Carbonyl Chemistry (12 Lectures)

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Aim of Course

- To build upon elements of Dr E.H. Smith's and Dr. D.C. Braddocks's course.
- To introduce the chemistry of the carbonyl functional groups.

Course Objectives

At the end of this course you should be able to:

- Identify the various functional groups that involve carbonyls
- Explain reaction mechanisms associated with each type of functional group

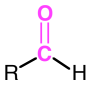
Recommended Texts

- Vollhardt, K.P.C. & Schore N.E. "Organic Chemistry" (2nd ed.)
- Clayden J., Greeves N., Warren S. & Wothers P. "Organic Chemistry"
- Sykes, P. "Mechanism in Organic Chemistry" (6th ed.)
- Warren, S. "Chemistry of the Carbonyl Group"

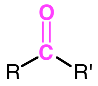
Aldehydes and Ketones

- We begin our study of carbonyl compounds with the study of **aldehydes** and **ketones** (the aldehyde/ketone oxidation level).
  - Carbonyl compounds are molecules containing the carbonyl group, **C=O**. These include:

- **Aldehydes**

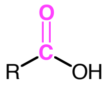


- **Ketones**



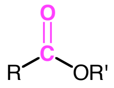
Note: two bonds to heteroatoms

- Carboxylic acids

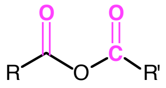


Carboxylic acid derivatives:

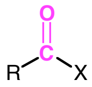
- Esters



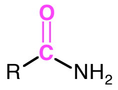
- Anhydrides



- Acid halides

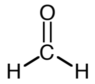


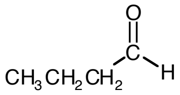
- Amides

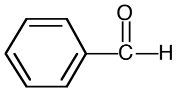


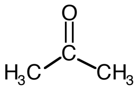
Nomenclature of Aldehydes and Ketones

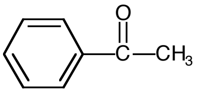
- Common names are used for the simplest aldehydes and ketones:

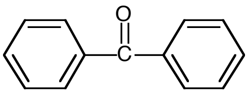

formaldehyde


butyraldehyde

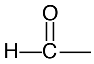

benzaldehyde

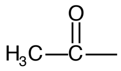

acetone

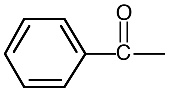

acetophenone


benzophenone

- Common names are also used for carbonyl-containing substituent groups, which are known collectively as ***acyl*** groups:

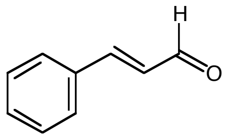

formyl

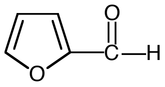

acetyl

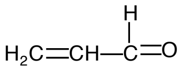

benzoyl

Nomenclature of Aldehydes and Ketones

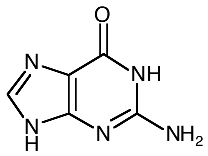
- Traditional names are used for a great many aldehydes and ketones which were recognized as substances long before systems of nomenclature were developed:

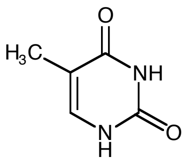

cinnamaldehyde

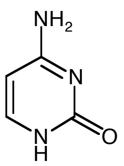

furfural


acrolein

- Three of the four bases which comprise DNA contain carbonyl groups (and all four bases are nitrogen heterocycles, which we will discuss later):


guanine (G)

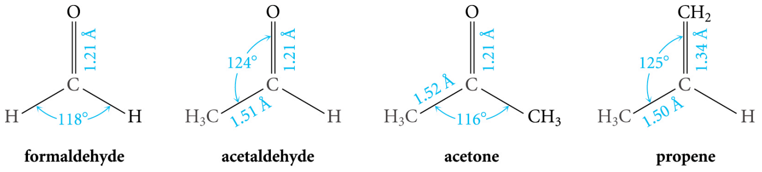

thymine (T)


cytosine (C)

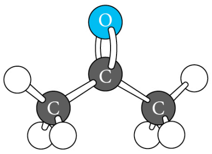
Structure of Aldehydes and Ketones

- The carbonyl carbon of an aldehyde or ketone is sp^2-hybridized.
- The bond angle is close to 120° (trigonal planar).
- The carbon-oxygen double bond consists of:
  - A σ C-O bond
  - A π C=O bond

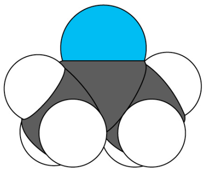
We can compare the C=O bond length to those of C=C double bonds



(a)



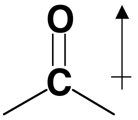
(b)



(c)

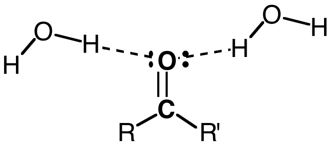
Properties of Aldehydes and Ketones

- Aldehydes and ketones are polar molecules because the C=O bond has a dipole moment:



For acetone:	*dipole moment = 2.7 D* *boiling piint = 56.5 °C*
For propene:	*dipole moment = 0.4 D* *boiling point = -47.4 °C*
For i-propanol:	*dipole moment = 1.7 D* *boiling point = 82.3 °C*

- Their polarity makes aldehydes and ketones have higher boiling points than alkenes of similar molecular weight.
- Aldehydes and ketones are not hydrogen bond donors (they can't donate a proton); therefore, they have lower boiling points than alcohols of similar molecular weight.
- Aldehydes and ketones are hydrogen bond acceptors; this makes them have considerable solubilities in water.

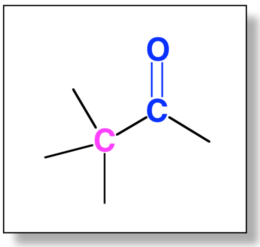


Ketones such as acetone are good solvents because they dissolve both aqueous and organic compounds

Recall that acetone is a ***polar, aprotic*** solvent.

Reactions of Aldehydes and Ketones

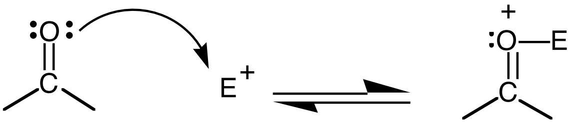
- The reactions of aldehydes and ketones can be divided into two main categories:
  - Reactions of the ***carbonyl group*** (Ch. 19)
  - Reactions involving the ***α-carbon*** (Ch. 22)



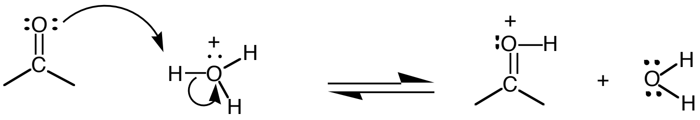
- ***Carbonyl group*** reactions fall into three main groups:
  - Reactions with acids
  - Addition reactions
  - Oxidation

Carbonyl Group Reactions

- Reactions with acids:
  - The carbonyl oxygen is weakly basic.
  - Both Bronsted and Lewis acids can interact with a lone pair of electrons on the carbonyl oxygen.

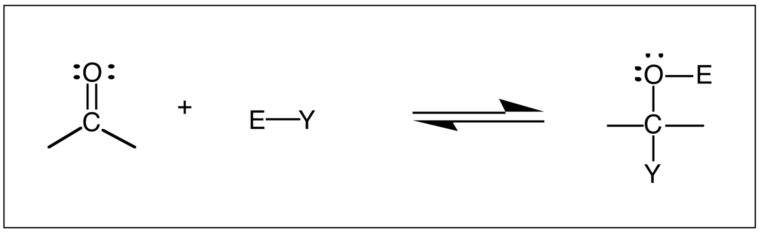


- For example, when the Bronsted acid H_3O^+ is used:



Carbonyl Group Reactions

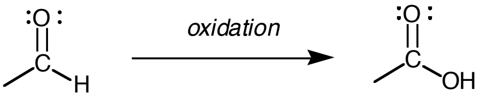
- Addition Reactions
  - Carbonyl groups in aldehydes and ketones undergo addition reactions.
  - This is one of the most important reactions of the carbonyl group.



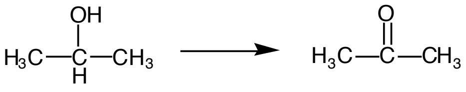
- Addition reactions occur by two different mechanisms:
  - Base-catalyzed addition (under basic or neutral conditions)
  - Acid-catalyzed addition (under acidic conditions)
- In some cases, we can carry out the same overall reaction using either set of conditions (acidic or basic).

Carbonyl Group Reactions

- Carbonyl groups in aldehydes and ketones may be oxidized to form compounds at the next “oxidation level”, that of carboxylic acids.

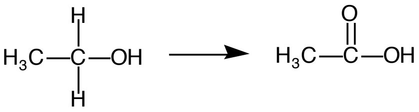


- Alcohols are oxidized to aldehydes and ketones
  (example: biological oxidation of ethanol to acetaldehyde)
- The carbonyl group may be further oxidized to carboxylic acids



$H_3C-\overset{OH}{\underset{H}{C}}-CH_3 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-CH_3$

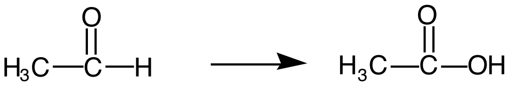
alcohol to **aldehyde**: <u>two</u> electron oxidation



$H_3C-\overset{H}{\underset{H}{C}}-OH \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-OH$

alcohol to **carboxylic acid**: <u>four</u> electron oxidation

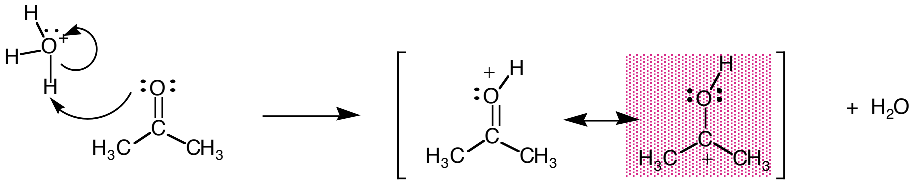
aldehyde to carboxylic acid:
<u>two</u> electron oxidation



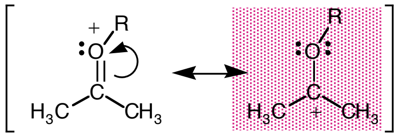
$H_3C-\overset{O}{\overset{\|}{C}}-H \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-OH$

Basicity of Aldehydes and Ketones

- Reactions which occur at the carbonyl *oxygen* of aldehydes and ketones:
  - The weakly basic carbonyl oxygen reacts with protons or Lewis acids
  - The protonated form of the aldehyde or ketone is resonance-stabilized
  - This gives the aldehyde/ketone conjugate acid carbocation character

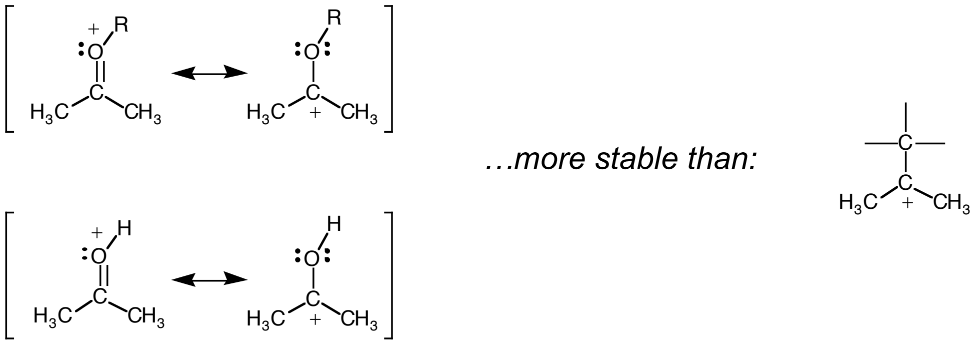


- Protonated aldehydes and ketones can be thought of as **α-hydroxy carbocations**
- When an alkyl group replaces (conceptually) the proton, an **α-alkoxy carbocation** is formed:



α-Hydroxy (Alkoxy) Carbocations

- α-Hydroxy (Alkoxy) carbocations are more stable than ordinary carbocations



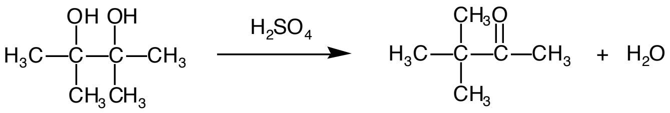
…more stable than:

- The polar effect of the oxygen in the carbon-oxygen bond attracts electrons.
- But… electron-attracting groups adjacent to carbocations are <u>de</u>stabilizing
- However, the resonance stabilization outweighs this destabilization

Stability of Protonated Aldehydes/Ketones

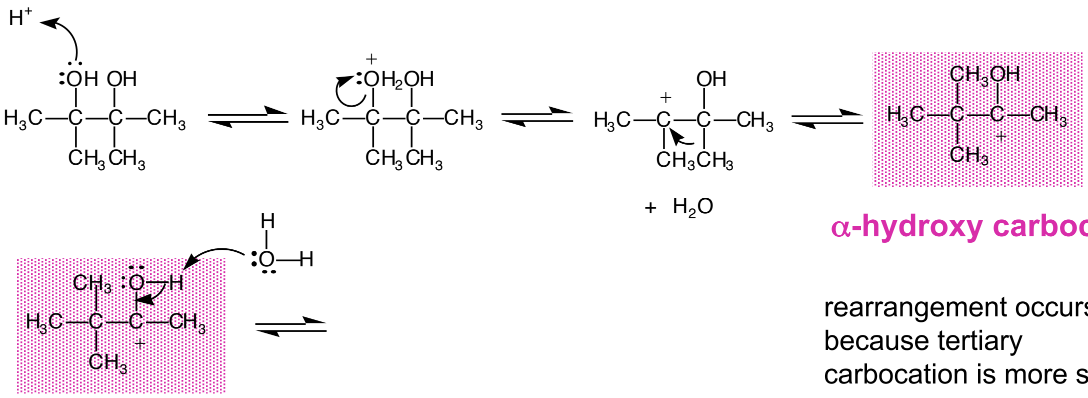
- The stability of α-hydroxy carbocations is demonstrated by a reaction known as the pinacol rearrangement of 1,2-diols:

overall reaction:



$$H_3C-C(OH)(CH_3)-C(OH)(CH_3)-CH_3 \xrightarrow{H_2SO_4} H_3C-C(CH_3)_2-C(=O)-CH_3 + H_2O$$

mechanism:



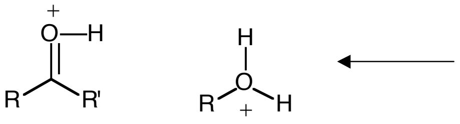
α-hydroxy carbocation

rearrangement occurs
because tertiary
carbocation is more stable

α-hydroxy carbocation

Basicity of Aldehydes and Ketones

- Compare pK_a values of the conjugate acids of aldehyde/ketones with those for the conjugate acids of alcohols:



pK_a: -7 -2.5

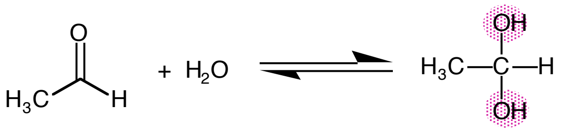
Protonated alcohols are less acidic; therefore alcohols are more basic than ketones

- Does this make sense?
  - Resonance stabilization of the protonated ketone should make it *<u>less</u>* acidic (less likely to lose a proton)
  - Hydrogen bonding explains this apparent contradiction:

    protonated alcohols can undergo hydrogen bonding with two protons, protonated ketones only with one

Reversible Additions to Aldehydes and Ketones

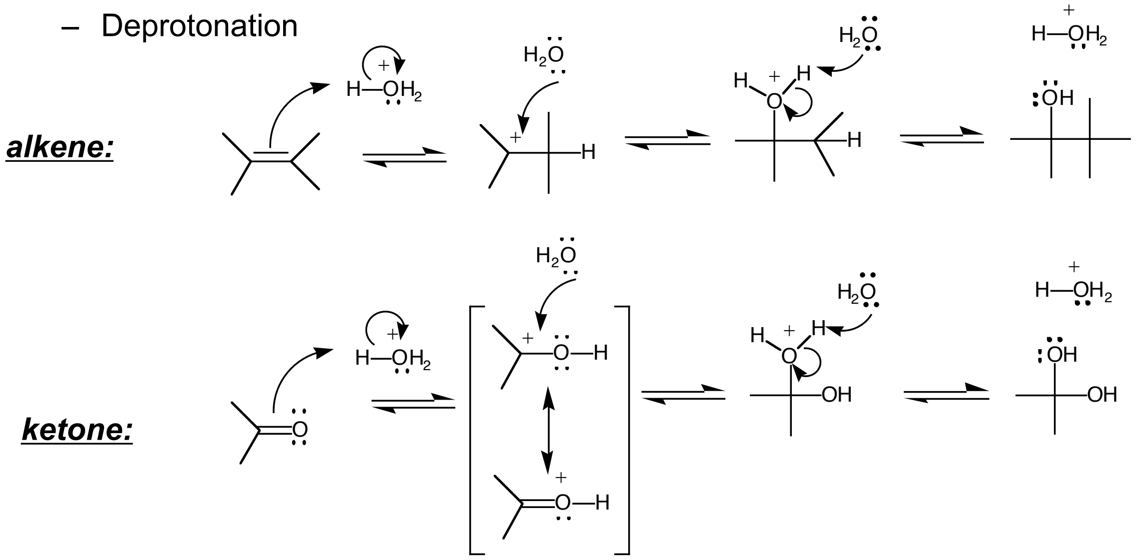
- Addition of water to an aldehyde or ketone gives a product called a ***hydrate*** or a ***gem-diol*** (two -OH groups on the same carbon).
- The reaction is both acid-catalyzed and base-catalyzed.



- The addition reaction is highly regioselective.
  - Addition always occurs with oxygen adding to the carbonyl *carbon* atom.
- The trigonal planar, sp^2-hydridized carbonyl becomes tetrahedral, sp^3-hybridized in the addition reaction.
- The addition reaction is reversible.
- The equilibrium conversion to the hydrate varies widely and depends on the nature of the groups attached to the carbonyl group.

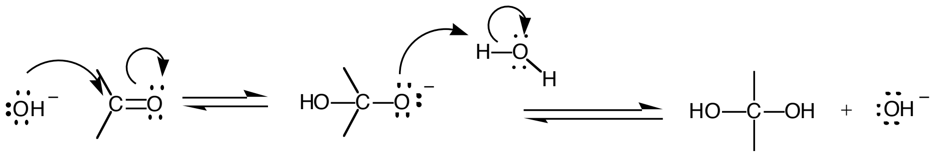
Addition Under Acidic Conditions

- Addition of water to carbonyl compounds under acidic conditions is analogous to addition of water to alkenes
- The reaction occurs in three steps:
  - Protonation
  - Addition
  - Deprotonation



Addition Under Basic Conditions

- Addition of water to carbonyl compounds under **basic** conditions has no analogy in reactions of alkenes
- The reaction occurs in two steps:
  - Addition of OH^- to carbonyl carbon
  - Protonation of carbonyl oxygen
- Addition occurs directly because OH^- is a more reactive nucleophile than H_2O



- Note that regioselectivity of addition is the same for acid or base catalyzed nucleophilic addition

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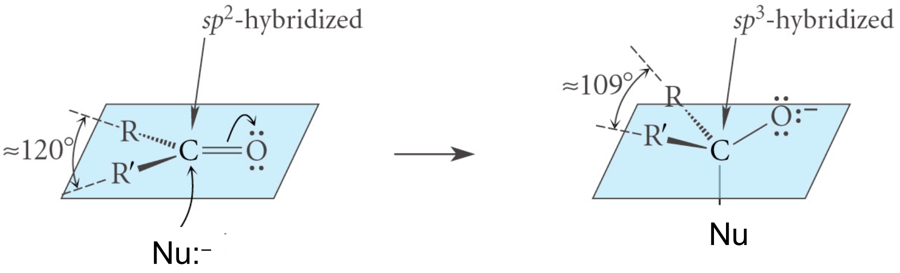
Geometry of Nucleophilic Attack on Carbonyl

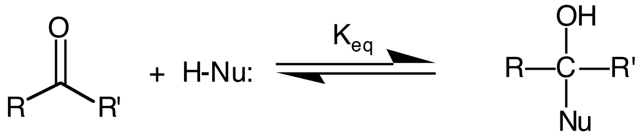
- The sp^2 hybridization of the carbonyl compound means that attack of the nucleophile on the carbonyl carbon may occur from either face.
- The resulting addition product is sp^3-hybridized.

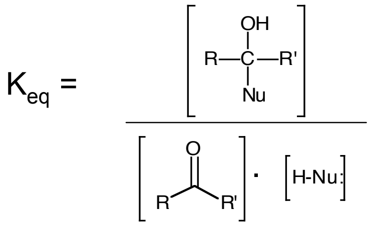


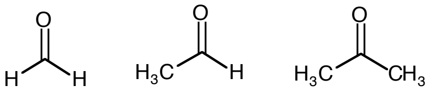
- We used the example of hydration (formation of gem-diols) to illustrate nucleophilic addition to carbonyl compounds; however, other nucleophiles can undergo the same reaction.
- There are other acid- and base-catalyzed examples.

Equilibria in Carbonyl-Addition Reactions

- Carbonyl addition reactions are reversible.
- The extent to which the reaction is able to proceed is defined by the magnitude of the equilibrium constant:







Compound:

K_{eq}: 2000 1 0.001

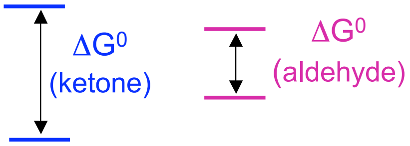
This trend can be explained by looking at factors which affect the stability of the *reactant* and factors which affect the stability of the *product*.

H-Nu = H_2O

Equilibria in Carbonyl Addition Reactions

- Reactant Stability:
  - Recall that alkyl groups stabilize double bonds (more highly substituted alkenes are more stable than less substituted alkenes)
  - This works for C=O double bonds, too
  - Ketones are more stable than aldehydes
  - Therefore, the addition to ketones is *less* favored than addition to aldehydes

Ketone:
reactant ***more*** stable,
product ***less*** stable



Aldehyde:
reactant ***less*** stable,
product ***more*** stable

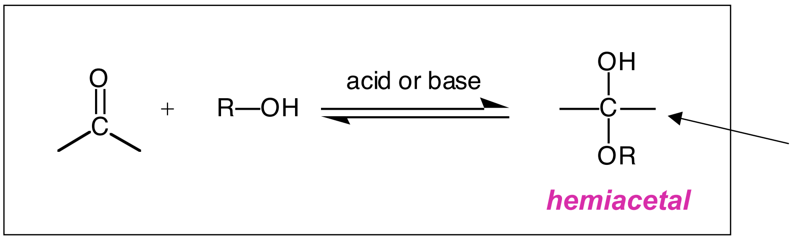
- Product Stability:
  - The four groups in the product are closer together than the three groups attached to the carbonyl carbon in the reactant.
  - Alkyl groups cause more steric destabilization in the tetrahedral addition product than does hydrogen
  - Therefore, the ketone addition product is *less* favored than the aldehyde addition product

Equilibria in Carbonyl Addition Reactions

- Electron-withdrawing groups attached to the carbonyl carbon make addition more favorable (larger K_{eq}).
- Electron-donating groups attached to the carbonyl carbon make addition less favorable (smaller K_{eq}).
- Conjugation with the carbonyl group makes addition less favorable (smaller (K_{eq}).
- Larger size of groups attached to the carbonyl carbon makes addition less favorable (smaller K_{eq}).

Formation of Hemiacetals and Acetals

- When an alcohol adds reversibly to an aldehyde or ketone, the product is called a hemiacetal.
  - *Recall our example of the reaction between CH_3OH and PhCHO.*
- Hemiacetals are formed in both acid- and base-catalyzed reactions.



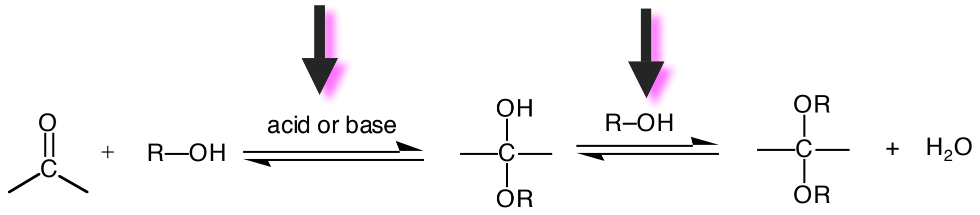
Note: this bond to carbon indicates that it may be either to an alkyl group or to hydrogen.

- Hemiacetals are unstable and can't be isolated in most cases.
- Hemiacetals undergo further reversible reactions under *<u>acidic conditions only</u>*.
  - This reaction involves carbocation chemistry.

Formation of Acetals

- Hemiacetals react further with alcohols under *acidic* conditions to form **acetals**.

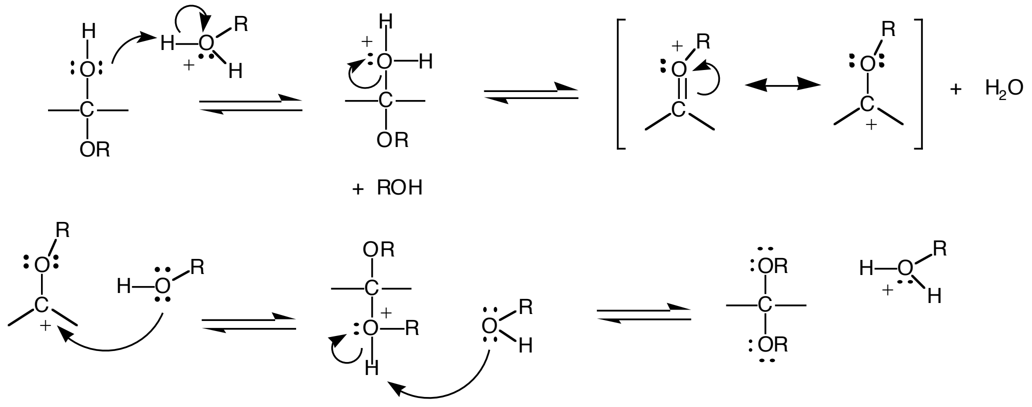
catalyzed by acid or base *catalyzed only by acid*



aldehyde or ketone ***hemiacetal*** ***acetal***

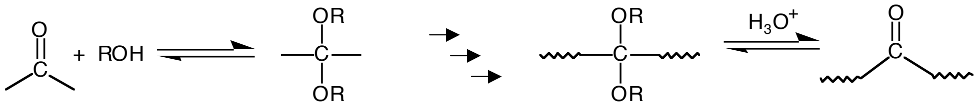
Mechanism of Acetal Formation

- Under acidic conditions, some of the alcohol becomes protonated ROH_2^+.
- The hemiacetal OH oxygen abstracts a proton from ROH_2^+.
- Loss of water gives a resonance-stabilized alkoxy carbocation.
- Nucleophilic attack by the alcohol on the carbocation occurs.
- Deprotonation by a further alcohol molecule produces the acetal.



Acetals as Protecting Groups

- The reversibility of acetal formation along with the relative inertness of the RO-C-OR linkage make acetals useful as ***protecting groups***.
- Protecting groups are functional groups which may be introduced in a molecule by converting another functional group in a reversible reaction.
- If the protecting group is more inert than the original functional group, then other reactions may be carried out with this molecule without worrying about altering or destroying the protecting group.
- When the other desired reactions are completed, the original group may be restored by carrying out the reverse of the reaction which introduced the protecting group.



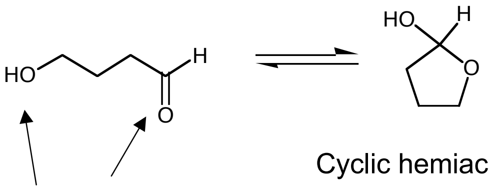
protection
(acetal formation)

further reactions

deprotection
(reverse of acetal formation)

Cyclic Hemiacetals

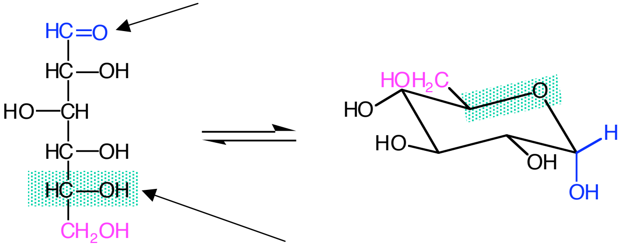
- Cyclic hemiacetals containing five and six atoms in the ring can form spontaneously from hydroxyaldehydes:



alcohol and carbonyl functions are contained in the same molecule

Cyclic hemiacetals are more stable than noncyclic hemiacetals; they can be isolated. They are favored under equilibrium (large K_{eq}) conditions.

- Five and six-carbon sugars are important biological examples of cyclic hemiacetals:

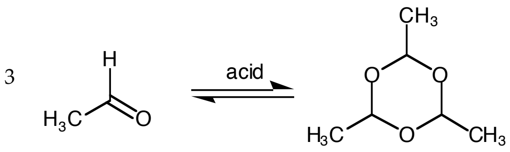


This oxygen becomes an OH group.

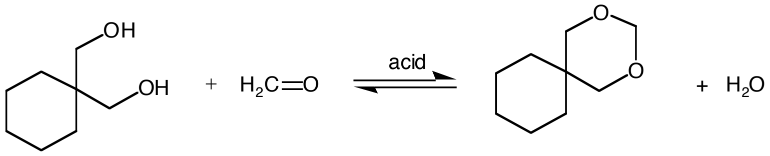
this oxygen ends up in the ring

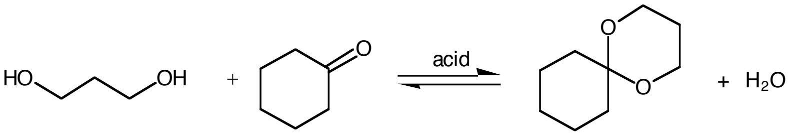
Cyclic Acetals

- Acetaldehyde forms a cyclic trimer when treated with acid:



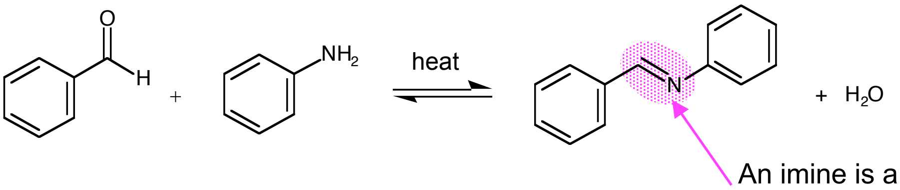
- Cyclic acetals are often used as protecting groups.





Reactions of Aldehydes and Ketones with Amines

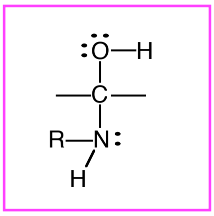
- Aldehydes and ketones react with primary amines to form ***imines,*** or ***Schiff bases***.



An imine is a compound with a **C=N** double bond (a nitrogen analog of an aldehyde or ketone

- The mechanism of imine formation involves the nucleophilic addition of the amine to the carbonyl carbon, forming a stable intermediate species called a ***carbinolamine***.

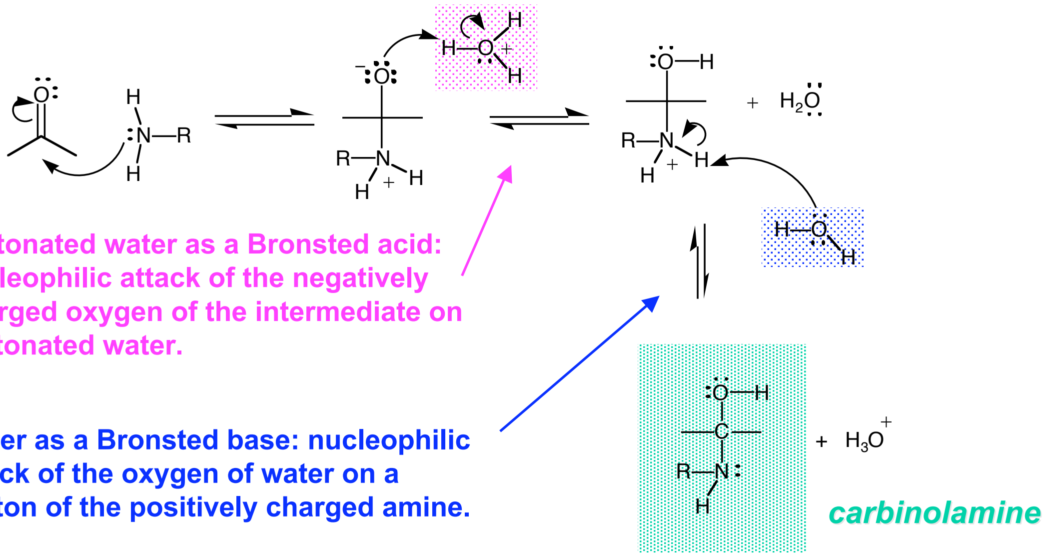
Carbinolamines are compunds with an amine group and a hydroxy group attached to the same carbon.



Carbinolamines are analogous to hemiacetals.

Mechanism of Carbinolamine Formation

- **Carbinolamine** formation begins with nucleophilic attack on the carbonyl carbon.
- The product of this attack is a neutral, charge-separated species.
- Water and its conjugate acid both play roles in the reaction.

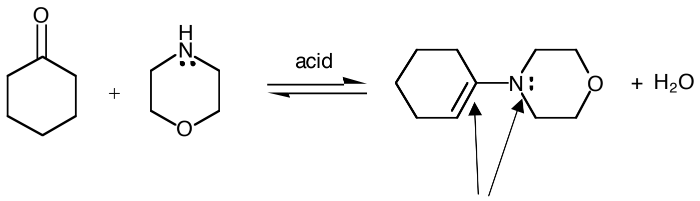


Protonated water as a Bronsted acid: nucleophilic attack of the negatively charged oxygen of the intermediate on protonated water.

Water as a Bronsted base: nucleophilic attack of the oxygen of water on a proton of the positively charged amine.

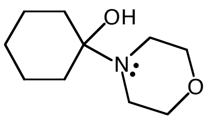
Reaction of Aldehydes/Ketones with 2° Amines

- Aldehydes and ketones react with secondary amines to form ***enamines*.**

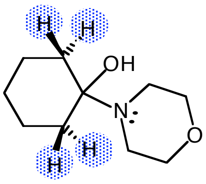


Enamines have a nitrogen bound to a carbon which is part of a C=C double bond.

- The mechanism involves nucleophilic addition of the amine to the carbonyl to form a carbinolamine.
- Enamines form only if the carbonyl compound has at least one hydrogen on a carbon adjacent to the carbonyl carbon.
- Formation of the alkene may be recognized as an elimination reaction.



carbinolamine



Irreversible Addition of Aldehydes and Ketones

- Aldehydes and ketones also undergo addition reactions which are essentially irreversible.
- These reactions use organometallic reagents to add alkyl groups to the carbonyl carbon atom.
- These reactions are nucleophilic additions; this means that the organic group added is acting as a nucleophile in the reaction.

We're accustomed to electrophilic behavior of alkyl groups (I.e., carbocations), but how does an alkyl group act as a nucleophile?

R-Li

R-MgX
(Grignard Reagent)

think of as….

$R{:}^{-}$ Li^{+}

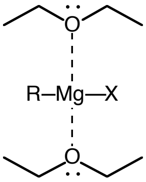
$R{:}^{-}$ MgX^{+}

The alkyl groups act as if they were free carbanions

Organometallic Reagents

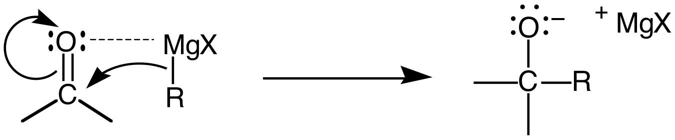
- The actual structure of Grignard reagents in solution is complex.
- These reagents are always prepared in ethereal solvents, and in fact two ether molecules are associated with the Grignard reagent.

Grignard reagent prepared in diethyl ether



Grignard reagents are highly polar compounds and are very strong Lewis bases.

- Mechanism of addition of a Grignard reagent to a carbonyl compound:



The product of this reaction step is a ***halomagnesium alkoxide***

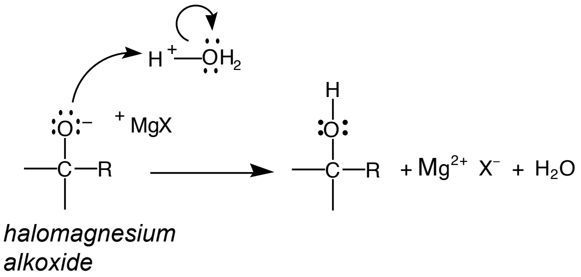
Lewis acid-base interaction between basic carbonyl oxygen and Mg makes the carbonyl carbon more reactive toward the alkyl group.

Addition Using Organometallic Reagents

- Formation of alcohols via addition of Grignard reagents to aldehydes and ketones is carried out in two separate steps

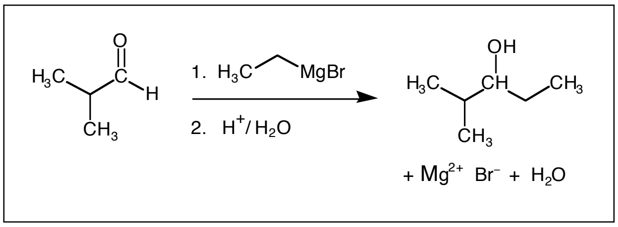
  Step 1: Addition of the nucleophilic alkyl group to the carbonyl carbon, aided by Lewis acid interaction between MgX^+ and the carbonyl oxygen. The product of this step is a halomagnesium alkoxide (see previous slide).

  Step 2. Protonation of the alkoxide oxygen. The product of this step is an alcohol.



Step 2.

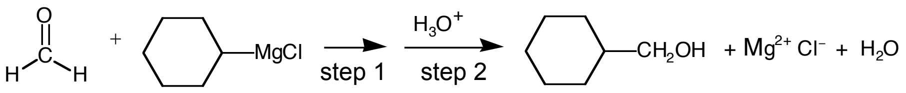
This notation makes it clear that the overall reaction occurs in two separate steps:



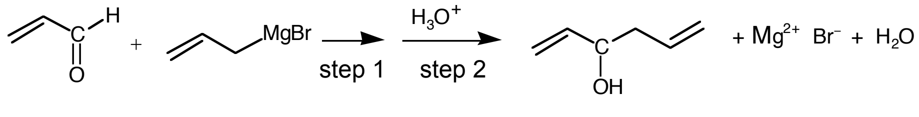
Addition Using Grignard Reagents

- Primary, secondary and tertiary alcohols may be formed in the reactions of aldehydes or ketones with Grignard reagents.

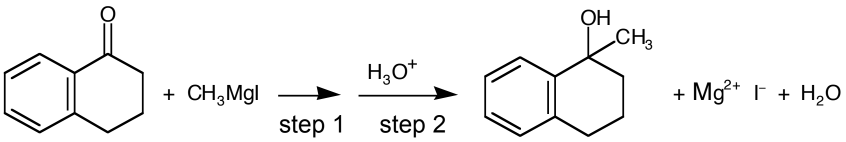
primary alcohols from formaldehyde



secondary alcohols from aldehydes



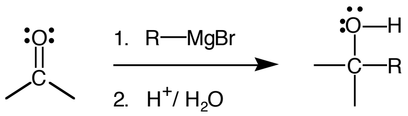
tertiary alcohols from ketones



Additions Using Organometallic Reagents

- The net effect of the reaction of a Grignard reagent with an aldehyde or ketone in the addition of the components R and H across the C=O double bond.
- Compare to nucleophilic addition of HCN:

Grignard:

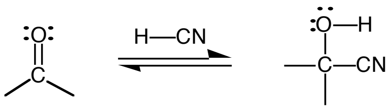


Nucleophile attacking the carbonyl carbon: → “ R^- ”

A separate step is needed to produce the alcohol from the halomagnesium alkoxide

irreversible reaction

Nucleophilic addition of HCN



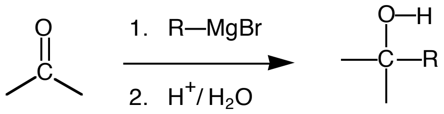
Nucleophile attacking the carbonyl carbon: → CN^-

“one-pot” reaction (multi-step mechanism, but all components may be added at once).

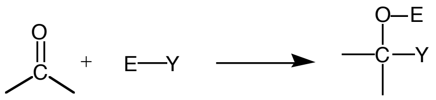
reversible reaction

Addition Reactions Using Organometallic Reagents

- Addition reactions to aldehydes and ketones using Grignard reagents are among the most important reactions in organic synthesis.
- These reactions are ***carbon-carbon bond forming reactions***.
- The net result of the reaction is the addition of the elements of R-H across the C=O double bond



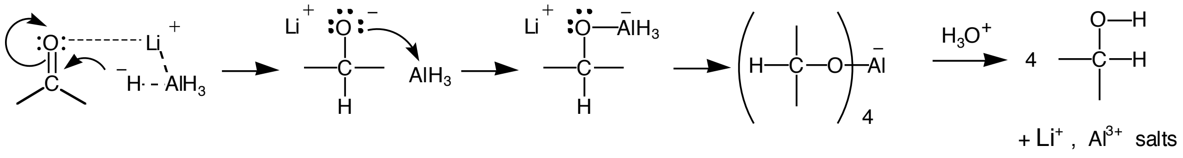
compared to..



- Other metal-based reagents also add components across the C=O bond in an analogous way:
  - Metal hydrides add H^- and H^+ across the C=O double bond.
  - When we add H-H to a double bond, we call the reaction a *reduction*.

Metal Hydrides

- $LiAlH_4$ and $NaBH_4$ act in a fashion similar to Grignard reagents.
- The hydride ion H^- acts as the nucleophilic reagent adding to the carbonyl carbon atom of an aldehyde or a ketone.

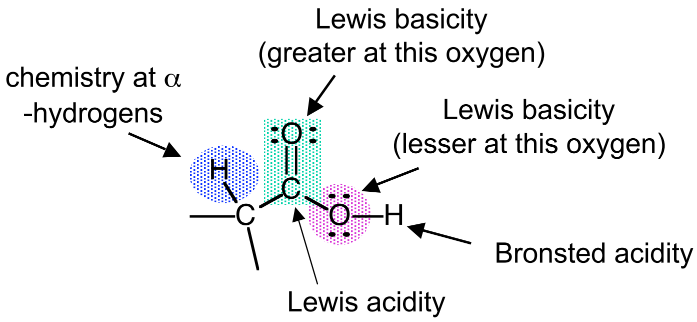


- The hydride ion in $LiAlH_4$ is more basic than the hydride ion in $NaBH_4$, and therefore it is more reactive.
- Some functional groups which may be reduced by $LiAlH_4$ are unreactive with $NaBH_4$ (e.g., alkyl halides R-X, nitro groups $-NO_2$)
  - Therefore $NaBH_4$ may be used to reduce C=O bonds in the presence of such groups.

Carboxylic Acids

- Carboxylic acids represent the next higher “oxidation level” up from aldehydes/ketones.

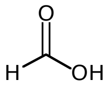
- Carboxylic acids occur widely in nature.
- Carboxylic acids serve important roles in organic synthesis.



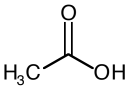
- **reactions at the carbonyl group**
- **reactions at the carboxylate oxygen**
- **reactions involving α-hydrogens**

Nomenclature of Carboxylic Acids

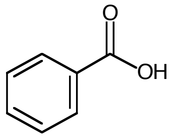
- Many carboxylic acids are known by their common names.
- These common names are often formed by adding the suffix “ic” + acid to the common names for aldehydes and ketones.



formic acid

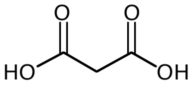


acetic acid

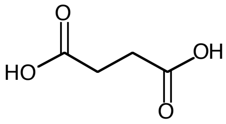


benzoic acid

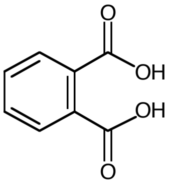
- Carboxylic acids may also contain two carboxy groups. These compounds are called dicarboxylic acids.



malonic acid



succinic acid

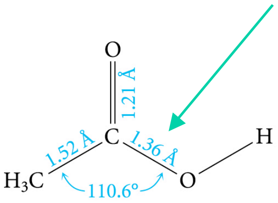


phthalic acid

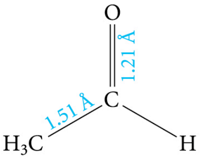
Structure and Properties of Carboxylic Acids

- Compare bond lengths and angles to other C=O and C-O containing compounds:

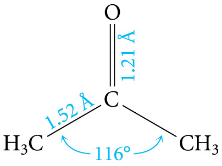
sp^2–sp^3 single bond is shorter than sp^3–sp^3 bond



acetic acid

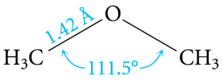


acetaldehyde

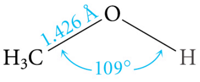


acetone

C=O bond length is the same in aldehydes, ketones, and carboxylic acids

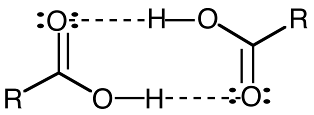


dimethyl ether



methanol

- Carboxylic acids have high boiling points due to their ability to act as both donors and acceptors in hydrogen bonding.

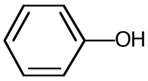


Carboxylic acids can exist as dimers in solution

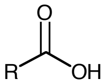
Acidity of Carboxylic Acids

- Carboxylic acids are much more acidic than alcohols.
- Two main reasons explain this acidity:
  - Resonance stabilization of the conjugate base, $RCOO^-$.
  - Electrostatic stabilization of the negative charge by the adjacent polar carbonyl group.

ROH $pK_a = 15\text{-}17$

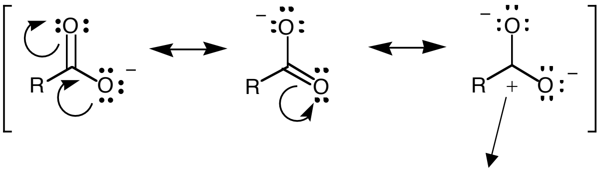


$pK_a = 10$

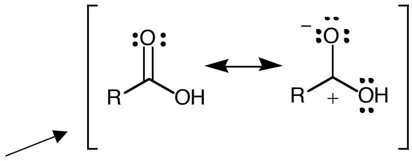


$pK_a = 3\text{-}5$

conjugate base:

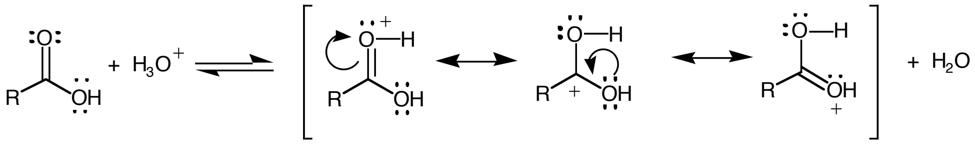


Separation of charge in the carbonyl C and O is already partially developed in carboxylic acid

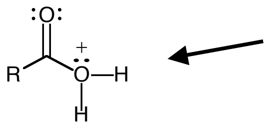


Basicity of Carboxylic Acids

- As in aldehydes and ketones, the carbonyl oxygen of carboxylic acids is weakly basic.
- The carbonyl carbon of carboxylic acids reacts with protons to form a resonance-stabilized conjugate acid.



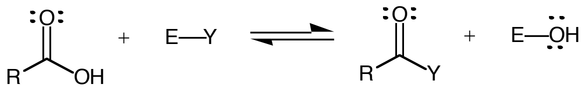
- Why does protonation occur only at the carbonyl oxygen, and not at the carboxylate oxygen?



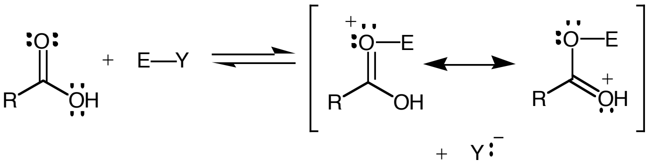
- Protonation at the carboxylate oxygen would result in a species like this
- This species is not resonance-stabilized, so its formation is much less favorable

Reactions at the Carbonyl Group

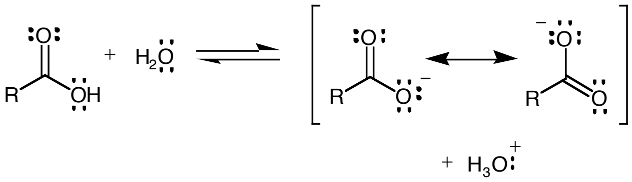
- The most typical reaction at the carbonyl group of carboxylic acid is substitution at the carbonyl carbon:



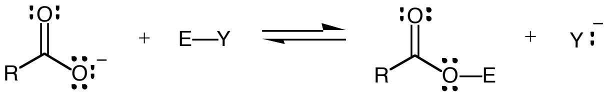
- Another important reaction is the reaction of the carbonyl oxygen with an electrophile:



- Reaction at the carboxylate oxygen results in ionization:

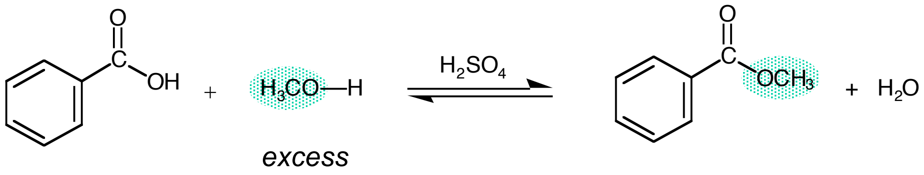


- The carboxylate oxygen anion can act as a nucleophile:



Conversion of Carboxylic Acids into Esters

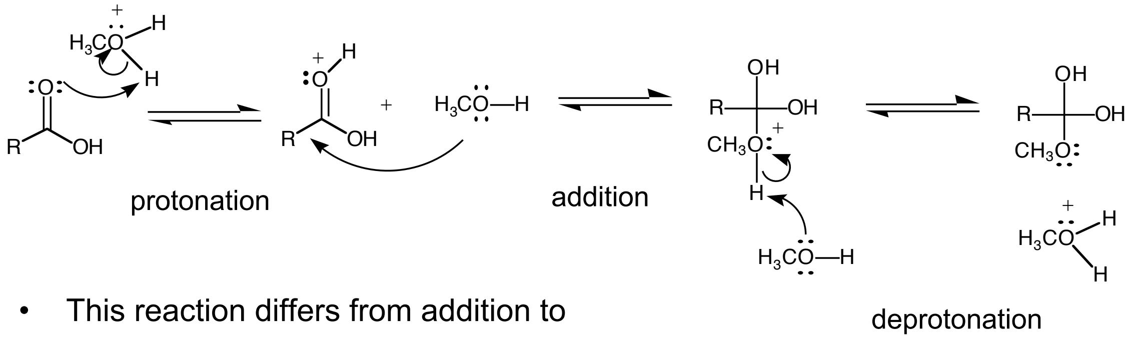
- The acid-catalyzed preparation of ***esters*** from carboxylic acids is known as Fischer esterification.
  - Esters are carboxylic acid derivatives with the carboxylate -OH group replaced by an alkoxy group.
  - Treating a carboxylic acid with an excess of an alcohol gives esters.



- This is an example of substitution at the carbonyl carbon.
- The reaction is driven forward by using a large excess of alcohol (usually as solvent), an application of Le Chatelier's priniciple.
- This esterification can't be carried out with tertiary alcohols (why?) or with phenols.

Mechanism of Acid-Catalyzed Esterification

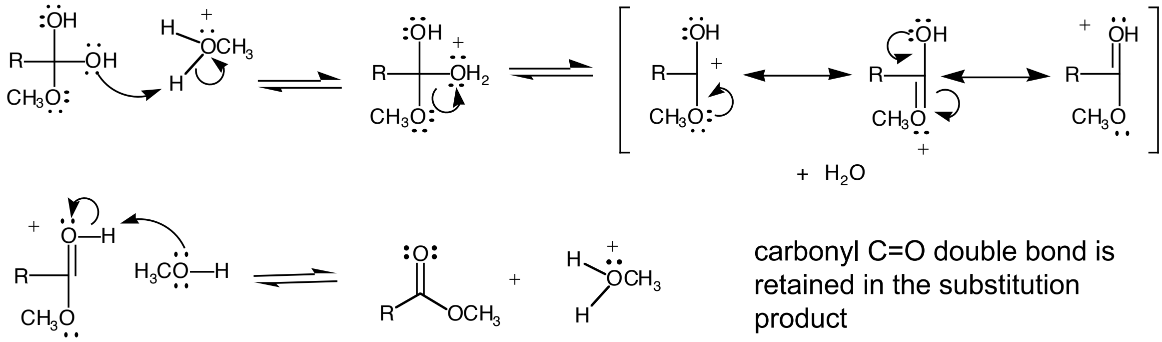
- The first steps of the reaction are familiar to us from aldehyde/ketone nucleophilic addition:
  - Protonation of the carbonyl oxygen by $CH_3OH_2^+$.
  - Nucleophilic attack of the alcohol on the carbonyl carbon by CH_3OH.
  - Deprotonation of the tetrahedral intermediate by CH_3OH.



- This reaction differs from addition to aldehydes and ketones in the *next* step -- in what happens to the tetrahedral intermediate.

Mechanism of Acid-Catalyzed Esterification

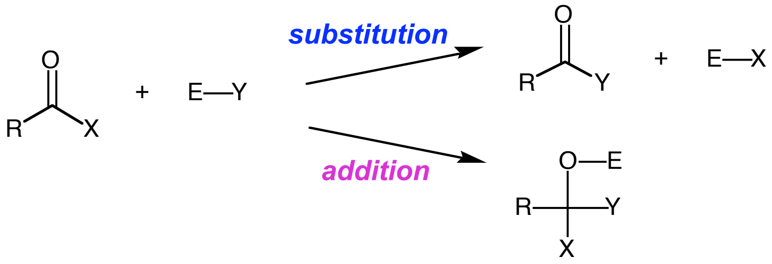
- In acid-catalyzed reactions of aldehydes and ketones, the tetrahedral alcohol species formed in these three steps (protonation, addition, deprotonation) is a hemiacetal. It may undergo further reactions, but the ultimate product will be a tetrahedral ***addition product***.
- In acid-catalyzed reactions of carboxylic acid, this tetrahedral species is not stable and undergoes further reaction, ultimately producing a ***substitution product*** and not an addition product.



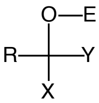
carbonyl C=O double bond is retained in the substitution product

Substitution vs. Addition

- Aldehydes and ketones undergo ***addition*** reactions while carboxylic acids undergo ***substitution*** reactions.



- In both reactions, a tetrahedral product is initially formed.
- The choice between substitution and addition depends on how good the leaving group, X, is.



tetrahedral (intermediate) product

For aldehydes and ketones: X = R, H
Cannot act as leaving group

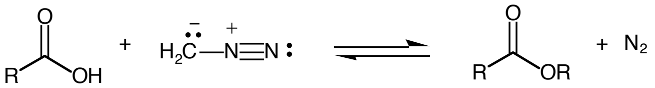
For carboxylic acids: X = OH, protonated to OH_2^+
Can act as leaving group

Esterification by Alkylation

- Another route to esterification of carboxylic acids involves one of the other types of reactions we outlined at the beginning of the discussion of carboxylic acids.

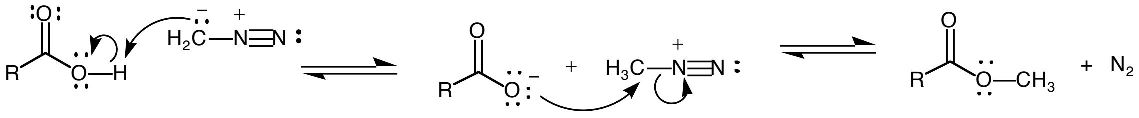
reactivity at the carboxylate oxygen

- Alkylation of the carboxylate oxygen may be carried out using diazomethane, a toxic, explosive, allergenic gas.



diazomethane

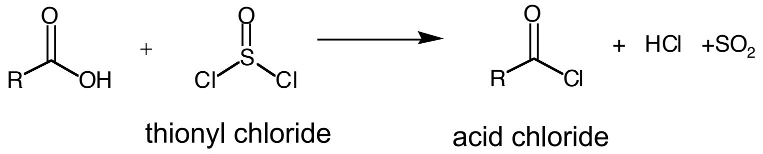
mechanism:



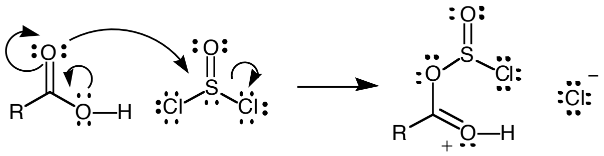
both steps involve the carboxylate oxygen and not the carbonyl oxygen

Synthesis of Acid Chlorides from Carboxylic Acids

- Acid chlorides are prepared from carboxylic acids using either thionyl chloride ($SOCl_2$) or phosphorus pentachloride (PCl_5).



- This reaction fits the pattern of substitution at the carbonyl group; however, the mechanism proceeds slightly differently from that of Fischer esterification.
- The first step involves attack of the sulfur of thionyl chloride by the carbonyl oxygen acting as a Lewis base.

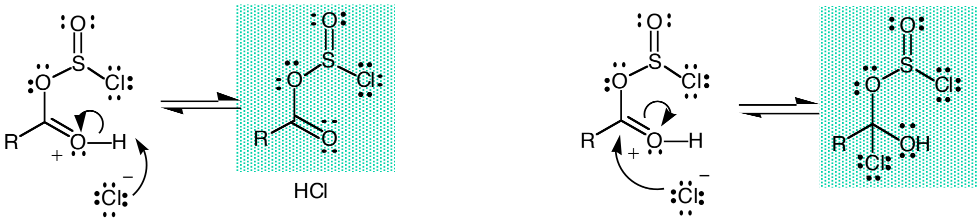


The sulfur is very electrophilic; why?

Preparation of Acid Chlorides

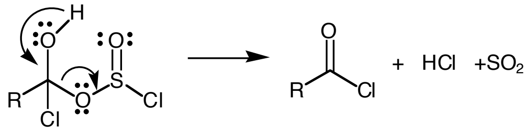
Compare reaction of carboxylic acids with $SOCl_2$ to reaction with alcohols.

- Carbonyl oxygen acts as a Lewis base to attack the electrophilic sulfur atom instead of attacking a proton.
- The protonated product of this first step is a very powerful electrophile.
  - The Cl^- anion can abstract a hydrogen, giving an unstable intermediate…
  - Or, the Cl^- anion can undergo nucleophilic attack on the carbonyl carbon (because this species is so electrophilic, even a weak nucleophile like Cl^- can undergo this reaction).



Preparation of Acid Chlorides

- The last step is the elimination of the thionyl chloride group as SO_2 and HCl. This step is irreversible because SO_2 is a gas.

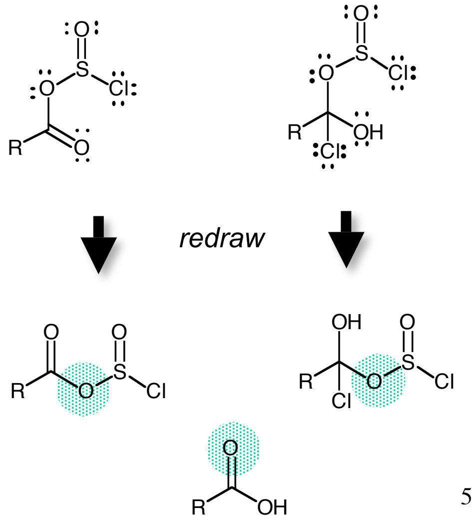


Redraw two of the intermediates in this mechanism:

Drawn this way, it makes it look like a simple substitution at the carboxylate oxygen.

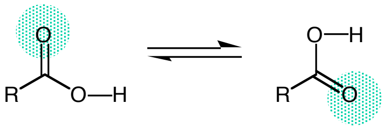
However, if we look back at the mechanism, we can see that the thionyl chloride adds to oxygen in a carbonyl group, not to oxygen in a carboxylate group.

The reaction occurs this way because the carbonyl oxygen is more strongly Lewis basic than is the carboxylate oxygen.

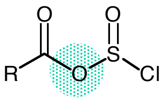


Attack via the Carbonyl Oxygen

- The oxygens in a carboxylic acid are indistinguishable. The proton moves rapidly back and forth from one to the other.



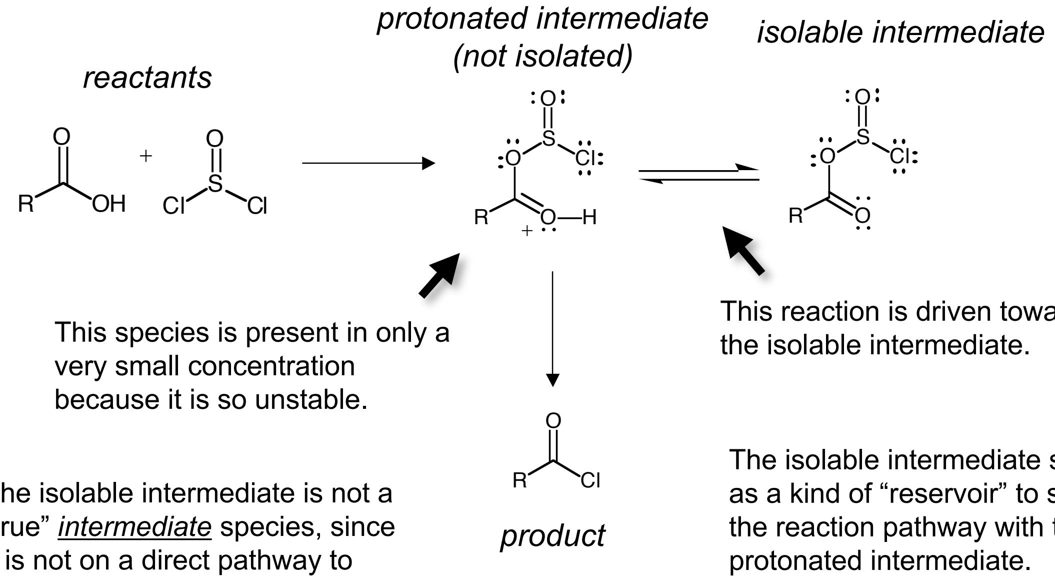
….however, when the reaction takes place, it does so via attack by the more Lewis basic carbonyl oxygen (whichever one that happens to be at that instant in time), and *not* via the less basic carboxylate oxygen.



The oxygen that is a carbonyl in this intermediate was a carboxylate when the reaction started.

Preparation of Acid Chlorides

- Another interesting point about the mechanism of acid chloride formation is the role of the thionyl intermediate.



This species is present in only a very small concentration because it is so unstable.

This reaction is driven towards the isolable intermediate.

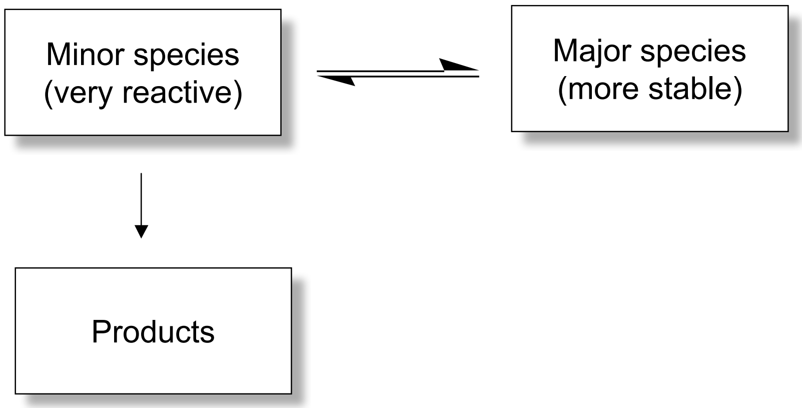
The isolable intermediate is not a "true" *intermediate* species, since it is not on a direct pathway to the product.

The isolable intermediate serves as a kind of "reservoir" to supply the reaction pathway with the protonated intermediate.

Can you recall an analogous example?

Reactive Intermediates Have Low Concentrations

- If the minor species is *too* reactive, a high concentration might make it subject to unwanted side reactions.
- The concentration of the minor species is kept low by virtue of its reversible reaction to form the more stable major species.
- This "reservoir" meters the concentration of the minor species so that it reacts immediately to products and can't build up in concentration.



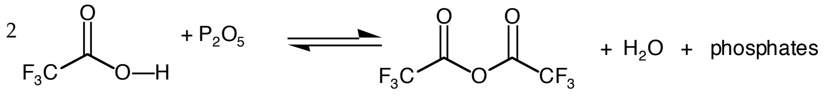
Minor species
(very reactive)

Major species
(more stable)

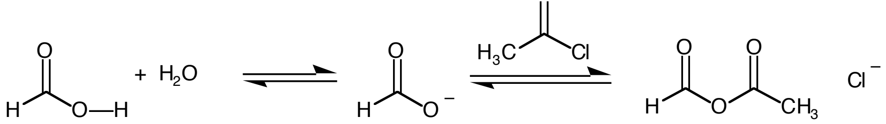
Products

Preparation of Acid Anhydrides

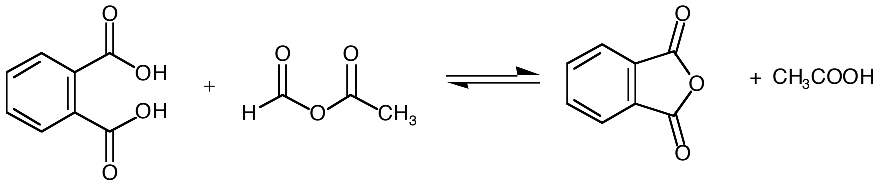
- Acid anhydrides may be thought of as the condensation product of two carboxylic acids, with loss of water.
- Anhydrides are formed by treatment of carboxylic acids with strong dehydrating reagents.



- Anhydrides may be formed by reaction between an acid chloride and the conjugate base of a carboxylic acid.

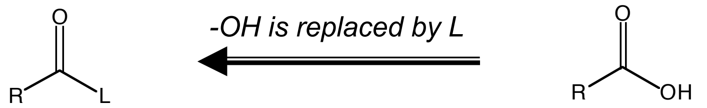


- Cyclic anhydrides may be formed by treating a dicarboxylic acid with another anhydride.

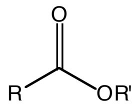


Carboxylic Acid Derivatives

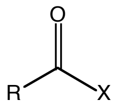
- Carboxylic acid derivatives have the general formula:



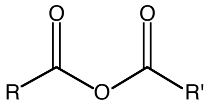
carboxylic acid derivative *carboxylic acid*



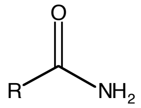
esters, L = OR’



acid halides, L = X = halogen (usually Cl)



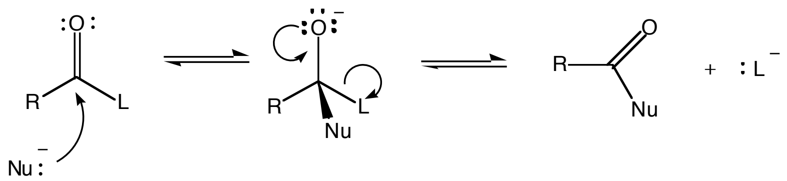
acid anhydrides, L = OCOR’



amides, L = NH_2, NHR’, NHR’R”

Carboxylic Acid Derivatives (Acyl Compounds)

- Not only are the structures of these compounds related, but their chemistries are related also.
- One of the most important types of reactions these compounds undergo are nucleophilic addition-elimination reactions resulting in the replacement of L with another nucleophile.

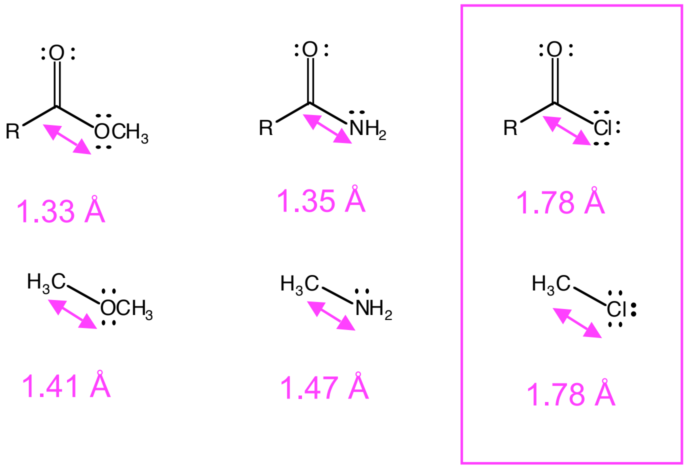


addition of Nu:⁻ elimination of L:⁻

- The two most important factors governing the chemistry of these transformations are:
  - The stability of the starting carboxylic acid derivative
  - The characteristics of the leaving group L:⁻

Structure and Stability of Acyl Compounds

- Compare the C-O bond lengths of acyl compounds with their related single-bonded compounds:

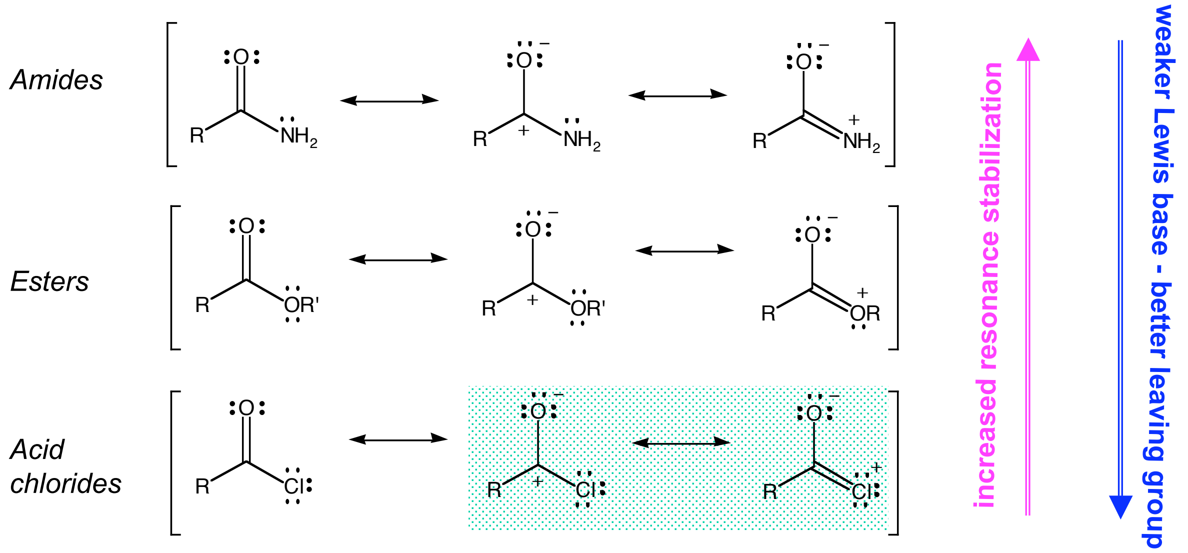


The C-Cl bond in an acyl chloride is not shortened compared to that of an alkyl chloride

- Acyl compounds are resonance-stabilized.
- The C-O and C-N bonds in esters and amides are shortened compared to ethers and amines because of their double bond character.

Structure and Stability of Acyl Compounds

- Look at the resonance-stabilized structures:



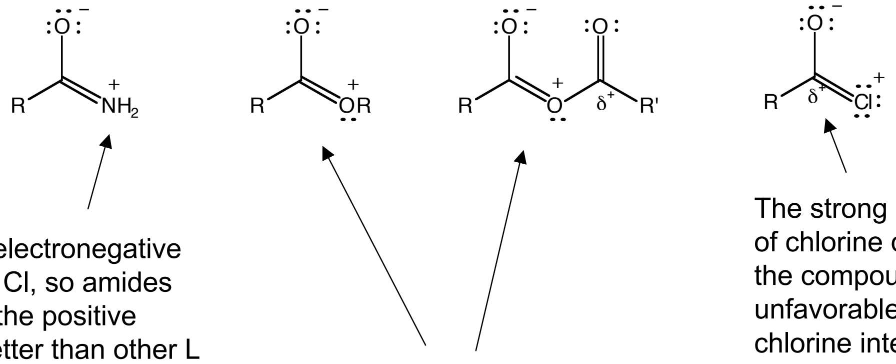
higher energy resonance forms

- Acyl chlorides are the least resonance-stabilized of the acyl compounds
- Halides are the best leaving groups of the acyl compound “L” groups

---

Structure and Stability of Acyl Compounds

- Let’s take a look at one of the high energy resonance forms and compare them for the different acyl compounds.



N is less electronegative than O or Cl, so amides can bear the positive charge better than other L groups. The result is a more polar C=O group and a more basic carbonyl oxygen.

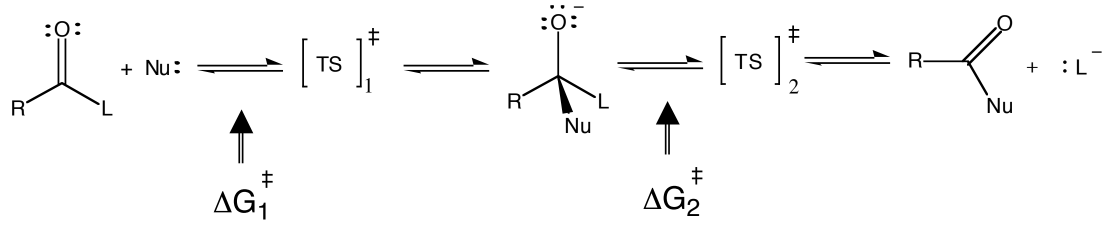
Oxygen is more electronegative than nitrogen and likes bearing the positive charge less.

Anhydrides exhibit charge repulsion between the carbon in the leaving acyl group and the carboxylate oxygen

The strong polar effect of chlorine destabilizes the compound via an unfavorable carbon-chlorine interaction - the most unfavorable in this series.

Reactivity in Nucleophilic Acyl Substitution

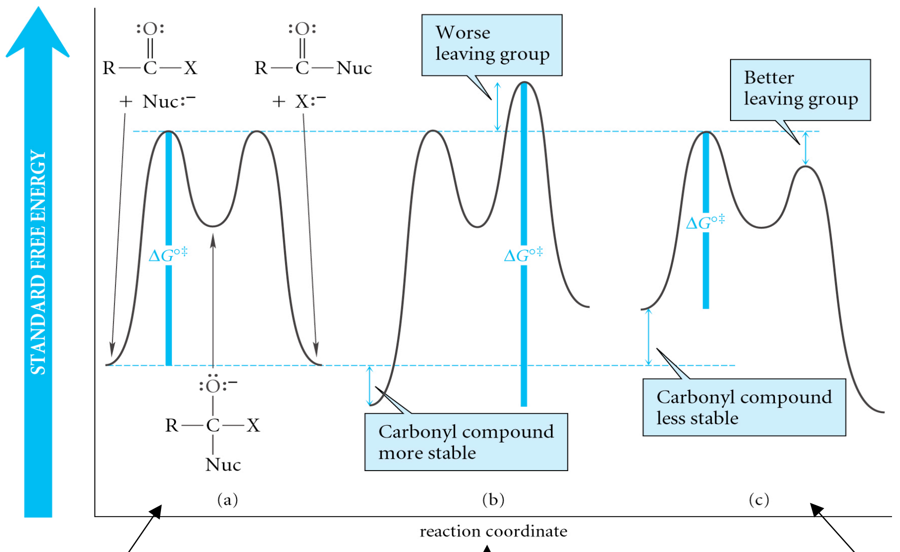
- The relative reactivity of acyl compounds in nucleophilic acyl substitution is affected by both of the factors we have discussed:
  - Stability of the starting acyl compound
  - Ability of the “L” group to act as a leaving group
- We can use activation energy to show this more clearly.



The height of the first transition state will depend on the stability of the starting acyl compound

The height of the second transition state will depend on the proficiency of **L** as a leaving group

Reactivity in Nucleophilic Acyl Substitution



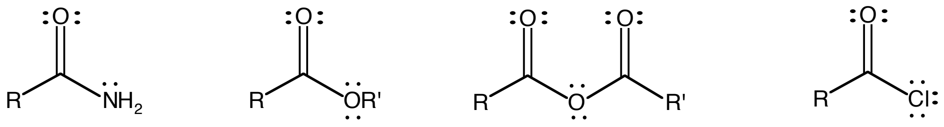
Case (a): transition states for formation and breakdown of tetrahedral intermediate are similar in energy (Nuc:⁻ and L:⁻ are similar).

Case (b): reactant is more stable relative to transition state 1 and L is a worse leaving group compared to Case (a).

Case (c): reactant is destabilized compared to Case (a), and L:⁻ is a better leaving group in this case.

Reactivity in Nucleophilic Acyl Substitution

- The trends for reactant stability and leaving group ability tend to work together (both contributing to make the compound more reactive or both contributing to make the compound less reactive)



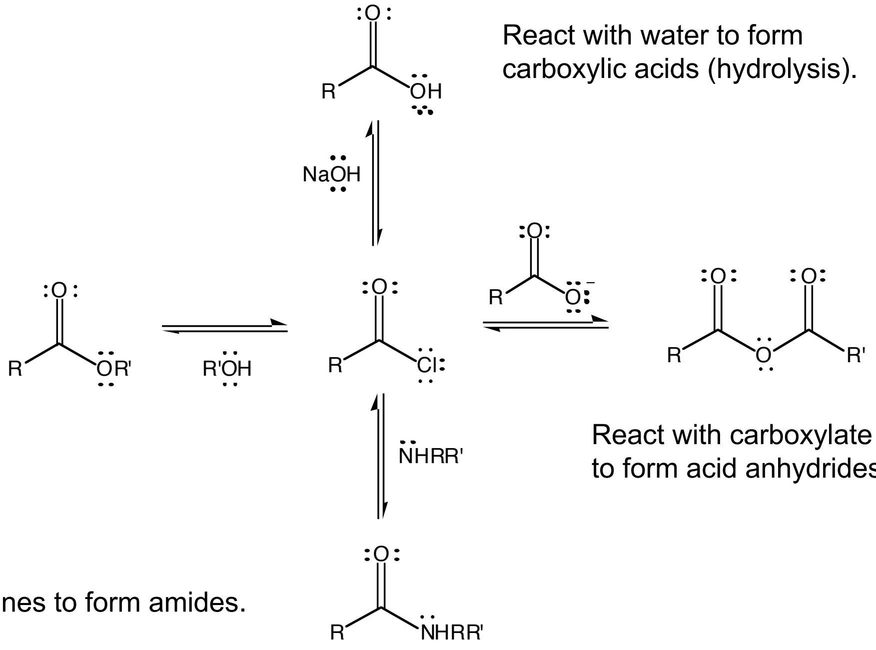
INCREASING REACTIVITY →

decreased resonance stabilization →

weaker Lewis base - better leaving group →

Reactivity of Acid Chlorides

- Acid chlorides are the most reactive of the acyl substituted carboxylic acid derivatives, and they readily undergo a variety of nucleophilic addition-elimination reactions.



React with water to form carboxylic acids (hydrolysis).

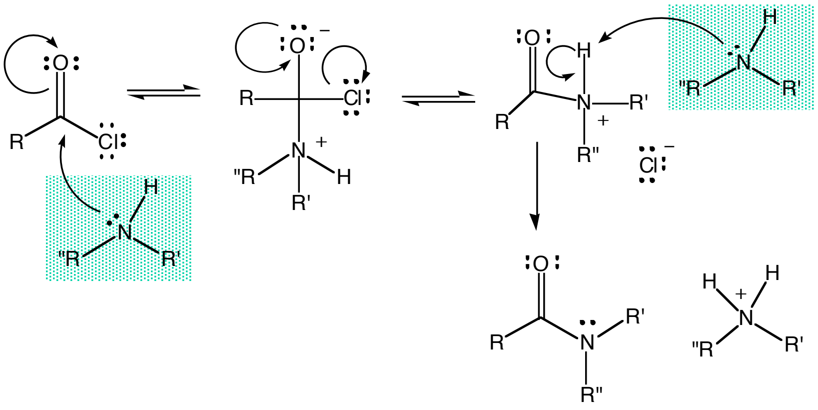
React with alcohols to form esters.

React with carboxylate anions to form acid anhydrides.

React with amines to form amides.

Reactivity of Acid Chlorides

- Acid chlorides react with NH_3, primary and secondary amines to give amides.

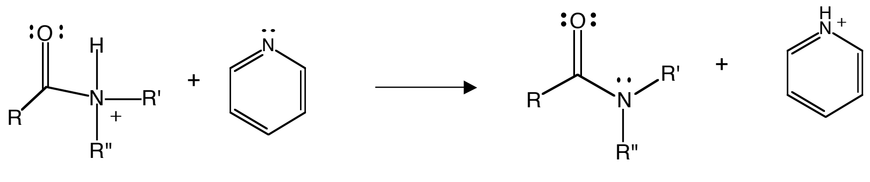


Notice that ***two*** moles of the amine are required to complete the reaction: one to act as the nucleophile which substitutes for Cl, and one to act as a base to deprotonate the ammonium ion.

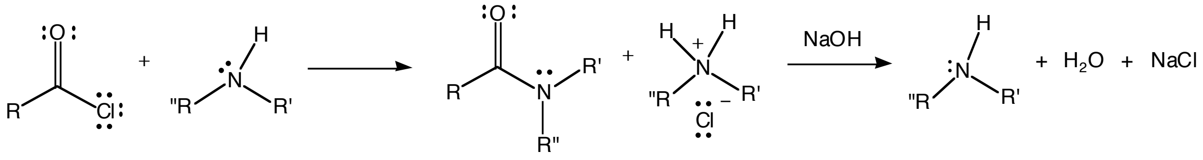
- Other methods for carrying out the proton transfer step have been developed for cases where the amine is too costly to waste in the final proton transfer step.
  - Add a tertiary amine to carry out the final proton transfer step (why tertiary?)
  - Run a two-phase reaction with a strong base (OH^-) preent in the aqueous layer.

Formation of Amides From Acid Chlorides

- Tertiary amines such as pyridine or triethylamine can carry out the proton transfer step:

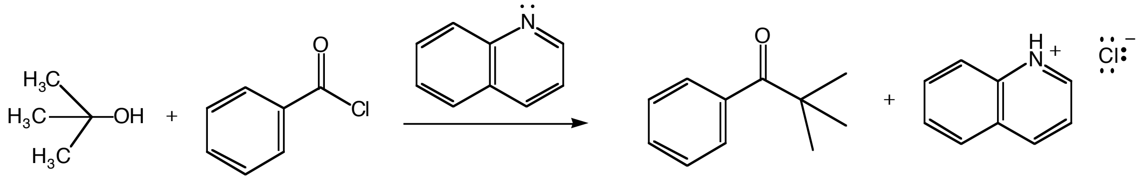


- The protonated amine may be deprotonated via extraction into an aqueous phase where a strong base is present.

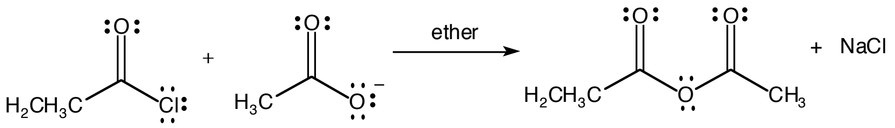


Reaction of Acid Chlorides

- Esters are formed from the nucleophilic substitution of acid chlorides with alcohols.
  - Hydrochloric acid is a by-product of this reaction. In practice, tertiary amines are often added to neutralize the HCl.

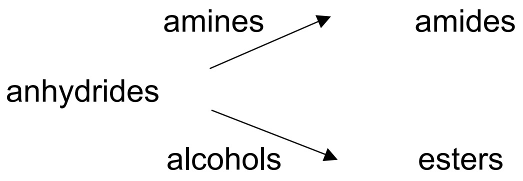


- Anhydrides are formed from acid chlorides and salts of carboxylic acids.
  - This provides a way to prepare mixed anhydrides (R and R' may be different groups).



Reactions of Anhydrides and Esters

- Anhydrides react with nucelophiles in substitution-elimination reactions in a manner similar to acid chlorides.

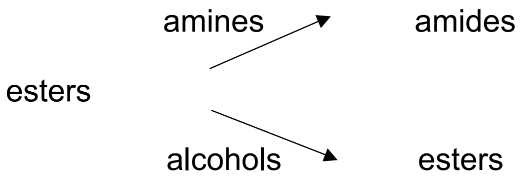


amines → amides

anhydrides

alcohols → esters

- Esters react with nucelophiles in substitution-elimination reactions in a manner similar to acid chlorides, although they are much less reactive towards these nucleophiles.



amines → amides

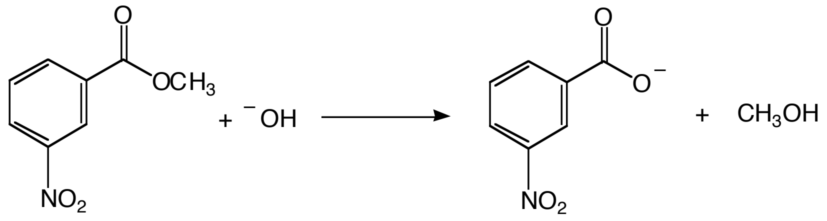
esters

alcohols → esters

When an ester reacts with an alcohol to give another ester, the reaction is known as a ***transesterification.***

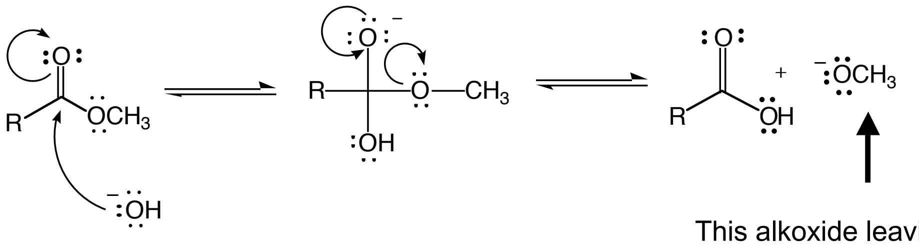
Hydrolysis Reactions

- Carboxylic acid derivatives undergo a cleavage reaction with water (hydrolysis) to yield carboxylic acids.
  - When the reaction is acid-catalyzed, the mechanism is the reverse of the Fischer esterification of carboxylic acids.
  - When the reaction occurs under basic conditions, the base is not a catalyst but is consumed in the reaction.
  - Under basic conditions, the reaction is effectively irreversible.



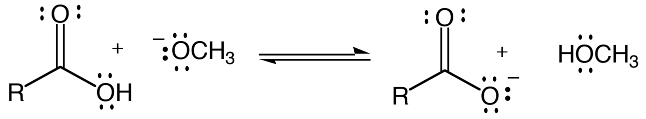
Mechanism of Ester Saponification

- Conversion of esters to carboxylic acids under basic conditions is called “saponification.”



This alkoxide leaving group reacts with the acid -- why?

Look at the pK_a values:



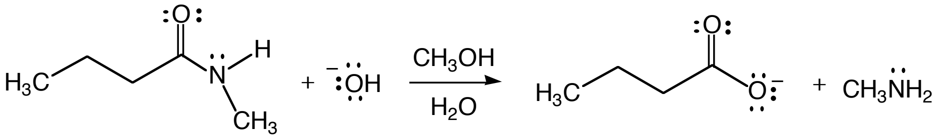
pK_a = 4.5 *pK_a = 15*

We can’t regenerate OH^-, so the reaction is not catalytic in OH^-, but instead consumes OH^- as a reactant.

The reaction is strongly driven toward the right.

Hydrolysis Reactions

- Hydrolysis of amides can also be carried out under acidic (acid-catalyzed) or basic conditions, but the reaction is slower and must be heated to make it proceed.
  - Why it this reaction slower than that of acid chlorides or esters?

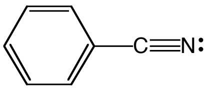


- Compare the leaving group in this reaction (-NHR) with that is an ester hydrolysis (-OR)
- (-NHR) is a much stronger base (its conjugate acid is much weaker) and therefore it's a poor leaving group

Leaving group	conjugate acid	(pK_a)
-OR	ROH	15
-NHR	NH_2R	35

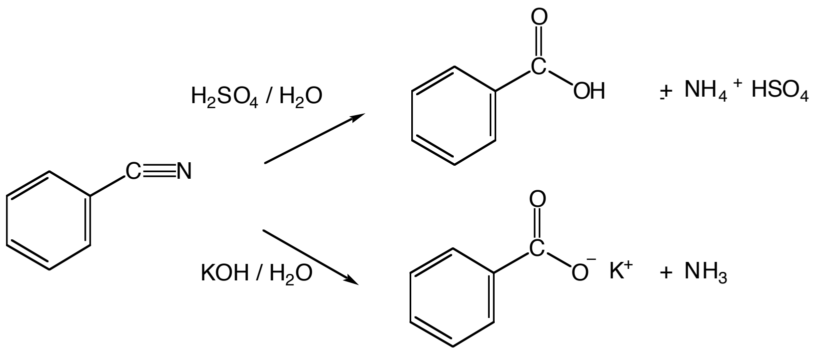
Chemistry of Nitriles

- Nitriles are compounds of the same "oxidation level" as carboxylic acids and carboxylic acid derivatives (three bonds to heteroatoms).



benzonitrile

- Nitriles undergo hydrolysis reactions similar to carboxylic acid derivatives. Hydrolysis occurs in both acid and base media, but the reactions are slower than those with esters or amides.



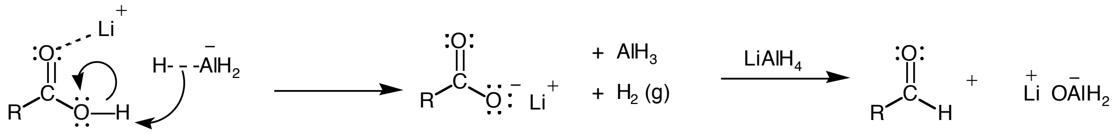
Note that the reaction stoichiometry under acidic conditions requires two moles of water for each mole of nitrile converted.

Hydrolysis of Nitriles

- Hydrolysis of nitriles under both acidic and basic conditions involves the formation of an amide, which is then hydrolyzed to a carboxylic acid as we have already discussed.
- Nitriles behave mechanistically like carbonyls.
  - Acid-catalyzed hydrolysis begins with protonation of the nitrile nitrogen, followed by addition and a series of protonation-deprotonation steps to form the amide.
  - Hydrolysis under basic conditions involves attack of OH^- on the nitrile carbon as the first step.

Reduction of Carboxylic Acid and Acid Derivatives

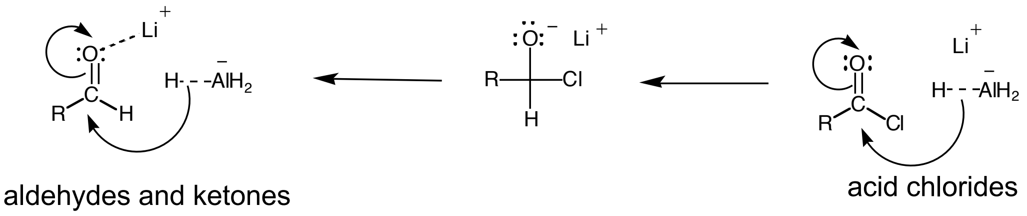
- Metal hydrides react with carboxylic acids to produce alcohols.
- The first step is different from the reaction between $LiAlH_4$ and aldehydes or ketones:
  - the basic hydride abstracts a proton to create a carboxylate ion and H_2(g).



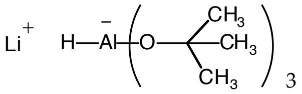
- A carboxylate salt is not a good electrophile!
- However, the $LiAlH_4$ is able to undergo nucleophilic attack and reduce the carbonyl to an aldehdye (the mechanism still under debate, so we won't go into the details of this step).
- Aldehydes react quickly with remaining $LiAlH_4$ to produce alcohols as we have already discussed.

Reduction of Carboxylic Acid and Acid Derivatives

- $LiAlH_4$ reduces acid chlorides to alcohols in a manner similar to the mechanism for aldehyde reduction.
  - The acid chloride is so reactive, the hydride ion can attack the carbonyl carbon directly without the carbonyl oxygen-Li^+ interaction



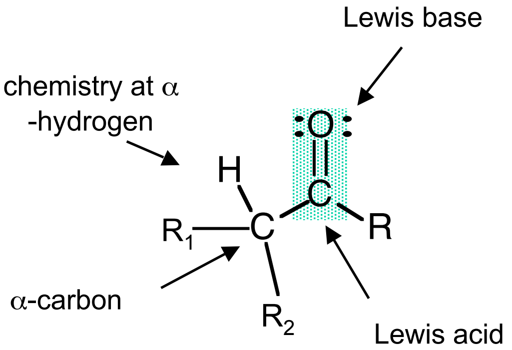
- The acid chloride is reduced to an aldehdye which is then reduced to an alcohol.
- Reduction from aldehyde to alcohol can be prevented by using a less reactive hydride reagent:



$$Li^+ \quad H-\overset{-}{Al}\left(O-C(CH_3)_3\right)_3$$

Chemistry at the α-Carbon of Carbonyl Compounds

- We have learned that the oxygen of a carbonyl group can act as a Bronsted or a Lewis base by attacking protons or other electrophiles.
- We have shown how the carbon of a carbonyl group can act as a Lewis acid resulting in addition of a nucleophile.
- Now we will explore chemistry at the carbon atom adjacent to the carbonyl carbon (α-carbon).

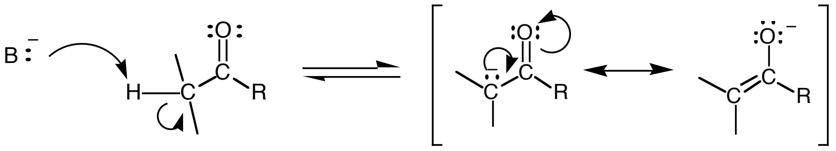


- What makes the α-carbon special?
  - Hydrogens attached to the α-carbon of aldehydes and ketones are weakly acidic.
  - How acidic are they?

    pK_a values range from ca. 15-20 (similar to alcohols).

Bronsted Acidity of Aldehydes and Ketones

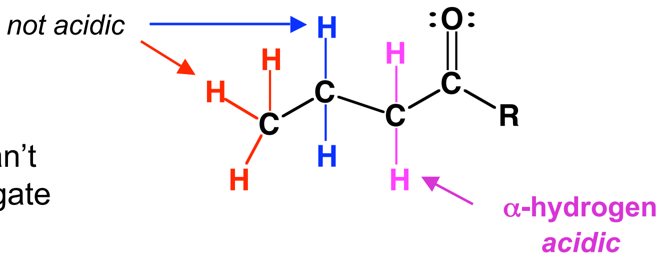
- Ionization of a proton from the α-carbon of an aldehyde or a ketone via attack by a Bronsted base results in formation of an anion called an ***enolate***.



pK_a = 16

+ B—H

- Compare to the ionization of an proton further removed from the C=O bond:

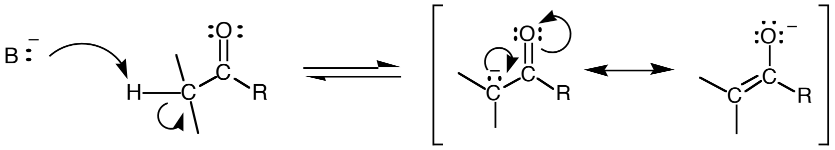


Hydrogens on carbon atoms not adjacent to the carbonyl carbon can't form ***resonance-stabilized*** conjugate bases

---

Bronsted Acidity of Aldehydes and Ketones

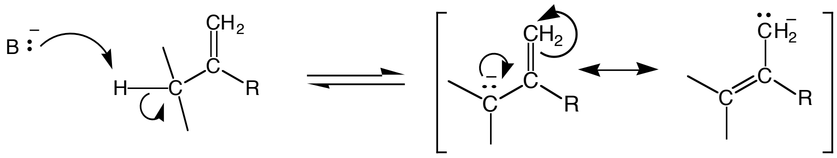
- Ionization of a proton from the α-carbon of an aldehyde or a ketone via attack by a Bronsted base results in formation of a resonance-stabilized anion called an ***enolate***.



pK_a = 16

+ B—H

- Compare to the ionization of an olefin which forms a resonance stabilized allyl anion:



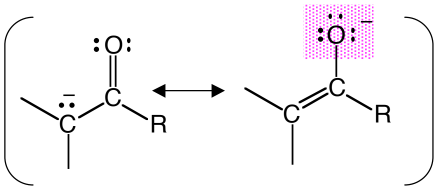
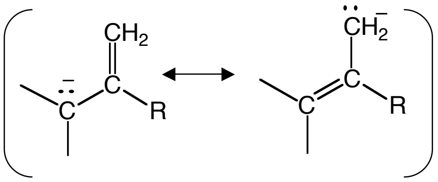
pK_a = 42

+ B—H

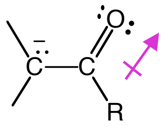
- Why is the aldehyde or ketone α-hydrogen so much more acidic?

Acidity of α-Hydrogens

- Enolate anions are resonance-stabilized.
- The extra stability afforded the conjugate base by resonance stabilization makes the α-hydrogen of an aldehyde or a ketone more acidic than an α-hydrogen on a compound which can't form resonance-stabilized intermediates.
- But this can't be the whole picture…..

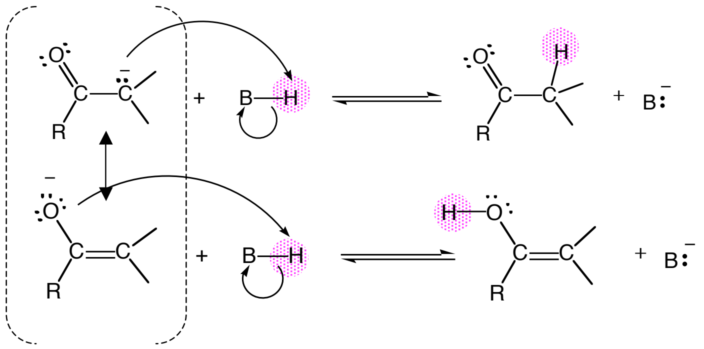
- It's oxygen's electronegativity that makes the difference.
- Delocalizing charge onto a more electronegative atom adds stability to the enolate anion
- The polar effect of the C=O dipole also stabilizes the enolate anion:



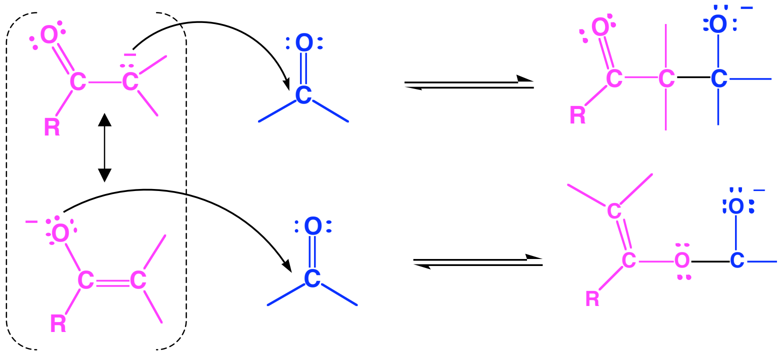
favorable charge-dipole interaction

Reactions of Enolate Ions

- Enolate ions are Bronsted bases.



- Enolate ions are Lewis bases (nucleophiles).

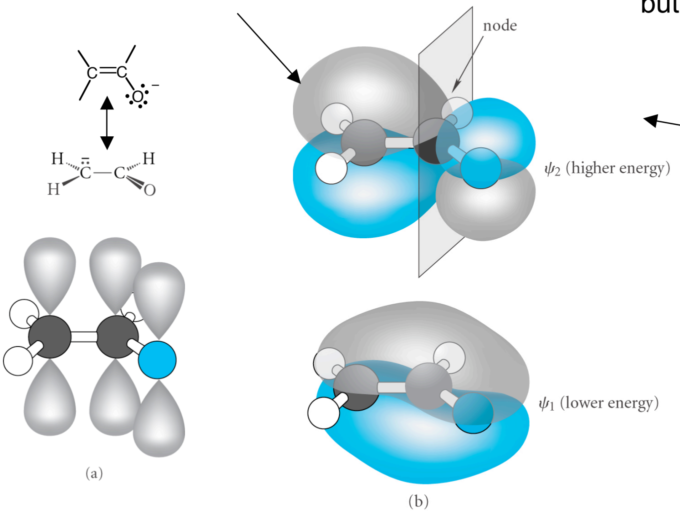


Molecular Orbitals of Enolate Ions

- The two highest occupied molecular orbitals of the enolate ion are shown below.

Note that this higher energy orbital is distorted toward carbon .

In the highest energy occupied orbital, the oxygen has more of the negative charge but the carbon has more of the orbital



This higher energy orbital is where the electrons come from when the enolate ion acts as a Lewis base.

The lower energy orbital shows orbital overlap over the entire ion.

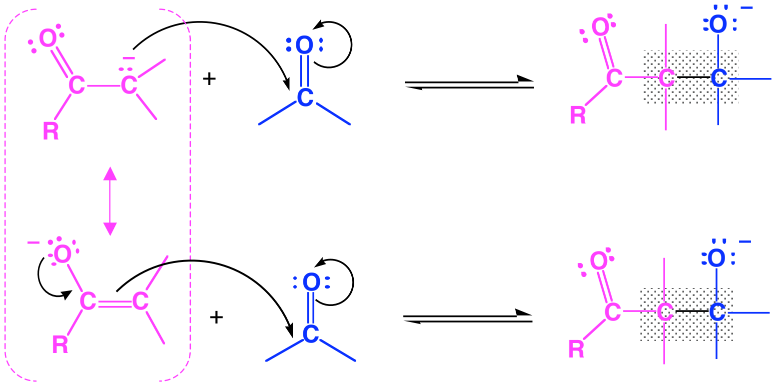
There are three M.O.'s of the enolate ion, derived from the three 2*p* orbitals involved in the overlap; the third (not shown) is an unoccupied antibonding orbital.

Reactions of Enolate Ions

- How do we know whether the attack of the enolate ion will occur at the α-carbon or at oxygen?
- The molecular orbital picture tells us that:
  - The enolate electrons which will participate in a nucleophilic attack reside predominantly on the oxygen.
  - The orbital which participates in the nucleophilic attack is distorted toward the α -carbon.
- Reactions which are dominated by charges and electrostatic interactions occur at the oxygen.
- Reactions which are dominated by orbital interactions occur at the α-carbon.

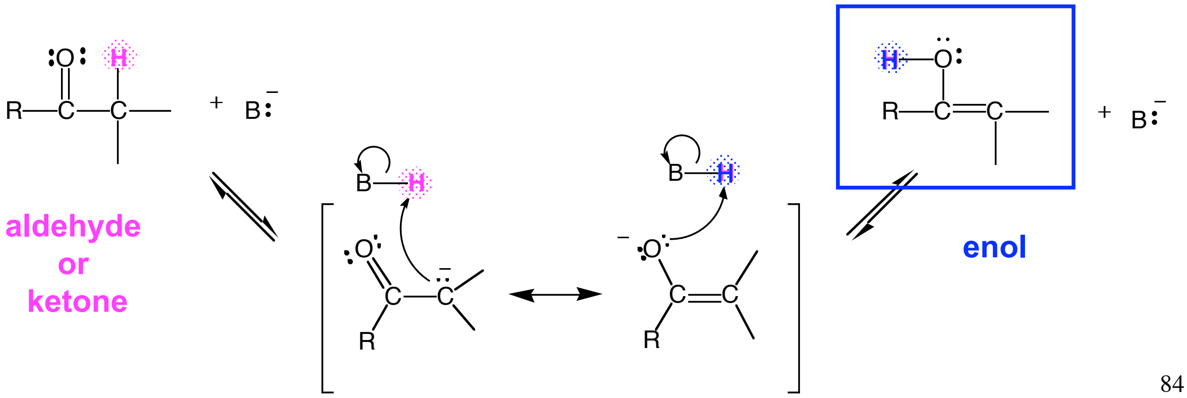
Reactions of Enolate Ions

- Remember that resonance structures are not separate entities, but that the molecule is some weighted average of these structures.
- We can write the curved arrow mechanism using either resonance structure.
  - Example: attack of the *enolate carbanion* on a carbonyl carbon:



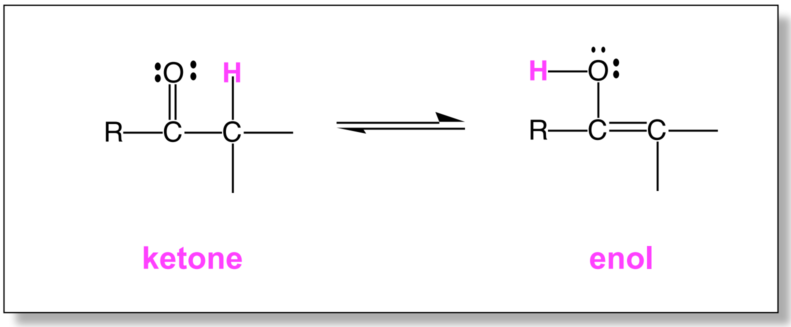
Bronsted Basicity of Enolate Ions

- When the enolate ion acts as a Bronsted base, it may use either the α-carbon or the oxygen to attack a **proton**.
  - When enolate ions attack **protons**, either a C-H bond or an O-H bond may be formed.
  - If a C-H bond is formed, the original aldehyde or ketone is regenerated.
  - If a O-H bond is formed, the product is an isomer of the aldehyde or ketone known as an ***enol***.



Formation of Enols

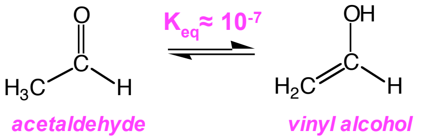
- The conversion of a carbonyl compound into its enol is an isomerization reaction called ***enolization***.



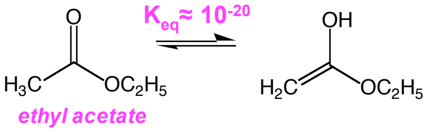
- For most simple aldehydes and ketones, the equilibrium concentration lies far on the side of the ketone.
- The reaction is catalyzed by both acids and bases.
- The mechanisms for acid- and base-catalyzed enolization are different.

Stability of Enols

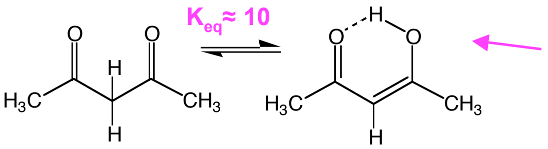
- Carbonyl compounds with α-hydrogens are in equilibrium with small amounts of their enol isomers.



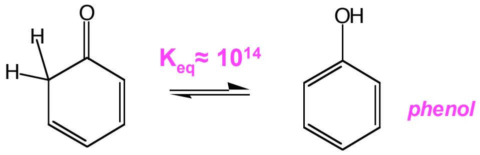
Simple aldehydes and ketones have very small equilibrium constants for enol formation.



Esters are even less favored to form enols.



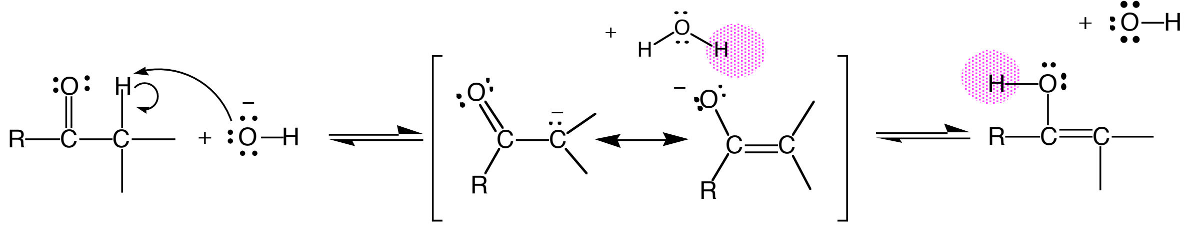
β-dicarbonyl compounds form relatively stable enols due to resonance stabilized conjugation and the opportunity for hydrogen bonding.



Phenol is the “ultimate enol”. Its aromaticity makes it significantly more stable than its keto form.

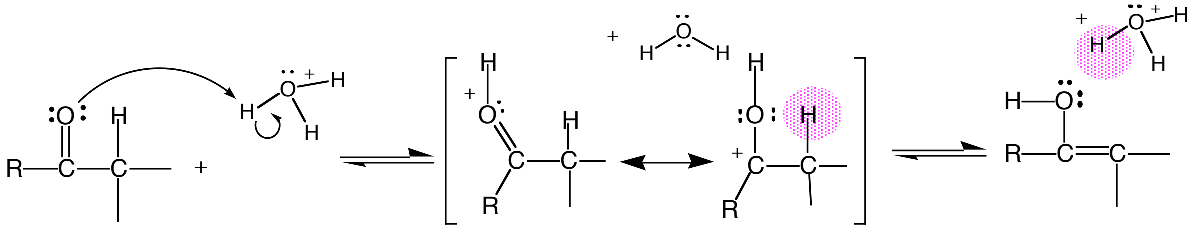
Mechanisms of Enolization

- The ***enolate ion*** is the intermediate species in base-catalyzed enolization of aldehydes and ketones.



ketone **enolate ion** **enol**

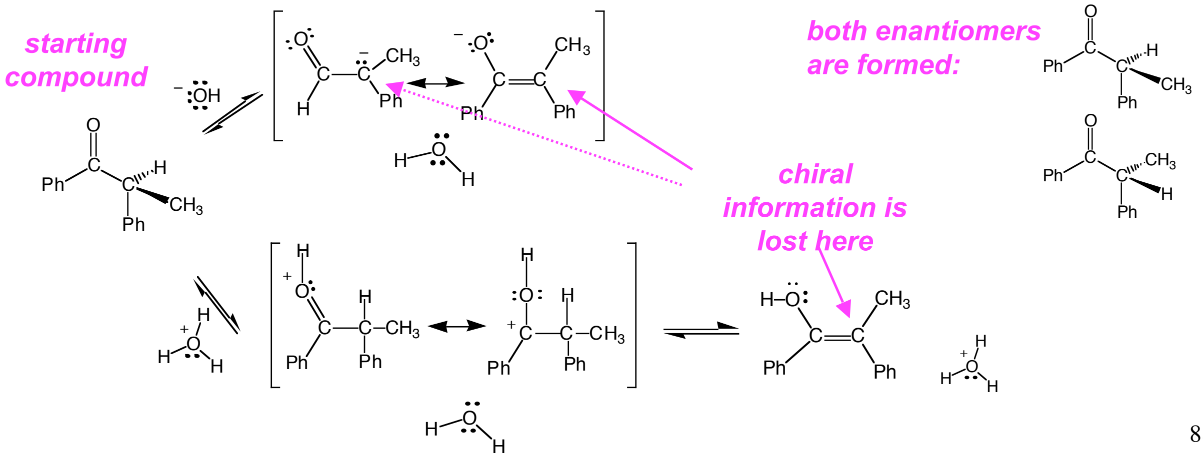
- A ***protonated keto/enol*** is the intermediate species in acid-catalyzed enolization of aldehdydes and ketones.



ketone **protonated keto/enol** **enol**

Implications of Enol Formation

- In base-catalyzed enol formation, enolate ions are resonance-stabilized species in which the C-C-O linkage becomes trigonal planar and sp^2-hybridized.
  - This means that any chiral information contained in the aldehyde or ketone is lost upon formation of the enolate ion.
- In acid-catalyzed enol formation, the α-hydrogen is removed to form a trigonal planar sp^2-hybridized C=C bond.
  - Chiral information in the aldehyde or ketone is lost in formation of the enol.



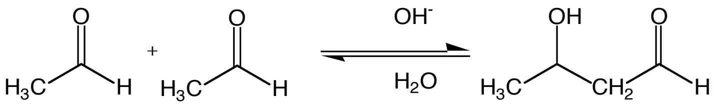
starting compound

both enantiomers are formed:

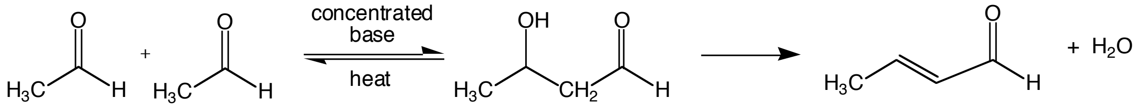
chiral information is lost here

Aldol Addition and Aldol Condensation Reactions

- Aldehydes and ketones undergo a reaction called the ***aldol addition*** to form ***β-hydroxy aldehydes and ketones***:



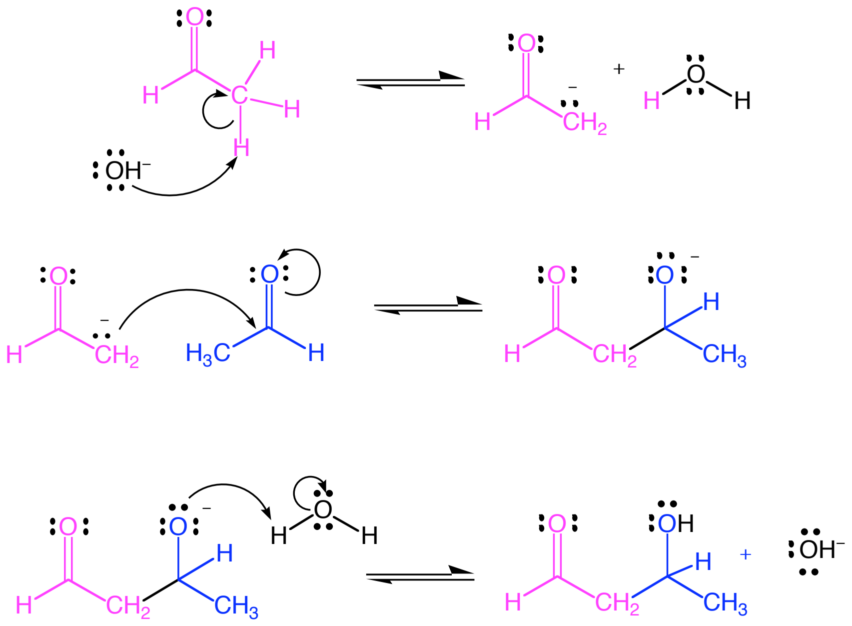
- Under more severe basic conditions, or under acidic conditions, the reaction proceeds further.
- Dehydration to form an α,β-unsaturated carbonyl compound is called the ***aldol condensation***:



- These reactions are addition-elimination reactions which proceed via acid and base-mediated mechanisms which should be familiar to us by now.

Mechanisms of the Aldol Reaction

- The base-catalyzed aldol reaction proceeds via an enolate intermediate:



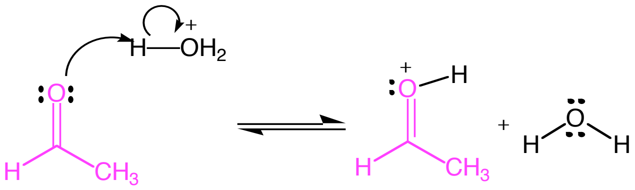
formation of the enolate ion

addition of the enolate ion to the carbonyl carbon of the second aldehyde molecule

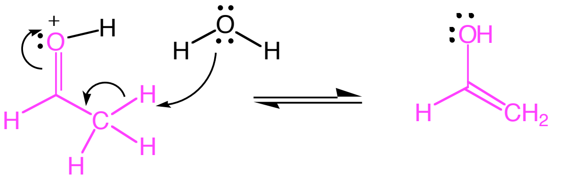
protonation of the addition product

Mechanisms of the Aldol Reaction

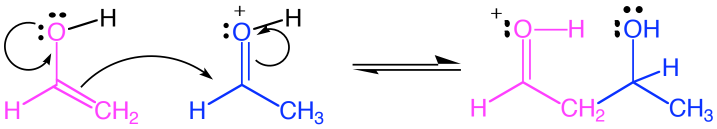
- The acid-catalyzed aldol reaction proceeds via an enol intermediate:



protonation of the aldehyde



deprotonation to form the enol



Addition of the enol to a second protonated aldehyde molecule

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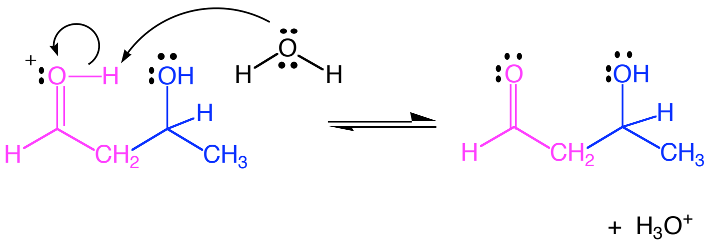
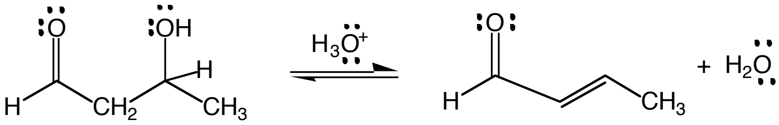
Acid-Catalyzed Aldol Condensation

- The β-hydroxy aldehyde is deprotonated to form the aldol addition product:



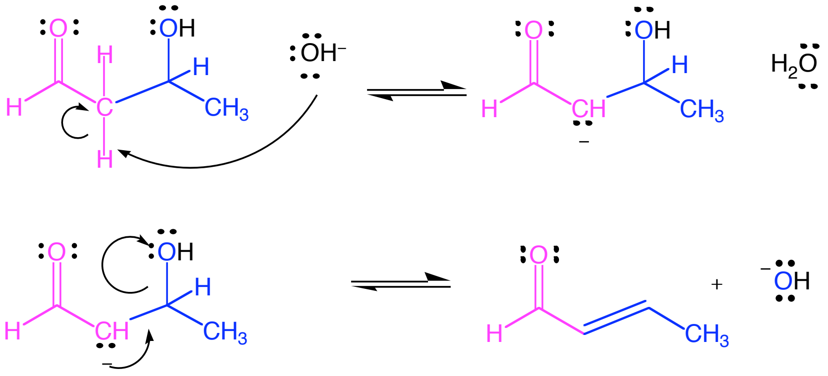
- Under acidic conditions, the aldol addition product is not stable; it undergoes acid-catalyzed dehydration to form the aldol condensation product:



(write the mechanism of this dehydration)

Base-Catalyzed Aldol Condensation

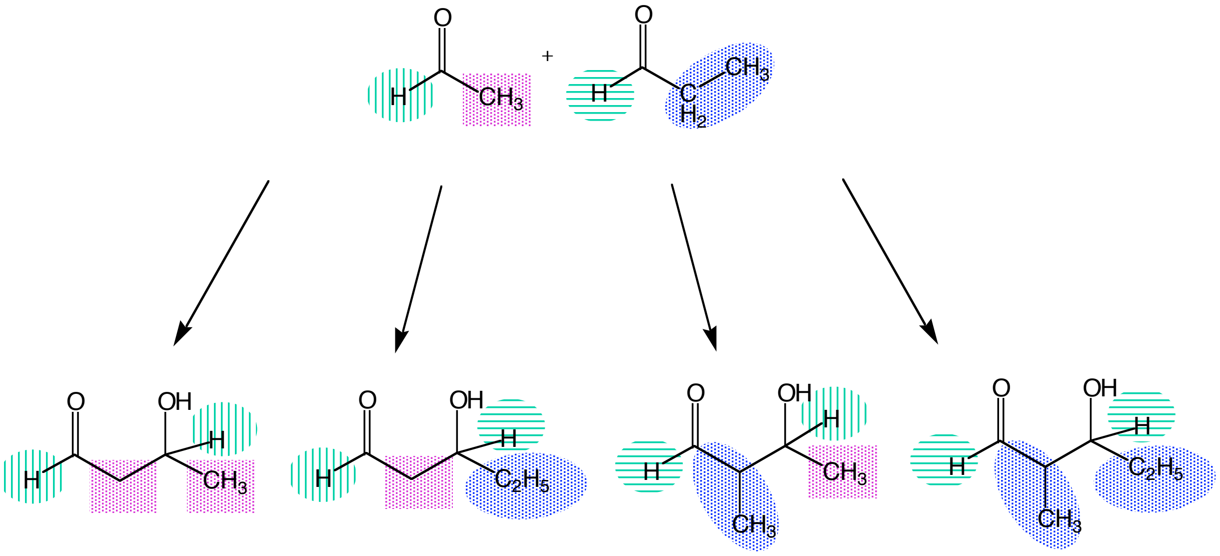
- Aldol condensation also occurs under basic conditions.
- Dehydration is more difficult in base because OH^- is a poor leaving group.
- More concentrated base or heat helps to drive the reaction.



- Simple alcohols do not dehydrate under basic conditions.
- Why does this reaction proceed for β-hydroxy aldehydes and ketones?

Crossed Aldol Additions

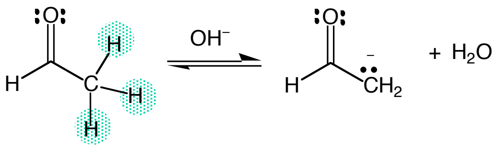
- What happens if an aldol addition reaction is carried out with two different carbonyl compounds?



- Four different aldol addition products are possible!

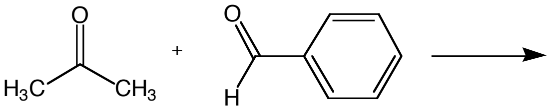
Claisen-Schmidt Condensation

- How can we limit the number of combinations possible in a base-catalyzed aldol condensation reaction?
  - Think about the intermediate species



We can't form an enolate unless we have α-hydrogens

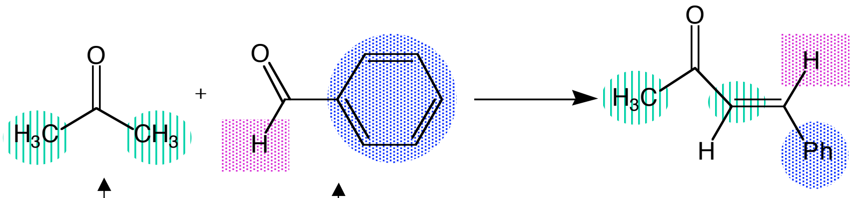
- If only one of the two carbonyl compounds has α-hydrogens, only one can form an enolate ion.
  - So now we're down to a maximum of two possible products.
  - Can we be even more selective? What reaction product(s) do we expect from this reaction?



?????

Claisen-Schmidt Condensation

- This reaction gives only one product, the "cross" condensation product:



can't form an enolate

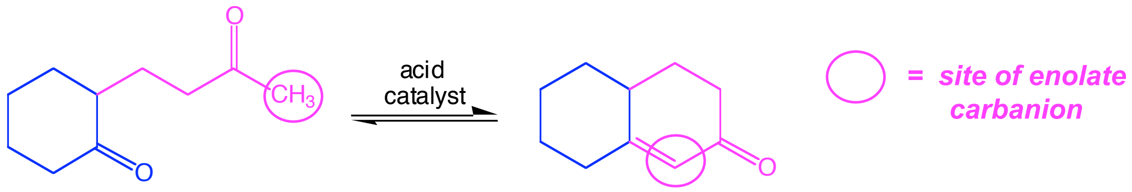
condensation cross product

forms an enolate which reacts much faster with its aldehyde partner than with itself

- Remember that ketones are generally more stable than aldehydes.
  - This means that ketones generally have a greater "energy hill" to climb to reach the transition state, and the rate is slower than for aldehydes.
- Addition to an aldehyde is also generally more favorable thermodynamically.
  - This means that the balance of products at equilibrium lies toward the cross product shown above.

Intramolecular Aldol Condensation

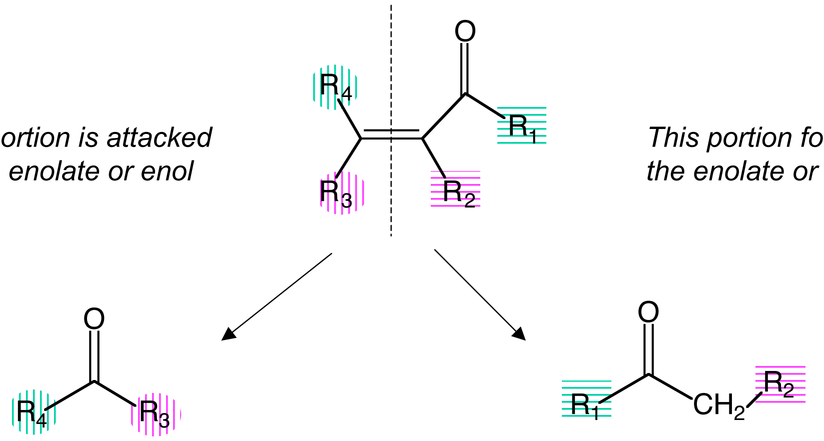
- If a molecule has two carbonyl functions, there is a possibility that ***intramolecular*** aldol condensation may occur.



- ***Intramolecular*** aldol condensation is favorable when five- or six-membered rings may be formed.

Synthesis with the Aldol Condensation

- With what we know about the mechanism of the aldol condensation, we should be able to deconvolute the origins of any aldol condensation product.
  - Identify the carbonyl compound which was the enolate or enol compound.
  - Identify the carbonyl compound which was attacked by the enolate or enol.
  - Then ask the question: is this a feasible reaction? How complex will the product mixture be?

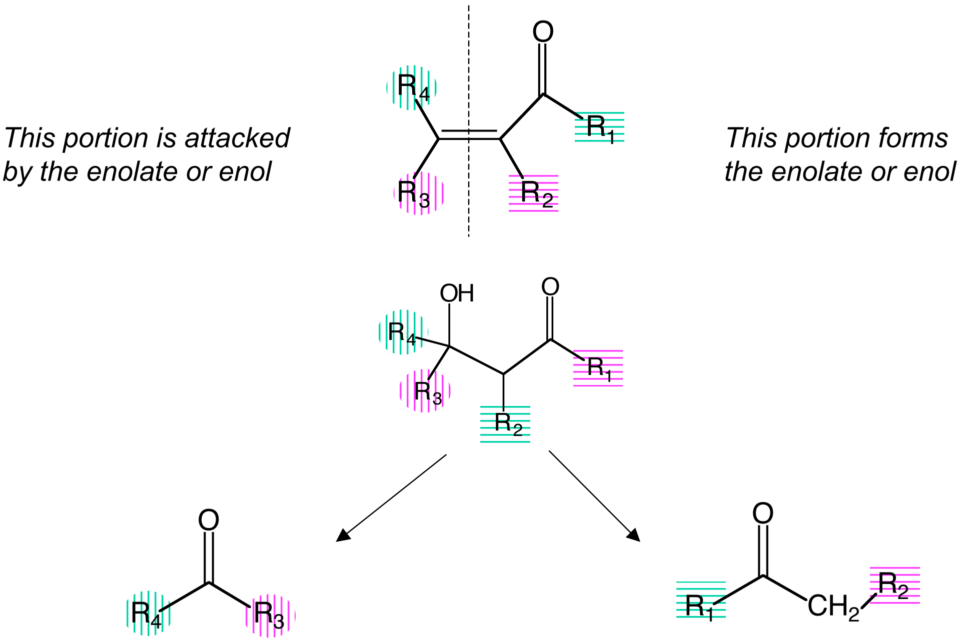


This portion is attacked by the enolate or enol

This portion forms the enolate or enol

Synthesis With the Aldol Condensation

- We can also identify the β-hydroxy aldehyde or ketone which was formed from our starting materials as the first step before the aldol condensation.

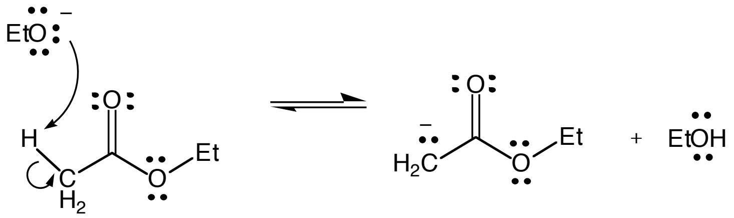


This portion is attacked by the enolate or enol

This portion forms the enolate or enol

Enolate Ester Ions

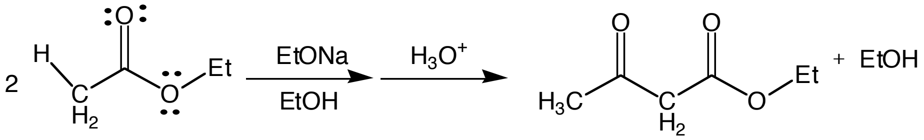
- Esters also form enolates via attack by strong bases:



$pK_a \approx 25$
(α-proton is less acidic than α-protons in aldehydes/ketones)

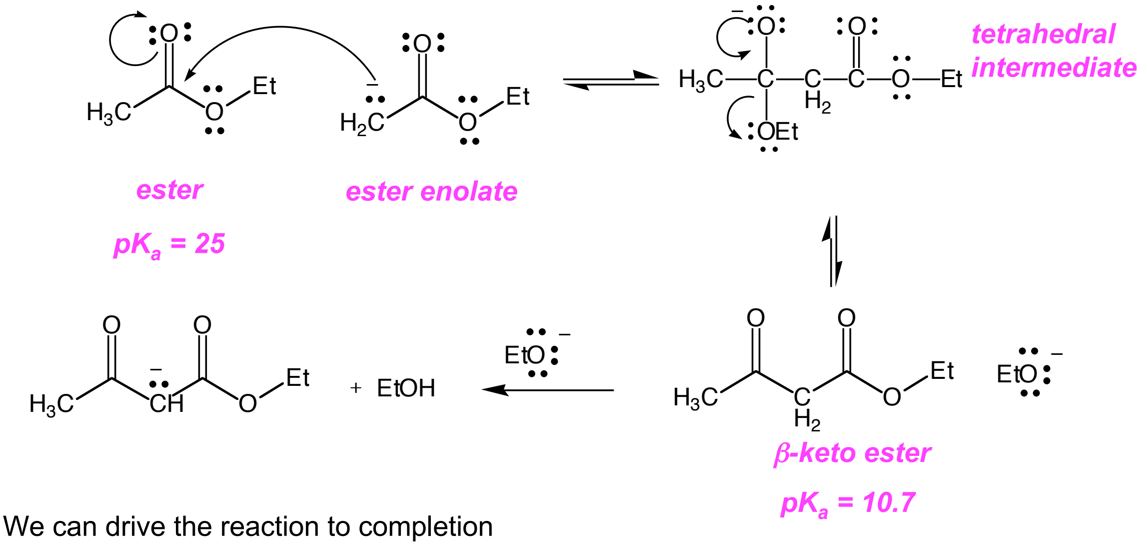
ester enolate ion

- The ester enolate ion is active as a nucleophile in condensation reactions involving esters, called the **Claisen condensation**:



Claisen Condensation

- An ester enolate ion attacks an ester to form a β-keto ester:

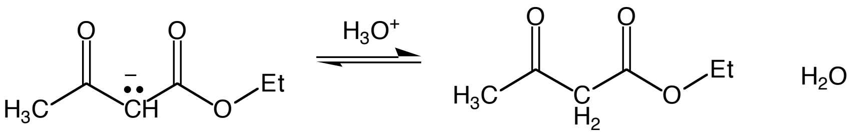


We can drive the reaction to completion by using **one equivalent of the ethoxide** base instead of a catalytic amount

β-keto esters are much less stable than the ester starting material.

Claisen Condensation

- We can use the acidic hydrogen adjacent to the two carbonyl groups to form the salt.
- We acidify the solution afterwards to regenerate the unionized β-keto ester.



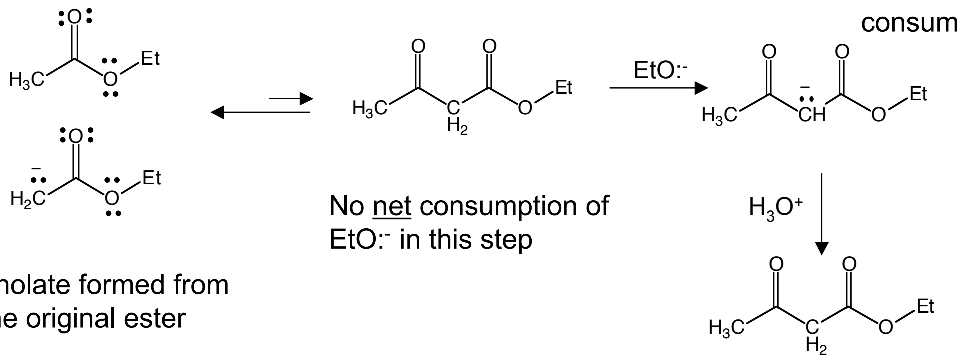
This means that we need to have at least two α-hydrogens on our ester;

- one to form the original enolate ion to form the C-C bond.
- one to form the ionized β-keto ester product.

(the starting ester in this example actually had three α-hydrogens)

Claisen Condensation: Summary

- We need to have at least <u>two</u> α-hydrogens on our ester;
  - one to form the original enolate ion to form the C-C bond.
  - one to form the ionized β-keto ester product.



enolate formed from the original ester

formation of β-keto ester is ***unfavored***

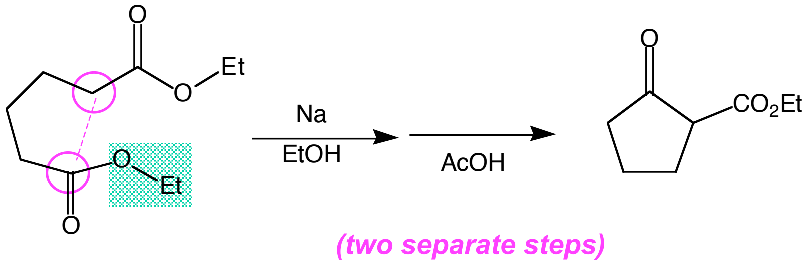
No <u>net</u> consumption of EtO:⁻ in this step

formation of enolate from β-keto ester consumes EtO:⁻

acidification in a <u>separate</u> step

Enolate Ester Reactions

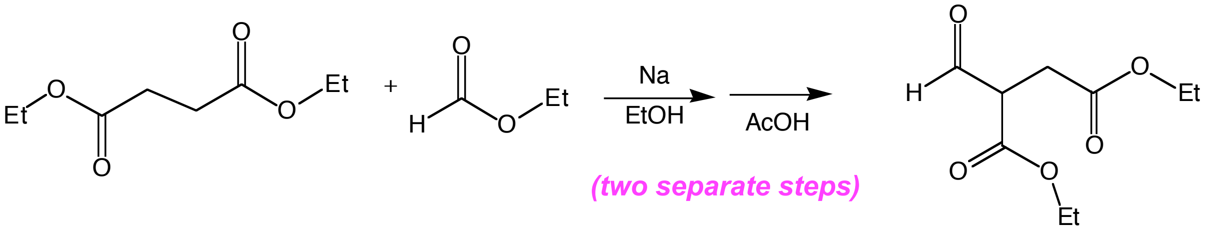
- The Claisen condensation has an intramolecular form just as aldol condensation does:



What is the role of Na?

(two separate steps)

- There is also a crossed Claisen condensation, which works best if one ester has no α-hydrogens or if one ester is especially reactive.

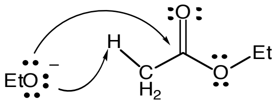


(two separate steps)

Summary of the Claisen Condensation

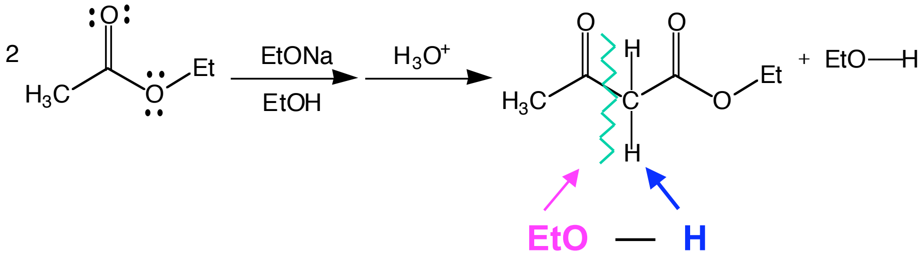
- The Claisen condensation consists of the following five steps:
  1. Formation of an ester enolate anion
  2. Addition of the enolate to the ester (carbon-carbon bond forming step)
  3. Elimination of alkoxide from the tetrahedral intermediate species
  4. Removal of α-hydrogen from the β-keto ester (to form another enolate)
  5. Acidification (in a separate reaction) to regenerate the β-keto ester
- Base is a reactant, not a catalyst in the Claisen condensation:
  - one full equivalent of base is required in order to form the the ionized product in step 4 above.
- The base used should be the same alkoxide ($-OR^-$) as is present in the ester.

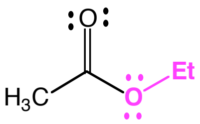
  (why??)



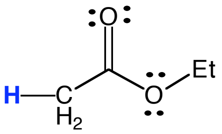
Synthesis With the Claisen Condensation

- A Claisen condensation product may be thought of as the result of adding the elements of an alcohol R-OH across the carbon-carbon bond between the two carbonyl groups.





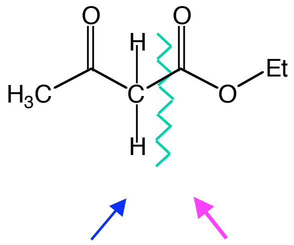
acceptor carbonyl compound



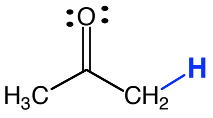
enolate component

Synthesis With the Claisen Condensation

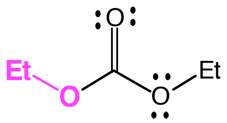
- There are always two different ways to break up (mentally) a Claisen condensation product
  - this time we'll break it up on the other side of the carbon in between the two carbonyl groups):



H — OEt



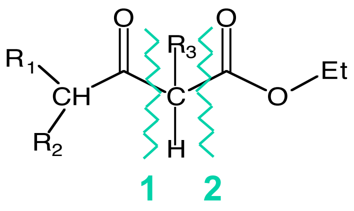
enolate component



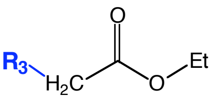
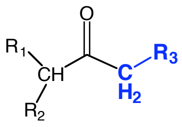
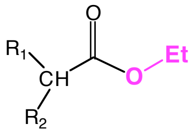
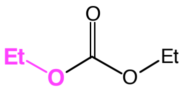
acceptor carbonyl compound

Synthesis With the Claisen Condensation

- After we determine the potential starting materials for a Claisen condensation, we can then examine them and ask whether the reaction will be practical.
  - Will the reaction give the desired product in good yield or will there be a mixture of products?
  - Are the starting materials inexpensive and easily obtained?

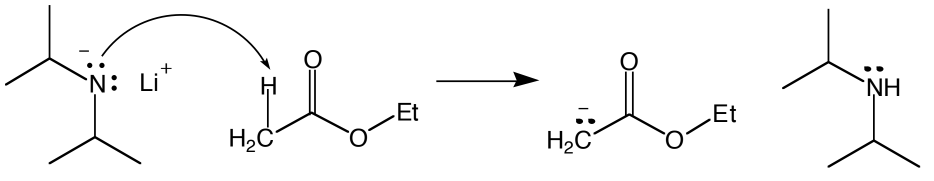


Work backwards from the product

	1	**2**
enolate component:		
acceptor carbonyl compound:		

Alkylation of Enolate Ions

- Esters may be converted completely to enolate ions using very strong, branched bases like lithium diisopropylamide (LDA):



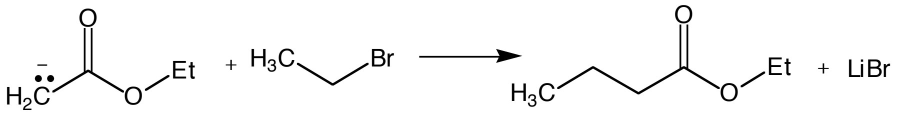
LDA

$pK_a \approx 25$

The reaction is driven to the right

$pK_a \approx 35$

- The enolate ion that is formed may be used in a subsequent (separate) step as a nucleophile to attack alkyl halides in an S_N2 reaction.

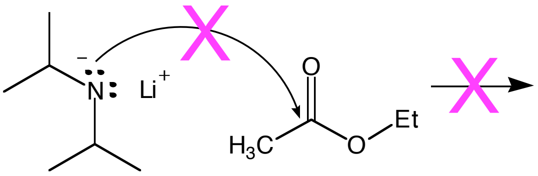


__All__ of the ester is turned into enolate in the first step

---

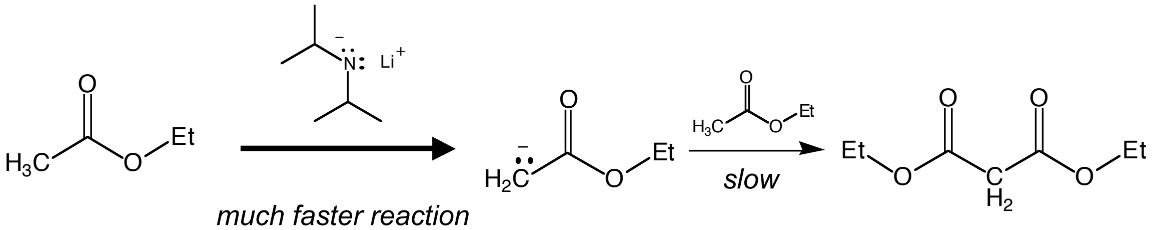
Selectivity in the Alkylation of Esters

- Why doesn't the strong base attack the Lewis acidic carbonyl carbon?



The bulky alkyl groups on LDA experience severe van der Waals repulsions with groups on the carbonyl compound, retarding the rate of reaction at the carbonyl C compared to reaction at the α-hydrogen.

- Why doesn't the enolate ion attack its own ester?

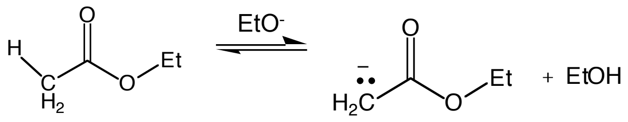


much faster reaction

The ester is totally consumed before (enolate+ester) have time to react together

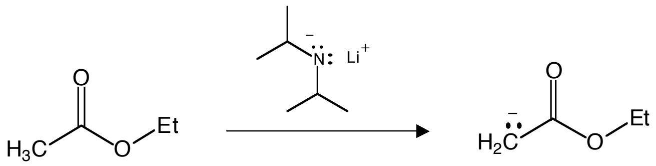
Enolate Formation and Reactivity

- When bases such as ethoxide attack esters to form ester enolate ions, the reaction is never complete (it’s driven to the left).
  - This means that the solution will consist of a mixture of the starting ester and a small fraction of its enolate anion.
  - This allows the Claisen condensation to take place.



ester and enolate both exist in solution

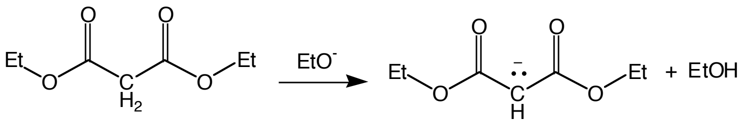
- When much stronger bases such as LDA are used, enolate formation is rapid and complete (it’s driven to the right).
  - This means that the solution will consist solely of the enolate anion.
  - This allows us to carry out alkylation without Claisen condensation as a side reaction.



enolate only exists in solution

Malonic Ester Synthesis

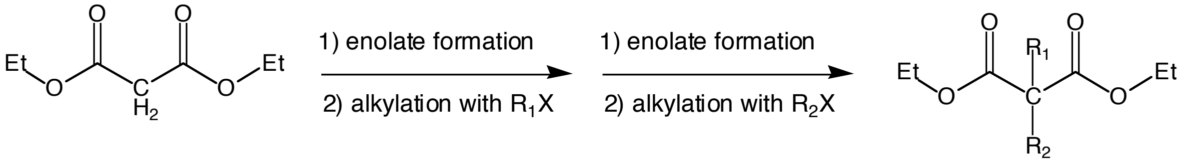
- Dicarbonyl compounds like diethyl malonate (malonic ester) have especially acidic α-hydrogens.
  - Such compounds can form enolate ions completely with weaker bases than LDA.



pK_a = 12.9

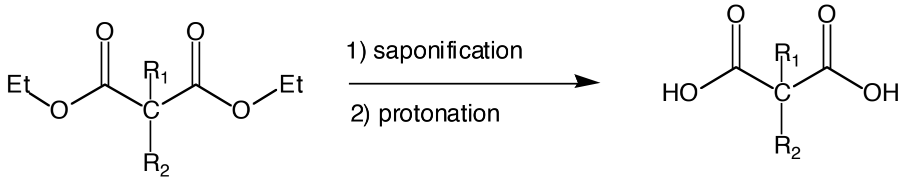
pK_a = 16

- The enolate may be alkylated with alkyl halides as we have just shown.
- A second alkylation may also be carried out using a different alkyl halide (in a separate step!).
  - This provides flexibility in synthesis, creating two C-C bonds in the same molecule.



Malonic Ester Synthesis

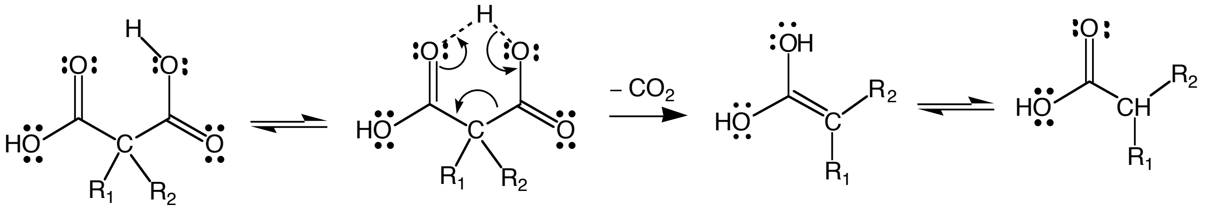
- Carboxylic acids may be prepared after alkylation by reaction steps that we know:



1) saponification

2) protonation

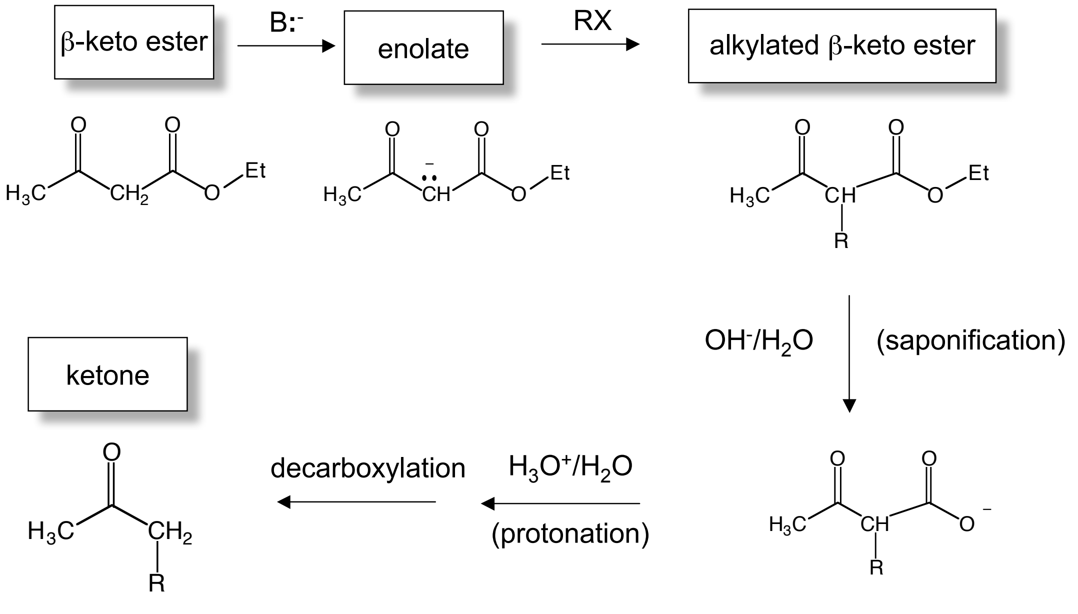
- Malonic acids and their derivatives decarboxylate (lose CO_2) upon heating. The mechanism involves formation of an enol-like intermediate:



– CO_2

Acetoacetic Ester Synthesis

- Ketones may be formed from β-keto esters like ethyl acetoacetate via a series of reactions that proceeds via formation of an enolate ester anion.



β-keto ester

B:⁻

enolate

RX

alkylated β-keto ester

OH^-/H_2O (saponification)

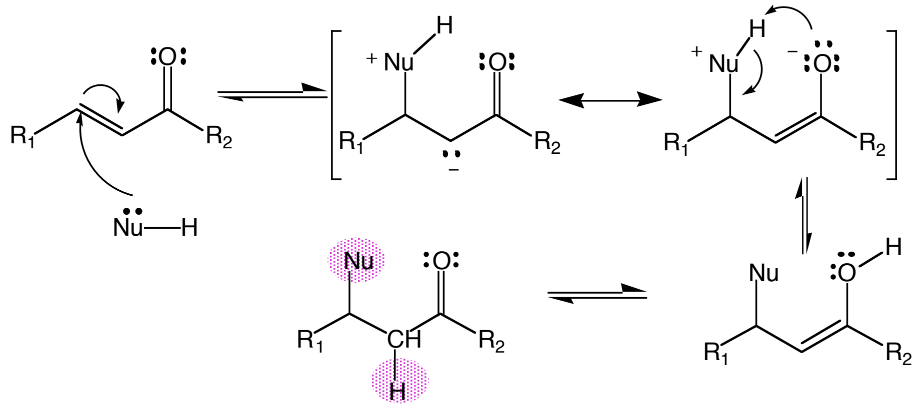
ketone

decarboxylation

H_3O^+/H_2O (protonation)

Conjugate Addition Reactions

- We learned that β-hydroxy aldehydes and ketones undergo dehydration to form α,β-unsaturated carbonyl compounds.
  - These compounds undergo further reactions ***at the C=C bond*** which are not found in the reactions of simple alkene compounds.
- Nucleophilic addition to the C=C bond can occur: why?
  - A resonance-stabilized enolate intermediate is formed.
  - The overall observed reaction is the net addition to the double bond.

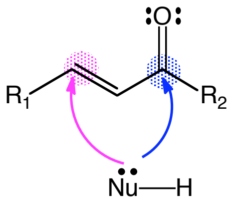


Conjugate Addition vs. Carbonyl Group Reactions

- We know that nucleophiles can attack the Lewis acidic carbonyl carbon atom.
- Thus it seems reasonable that the conjugate addition reaction we've just described may compete with nucleophilic attack at the carbonyl carbon.
- How can we tell which reaction will dominate?

attack at C=C carbon:

conjugate addition



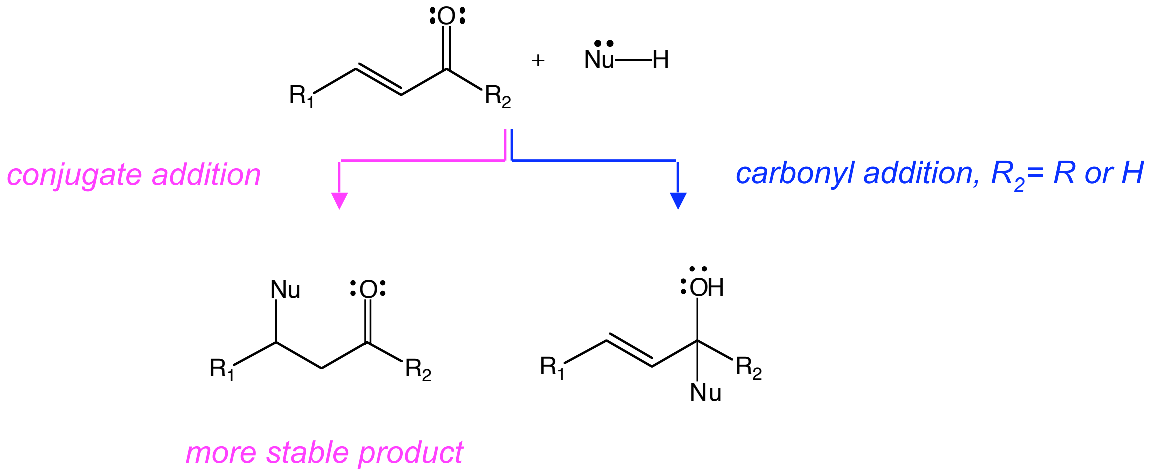
attack at C=O carbon:

carbonyl addition, R_2= R or H
carbonyl substitution, R_2= OR

- We must consider both kinetics and thermodynamics to answer this question:
  - Kinetics: which reaction is faster?
  - Thermodynamics: which reaction gives a more stable product?

α,β-Unsaturated Carbonyl Compounds

- Thermodynamics: Which reaction product is more stable?
  - C=O bonds are stronger than C=C bonds.
  - Conjugate addition retains the stronger C=O bond at the expense of the C=C bond.
  - The conjugate addition product is ***more stable and is thermodynamically favored.***



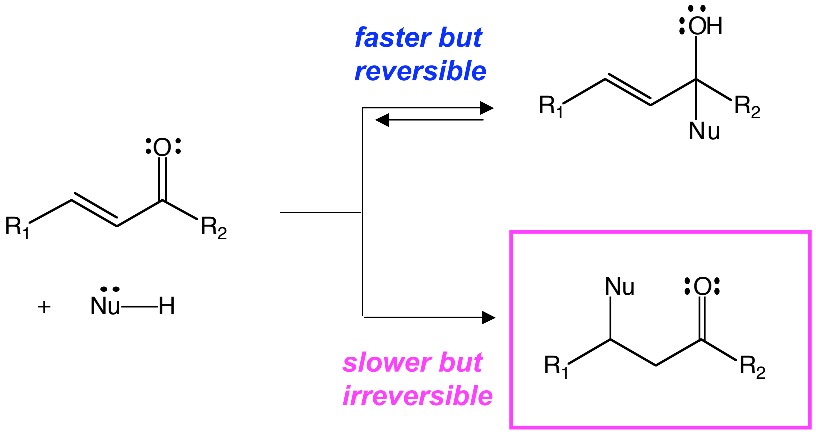
conjugate addition

carbonyl addition, R_2= R or H

more stable product

Competition in Reactions of Aldehydes and Ketones

- Kinetics: which reaction proceeds faster?
  - Often the addition to the carbonyl carbon proceeds faster (because the carbonyl carbon is a stronger Lewis acid than the C=C carbon)
  - Therefore the carbonyl addition reaction usually proceeds faster.
- Who wins? Thermodynamics or Kinetics?



faster but reversible

slower but irreversible

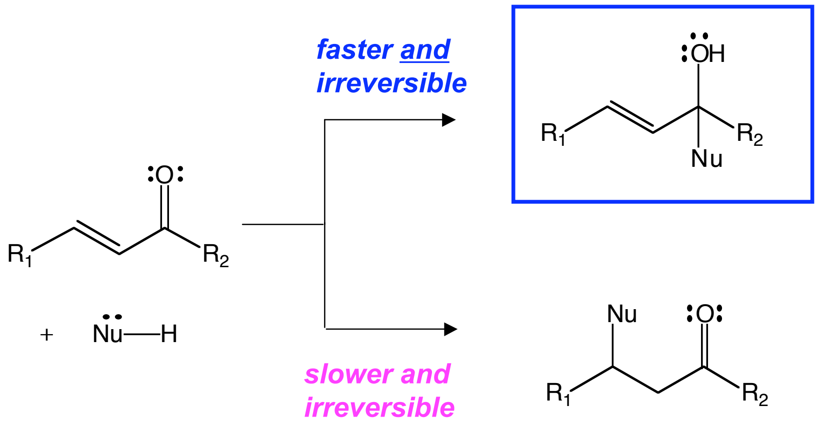
In ***reversible reactions***, the kinetically favored product eventually “drains” back through to the more stable thermodynamically favored product.

When carbonyl additions are reversible, ***conjugate addition wins out***.

- Reversible carbonyl additions occur with weak bases as nucleophiles (CN^-, amines, enolates derived from β-dicarbonyl compounds)

Competition in Reactions of Aldehydes and Ketones

- When carbonyl additions are irreversible, ***carbonyl addition wins out***.



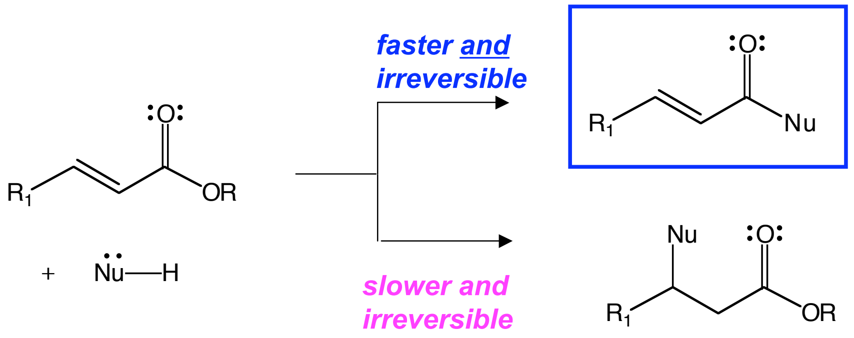
faster and irreversible

slower and irreversible

The **carbonyl addition product** dominates with more powerful nucleophiles like concentrated OH^-.

Competition in Reactions of α,β-Unsaturated Esters

- Kinetics vs. Thermodyamics in nucleophilic attack on α,β-unsaturated esters:
  - With esters, when nucleophilic attack of a strong base occurs at the carbonyl carbon, the result is an **acyl substitution** instead of addition to the carbonyl carbon.
  - In contrast to aldehydes and ketones, these reactions at the carbonyl carbon are not reversible (think of saponification).
- Acyl substitution products dominate in the nucleophilic attack of esters with **strong bases**.



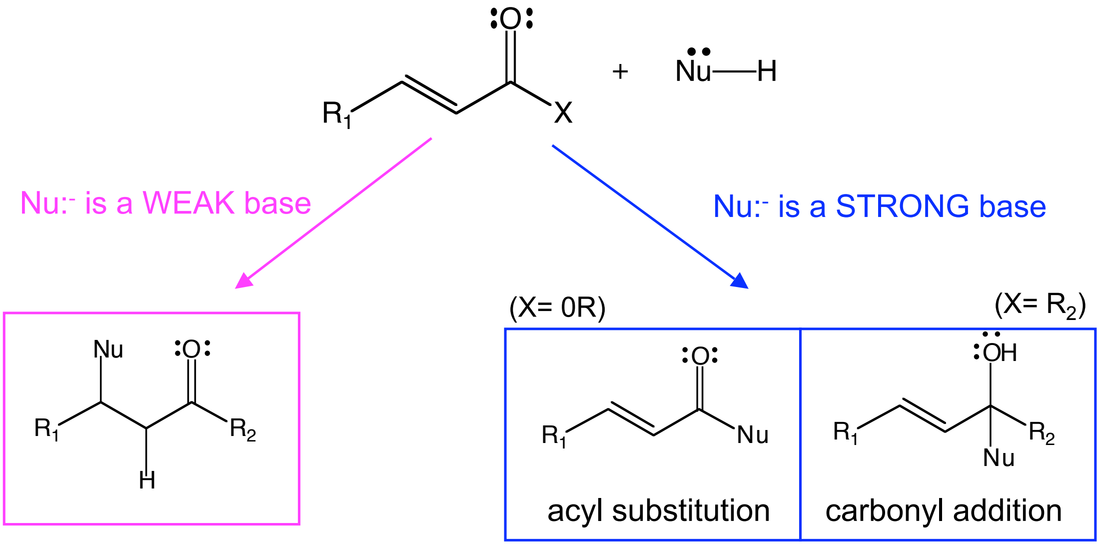
faster and irreversible

slower and irreversible

Nu = OH^-

Competition between C=C and C=O Reactions

- Summary:
  - Conjugate addition occurs with nucleophiles that are relatively weak bases.
  - Irreversible carbonyl reactions (addition or acyl substitution) occur with stronger bases.



Nu:$^-$ is a WEAK base

Nu:$^-$ is a STRONG base

(X= 0R)

(X= R$_2$)

acyl substitution

carbonyl addition

Weak and Strong Bases

- Which base to use for which reaction?

- Conjugate addition:

  We need relatively weak bases; look at the pK_a values of the conjugate acids.

  Good candidates:
  - Cyanide ion:

    H-CN pK_a = 9.4
  - Amines:

    $R_3N\text{-}H^+$ (pK_a = 9-11)
  - Thiolate ions (from thiols)

    $C_2H_5S\text{-}H$ (pK_a = 10.5)
  - Enolate ions derived from β-dicarbonyl compounds

    e.g.: diethyl malonate (pK_a =12.9)

    ethyl acetoacetate (pK_a = 10.7)
  - $(CH_3)_2CuLi$

- Carbonyl addition:

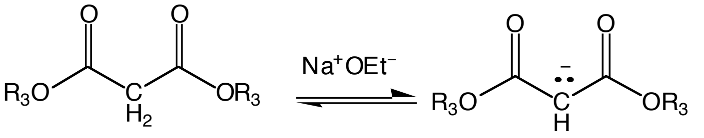
  We need relatively strong bases in order to make the reaction reversible:

  Good candidates:
  - OH^-
  - OR^-
  - Enolates derived from esters
  - Enolates derived from aldehydes and ketones
  - PhLi

Note: Grignard reagents tend to give a mixture of carbonyl addition and conjugate addition products!

Michael Additions

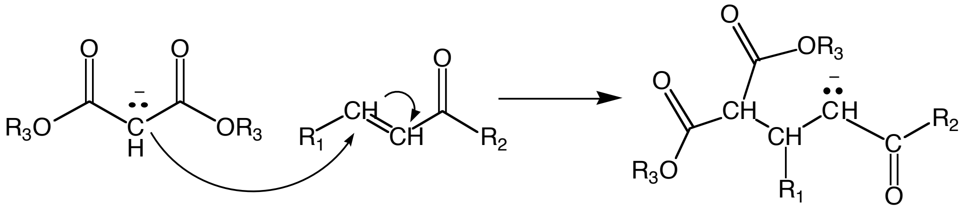
- When the nucleophile in a conjugate addition to an α,β-unsaturated carbonyl compound is an ester enolate anion, this reaction is called a Michael addition.
- The first step of the addition reaction results in the formation of another enolate ion with the carbon alpha to the carbonyl group in the α,β-unsaturated carbonyl compound



malonic ester

ester enolate ion

Malonic ester enolates are particularly useful in Michael additions because they are weaker bases than normal ester enolates



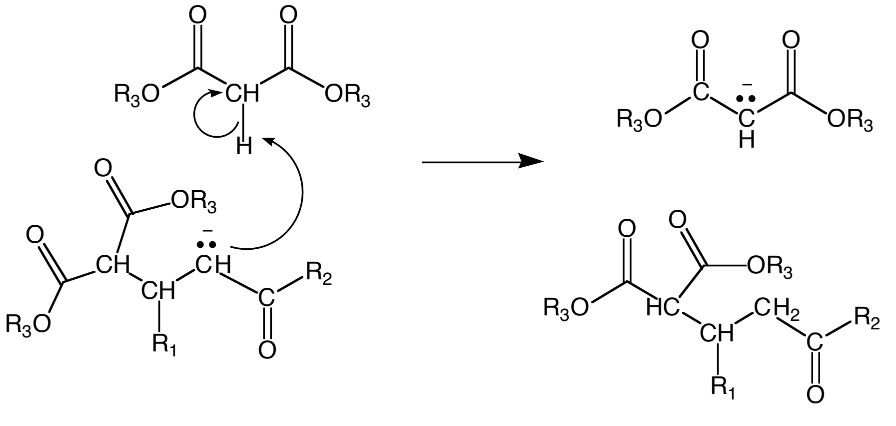
ester enolate ion

α,β-unsaturated carbonyl compound

enolate ion

Michael Additions

- The enolate ion that is formed from the addition reaction then goes on to deprotonate another molecule of the original ester.
  - This forms the neutral addition product and regenerates an ester enolate anion.
- Thus, this reaction is catalytic in base: only a small amount of base is required (compare to Claisen condensation, which requires one equivalent of base)
  - once the original base forms some ester enolate anion, the reaction proceeds without further need of the base.



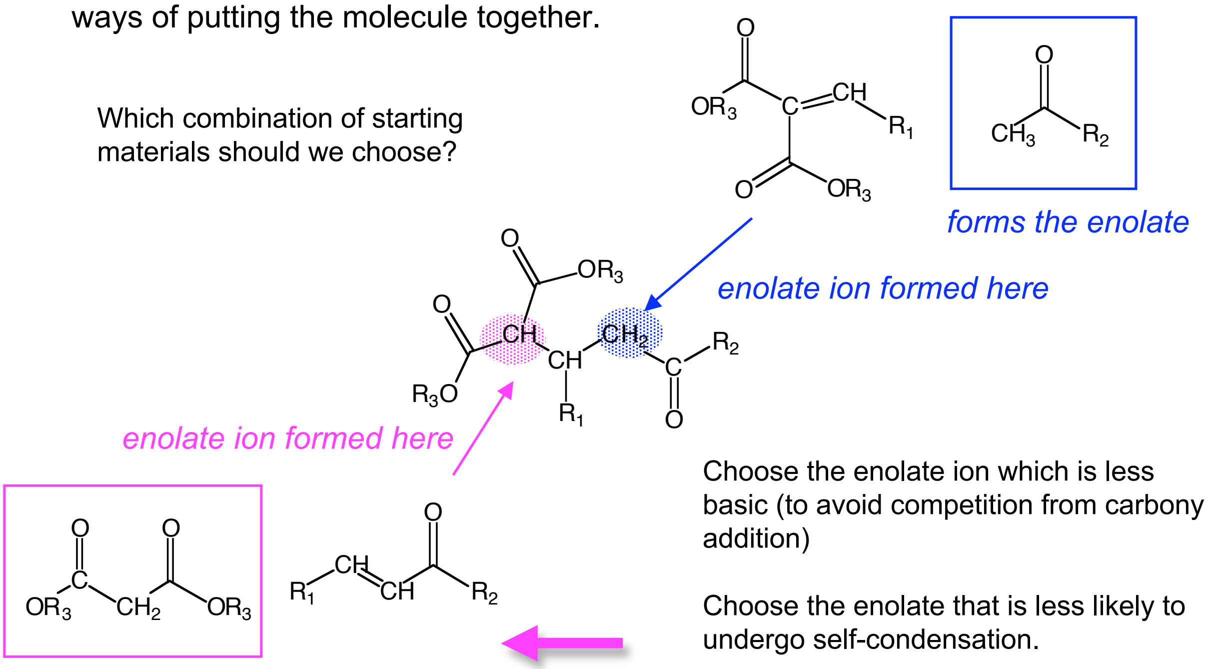
another ester enolate anion is formed

Michael addition product is formed

Synthesis With Michael Additions

- Working backwards from the Michael addition product, we can envision two ways of putting the molecule together.

Which combination of starting materials should we choose?



forms the enolate

enolate ion formed here

enolate ion formed here

forms the enolate

choose this

Choose the enolate ion which is less basic (to avoid competition from carbonyl addition)

Choose the enolate that is less likely to undergo self-condensation.