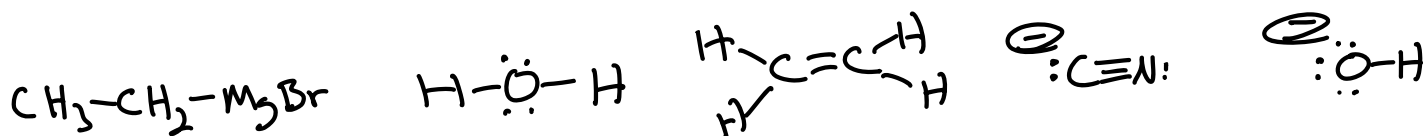# Nucleophiles react with electrophiles to MAKE A BOND
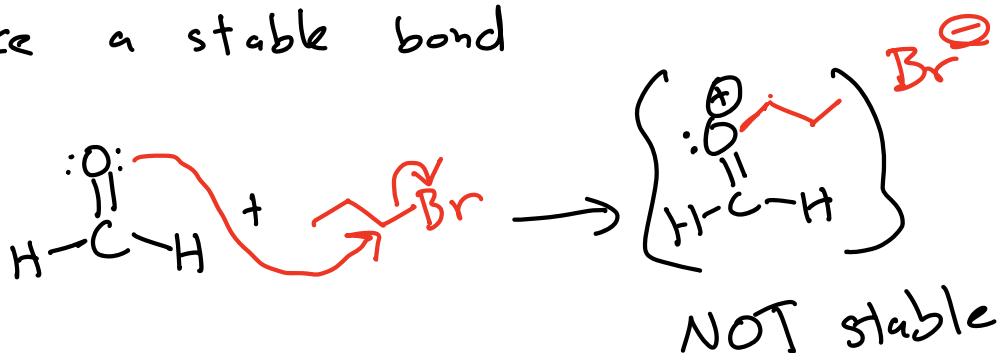
## When trying to recognize nucleophiles:

Area of high electron density {  Lone pair or bond AND they can make a new bond that is STABLE

$CH_3-CH_2-MgBr$     $H-\ddot{O}-H$     $H_2C=CH_2$ (H-C=C-H)     $^{\ominus}:C\equiv N:$     $^{\ominus}:\ddot{O}-H$
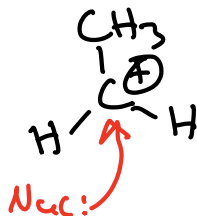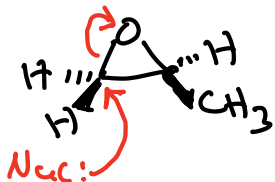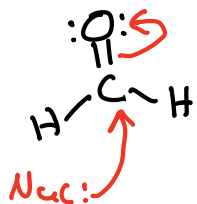
The O atom of a carbonyl is NOT a nucleophile because reacts at the lone pair and cannot make a stable bond
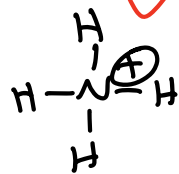


NOT stable

## When trying to recognize electrophiles: .

Usually an area of low electron density {  Can accept a new bond that is STABLE
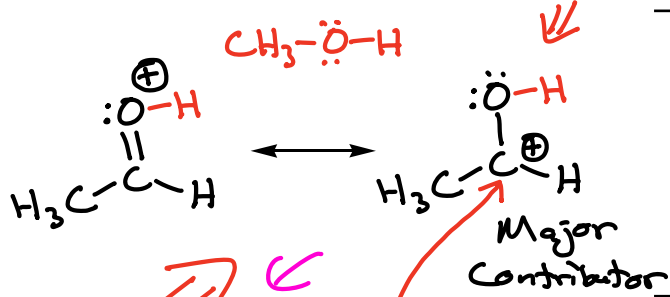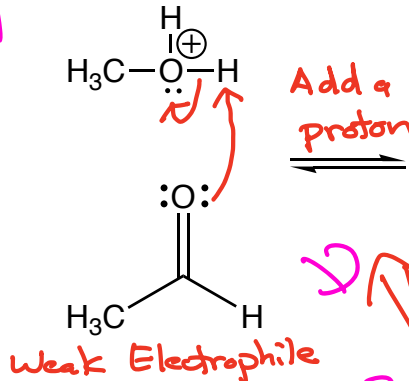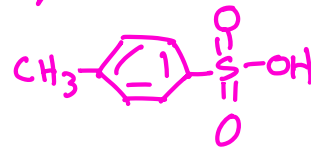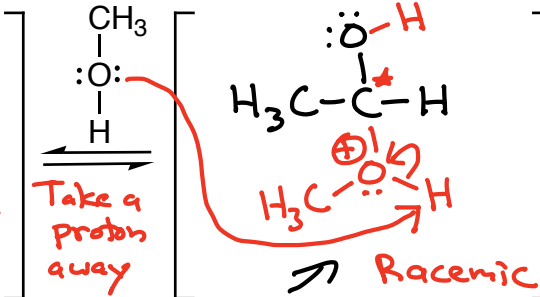
Cannot make a new bond



NOT an electrophile!

Nuc: → $:\ddot{B}r-\ddot{B}r:$     $H_2C=\ddot{O}:$ (H-C-H)     ...     ...

Nuc:     Nuc:     Nuc:

TsOH
Tosylic Acid

CH₃—⟨ ⟩—S—OH (sulfonic acid structure)

H₂SO₄

"Hey, does that thing have a hemi in it?" "SWEET!" !"

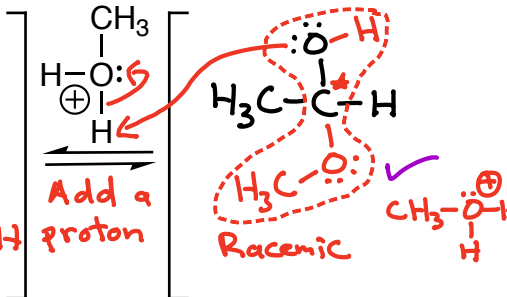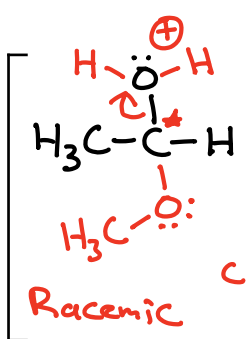*Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone*

H₃C—O⊕—H   Add a proton   CH₃—Ö—H   Red Hot Electrophile

:O:
‖
H₃C—C—H
Weak Electrophile

Mechanism

:O⊕—H
‖
H₃C—C—H   ↔   H₃C—C⊕—H   Major Contributor

Make a bond

H₃C—Ö—H

H⊕—Ö—H
|
H₃C—C—H ★
|
H₃C—Ö:
Racemic

Break a bond

H—O⊕:—S
|
H
CH₃—Ö—H   Add a proton

CH₃
|
:Ö—H
H₃C—C★—H
|
H₃C—Ö:
Racemic
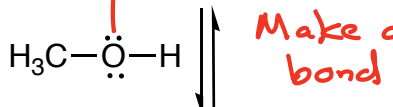
Hemiacetal intermediate   Not stable

Take a proton away

CH₃
|
:O:
|
H
CH₃—Ö⊕H
H

:Ö—H
|
H₃C—C—H ★
|
H₃C—Ö⊕—H
Racemic

H—Ö—H

H₃C—C⊕—H
|
H₃C—Ö:
Major Contributor
↔
H₃C—C—H
‖
H₃C—Ö⊕

Make a bond

H₃C—Ö—H

H₃C—Ö⊕—H
|
H₃C—C★—H
|
H₃C—Ö:
Racemic

Take a Proton away

H₃C—Ö—H

Stabilized by Charge Delocalization
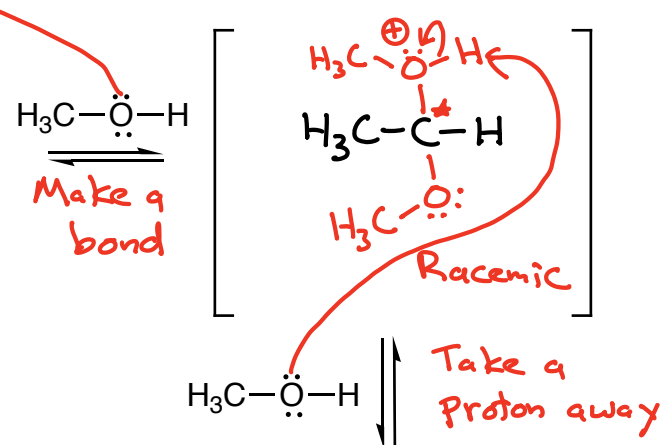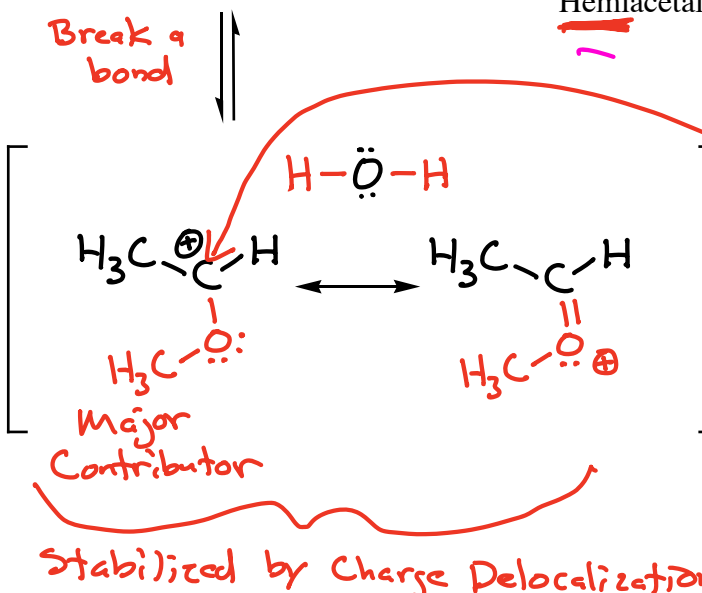
Key Recognition Element (KRE):

Two bonds to ether O atoms to an sp³ C atom

An acetal

H₃C—Ö:
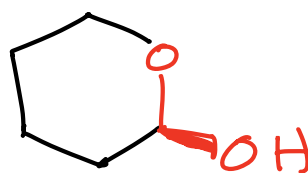|
H₃C—C—H
|
H₃C—Ö:

CH₃—Ö⊕H
|
H
Catalytic in acid

Products
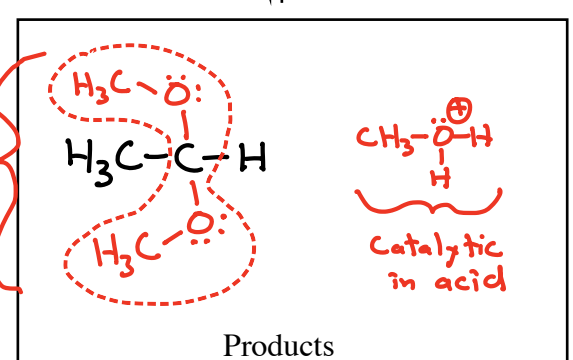
# Recap

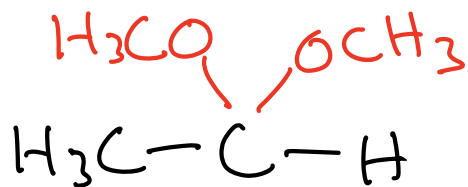**Hemiacetal** → One alcohol and one ether on same C atom
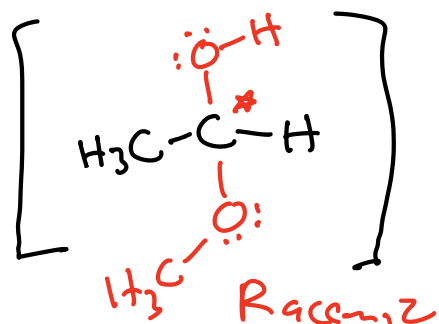


Not Stable
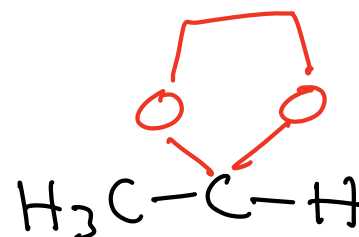


Stable
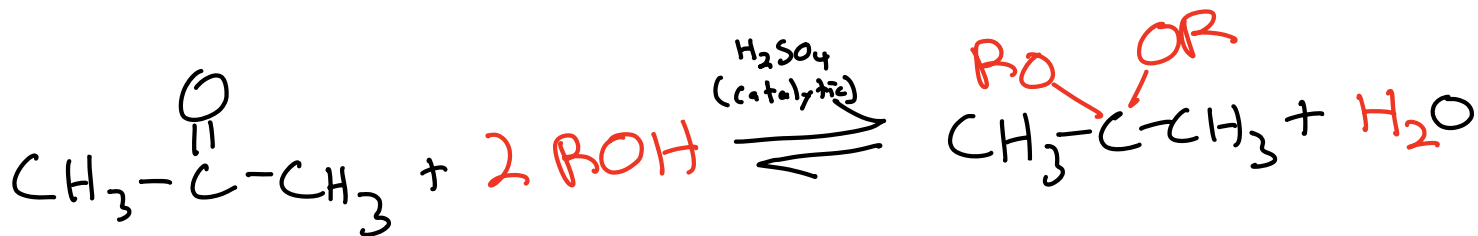(Chelate effect)

**Acetal** → two ethers on same C atom



Stable



More Stable
(Chelate effect)

# Acetal Formation is Reversible

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + 2\ ROH \underset{\longleftarrow}{\overset{H_2SO_4\ (catalytic)}{\rightleftharpoons}} CH_3-\overset{\overset{\displaystyle RO}{\diagdown}\overset{\displaystyle OR}{\diagup}}{C}-CH_3 + H_2O$$
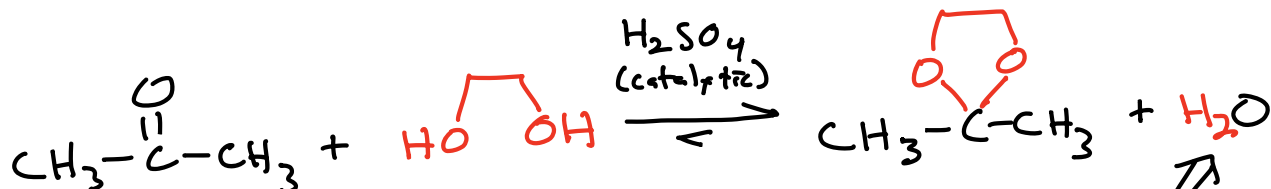
Add more ROH and acetal side
is favored.
Add more $H_2O$ and ketone side
is favored.

This is how cyclic acetal protecting
groups are added to a carbonyl

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + HO\diagdown OH \underset{\longleftarrow}{\overset{H_2SO_4\ (catalytic)}{\longrightarrow}} CH_3-\overset{O\diagdown\diagup O}{C}-CH_3 + H_2O$$

↗ Removed as
it is formed,
driving
reaction to
this side

# Le Chatier's Principle

This is how cyclic acetal protecting
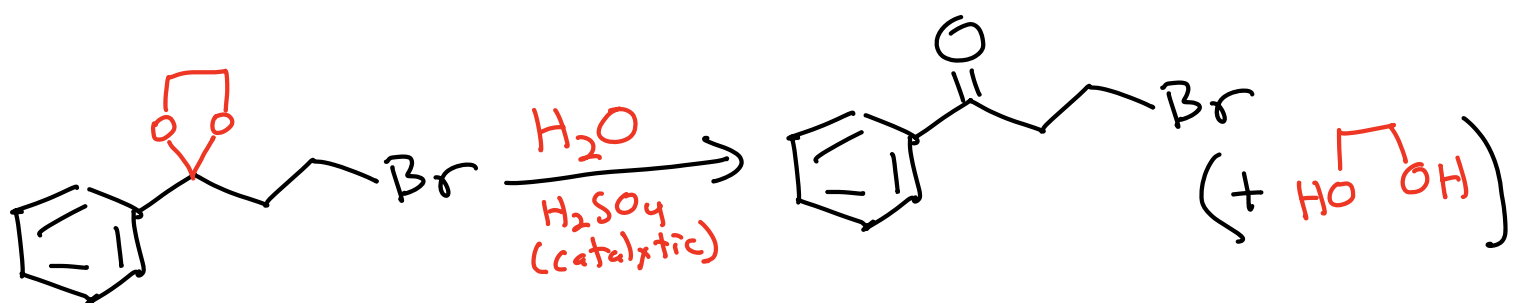groups are removed to get back a carbonyl

$$CH_3-\overset{O\diagdown\diagup O}{C}-CH_3 + H_2O \underset{\longleftarrow}{\overset{H_2SO_4\ (catalytic)}{\longrightarrow}} CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + HO\diagdown OH$$
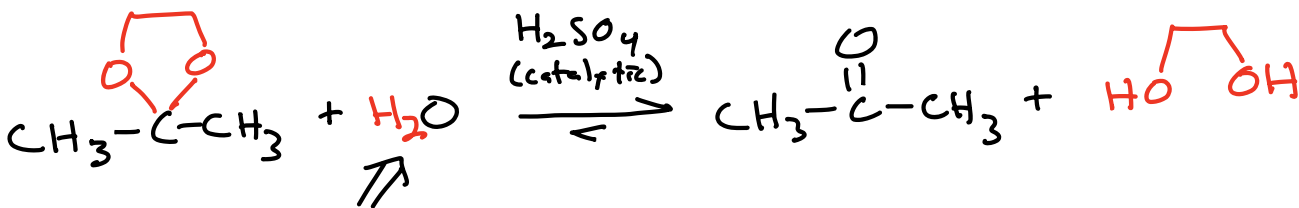
↗ Excess $H_2O$ is
added to drive
reaction to the
ketone side

# Protecting Group "ON"

A phenyl ketone with a $-CH_2CH_2-Br$ chain, reacted with $HO\!-\!OH$ (ethylene glycol) and $H_2SO_4$ (catalytic), forms the cyclic acetal (dioxolane) product with the $-Br$ chain. ($+H_2O$)

# Protecting Group "OFF"

The cyclic acetal (dioxolane) with the $-Br$ chain, reacted with $H_2O$ and $H_2SO_4$ (catalytic), regenerates the phenyl ketone with the $-Br$ chain. ($+$ $HO\!-\!OH$)
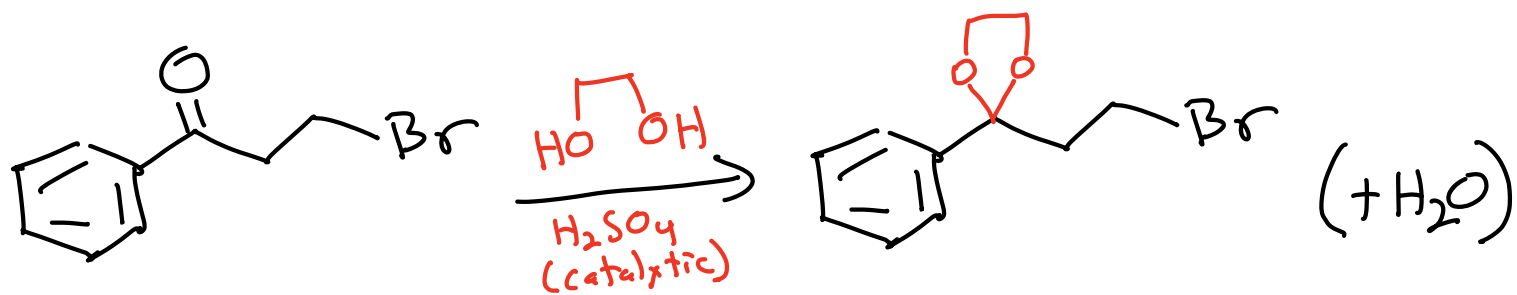
# Changing Personality:
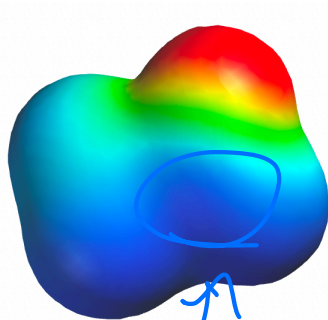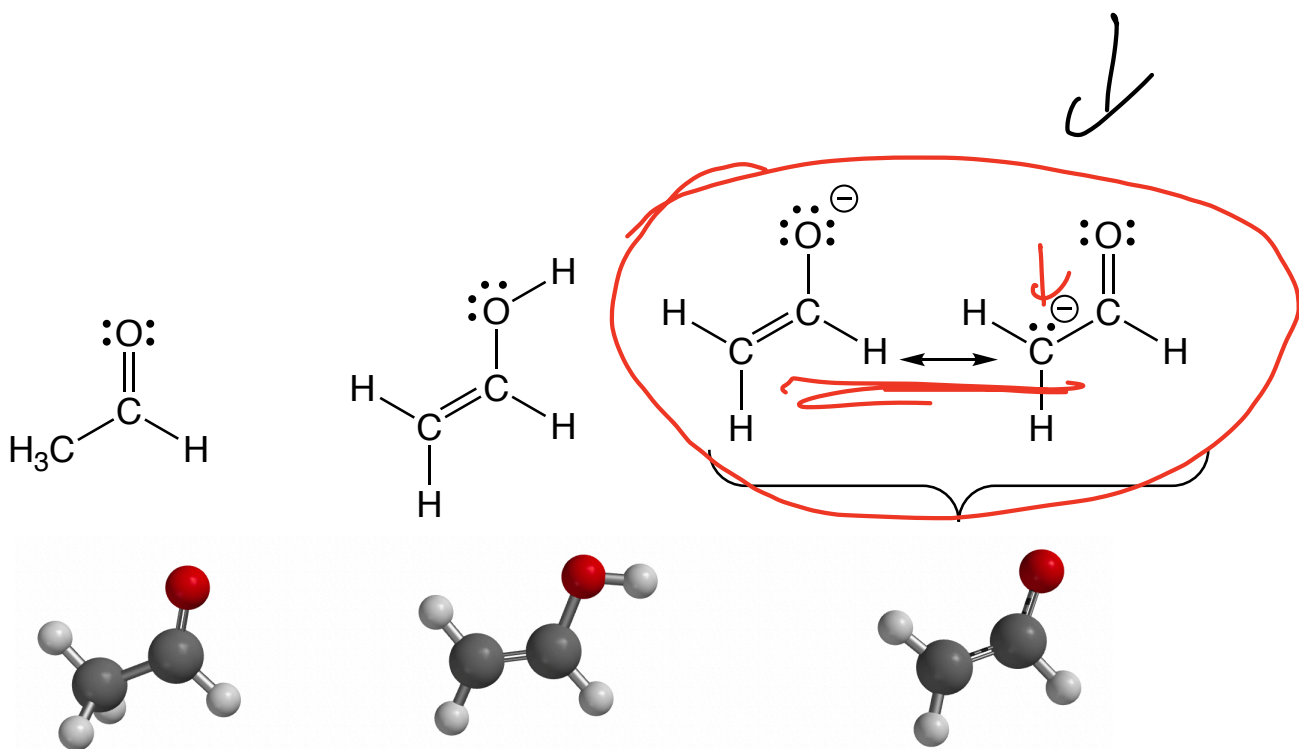


electrophile
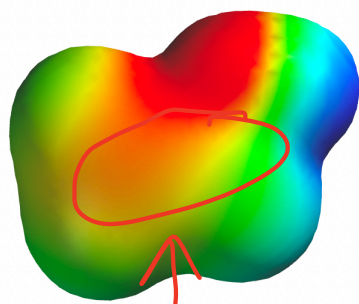
nucleophile

strong nucleophile

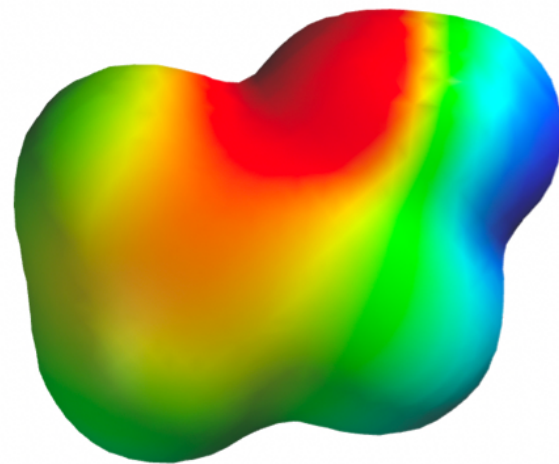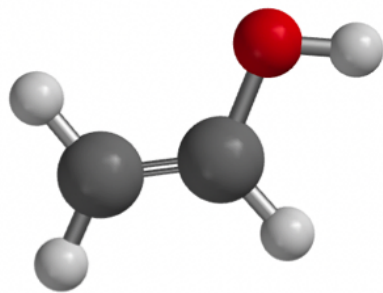Br₂

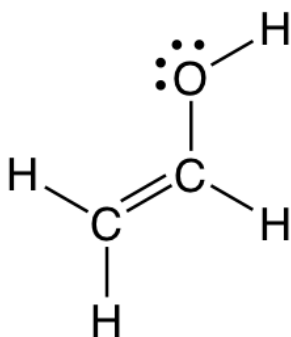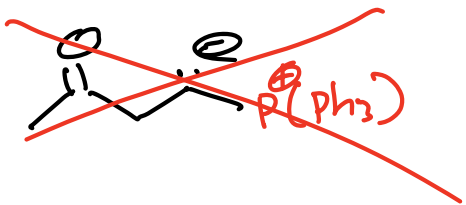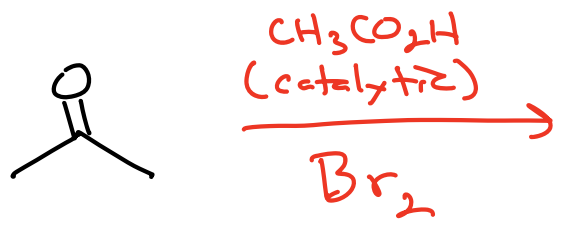$$CH_3-C(=O)-CH_3 \xrightarrow[\text{(catalytic)}]{\underset{CH_3CO_2H}{Br_2}} CH_3-C(=O)-CH_2Br + HBr$$
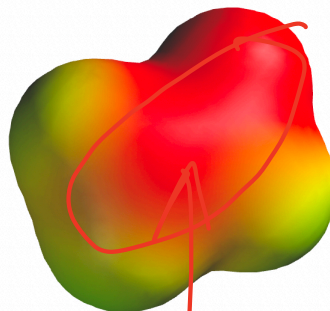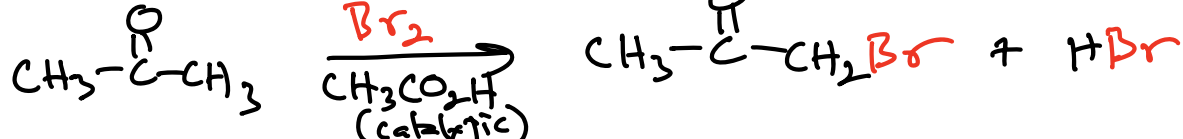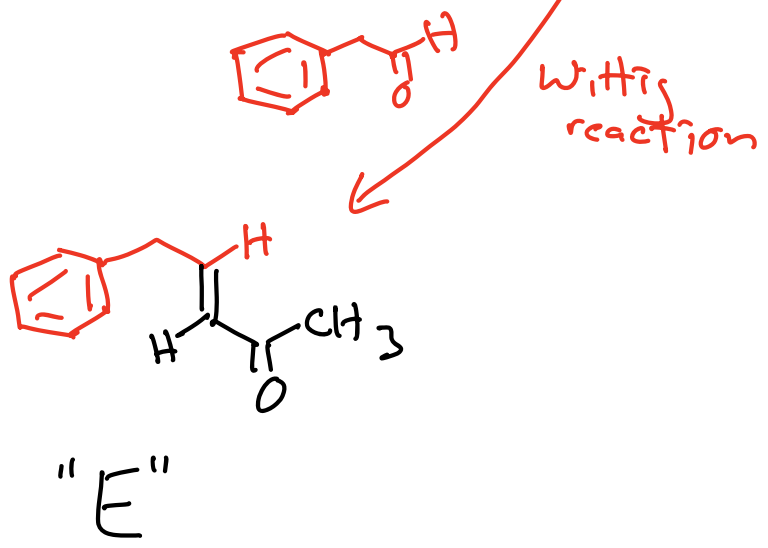
*α-Halogenation of an Aldehyde or Ketone Catalyzed by Acid*

Keto form
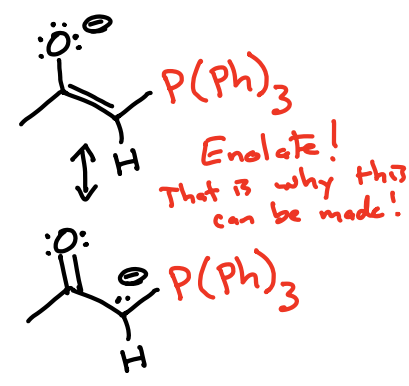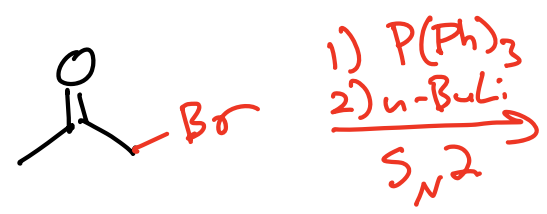
**Add a proton**

**Take a proton away**

Enol

**Nucleophile!**

electrophile ⟹ :Br—Br:

**Make a bond**

**Take a proton away**

:Br:⁻

Products
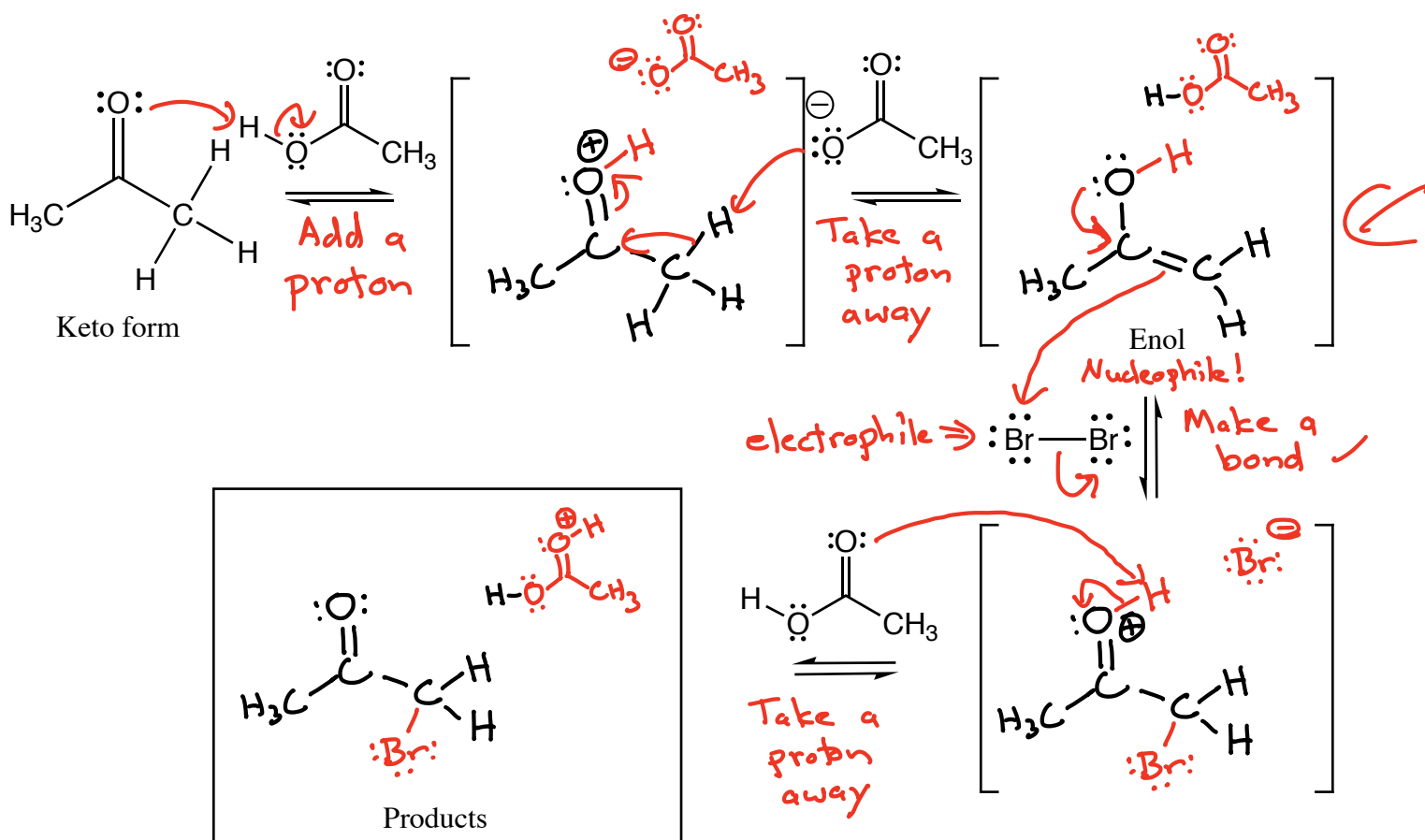
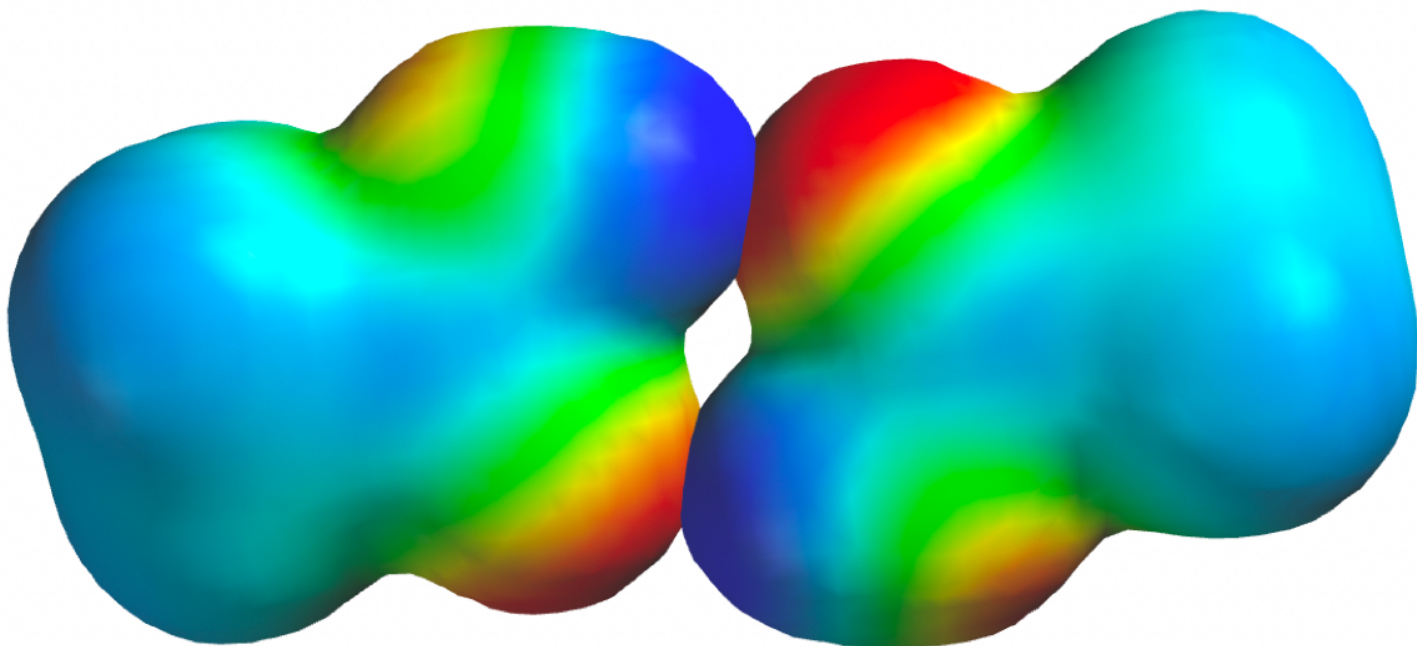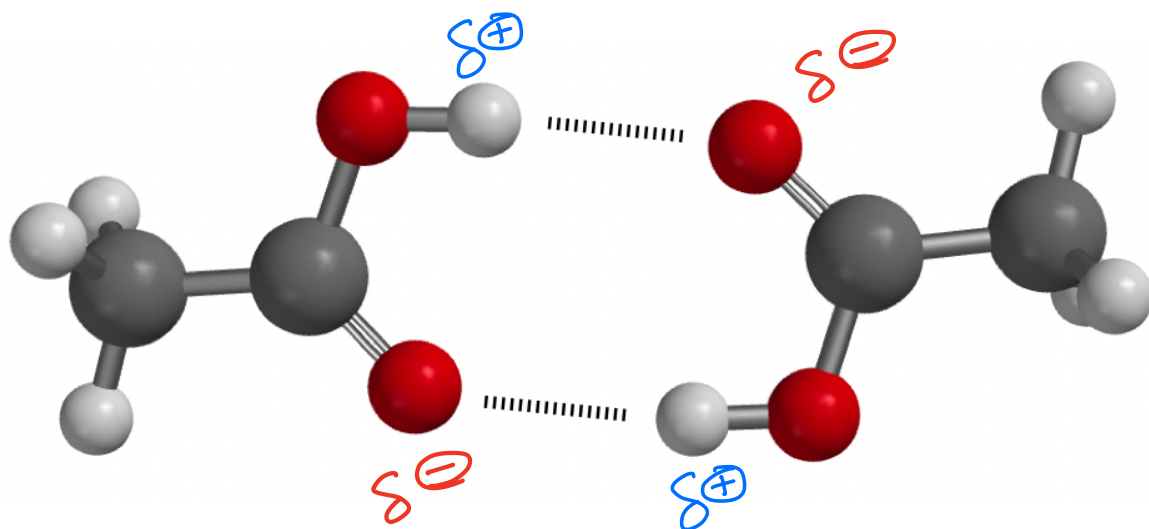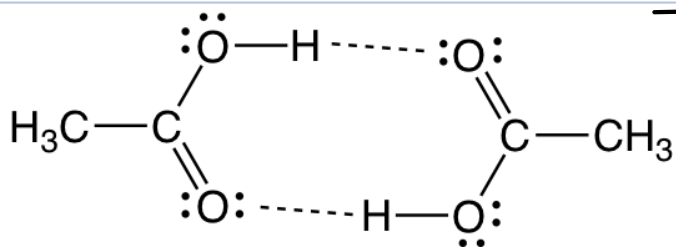KRG: A new bond to Br at the α-carbon position
Prefers methyl groups
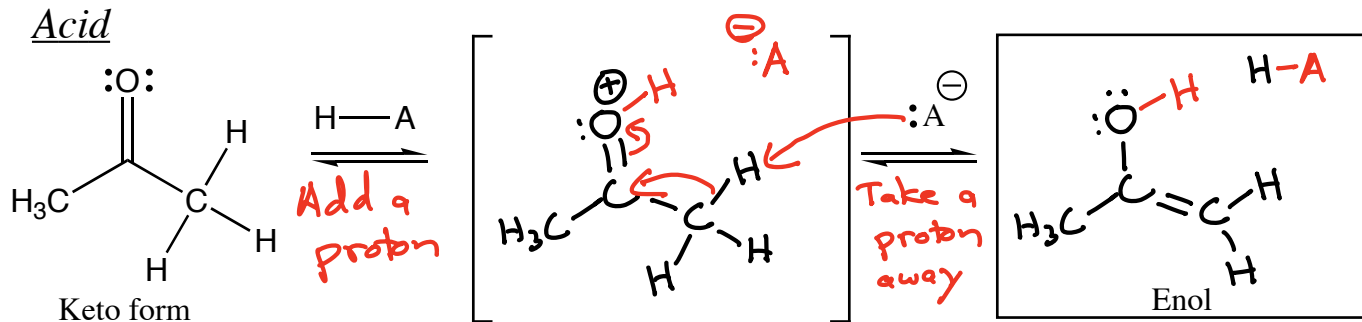
# Example

Carbonyl would react so this cannot be made.

CH₃CO₂H (catalytic) / Br₂

1) P(Ph)₃
2) n-BuLi:
S_N2

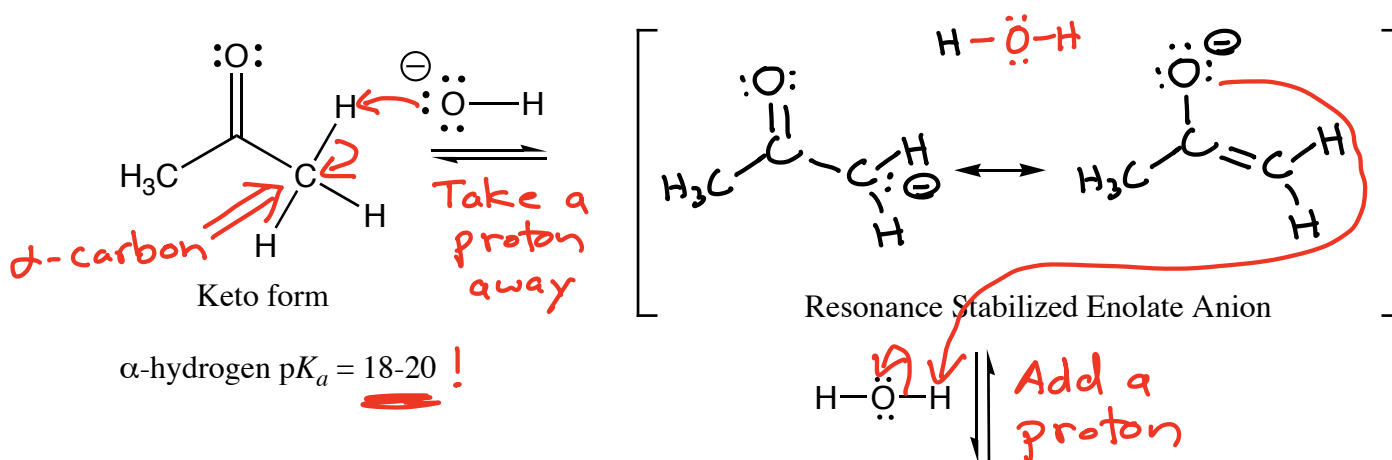Enolate! That is why this can be made!

Wittig reaction

"E"

The process of interconverting the keto and enol forms is called "tautomerization"

*Keto-Enol Equilibrium Catalyzed by Acid or Base*

*Acid*



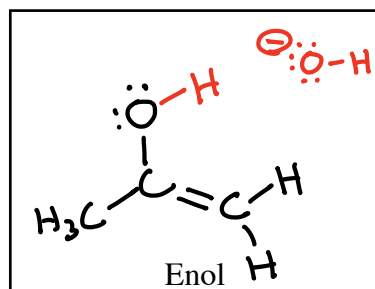Keto form

H—A

Add a proton

Take a proton away

Enol

*Base*



α-carbon

Keto form

Take a proton away

α-hydrogen $pK_a$ = 18-20 !

Resonance Stabilized Enolate Anion

Add a proton

keto and enol forms are called "tautomers"

Enol

For both aldehydes and ketones, the keto form predominates at equilibrium, because ___$C=O$___ bonds are stronger than ___$C=C$___ bonds.

Enols are significant, however, because they react like ___nucleophile___, not carbonyls, and this is important in certain situations.
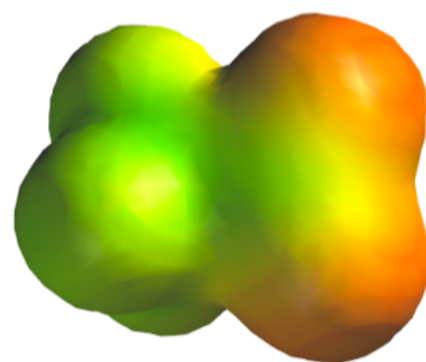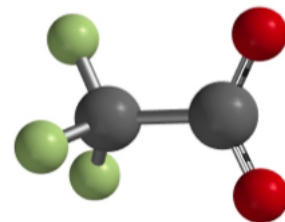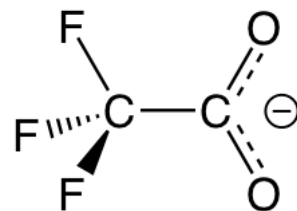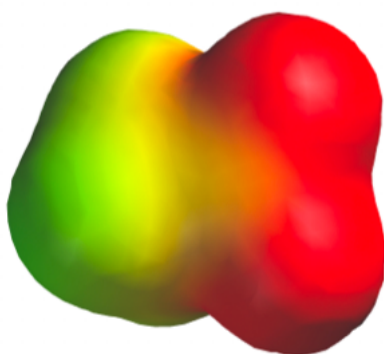
# Acidity Revisited

$$H-A \rightleftharpoons H^{\oplus} + :A^{\ominus}$$
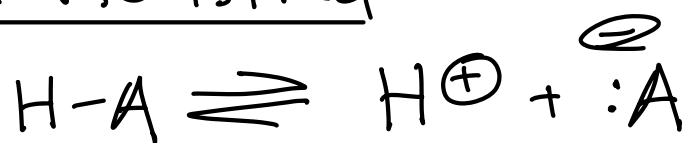
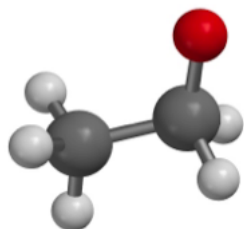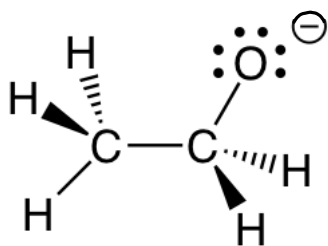$$K_a = \frac{[A:^{\ominus}][H^{\oplus}]}{[HA]}$$

$$pK_a = -\log_{10} K_a$$
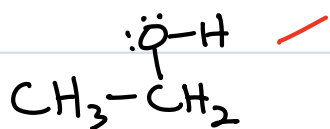
The lower the pKa value, the stronger the acid

If an anion is created when an acid dissociates → the more stable the anion, the stronger the acid
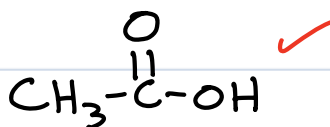
Anions are stabilized when the negative charge is distributed over more atoms

CH₃−CH₂ :Ö−H ✓
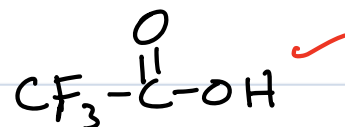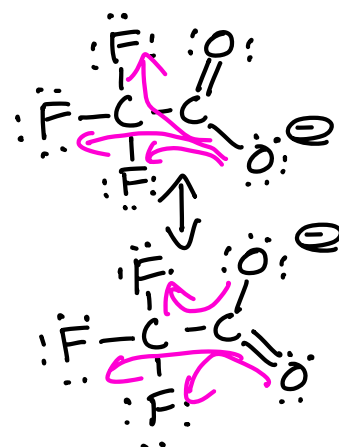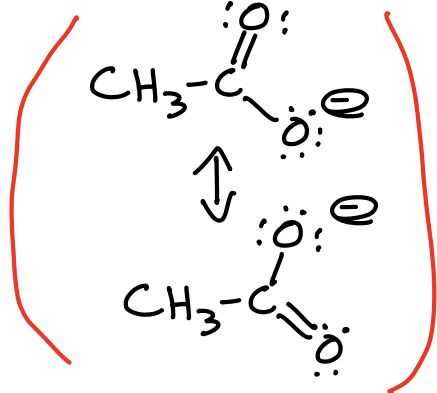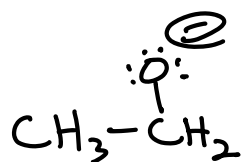
CH₃−C(=O)−OH ✓

CF₃−C(=O)−OH ✓
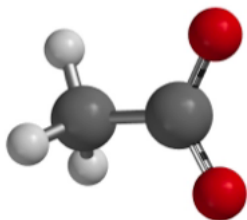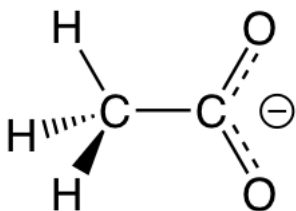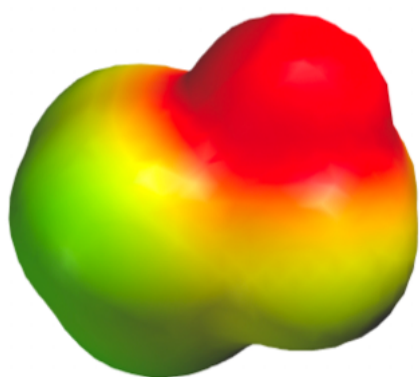
$pK_a = 16$

$pK_a = 3-5$

$pK_a = 0.3$

Inductive effect

# For an acid H-A

$$K_a = \frac{[A:^{\ominus}][H^{\oplus}]}{[HA]}$$

$$pK_a = -\log_{10} K_a$$
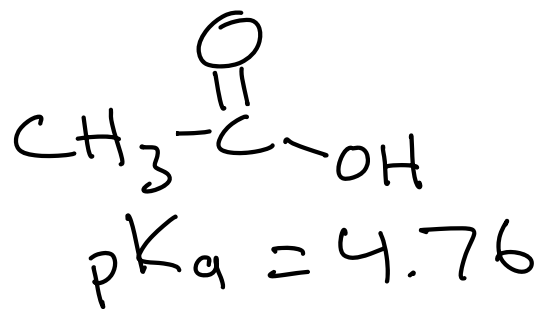
$$pH = -\lg_{10}[H^{\oplus}]$$

$$\frac{K_a}{[H^{\oplus}]} = \frac{[A:^{\ominus}]}{[HA]} = 10^{(pH - pK_a)}$$

If pH = 7 and pKa ⬭3⬭

$$\frac{[A:^{\ominus}]}{[HA]} = 10^{(pH - pK_a)} = 10^{(7-3)} = 10^4$$

1) If the pH of a solution is above (larger) than the pka of an acid, the acid will be largely deprotonated

2) If the pH of a solution is below (smaller) than the pKa of an acid, the acid will be largely protonated

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

$$pKa = 4.76$$

at pH 7.0

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O^{\ominus}$$

Deprotonated

at pH 2.0

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$
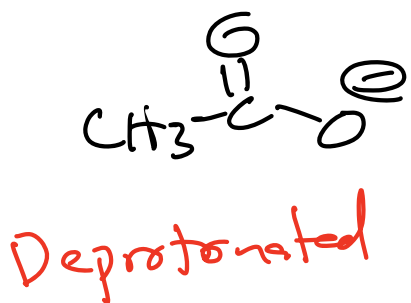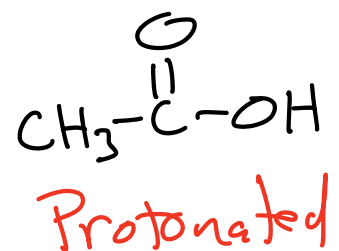
Protonated

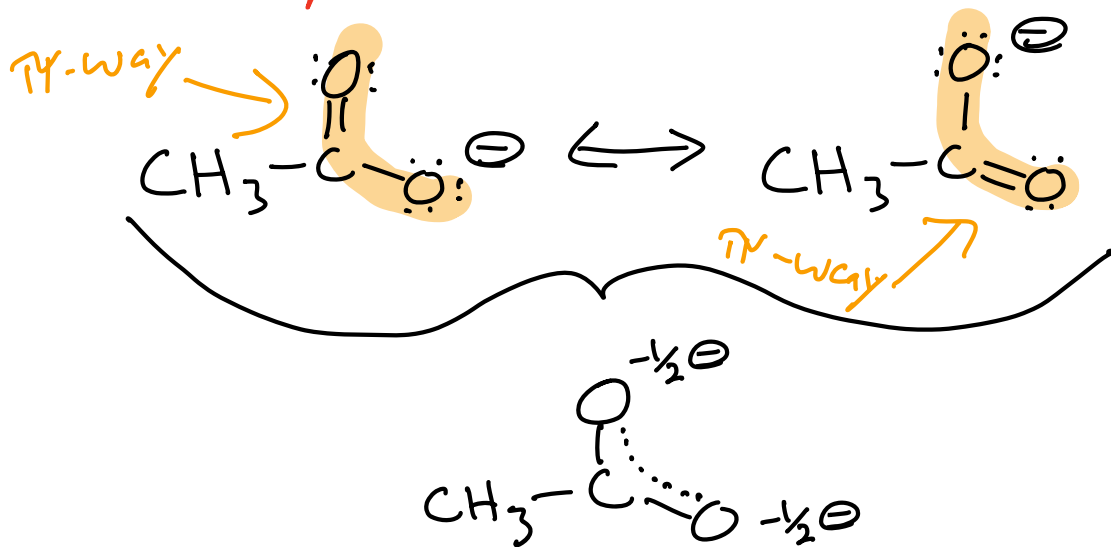In biochemistry → at or near neutral pH, carboxylic acids are deprotonated and negatively charged!

---

## Stability of anion Part II



π·way →

$CH_3-C \overset{\ddot{O}}{\underset{\ddot{\ddot{O}}:}{\Vert}} \ominus$ ⟷ $CH_3-C \overset{:\ddot{O}: \ominus}{\underset{\ddot{O}:}{=}}$

π-way ↗

$CH_3-C \overset{O^{-\frac{1}{2}\ominus}}{\underset{O^{-\frac{1}{2}\ominus}}{\cdots}}$

Not only is the negative charge split between two O atoms, there is a "π-way", namely a π bond that extends over all three atoms: