of valency. for example octet rule must apply to second row main group atoms. no expanded octet allowed
5. the resonance hybrid is more stable than any individual resonance form. *Generally speaking* the more resonance forms the more stable as electrons are more spread out.

2 polar covalent bonds; acids and bases

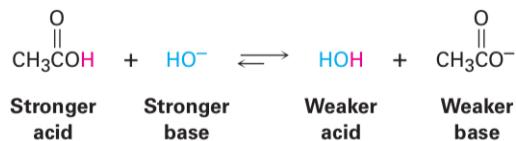
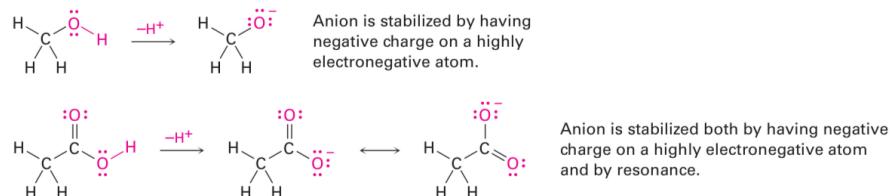
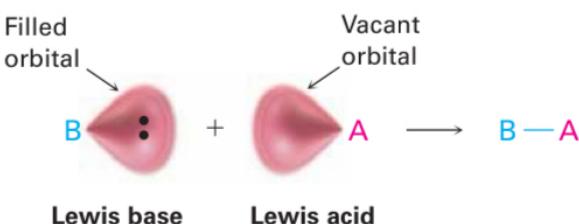


Figure 1: One may predict acid base reaction from pKa values

Recall higher pKa means stronger acid. Consider some reasons for acidity of an organic acid



2.1 lewis acids and bases



The fact that a lewis acid is able to accept an electron pair means that it must have either a low energy orbital or a polar bond

Example 3

Mg^{2+} , BF_3 are lewis acids. H_3O^+ are lewis bases

2.2 protonation vs deprotonation

Summary: How Protonation and Deprotonation Affect Reactivity

- The reactivity of a molecule is greatly affected by losing a proton (H^+) to form its **conjugate base**, or by gaining a proton to give its **conjugate acid**.
- Deprotonation makes a molecule a **better nucleophile** because the deprotonated atom becomes more electron-rich.

- "the conjugate base is always a better nucleophile"
- Protonation of a molecule makes it a **better electrophile** (leaving group) because it becomes more electron-poor.

- "the conjugate acid is always a better leaving group"
- Through **resonance**, acid-base reactions can affect the **electron-density of neighboring atoms**. For example, protonating the oxygen below also makes the adjacent carbon more electron-poor (more electrophilic) through resonance.

By protonating oxygen, we actually make the carbon more electron poor!

Gain or loss of H^+ (proton)

3 organic compounds: alkanes and their stereochemistry

Definition 4

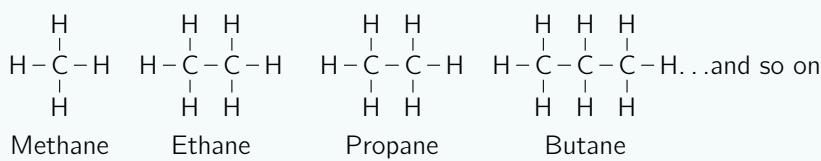
A **functional group** is a group of atoms within a molecule that has a characteristic chemical behavior.

Fact 5

Alkanes are often described as **saturated hydrocarbons**: *hydrocarbons* because they contain only carbon and hydrogen and *saturated* because they contain the maximum number of hydrogens per carbon

Example 6

The **alkane** family



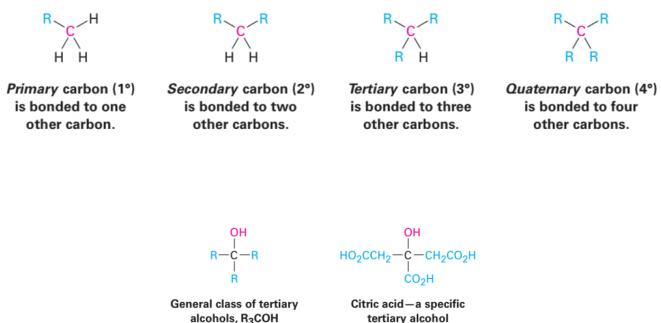
Definition 7

and the **alkyl** functional group which is basically alkane but with *H* on one end "removed"

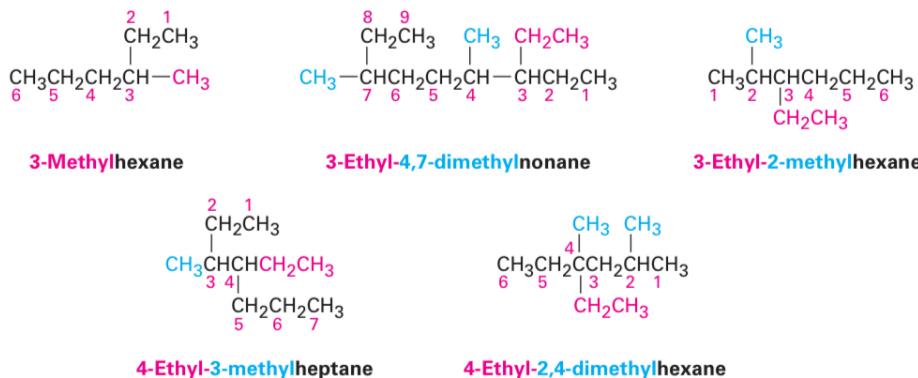
TABLE 3-4 Some Straight-Chain Alkyl Groups

Alkane	Name	Alkyl group	Name (abbreviation)
CH ₄	Methane	—CH ₃	Methyl (Me)
CH ₃ CH ₃	Ethane	—CH ₂ CH ₃	Ethyl (Et)
CH ₃ CH ₂ CH ₃	Propane	—CH ₂ CH ₂ CH ₃	Propyl (Pr)
CH ₃ CH ₂ CH ₂ CH ₃	Butane	—CH ₂ CH ₂ CH ₂ CH ₃	Butyl (Bu)
CH ₃ CH ₂ CH ₂ CH ₂ CH ₃	Pentane	—CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	Pentyl, or amyl

Primary Secondary Tertiary Carbons/Alcohols



3.1 naming alkanes



The steps are

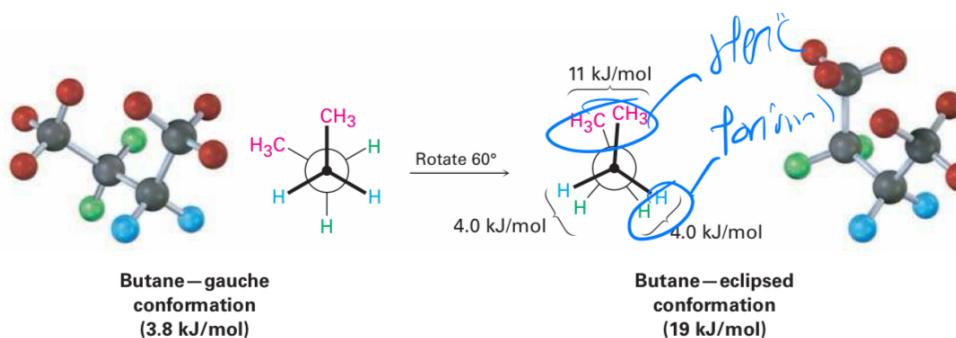
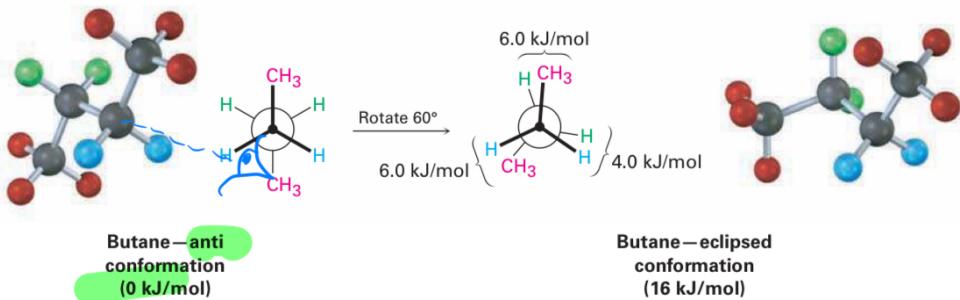
1. Find the parent hydrocarbon
2. Number atoms in the longest chain
3. Identify and number the substituants
4. write the name as a single word

The general format is

Locant+prefix+parent+suffix

- Locant: where are the substituents and functional groups
- Prefix: what are the substituents
- Parent: how many carbons
- Suffix: What is the primary functional group(eg. in our case it is "-ane")

3.2 conformations of alkanes



Gauche is due to methyl groups being near each other so have some steric strain although not as bad as directly eclipsed. Energy tables

TABLE 3-5 Energy Costs for Interactions in Alkane Conformers			
Interaction	Cause	Energy cost	
		(kJ/mol)	(kcal/mol)
H \leftrightarrow H eclipsed	Torsional strain	4.0	1.0
H \leftrightarrow CH ₃ eclipsed	Mostly torsional strain	6.0	1.4
CH ₃ \leftrightarrow CH ₃ eclipsed	Torsional and steric strain	11.0	2.6
CH ₃ \leftrightarrow CH ₃ gauche	Steric strain	3.8	0.9

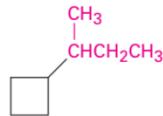
4 cycloalkanes

4.1 naming cycloalkanes

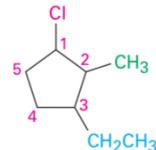
Same as for alkanes just different suffix



1-Bromo-3-ethyl-5-methylcyclohexane



(1-Methylpropyl)cyclobutane
or sec-butylcyclobutane



1-Chloro-3-ethyl-2-methylcyclopentane

4.2 cis-trans isomerism in cycloalkanes

Constitutional isomers
(different connections between atoms)

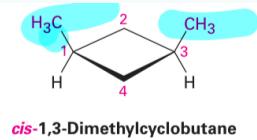


Stereoisomers
(same connections but different three-dimensional geometry)

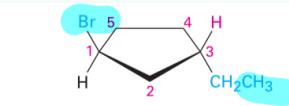


Example 8

A subclass of stereoisomers are called **cis-trans isomers**. Cis in latin means "same side" while Trans means "across"



cis-1,3-Dimethylcyclobutane



trans-1-Bromo-3-ethylcyclopentane

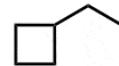
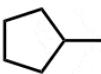
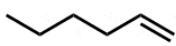
Example 9

Straight chain vs branched alkanes are examples are constitutional isomers

In all we have

Types of Isomers - Constitutional Isomers, Stereoisomers, Diastereomers

- Isomers are molecules that share the same **molecular formula**, e.g. C₆H₁₂
- **Constitutional isomers** have the same molecular formula but different connectivity



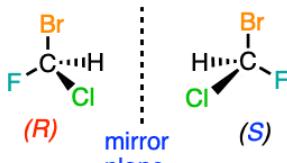
some isomers of C₆H₁₂

an important clue for different connectivity is that the molecules have different IUPAC names (without having to use R/S or E/Z descriptors)

- **Stereoisomers** have the same connectivity but differ in the arrangement of their atoms in space

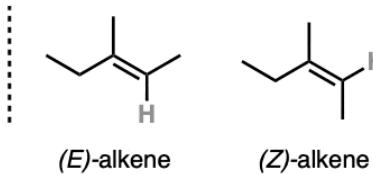
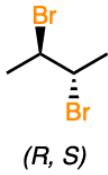
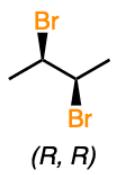
an important clue that molecules are stereoisomers are that they have the same IUPAC name but differ in their R/S and/or E/Z descriptors

- **Enantiomers** are stereoisomers that are non-superimposable mirror images.
(Molecules that are superimposable mirror images are considered to be identical).



Enantiomers always have opposite R,S descriptors

- **Diastereomers** are stereoisomers that are **not** enantiomers.



Share at least one (but not all) R,S descriptors, or differ in at least one E,Z descriptor

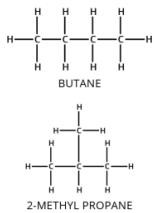
A BRIEF GUIDE TO • TYPES OF ISOMERISM IN ORGANIC CHEMISTRY •

A GUIDE TO THE FIVE MAIN TYPES OF ISOMERISM THAT CAN BE EXHIBITED BY ORGANIC COMPOUNDS

AN ISOMER OF A MOLECULE IS A MOLECULE WITH THE SAME MOLECULAR FORMULA BUT A DIFFERENT STRUCTURAL OR SPATIAL ARRANGEMENT OF ATOMS. THIS VARIATION CAN LEAD TO A DIFFERENCE IN PHYSICAL OR CHEMICAL PROPERTIES.

STRUCTURAL ISOMERISM

CHAIN



POSITION

BUTANE

FUNCTIONAL

POSITION

BUT-2-ENE

BUT-1-ENE

CYCLOBUTANE

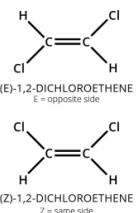
FUNCTIONAL

BUT-2-ENE

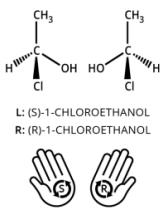
CYCLOBUTANE

STEREOISOMERISM

GEOMETRIC



OPTICAL



NON-SUPERIMPOSABLE MIRROR IMAGES OF THE SAME MOLECULE

Commonly exhibited by alkenes, the presence of two different substituents both with atoms at either end of the double bond can give rise to two different, non-superimposable isomers due to the restricted rotation of the bond.



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4.3 conformations of cyclohexane

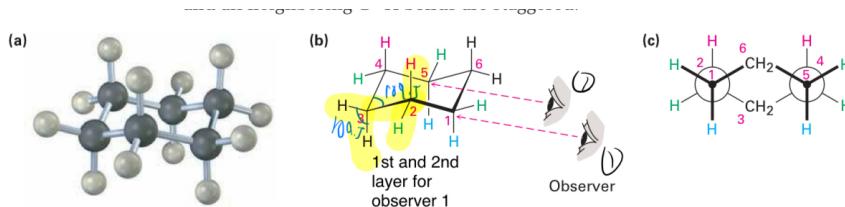


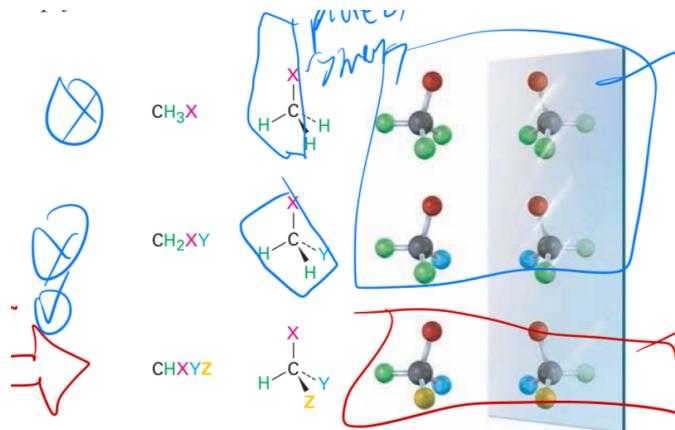
FIGURE 4-7 The strain-free chair conformation of cyclohexane. All C–C bond angles are 111.5°, close to the ideal 109° tetrahedral angle, and all neighboring C–H bonds are staggered.

Figure 2: the vertical H correspond to axial bonds while the horizontal equatorial bonds

This the most stable for cyclohexane(strain free) is known as the **chair conformation**

5 stereochemistry and tetrahedral centers

5.1 enantiomers and the tetrahedral carbon



See that the first 2 of not enantiomers but the last one is. The first 2 the mirror image can rotate and possibly get the same as original but not the last one. Alternatively you try to find a plane of symmetry as shown above and you will see you can find for only the first 2.

Definition 10

Molecules that are not identical to their mirror image are known as **enantiomers** (in greek enantio means opposite)

5.2 reasons for handedness: chirality

Definition 11

A molecule that is not identical to its mirror image is said to be **chiral** and **achiral** otherwise

Definition 12

If the cause of chirality is due to the presence of a tetrahedral carbon atom bonded to four different groups then the central atom is called a **chirality center**

For example the C in the 3 molecule in the figure above is one such chirality center. Still have some stuff but not v interested...to be continued

6 an overview of organic reactions

Fact 13

The electron rich double bond and can serve as a nucleophile not just negative charges

You will see examples in later sections

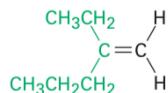
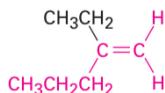
6.1 using curved arrows in polar reaction mechanisms

The rules are

1. Electrons move from a nucleophilic source to an electrophilic sink. The nucleophilic source must have an electron pair available (usually either a lone pair or in a multiple bond)
2. the nucleophile can be either negatively charged or neutral
3. the electrophile can be either positively charged or neutral
4. octet rule must be followed for second row atoms and below

7 alkenes: structure and reactivity

7.1 naming alkenes

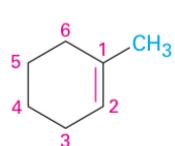


Named as a **pentene**

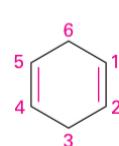
NOT

as a hexene, since the double bond is
not contained in the six-carbon chain

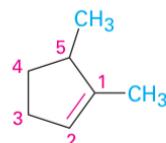
Figure 3: Obviously must contain the double bond in the parent group



1-Methylcyclohexene



1,4-Cyclohexadiene
(New: Cyclohexa-1,4-diene)



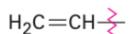
1,5-Dimethylcyclopentene

Note the naming process is the same as the top but other than changing the name of suffix also must specify the location of the double bond in the alkene parent group too.

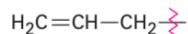
Now consider its substituents



A methylene group



A vinyl group



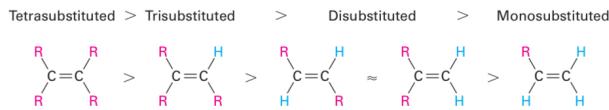
An allyl group

7.2 stability of alkenes

Factor 1

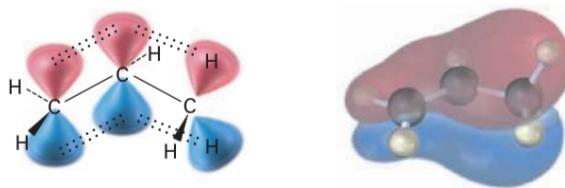


clearly more steric in cis Factor 2



Definition 14

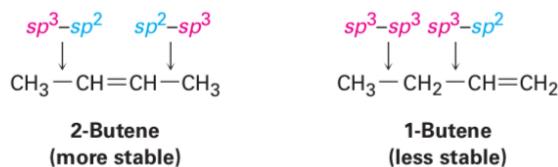
The reason is due **hyperconjugation** which is a stabilizing interaction between the $C = C \pi$ bond and the adjacent $C - H \sigma$ bonds on substituents.



In molecular orbital description there is a bonding MO that extends over the 4 atoms $C = C - C - H$ grouping. In hyperconjugation, a sigma bond (usually a C–H bond) adjacent to a system that has a vacant p-orbital (such as a carbocation), a π -bond (as in alkenes), or a radical donates electron density into that system. This leads to delocalization of charge or electron density, which provides stability to the molecule. Hyperconjugation is often referred to as the no-bond resonance or sigma-pi conjugation. See more in 17

Example 15

For example

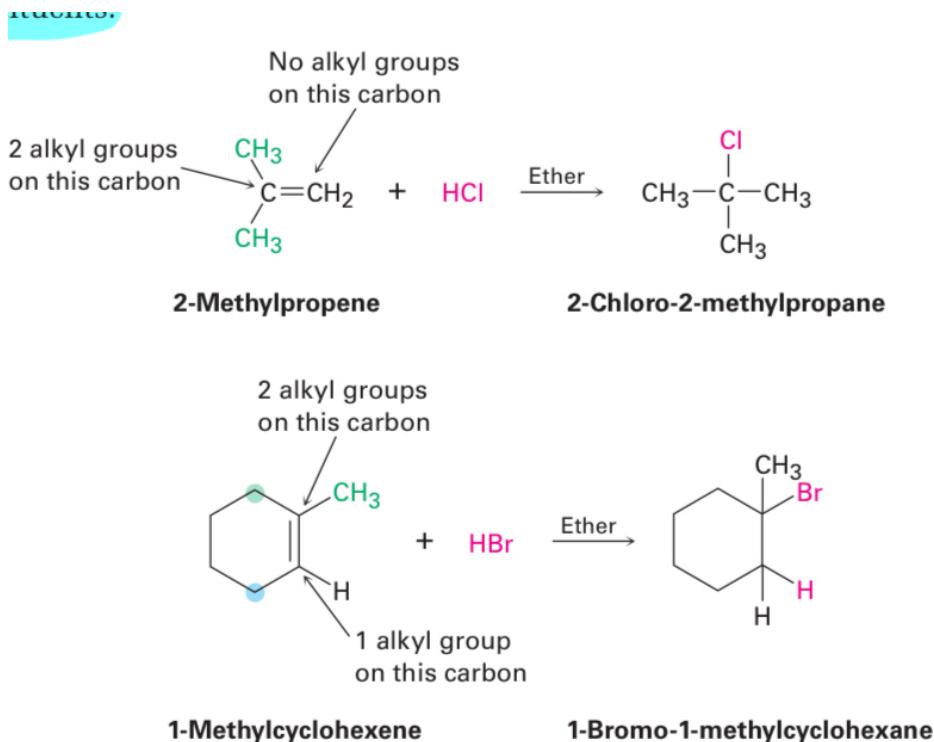


7.3 orientation of electrophilic additions: markovnikov rule

Fact 16

Markovnikov rule states that in the addition of HX to alkene the H attaches to the carbon with fewer alkyl substituents and the X attaches to the carbon with more alkyl substituents

For example



the reason for markonikov rule is due to carbocation stability.

7.4 carbocation structure and stability

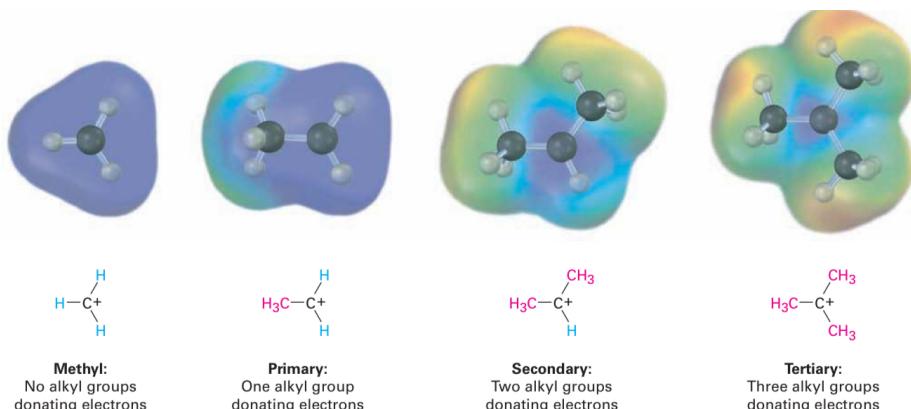


FIGURE 7-11 A comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups that are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron-poor (blue in electrostatic potential maps).

See that the stability order for carbocations follows

methyl → primary → secondary → tertiary

There are 2 reasons for this. First is due to **inductive effects**. The positive charge results in shifting of electron clouds on nearby σ bonds to it. Hence the relatively larger and more polarizable (consider that C is more electronegative than H) alkyl groups can shift more easily than the electron from an hydrogen.

Fact 17 (hyperconjugation)

The second reason is due to **hyperconjugation**. Hyperconjugation involves overlap between a sigma orbital (usually from a C–H bond) and an adjacent empty or partially filled orbital (like an empty p-orbital in a carbocation, or the π -system in an alkene).

The electrons from the sigma bond are delocalized into the adjacent system, reducing the electron deficiency or stabilizing the system by distributing electron density.

In resonance structures, hyperconjugation can be depicted as the breaking of a C–H bond with the hydrogen completely detached from the molecule, leaving a partial positive charge on the hydrogen and delocalizing electron density into the adjacent system.



7.5 Evidence for mechanism of electrophilic additions : carbocation rearrangements

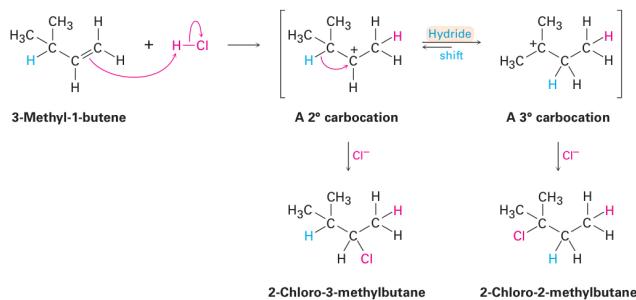


Figure 4: Hydride shift

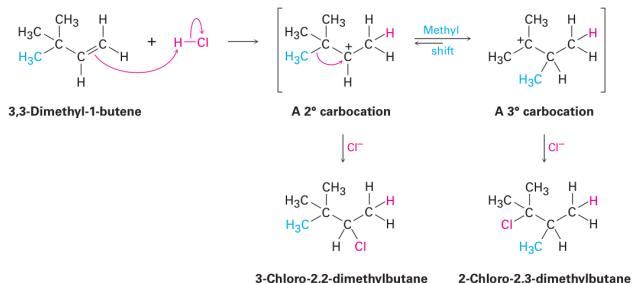


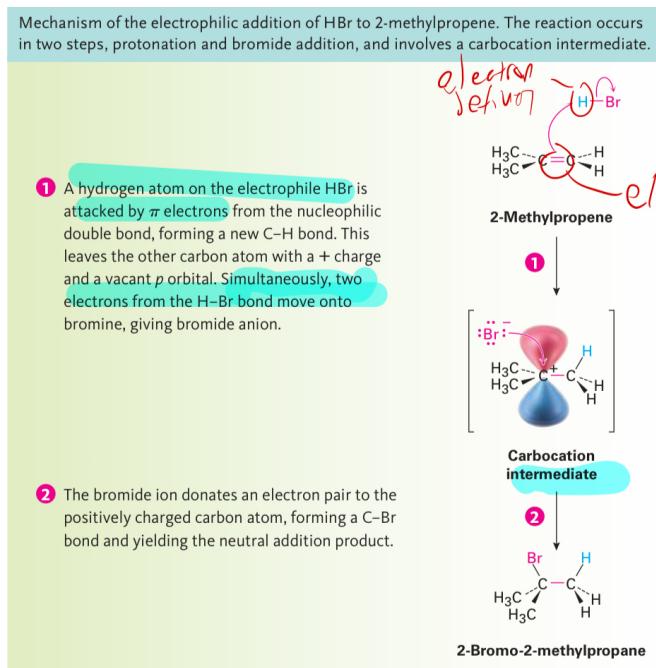
Figure 5: methyl shift

Note that in both cases a more stable carbocation results. This is because recall due to hyperconjugation the more highly substituted carbocation is more stable. See in this case the 3° is higher than 2°.

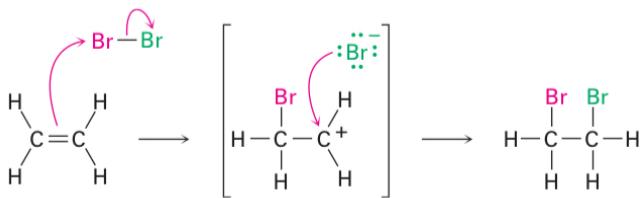
8 preparing alkenes: a preview of elimination reactions

8.1 halogenation of alkenes: addition of X₂

First consider electrophilic addition of HX to alkene

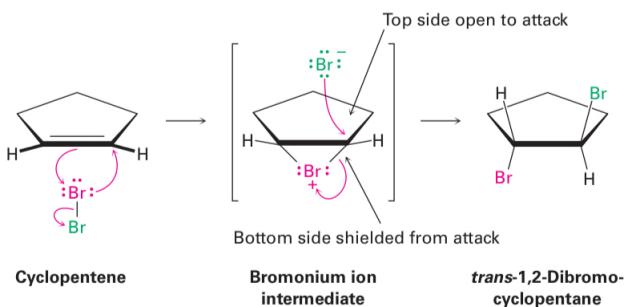


This still follows Markovnikov. But the stereochemistry of this reaction is neither anti or symmetric, that is we get a **racemic** mixture. However the following is untrue for the following

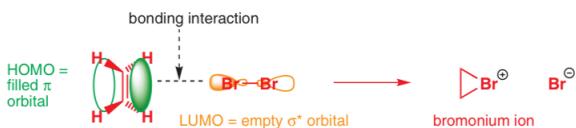


Remark 18. Note that Br could act as an electrophile here because Br_2 is highly polarizable since Br^- is a relatively weak base (doesn't hold electrons very tightly). Now that means the electron density can shift between each Br relatively easily

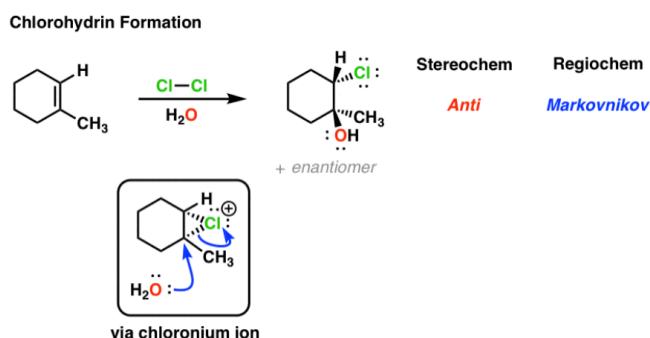
To see this consider that this happens



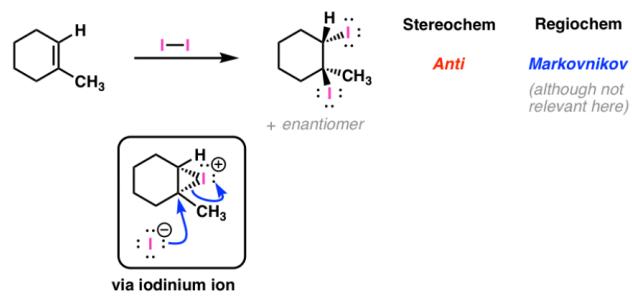
so we get **anti stereochemistry** meaning that the two bromine atoms come from opposite faces of the double bond. Why does this happen?



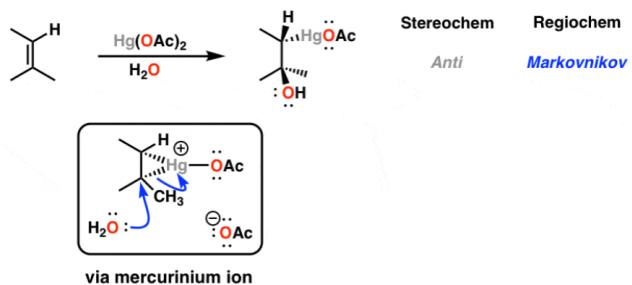
Consider how the bonding occurs. The antibonding orbital on Br will approach the center of the top of the π bond where the bonding orbital is where electron density is the greatest. So orientation wise this reflects the fact that Br approached the π bond at the center. Then why doesn't HX behave the same way? Well H does not have the lone pair to form a second bond with another carbon. This sort of reaction is known as a **3 member member ring pathway**. Other family members other than Br include



Iodination of Alkenes



Oxymecuration



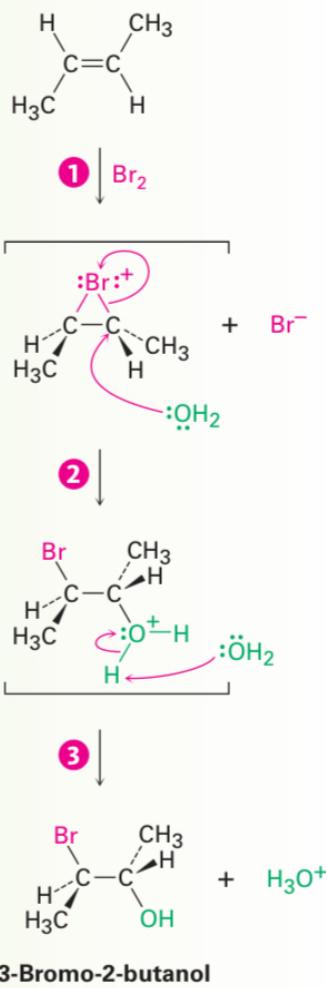
Note the last one(oxymecuration) is anti stereochem don't mind the grey color gradient

8.2 halohydrins from alkenes: addition of HOX

- 1 Reaction of the alkene with Br_2 yields a bromonium ion intermediate, as previously discussed.

- 2 Water acts as a nucleophile, using a lone pair of electrons to open the bromonium ion ring and form a bond to carbon. Since oxygen donates its electrons in this step, it now has the positive charge.

- 3 Loss of a proton (H^+) from oxygen then gives H_3O^+ and the neutral bromohydrin addition product.

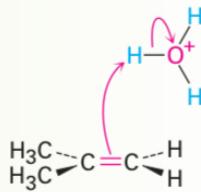


the difference here is that instead of Br^- attack, OH attack.

8.3 hydration of alkenes: addition of water by oxymecuration

Mechanism of the acid-catalyzed hydration of an alkene to yield an alcohol. Protonation of the alkene gives a carbocation intermediate, which reacts with water. The initial product is then deprotonated.

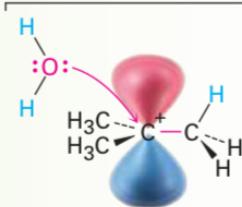
- 1 A hydrogen atom on the electrophile H_3O^+ is attacked by π electrons from the nucleophilic double bond, forming a new C-H bond. This leaves the other carbon atom with a + charge and a vacant p orbital. Simultaneously, two electrons from the H-O bond move onto oxygen, giving neutral water.



2-Methylpropene

1

- 2 The nucleophile H_2O donates an electron pair to the positively charged carbon atom, forming a C-O bond and leaving a positive charge on oxygen in the protonated alcohol addition product.



Carbocation

2

- 3 Water acts as a base to remove H^+ , regenerating H_3O^+ and yielding the neutral alcohol addition product.

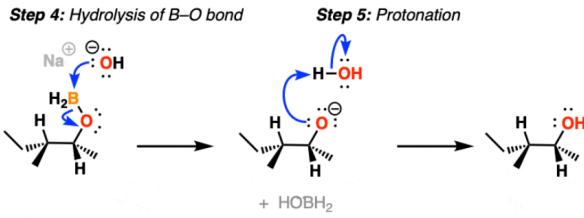
Protonated alcohol

3



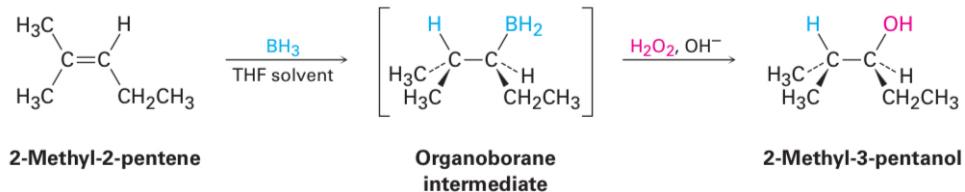
2-Methyl-2-propanol

Note that marokovnikov **reigochemistry** is followed here cos you want to pos charge corresponding to the cavant p orbital to be adjacent to more sigma bonds(H₃C) on that side. Again like the HX electrophilic example covered above this is neither anti or sym stereochemistry.

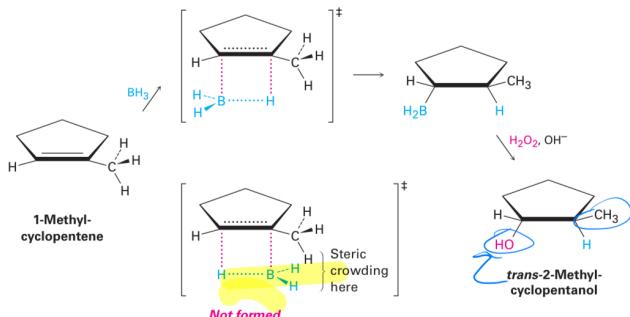


8.4 hydration of alkenes: addition of water by hydroboration

Borane BH_3 is very reactive as lewis acid since it only has six electrons in its valence shell so it will wanna accept a lone pair to gain octet. So it electrophilic and hence the first reaction. The second is due to oxidation Note that hydrogen being in a higher row than boron is more electronegative than it! Check internet. Thats why the base attacked B. Recall that OH^- is a strong base as it doesn't stabilize the negative charge well.



We will illustrate why with rings. Essentially it is due to steric crowding



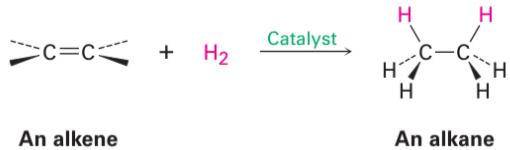
8.5 reduction of alkenes: hydrogenation

Definition 19

In organic chemistry a **reduction** is a reaction that results in a gain of electron density for carbon

Increases electron density on carbon by:
 - forming this: $\text{C}-\text{H}$
 - or breaking one of these: $\text{C}-\text{O}$ $\text{C}-\text{N}$ $\text{C}-\text{X}$

A reduction:



Note that hydrogenation usually occurs with syn stereochemistry meaning that both hydrogens add to the same face

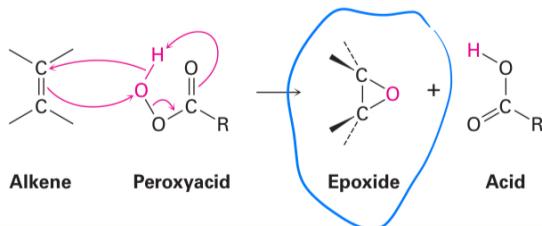
8.6 oxidation of alkenes: epoxidation and hydroxylation

Definition 20

In organic chemistry **oxidation** is a reaction that results in a loss of electron density for carbon

Decreases electron density on carbon by

- forming one of these : $\text{C}-\text{O}$, $\text{C}-\text{N}$, $\text{C}-\text{X}$
- or breaking this: $\text{C}-\text{H}$

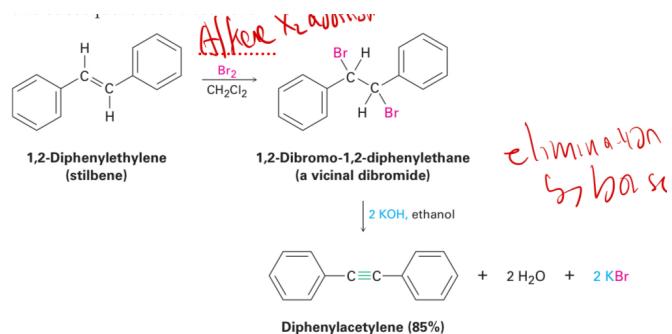


This reaction by breakage of the relatively weak O–O and C–C pi bonds (bond dissociation energies of about 45 kcal/mol and 60 kcal/mol, respectively) in exchange for two relatively strong C–O sigma bonds (about 90 kcal/mol)

8.7 oxidation of alkenes: cleavage to carbonyl compounds

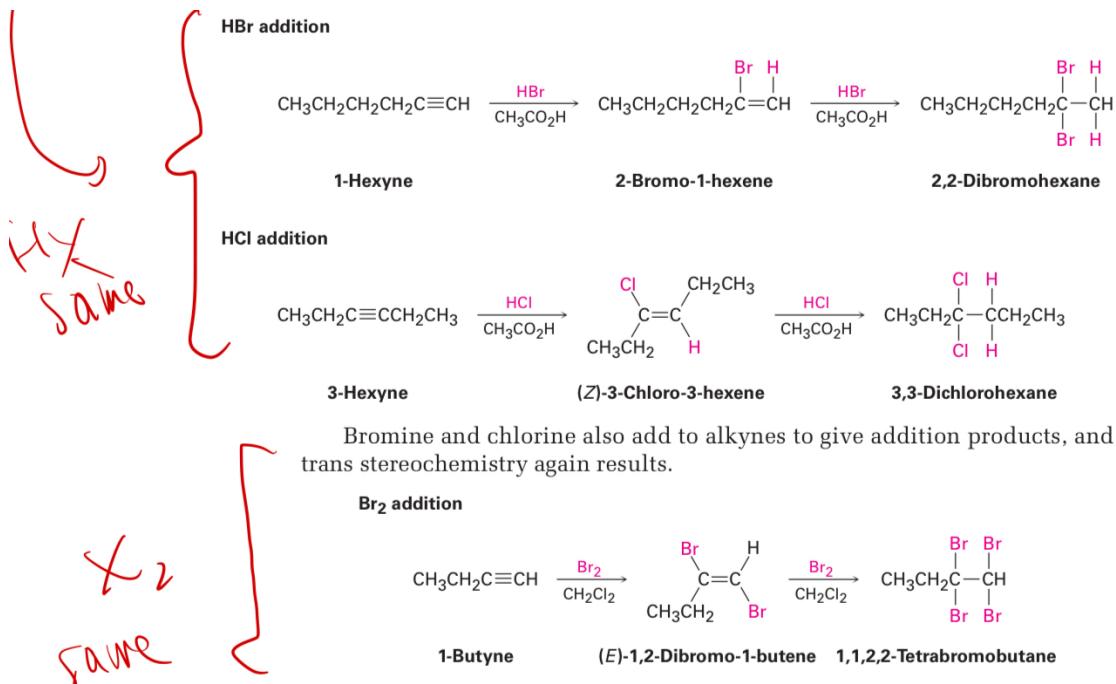
9 alkynes: an introduction to organic synthesis

9.1 preparation of alkynes: elimination of reactions of dihalides



The second step shown is known as elimination which will study more later

9.2 addition of HX and X_2

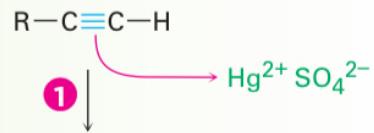


In general the addition the addition is the space as that of alkenes and the regiochemistry also follows marknovidov

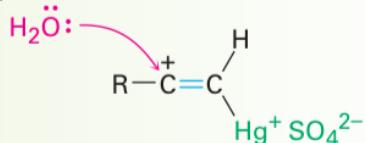
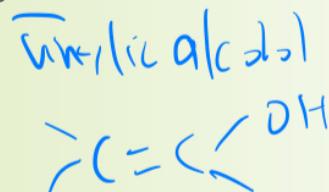
9.3 hydration of alkynes

Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone. The reaction occurs through initial formation of an intermediate enol, which tautomerizes to the ketone.

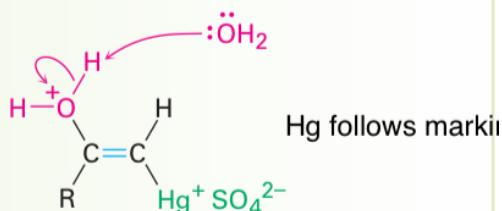
- 1 The alkyne uses a pair of electrons to attack the electrophilic mercury(II) ion, yielding a mercury-containing vinylic carbocation intermediate.



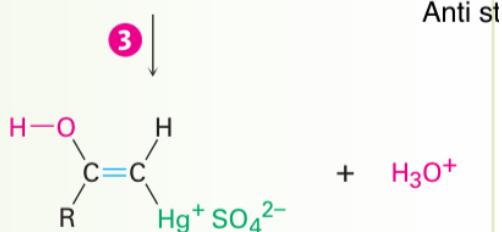
- 2 Nucleophilic attack of water on the carbocation forms a C–O bond and yields a protonated mercury-containing enol.



2

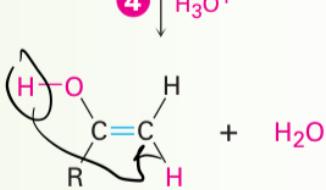


- 3 Abstraction of H^+ from the protonated enol by water gives an organomercury compound.



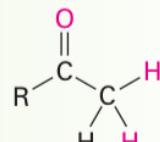
3

- 4 Replacement of Hg^{2+} by H^+ occurs to give a neutral enol.

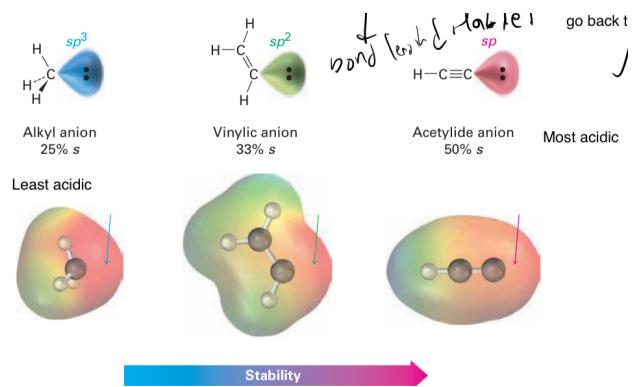


4

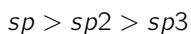
- 5 The enol undergoes tautomerization to give the final ketone product.



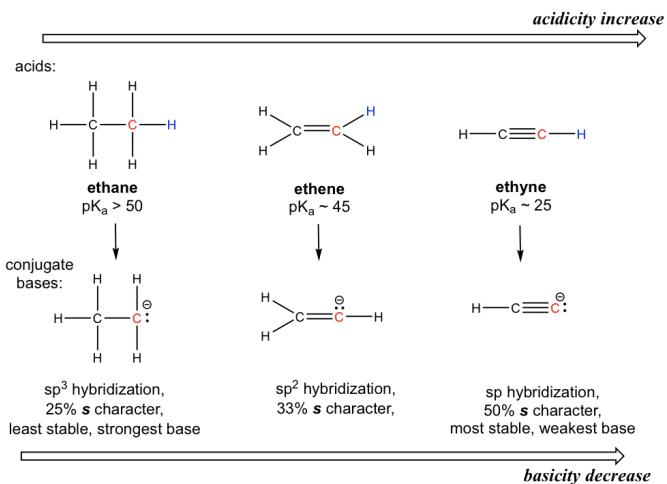
9.4 alkyne acidity: formation of acetylide anions



Think of the following anions as conjugate bases. A vinylic anion has an sp^2 hybridized carbon with 33% s character and an alkyl anion (sp^3) has only 25% s character. The main reason is that S orbitals are lower in energy than p orbitals so therefore acetylide anion stabilized negative charge/electrons the most meaning its corresponding acid the strongest. Refer to [MOC acidity factors](#) for more. From this we also know that the electronegativity of carbon is ranked in this order



again same reason, more s character, electron cloud closer to nucleus, lower energy.



10 reactions of alkyl halides: nucleophilic substitutions and eliminations

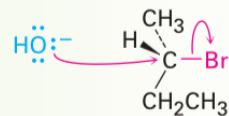
10.1 SN2

The mechanism

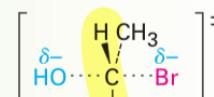
The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

1 The nucleophile ^-OH uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a transition state with a partially formed C-OH bond and a partially broken C-Br bond.

2 The stereochemistry at carbon is inverted as the C-OH bond forms fully and the bromide ion departs with the electron pair from the former C-Br bond.

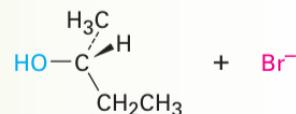


1

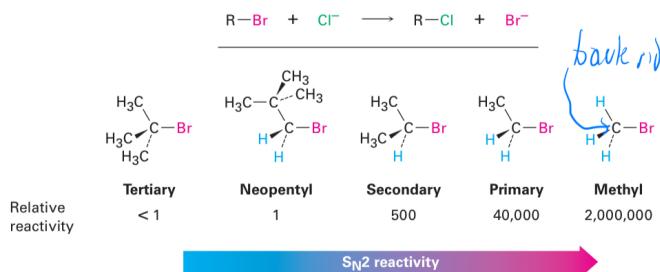


Think of it there

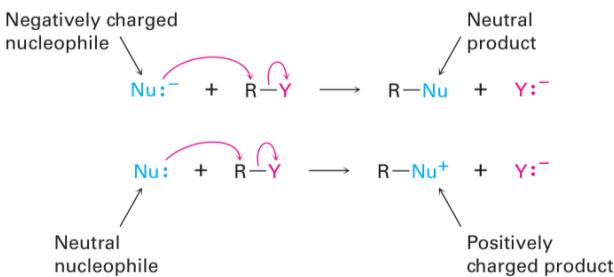
2



Factors that affect S_N2 . The substrate



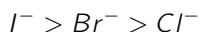
the nucleophile



Periodic trends that determine nucleophile suitability

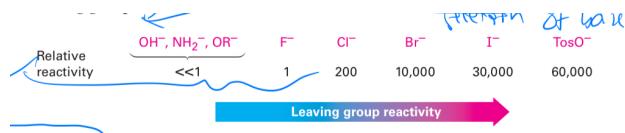
- nucleophilicity roughly parallels basicity

- nucleophilicity usually increases going down a column of the periodic table. Since their valence electrons are in successively larger shells where they are further away from the nucleus and hence less tightly held and consequently more reactive eg



- negatively charged nucleophiles are usually more reactive than neutral ones

the leaving group

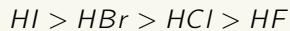


Periodic trends that determine a good leaving group

- the ones that best stabilize a negative charge in the transition state(see below) - that is weak bases like Tosolate, Cl^- , Br^- while strong bases such as OH^- , NH_2^- make poor leaving groups

Fact 21

In terms of acid strength in descending order we have



This is because the strength of the bond weakens down the group for halides.

- bond length. Down the group, the overlap becomes less proportionately as the bond increases so easier lose proton stronger acid
- electronegativity difference becomes smaller down the group so the bond strength goes down making it a stronger acid(lose proton more easily)

Remark 22. note the strength of bond is similar ranked in decreasing order for



again also the size of atom increases more than proportionately compared volume of orbital overlap resulting in decreasing bond strength(see saylor page 146 chapter 8.8)

what about its conjugate bases?

Fact 23

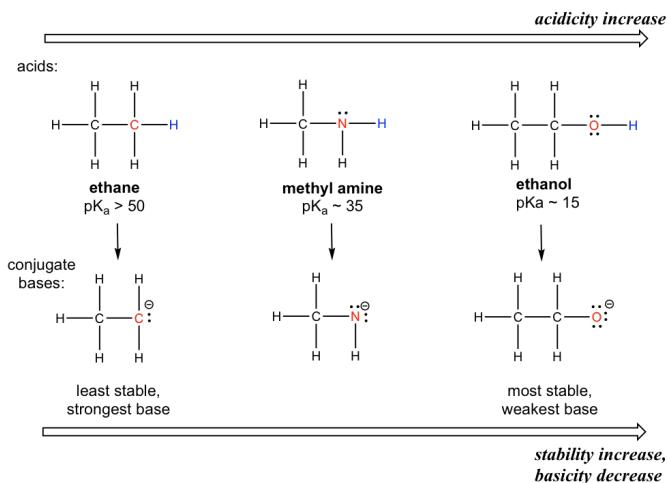
In terms of basicity in ascending order we have



Note that typically the more electronegative the weaker the base since less likely to give up electrons. However in this case charge density plays a bigger role than decreasing electronegativity here, I^- being the largest has the lowest charge density therefore making it a weaker base(less reactive,more stable) than F^-

Fact 24

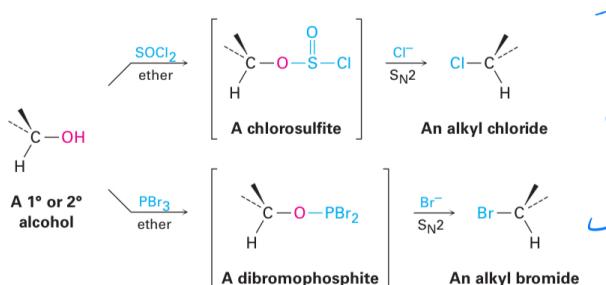
Hence now if you compare NH_2^- and OR^- since now same period, charge density and size plays a smaller role. Instead since O is more electronegative, it holds on negative charge more tightly making it a weaker base than NH_2^-



This figure was sourced from this [site](#) as well as some other figures used below

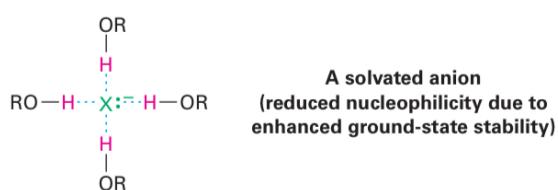
Remark 25. Notice that $S\text{N}2$ favours a stronger base(hence more reactive wanna give away electrons/accept proton attack C - **nucleophilic substitution**) as nucleophile and weaker base as leaving group. But not too strong...or $E2$ will dominate instead see below for more

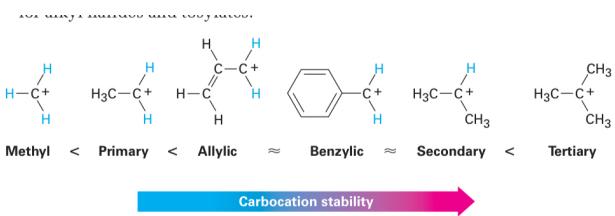
So typically poor leaving groups like OH don't undergo $S\text{N}2$ hence it is necessary to convert them into better leaving groups to do so like this Convert OH to good leaving group.



We will discuss this more in the alcohols section below.

Now finally the last factor that determines suitability of $S\text{N}2$ is the solvent. Typically **protic solvents**(those that contain $-OH$ or $-NH$ group ar generally the worst for $S\text{N}2$ reactions while **polar aprotic solvents**(which are polar but don't have an $-OH$ or NH group are the best)



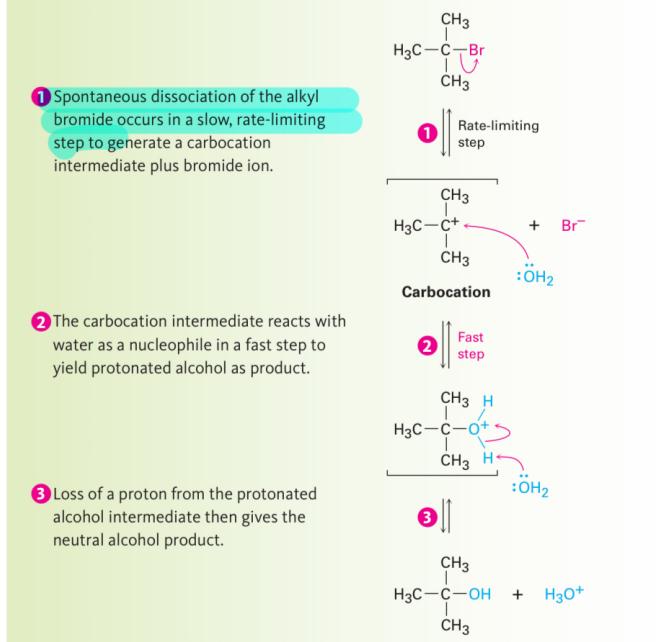


Polar aprotic solvents such as DMSO, acetone, DMF and acetonitrile are often chosen for SN2 reactions since they are polar enough to dissolve the reaction partners, but cannot form hydrogen bonds to the nucleophile which are the only intermolecular forces strong enough to solvate and "cage" the nucleophile

10.2 SN1

Consider the mechanism of SN1

The mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H_2O involves three steps. Step ①—the spontaneous, unimolecular dissociation of the alkyl bromide to yield a carbocation—is rate-limiting.

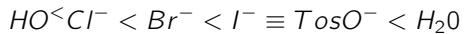


Unlike what occurs in an SN2 where the leaving group is displaced while the incoming nucleophile approaches the SN1 reaction takes place by loss of the leaving group spontaneously before the nucleophile approaches. This means the first step of spontaneous dissociation is a rate limiting step. Now then the favourability of the reaction depends on the stability of the intermediate state upon the loss of the leaving group which in this case is the carbocation but recall from 7.4 that the more methyl substituted the molecule the more the stable the alkyl carbocation is due to **hyperconjugation** 17. To this list we extend it to **allyl** cations. Consider See that the stabilization of allylic and benzyl carbocations are due to resonance stabilization. Why it is specifically in the middle and lesser than tertiary idk.

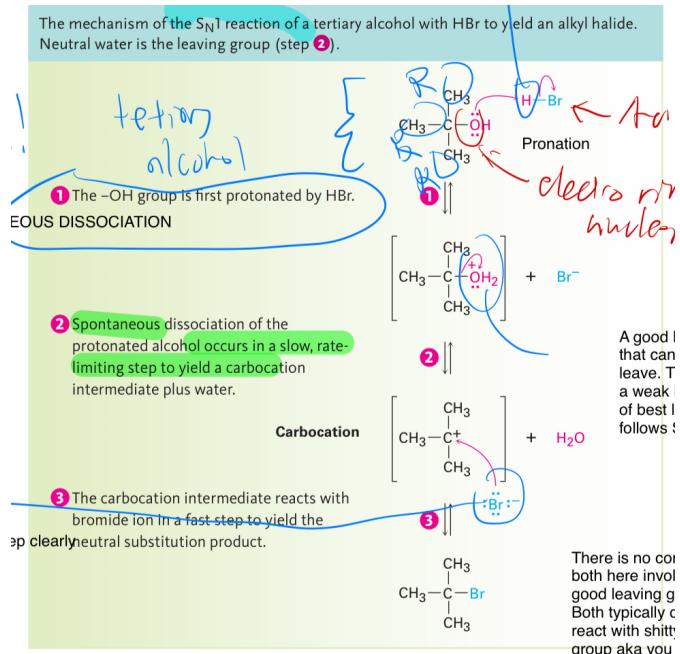
Remark 26. Notice that this is the exact opposite of SN1 which would like more substituted, ring substrates due to steric effects which block the nucleophilic attack!

However for **leaving groups** they follow the same trend as SN2 that is the more stable the conjugate base the

better the leaving group so in ascending order of leaving group suitability we have

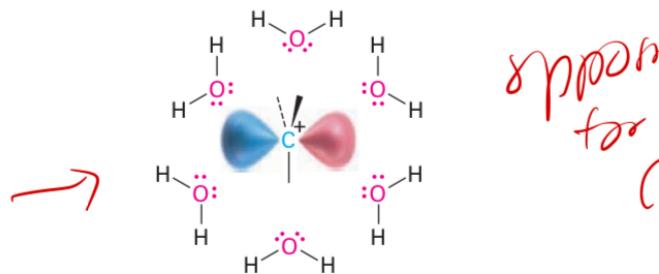


note that this time unlike SN2 we have H_2O at the end because SN1 is often carried out under acidic conditions so neutral water is sometimes the leaving group. To illustrate this consider



Comparing with 10.1 See that this is another way to turn OH into a better leaving group but SN1 version. Now as for the **nucleophile** since the first step is by spontaneous rate limiting step, the nucleophile does not play a major role in SN1. That is regardless if X is Cl , Br , or I SN1 proceeds at same rate.

Finally we discuss the **solvent**. This time unlike SN2, SN1 favours protic solvents because it solvates the carbocation(since can form hydrogen bonds) lowering its transition state energy and making it more stable.



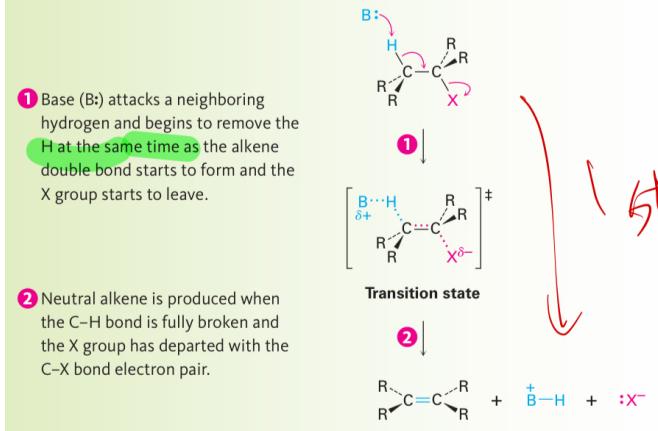
recall that this is not applicable to SN2 which happens in one step (there is not carbocation). Instead it's transition state is some kind of partial charge between the leaving and attacking group refer above.

10.3 the E2 reaction and the deuterium isotope effect

Consider the E2 mechanism. This occurs in a single step under strongly basic conditions. Also like SN2 that happens in a single step by nucleophilic attack so it would prefer an polar aprotic solvent that will not form hydrogen bonds

with the anion and solvate it

Mechanism of the E2 reaction of an alkyl halide. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.



Note the use of the word strongly basic. Experimentally SN2 substitution occurs if a weakly basic nucleophile is used in a polar aprotic solvent. E2 elimination predominates if a strong base is used. Think about it, im so strong i not just will attack the carbon imma also rip the H off the carbon too.

10.4 the e1 and e1cb reactions

Unlike e2 it is not 1 step. it is has 2, the first begin rate limiting. You can see how the relationship between e1 and e2 is an anlogue of that of sn1 vs sn2. Therefore the best e1 substrates are also the best sn1 substrates.

MECHANISM

Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.

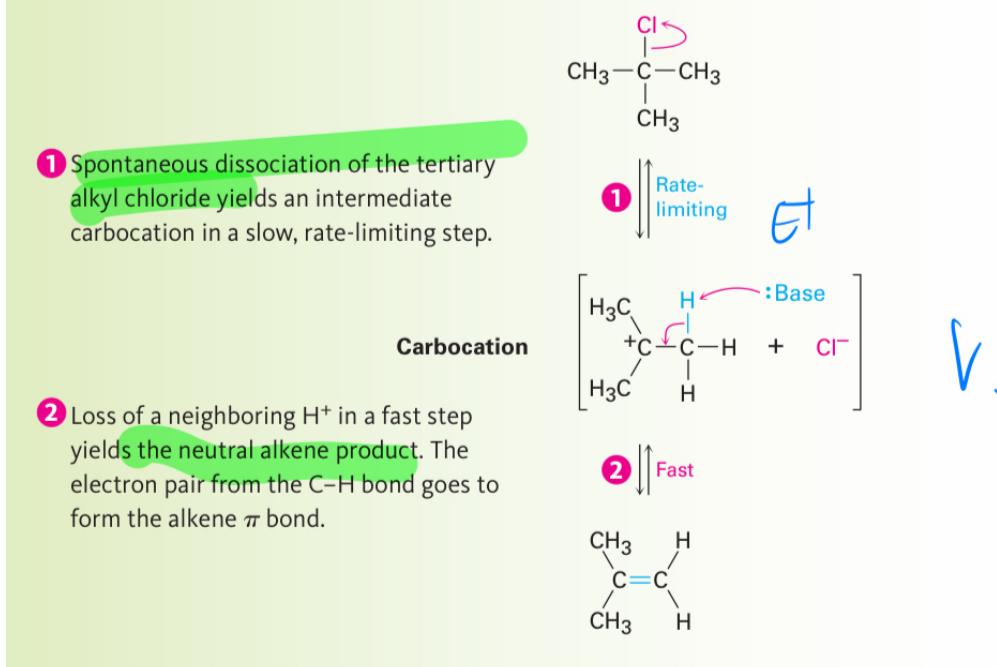


Figure 6: e1

In contrast to the e1 reaction which involves a carbocation intermediate the e1cb reaction takes place through a **carbonion intermediate** which has an anion instead.

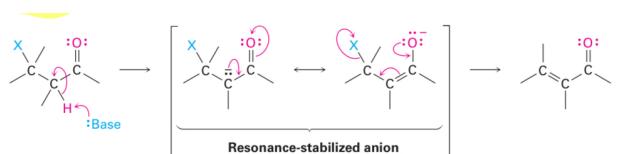


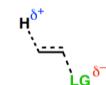
Figure 7: e1cb

This reaction typically happens when the substrates involved have a poor leaving group such as -OH and two carbons are removed from a carbonyl group. The poor leaving group then disfavours the alternative E1 and E2 possibilities while the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of the anion intermediate.

10.5 E1 vs E2 vs E1cb

You could see E1 and E1cb as the 2 extremes and E2 as the middle

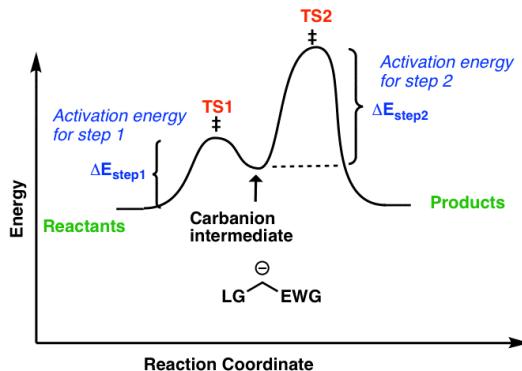
Comparing the E1, E2, and E1cB Mechanisms

E1	E2	E1cB
Two steps	One step	Two steps
1) C–LG breaks 2) C–H breaks C–C (pi) forms	C–H breaks, C–C (pi) forms C–LG breaks, all at same time	1) C–LG breaks 2) C–C (pi) forms
		
Carbocation intermediate Carbocation stabilized by electron donating groups Assisted by good leaving groups No strict requirement on stereochemistry of C–H and C–LG	No intermediate (concerted)	Carbanion intermediate Carbanion stabilized by electron withdrawing groups Assisted by poor leaving groups No strict requirement on stereochemistry of C–H and C–LG

Comparing their reaction coordinate we have

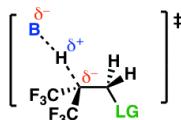
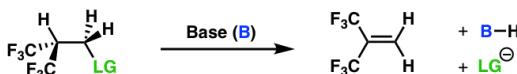
Reaction Coordinate Diagram For An E_{cB} Reaction

*for a case where deprotonation is fast, and elimination is slow

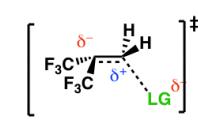


• **Step 2 is rate determining.** The activation energy for Step 2 (elimination, $\Delta E_{\text{step}2}$) is greater than that for Step 1 (deprotonation to give carbanion, $\Delta E_{\text{step}1}$)

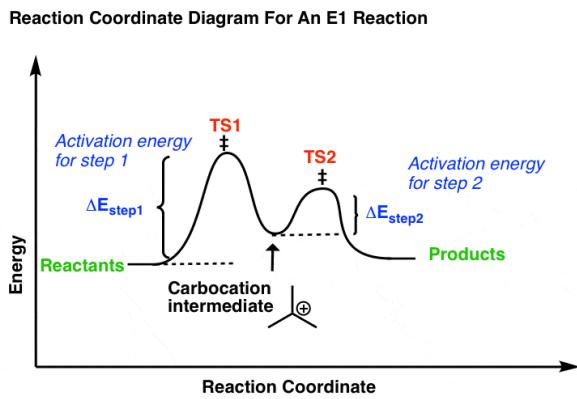
For example



Transition state 1 (**TS1**)
Deprotonation to give carbanion (fast step)

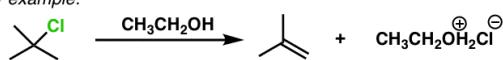


Transition state 2 (**TS2**)
Formation of pi bond with loss of leaving group (rate determining step)

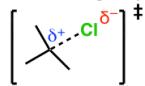


- **Step 1 is rate determining.** The activation energy for Step 1 (loss of leaving group to give the carbocation, $\Delta E_{\text{step}1}$) is greater than that for Step 2 (elimination, $\Delta E_{\text{step}2}$)

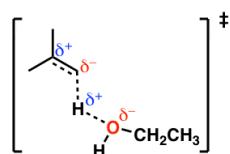
for example:



Transition state 1 (**TS1**)
Loss of leaving group
(Rate determining step (slow))

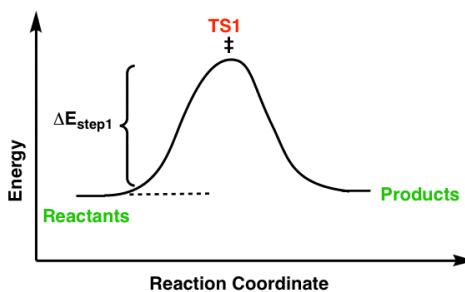


*Transition state 2 (**TS2**)
Elimination reaction
(fast step)*



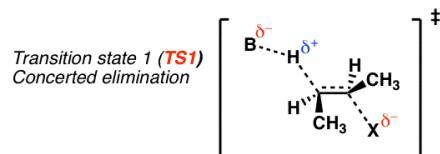
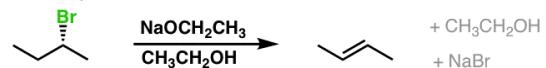
See that E1 and E1cb reaction coordinate diagrams are mirror images of each other because for the former the 1st step is rate determining while for the latter it is the second step that is rate determining. See how all this makes sense now, the lousy leaving group makes it the "spontaneous rate determining step" of E1cb which is analogous to the first step of E1. The acidic alpha hydrogen makes the 1st step fast, which is the analogous of the 2nd step for E1 since the nucleophile wants to add to the electrophilic carbocation asap which makes the 2nd step fast.

Reaction Coordinate Diagram for an E2 Reaction



- There is only one step. The reaction proceeds from reactants to products through the transition state TS1 with activation energy ΔE_1

for example:



As for E2 it is only 1 step with no transition state so there is only 1 peak.

11 benzene and aromaticity

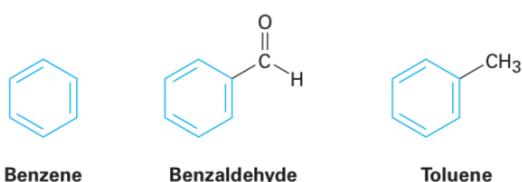
11.1 naming aromatic compounds

Definition 27

we use the word **aromatic** to refer to the class of compounds that contain six membered like rings with three double bonds.

Example 28

For example



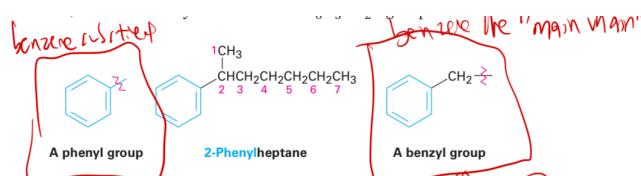
Consider the following common names of some aromatic compounds

TABLE 15-1 Common Names of Some Aromatic Compounds

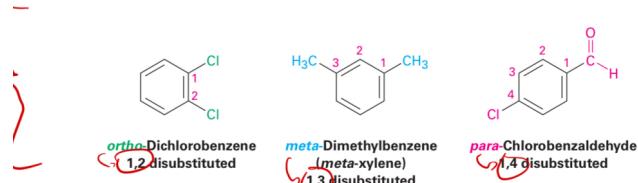
Structure	Name	Structure	Name
	Toluene (bp 111 °C)		Benzaldehyde (bp 178 °C)
	Phenol (mp 43 °C)		Benzoic acid (mp 122 °C)
	Aniline (bp 184 °C)		<i>ortho</i> -Xylene (bp 144 °C)
	Acetophenone (mp 21 °C)		Styrene (bp 145 °C)

Fact 29

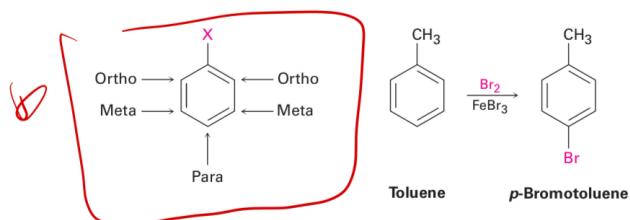
Alkyl substituted benzenes are sometimes referred to as **arenes**. The name **phenyl** is used for the $-C_6H_5$ unit when the benzene ring is considered a substituent



Note that disubstituted benzenes are named using the prefixes **ortho(o),meta(m),para(p)**



'where the positions are defined at

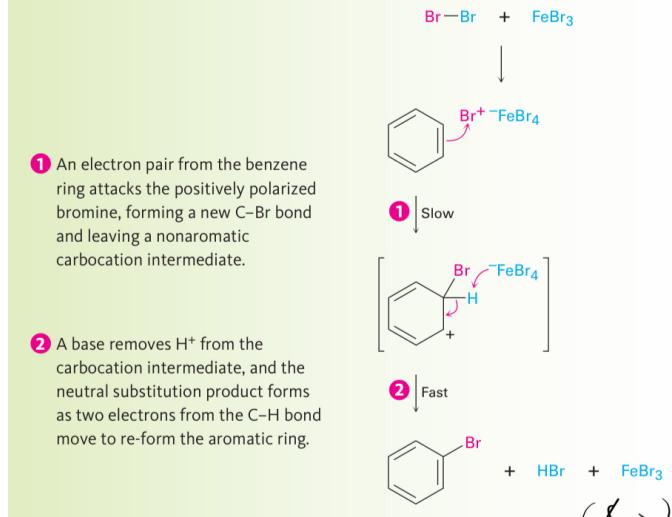


12 chemistry of benzene: electrophilic aromatic substitution

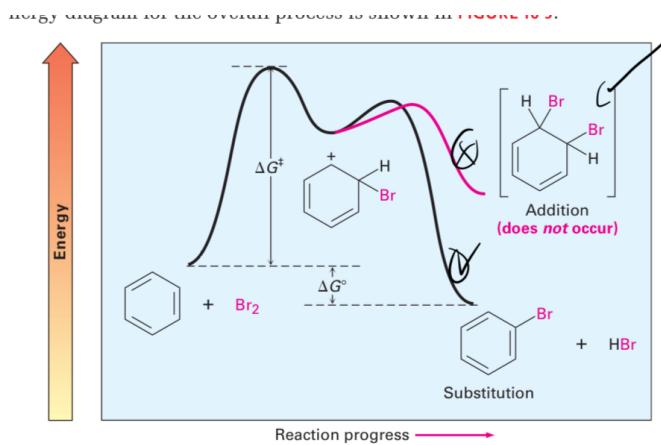
12.1 electrophilic aromatic substitution reactions: bromination

Consider the mechanism

The mechanism for the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.



You might be wondering unlike akenese why thet second step doesnt get addition but instead we get substitution. Consider that substitution retains the aromatic ring and hence resonance stabilization. note that FeBr_3 gives Br^+ more electrophilic in order to catalyze the raction.



12.2 alkylation and acylation of aromatic rings: the friedel crafts reaction

Consider recall akyllation(7)

FIGURE 16-7

MECHANISM

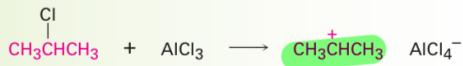
Mechanism for the Friedel-Crafts alkylation reaction of benzene with 2-chloropropane to yield isopropylbenzene (cumene). The electrophile is a carbocation, generated by AlCl₃-assisted dissociation of an alkyl halide.

You see why AlCl₃ needed now? If even C=O (the rest all hydrocarbons like in ketones and aldehydes) electronegativity difference not enough unless catalyzed

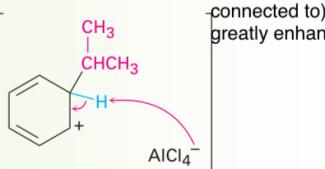
Then what say for C-Cl which is even worse aromatic ring attacks the carbocation, forming a C-C bond and yielding a new carbocation intermediate.

- ② Loss of a proton then gives the neutral alkylated substitution product.

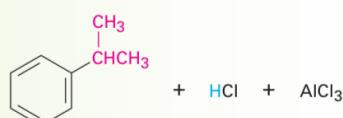
Now you begin to see pattern this just nucleophilic addition! Clearly the rest of hydrocarbons (all just R groups) all are shitty leaving groups. So no substitution



①



②

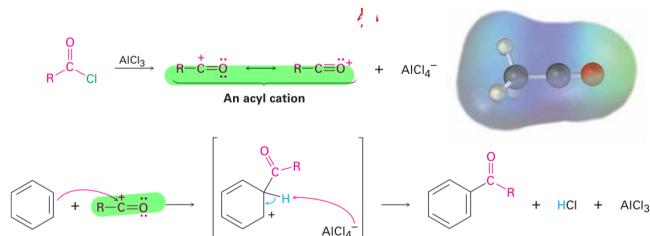


Electrophilicity of C (where a an electronegative element was connected to) here is now greatly enhanced

Note that AlCl₃ plays the same kind of role as FeBr₃ in 12.1. Both are lewis acids 3. Also again substitution instead of addition since the ring is preserved. However for only **alkyl halides** can be used. We cannot use **aryl** or **vinylic** halides as aryl and vinylic carbocations are too high in energy to form under freidel crafts conditions

Remark 30. This is because the CX bonds is on a c that is sp² compared to sp³ for alkyl and acyl. Now since sp² is more more s character it is shorter and thus the bonds are stronger. Moreover it is less effective at stabilizing a positive charge on carbon. Recall more s character the better it stabilizes neg charge because lower energy orbital? Because of this it holds on to its electrons more tightly is less willing to accomodate a positive charge.

As hinted by the title the above friedel crafts works for **acyl halides** too



Again it requires a lewis acid to polarize the carbon atom, "activating it"

12.3 substituent effects in electrophilic substitutions

Note that substituents affect both the *reactivity* and *orientation* of the reaction

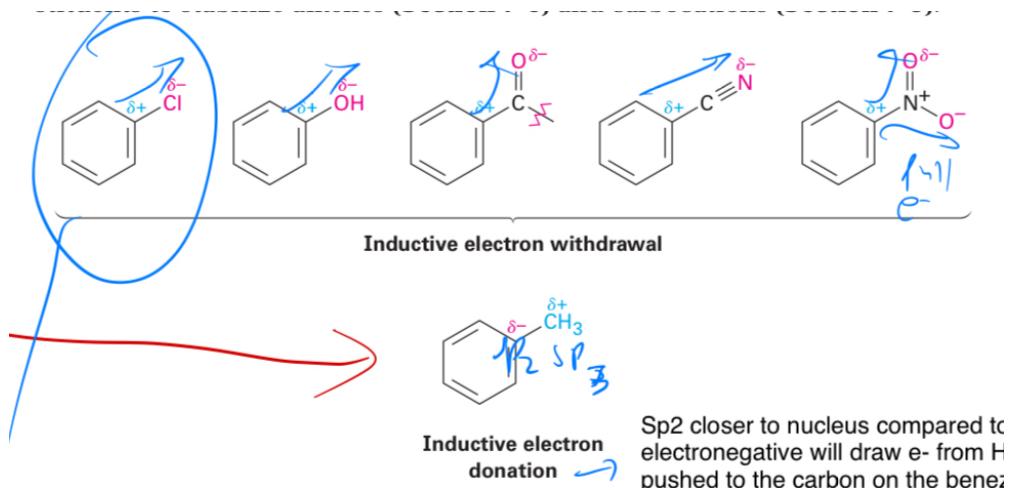
Fact 31

The common characteristic of **activating groups** is that they donate electrons to the ring thereby making the ring more electron rich stabilizing the carbocation intermediate. Conversely the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron poor, destabilizing the carbocation intermediate and raising the activation energy for its formation.

The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive* and *resonance* effects

Definition 32

the **inductive effect** is an withdrawal or donation of electrons through a σ bond due to electronegativity.

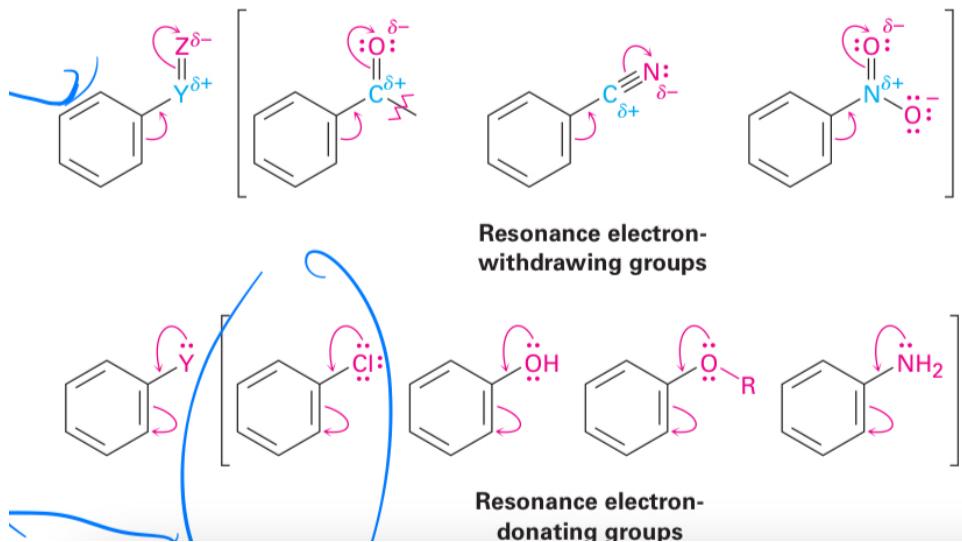


CH_3 is electron donating, to see this consider the electronegativity difference between the sp₂ ring carbon and the sp₃ c in ch₃. Hint recall 9.4

Remark 33. in the inductive electron donation example of alkyl notice that this is the same **hyperconjugation** donating effect we discussed in 17

Definition 34

a **resonance effect** is the withdrawal or donation of electrons through a π bond due to the overlap of a p orbital on the substituent with a p orbital on the aromatic ring



Remark 35. Note that oxygen is more electronegative than nitrogen. Recall "NOF"

Note that substituents with an electron withdrawing resonance effect have the general structure $-Y = Z$ where the Z atom is more electronegative than Y . This is a movement of lone pairs

Notice there are a few conflicts for example Cl according to the diagrams above is both resonance electron donating and inductive withdrawing. So is it withdrawing or donating? Turns out,

Fact 36

hydroxyl(-OH) alkoxyl(-RO) and amino(-NH₂) substituents are activators because their strong electron donation resonance effect outweighs their weaker electron withdrawing inductive effect.

Halogens(Cl, Br, I) however are deactivators because their stronger electron withdrawing inductive effect outweighs their weaker electron-donation resonance effect

Note that this is because in general elements in 3rd period and beyond due to poor overlap with the 2p carbon orbital. Eg. Cl is 3p overlap with 2p. However fluorine is an exception since it has both good overlap 2p and 2p and also very electronegative relative to carbon. So according to wikipedia in some positions the ring is deactivated while in others activated. Note for the case of N and O there is good orbital overlap so resonance effect outweighs (after all resonance effect is throughout, while the inductive is just local)

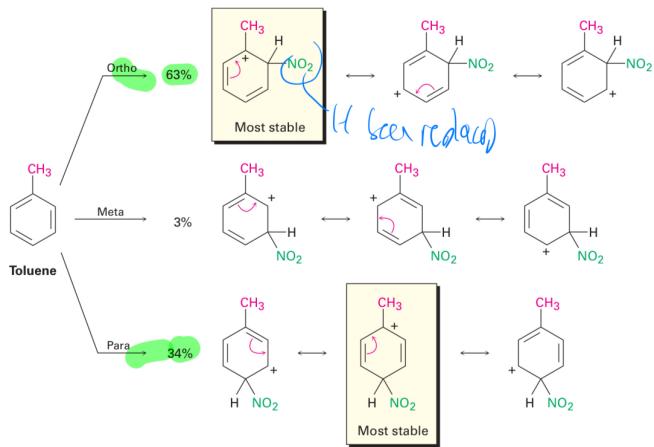


Figure 8: Ortho para directing activators: alkyl groups

See that when directly attached on the methyl substituted carbon can be stabilized by electron donating inductive effect of the methyl group.

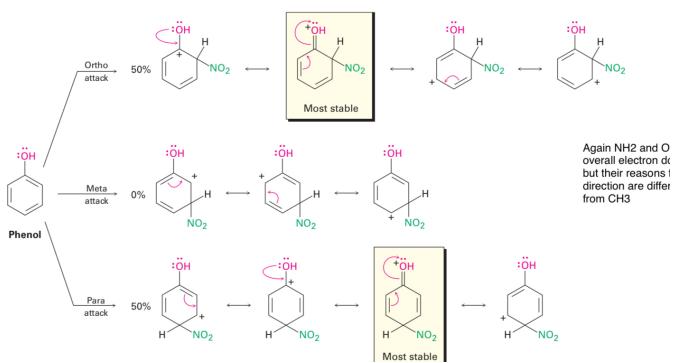


Figure 9: Ortho and para directing activators; OH and NH₂

Similarly can be stabilized by resonance donating resonance effect of the OH group at those positions.

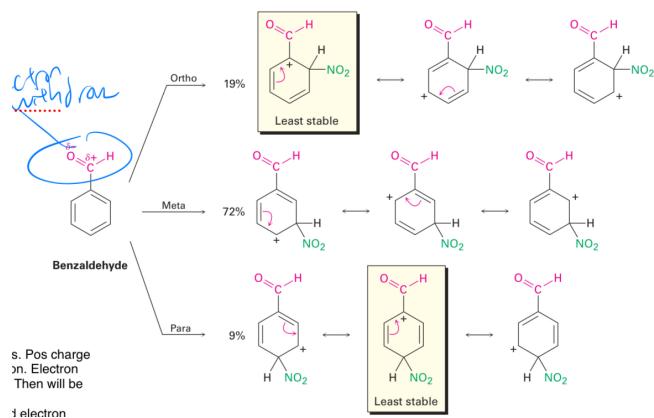
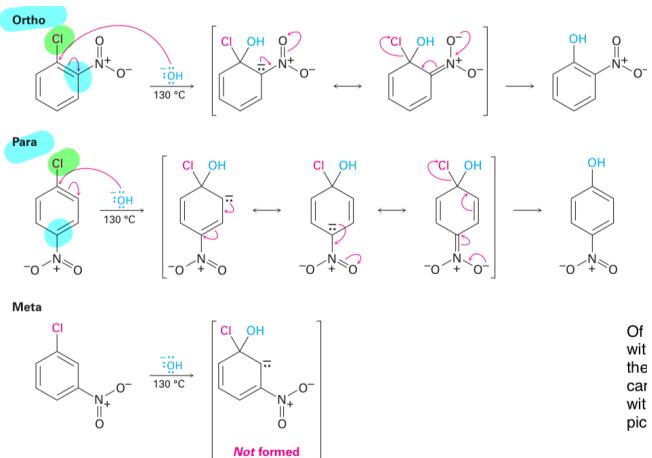


Figure 10: meta directing deactivators

however at those positions there is repulsion between the positive charge and the positively polarized carbon the aldehyde group.

12.4 nucleophilic aromatic substitution



Note that nucleophilic aromatic substitution occurs only if the aromatic ring has an *electron-withdrawing substituent* in a position *ortho* or *para* to the leaving group to stabilize the anion intermediate through resonance.

13 alcohols and phenols

13.1 naming alcohols and phenols



First find the longest chain containing the hydroxyl group. Essentially like alkenes you have to specify the position of their hydroxyl groups and if there are multiple have to put the prefixes to such as "1-4 **diol**"

13.2 properties of alcohols and phenols

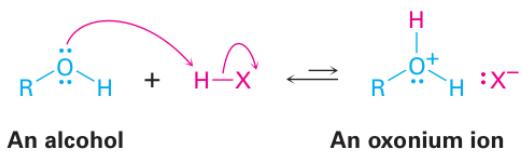


Figure 11: Alcohols as base

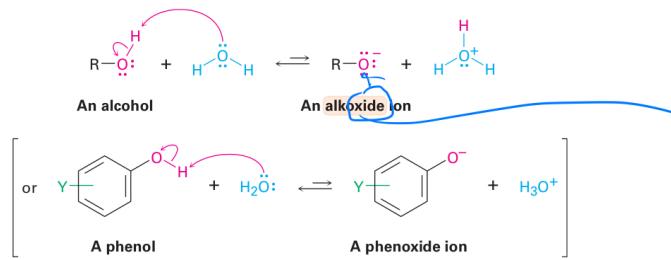
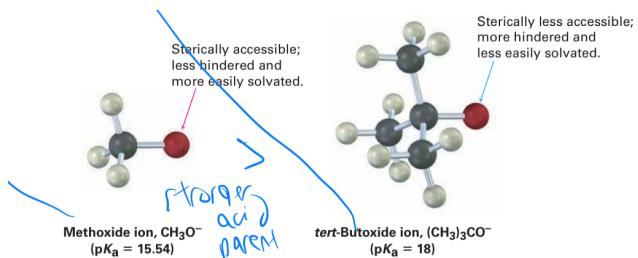


Figure 12: Alcohols as acids

acidity of alcohol is mainly due to solvation of the conjugate base. For example



less sterically hindered more easily solvated so associated acid more acidic. Also electron withdrawing groups can stabilize the alkoxide ion by spreading the charge over a larger volume stabilizing the conjugate base so its associated acid is more acidic.

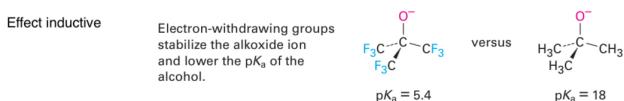
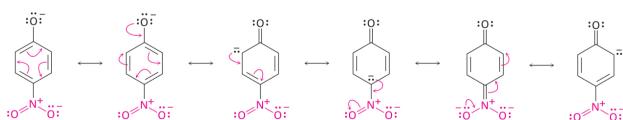


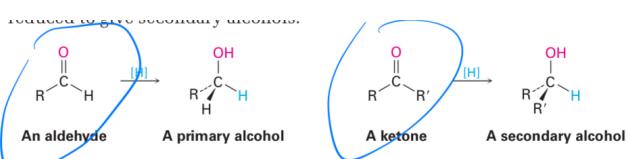
Figure 13: Caption

Phenols tend to even more acidic due to resonance. This acidity could be even enhanced further if the phenol is substituted with electron withdrawing groups



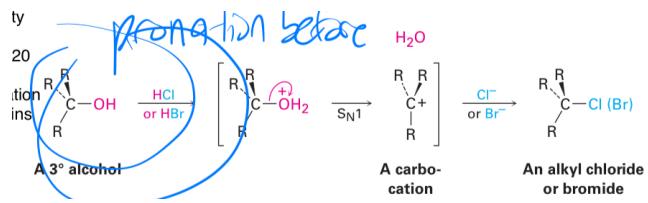
which further delocalizes the negative charge. In contrast phenols with electron donating groups are less acidic because it concentrates the negative charge instead.

13.3 alcohols from carbonyl compounds reduction

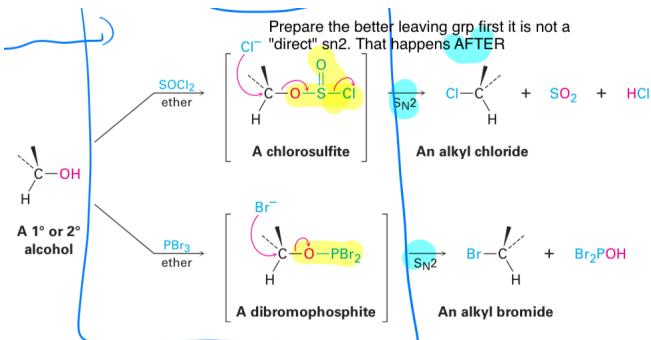


13.4 reactions of alcohols

Conversion of **alcohols into alkyl halides**. Via SN1 we have



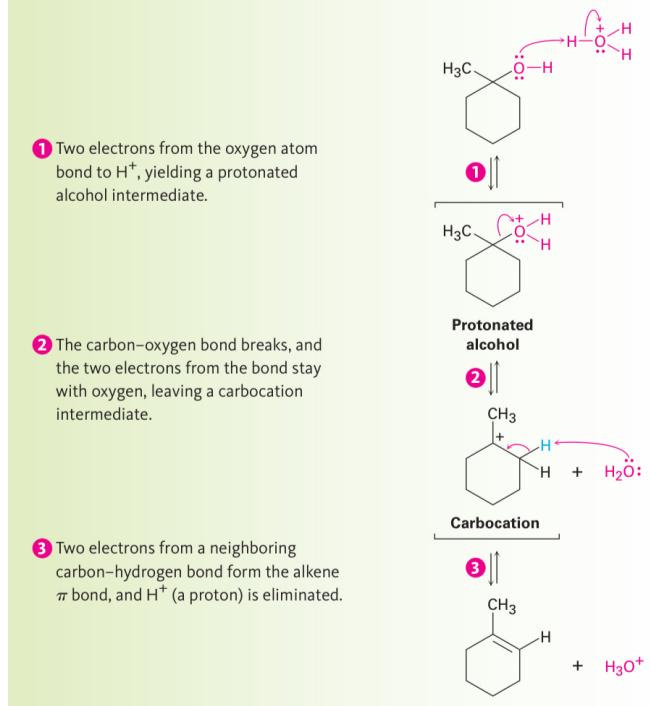
Recall how we have also discussed another way to convert OH into better leaving group using SOCl_2 or PBr_3 . That is precisely the SN2 way to convert alcohols into alkyl halides:



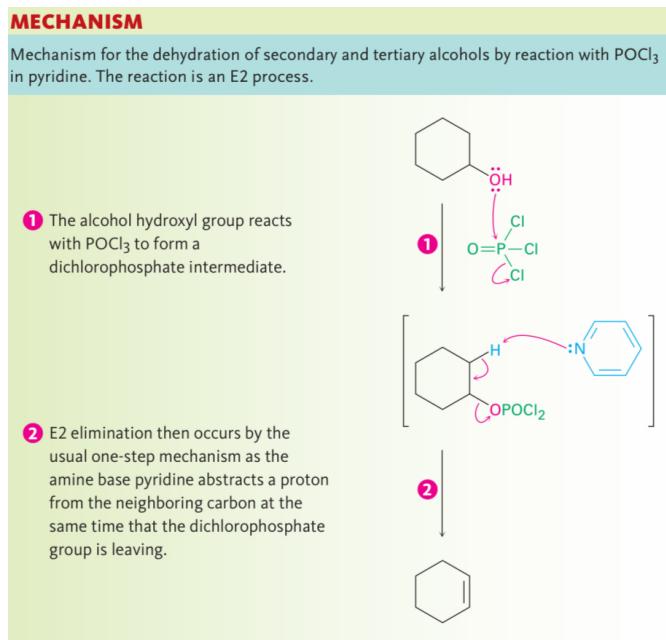
As for **dehydration** to E1 equivalent is

MECHANISM

Mechanism for the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.



and the e₂ equivalent is



13.5 oxidation of alcohols

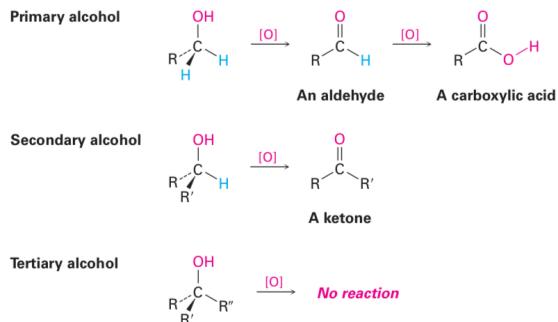
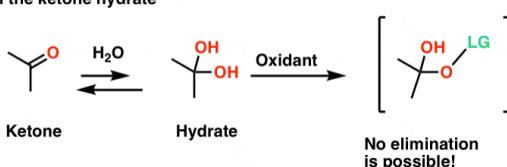


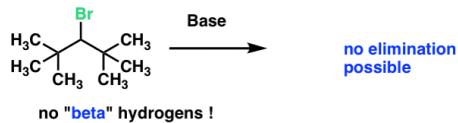
Figure 14: overview

So why don't ketones oxidize further?
Because there's no hydrogen that can be removed to form a new pi bond on the ketone hydrate

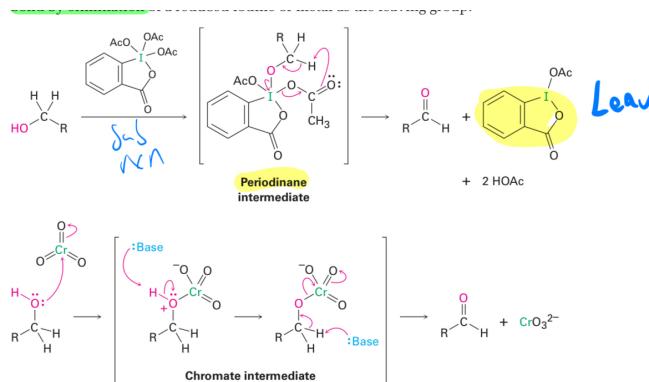


Same situation as

Similar to why E2 reactions don't happen on this alkyl halide

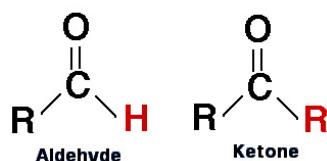
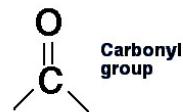


13.6 dessmartin



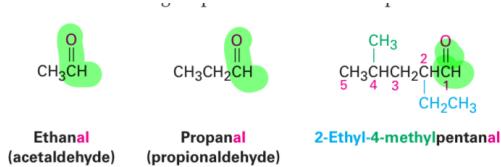
Just think of this as an E2 reaction with iodine or metal as the leaving group

14 aldehydes and ketones



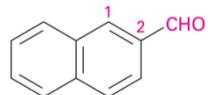
14.1 naming aldehydes and ketones

Aldehydes are named by replacing the terminal -e of the corresponding alkane name with -al. (Note in contrast to ketone one end must end with a H)



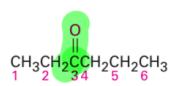


Cyclohexane**carbaldehyde**

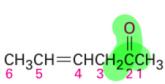


2-Naphthalene carbaldehyde

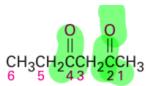
As for ketones



3-Hexanone
(New: Hexan-3-one)



4-Hexen-2-one
(New: Hex-4-en-2-one)

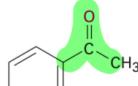


2,4-Hexanedione
(New: Hexane-2,4-dione)

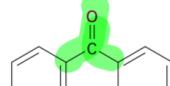
A few ketones are allowed by IUPAC to retain their common names.



Acetone



Acetophenone



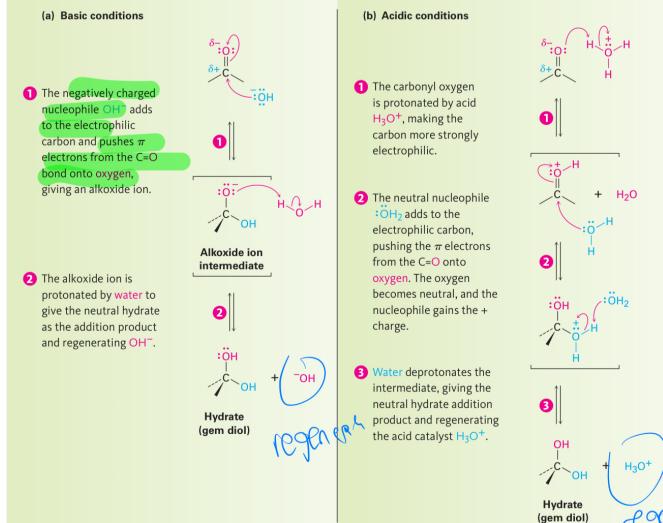
Benzophenone

Same kind of naming methods as the other group, gotta identify where the carbonyl are, if have multiple put the prefix in etc

14.2 nucleophilic addition

MECHANISM

The mechanism for a nucleophilic addition reaction of aldehydes and ketones under both basic and acidic conditions.
 (a) Under basic conditions, a negatively charged nucleophile adds to the carbonyl group to give an alkoxide ion intermediate, which is subsequently protonated. (b) Under acidic conditions, protonation of the carbonyl group occurs first, followed by addition of a neutral nucleophile and subsequent deprotonation.



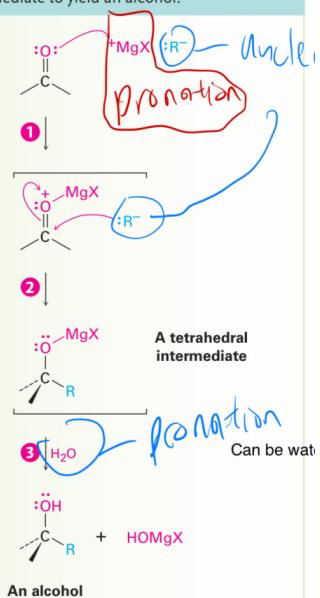
MECHANISM

Mechanism of the Grignard reaction. Complexation of the carbonyl oxygen with the Lewis acid Mg^{2+} and subsequent nucleophilic addition of a carbanion to an aldehyde or ketone is followed by protonation of the alkoxide intermediate to yield an alcohol.

- 1 The Lewis acid Mg^{2+} first forms an acid–base complex with the basic oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better acceptor.

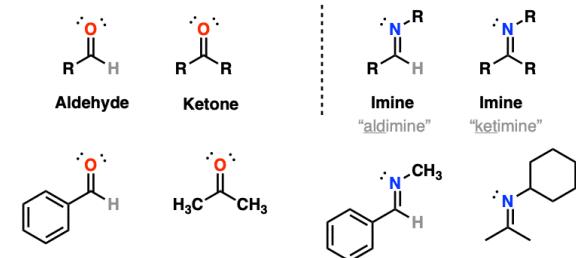
- 2 Nucleophilic addition of an alkyl group $:R^-$ to the aldehyde or ketone produces a tetrahedral magnesium alkoxide intermediate ...

- ... which undergoes hydrolysis when water is added in a separate step. The final product is a neutral alcohol.



14.3 imide and emamine formation

Imines are the nitrogen-containing “cousins” of aldehydes and ketones



Remark 37. we also call an imine a schiff base

MECHANISM

Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is the initial nucleophilic addition to yield a carbinolamine intermediate, which then loses water to give the imine.

① Nucleophilic attack on the ketone or aldehyde by the lone-pair electrons of an amine leads to a dipolar tetrahedral intermediate.

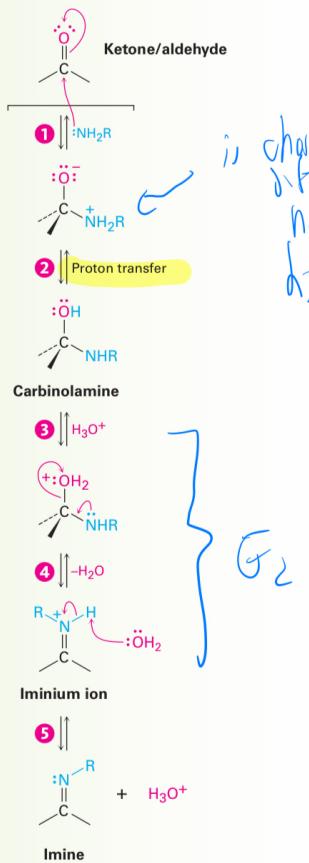
② A proton is then transferred from nitrogen to oxygen, yielding a neutral carbinolamine.

③ Acid catalyst protonates the hydroxyl oxygen.

Also making it a better leaving group

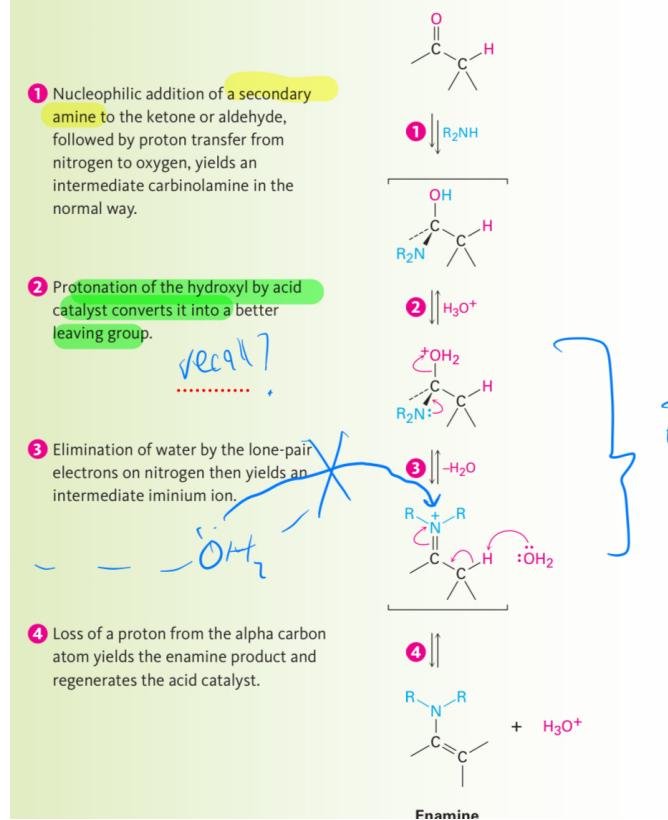
④ The nitrogen lone-pair electrons expel water, giving an iminium ion.

⑤ Loss of H⁺ from nitrogen then gives the neutral imine product.



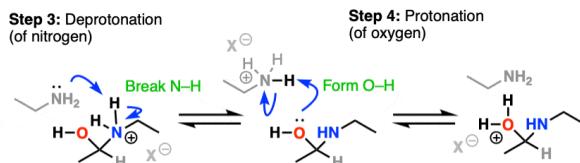
MECHANISM

Mechanism for enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH . The iminium ion intermediate formed in step 3 has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.



14.4 proton transfer

Note on proton transfer mech



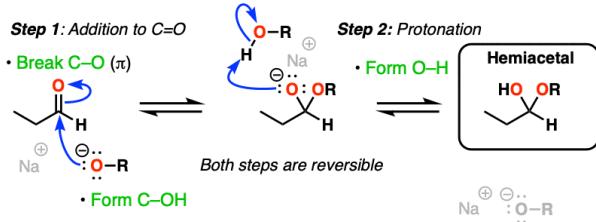
Together, steps 3 and 4 are generically called "proton transfer". The specific identity of the base (in step 3) and acid (in step 4) is generally not important, so it's OK to write B and $B-H$.

recall here that NH_2 is a strong resonance electron donating group. Secondly proton transfer via this "proton shuttle" is justified because **it results in a better leaving group**. Note that acid base reactions are all proton transfer events.

14.5 nucleophilic addition of alcohols: acetal formation

First consider the formation of hemiketal under basic conditions. We can do so under acidic conditions too. see below.

Mechanism: Hemiacetal Formation Under Basic Conditions

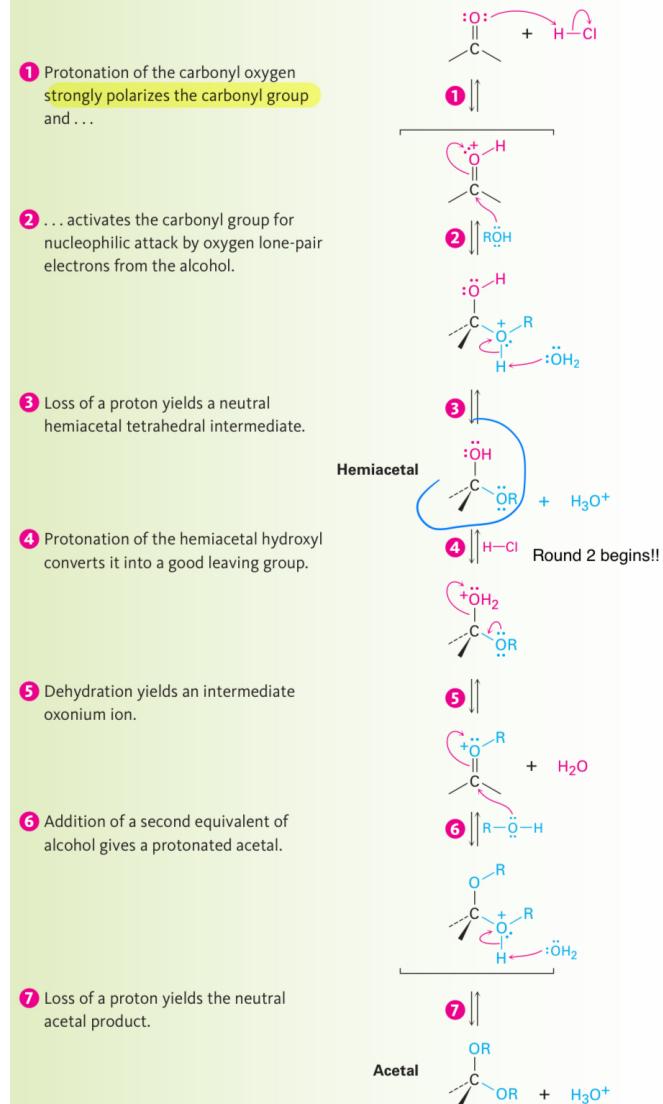


Overview

Overview - Hydrates, Hemiacetals, Acetals		
	$\xrightleftharpoons{H_2O}$	
		Hydrate
		<ul style="list-style-type: none"> • can be formed under basic, neutral, acidic conditions • equilibrium tends to favor aldehyde or ketone
	\xrightleftharpoons{ROH}	
		Hemiacetal
		<ul style="list-style-type: none"> • formed under basic, neutral, acidic conditions • equilibrium tends to favor aldehyde or ketone • cyclic hemiacetals possible
	$\xrightleftharpoons[H_3O^+]{ ROH / H^+ }$	
		Acetal
		<ul style="list-style-type: none"> • acetals formed from aldehyde/ketone by using alcohol (ROH) and H^+ • once formed, not in equilibrium with starting aldehyde/ketone • inert to nucleophiles • great protecting group; can be removed with aqueous acid

The last condition is specifically excess ROH and an acid catalyst H^+ . So essentially we have basic conditions. In that case as you will learn in biochemistry 1 . But once formed acetals in basic conditions do not proceed with the reverse reaction to get back hemiacetal unlike acidic conditions as shown below. To see why first consider that acetal has no good leaving groups. Secondly it does not have a carbonyl carbon(electrophilic site) where an $SN2$ addition can occur. well you require the double bond because to add to a carbonyl carbon(forming a bond with it) you need to break an existing bond of the carbonyl or you are going to violate octet. And clearly there are no double bonded carbonyl oxygen - carbon pair anywhere in acetal.

Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.

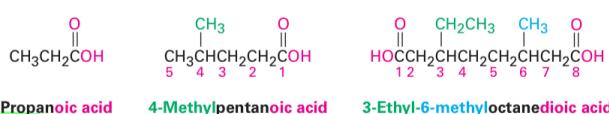


15 carboxylic acids and nitriles

15.1 naming carboxylic acids and nitriles

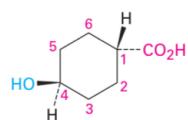
Definition 38

carboxylic acids take the form RCO_2H where R consists of C, H eg. $-\text{CH}_3, -\text{CH}_2\text{CH}_3$

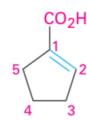


Essentially like the other groups find the longest chain containing CO_2H and by default it is labelled 1. And note we

also have identify the location of the CO_2H and add the prefix when there are multiple in the chain such as dioicacid.
As a substituent the CO_2H group is called a **carboxyl group**



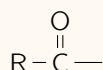
trans-4-Hydroxycyclohexanecarboxylic acid



1-Cyclopentenecarboxylic acid

Definition 39

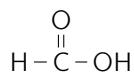
Acyl is basically CO_2H but with OH removed that is



The common names of some carboxylic acid and acyl groups are

Structure	Name	Acy group
HCO_2H	Formic	Formyl
$\text{CH}_3\text{CO}_2\text{H}$	Acetic	Acetyl
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	Propionic	Propionyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Butyric	Butyryl
$\text{HO}_2\text{CCO}_2\text{H}$	Oxalic	Oxaryl
$\text{HO}_2\text{CCH}_2\text{CO}_2\text{H}$	Malonic	Malonyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Succinic	Succinyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Glutaric	Glutaryl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Adipic	Adipoyl

Note the first group is just this but add CH_2 to the chain successively

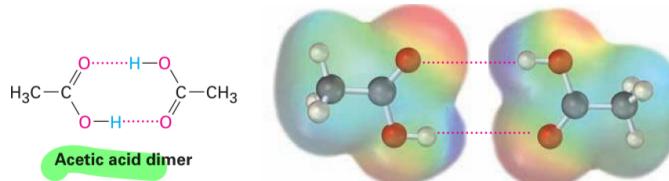
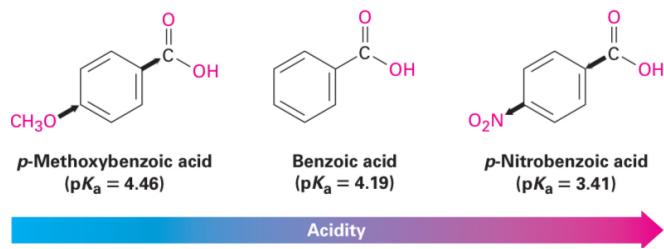


Note the second group is just this but add CH_2 to the chain successively



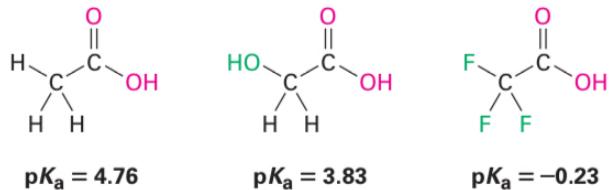
15.2 structure and properties of carboxylic acids

Note the carboxylic acids tend to have higher boiling points as they hydrogen bondedd dimers.

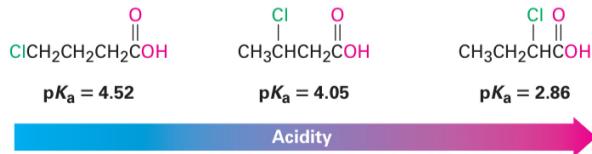


The most obvious property of carboxylic acids is implied by their na

15.3 substituent effects on acidity



The 3 electron withdrawing fluorine atoms delocalize the negative charge in the trifluoroacetate anion thereby stabilizing the ion and increasing acidity. Which can also seen as making the carbonyl carbon more electrophilic.



The halogen substitution decreases as the substituent moves further from the carboxyl. Similar trend for phenol substituents. Note that CH_3O is activating while NO_2 is withdrawing.

16 carboxylic acid derivatives: nucleophilic acyl substituent reactions

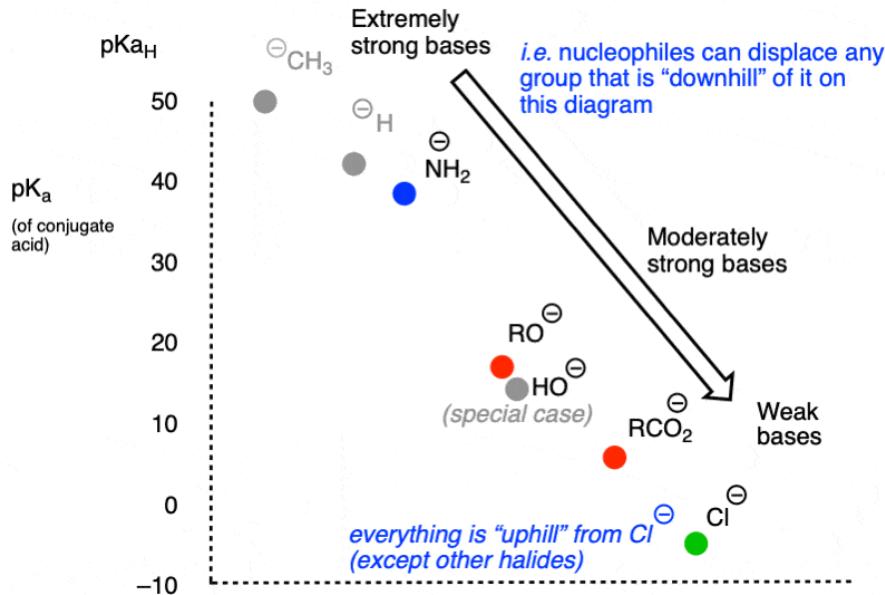
16.1 naming carboxylic acid derivatives

TABLE 21-1 Nomenclature of Carboxylic Acid Derivatives

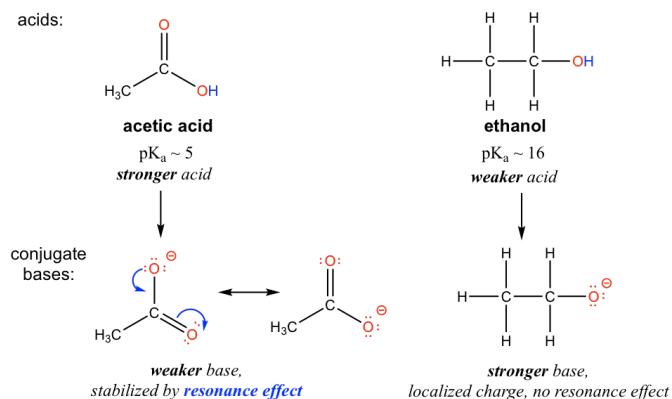
Functional group	Structure	Name ending
Carboxylic acid		-ic acid (-carboxylic acid)
Acid halide		-oyl halide (-carbonyl halide)
Acid anhydride		anhydride
Amide		-amide (-carboxamide)
Ester		-oate (-carboxylate)
Thioester		-thioate (-carbothioate)
Acyl phosphate		-oyl phosphate

In general the reactivity order follows. Essentially as usual the weaker conjugate base the more stable and the more reactive carboxylic acid derivative is nucleophilic substitution.

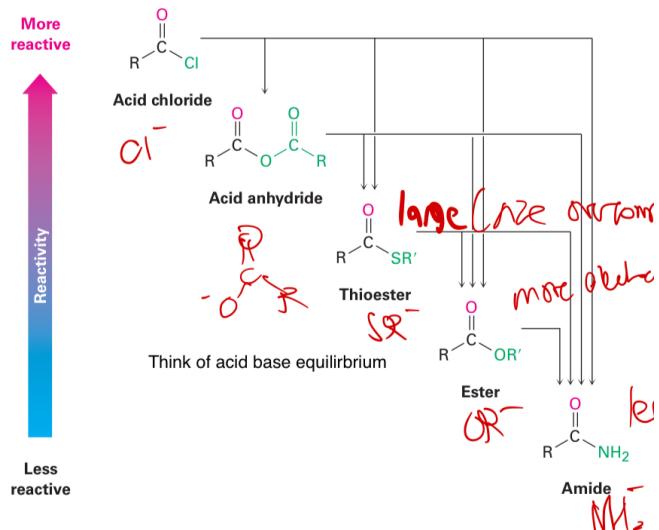
General rule for nucleophilic acyl substitution: if **leaving group** is a **weaker base** than the **nucleophile**, the reaction will be **favored**



Note that we have discussed the relative basicity in 24. As for RO^- vs HO^- consider that $R = CH_3$ is an electron donating group which further destabilizes the negative charge so $RO^- > OH^-$ in terms of basicity.



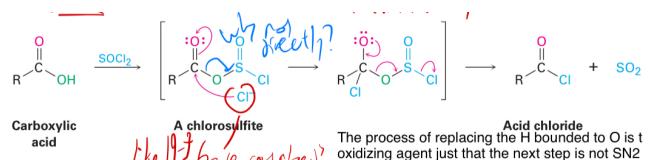
so Cl^- still the most stable hence acid chloride most reactive. In practice this is what the order we need to know



In general just use the general trend in basicity as shown above. Comparing within same row(period) the less electronegative(more left) conjugate base is more basic. For example SR^- vs Cl^- and OR^- vs NH_2^- . But comparing down groups(columns) the deeper column one is less basic since larger lower charge density which overcompensates for decrease in electronegativity(just like how shielding overcompensates effective nuclear charge). For example SR^- vs OR^- . The only special thing therefore acid anyhydride where the resonance stabilization of carboxylate makes it even more stable than SR^- but still not as stable as Cl^-

16.2 reactions of carboxylic acids

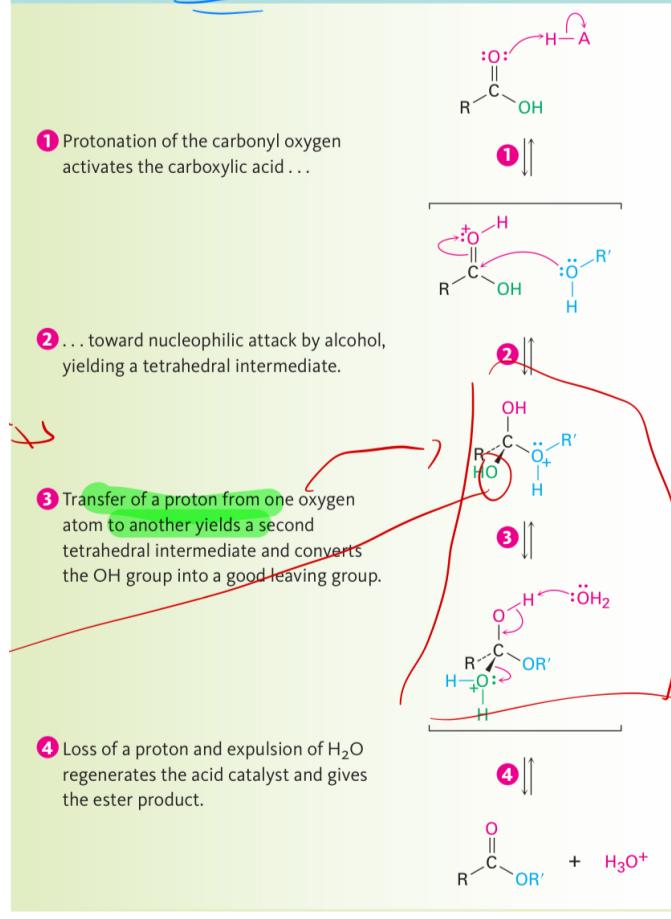
conversion of carboxylic acids into acid chlorides. just like 13.4 we use $SOCl_2$



Note that this what we call the **nucleophilic substitution with internal return(Sni)** - was actually what happened in 13.4 too we just didn't show there stereochemistry and details there. Not required to know for my purposes through you can read more [here](#) As for conversion of carboxylic acids into esters we have

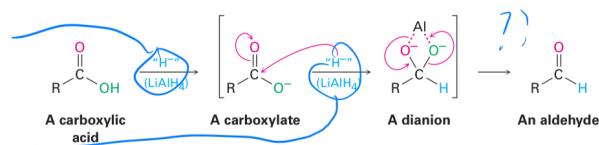
MECHANISM

Mechanism of Fischer esterification. The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.

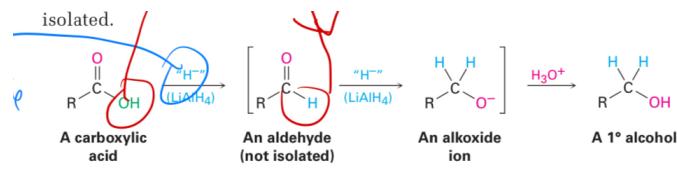


Esters can also be synthesized by an acid-catalyzed nucleophilic acyl

See that step 2 to 3 is a "proton shift" which just like 7.5 is justified as it results in a more stable configuration in this case a more stable leaving group. Recall 18.2(pronation of OH^- is one way we make it into a better leaving group) As we will see later. As for conversion of carboxylic acids into aldehydes we have



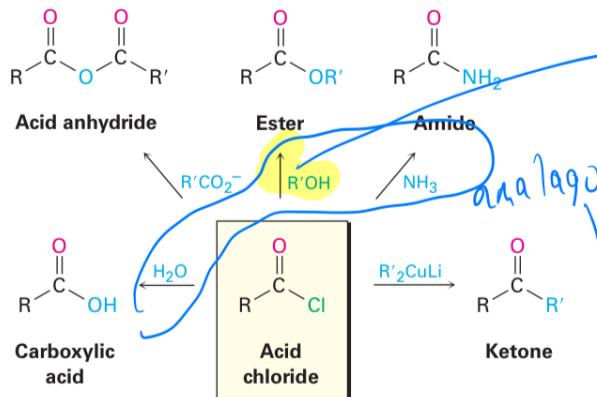
Then the aldehyde is further reduced to



For our purposes just note that LiAlH_4 contributes a powerful nucleophile H^- that essentially "forces substitution" of H even with leaving group is shit. For example there are "coordinating effects" such as in the dianion above that help achieve this(see that OH^- is a shit leaving group but still kicked out)

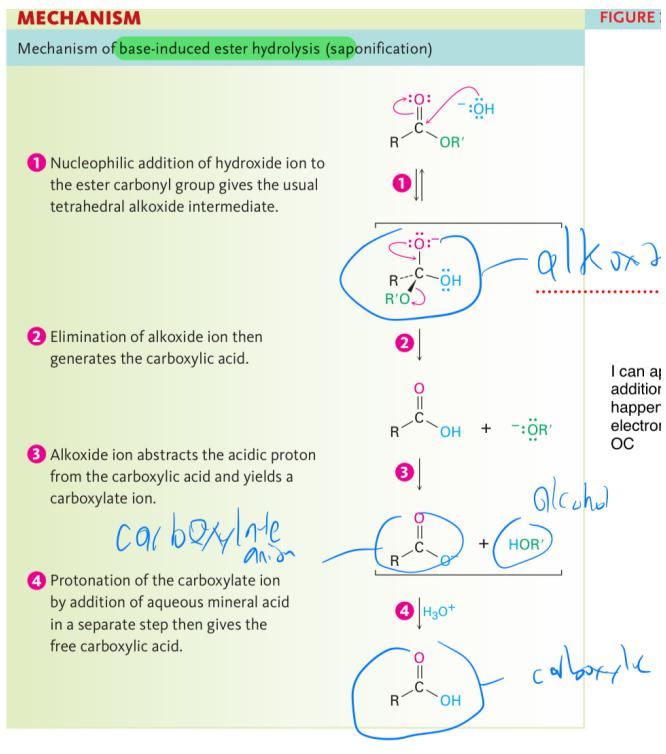
16.3 chemistry of acid halides

Recall that acid chlorides are the most reactive. It can go through nucleophilic acyl substitution with all the other carboxylic acid derivatives which are all have stronger conjugate bases than it recall 16.1



16.4 chemistry of esters

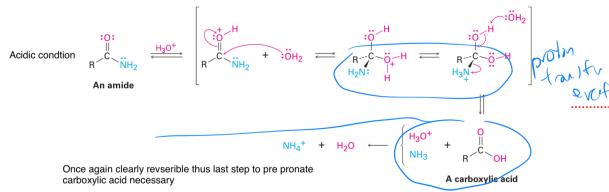
base catalyzed ester hydrolysis(saponification)



See that this is pretty logical. OR- is a better leaving group than OH-. this nucleophilic sub makes sense.

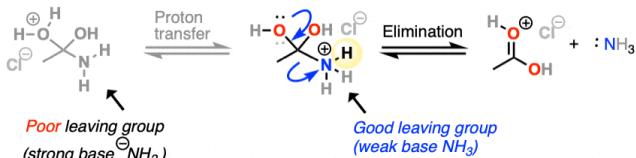
16.5 chemistry of amides

Amide hydrolysis



Recall that NH₂⁻ is one of the worst leaving groups so we use a proton transfer event to make it a better leaving group

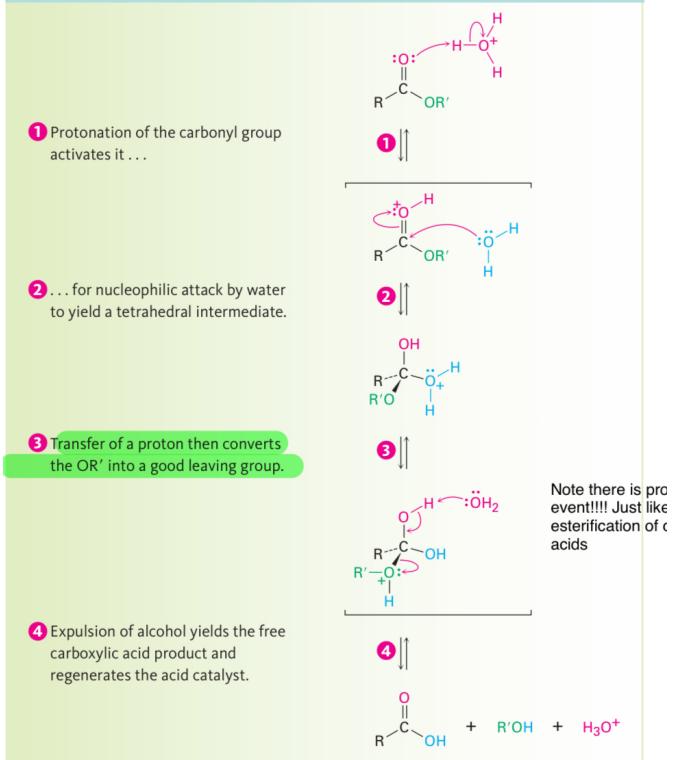
Proton transfer often precedes an elimination step



Acid catalyzed ester hydrolysis

MECHANISM

Mechanism of acid-catalyzed ester hydrolysis. The forward reaction is a hydrolysis; the back-reaction is a Fischer esterification and is thus the reverse of Figure 21-4.



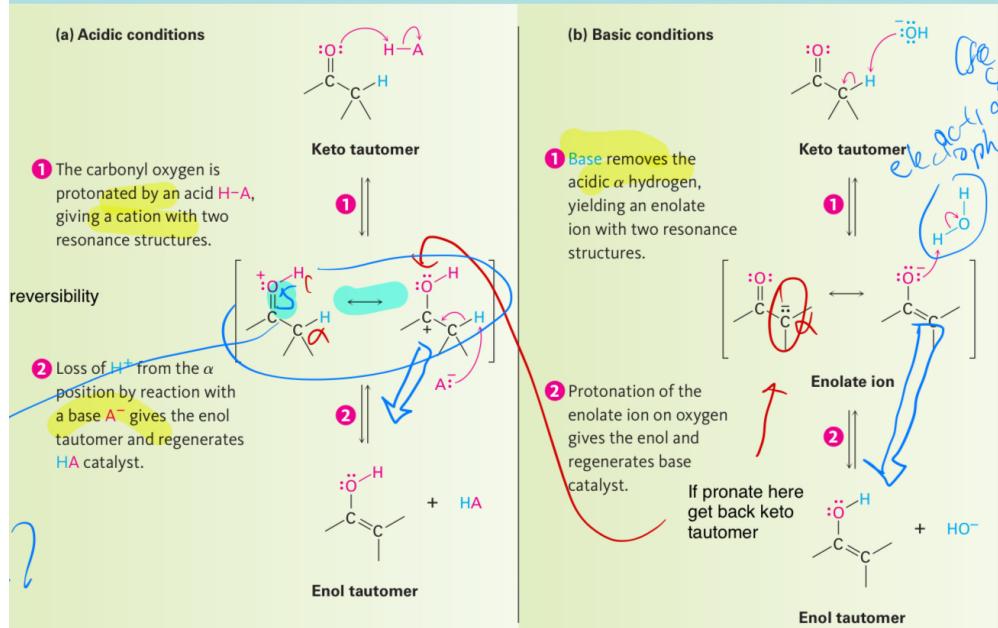
step to 2 to 3 is a proton transfer mentioned in 16.2 (which is simply the reverse reaction of this)

17 carbonyl alpha sub reactions

17.1 keto-enol tautomerization

MECHANISM

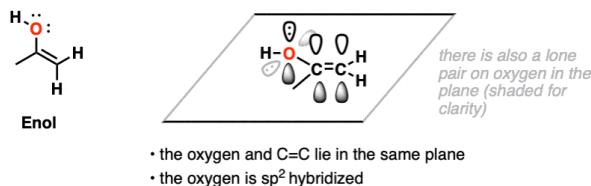
Mechanism of enol formation under both acid-catalyzed and base-catalyzed conditions. (a) Acid catalysis involves (1) initial protonation of the carbonyl oxygen followed by (2) removal of H^+ from the α position. (b) Base catalysis involves (1) initial deprotonation of the α position to give an enolate ion, followed by (2) reprotonation on oxygen.



Why this happens? First consider that OH is in conjugation with the pi bond

Structure of the enol tautomer

In the enol tautomer, a lone pair on oxygen is in conjugation with the pi-bond

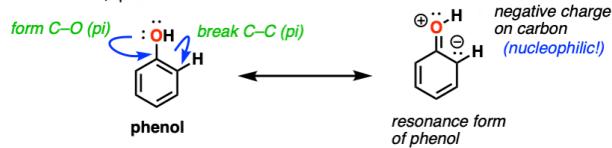


now recall that OH is a strong electron donating substituent

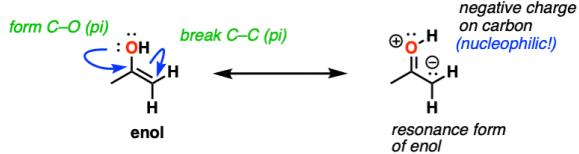
Phenols and Enols

Recall that the $-\text{OH}$ group on aromatic rings (e.g. phenol) is **strongly activating**, since a lone pair from O can increase electron density on carbon

This is called, "pi-donation"



Likewise, in the enol tautomer the lone pair on oxygen can act as a pi-donor, increasing the nucleophilicity on carbon



so then how did the tautomerization occur? They seem to structural isomers not resonance forms?

In both cases the atoms are too far apart for the necessary bonds to form

In this case the alpha-carbon is too far away from the proton on the oxygen, rendering protonation impossible

enol

keto

oxygen is sp^2 hybridized

the proton would have to reach this lobe of the p-orbital which is too far away

For keto-enol, the oxygen would have to remove a proton that is too far away

keto

enol

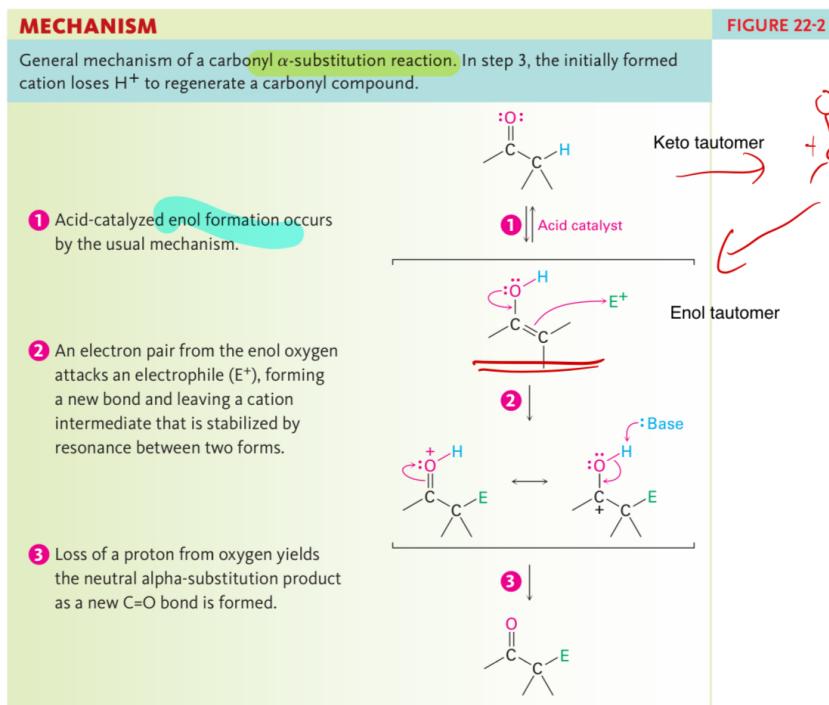
*because it is aligned with the orbitals of the $\text{C}=\text{O}$ pi bond

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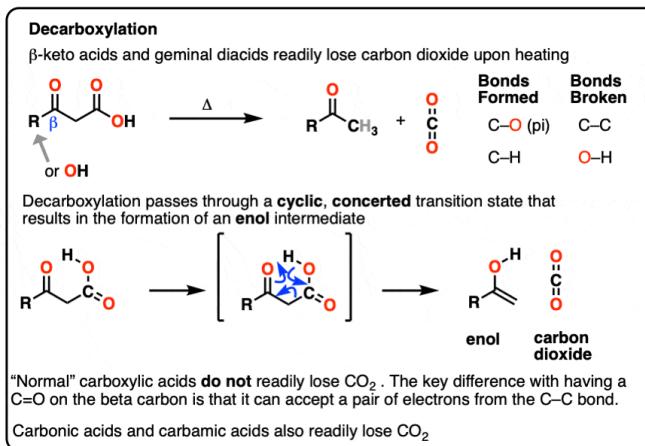
so in order facilitate the proton transfer we use helper functions such as acidic and basic conditions tautomerization outlined above

17.2 α-sub reactions



17.3 carboxylation

we will delve into this topic in preparation for the next two chapters to come.



Proposition 40

only beta-keto carboxylic acids decarboxylate readily. The others don't

There is something special about having a $\text{C}=O$ two carbons away from the CO_2H that allows decarboxylation to occur which we will look into now. The answer has got to do with the sigmatropic rearrangement mechanism of decarboxylation as shown in the figure above. the 2 carbons away is to ensure the symmetries line up. Unfortunately i

have a shot at MO theory in organic chem but really nothing makes sense. Anyway you won't know the theory till you know quantum so ill just leave it as it is for now...

17.4 malonic ester snythesis

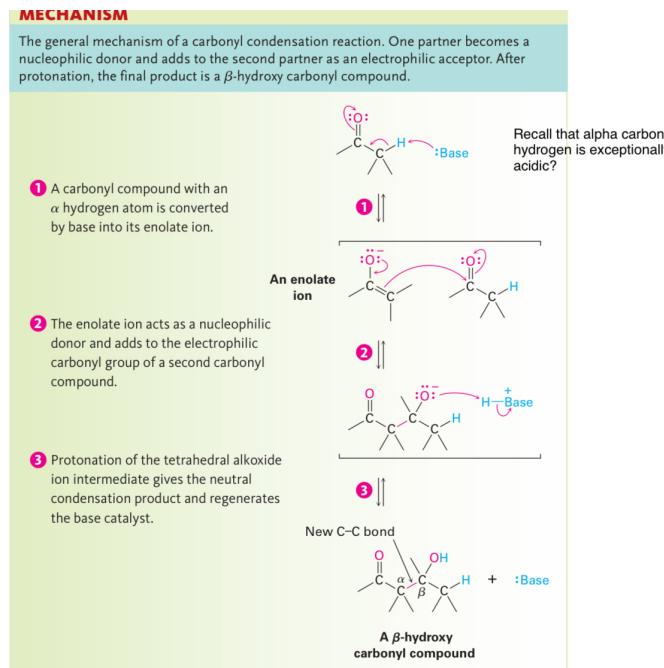
let us consider an interesting case of alkylation of enolate ions known as **malonic ester synthesis**.

17.5 acetocetic ester synthesis

Just as malonic ester synthesis converts an alkyl halide into a carboxylic acid, **acetocetic ester synthesis** converts an alkyl halide into a methyl ketone having three more carbons

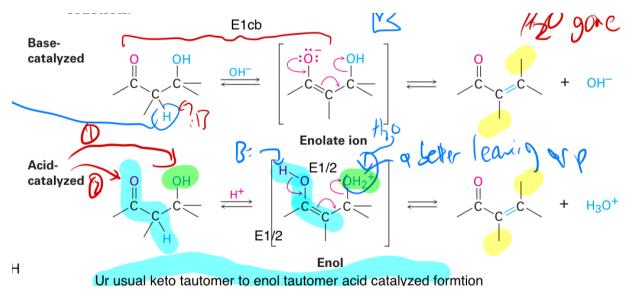
18 carbonyl condensation reactions

18.1 carbonyl condensations: the aldol reaction



Same as alpha sub but now instead of adding to say some halide(recall alpha bromination) we add to another carbonyl or another compound. This is just standard nucleophilic addition as shown earlier

18.2 dehydration of aldol products



Recall that we briefly introduce the E1cb reaction in 7 where X there is now OH^- here. Notice that OH^- which is a shitty leaving group is dispelled. Dafaq how? Well that because as eluded earlier, firstly the alpha hydrogen is unusually acidic due to

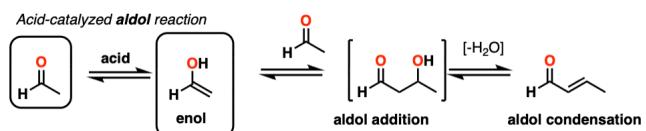
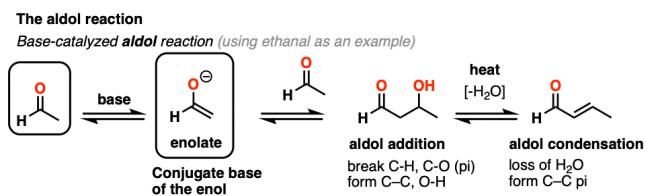
- electron withdrawing effects of the carbonyl oxygen
- resonance stabilization of the enolate ion

So in fact energetically we can even allow OH^- to be a leaving group much unlike alcohols which are in general resistant to dehydration by base (they require stuff like POCl_2 and PBr_3 etc to turn OH^- into a better leaving group first). We will discuss this topic more below

Remark 41. Dehydration is another word for condensation

18.3 base catalyzed:carbonyl condensations versus alpha sub

As an overview this is what we have



Hey! That's weird! Yes we covered base catalyzed aldol condensation the base catalyzed one is the E1CB one while the acid catalyzed one is the E1/E2 version we discussed in 18.2. But what is with the heat? It turns out that

Theorem 42

Elimination reactions are favoured by heat

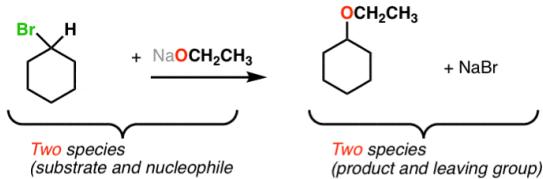
Proof. Consider

Lemma 43

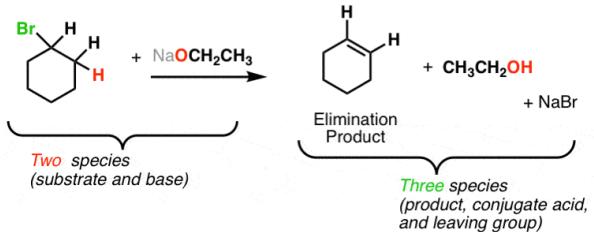
Consider that elimination results in more species but not substitution

Proof. consider

In Substitution Reactions The Number Of Species In Solution Generally Remains Constant



Elimination Results In An Increased Number of Species In Solution



Therefore by gibbs equation for entropy we can show that elimination is favoured via

The ΔS term in the Gibbs equation will increase more with heat for elimination than it will for substitution

As T increases, this term starts getting big

This will make ΔG more negative
making the reaction more favorable

$$\Delta G = \Delta H - T\Delta S$$

Therefore, all else being equal, heating tends to favor elimination over substitution

Then this means all things equal ΔG is more negative for elimination meaning more exothermic meaning more favourable! □

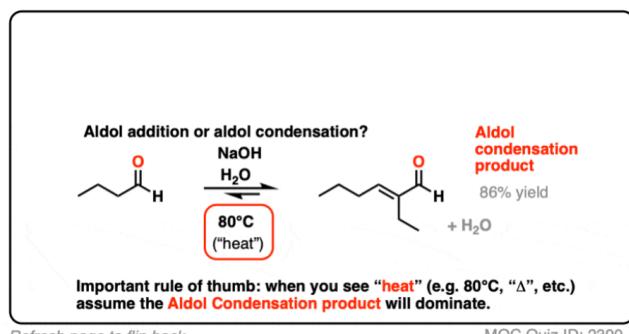
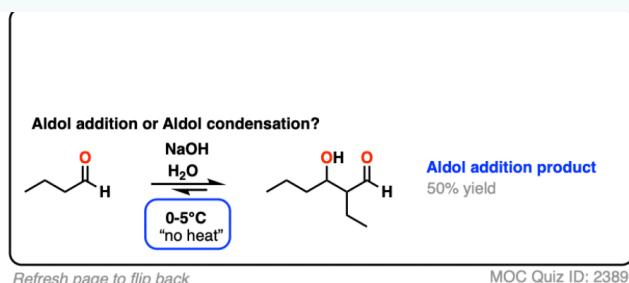
Therefore

Proposition 44

For base catalyzed aldol reactions, condensation(E1CB elimination) products are favoured over addition(Alpha substitution) products in the presence of heat

Example 45

this means for example



18.4 acid catalyzed: aldol condensation and addition

another thing is weird about 18.3. We did not discuss aldol addition and condensation products at all using the acid catalysed pathway. We do so now. Turns out it is also possible just like the base catalyzed pathway but it needs some additional help.

Proposition 46

enolates are stronger nucleophiles than **enols**

First let us consider their resonance forms

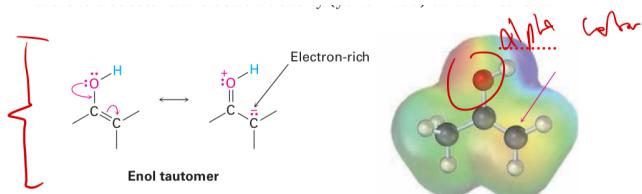


Figure 15: Resonance forms: enol

Note that it is quite clear that reactions(nucleophilic addition) will occur on the alpha carbon and not anywhere else(not so for enolates as we will see). In the first case the one of the lone pairs in π bond will perform the nucleophilic attack to form bonds in reaction, this is aided by the fact that OH is a strong electron resonance donating group which will further contribute to electron density in the pi bond area. The case for 2nd resonance form is obvious. So all in all as indicated by the figure, the electron density is concentrated on the alpha carbon.

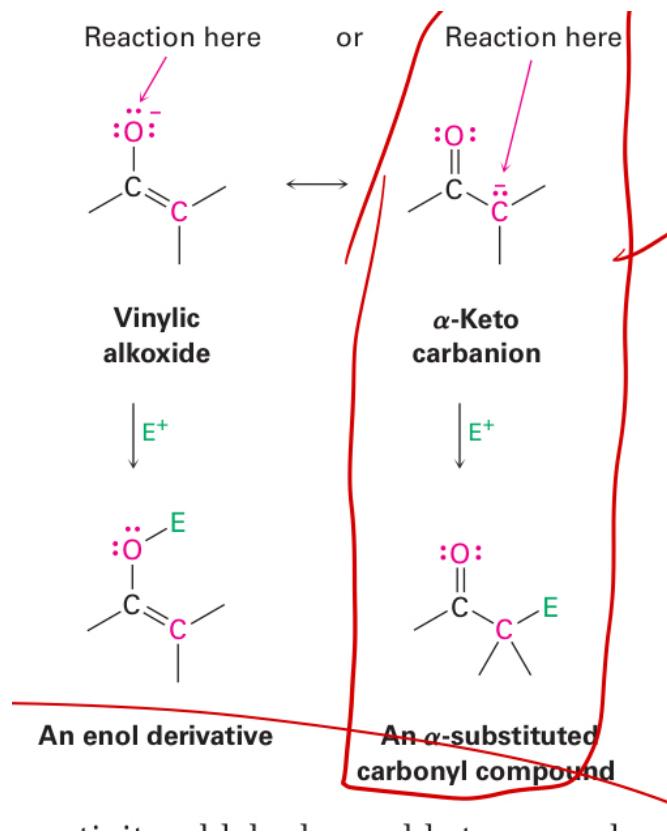


Figure 16: (1st row of image) Resonance forms: enolate

Note that the circled reaction (reaction on alpha carbon) is more common because its kinda blocked by the cation used in the base that got our enolate. To see this consider

Fact 47

Enolates tend to react at carbon rather than oxygen. One reason is that the oxygen tends to be tightly bound to the counter-ion of whichever base is used (e.g. Li^+ or Na^+). One way to get the oxygen to be more reactive is to use alkali metal salts that are bigger and form a weaker ionic bond with oxygen (e.g. potassium, K^+)

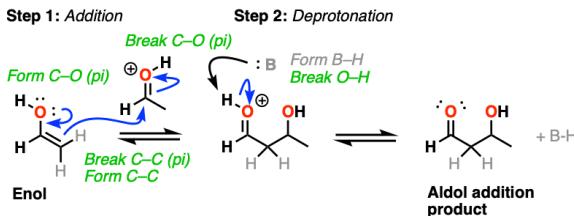
So we established that both are resonance stabilized. In which case ultimately enolates should be more reactive as nucleophiles because they differ by one proton(hydrogen). So its electron cloud is more diffuse.

Fact 48

In general ions tend to be more reactive than their neutral atom counterparts. Refer to periodic trends of ions in your Intro to solid state chemistry notes.

In that case, we will need additional help, in particular we require acid catalyst to proceed with an addition reaction like so

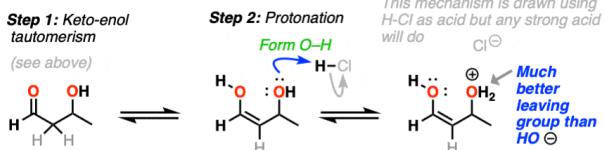
The second step of the acid-catalyzed aldol is addition of the enol to the protonated aldehyde (or ketone)



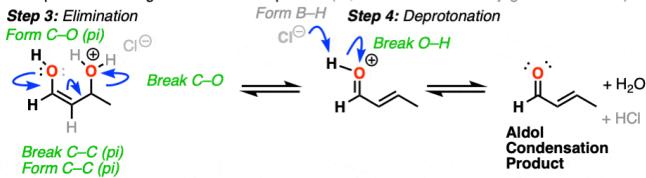
As for condensation we basically another round of acid catalyzed keto to enol tautomerization. Then protonation by the acid of OH turns it into a much better leaving group(recall 13.4)

Acid Catalysis of the Aldol Reaction, Part 3:
The Conjugate Acid Is A Better Leaving Group
The third stage of the acid-catalyzed aldol condensation is loss of water and formation of a new C-C pi bond.

Protonation of OH to give H₂O makes for a **much** better leaving group



One way to draw the final elimination step is through the simultaneous formation of the C-O bond and migration of the C-C pi bond ("1,4 elimination" or "conjugate elimination")



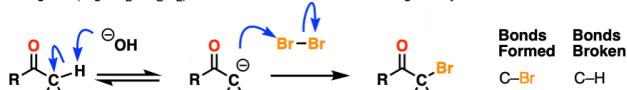
which is basically the E1/E2 reaction we discussed in 18.2. Recall that both E1 and E2 favour good leaving groups(unlike E1CB)

18.5 more enolate reactivity: alpha substitution enolates?

Beyond addition to another ketone, both enol and enolate generated in acid catalyzed and base catalyzed respectively can be halogenated. We have discussed the acid catalyzed halogenation of ketone(using acid to turn keto into enol first) in 18.1. So what about of base catalyzed halogenation of ketone?(use base to turn keto into enolate first) In theory yes this is indeed possible

Halogenation of enolates

Halogens (e.g. Cl₂, Br₂, I₂) will also react with enolates to give **alpha-halo ketones**.



- With NaOH/H₂O this reaction is hard to control since the product is more acidic than the starting material.
- Multiple halogenations can happen (haloform reaction)

this is actually more acidic than the starting ketone

Figure 17: OH- says: wow you even more acidic now i wanna attack your other H even more!

The problem is the alpha halogenated ketone is generally more acidic than the starting unsubstituted ketone because of the electron withdrawing inductive effect of the halogen atom so it is difficult to stop at the substituted product.

Example 49

For example

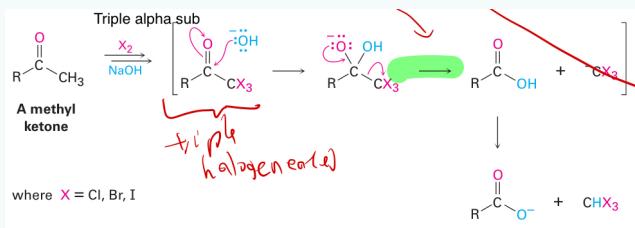


Figure 18: Get triple halogenated noob!

18.6 enolates of amines and esters

In general, for any group X, the more X donates its lone pair into the carbonyl, the more unstable will be the enolate of that species.

$\text{:X}-\text{C}(=\text{O})-\text{H} \leftrightarrow \text{X}^+-\text{C}(\text{H})=\text{O}^-$

pi donation of X

the more important this resonance form is, the less acidic this H will be, since the negative charge on carbon is less able to donate into the carbonyl

If you think back to aromatic rings, NR_2 is more activating than OR , which is more activating than Cl . That's because N is best able to donate its pi electrons to make a new pi bond, and Cl is worst able to donate pi electrons

$\text{R}-\overset{\text{N}^+}{\underset{\text{H}}{\parallel}}-\text{O}^-$ least acidic $\text{R}-\overset{\text{O}^+}{\underset{\text{H}}{\parallel}}-\text{O}^-$ $\text{R}-\overset{\text{Cl}^+}{\underset{\text{H}}{\parallel}}-\text{O}^-$ most acidic

So we should expect amides to be less acidic than esters, but acid halides to be more acidic
That is exactly what is observed.

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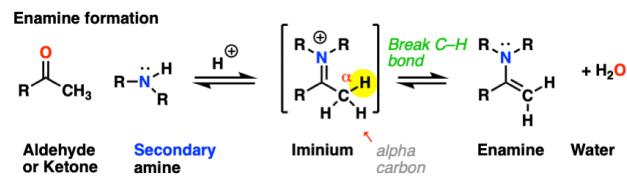
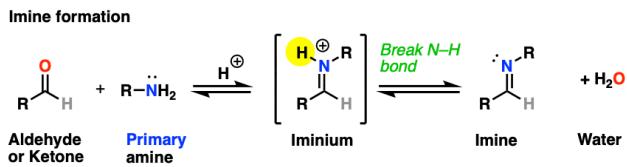
In the case of an ester the alpha-carbon actually becomes less acidic. Therefore ester enolates are less stable(stronger bases) than those of aldehydes and ketones where X above is R or H. Because the electron donation ability rank goes:



Why? Well N is less electronegative than O so inductive electron withdrawal that works against the stronger resonance donation of N and O is stronger for O. Now CH_3 is an inductive electron donator if you recall which is in general weaker than resonance electron donation(since induction is mainly localized while electron resonance is throughout unless you orbital overlap is so shit that inductive withdrawal outweighs like Cl) Note that this is also reflected in 16.1

19 amines and heterocycles

As a recap



20 orbitals and organic chemistry: pericyclic reactions

Fact 50

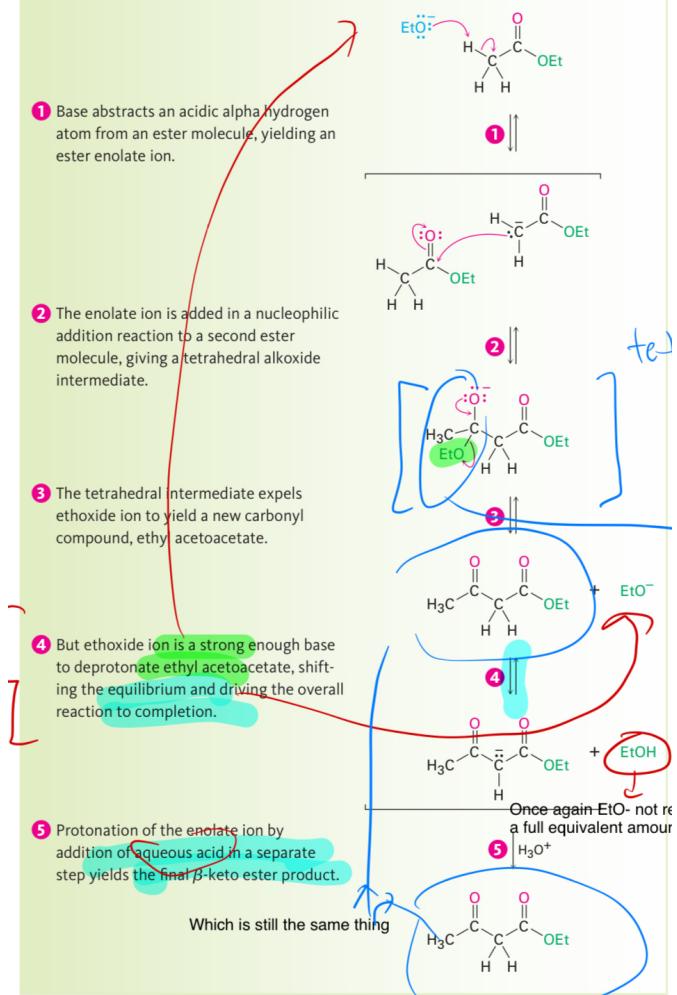
If the symmetries and product orbitals match up or correlate the reaction is said to be **symmetry -allowed**. If not the reaction is **symmetry-disallowed**. Symmetry allowed reactions often occur under relatively mild conditions but symmetry-disallowed reactions can't occur by concerted paths.

20.1 claisen condensation reaction

Note that Et stands for "ethyl" CH_3CH-

MECHANISM

Mechanism of the Claisen condensation reaction.



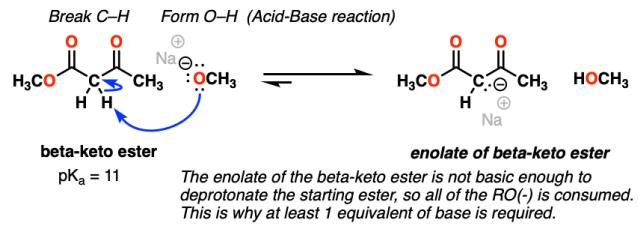
In step 2 to 3, Normally one wouldn't think of an alkoxide as a good leaving group (the pK_a of ethanol is 16, making $\text{CH}_3\text{CH}_2\text{O}^-$ a strong base) but elimination of RO^- is still a much more favorable pathway than reversal of the addition reaction to give the ester enolate (pK_a of the ester = 25) as obtained in step 1 to 2. (note that the weaker the acid the stronger the conjugate base) recall 18.6. See that



the electron donating group that contributes to O (that is directly bonded to the acidic H) is $\text{R}=\text{CH}_3\text{CH}_2$ here which is as mentioned previously not as good an electron donor as OR in ester. Note that the last step of adding aqueous acid is just a cleanup since

Claisen Condensation: Acid-Base Reaction of The Beta-Keto Ester Product

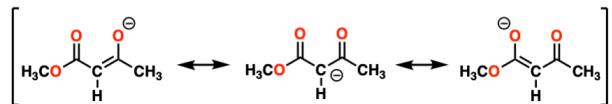
Since the beta-keto ester is considerably more acidic than RO⁻, it is quickly deprotonated to give the stable beta-keto enolate.



to remove the weak base enolate keto beta ester. This reaction occurs because

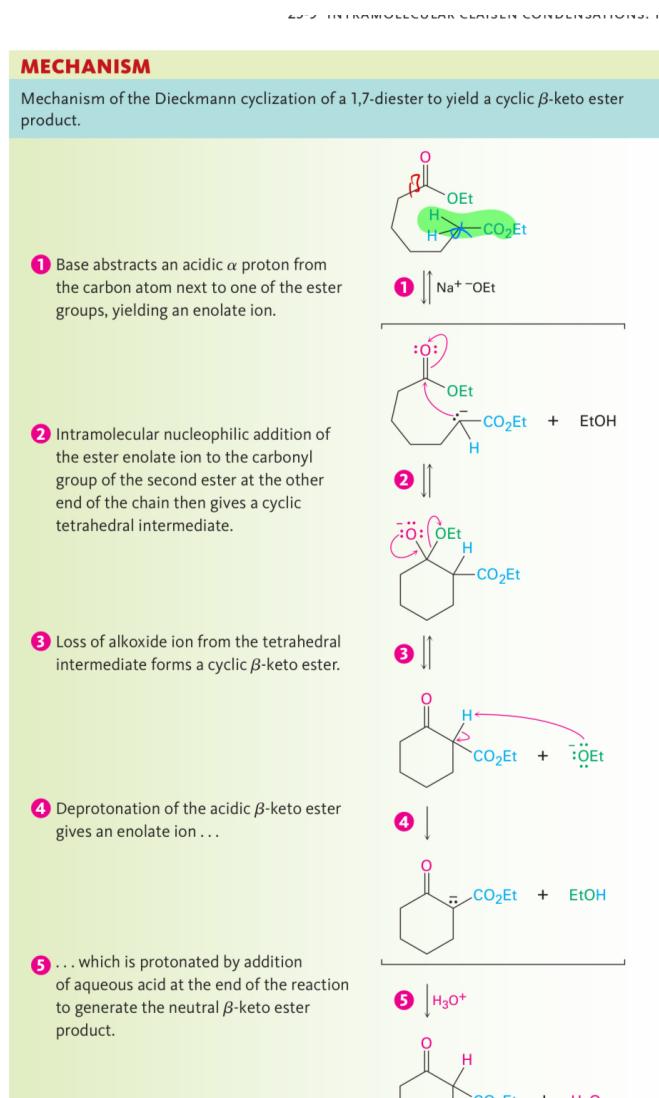
The Conjugate Base Of The β -Keto Ester Is Greatly Stabilized By Resonance

In the enolate of the beta-keto ester, the negative charge can be delocalized from the carbon either of two different oxygen atoms



beta keto acid is exceptionally acidic as visualized in this diagram above. Now strong acid + base yields to large extent a weak conjugate base and acid.

20.2 intramolecular claisen condensations: the dieckmann cyclization

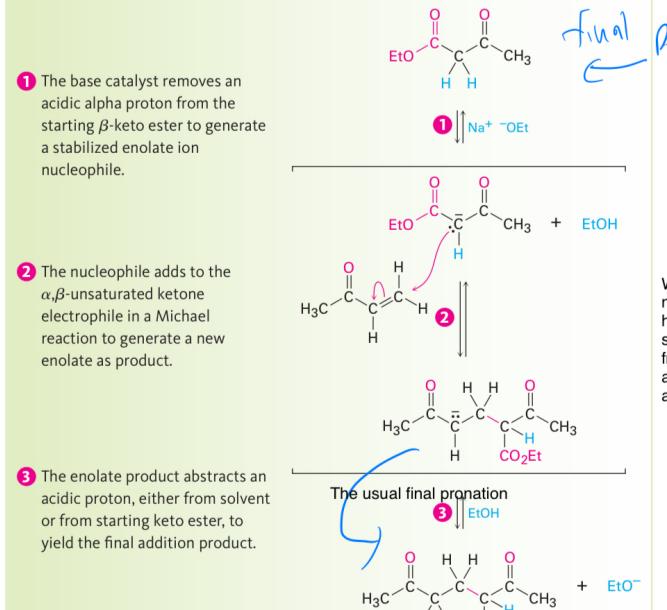


well this is just claisen but the 2 esters are in the same ring

20.3 conjugate carbonyl additions: the micheal reactions

MECHANISM

Mechanism of the Michael reaction between a β -keto ester and an α,β -unsaturated ketone. The reaction is a conjugate addition of an enolate ion to the unsaturated carbonyl compound.



20.4 electrocyclic reactions

No need do this anyway 5.06 chemistry(Biological Chemistry by chem dep mit) only requires up to claisen condensation(aka only 5.12 organic chem as clearly stated in prereq)...no need pericyclic at least until 5.07(which you only intend to do after quantum then back to advanced chem in that order)

Definition 51

a **electrocyclic reaction** is a pericyclic process that involves the cyliczation of a conjugated acyclic polyene.