

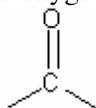
Carbonyl Chemistry - Fundamentals

Images and Information from:

Bruice, P. *Organic Chemistry*, Pearson Prentice Hall, 2004

Hardinger, S. *Chemistry 14D: Thinkbook*, 2006. Lecture Supplement: *Carbonyl Chemistry Fundamentals*

Carbonyl group – a carbon double bonded to an oxygen



Acyl group – carbonyl group attached to an alkyl or aryl group



Carbonyl compounds- compounds containing carbonyl groups

Carbonyl compounds can be divided into two classes:

Class I

- Has a group attached to the acyl group that can function as a leaving group

Compound	Structure
Carboxylic Acid	
Ester	
Amide	
Carboxylate	
Acyl chloride	
Anhydride	
Thioester	

o acyl halides, acid anhydrides, esters, thioesters, carboxylates, and amides are carboxylic

acid derivatives because they differ only by the chemical group that has replaced the OH group

Systematic Nomenclature for Class I

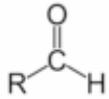
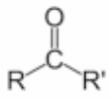
- **Carboxylic Acids**
 - o Functional group = carboxyl group
 - replace the terminal "e" of the alkane name with "oic acid"
 - Common names used for carboxylic acids with six or fewer carbons
 - widely found in nature because less reactive than acyl halides and acid anhydrides:
 - lactic acid in muscles, citric acid in citric fruits etc.
 - Carboxylic acids with amino group on the α -carbon = amino acids.
 - linked together by amide bonds to form peptides and proteins
- **Acyl Halides**
 - o OH group of the carboxylic acid replaced by: halogen
 - Replace "ic acid" with "yl chloride" or "yl bromide"
- **Acid Anhydrides**
 - o Loss of water from two molecules of a carboxylic acid results in an acid anhydride
 - Symmetrical anhydride = if two carboxylic acid molecules are the same
 - Replace "acid" with "anhydride"
 - Mixed anhydride = two carboxylic acid molecules are different
 - State names of both acids in alphabetical order, followed by "anhydride"
- **Esters**
 - o OH group of the carboxylic acid replaced by: OR group
 - Name the group (R') attached to the carboxyl oxygen first, followed by the name of the acid, with "ic acid" replaced by "ate"
 - Lactones = cyclic esters
 - commonly cause the fragrances of fruits and flowers
- **Amides**
 - o OH group of the carboxylic acid replaced by: NH₂, NHR, or NR₂ group
 - Named by using the acid name, replacing "oic acid" or "ic acid" with "amide"
 - Acids ending with "carboxylic acid," "ylic acid" is replaced with "amide"
 - Lactams = cyclic amides
 - Named "2-azacycloalkanones" [aza designates the N atom]

Structures of Carboxylic Acids and Carboxylic Acid Derivatives

- three sp² orbitals to form σ bonds to the carbonyl oxygen, the α -carbon, and a substituent.
 - o trigonal planar
 - o bond angles = 120 degrees
- carbonyl oxygen is sp² hybridized
 - o one sp² orbital forms a σ bond with the carbonyl carbon
 - each of the other two sp² orbitals contains a lone pair
 - o π bond forms between p orbital of carbonyl oxygen and p orbital of carbonyl carbon

Class II

- Does not have a group attached to the acyl group that can function as a leaving group

Compound	Structure
Aldehyde	
Ketone	

- H and alkyl or aryl (-R or -Ar) groups of aldehydes and ketones are too basic to be replaced by a nucleophile

Systematical Nomenclature for Class II

- Aldehyde

- o carbonyl carbon is bonded to a H and to an alkyl (or aryl) group
- o exception: formaldehyde = bonded to two H
 - replace terminal "e" from the name of the parent hydrocarbon with "al"
- o have pungent odors = ex. Vanillin

- ketone

- o carbonyl carbon is bonded to two alkyl (or aryl) groups
 - replace "e" from the name of the parent hydrocarbon and adding "one"
 - the chain is numbered in the direction that gives the carbonyl carbon the smaller number
- o tend to smell sweet = ex. Spearmint leaves
- o also have biological importance = ex: progesterone and testosterone

Physical Properties of Carbonyl Compounds

Relative Boiling Points

amide > carboxylic acid > nitril > ester ~ acyl chloride ~ aldehyde ~ ketone

Boiling Point

- the temperature at which the liquid form of a compound vaporizes into a gas.
- the attractive forces in the liquid must be overcome to become a gas.
- Carboxylic acids form intermolecular hydrogen bonds - high boiling point
- Amides have the highest boiling points because the resonance contributor with separated charges contributes significantly to the overall compound structure

Leaving Groups:

- the better the leaving group the more reactive:
 - 1) **Resonance** - the more resonance it gains from leaving the more its electrons are dispersed and the more stable it becomes - gains resonance = good LG
 - 2) **Atomic radius** - bigger - to house new electrons better
 - 3) **Electronegativity** - more electronegative
 - 4) **Inductive effect** - more electron withdrawing neighbors
- X) Formal Charge - moves from + → neutral
- aldehydes and ketones do not have leaving groups so cannot undergo substitution reactions like the carbonyl compounds of Class I

Relative Reactivities of Carbonyl Compounds Toward Nucleophiles

acyl halide > acid anhydride > aldehyde > ketone > ester ~ carboxylic acid > amide > carboxylate ion

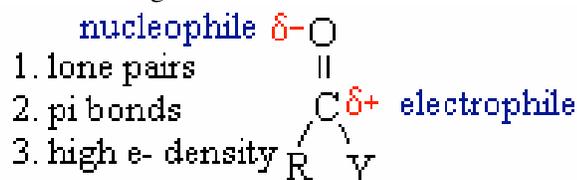
most reactive least reactive

Aldehydes and ketones are:

- less reactive than carbonyl compounds when Y- is a good LG (acyl halides and acid anhydrides)
- more reactive than carbonyl compounds when Y is a poor LG

CARBONYL COMPOUND REACTIVITY

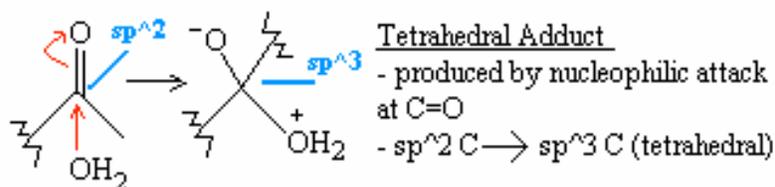
- resides in the polarity of the carbonyl group
 - o Oxygen is more electronegative than carbon.



3 Fundamental Carbonyl Group Mechanism Steps: (Thinkbook Lecture Supplement pg 26)

1. Accept Nucleophile at Carbonyl Carbon

- the highly EN oxygen accepts an electron pair
- all carbonyl addition and substitution mechanisms contain this step

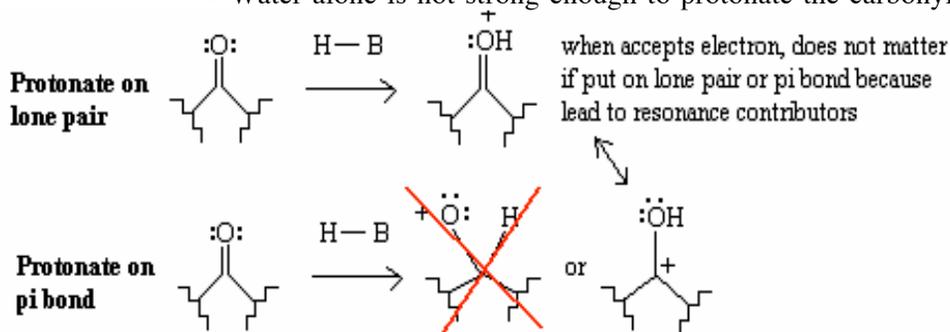


2. Accept Electrophile (Usually Proton at Oxygen)

- lone pairs and pi bond accept an electrophile
- Need strong, reactive acid

Ex. H_3O^+ , H_2SO_4 , ROH_2 etc.

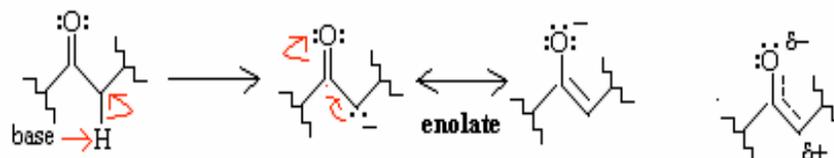
- Water alone is not strong enough to protonate the carbonyl oxygen

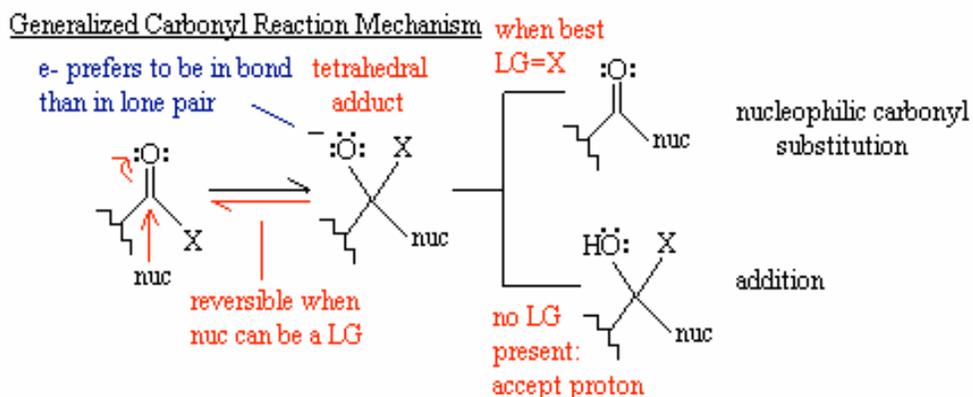


Conclusion: oxycation favored over Carbon's +ive charge

3. Enolate Formation

- driven by conjugate base resonance-stabilization





* Substitution occurs when C=O has a LG: Class I carbonyl compounds

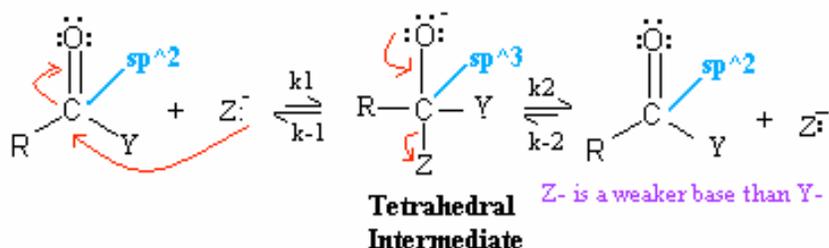
* Addition occurs when C=O does not have a LG: Class II carbonyl compounds

HOW CARBOXYLIC ACIDS AND CARBOXYLIC ACID DERIVATIVES REACT (CLASS I)

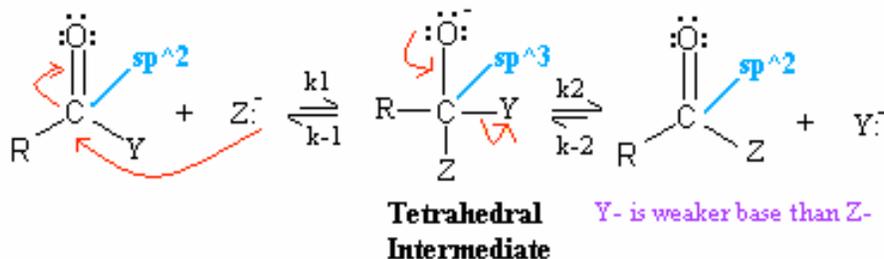
Whether X- or Z- is expelled depends on their relative basicities

- the weaker the base, the better it is as a LG

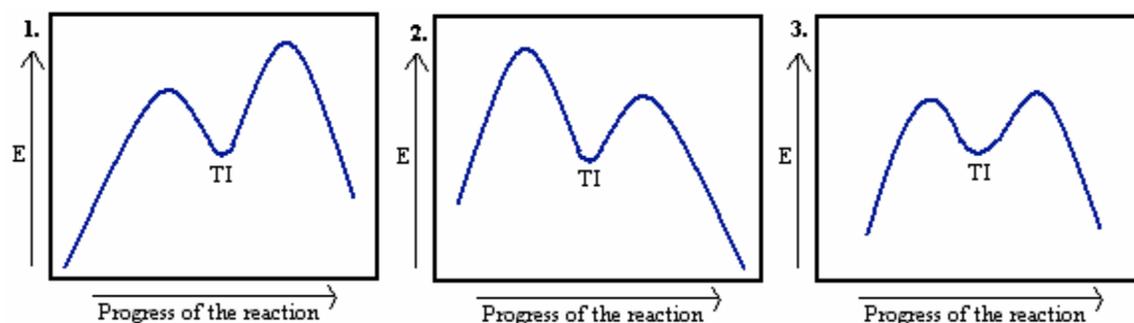
If Z- is much weaker base than Y-, Z- will be expelled



If Y- is a much weaker base than Z-, Y- will be expelled and a new product will be formed



Nucleophilic acyl substitution reaction = nucleophile replaces the substituent attached to the acyl group



1. If the new group in the tetrahedral intermediate is a weaker base than the group that was attached to the acyl group in the reactant, the new group is expelled and the reactants reformed.

- No reaction

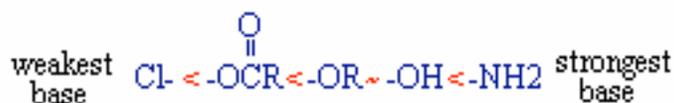
2. If the new group in the tetrahedral intermediate is a stronger base than the group that was attached to the acyl group in the reactant, the group in the reactant is expelled.

- Substitution product

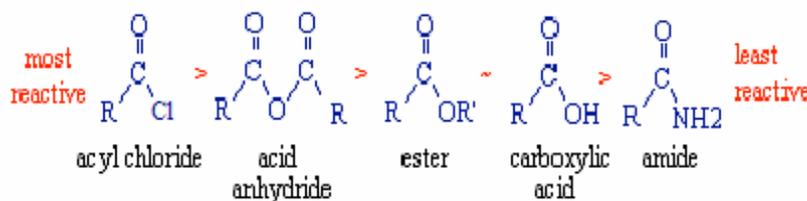
3. If both groups in the tetrahedral adduct have similar basicities, either groups are expelled
- Mixture of reactant and substitution

Relativities of Carboxylic Acids and Carboxylic Acid Derivatives

Relative basicities of the LGs



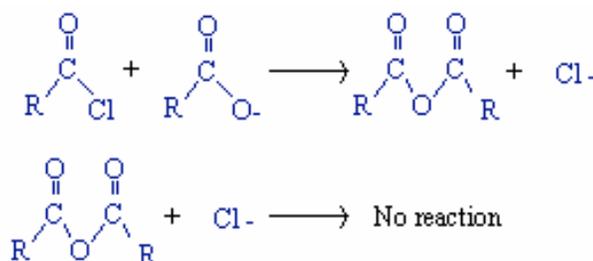
Relative reactivities of carboxylic acid derivatives



If nucleophilic attack allows the leaving group to gain resonance then the molecule is more reactive
If nucleophilic attack disrupts major resonance then the molecule is less reactive

Ex. The resonance between the carbonyl and the amine group is more important than the resonance between the carbonyl and an oxygen because N is less EN so shares its electrons more readily adding more stability

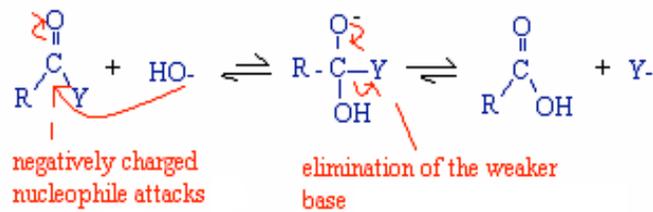
A carboxylic acid derivative will undergo a substitution reaction if the newly added group is not a weaker base than the original group in the reactant



General Mechanism for Nucleophilic Acyl Substitution Reactions

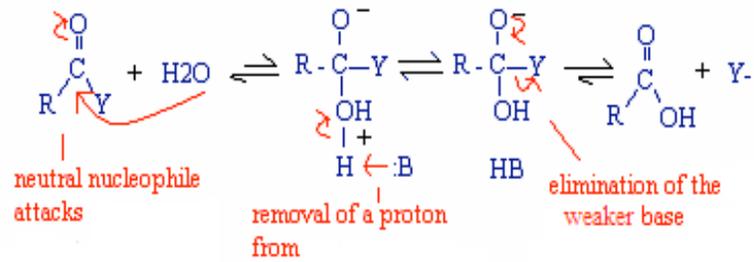
If the nucleophile is **negatively** charged:

Negative Nucleophile



If the nucleophile is **neutral**:

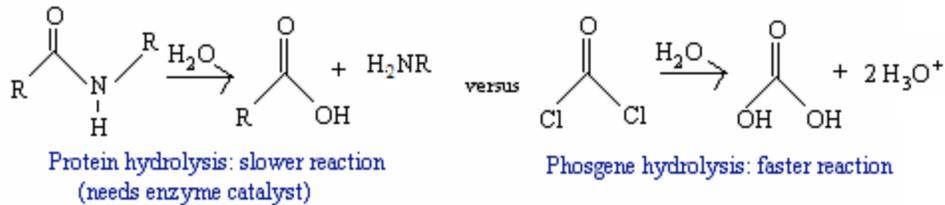
Neutral Nucleophile



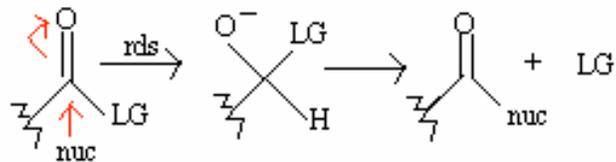
C=O Substitution Reactions

Example from Thinkbook Lecture Supplement pg 28

- Why is protein hydrolysis much slower than phosgene hydrolysis?



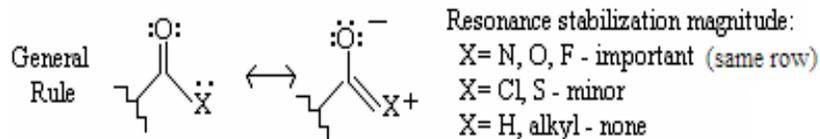
What is the rate-determining step?



RDS = 1st mechanism step: nucleophilic attack at C=O carbon

	Amide	Acid Chloride
Leaving Group	LG= -NR ₂ (nitranion) EN = 3.0	LG = Cl- EN = 3.0
Conclusion	Irrelevant because LG does not leave in RDS	Irrelevant because LG does not leave in RDS
Steric Effects	R unspecified	R unspecified
Conclusion	?	?

$\delta^+ \text{C}=\text{O}$	Nitrogen EN = 3.0 Magnifies carbonyl δ^+	Chlorine EN = 3.0 Magnifies carbonyl δ^+
Conclusion	?	?
Resonance		
Conclusion	More resonance stabilization Slower	



Second Mechanism Step: LG leaves

	Amide	Acid Chloride
LG	LG = -NR ₂ (a nitranion)	LG = Cl ⁻
Conclusion	Slower	Faster
Resonance	Gain resonance with oxygen	Gain resonance with oxygen
Conclusion	Same	Same

Conclusion: amide slower because slower LG

Very important that protein hydrolysis is slow or else our proteins would be constantly breaking into amino acids

Acid chloride > anhydride, thioester > ester ~ carboxylic acids > amide >> carboxylate

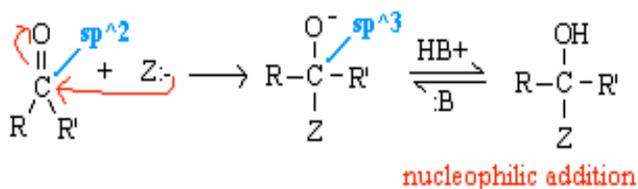
HOW ALDEHYDES AND KETONES REACT (CLASS II)

A substitution reaction does not occur because the carbonyl group of an aldehyde or a ketone is attached to a group that cannot leave

- undergo addition reaction

If the nucleophile (Z) adds to an aldehyde or ketone :

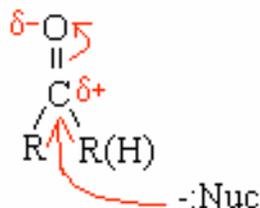
o forms alkoxide ion that can be protonated either by the solvent or added acid



Relative Reactivities of Class II Carbonyl Compounds

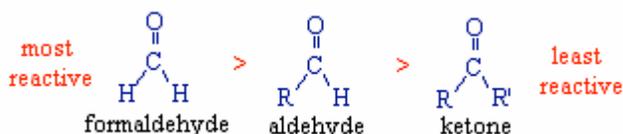
$\delta+$ on Carbonyl Carbon

- partial positive charge on the carbonyl carbon enables it to act as an electrophile and be attacked by a nucleophile



An aldehyde has a greater partial positive charge on its carbonyl carbon than a ketone
 - a ketone has electron donating alkyl groups.

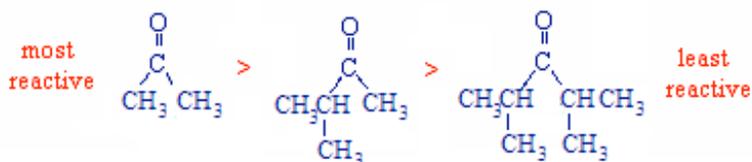
Conclusion: Aldehyde less stable and more reactive towards nucleophilic attack than a ketone



Steric Factors

Aldehyde carbonyl carbons are more accessible since the H groups are smaller than the alkyl groups of ketone

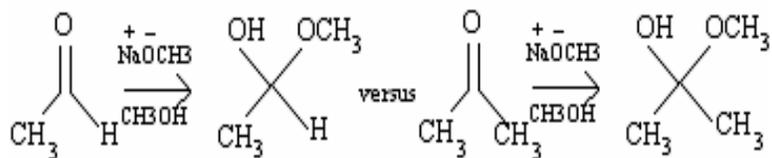
- ketones with small alkyl groups are more reactive than ketones with large alkyl groups



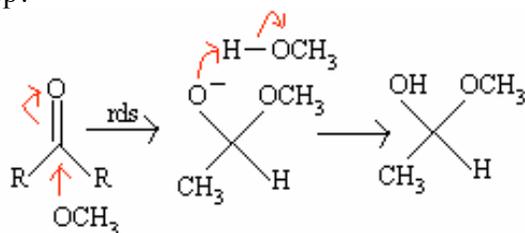
C=O Addition Reactions

Example from Thinkbook Lecture Supplement pg 29-30

Which is faster?



What is the rate-determining step?



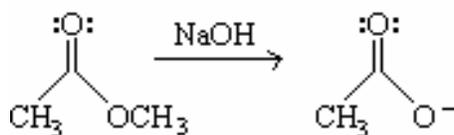
Rds = Nucleophilic attack on carbonyl carbon

	Ketone	Aldehyde
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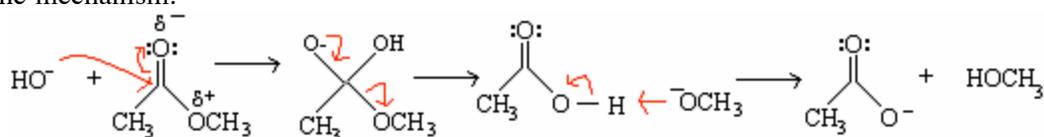
Steric Effects:	CH ₃ larger	H smaller
Conclusion	Slower	Faster
δ^+ C=O	CH ₃ is electron donor (decreasing nucleophilicity)	H is electroneutral
Conclusion	Slower because smaller δ^+	Faster

Aldehydes > ketones

** Problem (from Thinkbook Lecture Supplement pg 31):

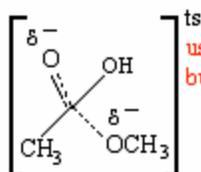


a) Write the mechanism:



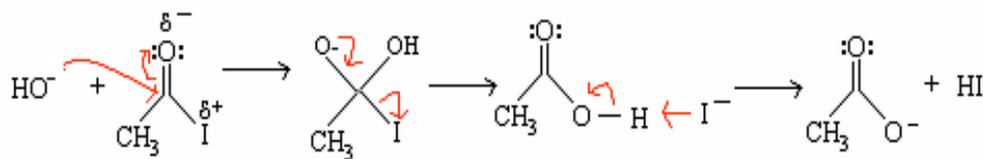
methyl never leaves

Tetrahedral
- eject LG (intra) faster
- accept H (inter)



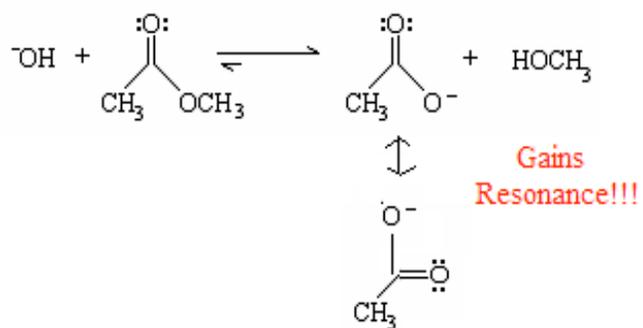
usually b/c O⁻ is very small, can't take new electrons
but if stabilize transition state then can leave
1. help delocalize charge, allows OR to leave
2. lone pairs repel, weaken bonds

b) Rewrite the reaction so it is obviously faster:



I⁻ is a better LG

c) Is $K_{eq} < 1$ (ester favored) or $K_{eq} > 1$ (carboxylate favored)?



Position of equilibrium usually controlled by resonance