Structure and Reactivity
of
Carboxylic Acid Derivatives

Three Keys to Understanding the Chemistry of Carboxylic Acids Derivatives

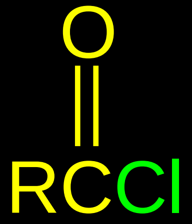
The key to managing the information in this chapter is the same as always: *structure determines properties.*

The key structural feature is how well the carbonyl group is stabilized.

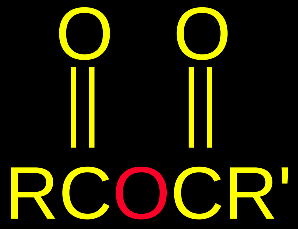
The key property is reactivity in nucleophilic acyl substitution.

most reactive

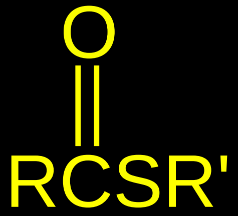
a carboxylic acid derivative can be converted by nucleophilic acyl substitution to any other type that lies below it in this table


$R\overset{O}{\overset{\|}{C}}Cl$

ethyl chloride


$R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R'$

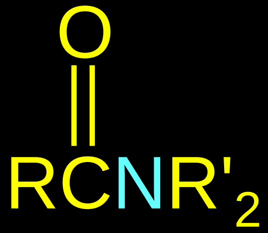
acetic anhydride


$R\overset{O}{\overset{\|}{C}}SR'$

ethyl thioacetate

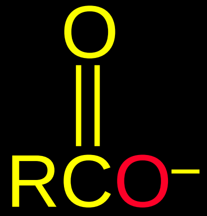

$R\overset{O}{\overset{\|}{C}}OR'$

ethyl acetate


$R\overset{O}{\overset{\|}{C}}NR'_2$

acetamide

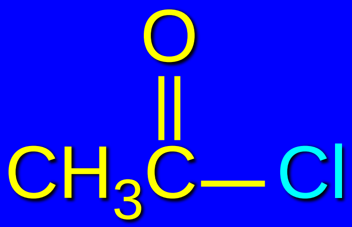
acetate

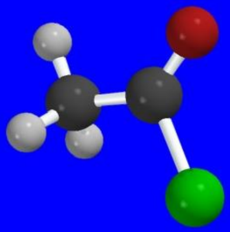

$R\overset{O}{\overset{\|}{C}}O^-$

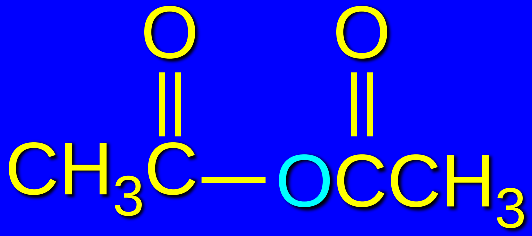
least reactive

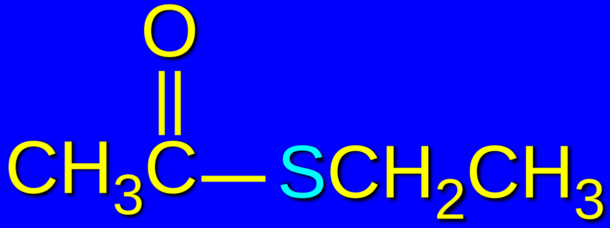
Most reactive

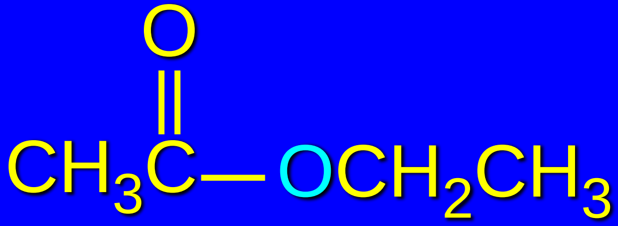
Least stabilized

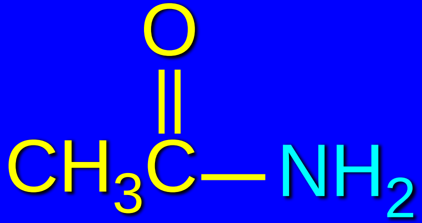

$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{Cl}$$

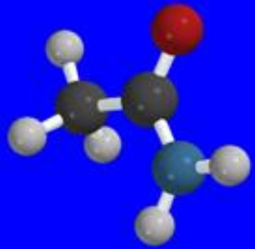



$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_3}$$


$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{SCH_2CH_3}$$


$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OCH_2CH_3}$$

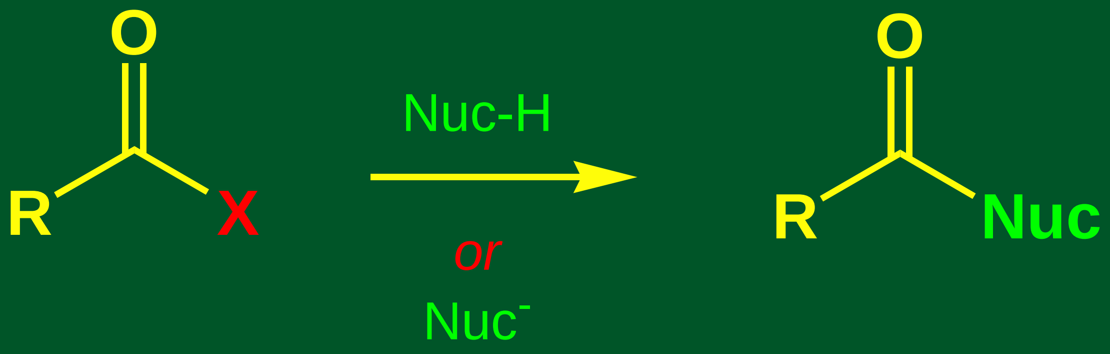

$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{NH_2}$$



Least reactive

Most stabilized

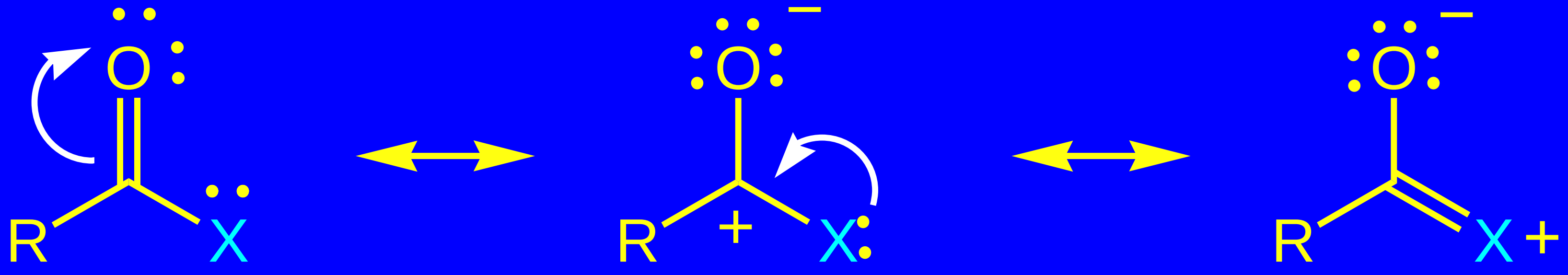
Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution



General Mechanism
for
Nucleophilic Acyl Substitution

Electron Delocalization and the Carbonyl Group

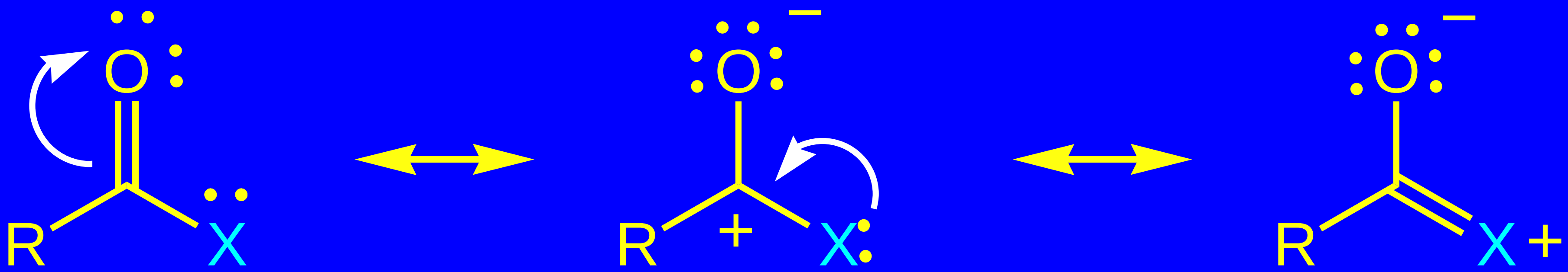
The main structural feature that distinguishes acyl chlorides, anhydrides, thioesters, esters, and amides is the interaction of the substituent with the carbonyl group. It can be represented in resonance terms as:



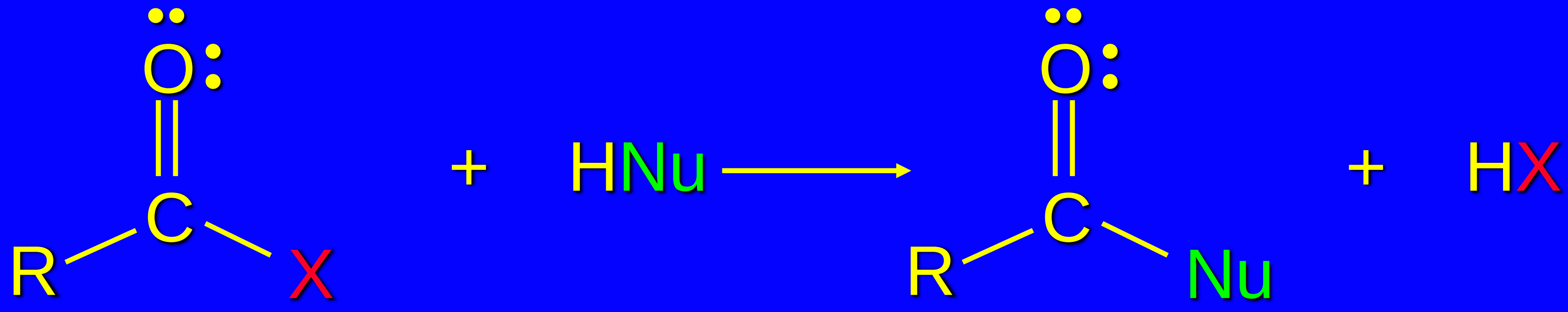
Electron Delocalization and the Carbonyl Group

The extent to which the lone pair on X can be delocalized into C=O depends on:

1) the electronegativity of X
2) how well the lone pair orbital of X interacts with the π orbital of C=O



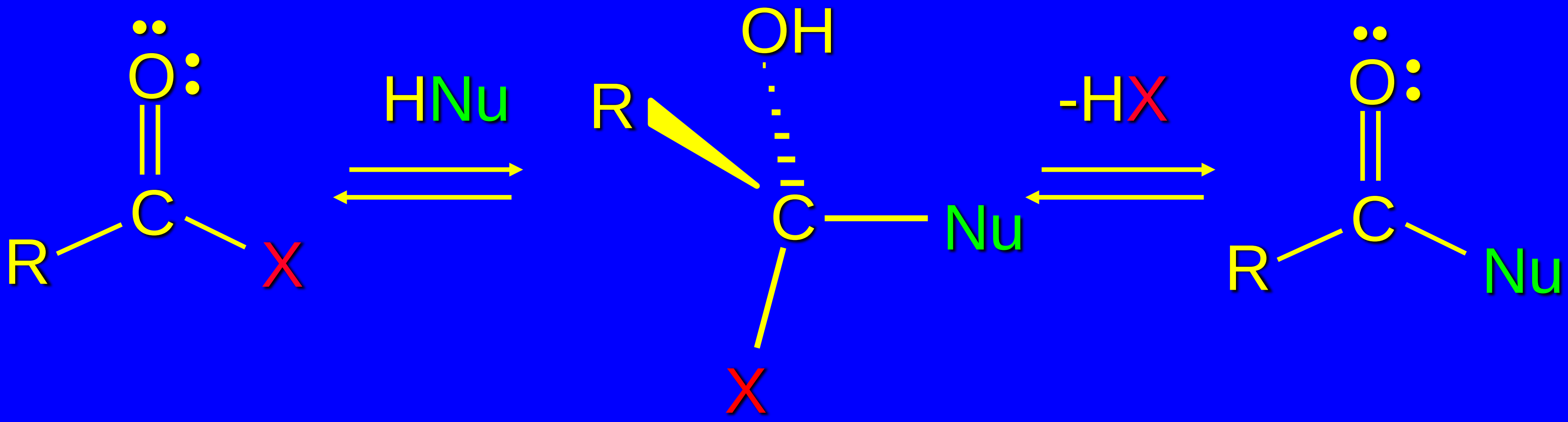
Nucleophilic Acyl Substitution



Reaction is feasible when a less stabilized carbonyl is converted to a more stabilized one (more reactive to less reactive).

Mechanism of Nucleophilic Acyl Substitution

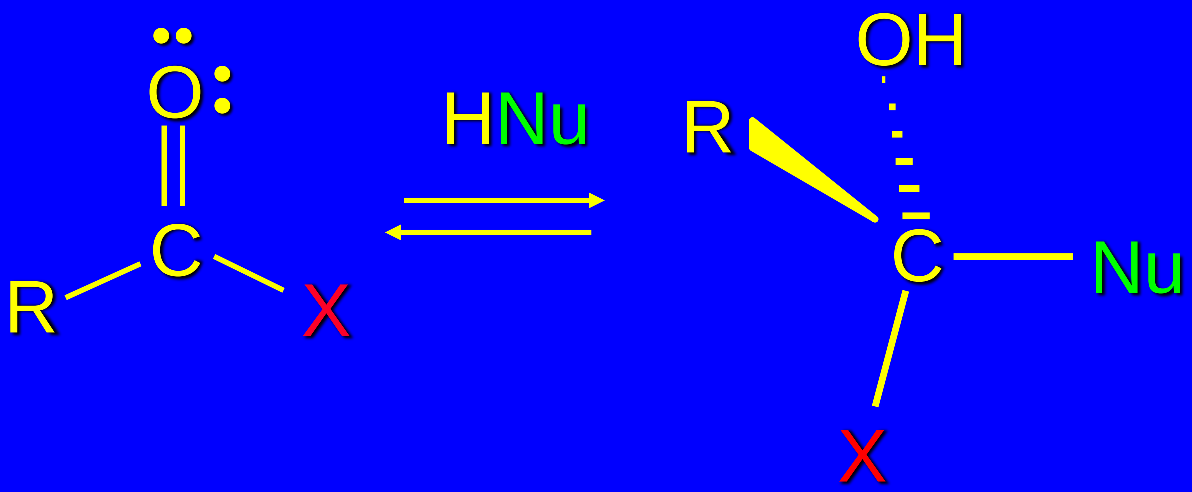
involves formation and dissociation
of a tetrahedral intermediate



Both stages can involve several elementary steps

Mechanism of Nucleophilic Acyl Substitution

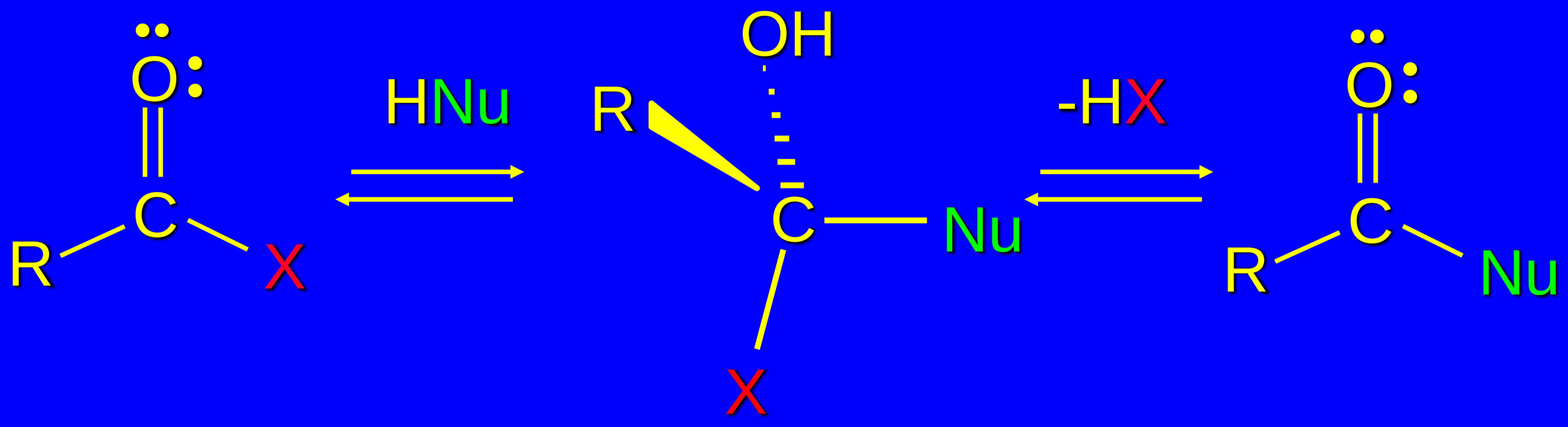
first stage of mechanism (formation of tetrahedral intermediate) is analogous to nucleophilic addition to C=O of aldehydes and ketones



Mechanism of Nucleophilic Acyl Substitution

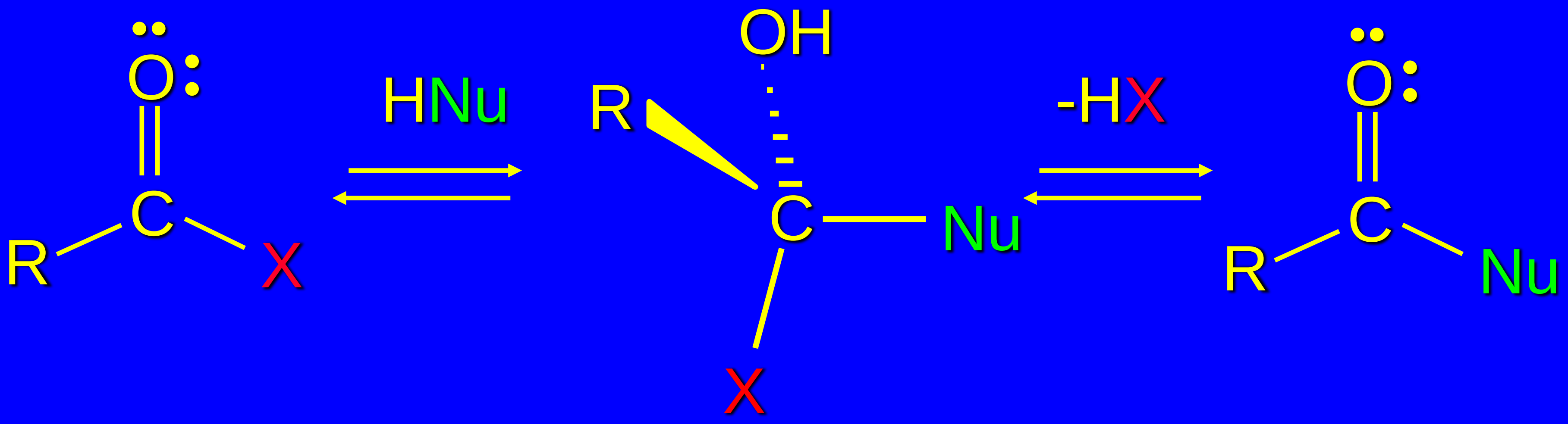
second stage is restoration of C=O by elimination

complicating features of each stage involve acid-base chemistry



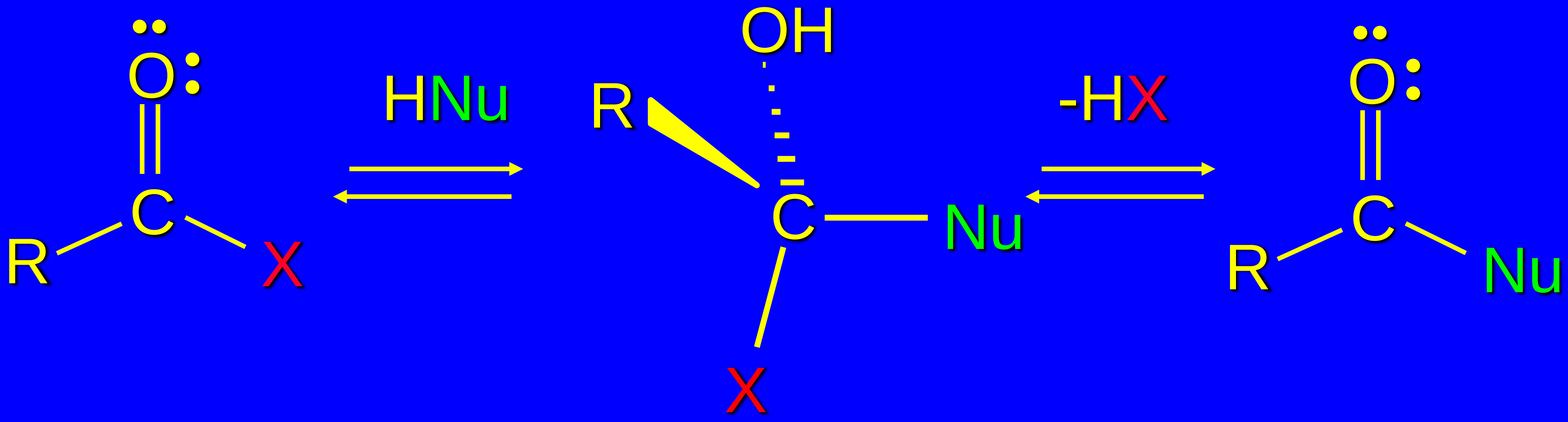
Mechanism of Nucleophilic Acyl Substitution

Acid-base chemistry in first stage is familiar in that it has to do with acid/base catalysis of nucleophilic addition to C=O.

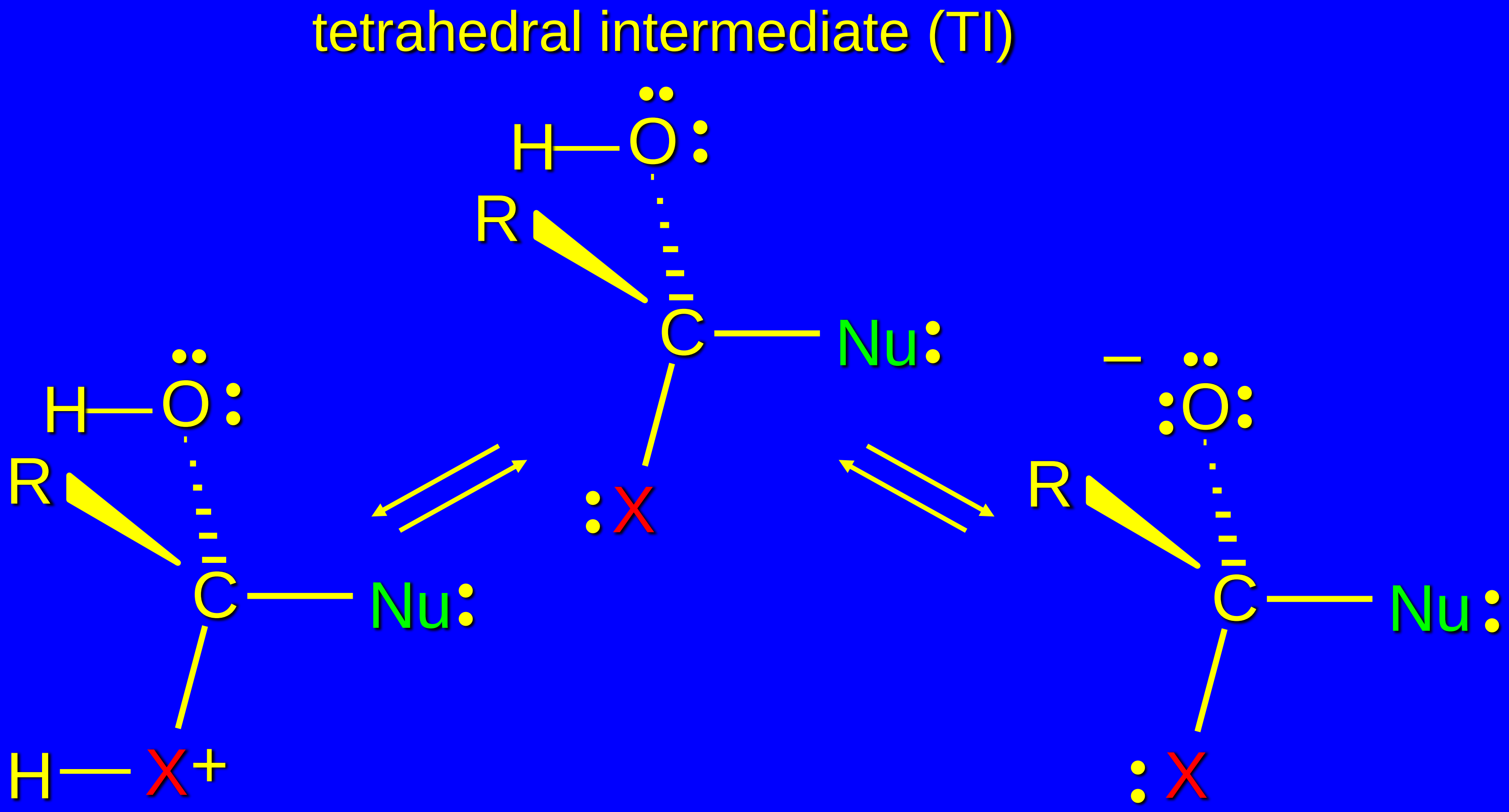


Mechanism of Nucleophilic Acyl Substitution

Acid-base chemistry in second stage concerns the form in which the tetrahedral intermediate exists under the reaction conditions and how it dissociates under those conditions.



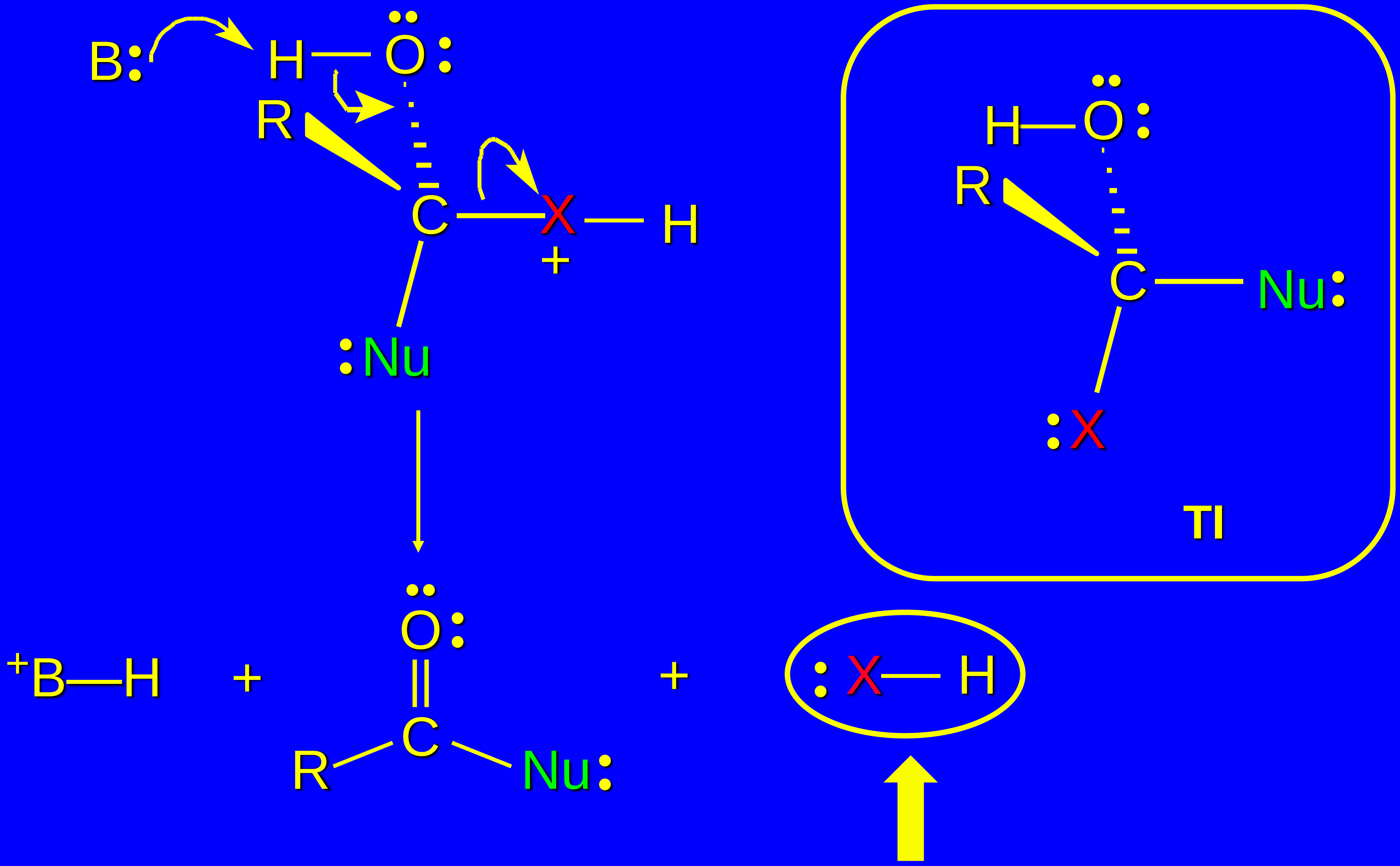
The Tetrahedral Intermediate



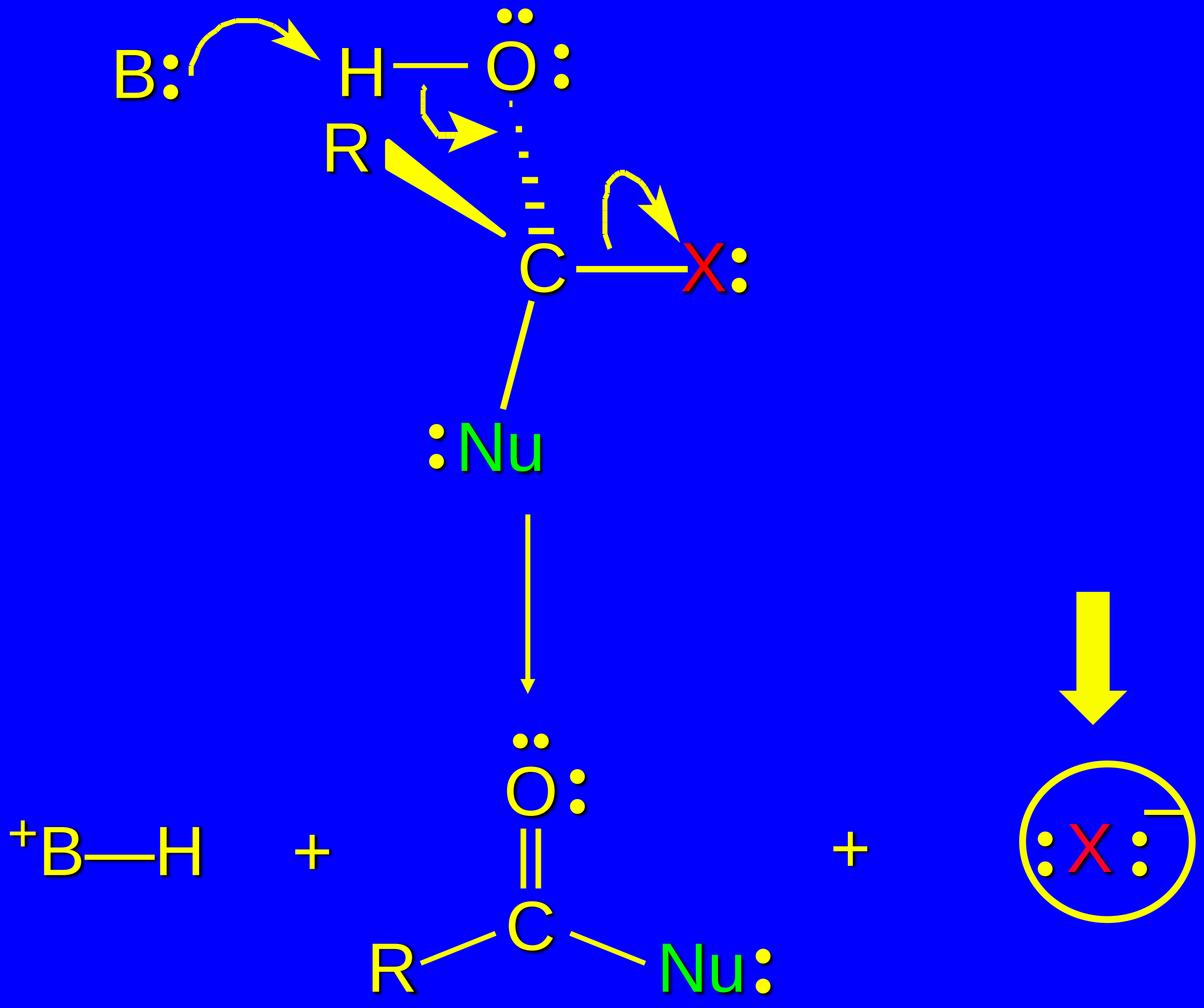
Conjugate acid of tetrahedral intermediate (TI^+)

Conjugate base of tetrahedral intermediate (TI^-)

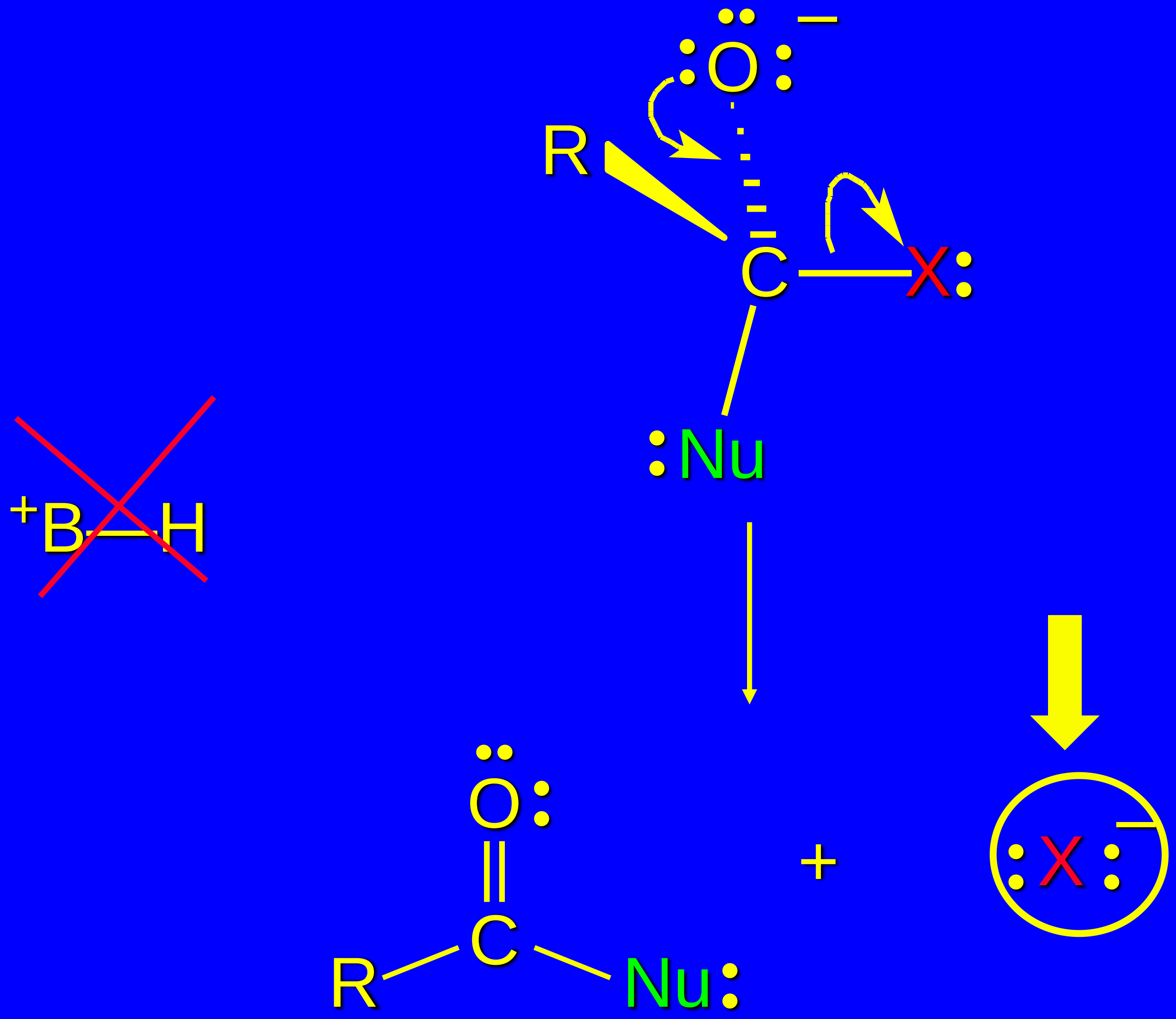
Dissociation of Protonated Tetrahedral Inter.



Dissociation of Neutral Tetrahedral Inter.

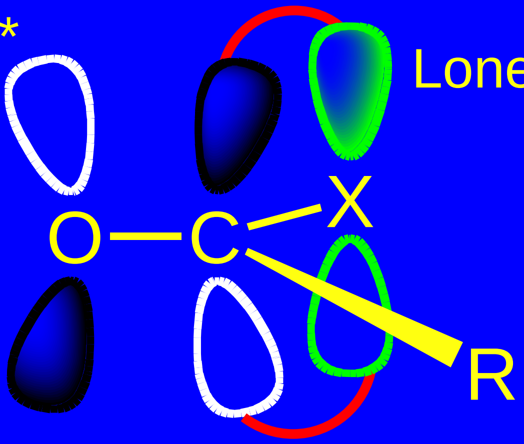


Dissociation of Anionic Tetrahedral Inter.



Eletronegativity and Reactivity of Carboxylic Acid Derivatives

Orbital Overlap in Carboxylic Acid Derivatives

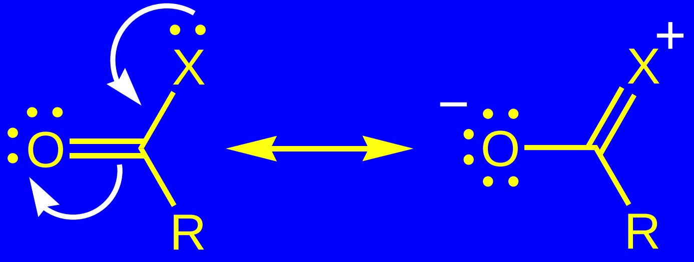


Orbitals Overlap

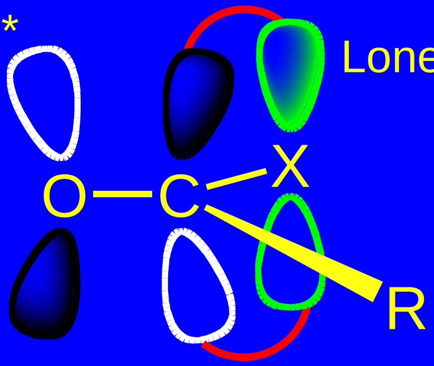
Empty π* orbital

Lone Pair

The p-π* orbital interaction can be represented in terms of resonance



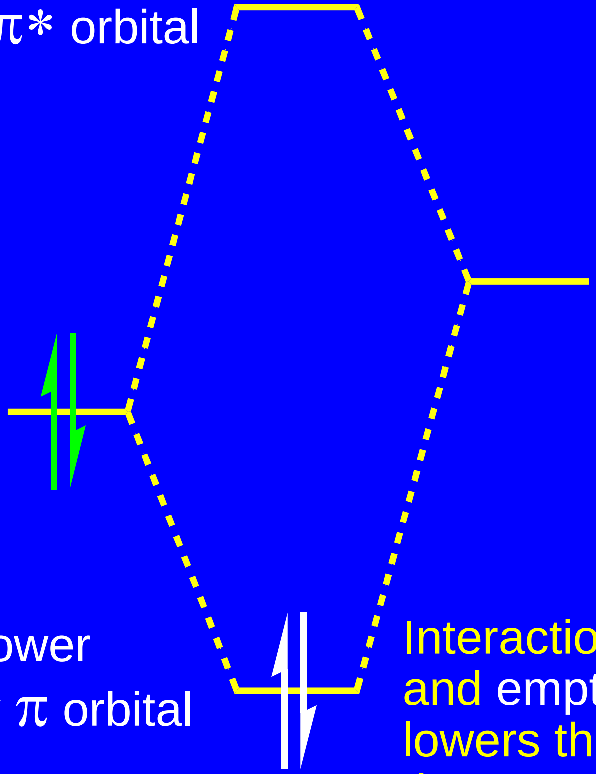
Orbital Overlap in Carboxylic Acid Derivatives



Orbitals Overlap

Empty π^* orbitial

Lone Pair



New, higher energy π^* orbital

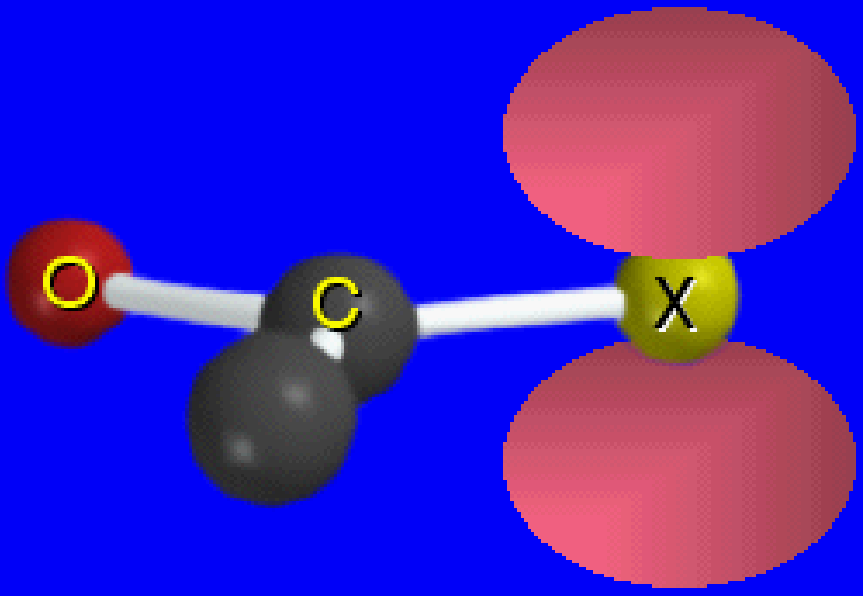
Empty π^* Orbital of CO group

Nitrogen Lone Pair

New, lower energy π orbital

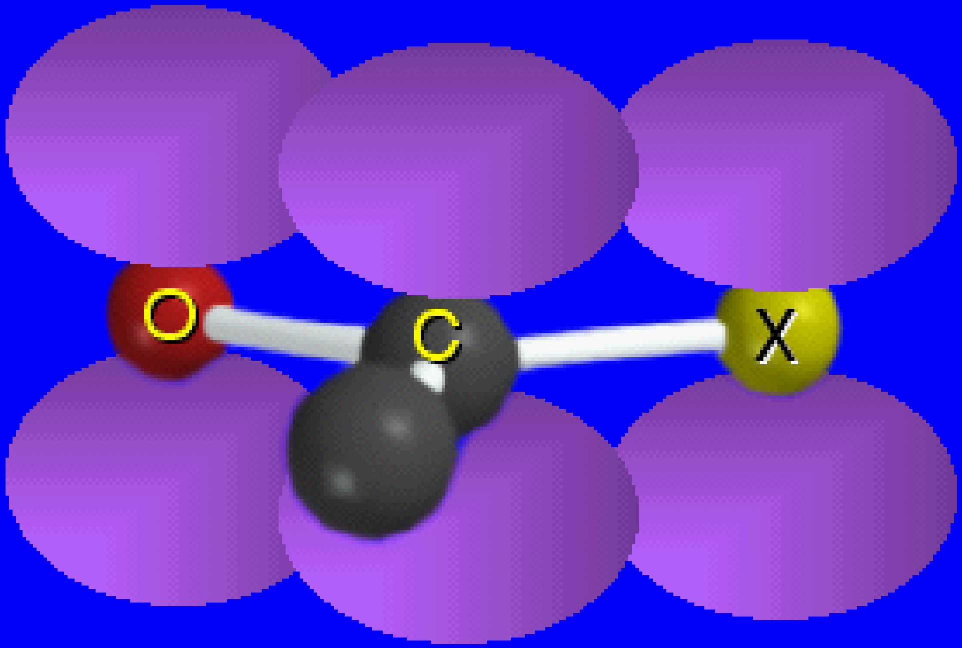
Interaction of filled and empty orbitals lowers the energy of thesystem

Orbital Overlap in Carboxylic Acid Derivatives



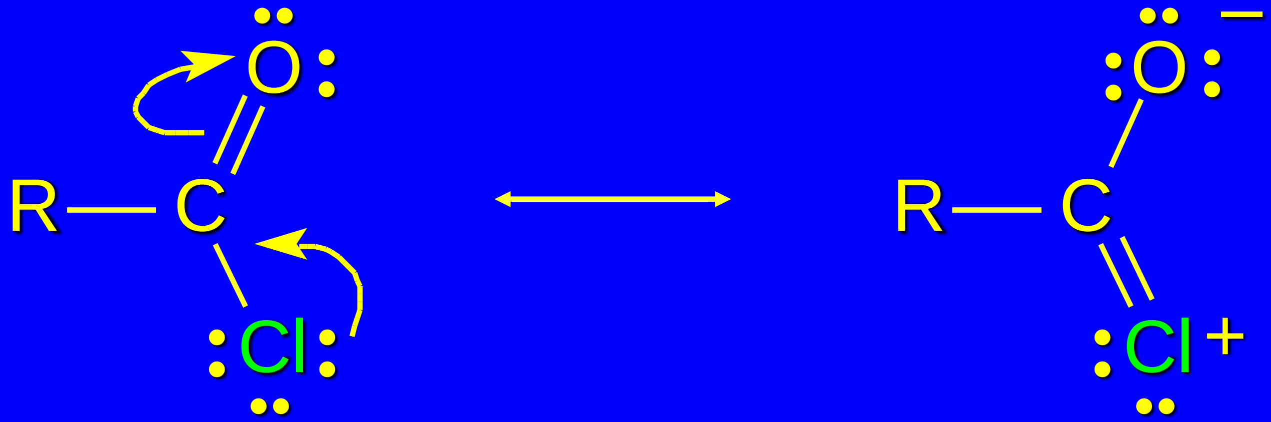
lone pair orbital
of substituent

Orbital Overlap in Carboxylic Acid Derivatives



electron pair of substituent delocalized into carbonyl π orbital

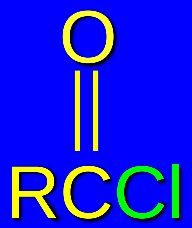
Orbital Overlap in Acyl Chlorides



Acyl chlorides have the least stabilized carbonyl group

Delocalization of lone pair of Cl into C=O group is not effective because C—Cl bond is too long

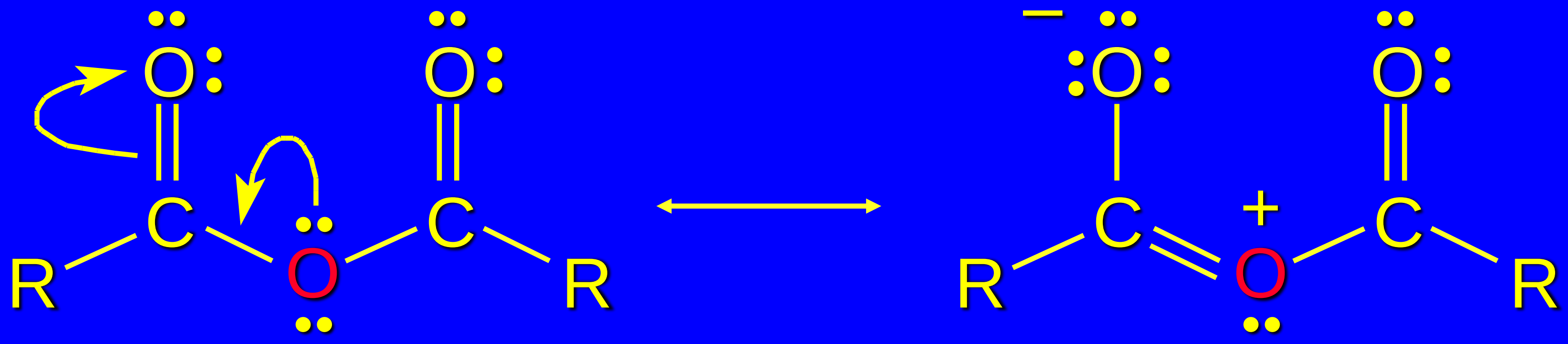
least stabilized C=O



$$R\overset{\overset{\displaystyle O}{\|}}{C}Cl$$

most stabilized C=O

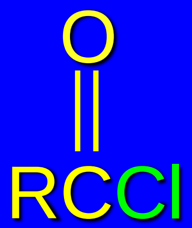
Orbital Overlap in Acid Anhydrides



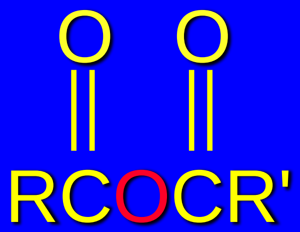
lone pair donation from oxygen stabilizes the carbonyl group of an acid anhydride

the other carbonyl group is stabilized in an analogous manner by the lone pair

least stabilized C=O



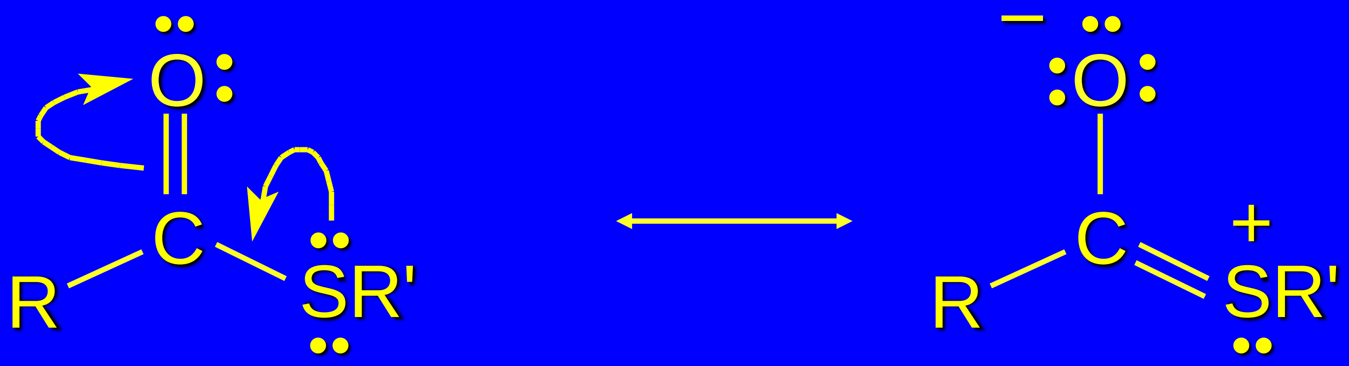
$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl}$



$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R'}$

most stabilized C=O

Orbital Overlap in Thioesters

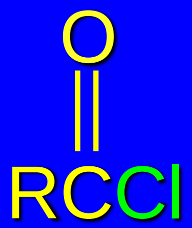


Sulfur (like chlorine) is a third-row element.

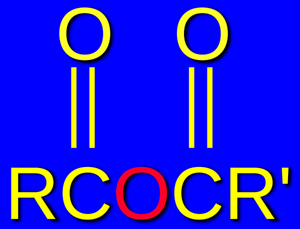
Electron donation to C=O from third-row elements is not very effective.

Resonance stabilization of C=O in thioesters is not significant.

least stabilized C=O



$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl}$

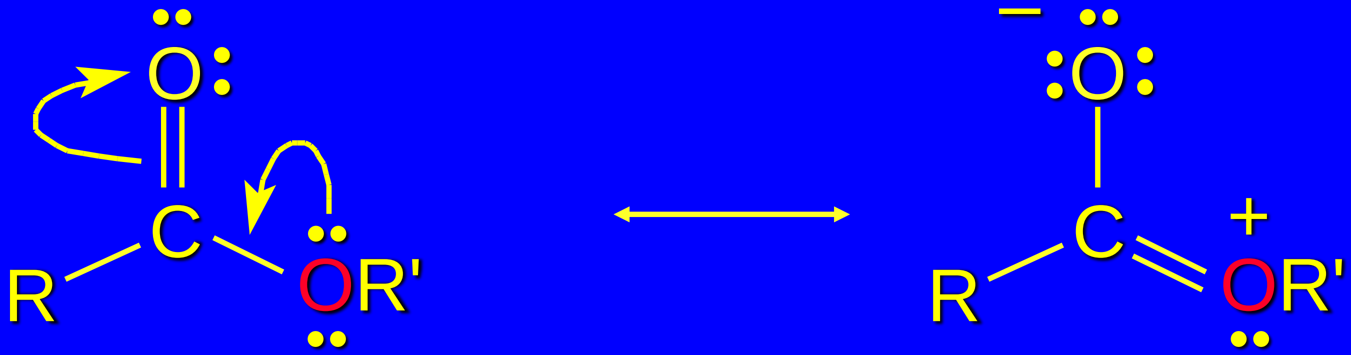


$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R'}$

$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{SR'}$

most stabilized C=O

Orbital Overlap in Esters



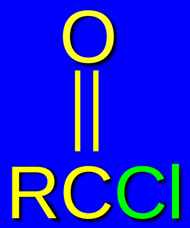
lone pair donation from oxygen stabilizes the carbonyl group of an ester

stabilization greater than comparable stabilization of an anhydride or thioester

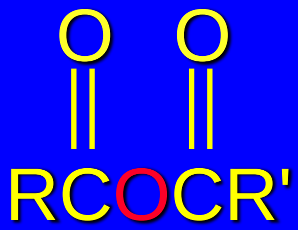
Estabilidade relativa de derivados de ácidos
Estruturas de ressonância

https://pt.khanacademy.org/science/organic-chemistry/carboxylic-acids-derivatives/formation-carboxylic-acid-derivatives-sal/v/relative-stability-of-amides-est

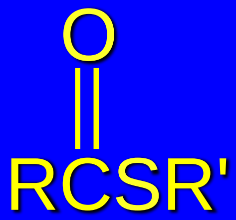
least stabilized C=O



$R\overset{O}{\overset{\|}{C}}Cl$



$R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R'$

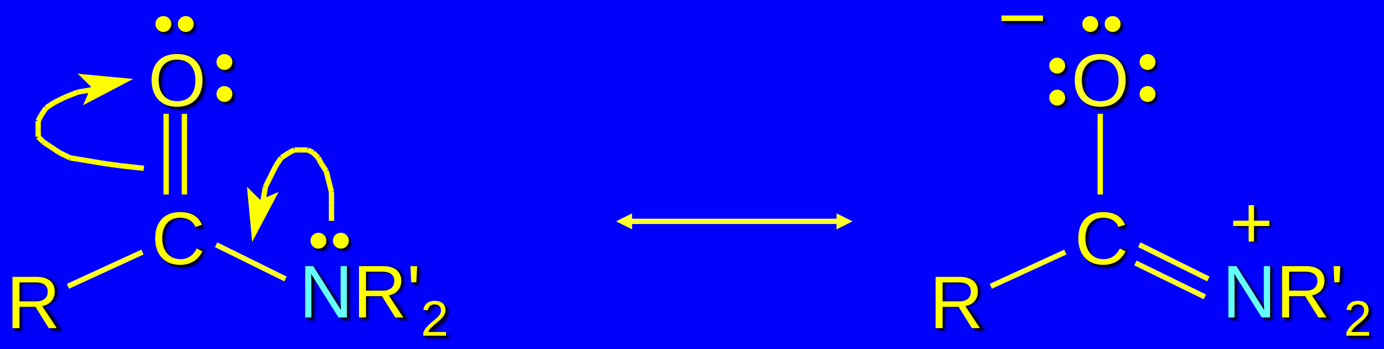


$R\overset{O}{\overset{\|}{C}}SR'$

$R\overset{O}{\overset{\|}{C}}OR'$

most stabilized C=O

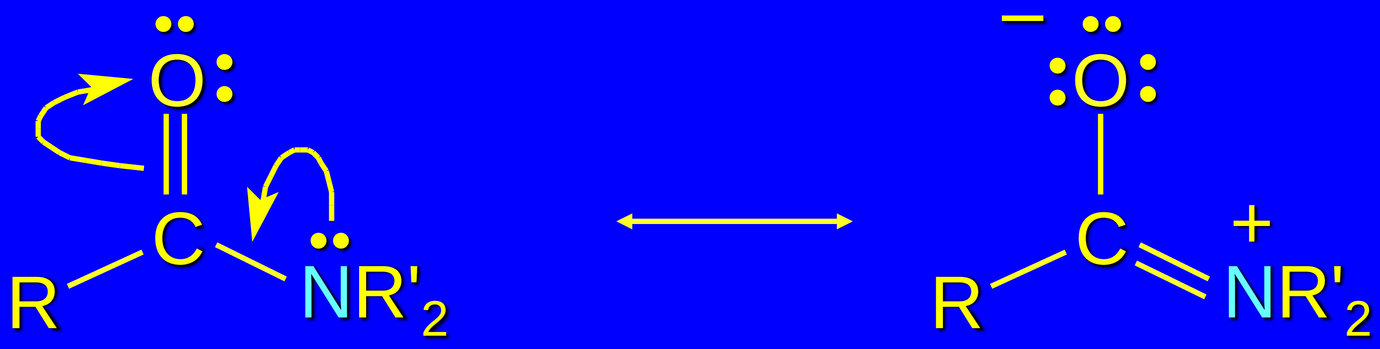
Orbital Overlap in Amides



lone pair donation from nitrogen stabilizes the carbonyl group of an amide

N is less electronegative than O; therefore, amides are stabilized more than esters and anhydrides

Orbital Overlap in Amides

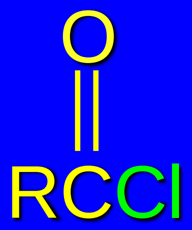


amide resonance imparts significant double-bond character to C—N bond

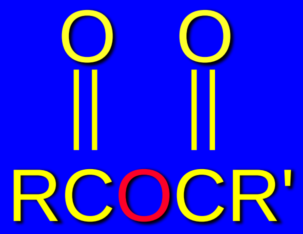
activation energy for rotation about C—N bond is 75-85 kJ/mol

C—N bond distance is 135 pm in amides versus normal single-bond distance of 147 pm in amines

least stabilized C=O



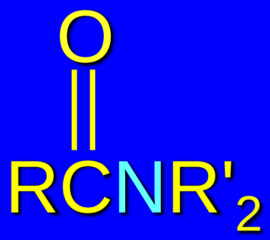
$\mathrm{R}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{Cl}$



$\mathrm{R}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{O}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{R'}$

$\mathrm{R}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{SR'}$

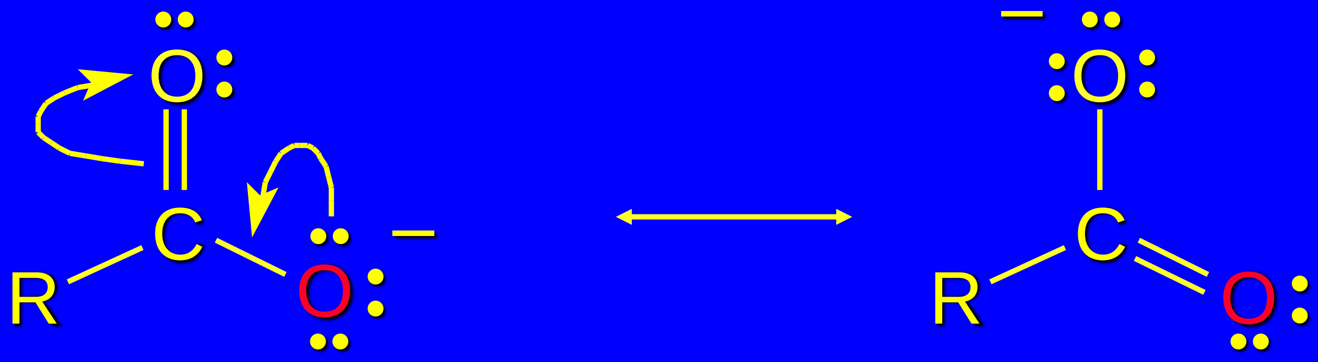
$\mathrm{R}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{OR'}$



$\mathrm{R}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{NR'_2}$

most stabilized C=O

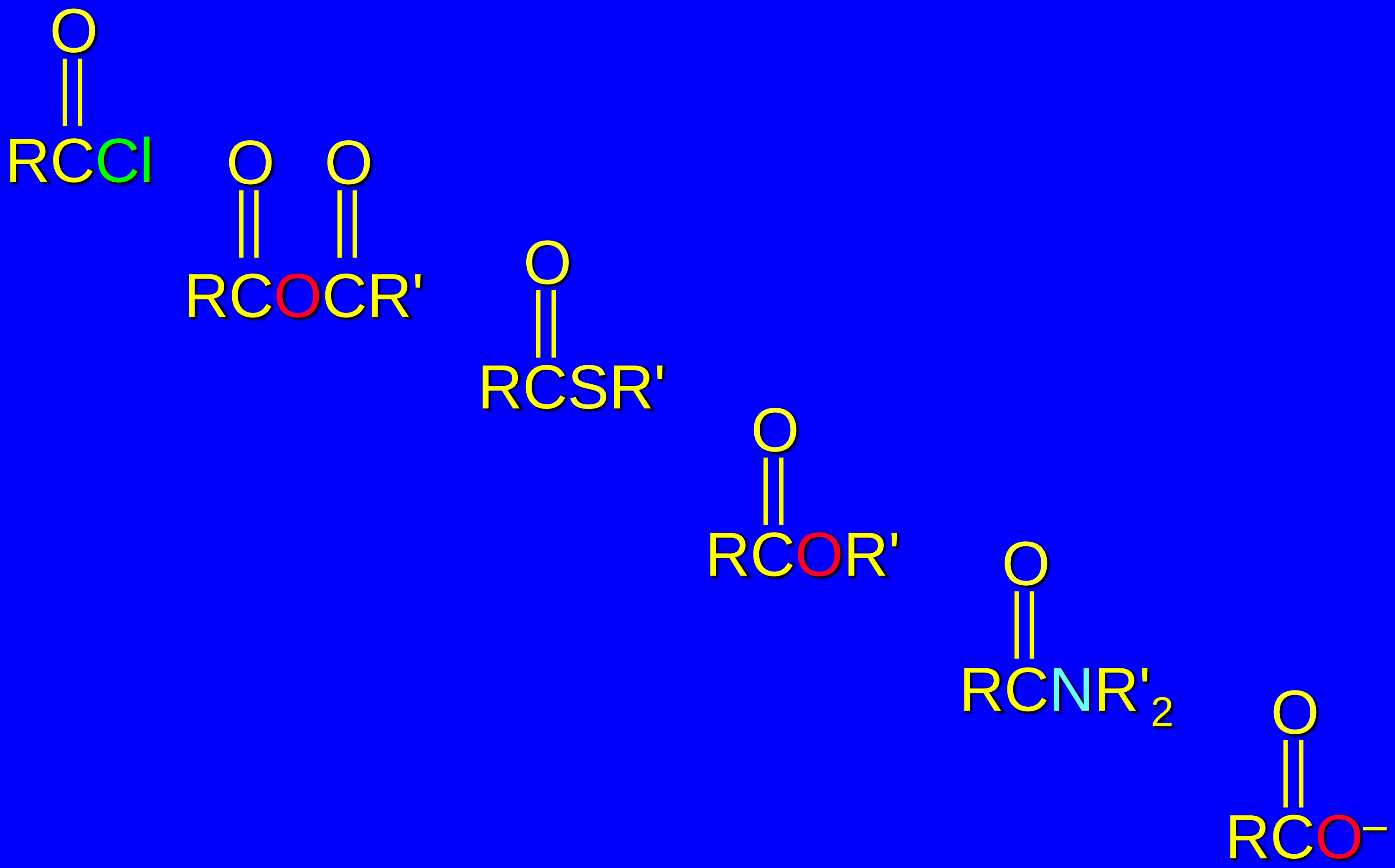
Orbital Overlap in Carboxylate Ions



very efficient electron delocalization and dispersal of negative charge

maximum stabilization

least stabilized C=O



$\mathrm{R\overset{O}{\overset{\|}{C}}Cl}$

$\mathrm{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R'}$

$\mathrm{R\overset{O}{\overset{\|}{C}}SR'}$

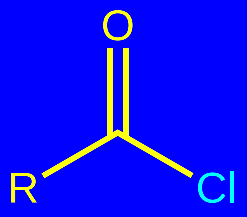
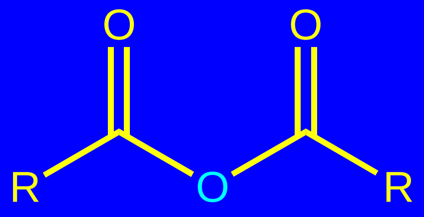
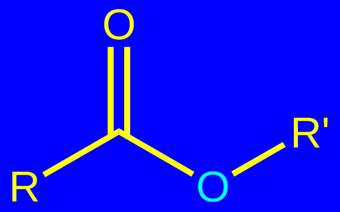
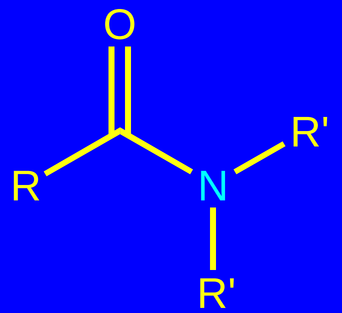
$\mathrm{R\overset{O}{\overset{\|}{C}}OR'}$

$\mathrm{R\overset{O}{\overset{\|}{C}}NR'_2}$

$\mathrm{R\overset{O}{\overset{\|}{C}}O^-}$

most stabilized C=O

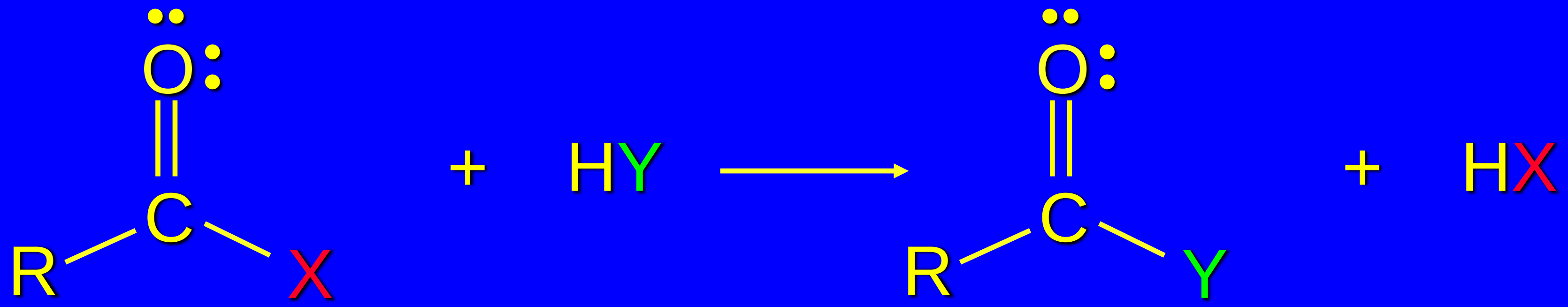
Reactivity is Related to Structure

	Stabilization	Relative rate of hydrolysis
	very small	10^{11}
	small	10^{7}
	moderate	1.0
	large	$<10^{-2}$

The more stabilized the carbonyl group, the less reactive it is.

Nucleophilic Acyl Substitution

In general:

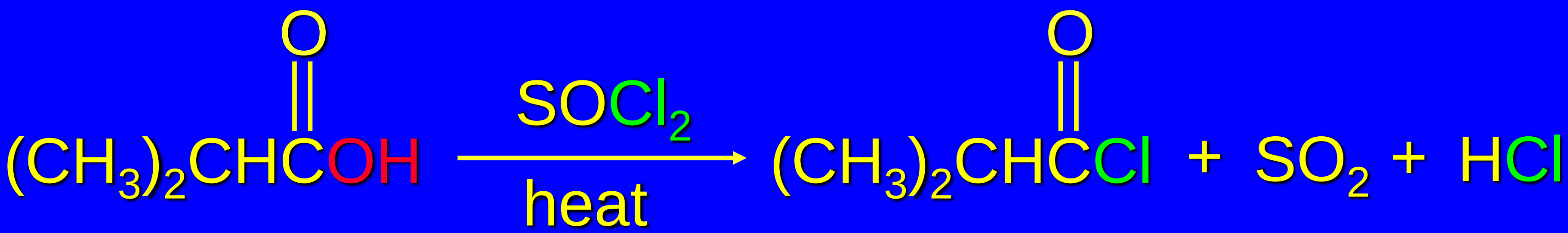


Reaction is feasible when a less stabilized carbonyl is converted to a more stabilized one (more reactive to less reactive).

Nucleophilic Substitution in Acyl Chlorides

Preparation of Acyl Chlorides

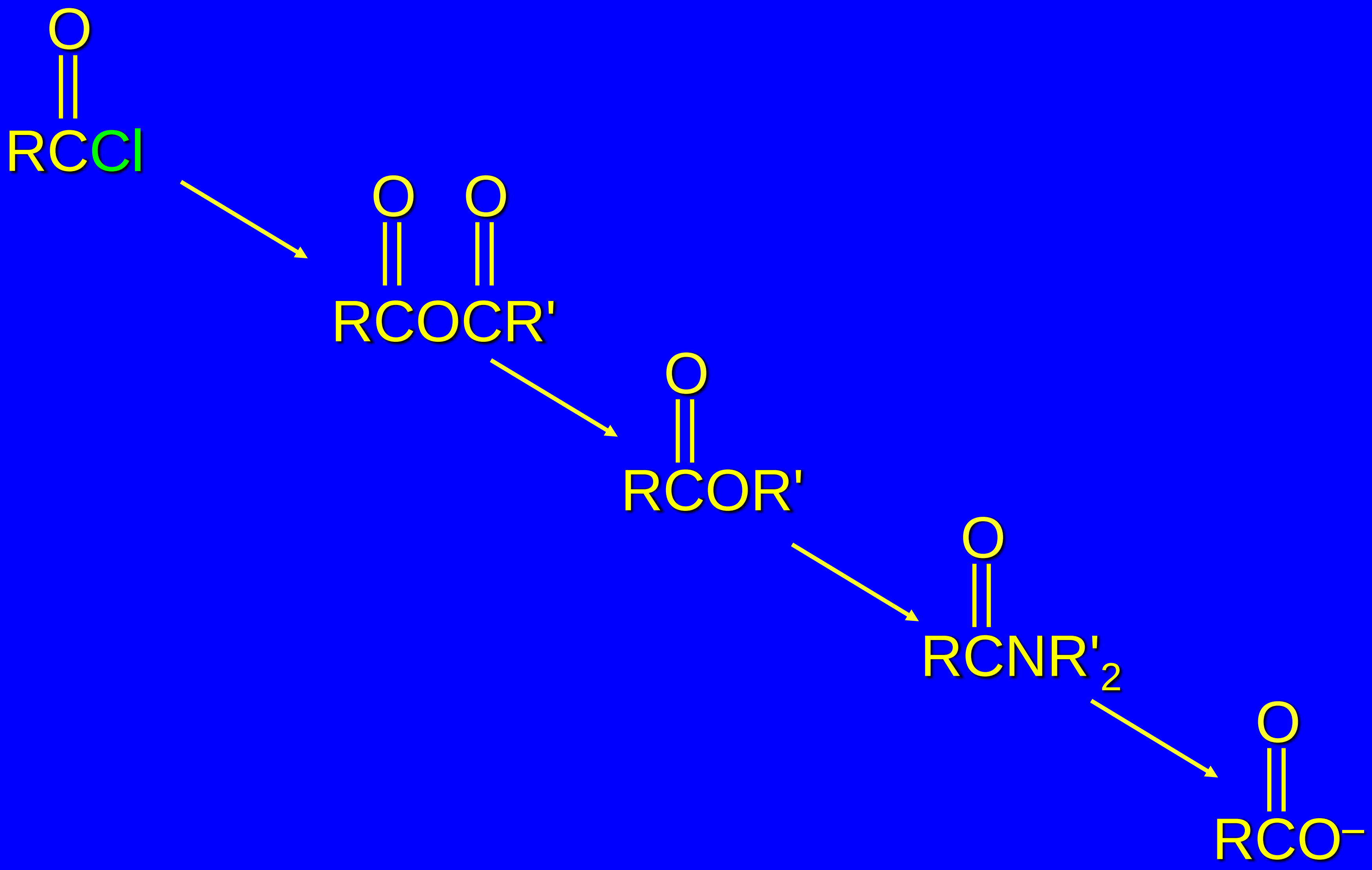
from carboxylic acids and thionyl chloride



$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}OH \xrightarrow[\text{heat}]{SOCl_2} (CH_3)_2CH\overset{\overset{O}{\|}}{C}Cl + SO_2 + HCl$$

(90%)

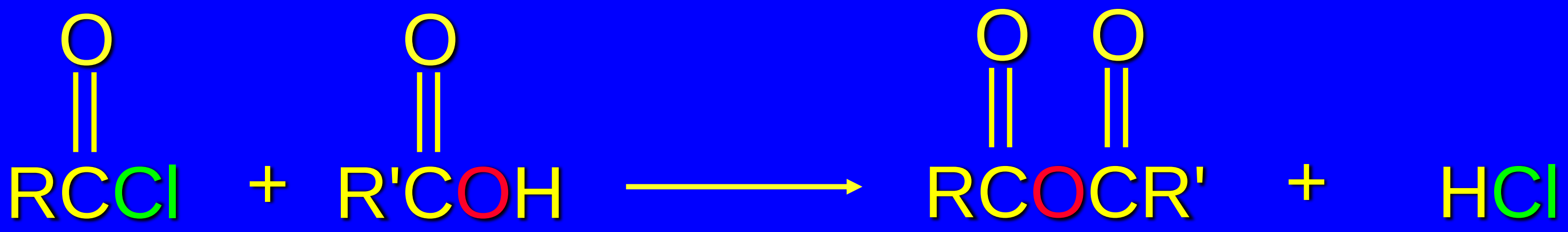
Reactivity and Reactions of Acyl Chlorides



$$R\overset{\overset{O}{\|}}{C}Cl \rightarrow R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R' \rightarrow R\overset{\overset{O}{\|}}{C}OR' \rightarrow R\overset{\overset{O}{\|}}{C}NR'_2 \rightarrow R\overset{\overset{O}{\|}}{C}O^-$$

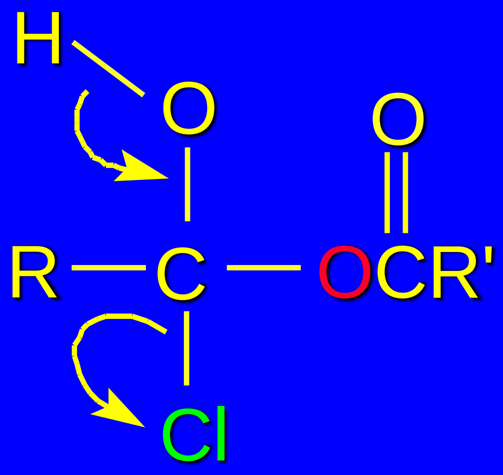
Reactions of Acyl Chlorides

Acyl chlorides react with carboxylic acids to give acid anhydrides:



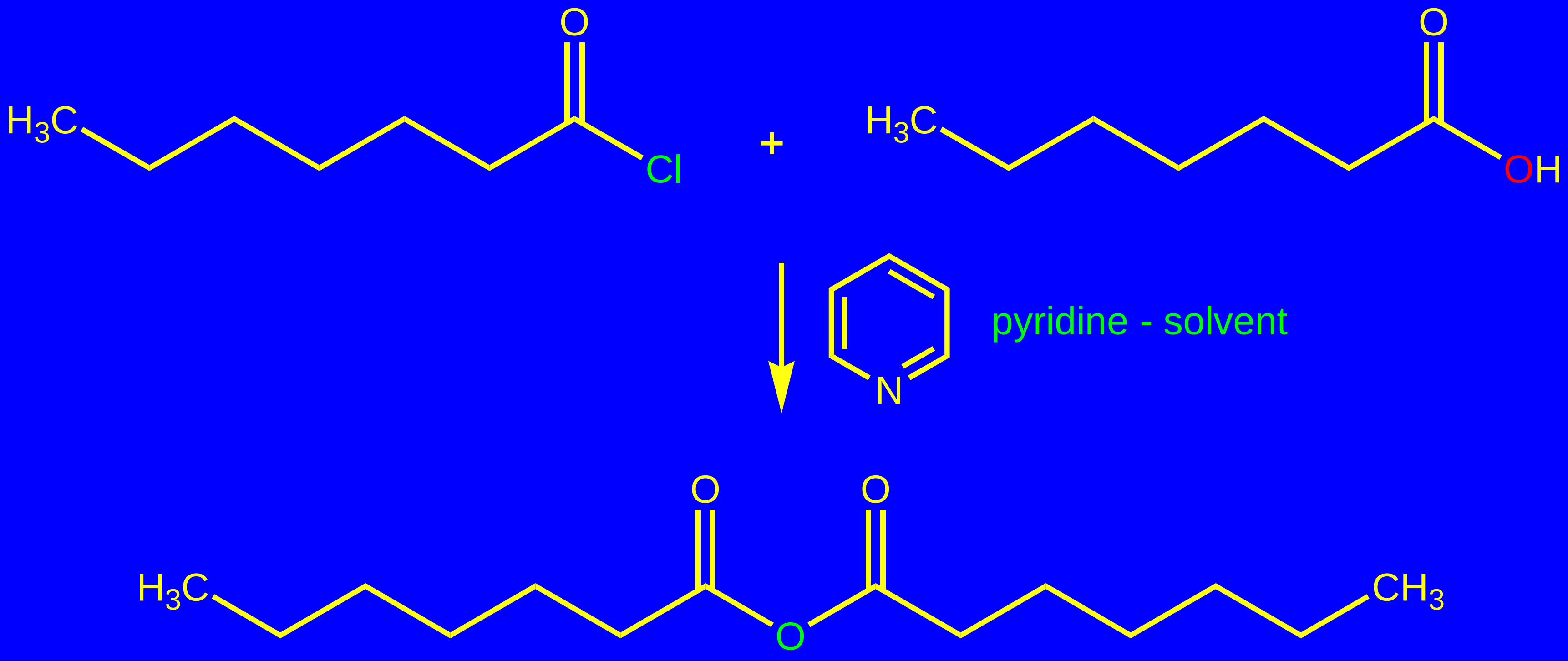
$$\mathrm{R\overset{\overset{O}{\|}}{C}Cl} + \mathrm{R'\overset{\overset{O}{\|}}{C}OH} \longrightarrow \mathrm{R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R'} + \mathrm{HCl}$$

via:



$$\mathrm{R-\underset{\underset{Cl}{|}}{\overset{\overset{HO}{|}}{C}}-O\overset{\overset{O}{\|}}{C}R'}$$

Reactions of Acyl Chlorides - Example

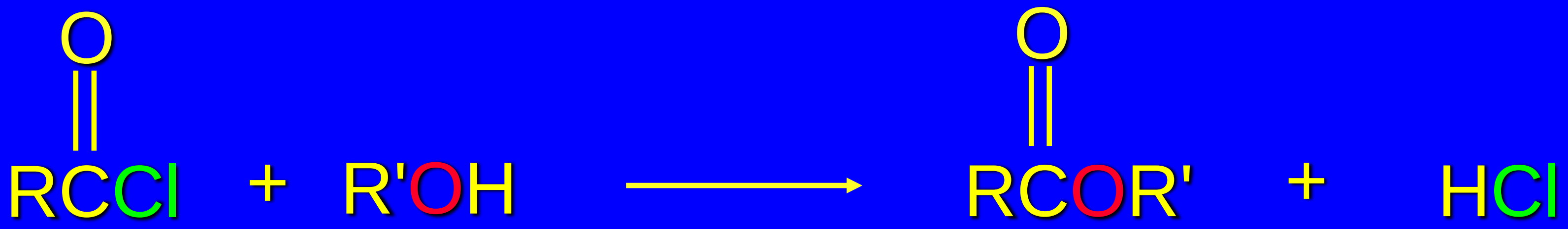


pyridine - solvent

(78-83%)

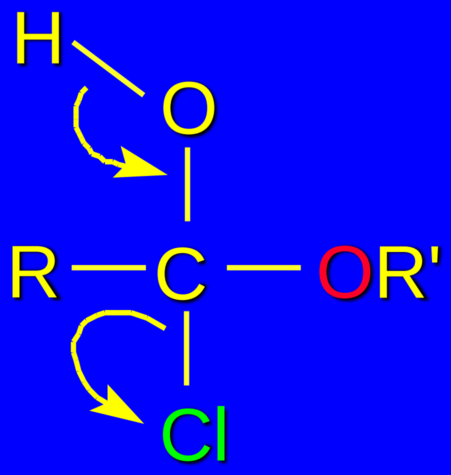
Reactions of Acyl Chlorides with Alcohols

Acyl chlorides react with alcohols to give esters:



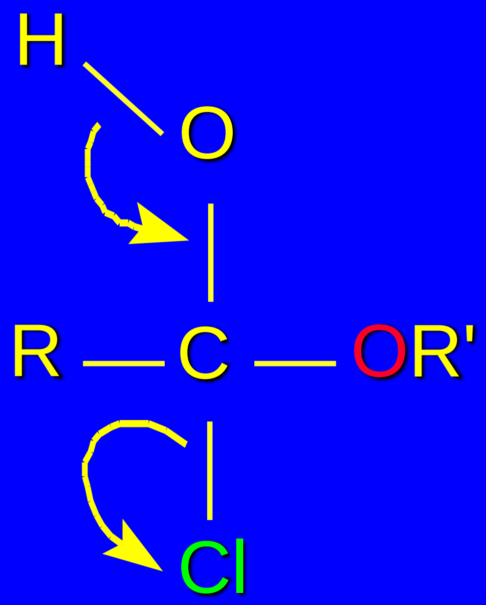
$$R\overset{O}{\overset{\|}{C}}Cl + R'OH \longrightarrow R\overset{O}{\overset{\|}{C}}OR' + HCl$$

via:

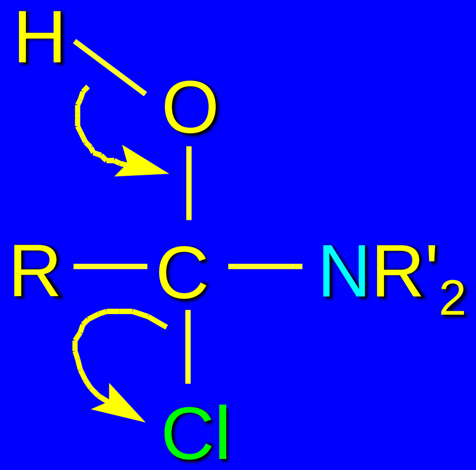


Reactions of Acyl Chlorides

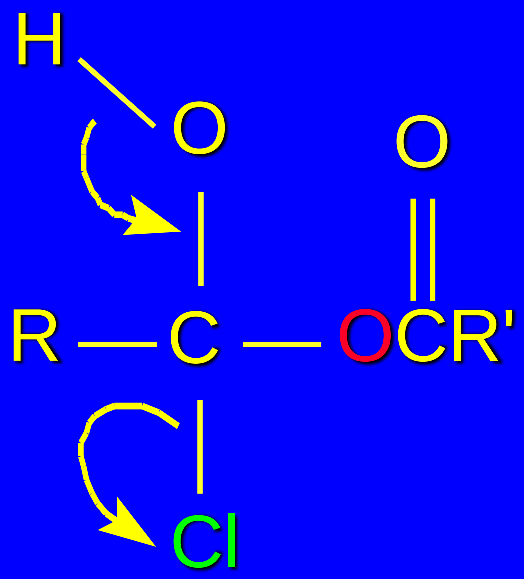
via:



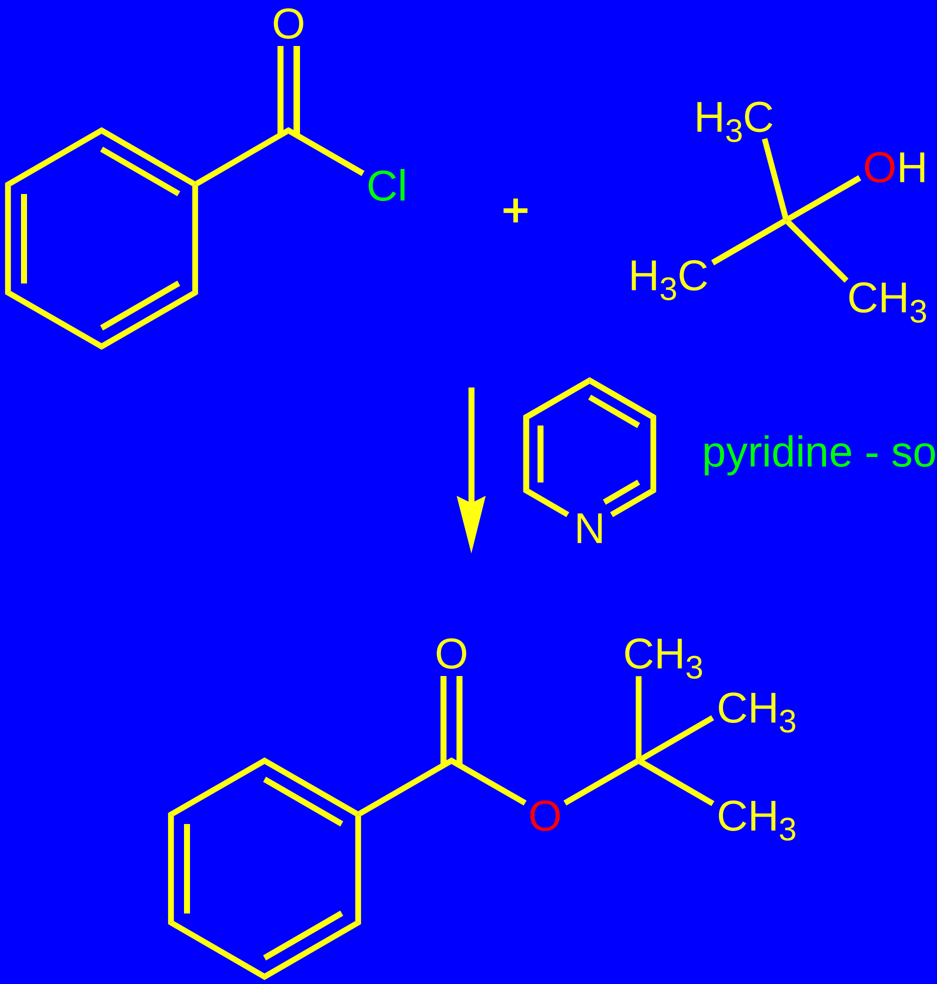
via:



via:



Acylation with Alcohols

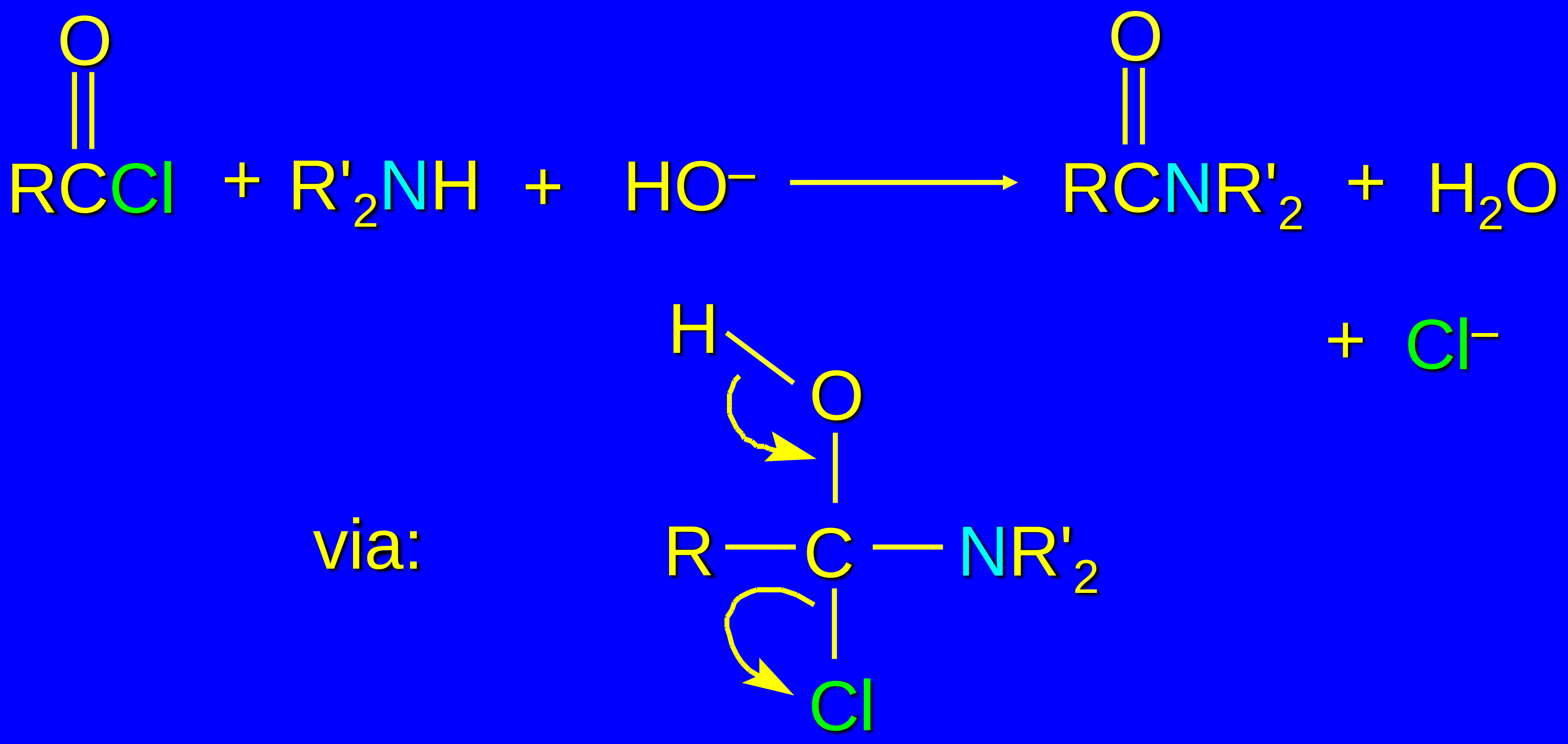


pyridine - solvent

(80%)

Acylation with Amines

Acyl chlorides react with ammonia and amines to give amides:

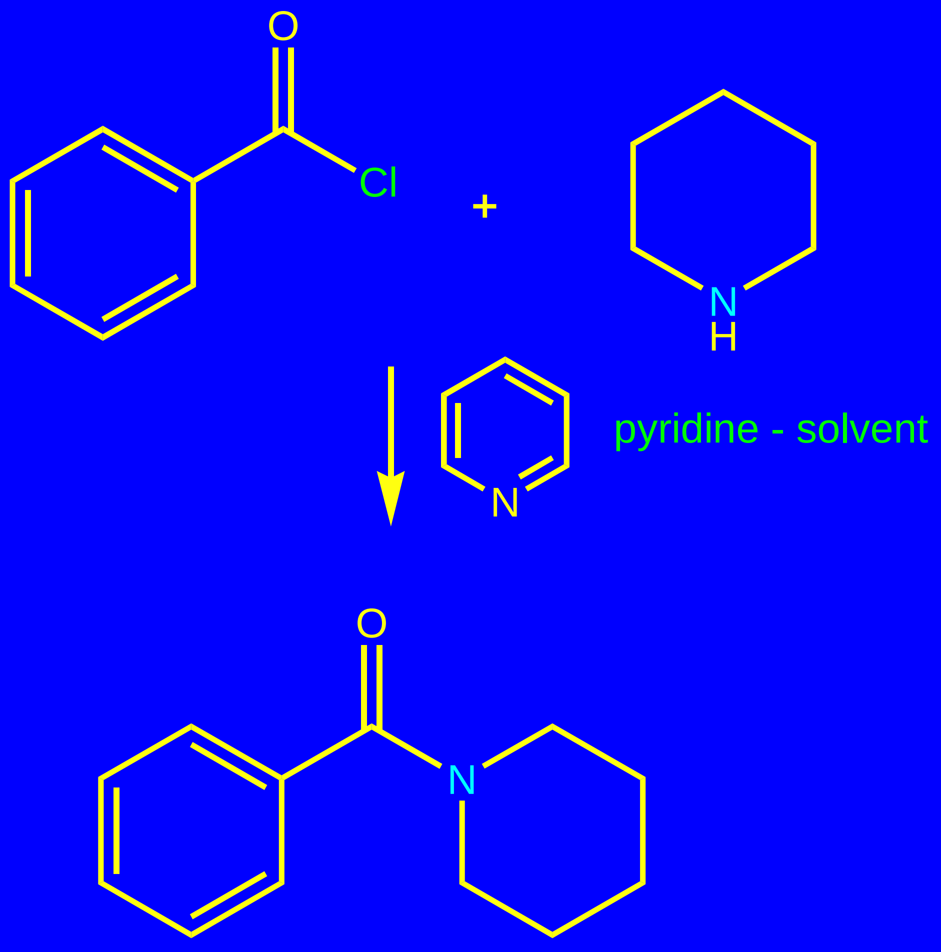


$$\mathrm{R}\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl} + \mathrm{R'_2NH} + \mathrm{HO^-} \longrightarrow \mathrm{R}\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NR'_2} + \mathrm{H_2O} + \mathrm{Cl^-}$$

via:

$$\mathrm{R}-\underset{\displaystyle \mathrm{Cl}}{\overset{\displaystyle \mathrm{HO}}{\mathrm{C}}}-\mathrm{NR'_2}$$

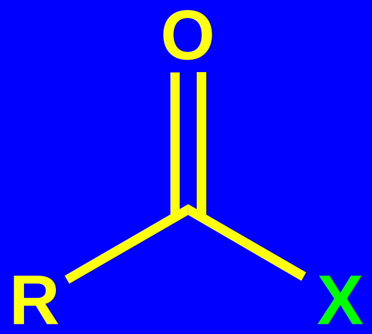
Acylation with Amines - Example



(90%)

Nomenclature of Carboxylic Acid Derivatives

Nomenclature of Acyl Halides

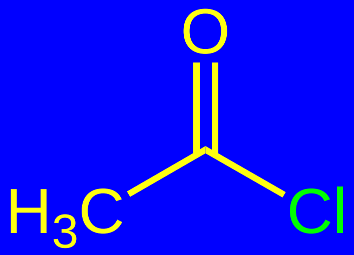


X = Halogen

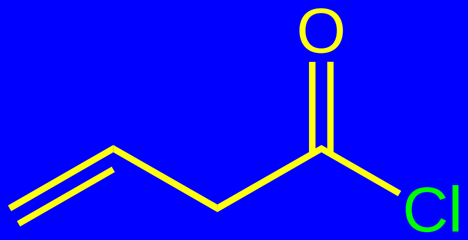
Name the acyl group and add the word *chloride*, *fluoride*, *bromide*, or *iodide* as appropriate.

Acyl chlorides are, by far, the most frequently encountered of the acyl halides

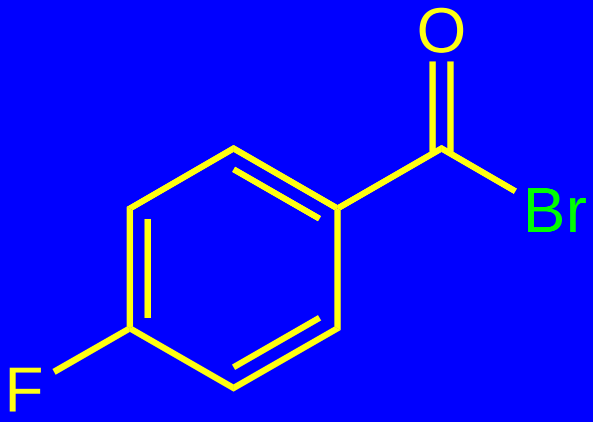
Nomenclature of Acyl Halides - Examples



acetyl chloride

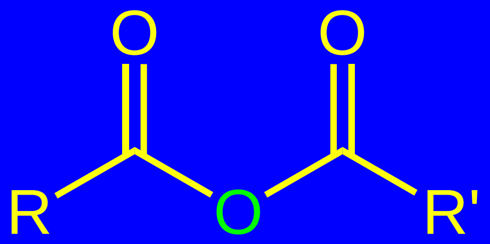


3-butenoyl chloride



p-fluorobenzoyl bromide

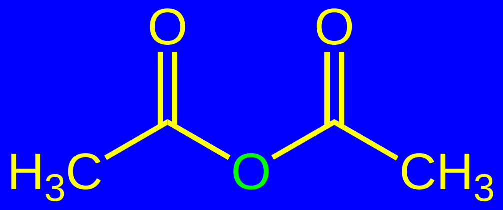
Nomenclature of Acid Anhydrides



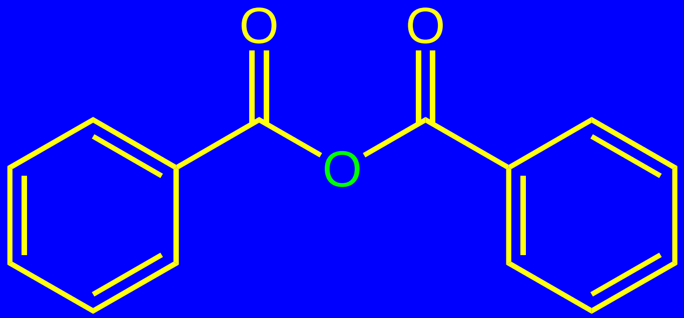
When both acyl groups are the same, name the acid and add the word *anhydride*

When the groups are different, list the names of the corresponding acids in alphabetical order and add the word *anhydride*

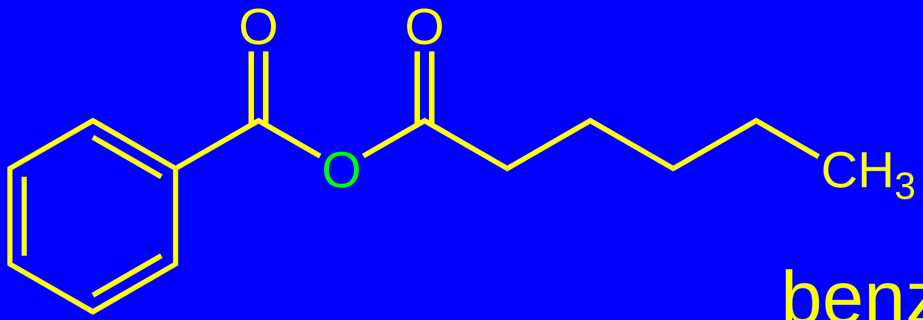
Nomenclature of Acid Anhydrides - Examples



acetic anhydride

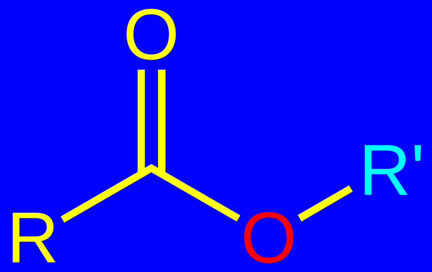


benzoic anhydride



benzoic heptanoic anhydride

Nomenclature of Acid Esters

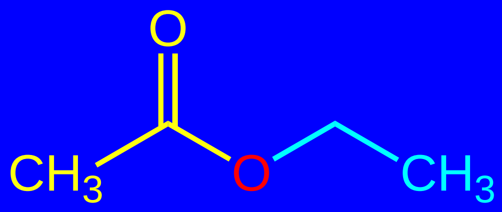


name as *alkyl alkanoates*

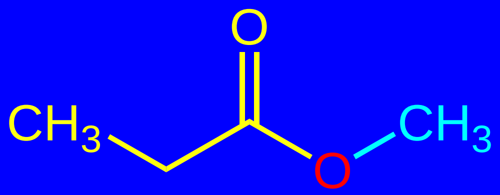
cite the alkyl group attached to oxygen first (R')

name the acyl group second; substitute the suffix *-ate* for the *-ic* ending of the corresponding acid

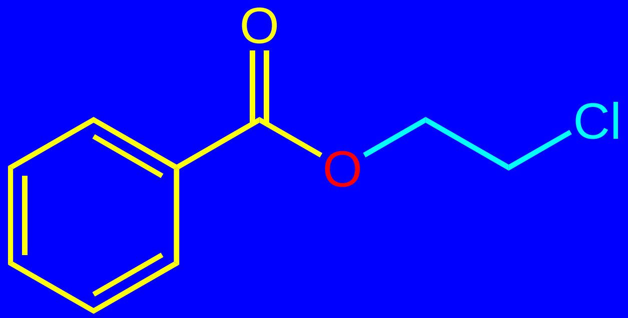
Nomenclature of Acid Esters - Examples



ethyl acetate

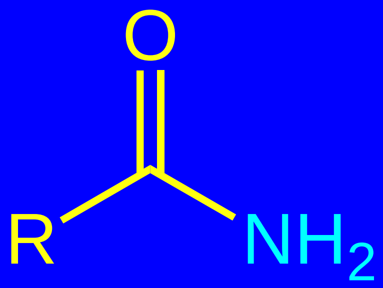


methyl propanoate



2-chloroethyl benzoate

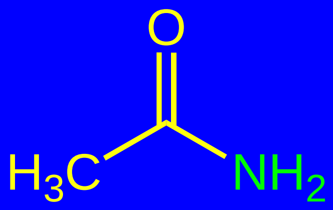
Nomenclature of Primary Amides



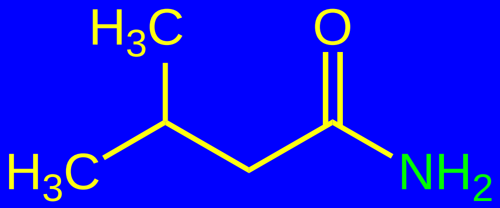
identify the corresponding carboxylic acid

replace the *-ic acid* or *-oic acid* ending by -amide

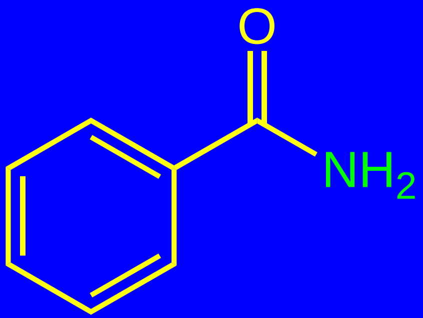
Nomenclature of Primary Amides - Examples



acetamide

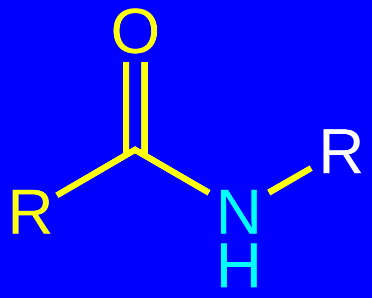


3-methylbutanamide

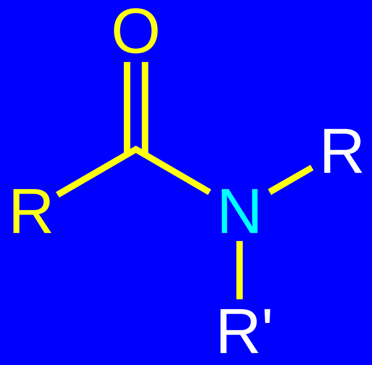


benzamide

Nomenclature of Secondary & Tertiary Amides



and

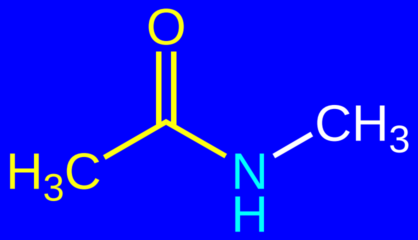


name the amide as before

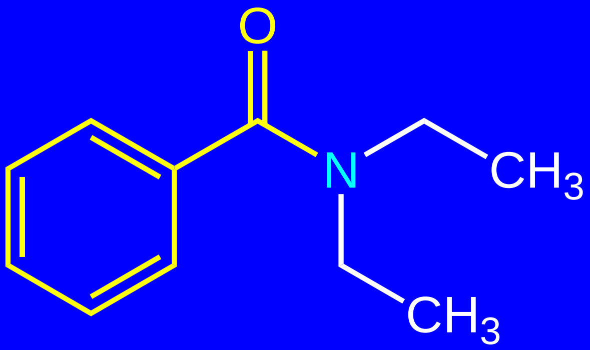
precede the name of the amide with the name of the appropriate group or groups

precede the names of the groups by the letter *N*- (standing for nitrogen and used as a locant)

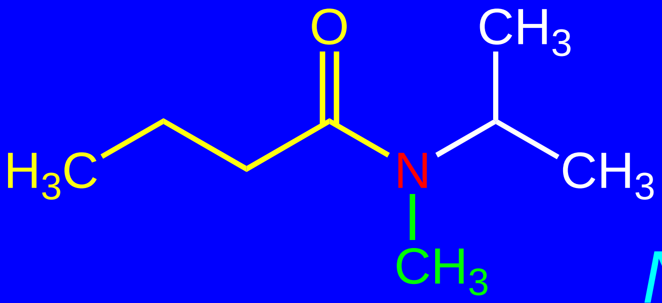
Nomenclature of Secondary & Tertiary Amides



N-methylacetamide



N,*N*-diethylbenzamide



N-isopropyl-*N*-methylbutanamide

Nomenclature of Cyanides

$$R-C\equiv N$$

add the suffix *-nitrile* to the name of the parent hydrocarbon chain (including the triply bonded carbon of CN)

or: replace the *-ic acid* or *-oic acid* name of the corresponding carboxylic acid by *-onitrile*

or: name as an *alkyl cyanide* (functional class name

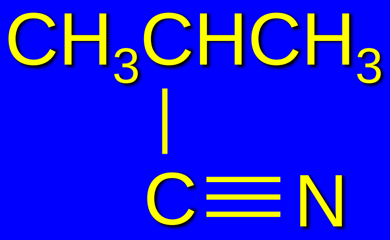
Nomenclature of Cyanides

$CH_3C\equiv N$

ethanenitrile
or: acetonitrile
or: methyl cyanide

$C_6H_5C\equiv N$

benzonitrile



$CH_3\underset{\underset{C\equiv N}{|}}{C}HCH_3$

2-methylpropanenitrile
or: isopropyl cyanide