

Summary Sheet: Two Key Concepts for Nucleophilic Substitution on Carbonyls plus a third bonus concept.

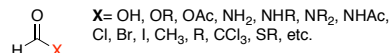
Predicting the **rate** of reaction at a carbonyl and the **fate** of the resulting tetrahedral intermediate depend on understanding two key concepts: 1. The electronic nature of the atoms adjoining the carbonyl. 2. Steric bulk around the carbonyl.

Key Concept #1: The importance of electronic factors

Take the simplest carbonyl: formaldehyde
It undergoes one type of reaction: nucleophilic addition.

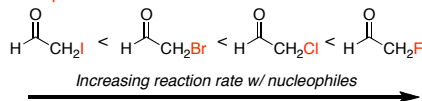


What happens when you substitute one of the hydrogens on formaldehyde for a different functional group?

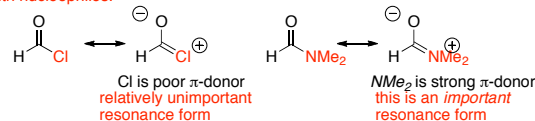


The **rate** of the reaction will depend on two key factors.

1) Electronegative functional groups make the carbonyl carbon more electropositive, which increases the rate of reaction with nucleophiles.



2) Donation of π -electrons by the X group makes the carbonyl carbon **less** electropositive, which decreases the rate of reaction with nucleophiles.



Does this discussion seem familiar from electrophilic aromatic substitution? It should! It's the same principle!
Recall from electrophilic aromatic substitution:

Strongly activating
NH₂, NHR, NR₂, OH, O[−]

Moderately deactivating
CO₂H, CO₂R, CN, CHO, COR

Moderately activating
NHCOCH₃, NHCOR, OCH₃, OR

Strongly Deactivating*
CF₃, CCl₃

Weakly activating
CH₃, C₂H₅, R, C₆H₅

*I left off NO₂ and SO₃H, which are important in electrophilic aromatic substitution but not here; in general, carbonyl groups attached to these functional groups are too unstable toward hydrolysis to be synthetically useful.

Weakly Deactivating*
F, Cl, Br, I
deactivating due to electronegativity but are π -donors

Note: look at the position of OH and O[−]. They are extremely strong π -donors. This is why carboxylic acids are resistant to attack under basic conditions; strong π -donation by O[−] into the carbonyl makes it extremely resistant toward nucleophilic attack.

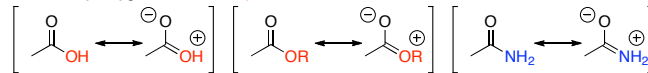
Just like with electrophilic aromatic substitution, π -donation trumps electronegativity. **The stronger the π -donor, the more resistant the carbonyl will be towards nucleophilic attack.**

In general

more nucleophilic = less electrophilic = faster rate of reaction with electrophiles = higher electron density = more Lewis basic = less Lewis acidic = more electron rich = less electropositive
more electrophilic = less nucleophilic = faster rate of reaction with nucleophiles = lower electron density = less Lewis basic = more Lewis acidic = less electron rich = more electropositive

* caveat: acidity/basicity is the position of a thermodynamic **equilibrium**, while nucleophilicity is measured by reaction **rate**

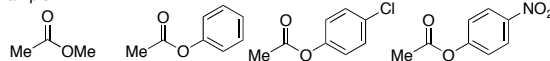
The presence of donating groups makes the carbonyl carbon less electrophilic and the carbonyl oxygen **more nucleophilic**. Recall these resonance forms



The carbonyl is the most nucleophilic (and Lewis basic) site. Therefore, it is protonated first.

A good proxy for donating ability is pKa, especially when the atom attached to the carbonyl is the same.

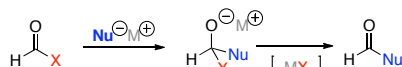
Example:



increasing susceptibility toward nucleophilic attack

pKa of alcohol: ~16, 10, 9.4, 7

The tetrahedral intermediate can undergo further reaction



How can you predict what will happen?

Leaving group ability is directly related to the pKa of the conjugate acid.

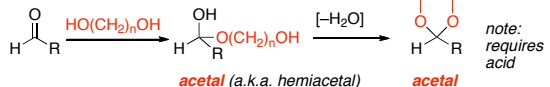
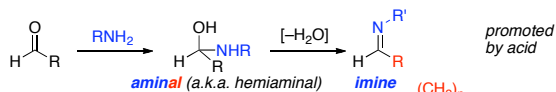
I > Br > Cl > OAc > OAr > OH[−], OMe > NRAc > NR₂ > H > CH₃, R
 good moderate poor these groups never leave
 −11 −9 −7 4 10 15 17 35 ~40 ~50

pKa of conjugate acid

*remember, however, that under basic conditions OH will be O[−] which means it would have to leave as O^{2−}: an extremely bad leaving group

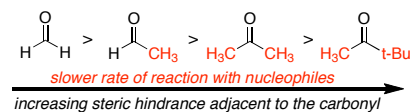
Advice: Know your pKa's cold. They are a great measure of leaving group ability and also of the electron donating ability of the conjugate base, which comes up again and again when discussing chemical reactivity.

Aldehydes and ketones:

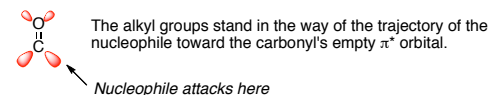


Key concept #2: The importance of steric factors

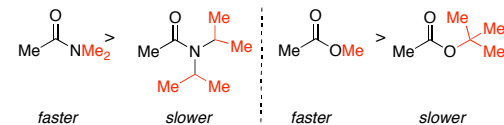
Formaldehyde again: as the hydrogens are replaced with progressively bulkier groups, the reaction rate goes down.



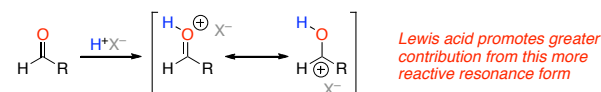
Why? Recall the antibonding (π^*) orbitals of the carbonyl group.



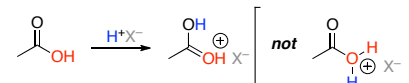
The same concept applies for the rate of reaction of nucleophiles with esters and amides:



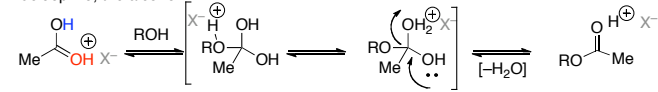
A final important concept: Lewis acids make carbonyls more electrophilic



For example, in the Fischer esterification, the first step is protonation of the carboxylic acid:



The protonated carbonyl, which is now more electrophilic, reacts with the relatively weak nucleophile, the alcohol:



Note in this example that the reaction between the Lewis acid (HCl) and nucleophile (EtOH) is reversible under the reaction conditions, whereas using, say, a Grignard reagent would result in irreversible protonation of the nucleophile (i.e. no reaction). Compatibility between Lewis acids and nucleophiles is treated with more detail in advanced level organic chemistry courses.

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