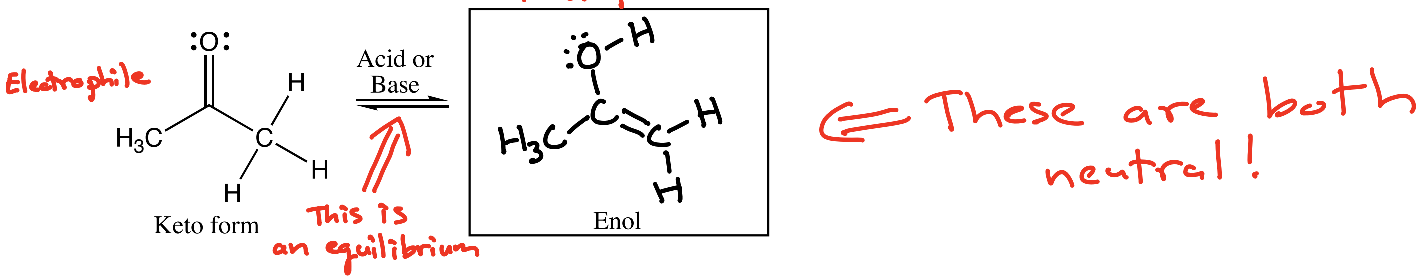
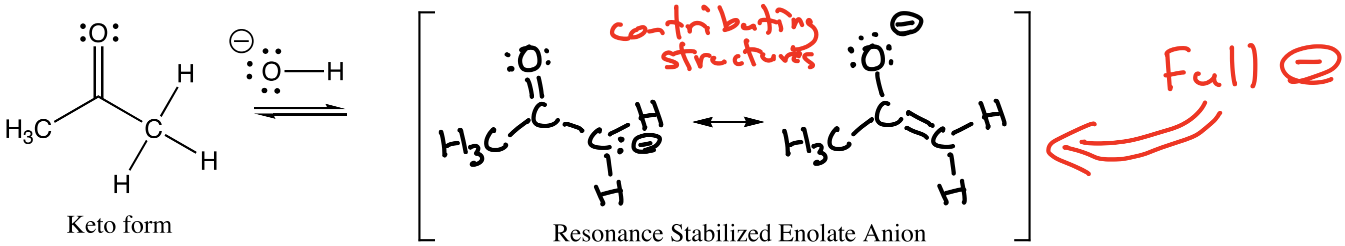
*Keto-Enol Tautomerization vs. Enolate Resonance*

## *Keto-Enol Tautomerization*



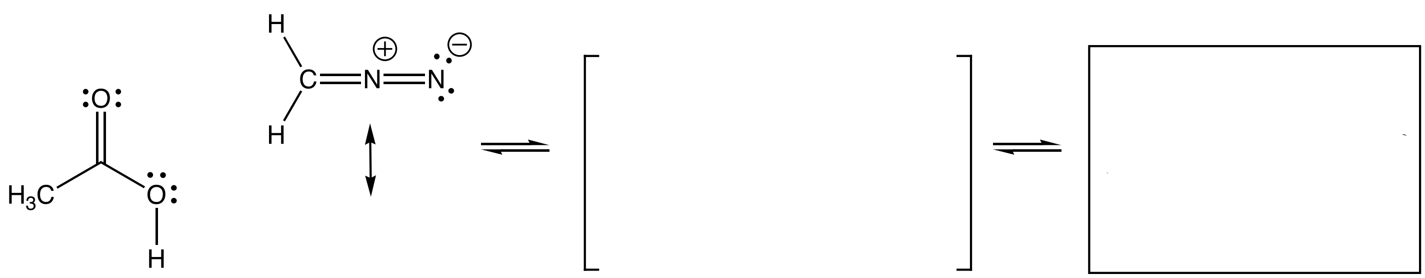

## *Enolate Resonance*




α-hydrogen p$K_a$ = 18-20

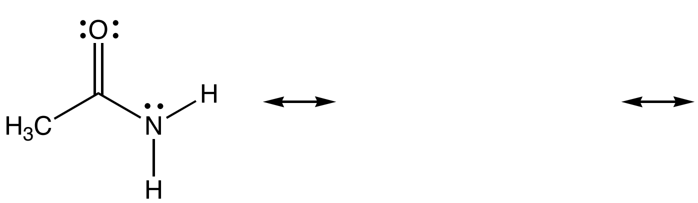
Strong nucleophile

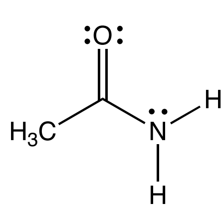
## *Diazomethane reaction*



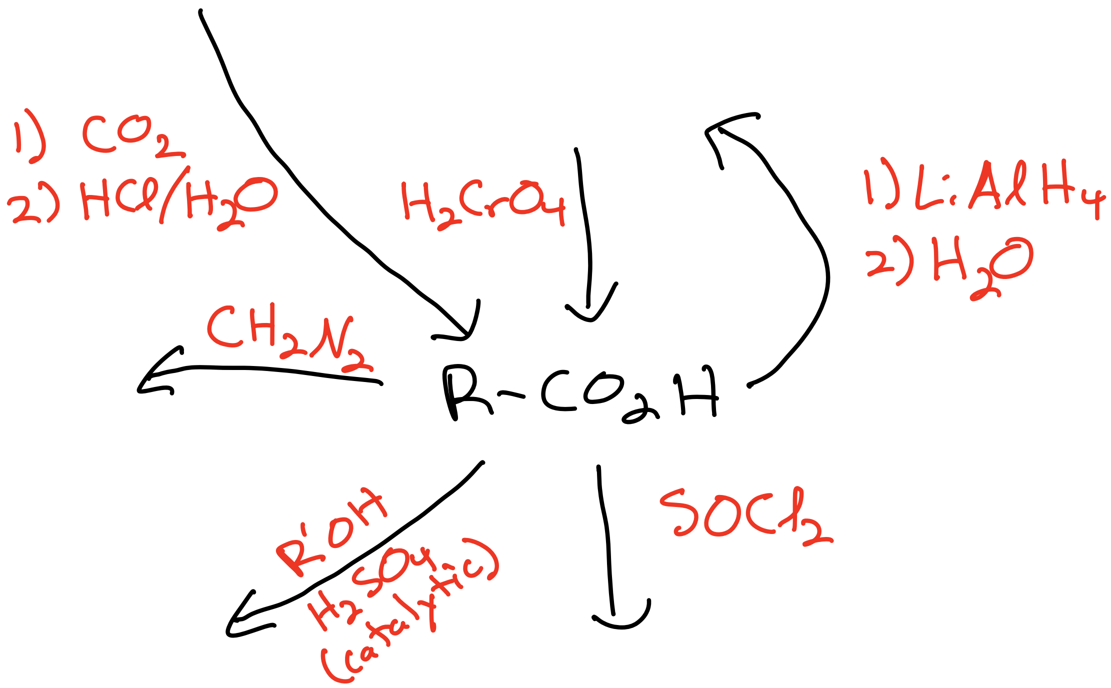
Diazomethane
contributing structures

## *Amide Resonance VERY IMPORTANT!!!!!!*



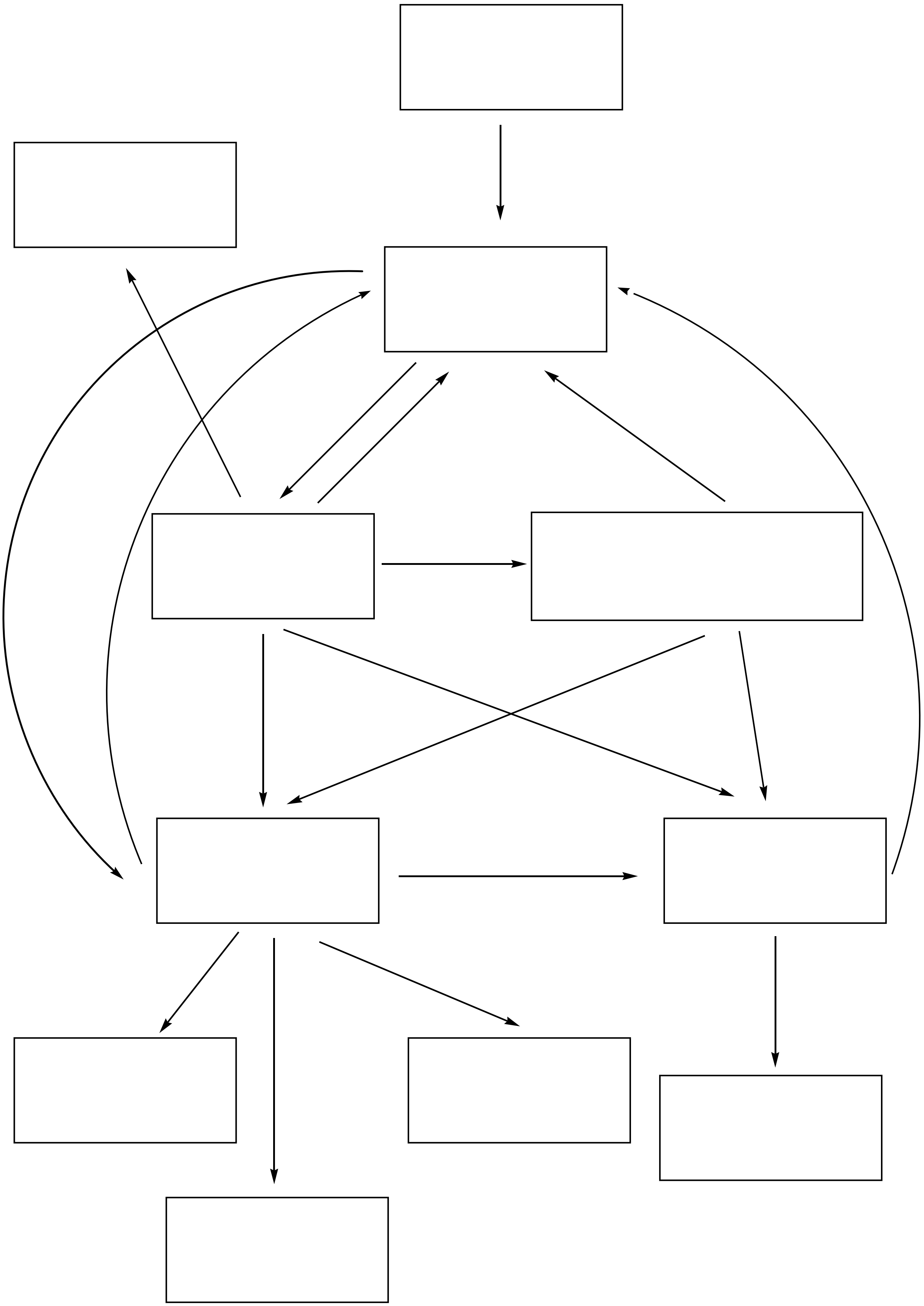


# Summary of Carboxylic Acid Reactions →



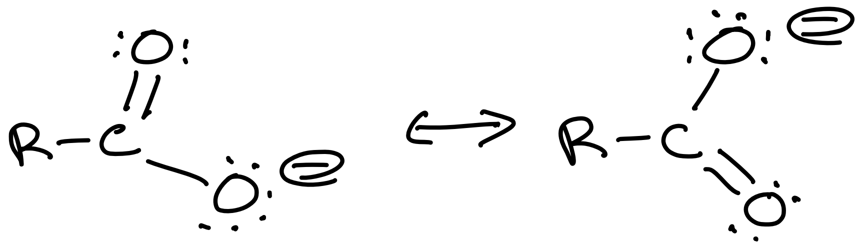
# Carboxylic Acid Derivatives

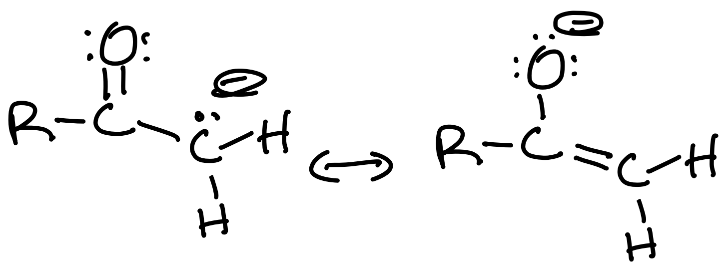
*Interconversion of Carboxylic Acid Derivatives*

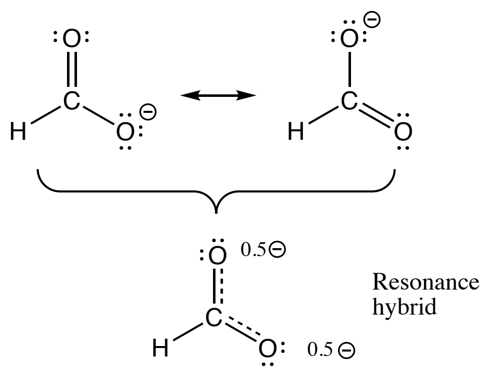


Key idea →

Resonance contributing structures you have seen before:



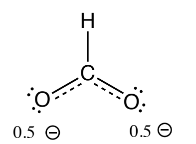





Carboxylate anion

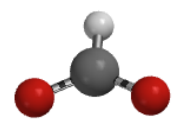
A common situation, and the one many resonance contributing structures describe, occurs when three 2p orbitals combine on adjacent atoms. A good example is the carboxylate anion. When three adjacent 2p orbitals interact (we add the three 2p orbital wave functions $\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$ ), three new molecular orbitals are produced; a low energy bonding "pi-way", a non-bonding orbital and an antibonding orbital as shown below. This pattern of three molecular orbitals is generally the same whenever three 2p orbitals interact even if there are different atoms involved, for example the enolate ion or allyl cation. There are four electrons in the pi system of the carboxylate anion, (you can see this by looking at either of the contributing structures; two electrons from the pi bond and two from the third lone pair on the negatively charge O atom). Note the non-bonding orbital contains the electron density of two electrons that are paired, do NOT think of it as having one upaired electron on each O atom. I know, weird, but remember it is best to think of bonding electrons as waves, not particles. Note the electron density on only the O atoms of the non-bonding orbital explains why the negative charge is localized on the O atoms in the carboxylate anion.

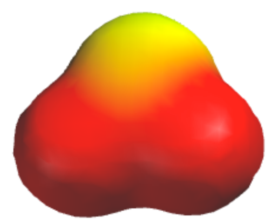
$$\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$$

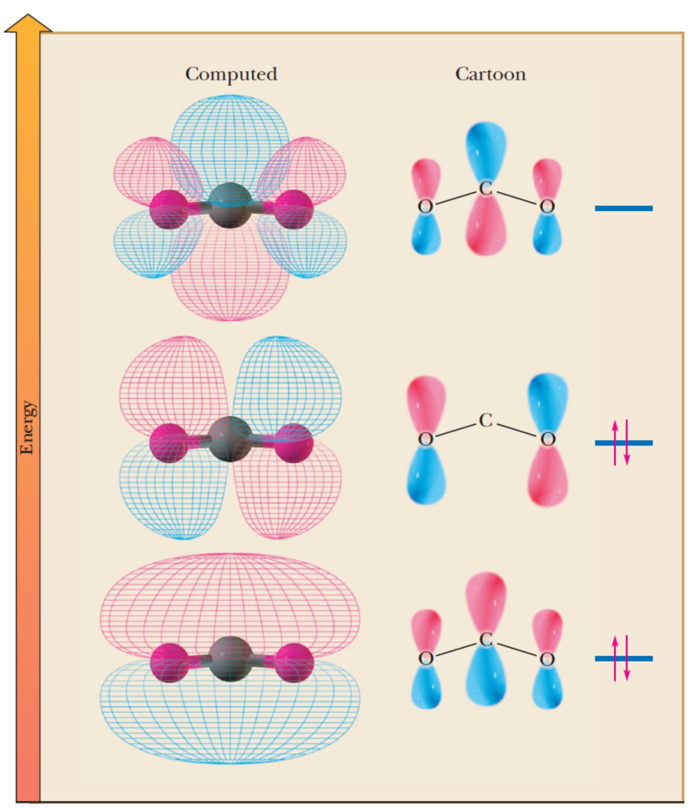


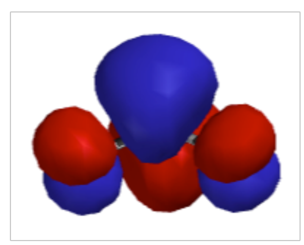

Carboxylate anion

Resonance
hybrid

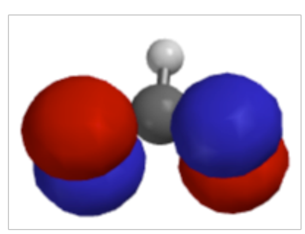




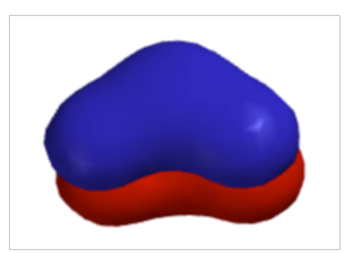


Antibonding orbital



Non-bonding orbital



"π-way" orbital

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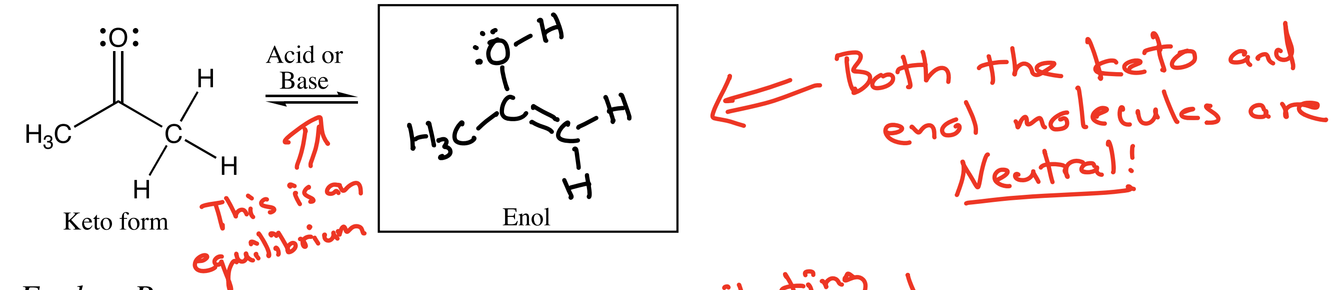
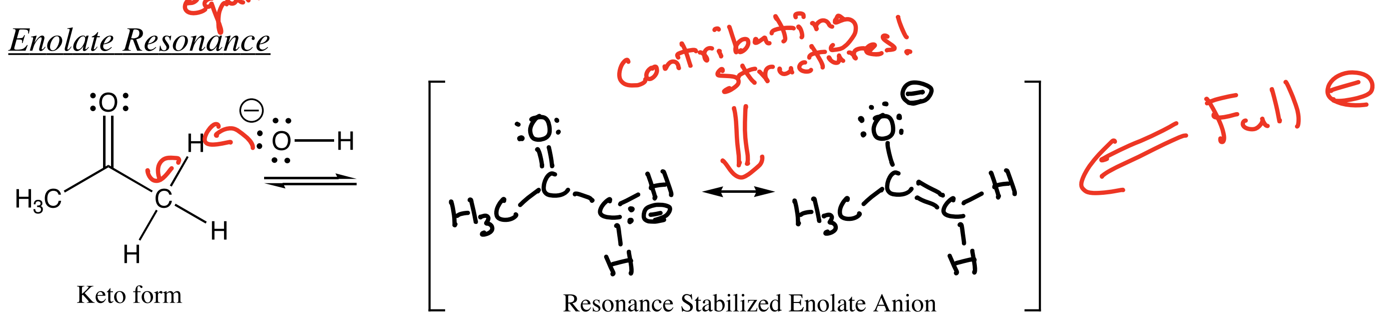



## *Enolate Resonance*

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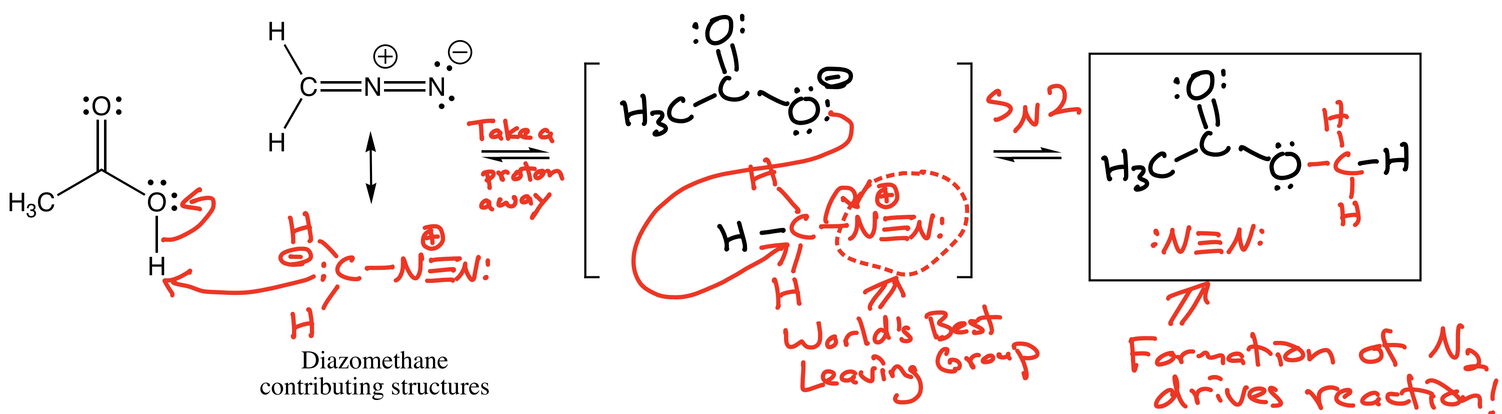
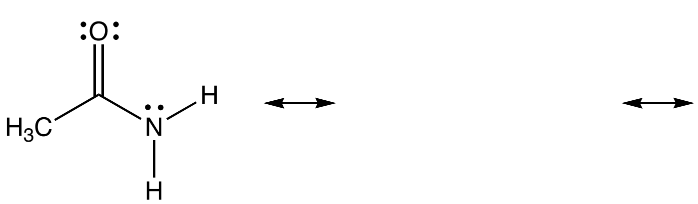
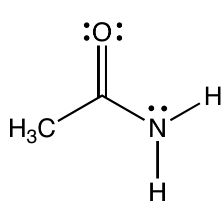


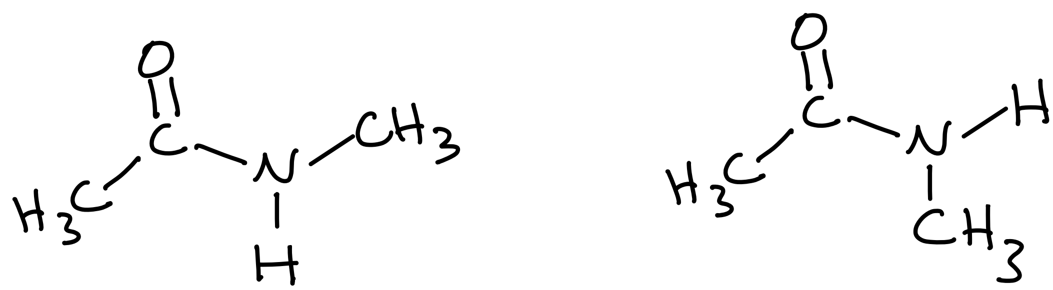

## *Amide Resonance  VERY IMPORTANT!!!!!!*





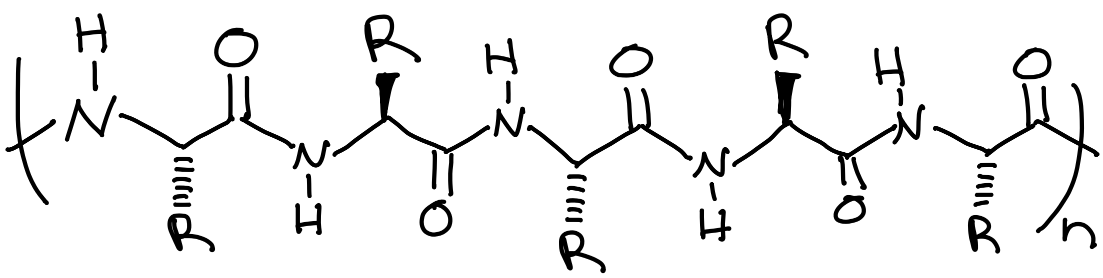
What does all of this mean for amide bonds?

1) The C–N bond of amides acts like a C=C bond so there can be cis and trans isomers!



2) The contributing structures verify there is more negative charge on O atom of amides than on the O atom of other carbonyls.

3) The C–N bond of amides does not rotate at room temperature.



We inherit DNA sequences from our parents →

The rigidity of the protein backbone due to the amide bonds is enough to provide for the stable folded three-dimensional structures!

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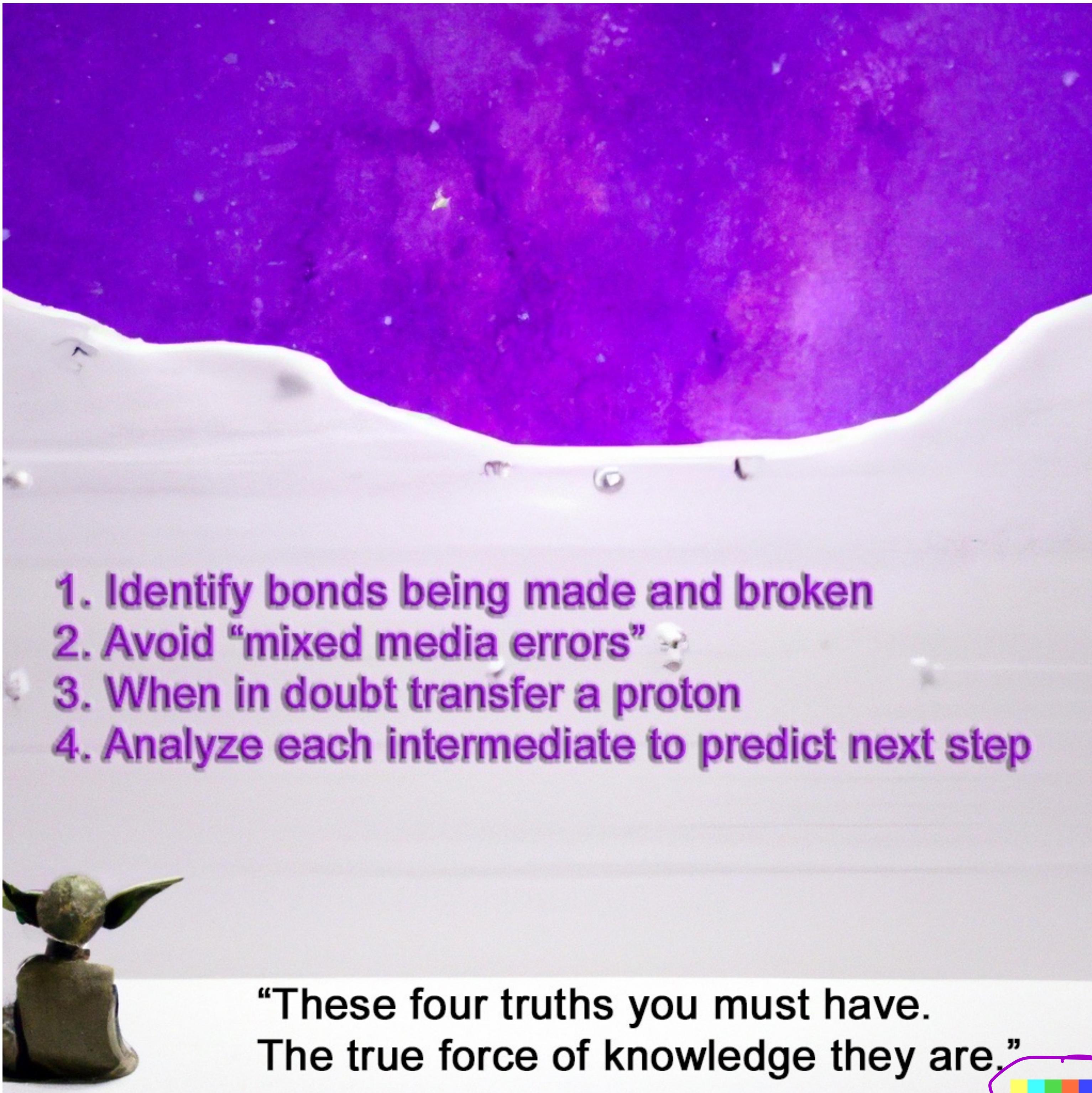

1. Identify bonds being made and broken
2. Avoid “mixed media errors”
3. When in doubt transfer a proton
4. Analyze each intermediate to predict next step
“These four truths you must have.
The true force of knowledge they are.”

For mechanisms, keep the following in mind:

1) Identify the bonds to be made and broken in the overall reaction

2) Avoid "mixed media errors"

3) When in doubt transfer a proton → protons move very fast

4) Analyze each intermediate carefully to predict the next step

# Here are the keys to understanding mechanisms in 320N!!

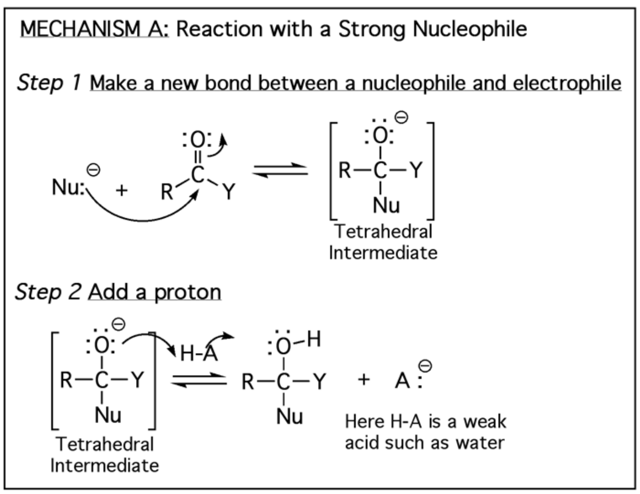
1) There are basically four different mechanisms elements that make up the steps of carbonyl reactions.

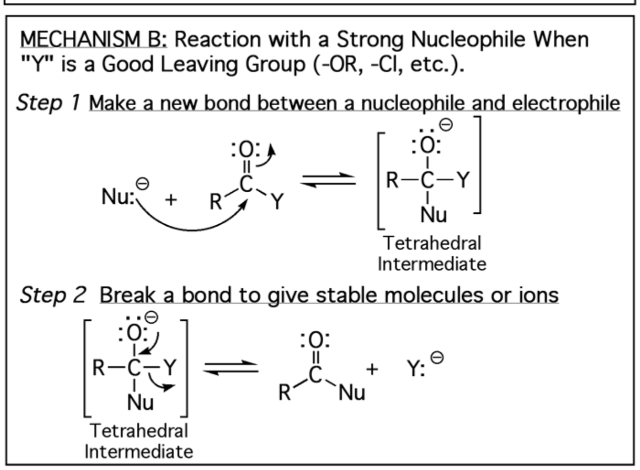
**A) Make a bond between a nucleophile and an electrophile**
**B) Break a bond to give stable molecules or ions**
**C) Add a proton**
**D) Take a proton away**

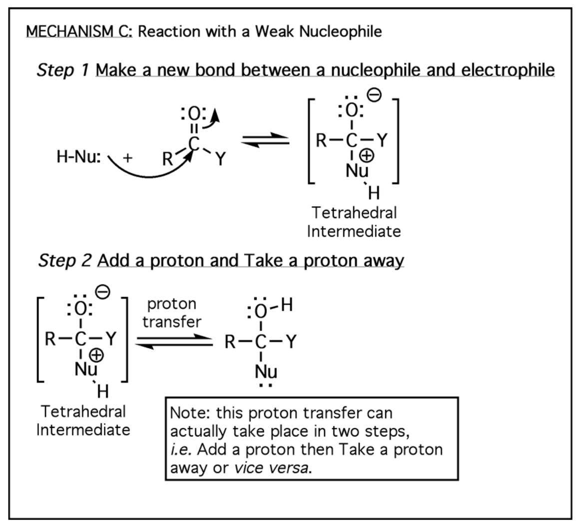
2) These same four mechanism elements describe most of the other mechanisms you have/will learn!!! (Yes, organic chemistry really is this simple if you look at it this way!!)

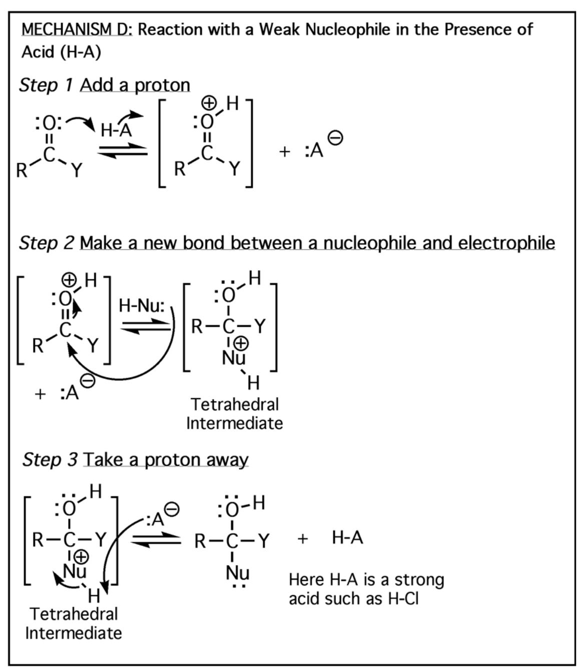
There are basically four different mechanisms that describe the vast majority of carbonyl reactions and these mechanisms are different combinations/ordering of the four mechanism elements listed above. In this class, I have termed them "Mechanism A", "Mechanism B", "Mechanism C", and "Mechanism D". They all involve a nucleophile attacking the partially positively charged carbon atom of the carbonyl to create a tetrahedral intermediate. Different reaction mechanisms are distinguished by the timing of protonation of the oxygen atom as well as the presence or absence of a leaving group attached to the carbonyl.

Four Mechanisms for the Reaction of Nucleophiles with Carbonyl Compounds

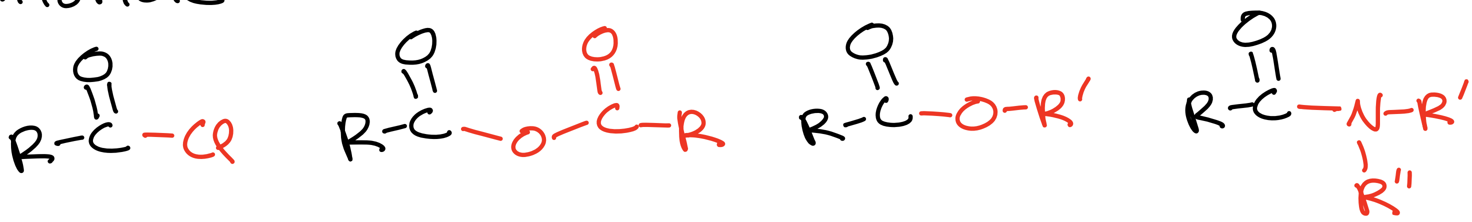


Acid Chloride | Anhydride | Ester | Amide

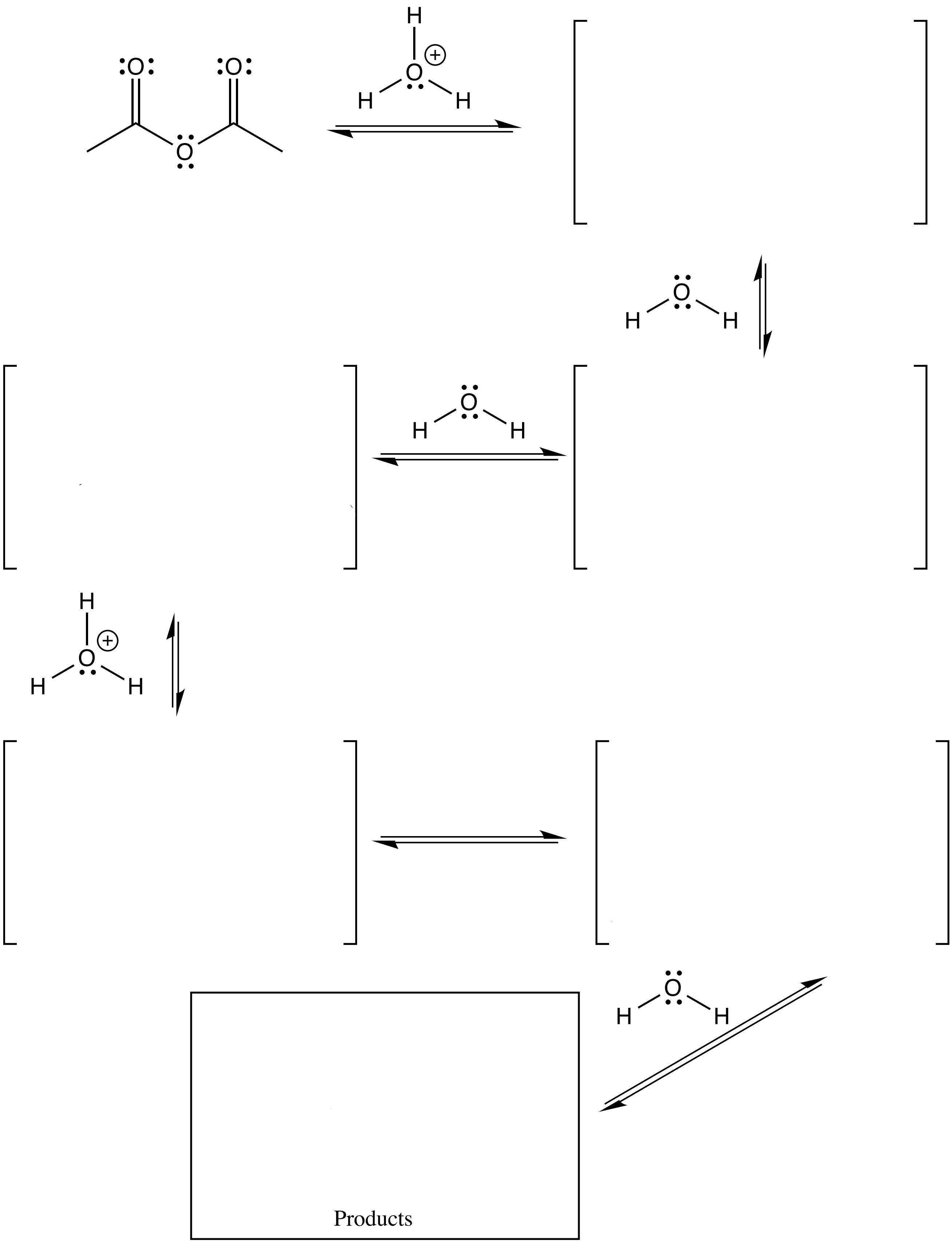



Leaving Group

Conjugate Acid

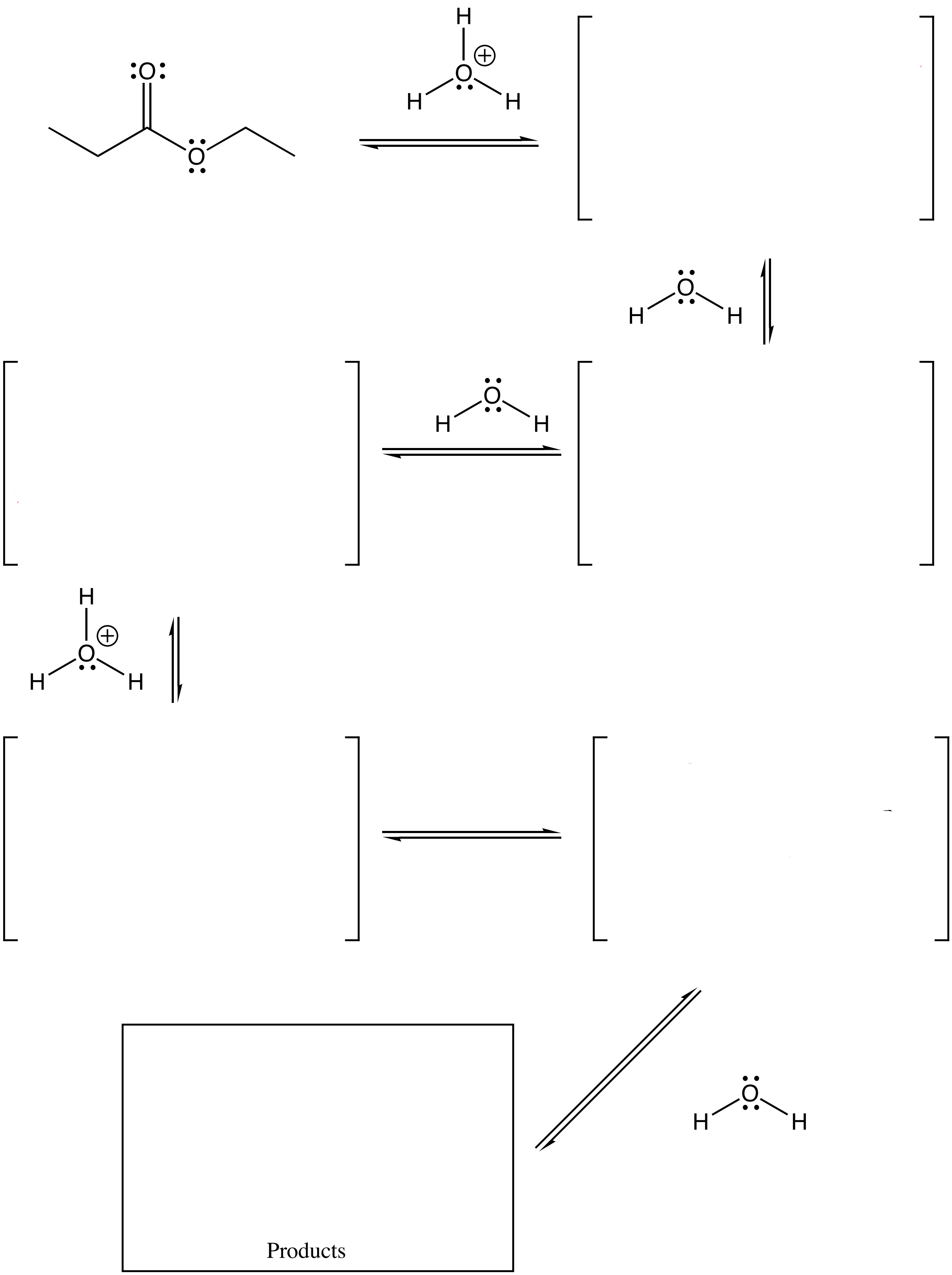
pKa

*Acid Catalyzed Anhydride Hydrolysis*

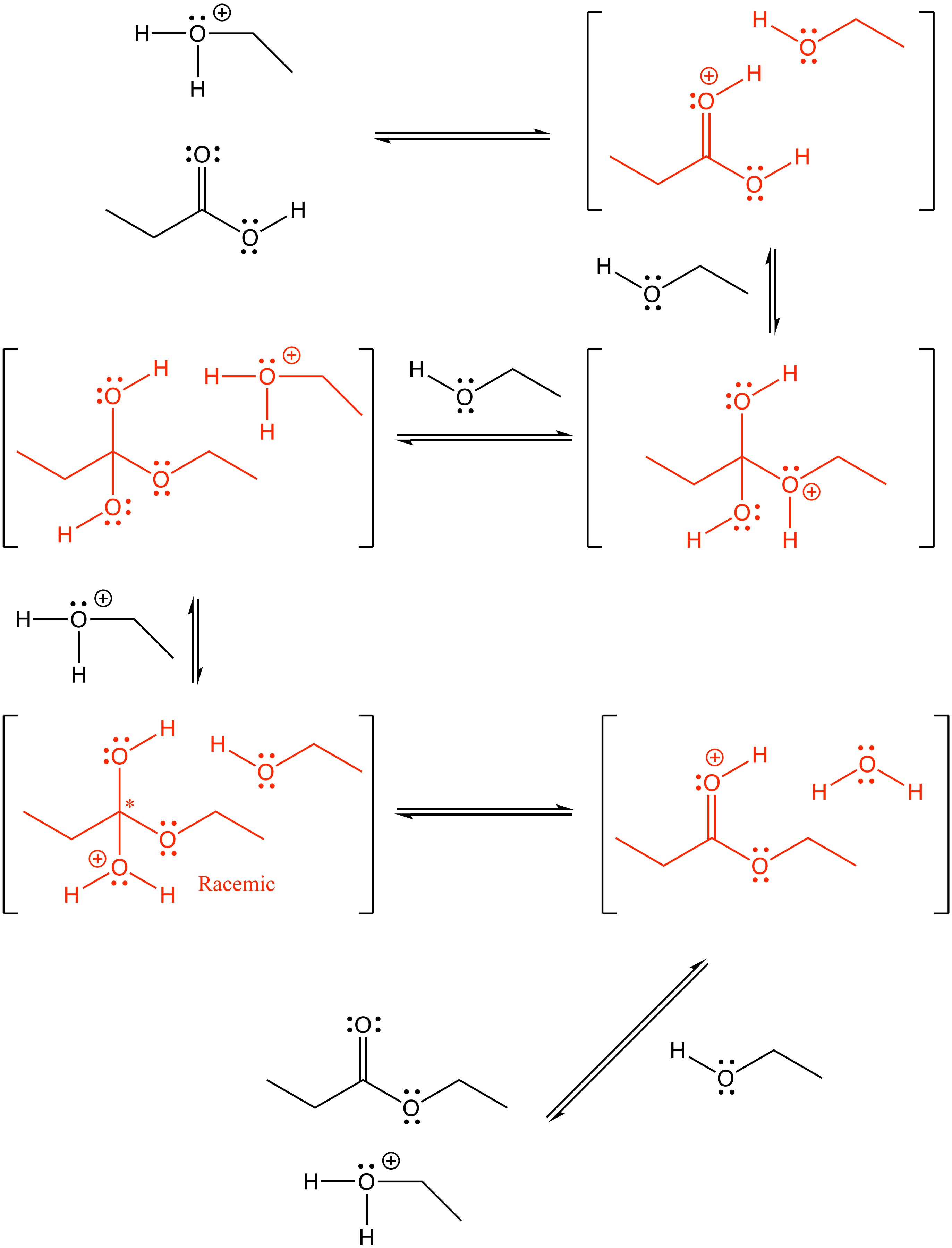



Products

# *Acid Catalyzed Ester Hydrolysis*



*Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification*



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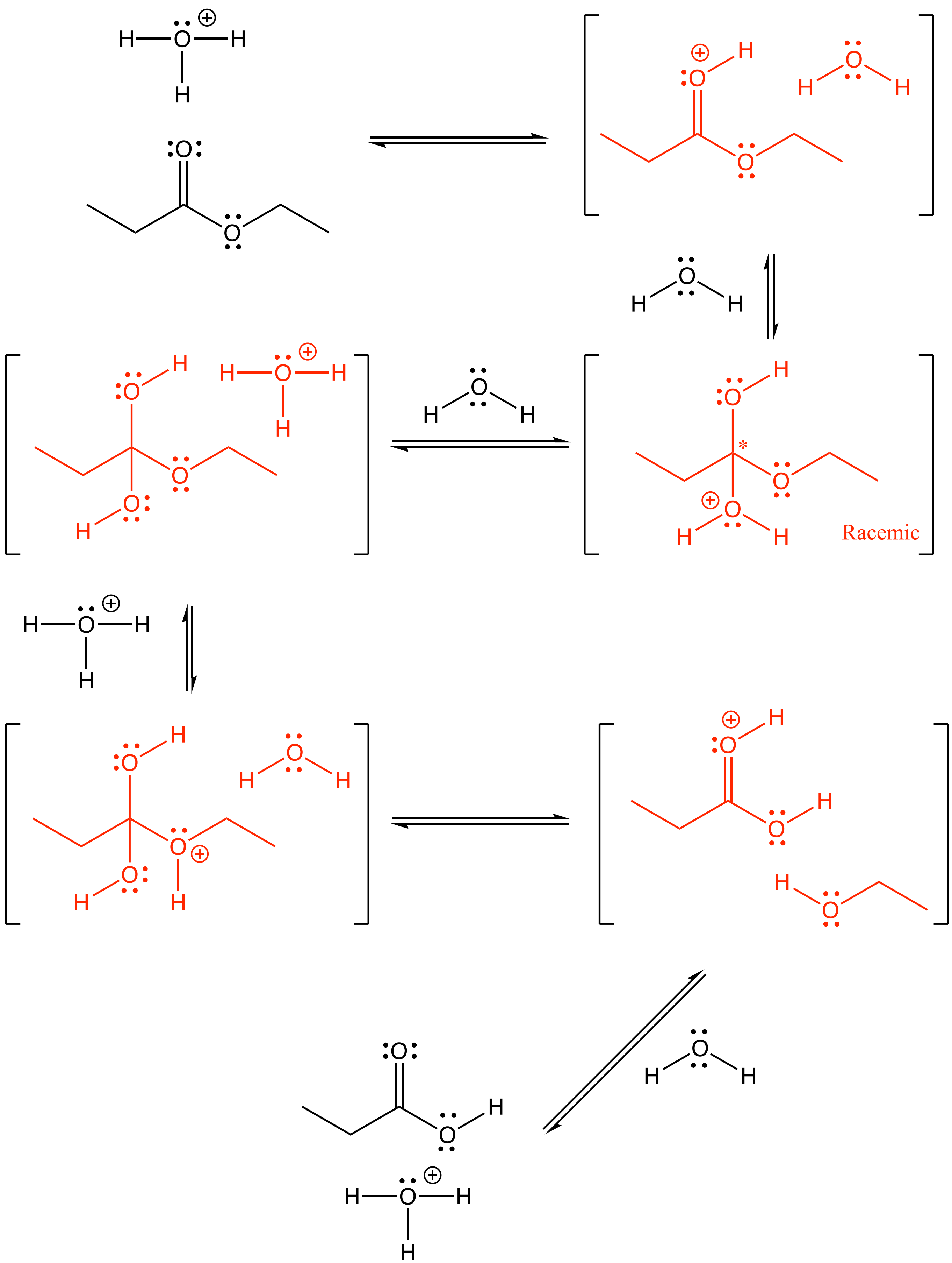
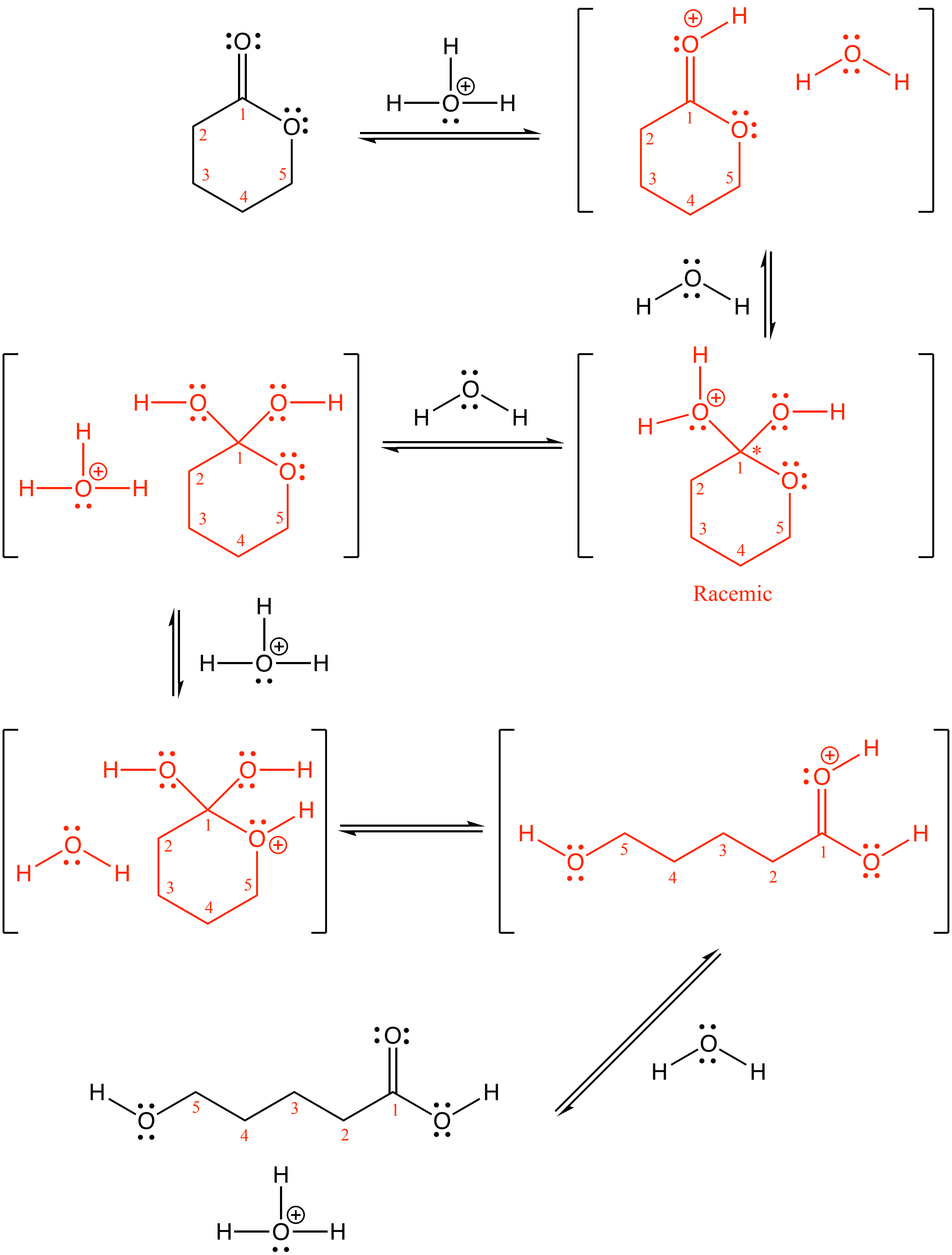


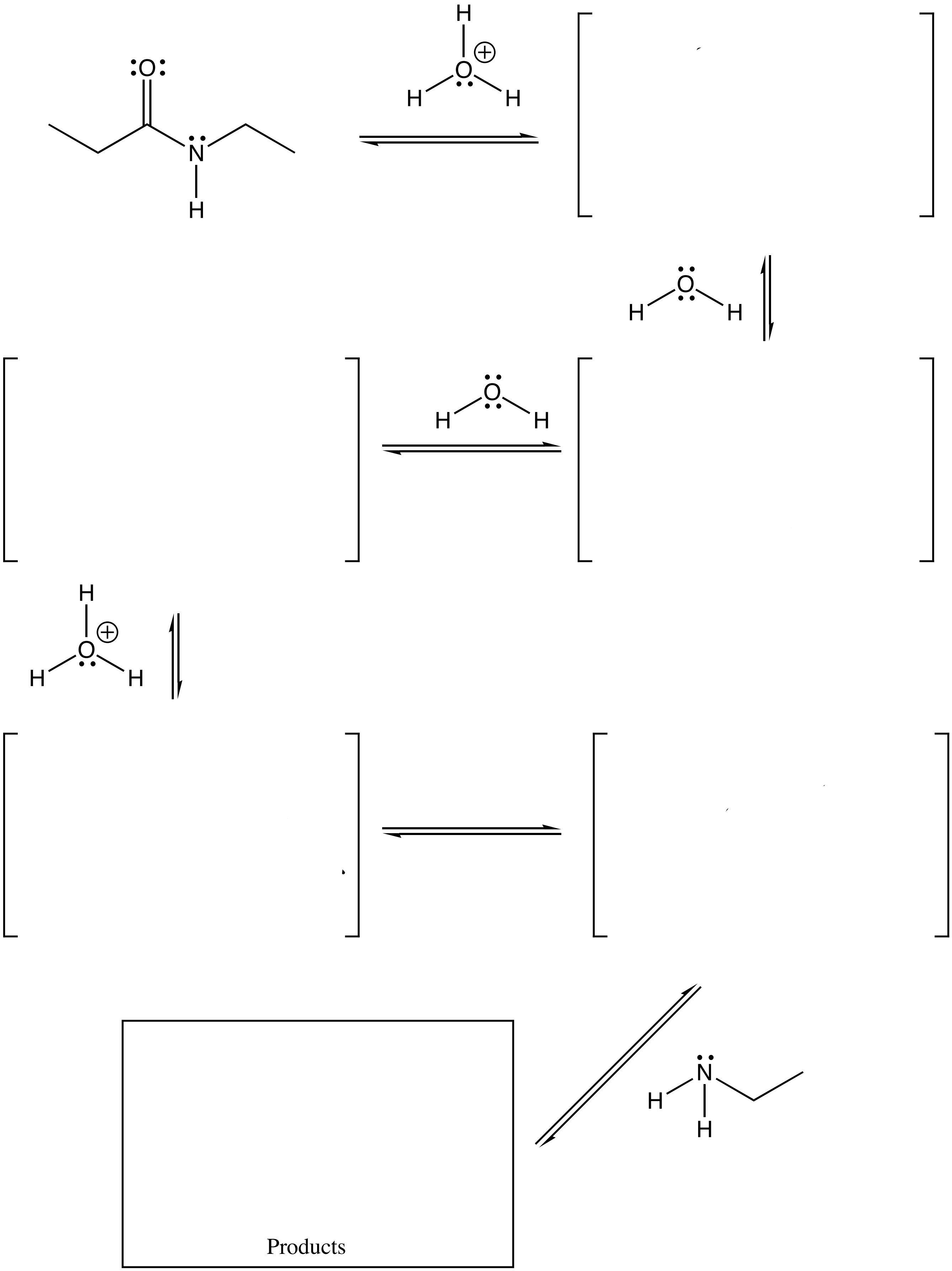
$$R{-}\overset{\overset{O}{\|}}{C}{-}OH + R'OH \xrightleftharpoons[]{H_2SO_4 \text{ (catalytic)}} R{-}\overset{\overset{O}{\|}}{C}{-}OR' + H{-}O{-}H$$

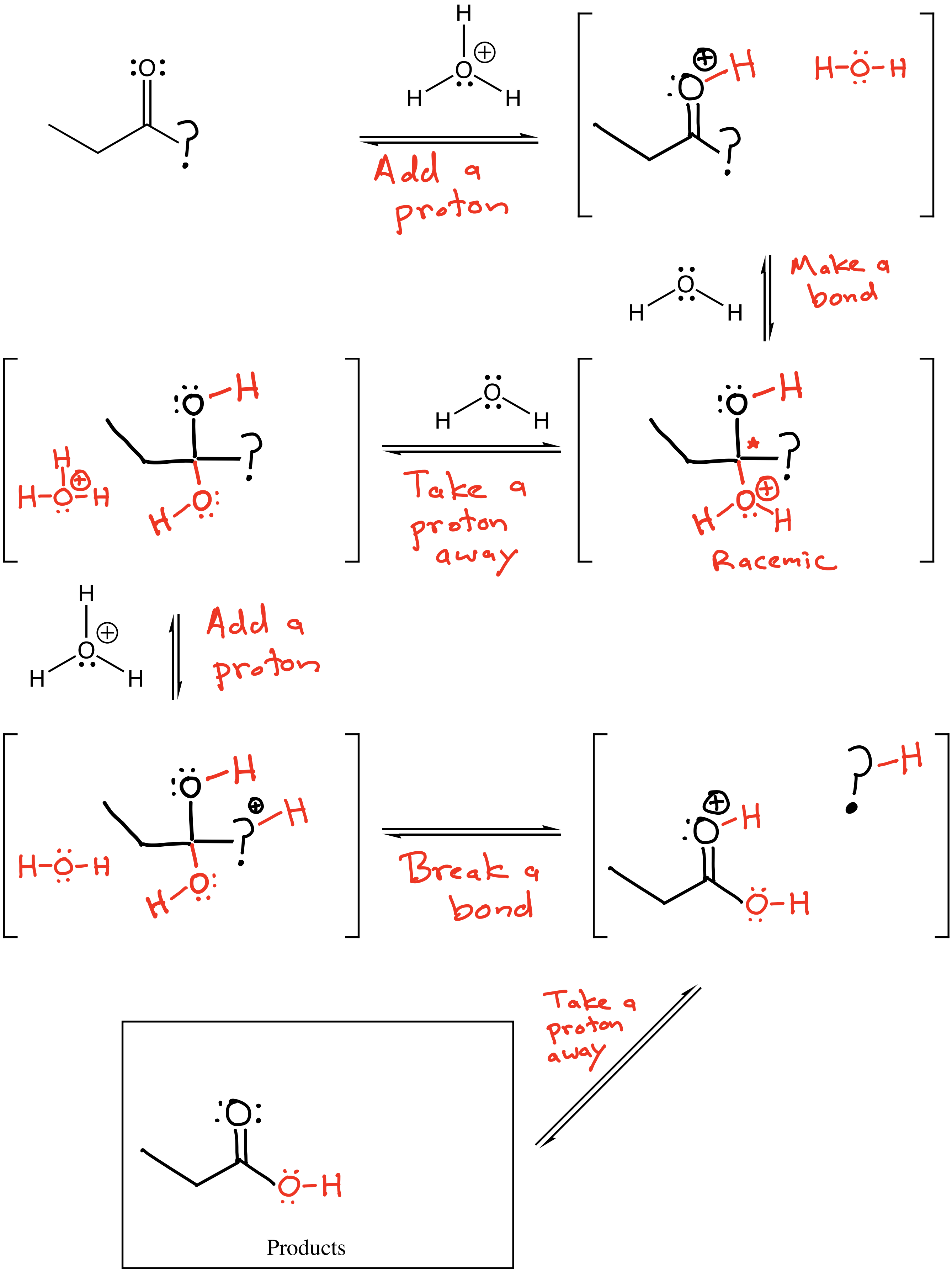
Microscopic Reversibility →

# *Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification*

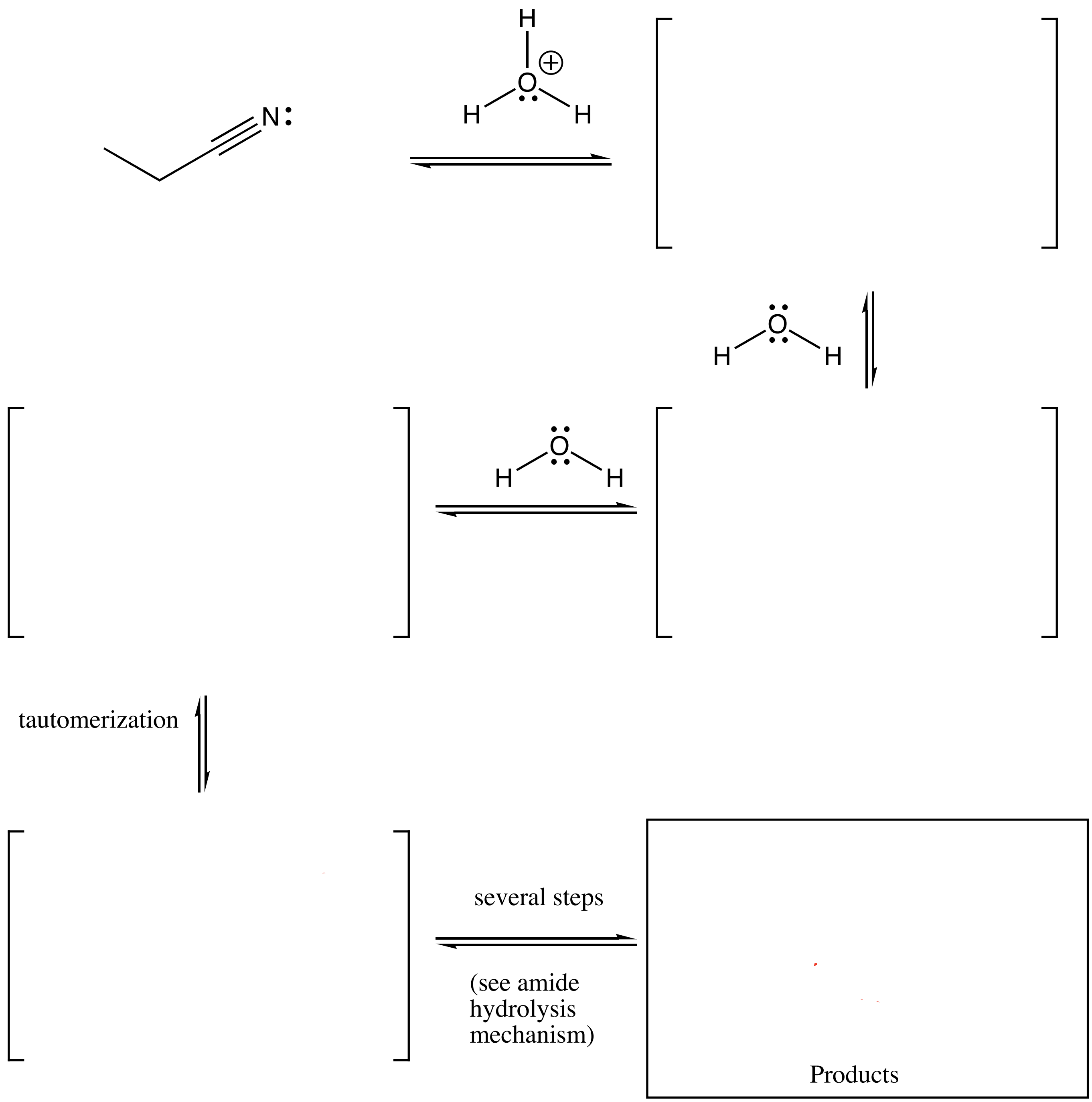


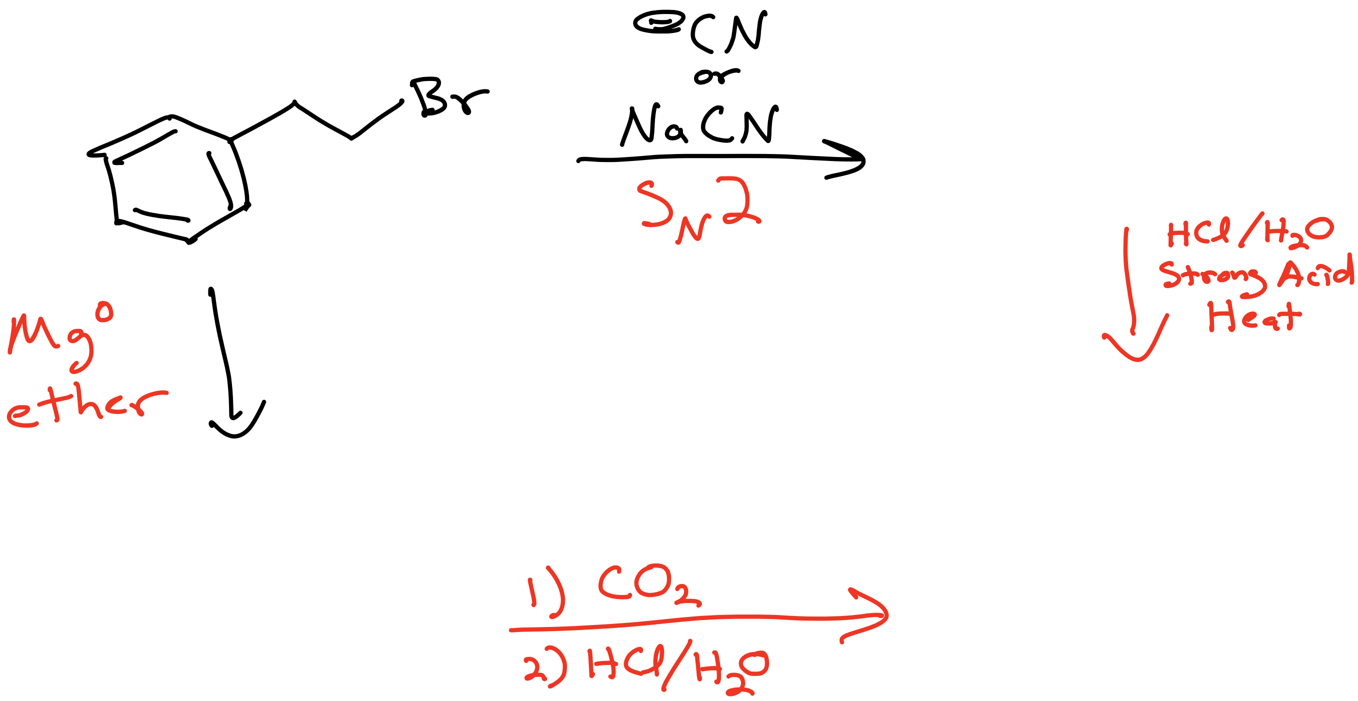
# *Acid Promoted Amide Hydrolysis*

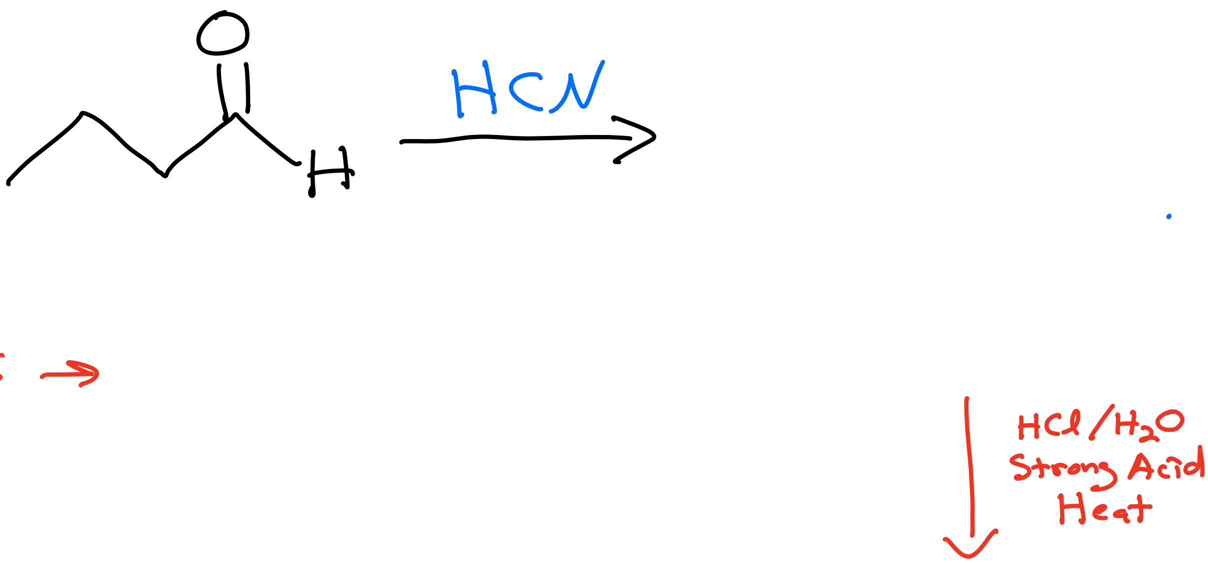



Add a proton
Make a bond
Take a proton away
Racemic
Add a proton
Break a bond
Take a proton away
Products

# *Acid Promoted Nitrile Hydrolysis*

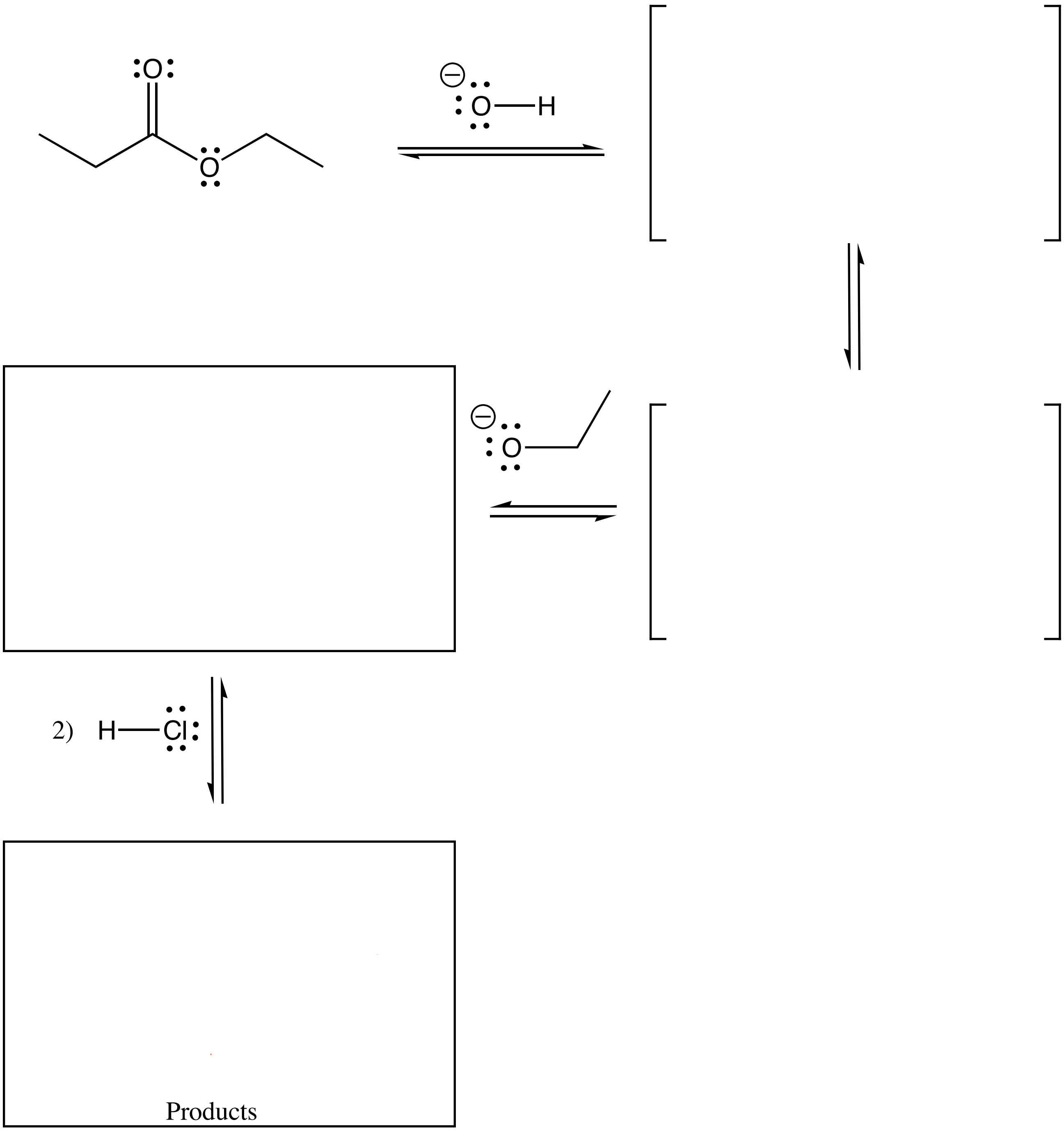



Br
⊖CN
or
NaCN
$S_N2$
$HCl/H_2O$
Strong Acid
Heat
$Mg^0$
ether
1) $CO_2$
2) $HCl/H_2O$

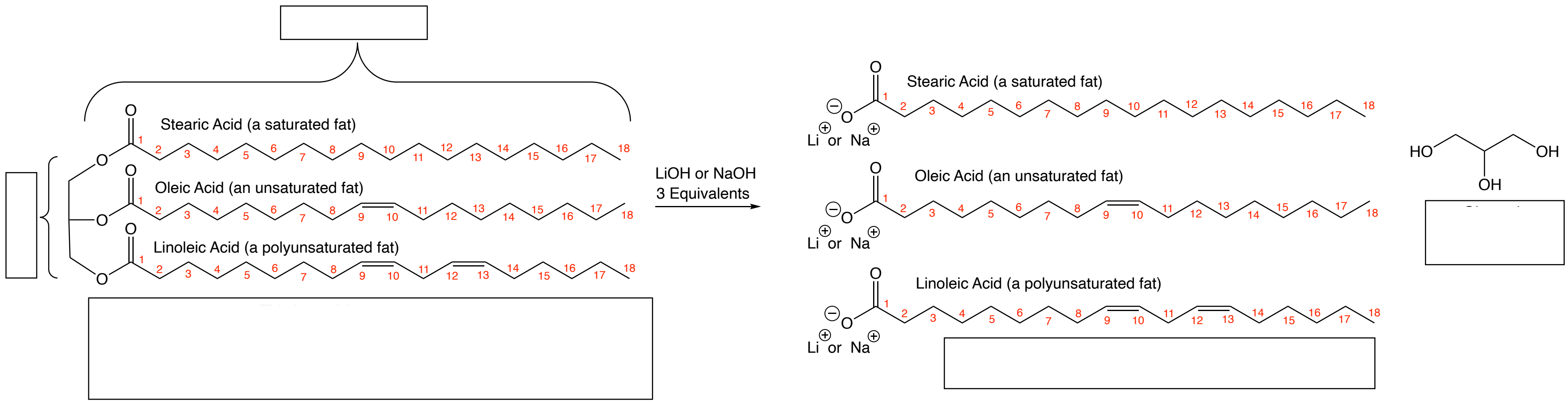

O
H
HCN
$HCl/H_2O$
Strong Acid
Heat

KRE →

*Base-Promoted Ester Hydrolysis - Saponification*

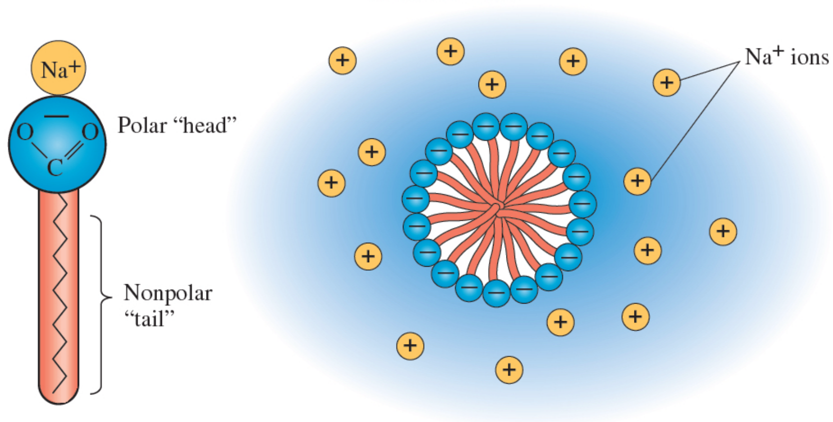



Driving force →

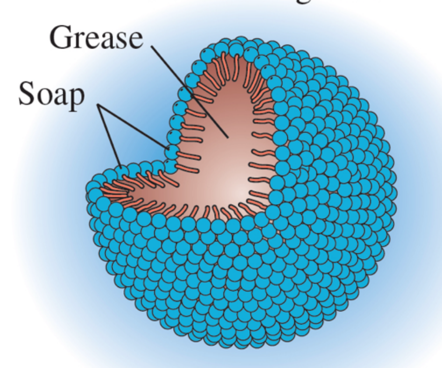



**(a)** A soap

**(b)** Cross section of a soap micelle in water




Soap micelle with "dissolved" grease

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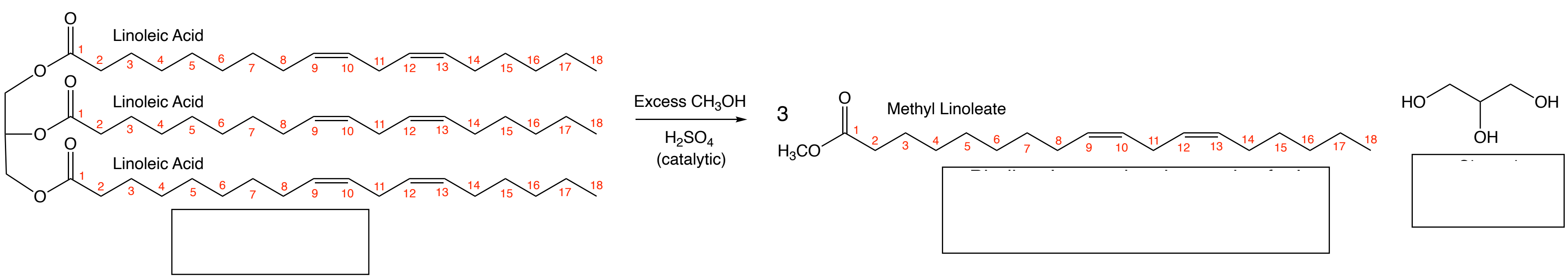

$$R-\overset{O}{\overset{\|}{C}}-OR' + H_2O \xrightarrow[\text{(catalytic)}]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-OH + R'OH$$

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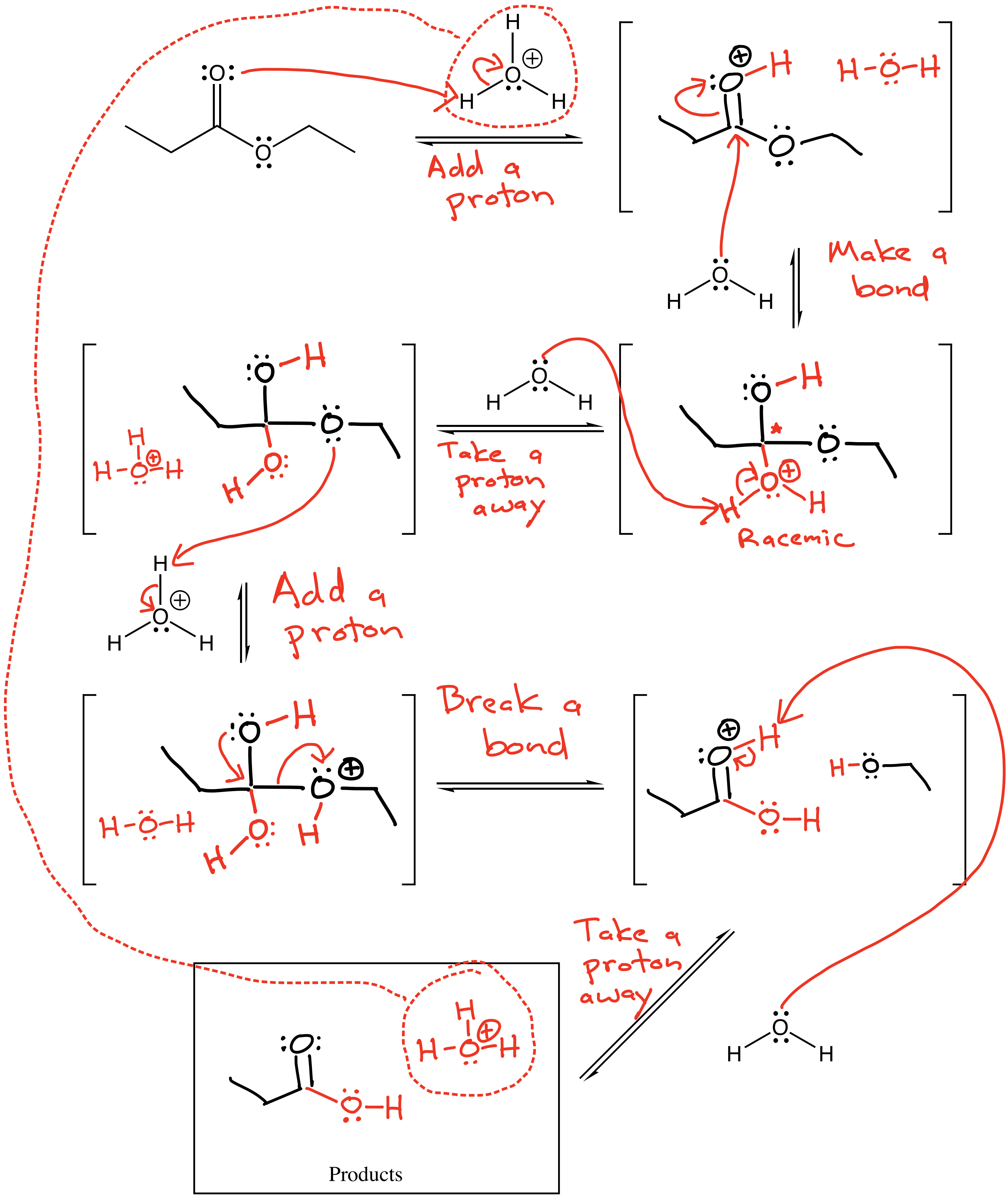

$$R-\overset{\displaystyle O}{\overset{\|}{C}}-OR' + R''OH \xrightleftharpoons[\text{(catalytic amount)}]{H_2SO_4}$$

Transesterification $\longrightarrow$

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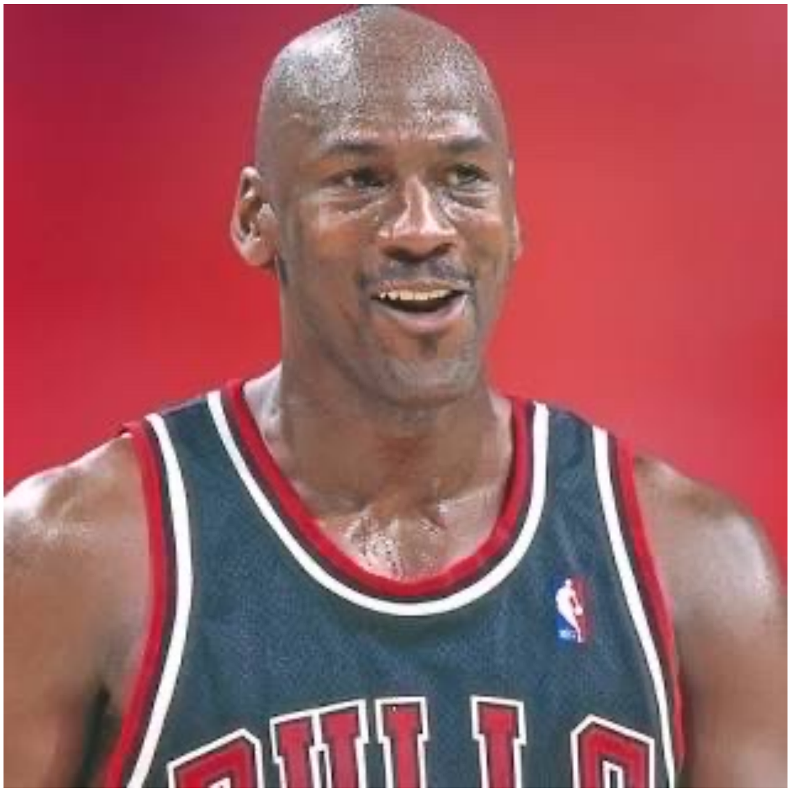
# Hydrolysis of Esters and Amides

Although either acid or base will work for both esters and amides, it is easiest (less harsh conditions required) to



“I've missed more than 9000 shots in my career. I've lost almost 300 games. 26 times, I've been trusted to take the game winning shot and missed. I've failed over and over and over again in my life. And that is why I succeed.”   Michael Jordan