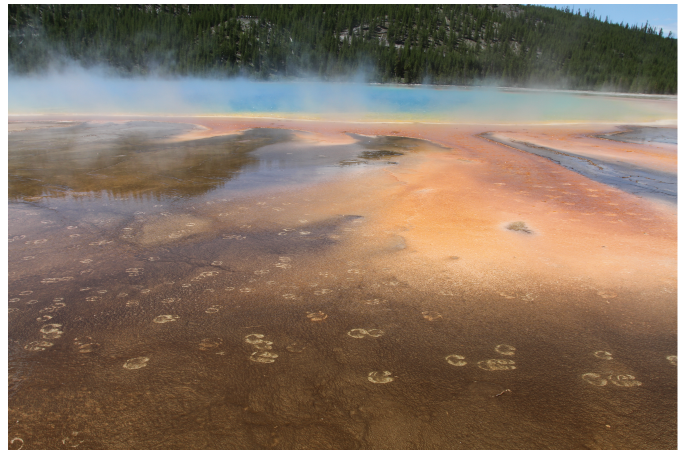
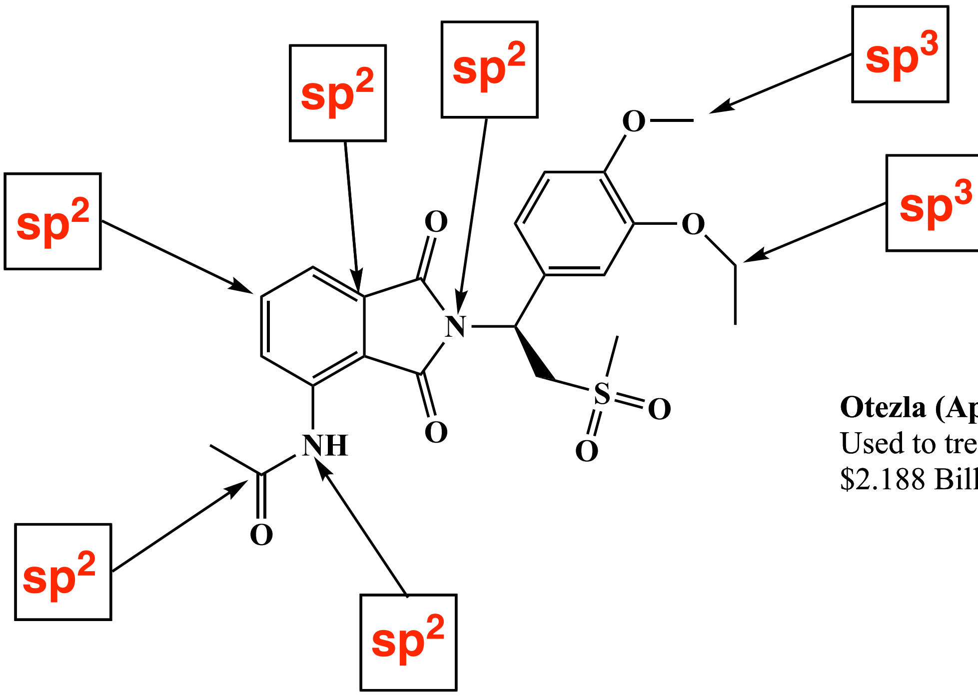
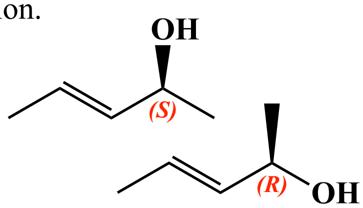


4. (1 pt each) In the boxes provided, write the hybridization state of the atoms indicated by the arrow.

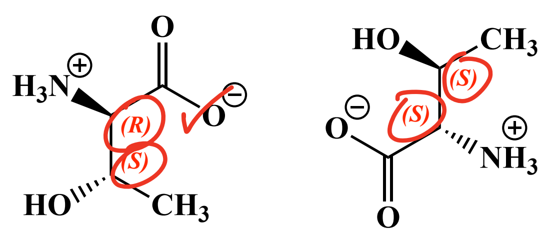


Otezla (Apremilast)
Used to treat plaque psoriasis
$2.188 Billion in sales 2023

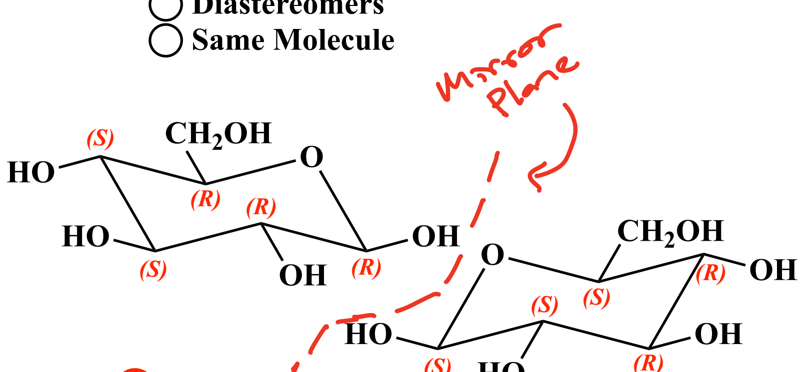
5. (3 pts each) Fill in the circle to identify the stereochemical relationship between each pair of molecules. Hint: You might want to determine *R* or *S* for each chiral center to help you answer the question.



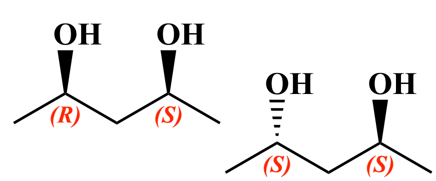
- ● Enantiomers
- ○ Diastereomers
- ○ Same Molecule



- ○ Enantiomers
- ● Diastereomers
- ○ Same Molecule

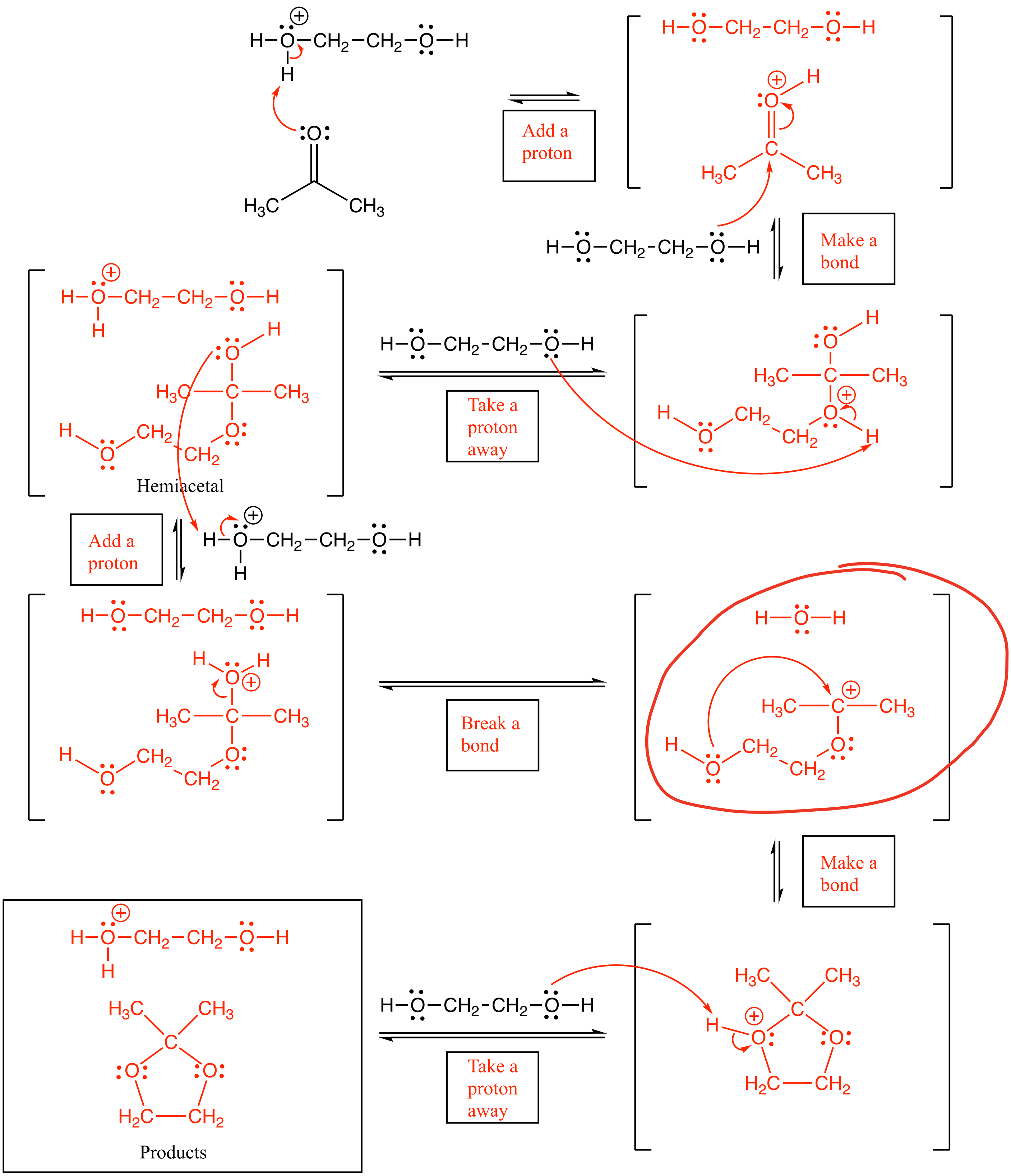


- ● Enantiomers
- ○ Diastereomers
- ○ Same Molecule



- ○ Enantiomers
- ● Diastereomers
- ○ Same Molecule

Signature______________________________ Pg 8 __________(45)



Signature__________________________ Pg 7 __________(-)

12. (45 pts) For the cyclic acetal reaction mechanism ON THE NEXT PAGE, use **arrows to indicate movement of all electrons, write all lone pairs, all formal charges, and all the products for each step.** Remember, I said all the products for each step. **IF A NEW CHIRAL CENTER IS CREATED IN AN INTERMEDIATE, MARK IT WITH AN ASTERISK AND LABEL THE MOLECULE AS "RACEMIC" IF APPROPRIATE. FOR ALL CHIRAL "PRODUCTS" YOU MUST DRAW ALL ENANTIOMERS WITH WEDGES AND DASHES AND WRITE "RACEMIC' IF APPROPRIATE. In the boxes provided by the arrows, write which of the 4 most common mechanistic elements describes each step (make a bond, break a bond, etc.).**

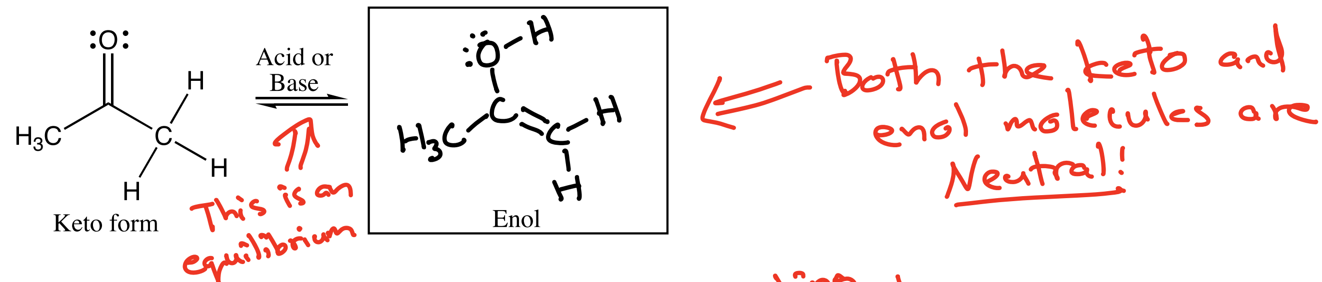
The mechanism did not fit on the same page as the directions, so use the directions on this page to fill in the mechanism on the next page!

Note: For intermediates that I drew as two contributing structures in class, you only need to draw one contributing structure. Either one will be correct. Just make sure your arrows are accurate for the contributing structure you draw.

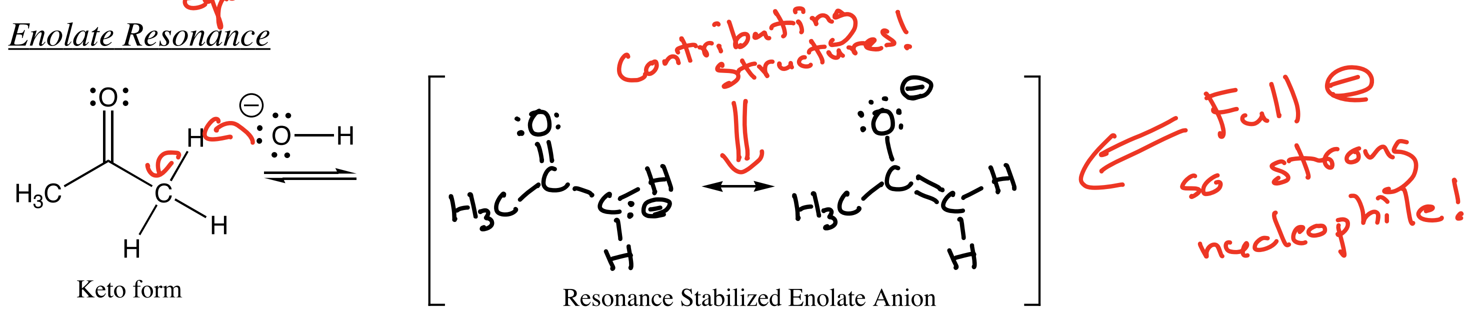
Enol has an "N" like Nucleophile
Keto keeps its electrons!

Keto-Enol Tautomerization vs. Enolate Resonance

Keto-Enol Tautomerization



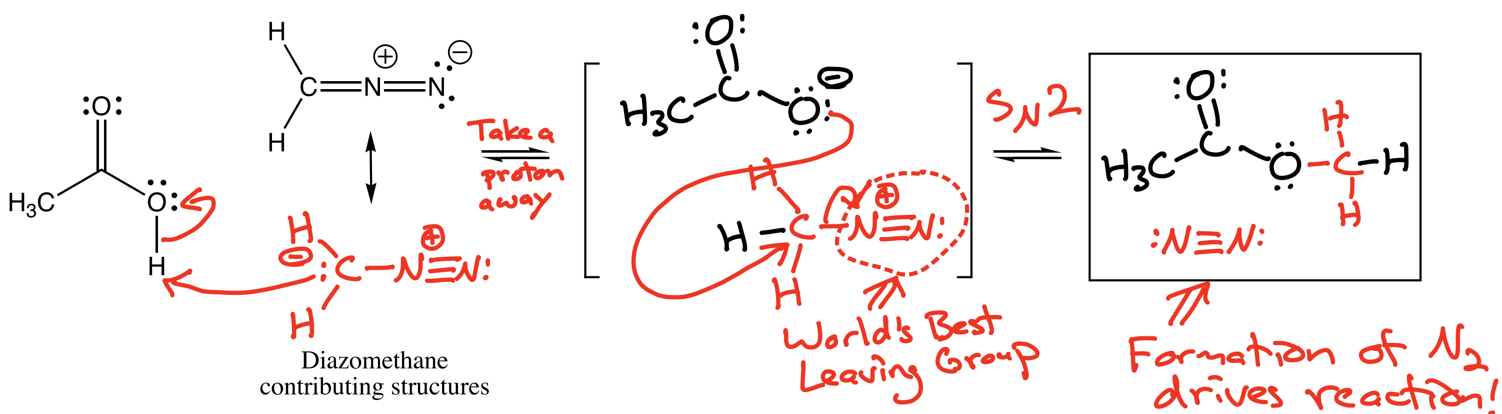
Enolate Resonance



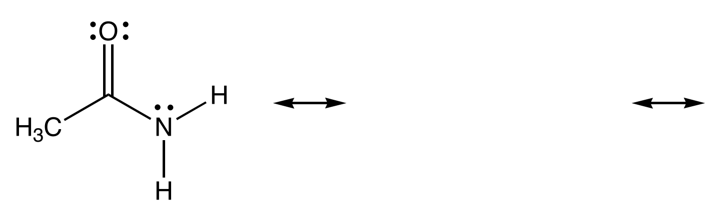
α-hydrogen pK_a = 18-20

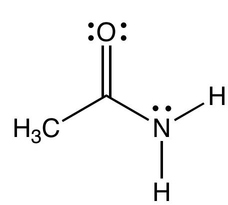
In an enolate something "ate" the H atom!

Diazomethane reaction

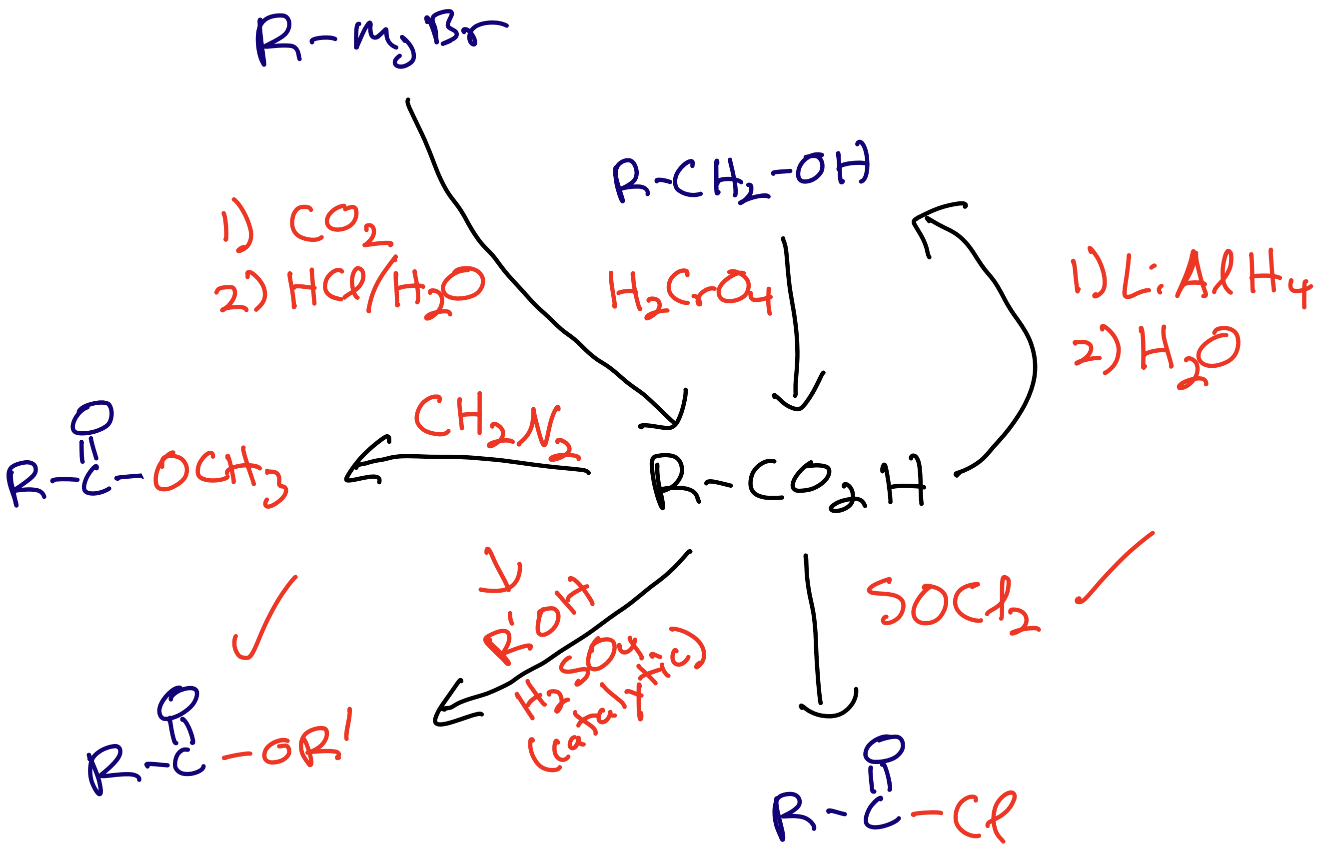


Amide Resonance VERY IMPORTANT!!!!!!



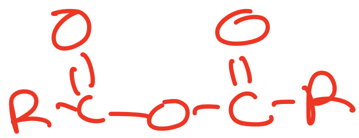


Summary of Carboxylic Acid Reactions →

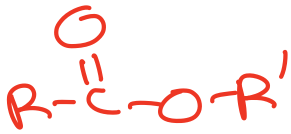


Carboxylic Acid Derivatives

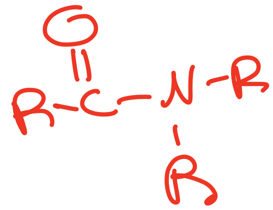
Acid Chloride



Anhydride

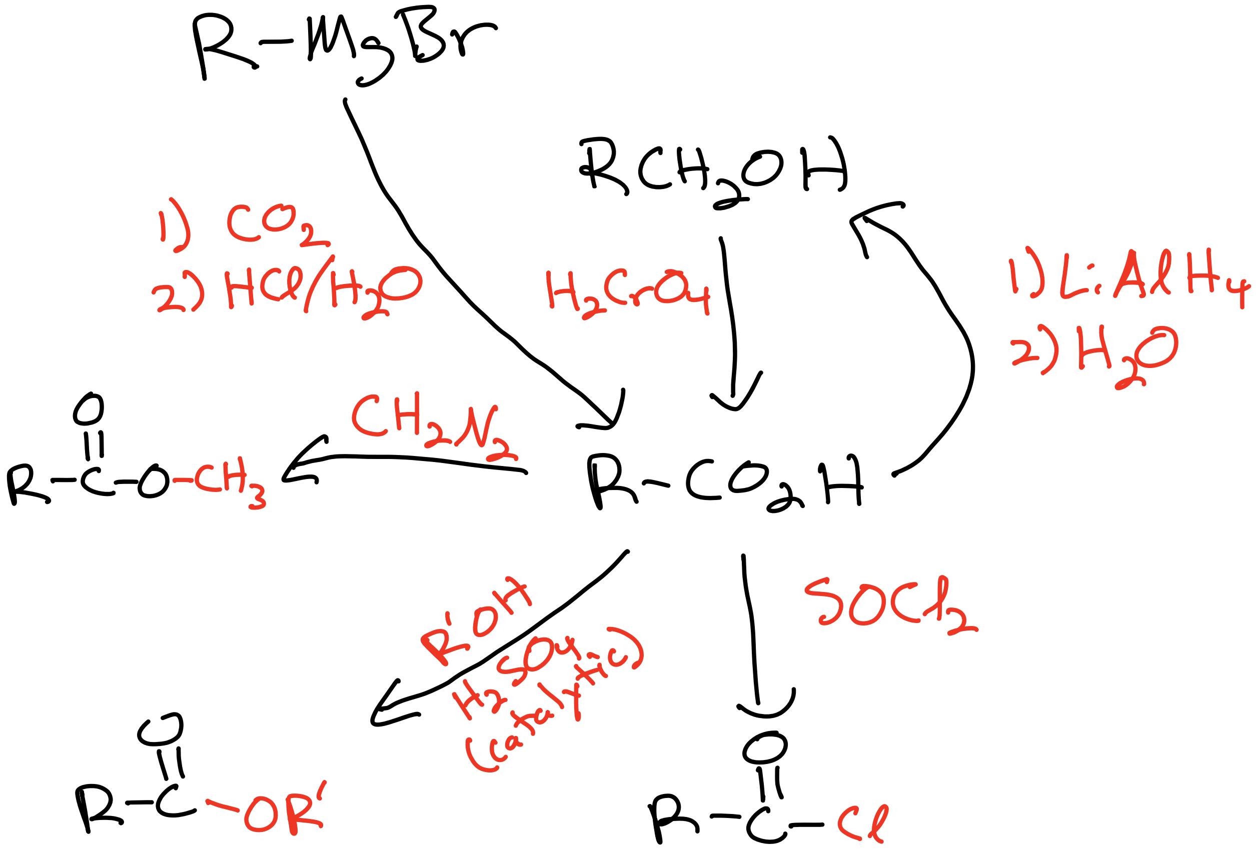


Ester

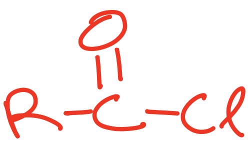


Amide

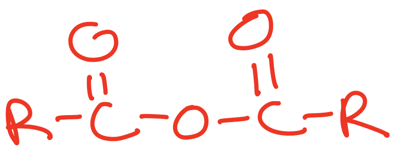
Summary of Carboxylic Acid Reactions → So Far...



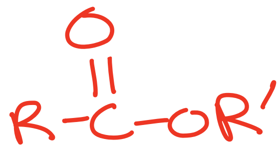
Carboxylic Acid Derivatives



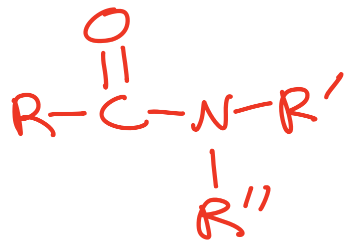
Acid Chloride



Anhydride

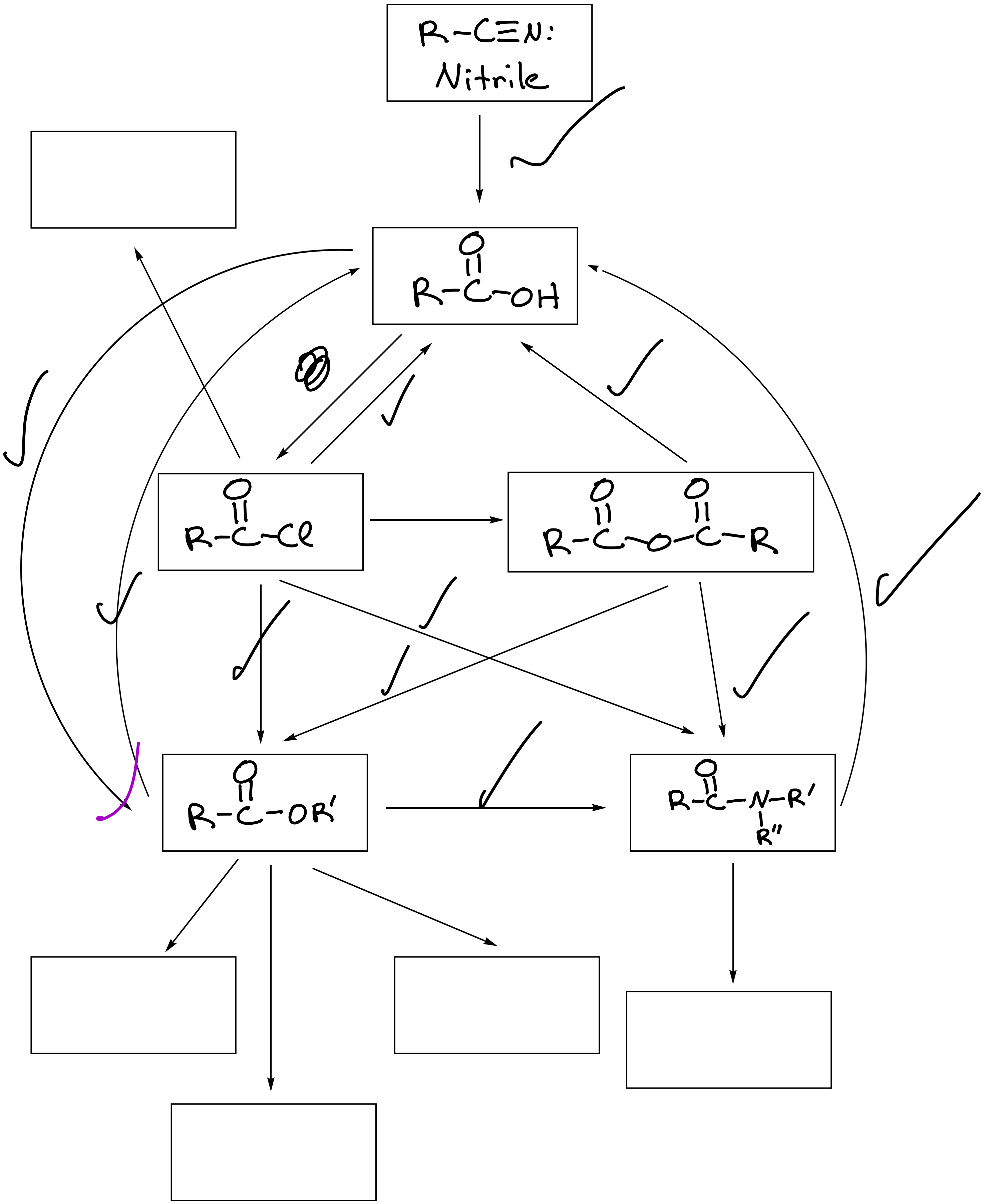


Ester



Amide

Interconversion of Carboxylic Acid Derivatives



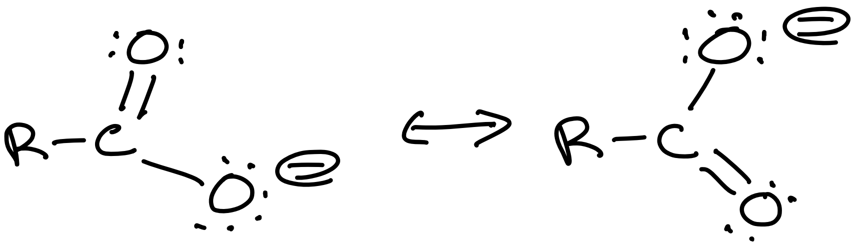
Key idea → A lone pair on an atom adjacent to a carbonyl is delocalized into the π bond of the C=O

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

VERY stabilizing

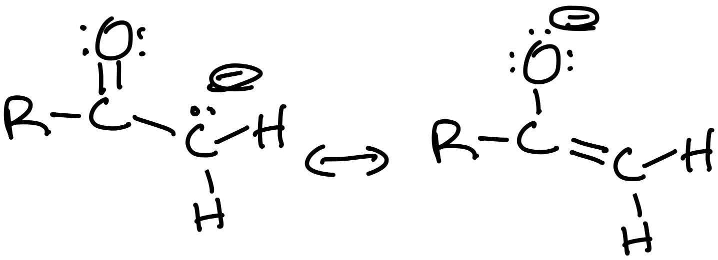
(Golden Rule of Chemistry)

Resonance contributing structures you have seen before:



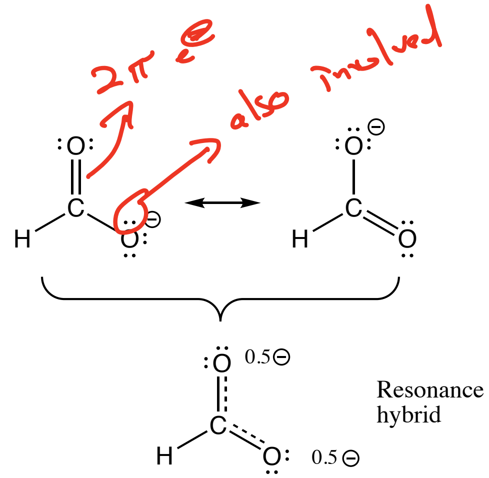
This also has a 3 atom π-way on the O–C–O atoms!!

We just never told you!



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

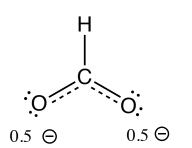
We just never told you!



Carboxylate anion

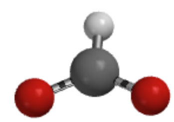
A common situation, and the one many resonance contributing structures describe, occurs when three 2p orbitals combine on adjacent atoms. A good example is the carboxylate anion. When three adjacent 2p orbitals interact (we add the three 2p orbital wave functions $\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$), 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.

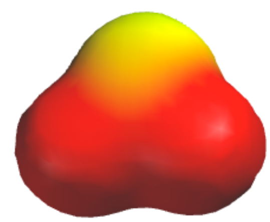
$$\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$$

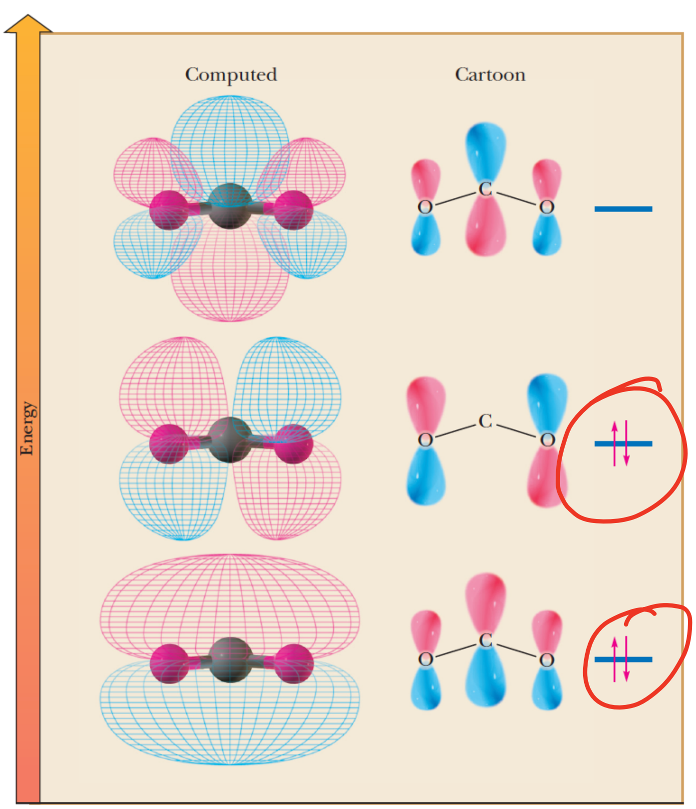


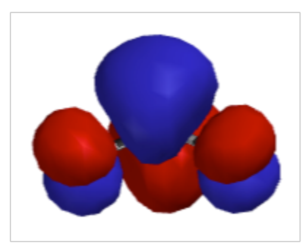
Carboxylate anion

Resonance hybrid

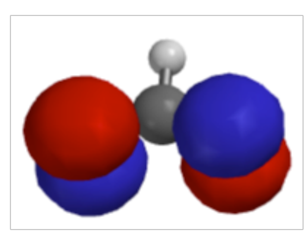




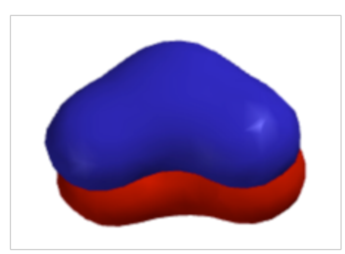




Antibonding orbital



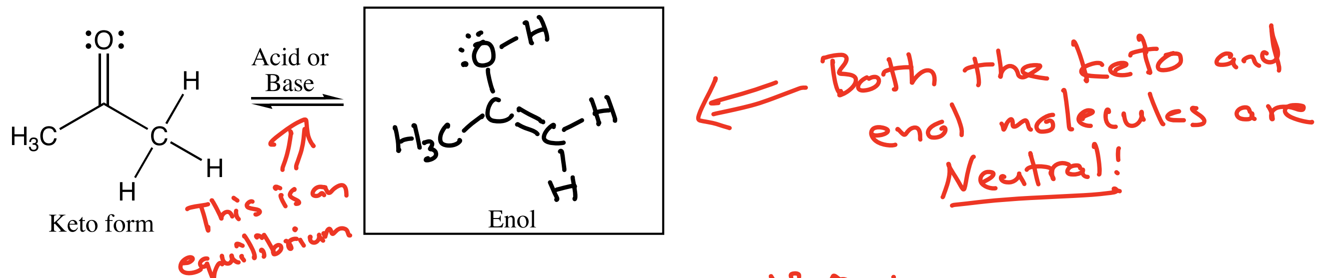
Non-bonding orbital



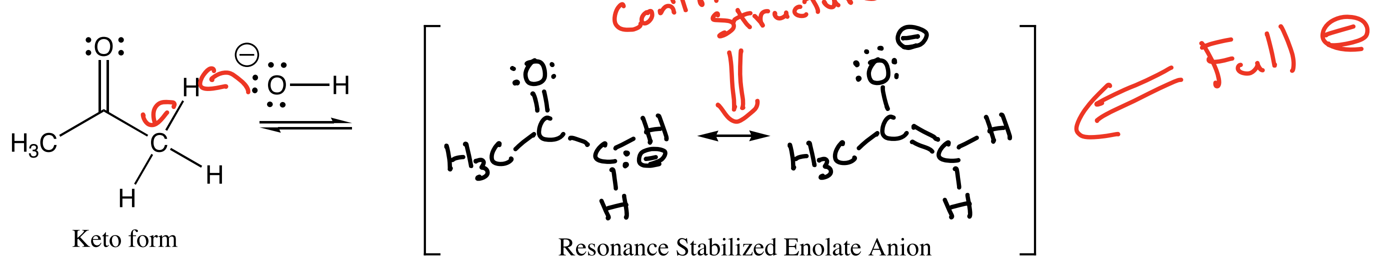
"π-way" orbital

Keto-Enol Tautomerization vs. Enolate Resonance

Keto-Enol Tautomerization

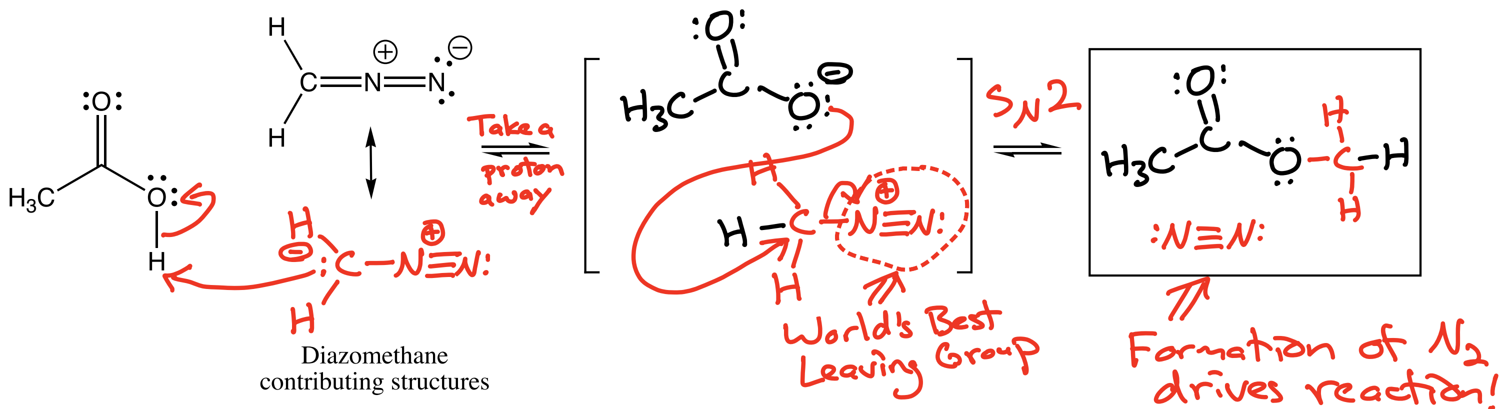


Enolate Resonance

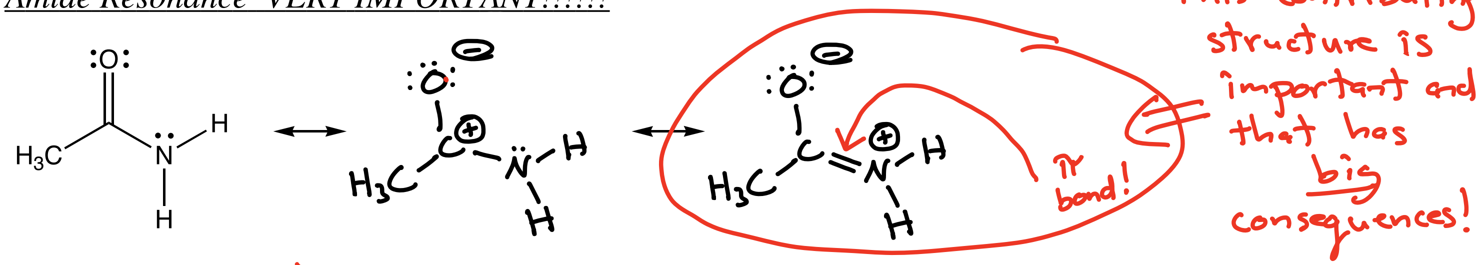


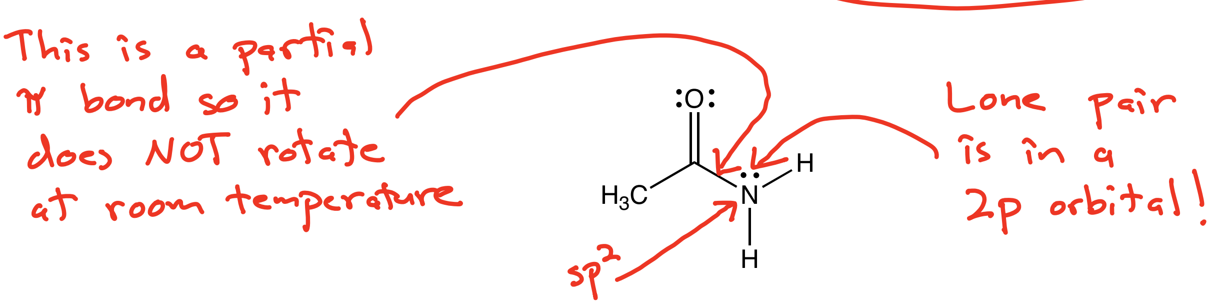
α-hydrogen pK_a = 18-20

Diazomethane reaction



Amide Resonance VERY IMPORTANT!!!!!!





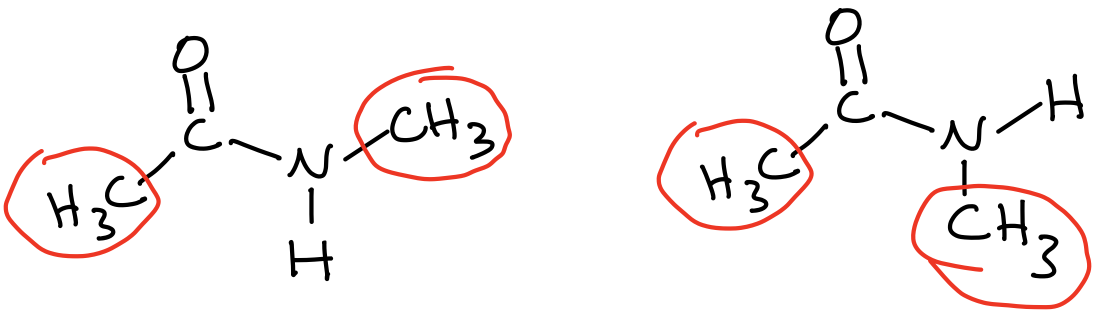
(Golden Rule of Chemistry)

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
<u>Favored</u>

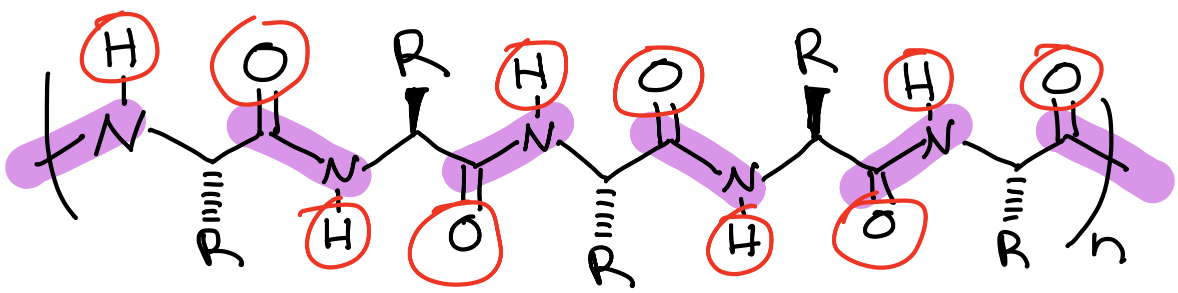
cis

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!

This interaction is still relevant but less important for esters → no real consequences so we can ignore it.

<u>Organic Chemistry</u> is the study of carbon-containing molecules. This class has two points.

The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing molecules on the planet!!

You will learn how MRI scans work. 1/14/26

You will learn the basic principles of pharmaceutical science and how many drugs work. 1/21/26

You will learn about the special bond that holds carbohydrates such as glucose in six-membered rings, connects carbohydrate monomers together to make complex carbohydrate structures and is critical to DNA and RNA structure. 2/2/26

You will learn how soap is made from animal fat and how it works to keep us clean.

You will learn the important structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 2/16/26

You will learn how important antibiotics like penicillins work, including ones that make stable covalent bonds as part of their mode of action.

You will learn why carrots are orange and tomatoes are red.

You will learn the very cool reason that the DNA and RNA bases are entirely flat so they can stack in the double helix structure.

You will learn how energy drinks work.

You will learn even more about why fentanyl is such a devastating part of the opioid problem and how Naloxone is an antidote for a fentanyl overdose.

You will learn even more details about why Magic Johnson is still alive, decades after contracting HIV, and how the same strategy is being used to fight COVID.

You will learn about the surprising chemical reason the Pfizer and Moderna mRNA vaccines elicit strong immune responses.

The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds, especially carbon-carbon bonds.

You will learn how carbon-metal bonds lead to new carbon-carbon bonds. 1/21/26

You will learn how most reactions of carbonyl compounds involve only the four common mechanistic elements operating in only a few common patterns. 1/21/26

You will learn how, by simply adding a catalytic amount of base like HO^- to aldehydes or ketones, you can make new carbon-carbon bonds, giving complicated and useful products.

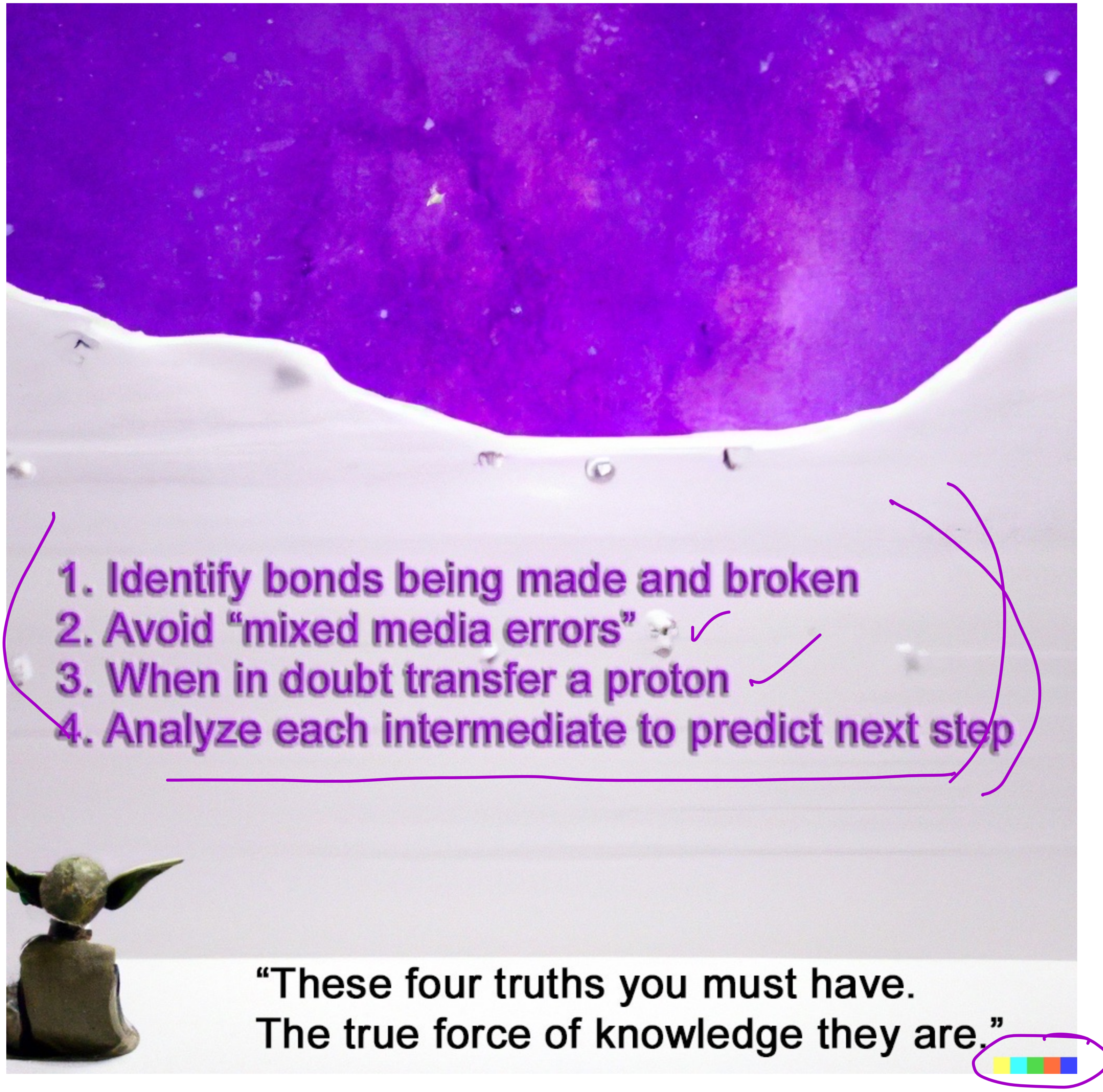
You will learn a reaction that can convert vinegar and vodka into a common solvent.

You will learn why molecules with six-membered rings and alternating double bonds are stable.

You will learn a reaction that can turn model airplane glue into a powerful explosive.

Most important, you will develop powerful critical thinking skills:

1. You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.
2. You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.


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, <u>all</u> the intermediates are positively-charged or neutral

   b) In base, <u>all</u> 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!!

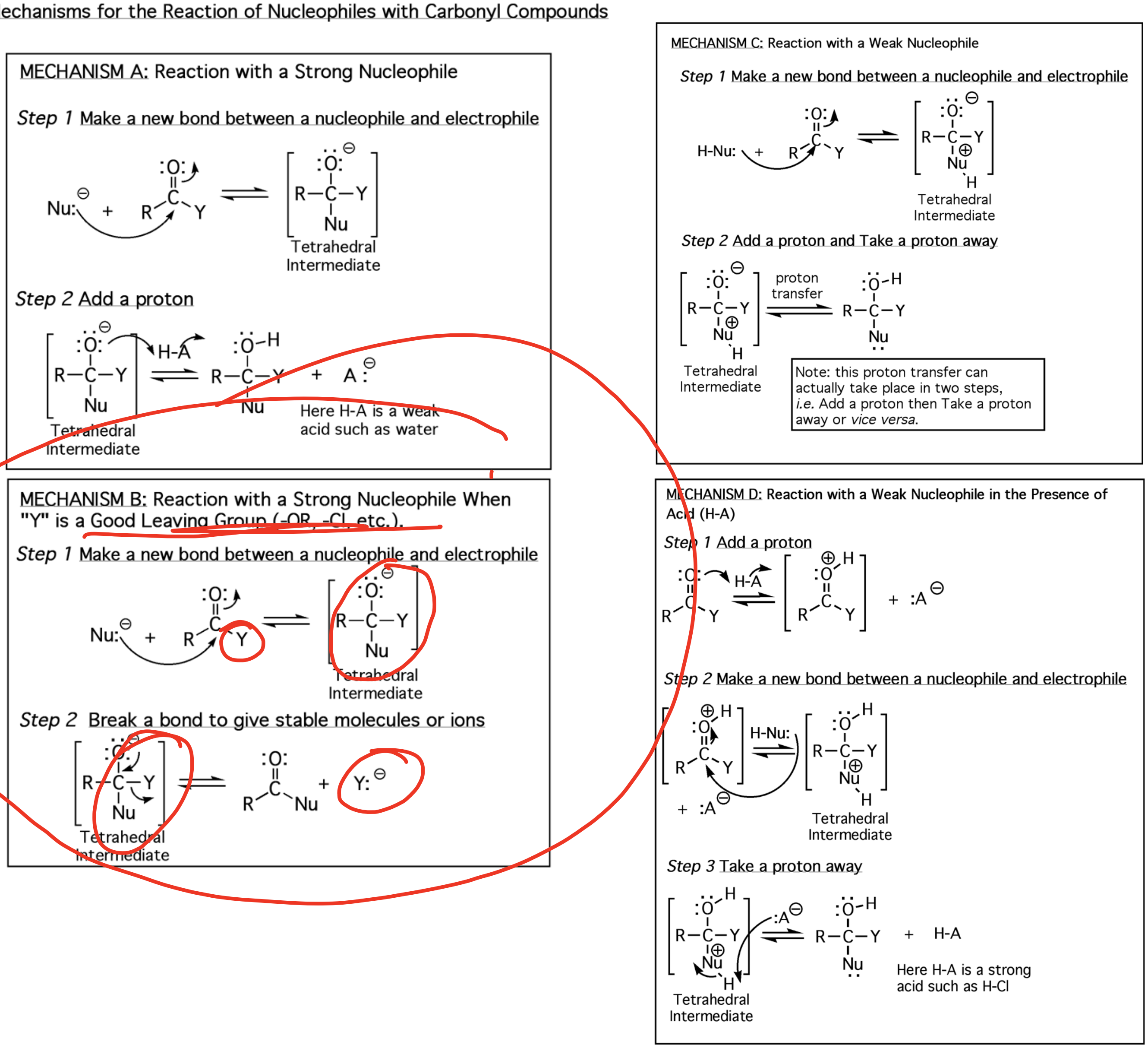
1) There are basically four different mechanisms elements that make up the steps of carbonyl reactions.

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

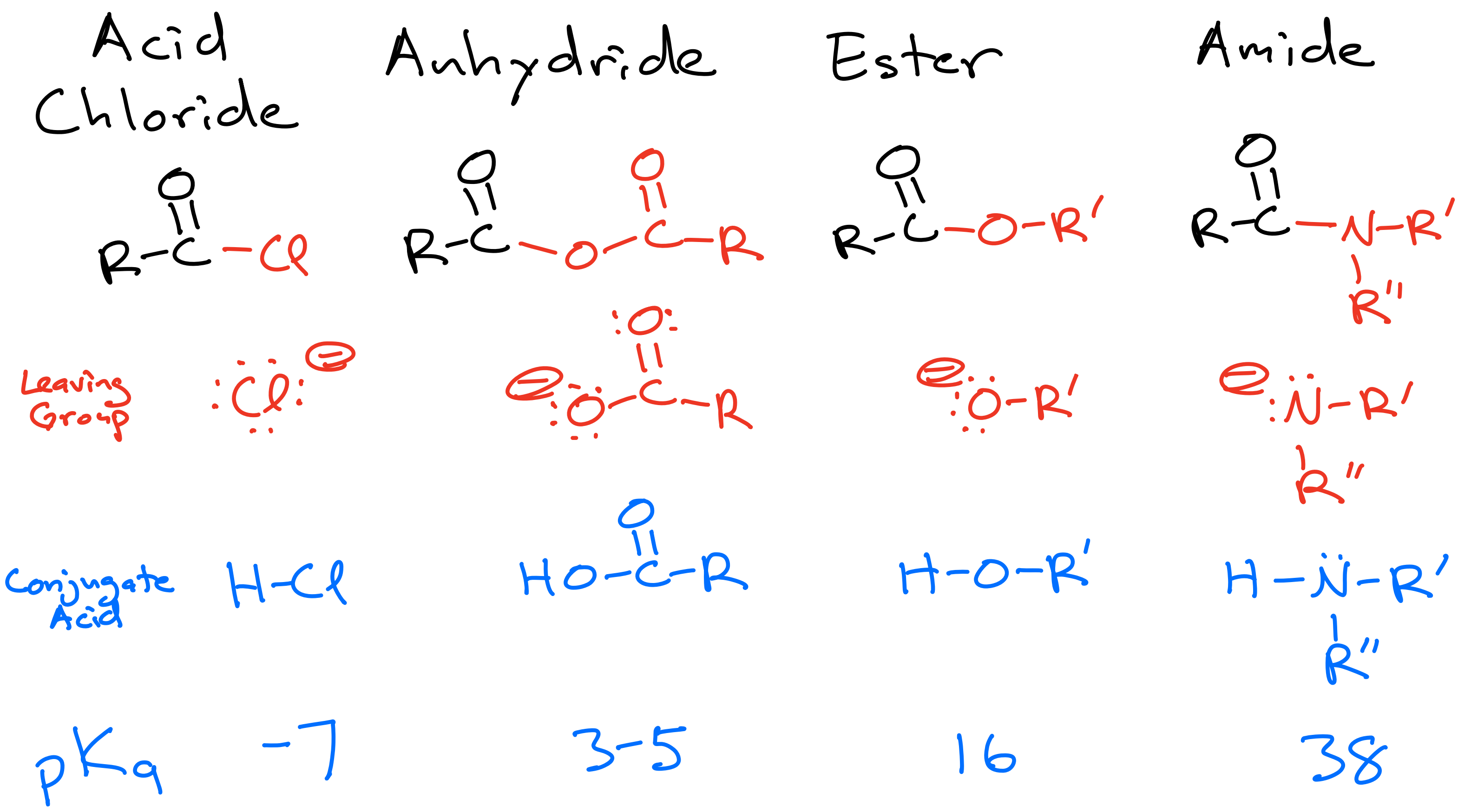
2) These same four mechanism elements describe most of the other mechanisms you have/will learn!!! (Yes, organic chemistry really is this simple if you look at it this way!!)

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



From Last Thursday's Lecture:



Anion Stability

Better Leaving Group Ability

Reactivity of Carboxylic Acid Derivative

Think of carboxylic acid derivatives
⟹ C=O with a leaving group attached