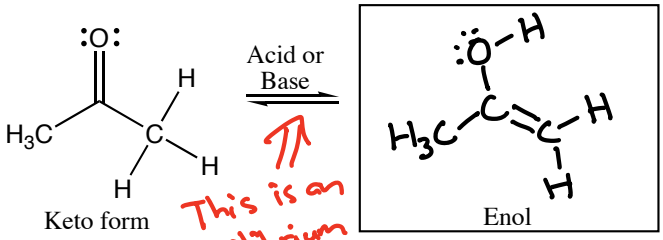
Key idea → A lone pair on an atom adjacent to a carbonyl is delocalized into the π bond of the C=O

creates a three atom π-way orbital that contains 2 electrons

VERY stabilizing
(Golden Rule of Chemistry)

Keto-Enol Tautomerization vs. Enolate Resonance

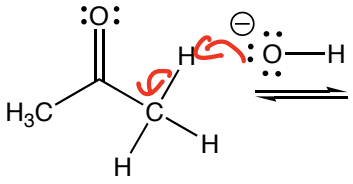
Keto-Enol Tautomerization

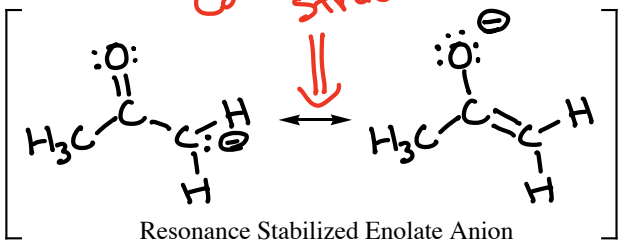


This is an equilibrium

Both the keto and enol molecules are Neutral!

Enolate Resonance



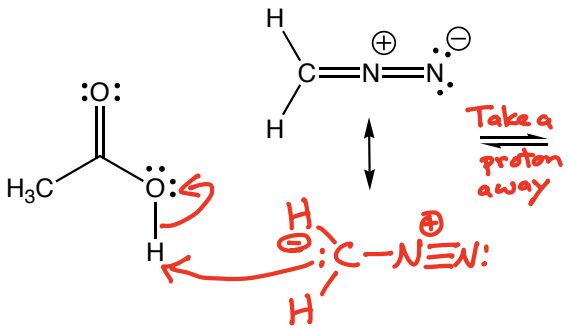


Contributing structures!

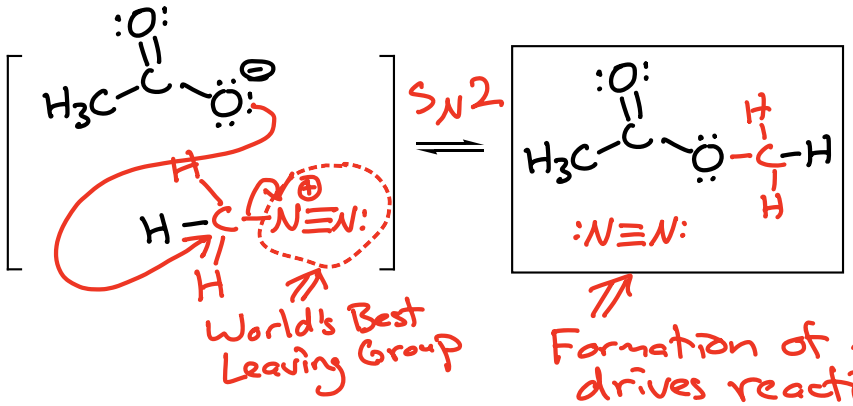
Full ⊖

α-hydrogen pK_a = 18-20

Diazomethane reaction



Take a proton away

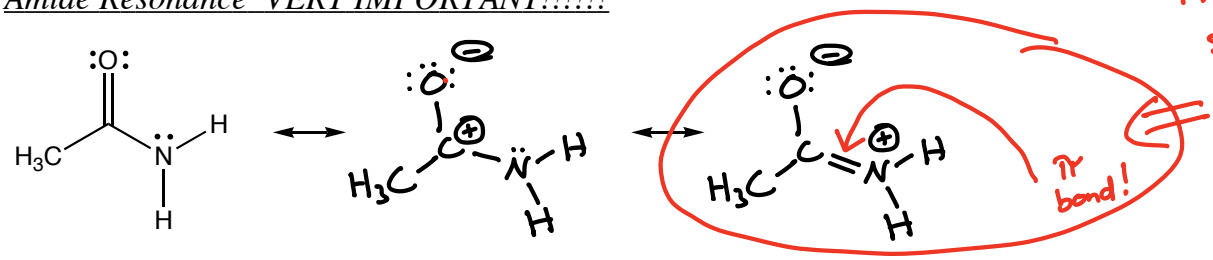


S_N2

World's Best Leaving Group

Formation of N_2 drives reaction!

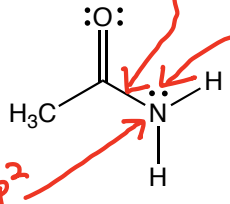
Amide Resonance VERY IMPORTANT!!!!!!



This contributing structure is important and that has big consequences!

π bond!

This is a partial π bond so it does NOT rotate at room temperature



Lone pair is in a 2p orbital!

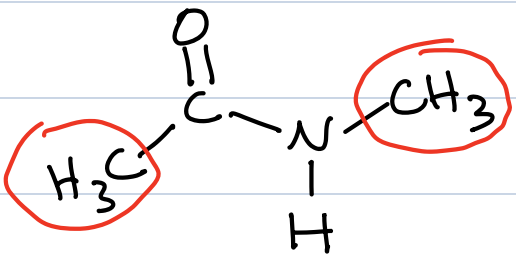
(Golden Rule of Chemistry)

A "π-way" is created from the overlap of 2p orbitals on the O, C, and N atoms → 3 atoms, 2 electrons → VERY STABILIZING!

What does all of this mean for amide bonds?

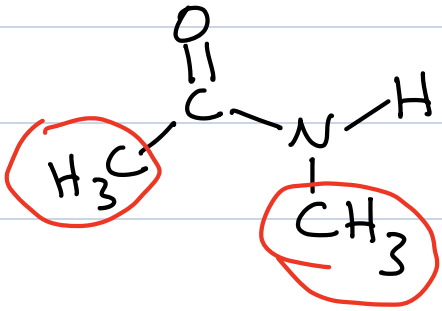
1) The C–N bond of amides acts like a C=C bond so there can be cis and trans isomers!

Amides prefer to be "trans" rather than "cis"



trans

Favored



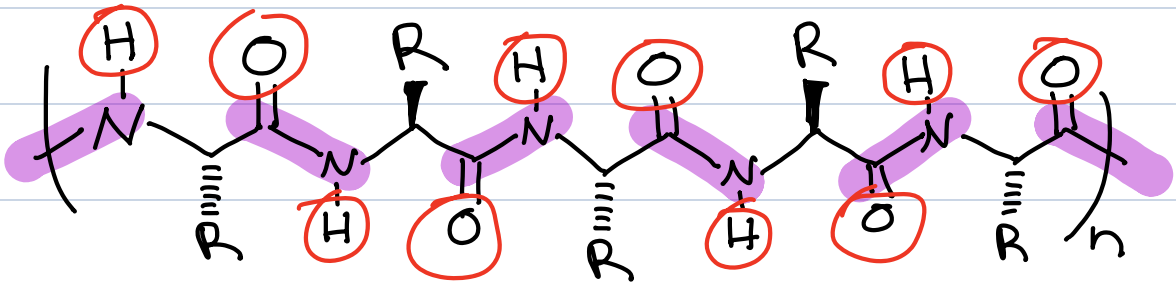
cis

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

Amides make strong hydrogen bonds! (See the Pictures of the day for today)

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

All of the C–N bonds in a protein backbone do not rotate so the protein backbone is rigid enough to fold into stable 3-d structures!



The protein backbone with amide bonds highlighted — the atoms with red circles make hydrogen bonds

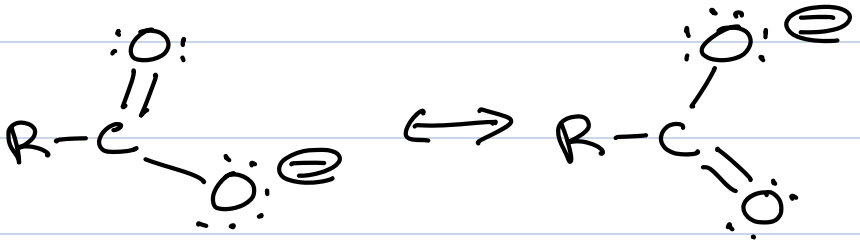
We inherit DNA sequences from our parents → code for one-dimensional chains of amino acids (called proteins) that fold into three-dimensional objects!

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

One-dimensional → three dimensional information → the secret of life on on this planet ⇒ owes it all to the rigidity of the humble amide bond

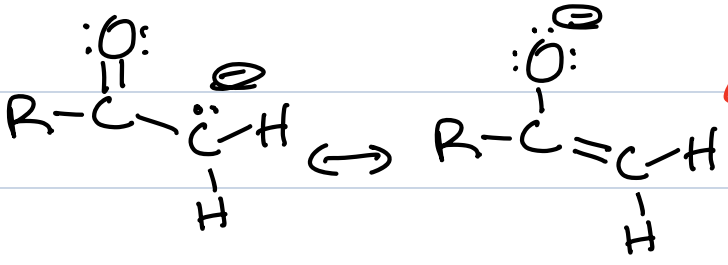
π-ways rule!

Resonance contributing structures you have seen before:



This also has a 3 atom π-way on the O-C-O atoms!!

We just never told you!



This also has a 3 atom π-way on the O-C-C atoms!!

We just never told you!

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"

   a) In acid, all the intermediates are positively-charged or neutral

   b) In base, all the intermediates are negatively-charged or neutral

   c) In neutral solution → the intermediates could be positively-charged, negatively-charged or neutral

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

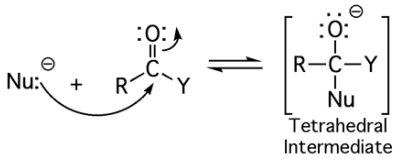
2) These same four mechanism elements describe most of the other mechanisms you have/will learn!!! (Yes, organic chemistry really is this simple if you look at it this way!!)

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.

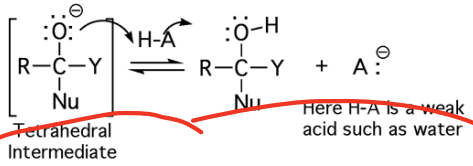
Four Mechanisms for the Reaction of Nucleophiles with Carbonyl Compounds

MECHANISM A: Reaction with a Strong Nucleophile

Step 1 Make a new bond between a nucleophile and electrophile

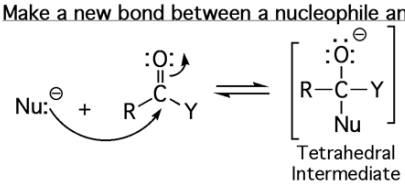


Step 2 Add a proton

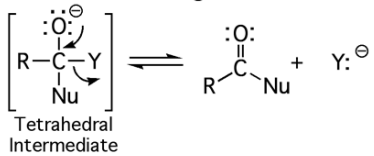


MECHANISM B: Reaction with a Strong Nucleophile When "Y" is a Good Leaving Group (-OR, -Cl, etc.).

Step 1 Make a new bond between a nucleophile and electrophile

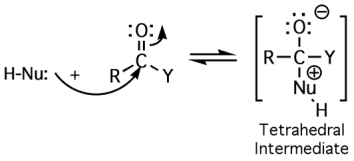


Step 2 Break a bond to give stable molecules or ions

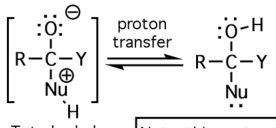


MECHANISM C: Reaction with a Weak Nucleophile

Step 1 Make a new bond between a nucleophile and electrophile



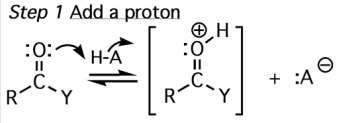
Step 2 Add a proton and Take a proton away



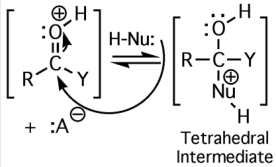
Note: this proton transfer can actually take place in two steps, *i.e.* Add a proton then Take a proton away or *vice versa*.

MECHANISM D: Reaction with a Weak Nucleophile in the Presence of Acid (H-A)

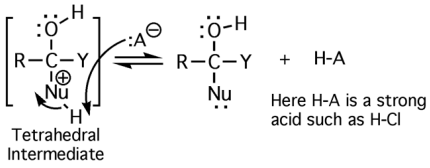
Step 1 Add a proton



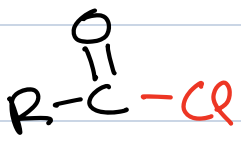
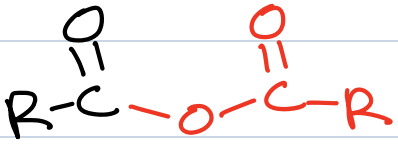
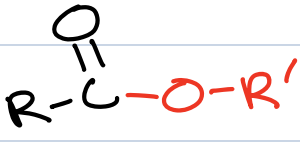
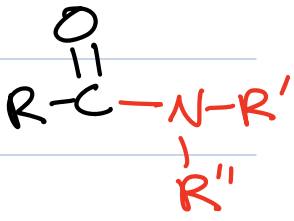
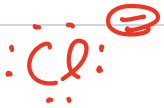
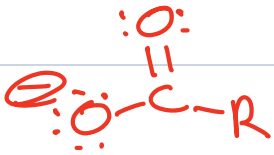
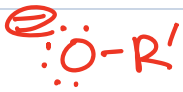
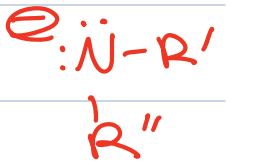
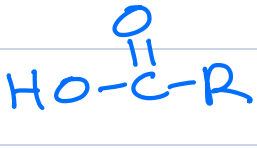
Step 2 Make a new bond between a nucleophile and electrophile

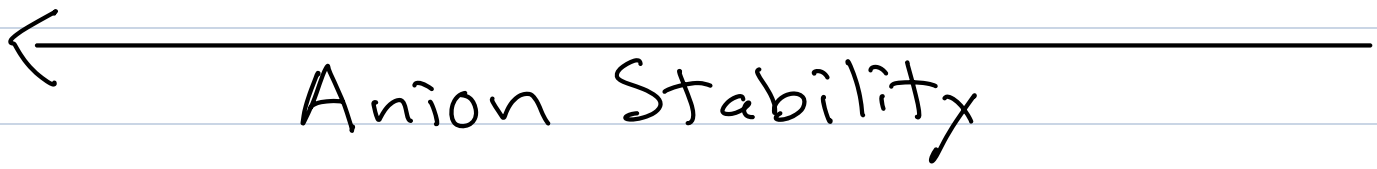


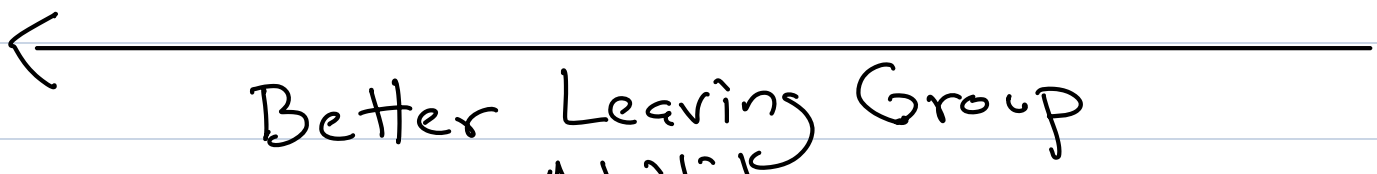
Step 3 Take a proton away

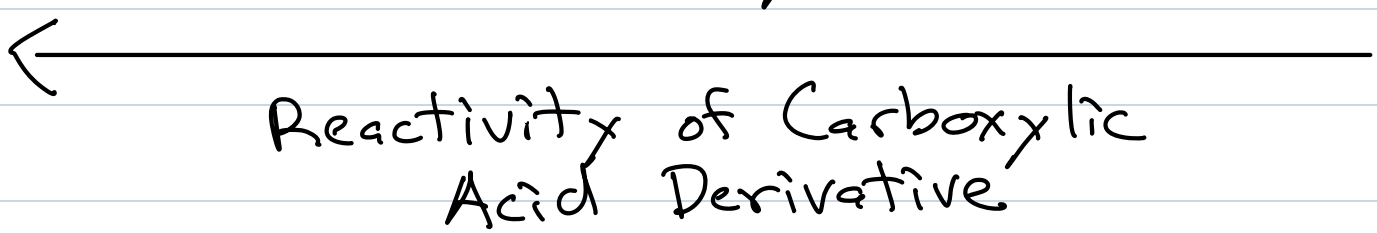


From Last Thursday's Lecture:

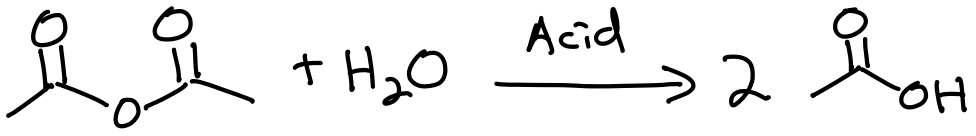
	Acid Chloride	Anhydride	Ester	Amide
				
Leaving Group				
Conjugate Acid				
pK_a	-7	3-5	16	38



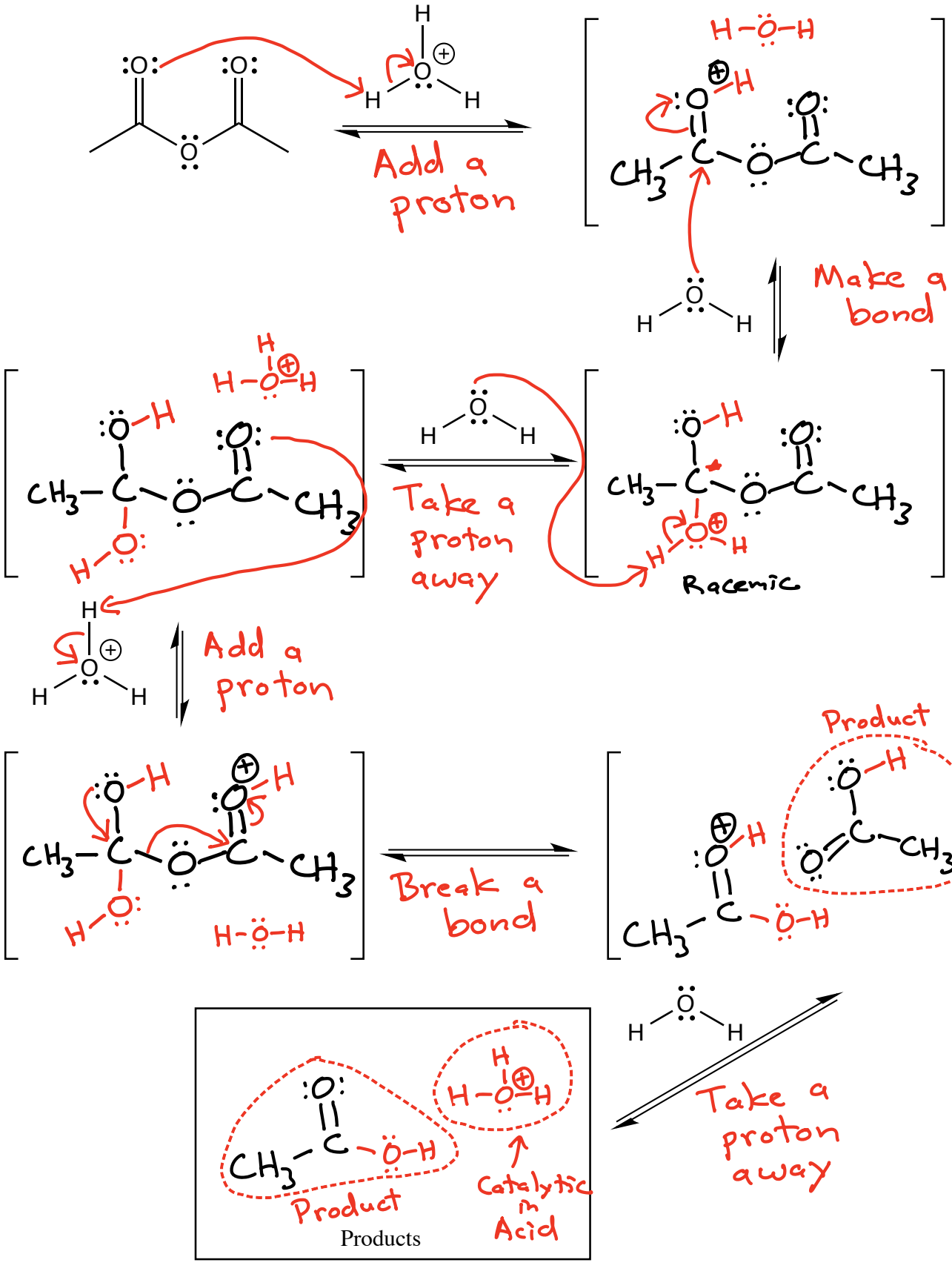


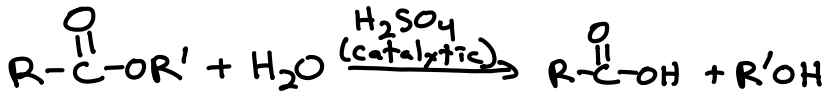


Think of carboxylic acid derivatives
$\Rightarrow$ C=O with a leaving group attached

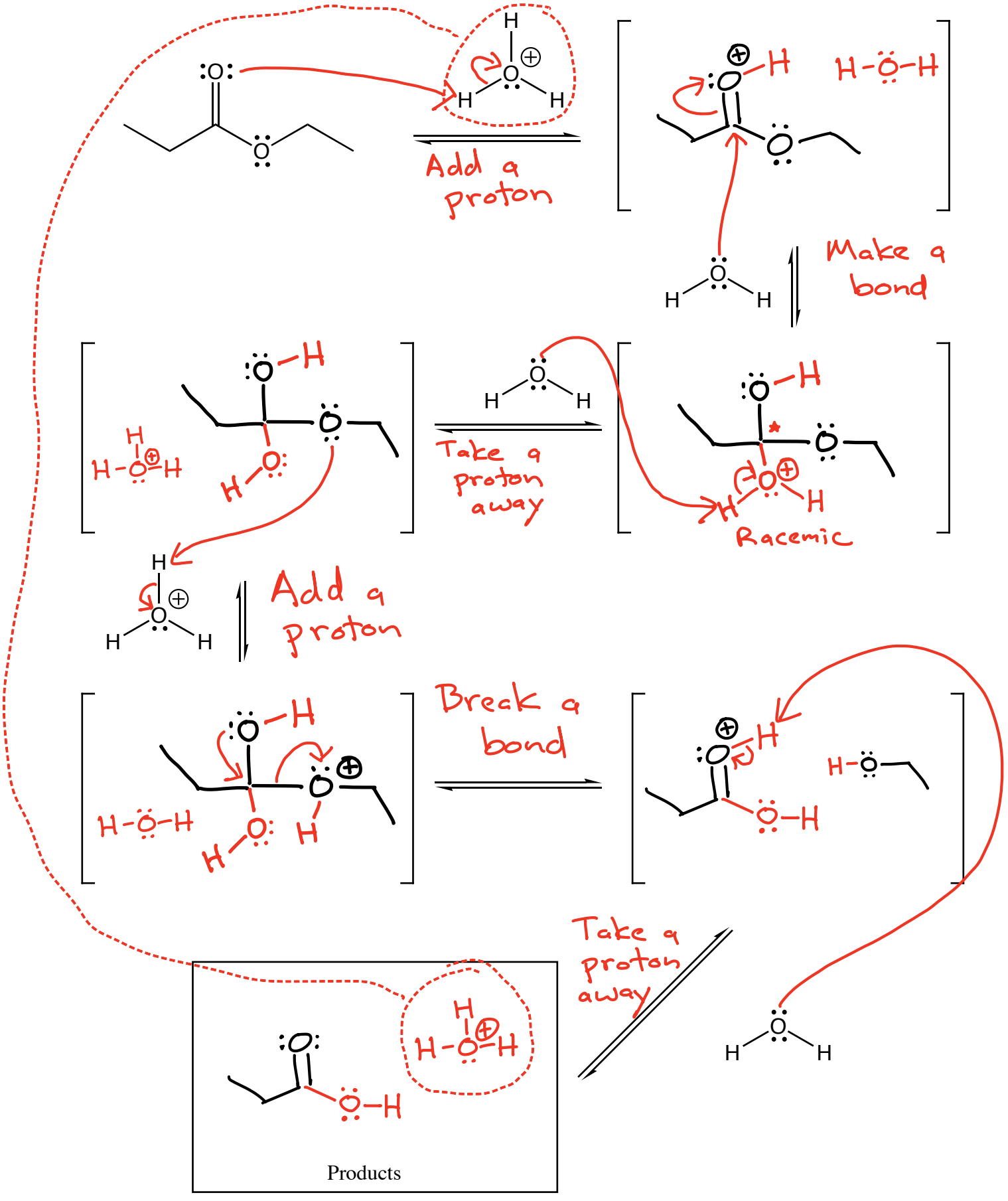


Acid Catalyzed Anhydride Hydrolysis

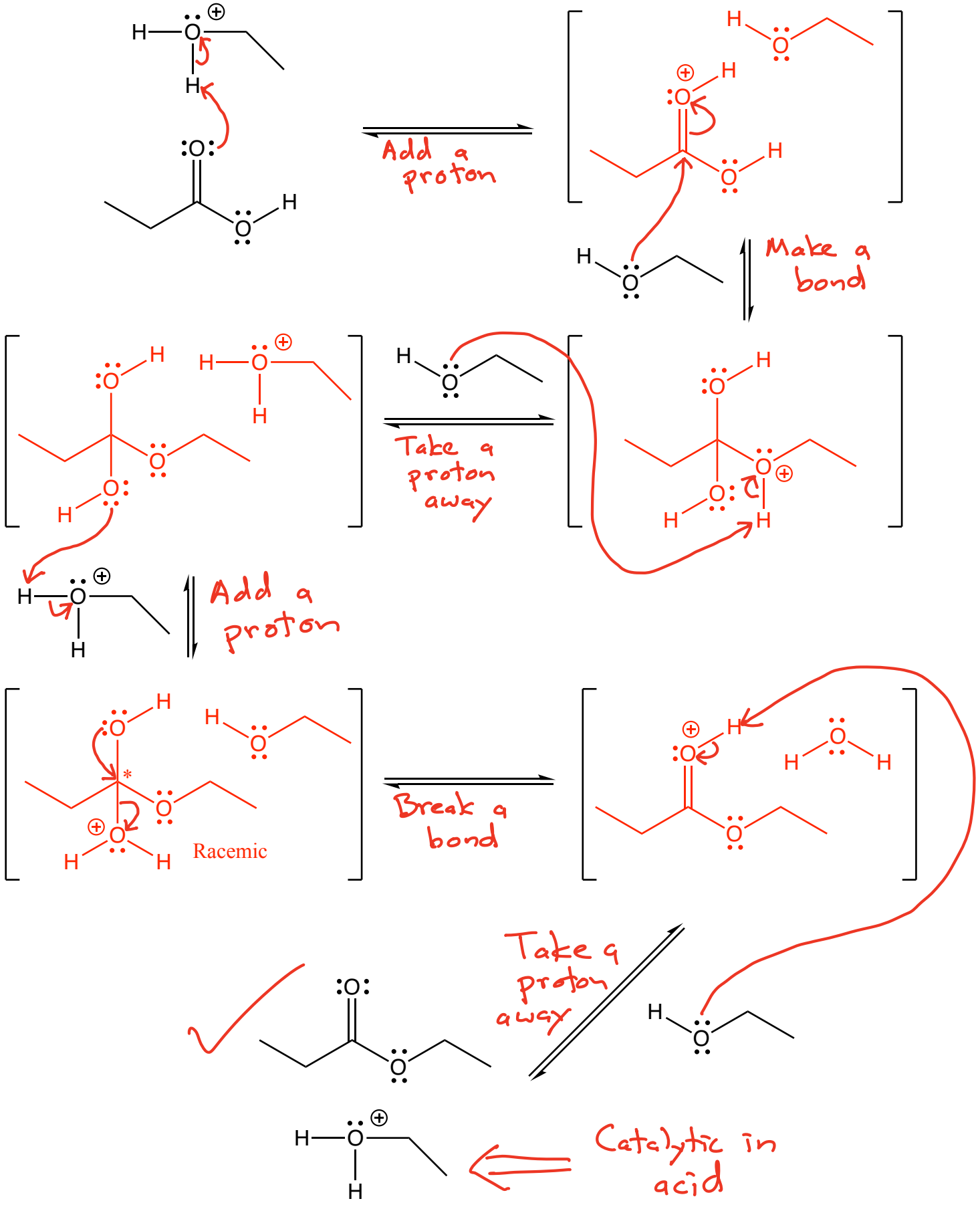




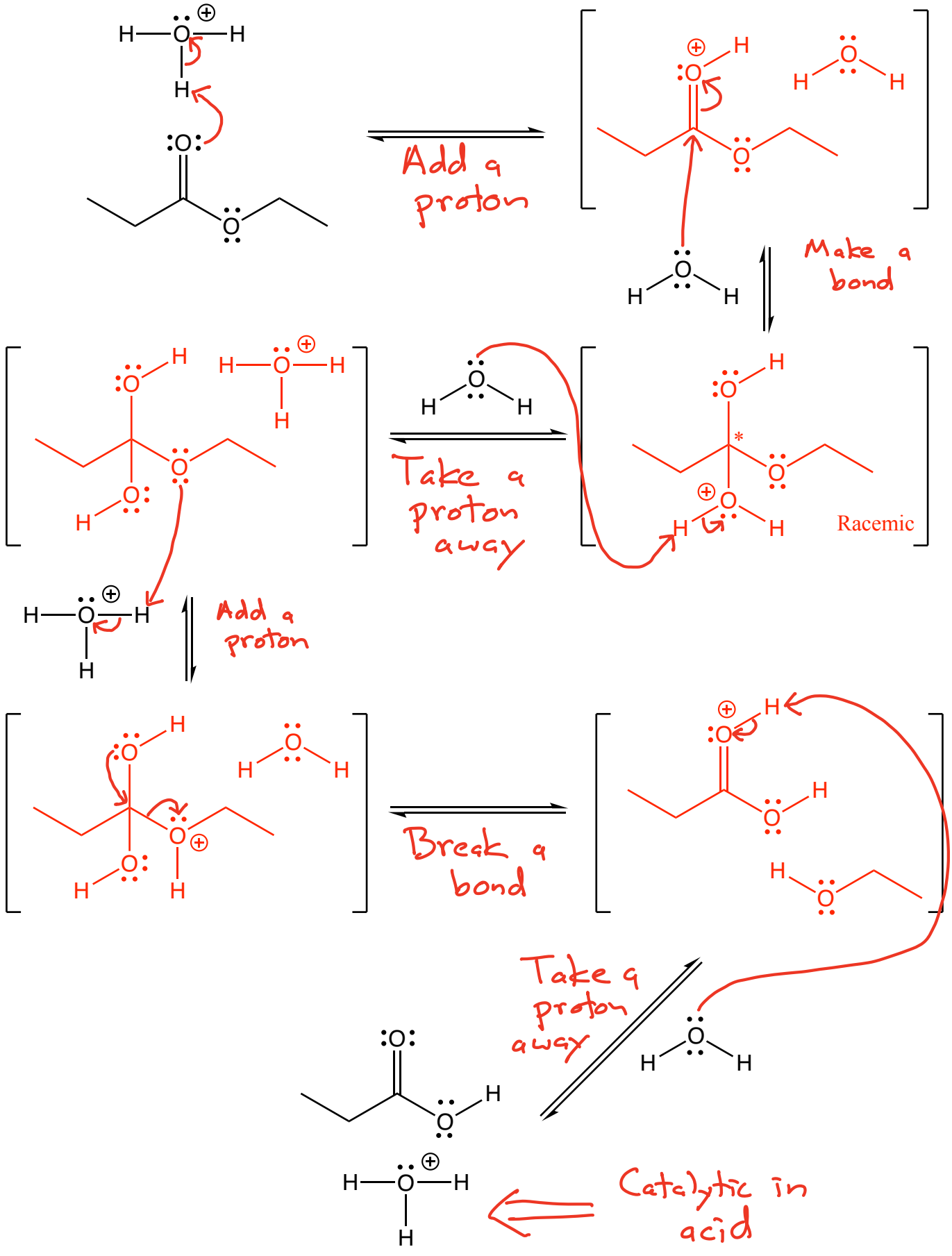
Acid Catalyzed Ester Hydrolysis



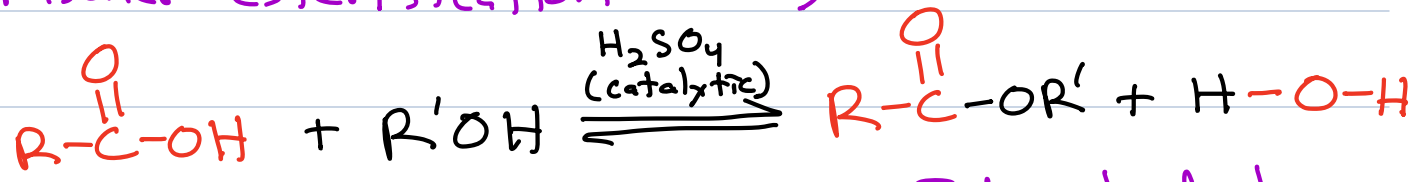
Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



Fischer esterification →



← Ester hydrolysis

This reaction is reversible

It has the same mechanism in both directions!

Important general rule

↓

Microscopic Reversibility → The mechanism of a reversible process is the same (same intermediates) in both directions!