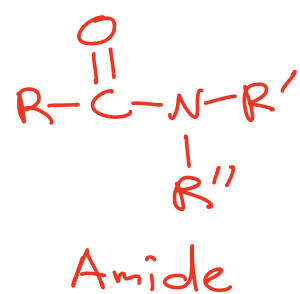
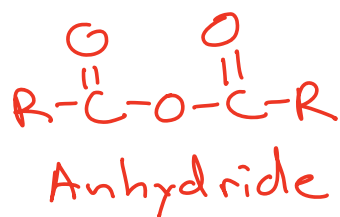
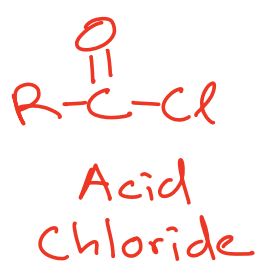
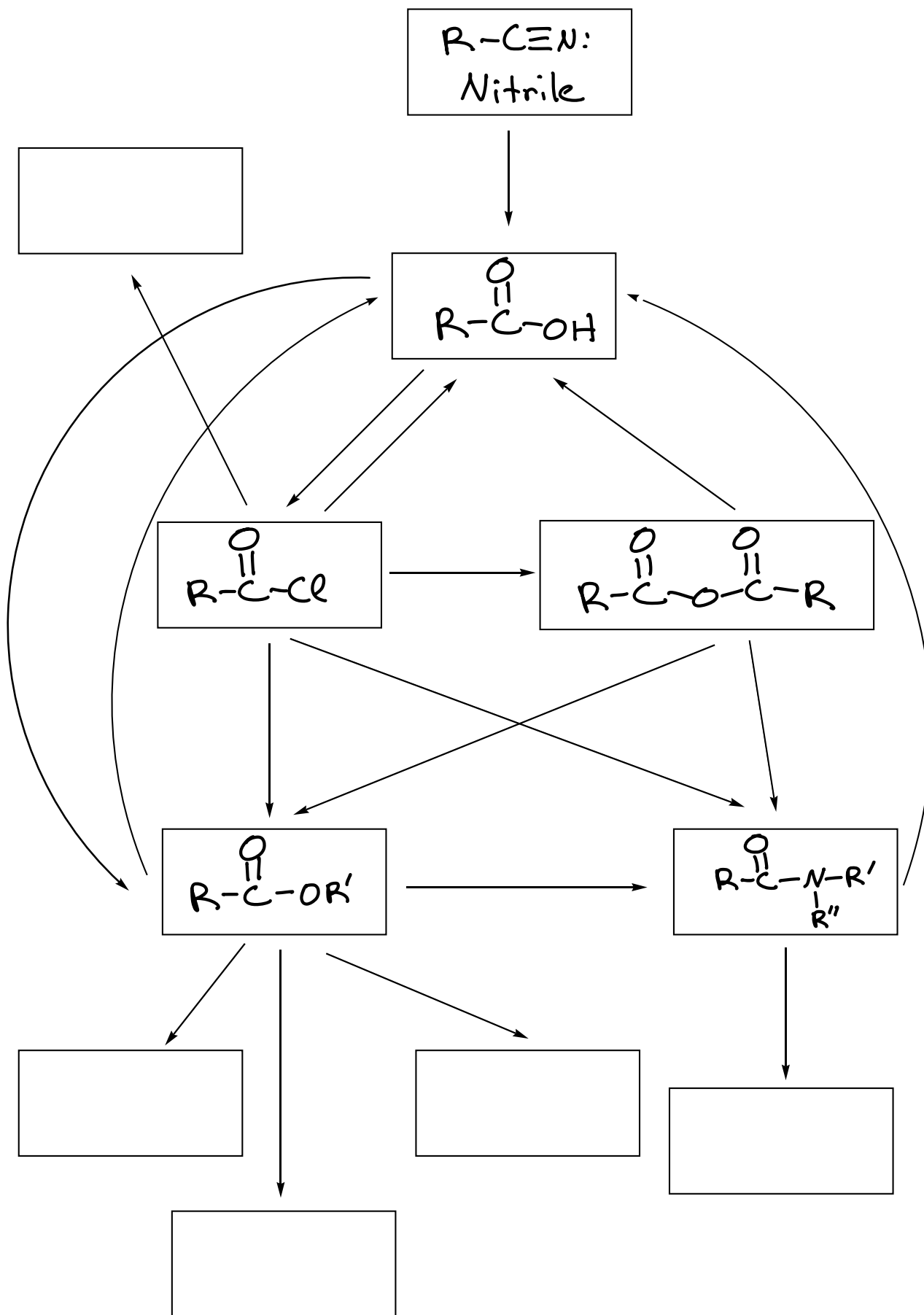


## Carboxylic Acid Derivatives



Interconversion of Carboxylic Acid Derivatives



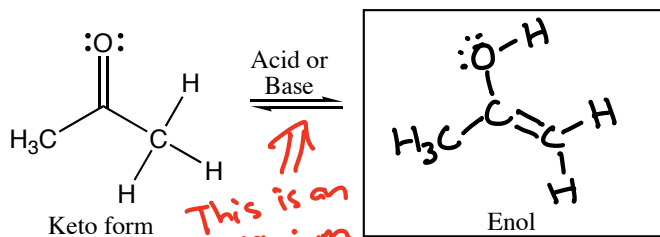
Key idea → A lone pair on an atom adjacent to a carbonyl (C=O) is delocalized into the  $\pi$  bonding of the C=O

The same type of delocalization is present in esters → but to a much lesser extent than amides



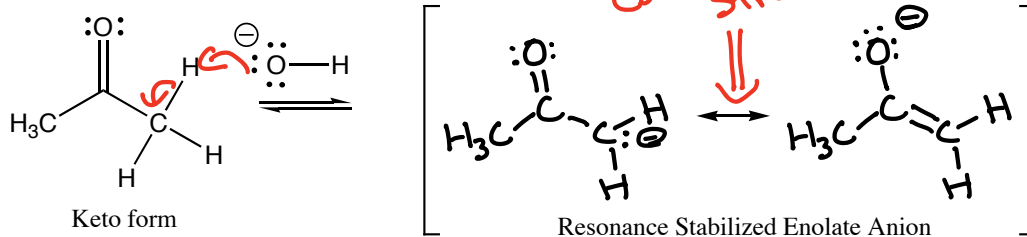
## Keto-Enol Tautomerization vs. Enolate Resonance

### Keto-Enol Tautomerization



Both the keto and enol molecules are Neutral!

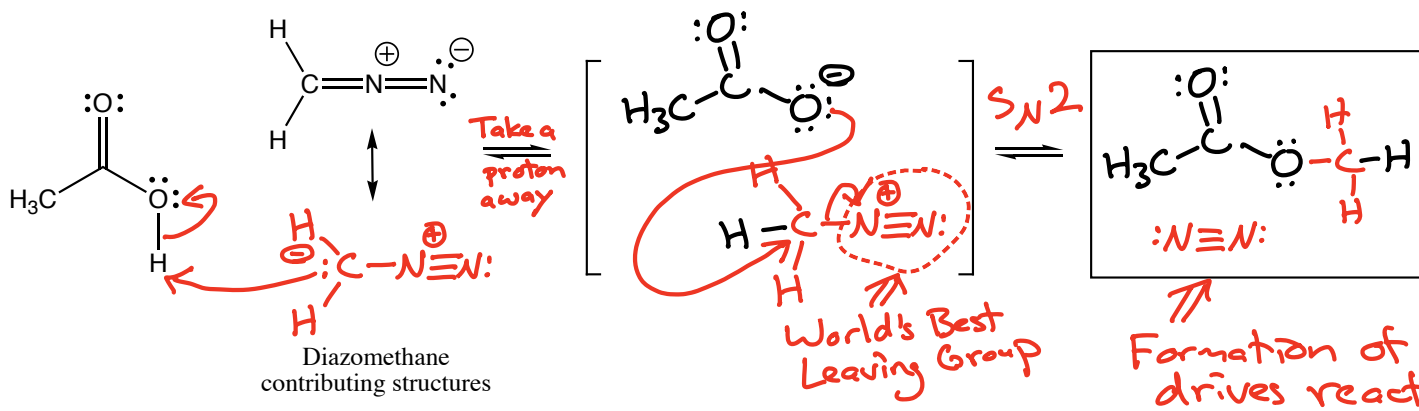
### Enolate Resonance



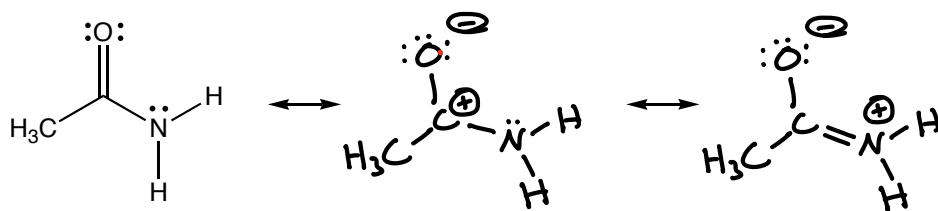
Full  $e^-$

$\alpha$ -hydrogen  $\text{p}K_a = 18-20$

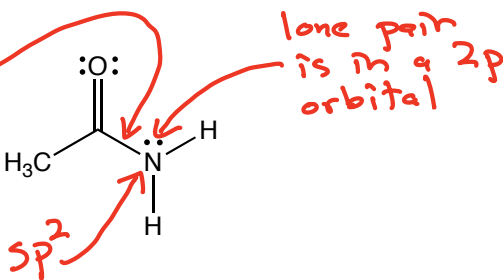
### Diazomethane reaction



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

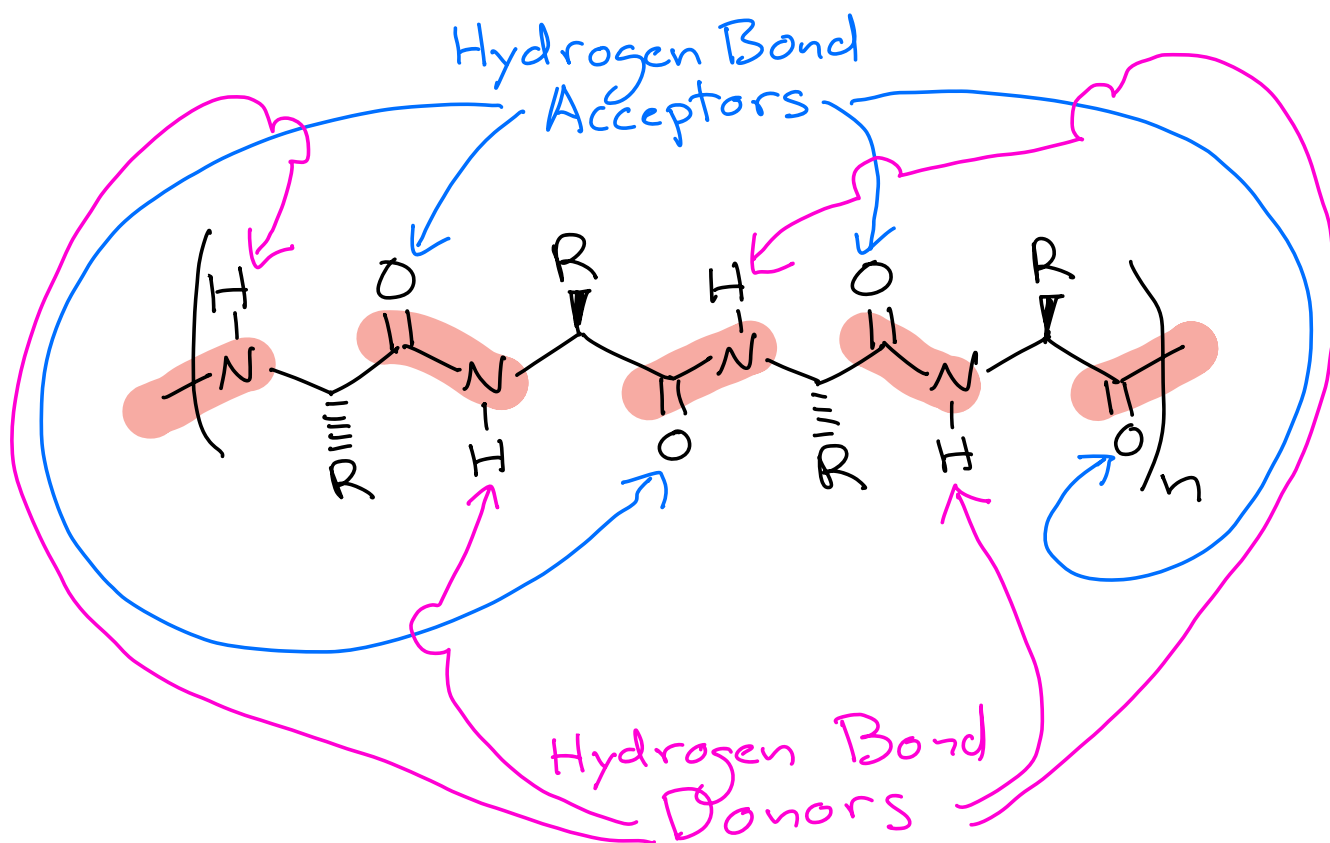


This is a partial  $\pi$  bond so it does not rotate at room temperature

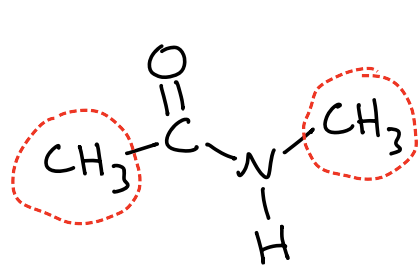


What does this mean for amides:

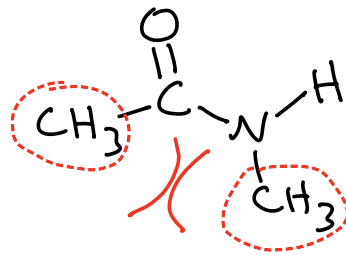
- 1) The amide group can make strong hydrogen bonds
- 2) The C-N bond **does not rotate** at room temperature



Amides in proteins strongly prefer to be trans



trans



cis

## 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  $\Rightarrow$  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 Chloride	Anhydride	Ester	Amide
	$R-\overset{\text{O}}{\parallel}{C}-Cl$	$R-\overset{\text{O}}{\parallel}{C}-O-\overset{\text{O}}{\parallel}{C}-R$	$R-\overset{\text{O}}{\parallel}{C}-O-R'$	$R-\overset{\text{O}}{\parallel}{C}-\underset{\text{R}''}{\text{N}}-R'$
Leaving Group	$:\ddot{Cl}:^{\ominus}$	$^{\ominus}:\ddot{O}:\overset{\text{O}}{\parallel}{C}-R$	$^{\ominus}:\ddot{O}-R'$	$^{\ominus}:\ddot{N}-R'$ $\quad \quad \quad  $ $\quad \quad \quad R''$
Conjugate Acid	$H-Cl$	$HO-\overset{\text{O}}{\parallel}{C}-R$	$H-O-R'$	$H-\underset{\text{R}''}{\text{N}}-R'$
pK <sub>a</sub>	-7	3-5	16	38

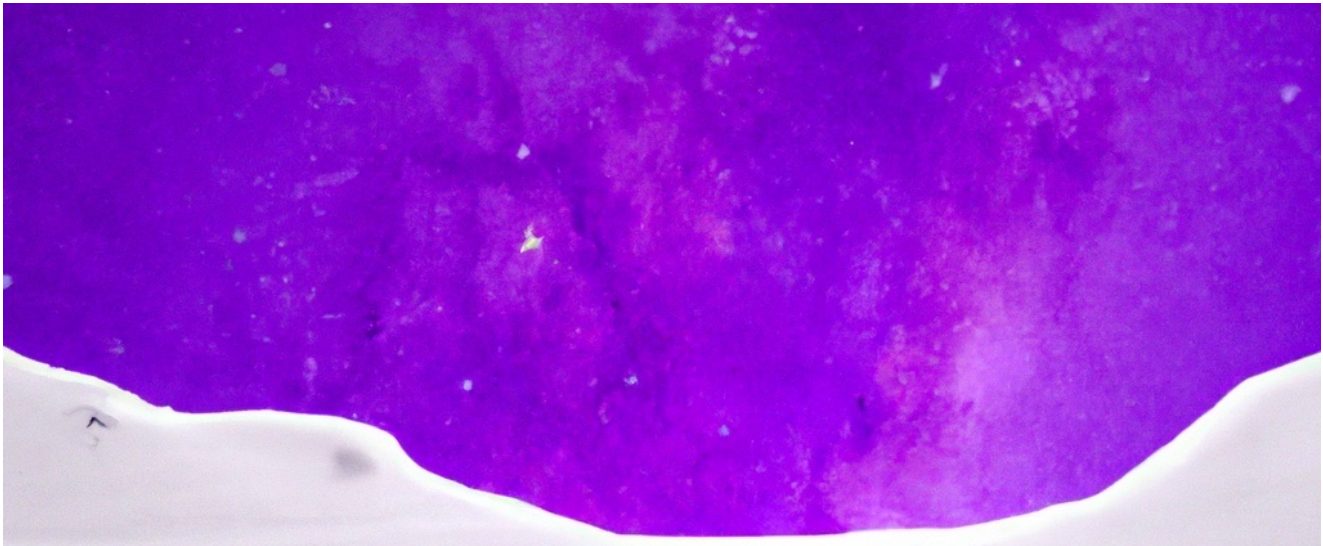
← Anion Stability

← Better Leaving Group Ability

← Reactivity of Carboxylic Acid Derivative


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



- 
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

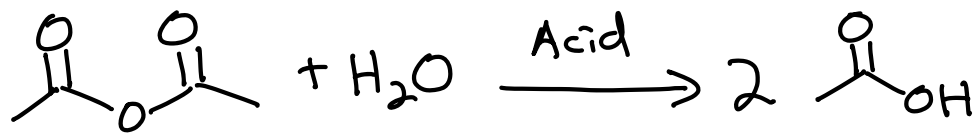


“These four truths you must have.  
The true force of knowledge they are.”



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  $\rightarrow$  the intermediates could be positively-charged, negatively-charged or neutral
- 3) When in doubt transfer a proton  $\rightarrow$  protons move very fast
- 4) Analyze each intermediate carefully to predict the next step



Acid Catalyzed Anhydride Hydrolysis

