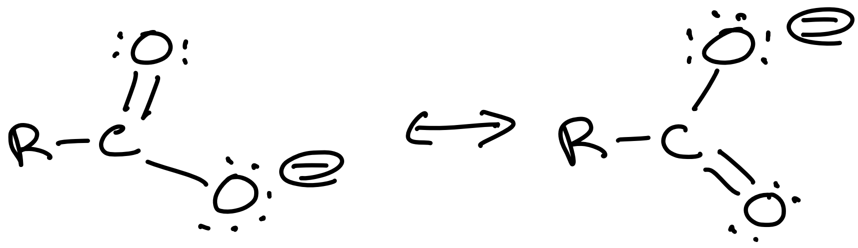
Key idea → A lone pair on an atom adjacent to a carbonyl is delocalized into the π bond of the $C=O$

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

VERY stabilizing
(Golden Rule of Chemistry)

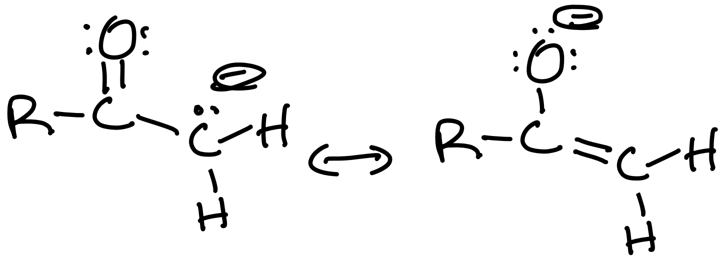

WAYNE'S WORLD

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!



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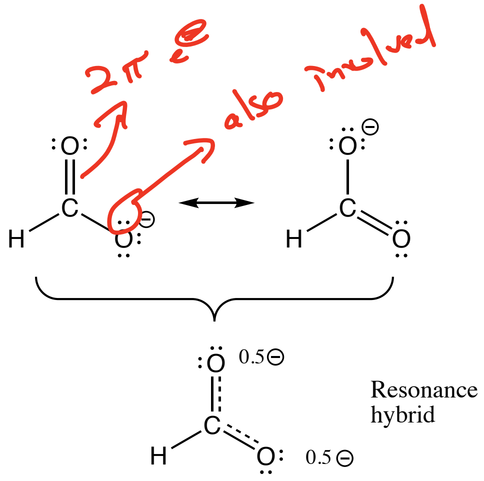
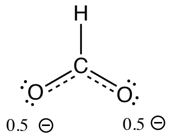


Carboxylate anion

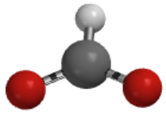
A common situation, and the one many resonance contributing structures describe, occurs when three 2p orbitals combine on adjacent atoms. A good example is the carboxylate anion. When three adjacent 2p orbitals interact (we add the three 2p orbital wave functions $\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$),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

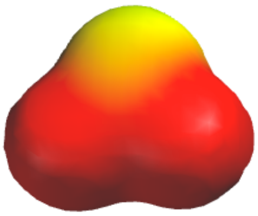
$$\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$$

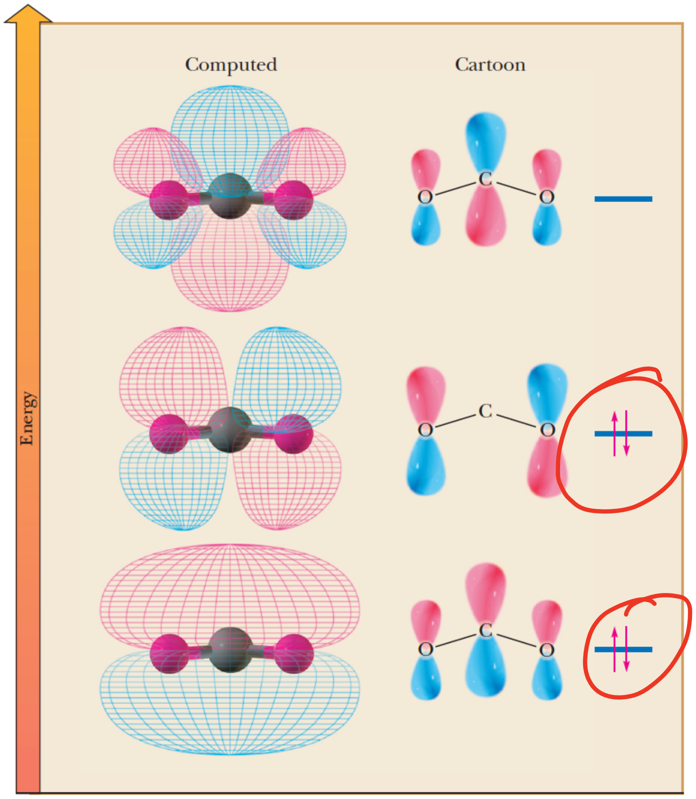


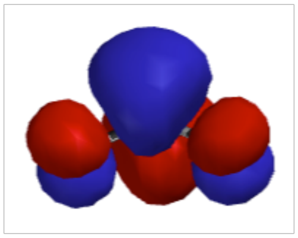
Carboxylate anion

Resonance hybrid

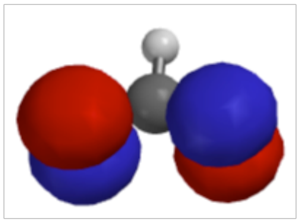




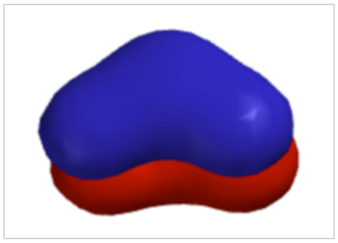




Antibonding orbital



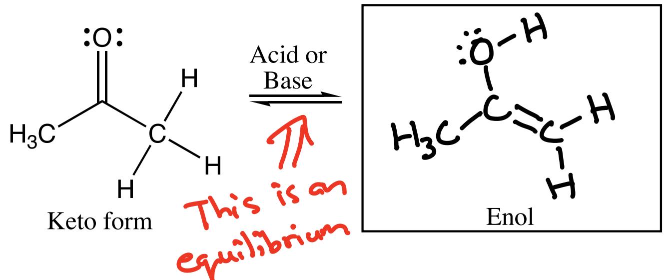
Non-bonding orbital



"π-way" orbital

Keto-Enol Tautomerization vs. Enolate Resonance

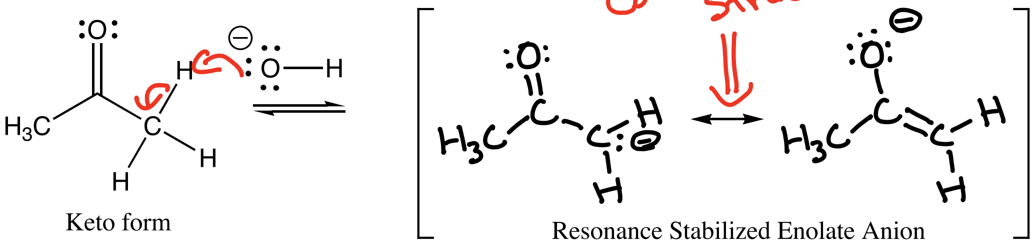
Keto-Enol Tautomerization



This is an equilibrium

Both the keto and enol molecules are Neutral!

Enolate Resonance



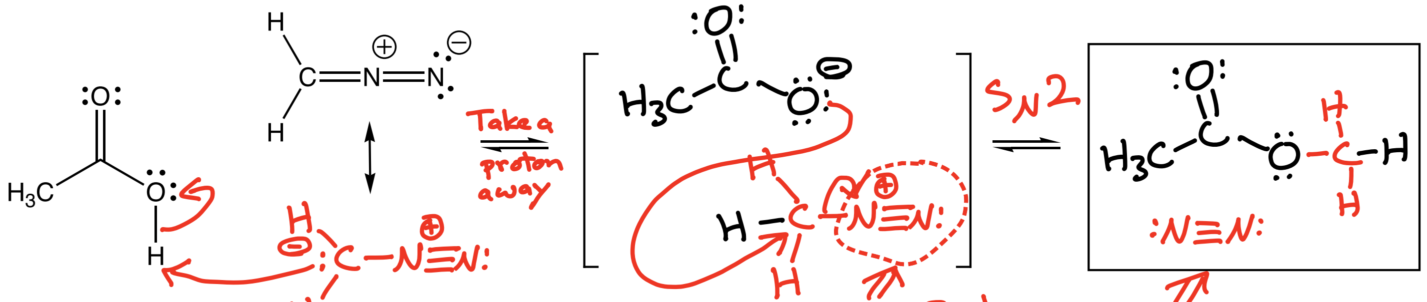
Resonance Stabilized Enolate Anion

Contributing structures!

Full ⊖

α-hydrogen pK_a = 18-20

Diazomethane reaction

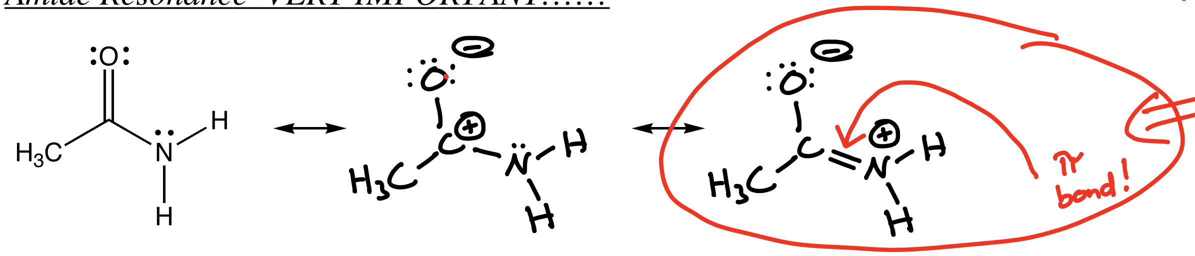


Diazomethane contributing structures

World's Best Leaving Group

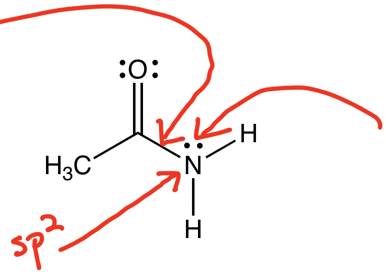
Formation of N_2 drives reaction!

Amide Resonance VERY IMPORTANT!!!!!!



This contributing structure is important and that has big consequences!

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



Lone pair is in a 2p orbital!

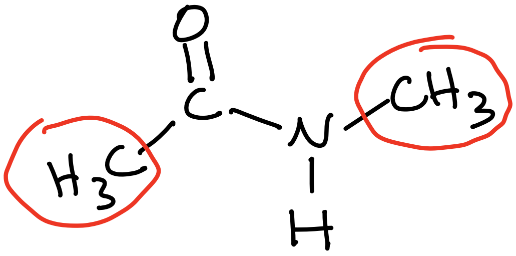
(Golden Rule of Chemistry)

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?

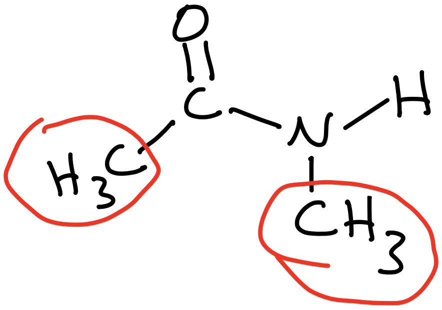
1) The C–N bond of amides acts like a C=C bond so there can be cis and trans isomers!

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



trans

<u>Favored</u>



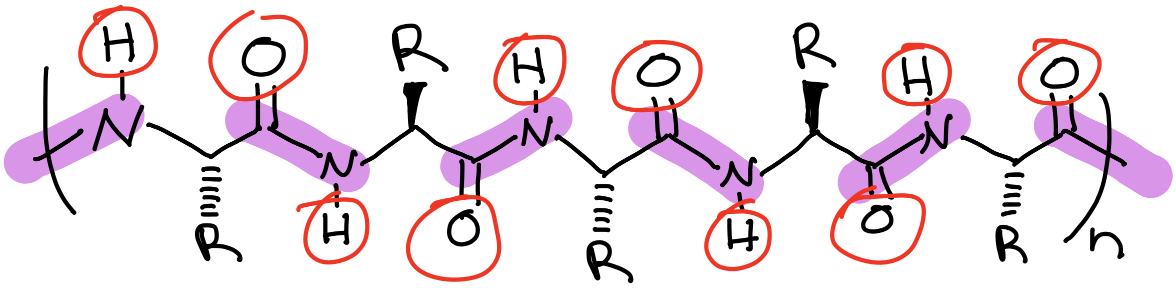
cis

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

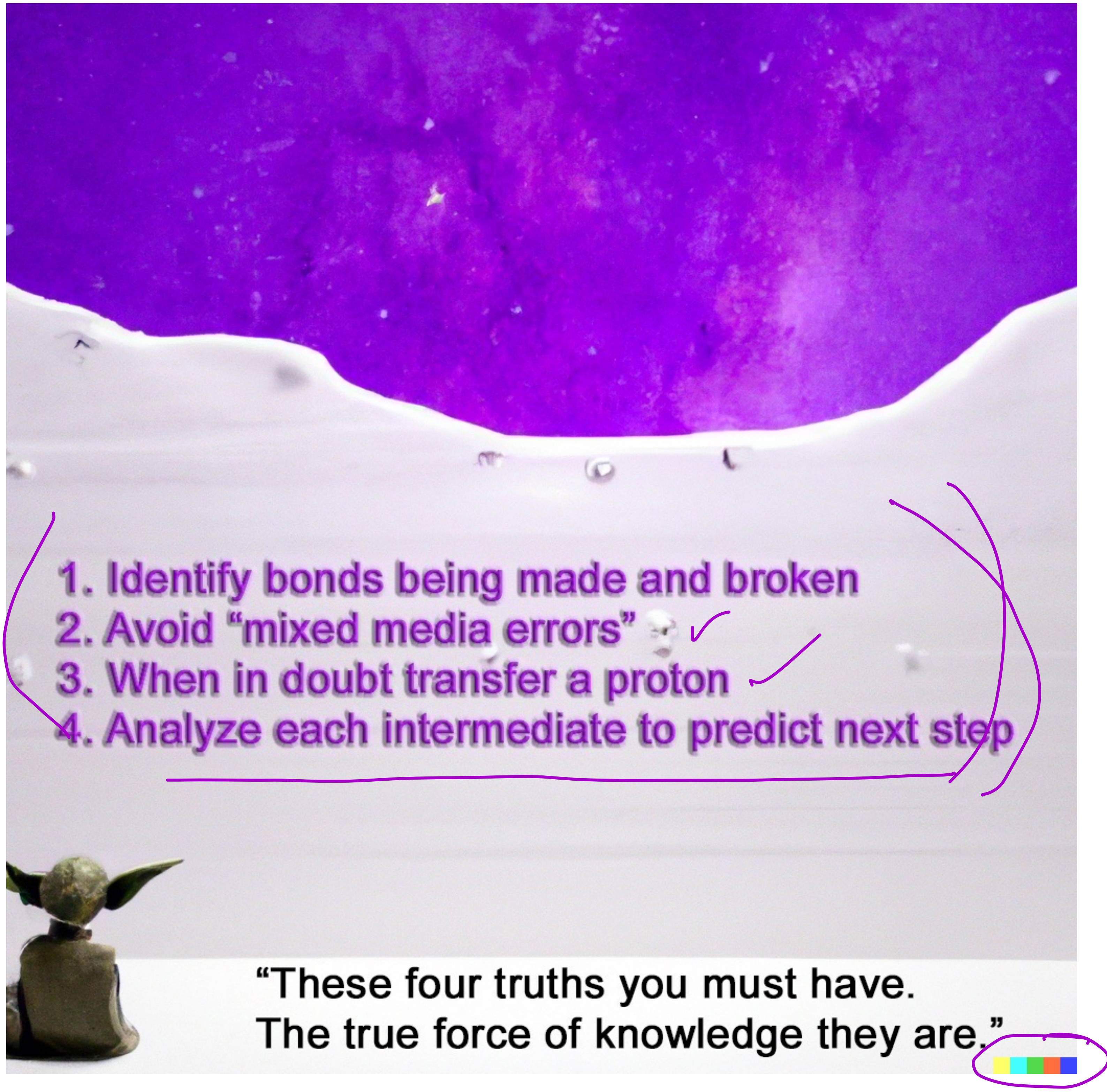
We inherit DNA sequences from our parents → code for one-dimensional chains of amino acids (called proteins) that fold into three-dimensional objects!

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.



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!!

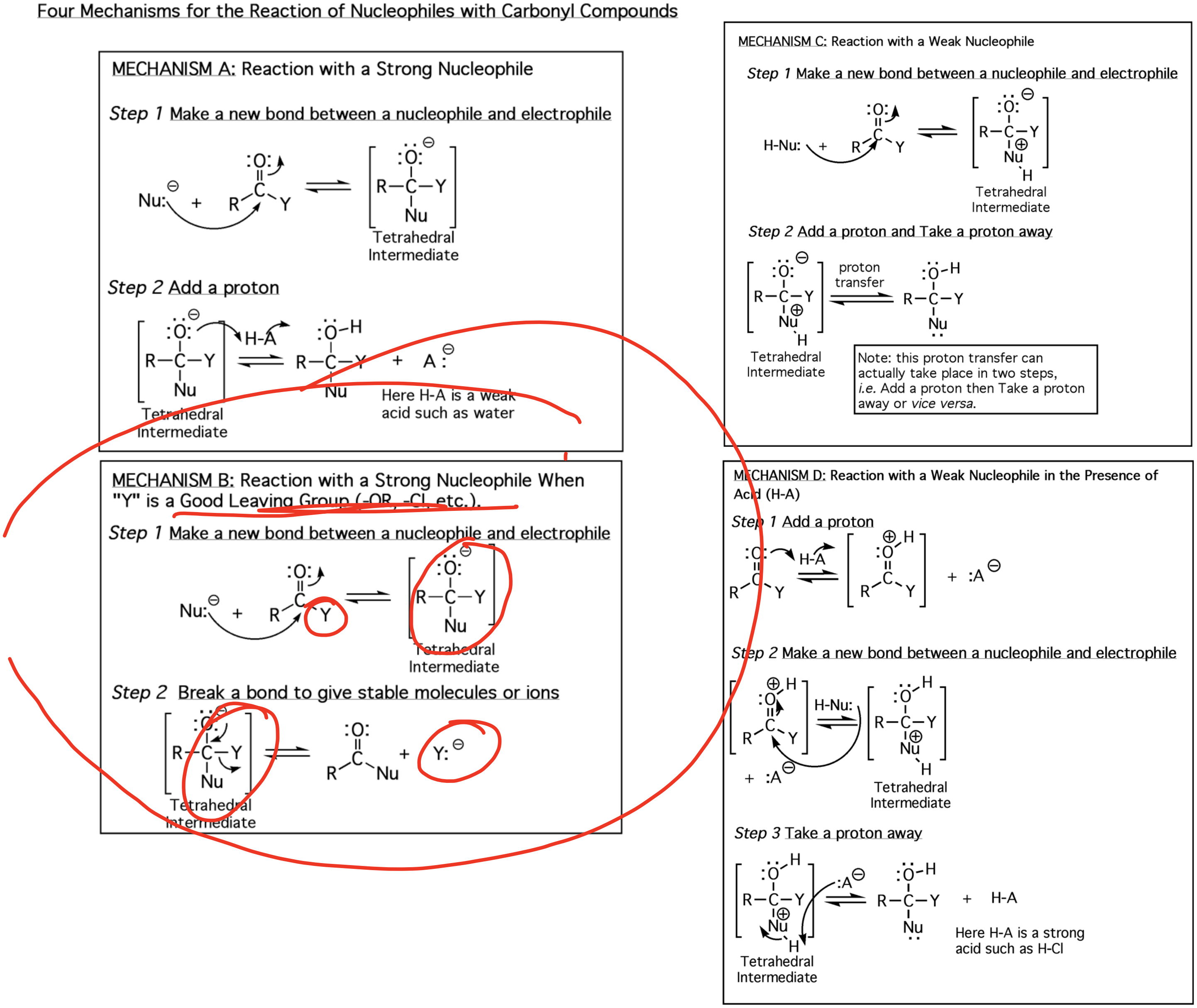
1) There are basically four different mechanisms elements that make up the steps of carbonyl reactions.

- **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



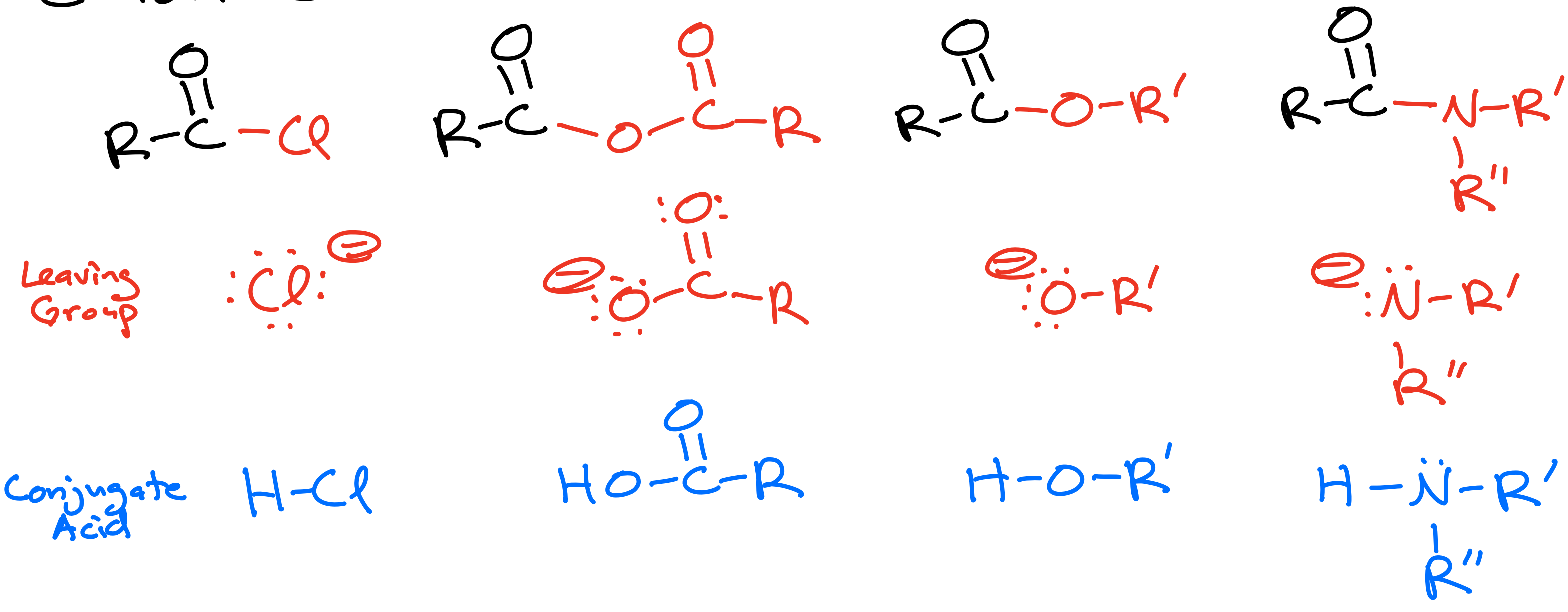
Here H-A is a weak acid such as water

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

Here H-A is a strong acid such as H-Cl

From Last Thursday's Lecture:

	Acid Chloride	Anhydride	Ester	Amide



pKa	-7	3-5	16	38

← Anion Stability

← Better Leaving Group Ability

← Reactivity of Carboxylic Acid Derivative

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

Characteristic Reactions of Carboxylic Acid Derivatives

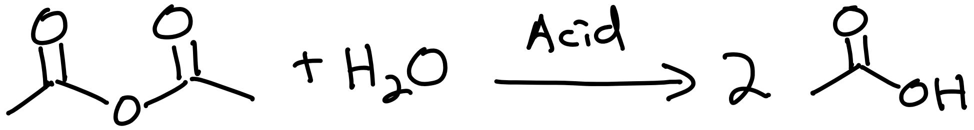
Mechanism B

The key issue is leaving group ability

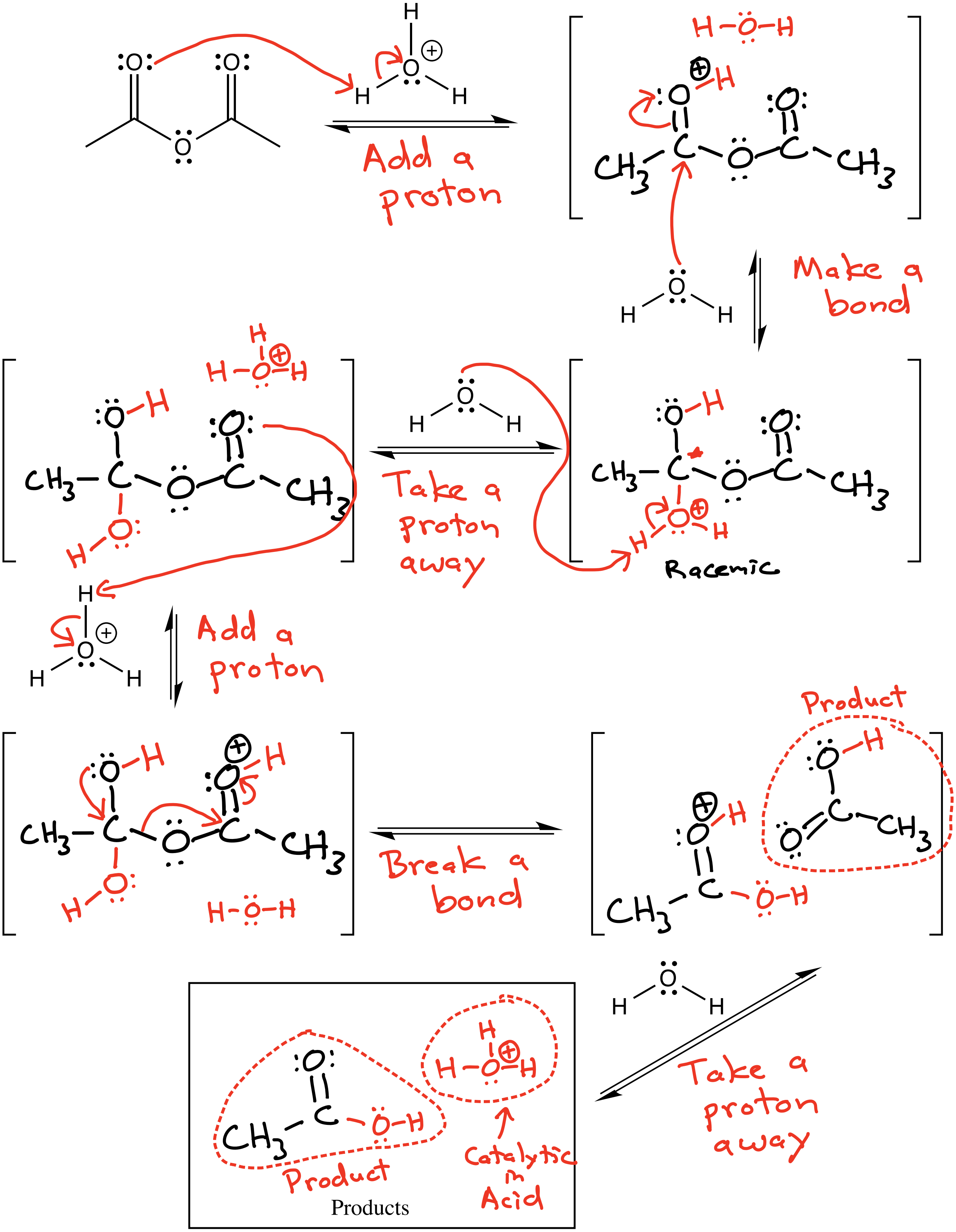
Both depend on anion stability

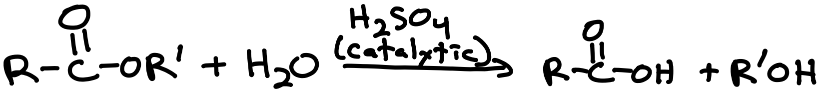
The more stable the anion of the leaving group, the better the leaving group ability ⇒ the more reactive the carboxylic acid derivative

The relative leaving group ability is correlated with the pK_a of the leaving group conjugate acid



Acid Catalyzed Anhydride Hydrolysis





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

Acid Catalyzed Ester Hydrolysis