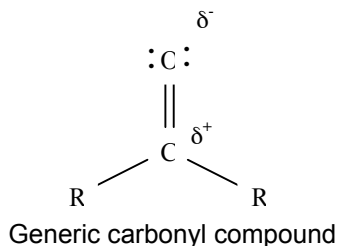


# Carbonyl Chemistry: Fundamentals

What is a carbonyl group and what are its properties?

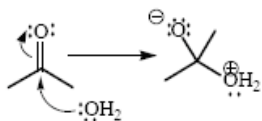
- A carbonyl is any compound that has a carbon double-bonded to an oxygen
- Carbonyls can behave as a nucleophile OR an electrophile
  - Nucleophilic oxygen: electron-rich pi bond, lone pairs on oxygen,  $\delta^-$  charge on oxygen
  - Electrophilic carbon:  $\delta^+$  charge on carbon
- $\delta^-$  and  $\delta^+$  charges due to more **electronegative** oxygen (EN=3.4) compared to carbon (EN=2.5)
- Geometry: trigonal planar,  $sp^2$  hybridized



\* It is somewhat erroneous to claim that these  $\delta^-$  and  $\delta^+$  charges arise from **resonance** because the resonance contributor, with a formal positive charge on carbon and a formal negative charge on oxygen (a carbocation), is too *minor* a contributor compared to that of the major contributor (shown here) that it is not considered.

Three Fundamental Carbonyl Mechanism Steps using Acetone

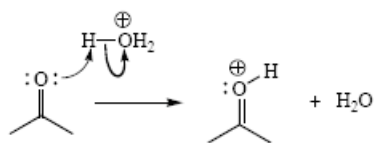
1) Nucleophilic attack at carbon



- 1) Moderate nucleophile  $H_2O$  attacks the electrophilic carbon end at same time the pi bond electrons are shifted to the more electronegative oxygen
- 2) Yields a *tetrahedral adduct* (intermediate=not product) that changes hybridization from  $sp^2 \rightarrow sp^3$

**TIP:** this generic step occurs in almost ALL carbonyl reactions

2) Accept electrophile at oxygen



- 1) Oxygen accepts proton from  $H_3O^+$
- 2) Yields new product with formal  $\oplus$  charge on oxygen
- 3) Does NOT matter whether the *pi bond* or *lone pair* on oxygen attacks proton of  $H_3O^+$  because results in same molecule (resonance contributors of each other)

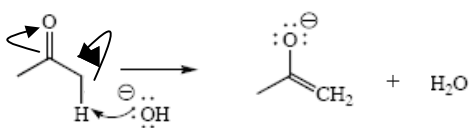
**TIP #1:** Protonation of oxygen end of carbonyl can ONLY occur in presence of STRONG acid (i.e.  $H_2SO_4$ ,  $ROH_2^+$ ,  $H_3O^+$ )

**TIP #2:** If there is strong acid present in a reaction, usually protonate the carbonyl first

3) Enolate Formation

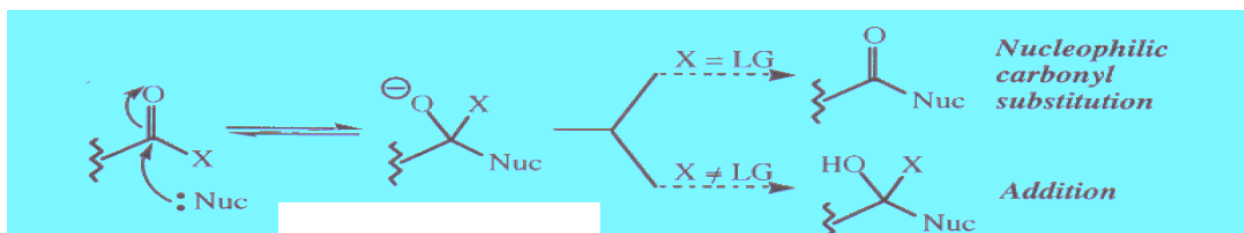
- 1) Strong base deprotonates R group of carbonyl
- 2) Yields enolate with new pi bond formed and negative charge on oxygen

**TIP:** Although incorrect in terms of reasoning, this step can be better remembered by seeing that it is very similar to the carbocation fate step "lose a proton, form a pi bond"



Depending on the nature of the **leaving group**, nucleophilic attack at carbon can lead to two results:

- 1) *Nucleophilic carbonyl substitution*: If there is a leaving group present, kick out the leaving group and form new pi bond = substitution product
- 2) *Addition*: If there is **no** leaving group present in the tetrahedral adduct= addition product



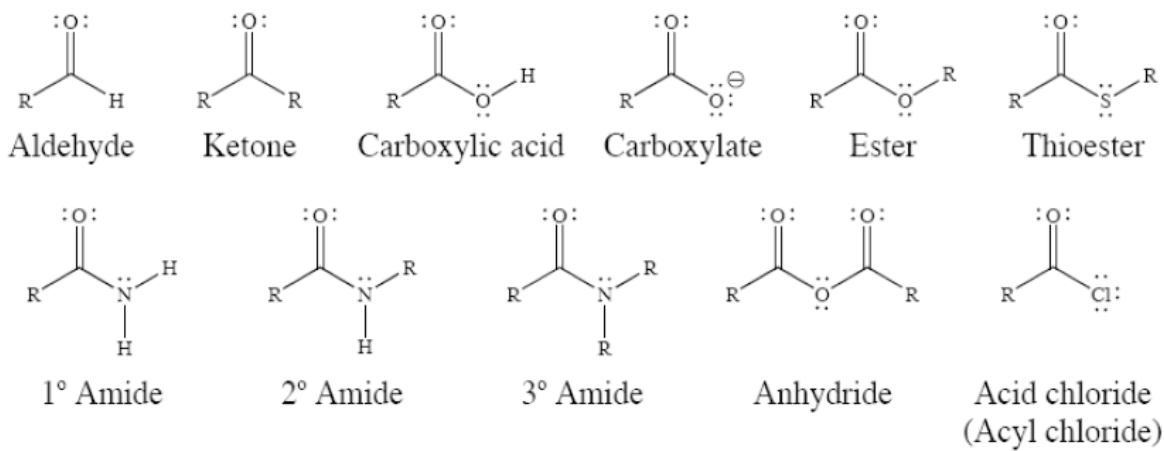
- If group X is a leaving group (i.e.  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $^+\text{OH}_2$ ) then pack its bags and kick it out (intramolecular step) and make new carbon-oxygen pi bond
- If group X is NOT a leaving group (i.e.  $\text{CH}_3$ ,  $\text{H}$ ,  $\text{F}$ ) and no other mechanism steps can occur, protonate the oxygen to make it neutral (intermolecular step)

**QUESTION:** Why not have the nucleophile attack the carbonyl and the leaving group leave *simultaneously* in a concerted action as in  $\text{S}_{\text{N}}2$  reactions?

**ANSWER:** Remember  $\text{S}_{\text{N}}2$  reactions ONLY occur at  $\text{sp}^3$  hybridized carbons; carbonyl compounds are  $\text{sp}^2$  hybridized

## What Four Factors to Consider in Finding Relative Reactivity of Carbonyl-containing Functional Groups

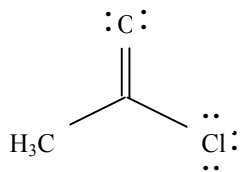
Remember the functional groups that contain carbonyls (these undergo similar reactions):



When asked to find the **fastest** reaction comparing compounds with different carbonyl-containing functional groups COMPARE:

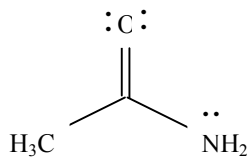
### A) Resonance

- GOOD resonance → slower reaction
- NO/POOR resonance → faster reaction
  - Carbonyl will be **less likely to react** due to resonance stabilization that reduces the partial  $\delta^+/\delta^-$  charges
  - ALSO, tetrahedral adduct less likely to form at the expensive cost of resonance
  - Loss of resonance will spike up the transition state energy for nucleophilic attack step
- ★ More significant resonance when there is resonance between **atoms that are in the same row** and **less electronegative**



**Acid chloride** functional group:  
Weaker resonance  
C is 2<sup>nd</sup> row element but Cl is 3<sup>rd</sup> row element

VS



**Primary Amide** functional group:  
**SIGNIFICANT** resonance  
C and N are both 2<sup>nd</sup> row elements

### B) Leaving Group

1. Better leaving group of tetrahedral adduct → faster reaction
  - What constitutes a GOOD leaving group? (review)
    1. **RESONANCE:** resonance will push leaving group to be expelled due to potential gain of energy-rich resonance (i.e. R-OSO<sub>3</sub>H)

- 2. ATOMIC RADIUS:** larger radius can better make room for newly-gained electron density
- 3. ELECTRONEGATIVITY:** more electronegative the atom, the more greedy it is about electron density, the more it can keep to itself when it leaves
- 4. INDUCTIVE EFFECT:** greater the inductive power of leaving group, the better the ability to accommodate extra electron density
- 5. FORMAL CHARGE:** if charge changes from positive/negative to neutral, the more stable the product, the better the leaving group

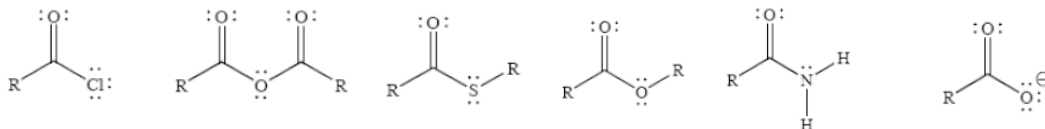
C) Magnitude of  $\delta^+$  charge on carbon

- Larger  $\delta^+$  charge on carbon will make carbon more electrophilic and more easily attacked by nucleophiles
  - Carbons with large  $\delta^+$  charge can be attacked by weaker nucleophiles
  - Neighboring groups with high electronegativity suck away electron density from carbon of carbonyl, rendering it more electrophilic or electron poor
  - $\delta^+$  charge on carbon can be reduced by neighboring electron-donating groups such as alkyl groups (-CH<sub>3</sub>)

D) Steric Effects

- Bulky substituents hinder nucleophilic attack → slower reaction

In general, acid chloride, anhydride, thioester > ester > amide >> carboxylate



Factors in finding reaction rates	Acid chloride	Anhydride	Thioester	Ester	Amide	Carboxylate
A) Resonance	Poor resonance—C and Cl NOT same row elements	Good resonance with two oxygen atoms—C and N same row elements, greater delocalization of charge	Poor resonance C and S NOT same row elements	Good resonance with oxygen atom — C and O same row elements	Great resonance with N — C and N same row elements and N is less electronegative than O = better resonance	Superior resonance with oxygen atom — C and O same row elements
B) Leaving group	Cl- good leaving group	-OCOR good leaving group due to gained resonance stabilization and	-SR good leaving group due to larger atomic size	-OR moderate leaving group due to highly electroneg	-NH <sub>2</sub> moderate/bad leaving group due to less	-O <sup>2-</sup> VERY poor leaving group due to 2- formal charge

		electronegative O		active O	electronegative N and small radius	
C) Magnitude of $\delta^+$ charge on carbon	Larger $\delta^+$ due to electronegative Cl atom	Larger $\delta^+$ due to electronegative O	Moderate $\delta^+$ due to less electronegative S	Larger $\delta^+$ due to electronegative O	Moderate/small $\delta^+$ due to less electronegative N and good resonance	Larger/moderate $\delta^+$ due to highly electronegative O but good resonance
D) Steric effects	Steric effects <b>hard to compare</b> among these functional groups, resonance trumps					

In the general mechanism steps for carbonyl chemistry, **what is the rate-determining step?**

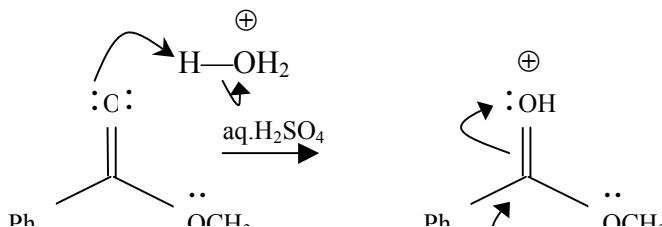
Carbonyl Reaction Steps	Rate-determining step?
<b>SUBSTITUTION</b>	
1. Nucleophilic attack	Neither nucleophilic attack or the expulsion of the leaving group can be clearly defined as the rate determining step: Since there is no clear-cut explanation why one step should be slower than the other, the rate-determining step happens to depend on many experimental, external conditions
2. Leaving group leaves	
<b>ADDITION</b>	
1. Nucleophilic attack	<b>Yes</b> , rate determining step because intermolecular step that involves breaking of C-O pi bond and formation of C-nucleophile bond
2. Protonation	<b>No</b> , because protonation is often very FAST

**Conclusion:** Although we can determine the faster reaction by comparing only the 1) magnitude of  $\delta^+$  charge on carbon and 2) steric effects for carbonyl addition reactions, we need to consider all 4 factors for nucleophilic carbonyl substitution

“To protonate or not protonate, that is the question.” – “Hardinger”

When do we know when or when not to protonate?

- Nucleophile: the better the nucleophile, the less necessary it is to protonate in the 1<sup>st</sup> step
- Electrophile: the better the electrophile, the less necessary it is to protonate in the 1<sup>st</sup> step
- If strong acid is present, protonate!

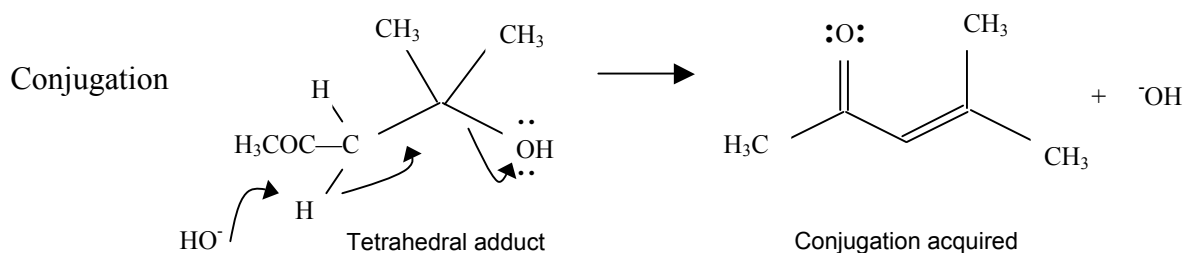
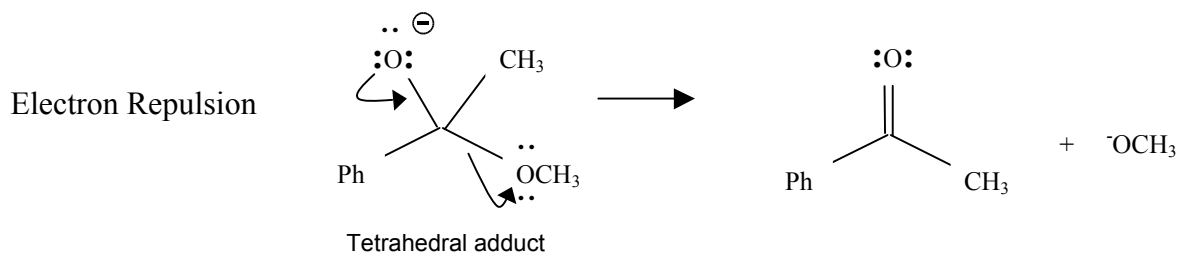


: OH<sub>2</sub>

- 1) **Strong acid** aq. H<sub>2</sub>SO<sub>4</sub> is present, protonate using H<sub>3</sub>O<sup>+</sup>!
- 2) Moderate nucleophile: H<sub>2</sub>O (presence implied by "aqueous")
- 3) **Resonance stabilization** makes carbonyl carbon less likely to undergo nucleophilic attack
- 4) δ<sup>+</sup> charge on carbonyl carbon larger due to even less electron density on carbonyl oxygen = **better electrophile**
- 5) Now moderate nucleophile H<sub>2</sub>O can attack carbonyl carbon more easily even with resonance present (carbonyl C turned into better electrophile)

When can <sup>-</sup>OH or <sup>-</sup>OR ever be a leaving group? I thought they can never leave!

- A) In the tetrahedral adduct when there is a **formal negative charge on the oxygen**, <sup>-</sup>OH or <sup>-</sup>OR can leave due to unfavorable *electron repulsion*
- B) If **conjugation** can be gained, <sup>-</sup>OH or <sup>-</sup>OR can be leaving groups (enolate mechanisms)



\*Some images and reactions taken from Chemistry 14D Thinkbook 2006 but otherwise created by Microsoft Word

