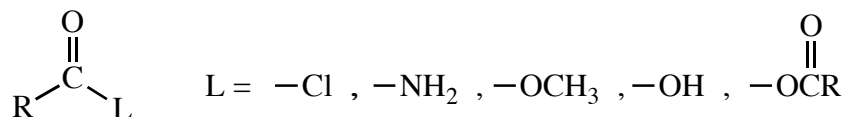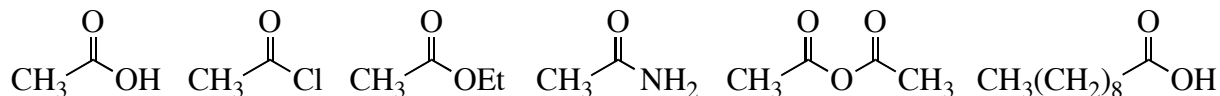Chapter 22 Carboxylic Acids and their Derivatives:
Nucleophilic Acyl Substitution

I. Structure and Physical Properties:

Type 2 carbonyl compounds (carboxylic acids and derivatives) contain the carbonyl group bonded to an atom that has at least one pair of non-bonding electrons.


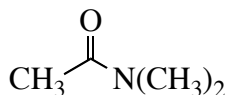$$L = -Cl \ , -NH_2 \ , -OCH_3 \ , -OH \ , -OCR$$

Physical properties:

BP

Sol.
in H_2O

- Both carboxylic acids and 1° and 2° amides can form hydrogen bonds, and therefore have higher bp's and greater solubility that other Type 2 compounds.
- Amides have higher boiling points than carboxylic acids because they have very strong dipole-dipole attractions (the resonance contributor with separated charges contributes significantly to the overall structure of the molecule.)
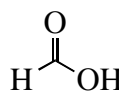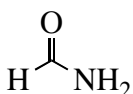
- Tertiary amides have significantly lower boiling points despite the fact that they have higher molecular weights because they cannot form hydrogen bonds.
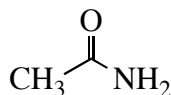
II. Some Famous Type 2 Carbonyl Compounds *(Carboxylic Acid Derivatives):*

cocaine

Novocaine

LSD

Diazepam (Valium)

caffeine

Penicillin G

Phenobarbital

prostaglandin A$_2$

citric acid

benzyl acetate

isopentyl acetate
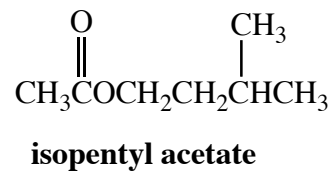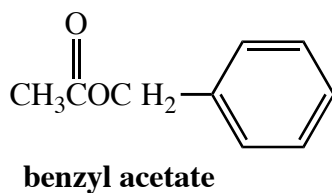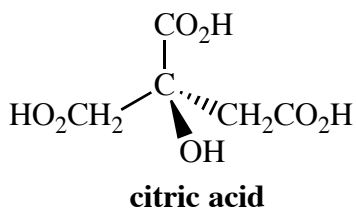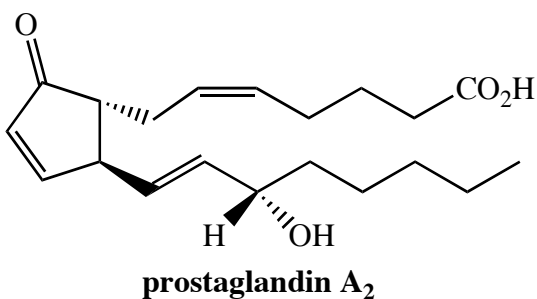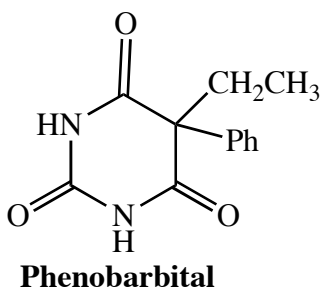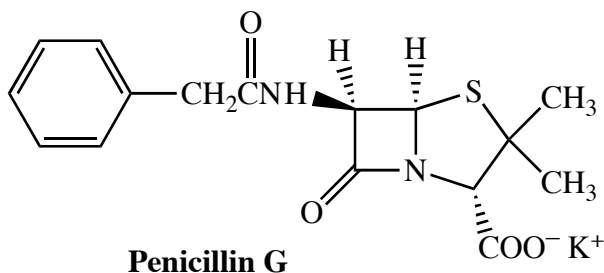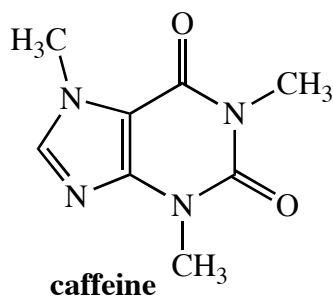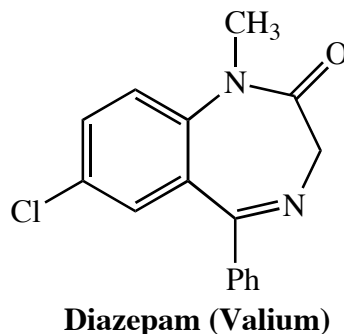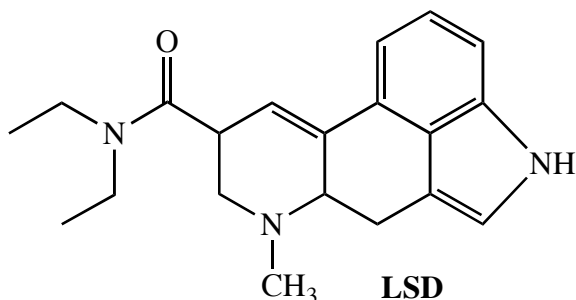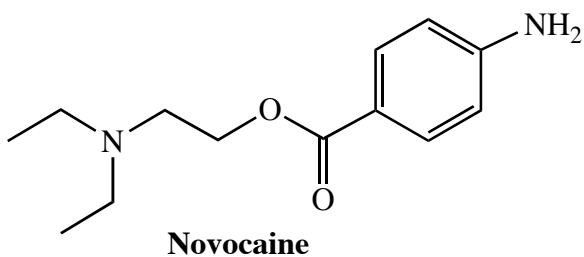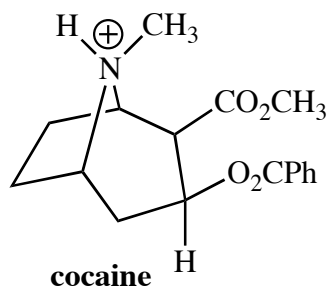
III. Nomenclature (*see handout & podcast*)

IV. Electrophilic Addition Reactions of Type 2 Carbonyl Compounds: Acyl Substitution

As we saw in chapter 20, when powerful nucleophiles add to Type 2 carbonyl compounds, the reaction is irreversible, and the result is acyl substitution.

> Strong Nucleophiles: Organolithium reagents, Grignard reagents, Hydride Reagents, Sodium alkynides

Example:
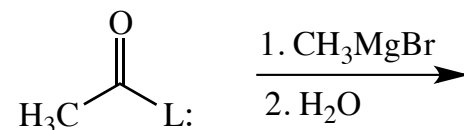
When weaker nucleophiles add to aldehydes & ketones, the reaction is reversible. The acyl substitution product will depend *not only* on the reactivity of the Type 2 carbonyl but also on the leaving group ability of L:

> Weaker Nucleophiles: water, alcohols, 1° and 2° amines, cyanide ion

V. Mechanism and Reactivity in Acyl Substitution Reactions

When a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative, the carbon-oxygen π-bond breaks and a tetrahedral addition intermediate is formed. The lone pair on oxygen then reforms the π-bond, and expels L⁻.
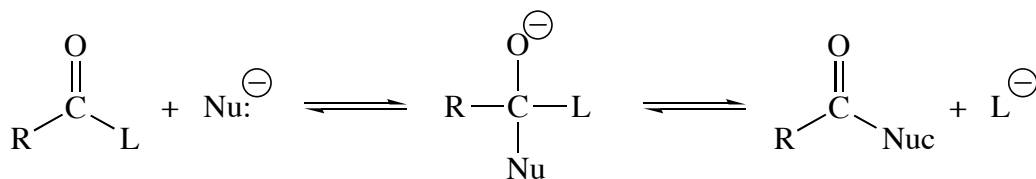
The rate of the reaction depends on two factors:

1. The stability of the carbonyl carbon derivative
2. The leaving group ability of L:-

A. The Stability of the Carboxylic Acid Derivative

The stability, and therefore reactivity of the various carboxylic acid derivatives varies widely, depending on the identity of L.

☛ *The least stable will be the most reactive.*

Recall: The stability is dependent on the concentration of positive charge on the carbonyl carbon, which is dependent on a combination of inductive and resonance effects *(see page 12-14 of the notes).*

Reactivity:

E ↑

_____ Acid Chloride
_____ Anhydride

_____ Ester, Carboxylic Acid
_____ Amide
_____ Carboxylate Anion
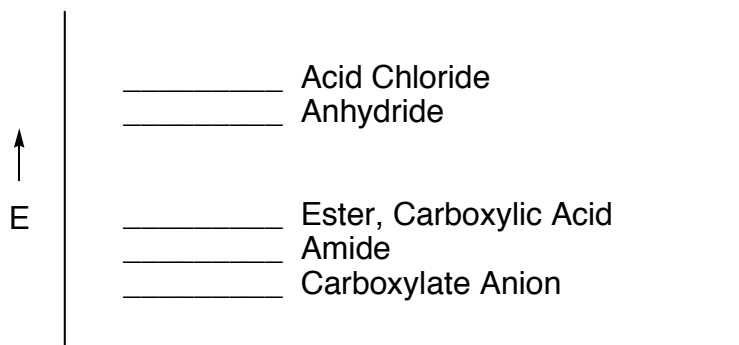
B. The Leaving Group Ability of L:–

The best leaving groups are weak bases ∴ *the weaker the base, the better the leaving group.*

Compare the leaving group abilities of the various carboxylic acid derivatives:

$$CH_3\overset{O}{\underset{}{\|}}Cl \qquad CH_3\overset{O}{\underset{}{\|}}O\overset{O}{\underset{}{\|}}CH_3 \qquad CH_3\overset{O}{\underset{}{\|}}OH \qquad CH_3\overset{O}{\underset{}{\|}}OEt \qquad CH_3\overset{O}{\underset{}{\|}}NH_2$$

pKa
conj.
acid
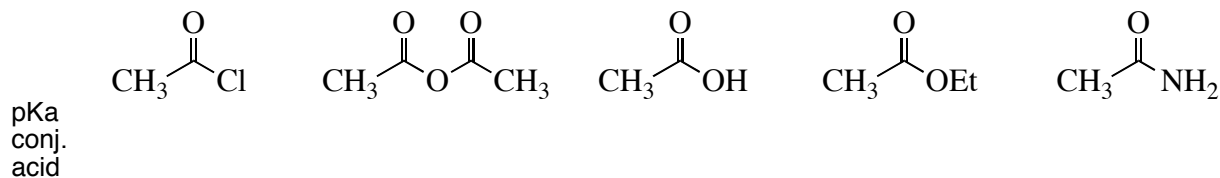
C. The Rate of the Reaction

Going back to the general reaction, we can see the effect that the stability of the carbonyl and leaving group ability has on the rate of the reaction. These two factors tend to operate together.
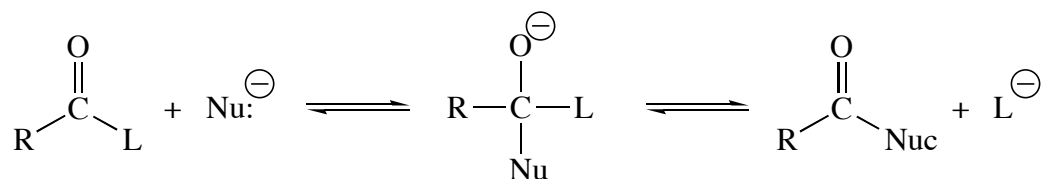
Look at the 1st energy diagram of a reaction in which the reactants and products are of comparable stability, and the transition states for formation and breakdown of the tetrahedral intermediates have the same energies:
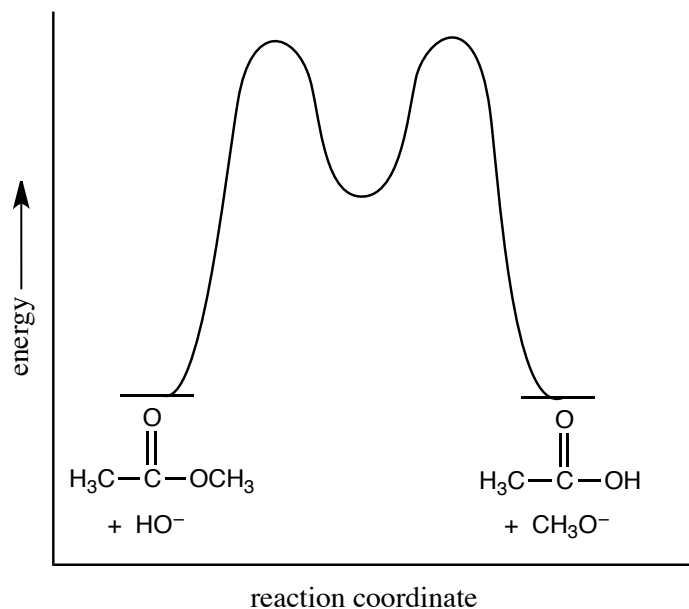
In the 2nd energy diagram, the carbonyl compound is stabilized by resonance and it contains a poor leaving group *(ie. an amide)*. In this graph, the rate of formation and breakdown of the tetrahedral intermediate are decreased, and nucleophilic substitution is slower.

reaction coordinate
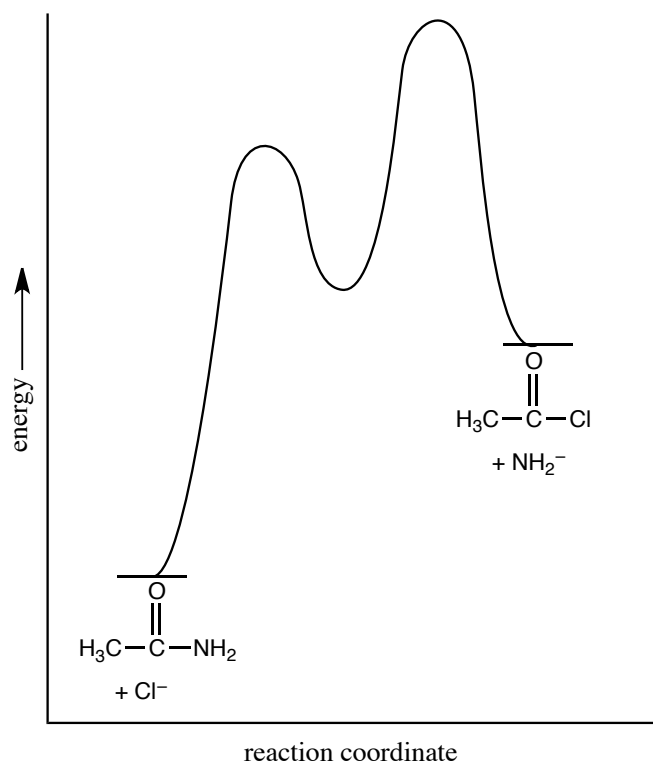
In the 3ʳᵈ energy diagram, the carbonyl compound is unstable and contains a good leaving group *(ie. an acid chloride)*. In this graph, the rates of both formation and breakdown of the tetrahedral intermediate are increased, and nucleophilic substitution is fast.

reaction coordinate
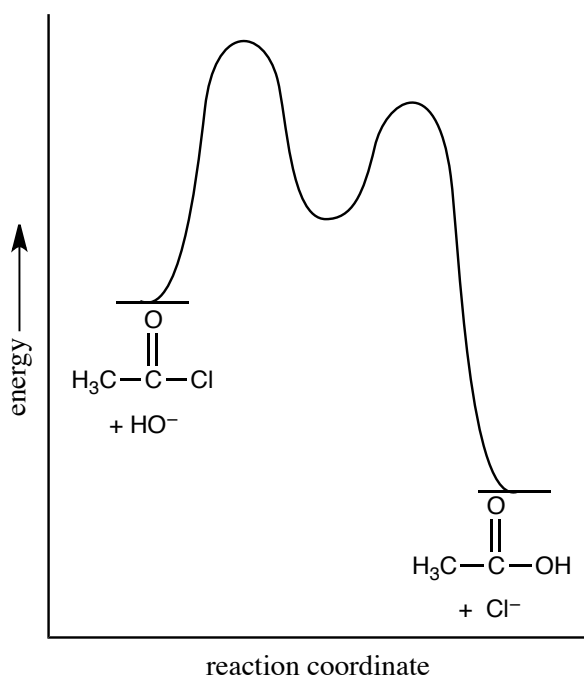
These factors can be summarized:

$$CH_3\overset{O}{\underset{}{\|}}Cl \qquad CH_3\overset{O}{\underset{}{\|}}O\overset{O}{\underset{}{\|}}CH_3 \qquad CH_3\overset{O}{\underset{}{\|}}OH \qquad CH_3\overset{O}{\underset{}{\|}}OEt \qquad CH_3\overset{O}{\underset{}{\|}}NH_2 \qquad CH_3\overset{O}{\underset{}{\|}}O^-$$
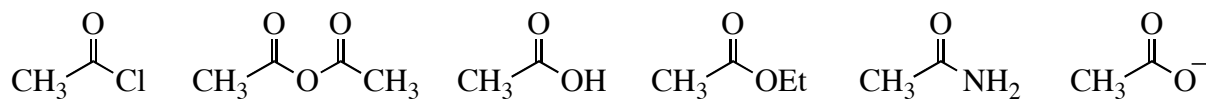
VI. Reactions of Acyl Halides

Being the most reactive, acid halides can easily be converted into all of the other carboxylic acid derivatives by acyl substitution.
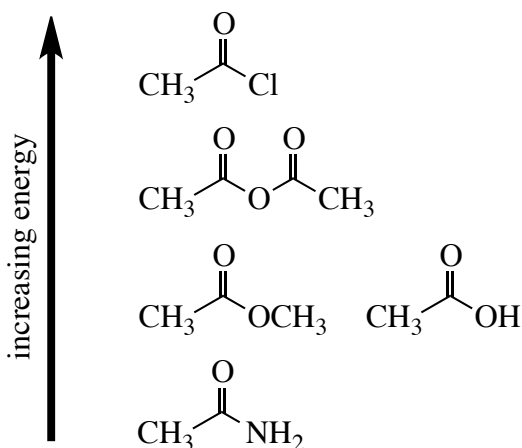
☛ **In general:** *Less* reactive acyl compounds can be easily synthesized from *more* reactive ones. Forming a *more* reactive acyl compound from a *less* reactive one requires **special reagents** or **forcing conditions**.

Examples of acyl substitution with acid chlorides:

$$CH_3\overset{\displaystyle O}{\overset{\|}{C}}Cl \quad + \quad CH_3\overset{\displaystyle O}{\overset{\|}{C}}O^{\ominus} \quad \longrightarrow$$

$$H_3C-\overset{\displaystyle O}{\overset{\|}{C}}-Cl \quad + \quad 2\,CH_3NH_2 \quad \longrightarrow$$
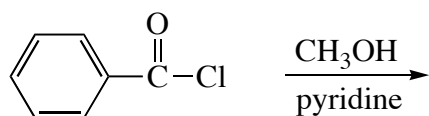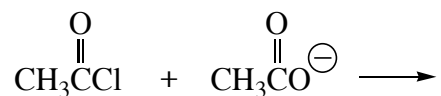
✳✳An extra equivalent of amine is needed in this reaction! *Why??*

- CH_3NH_2 will be protonated in this reaction. $CH_3NH_3{}^+$ is not nucleophilic!
- Reaction will stop at 50% conversion if only one equivalent of amine is used!

Q: Why not just deprotonate with the Cl⁻ generated in the reaction? Then you won't need a second equivalent of amine.

A: Even if you deprotonate with Cl⁻ you will generate HCl, which will react with the amine.

VII. Reactions of Anhydrides

Acid anhydrides are easily converted to esters, carboxylic acids, and amides, but cannot be used to form acid chlorides.
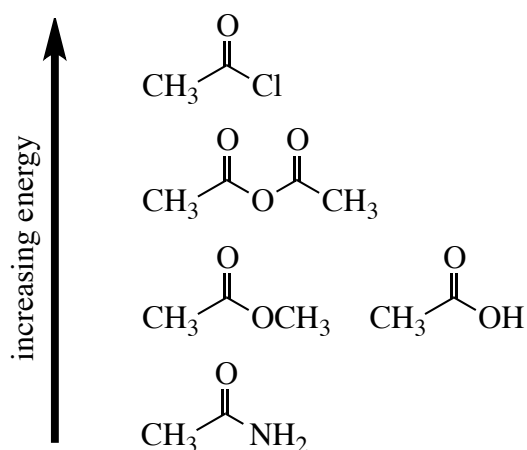
This can't happen:

Examples:

$$CH_3-C(=O)-O-C(=O)-CH_3 \xrightarrow{\ H_2O\ }$$

$$CH_3-C(=O)-O-C(=O)-CH_3 \xrightarrow{\ 2\ NH_3\ }$$
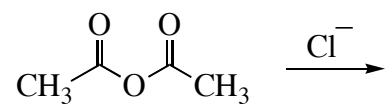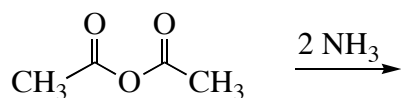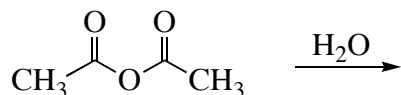
VIII. Reactions of Esters

Esters are easily converted to carboxylic acids, and amides, but cannot be used to form acid chlorides or anhydrides.

increasing energy ↑

$$CH_3-C(=O)-Cl$$

$$CH_3-C(=O)-O-C(=O)-CH_3$$

$$CH_3-C(=O)-OCH_3 \qquad CH_3-C(=O)-OH$$

$$CH_3-C(=O)-NH_2$$
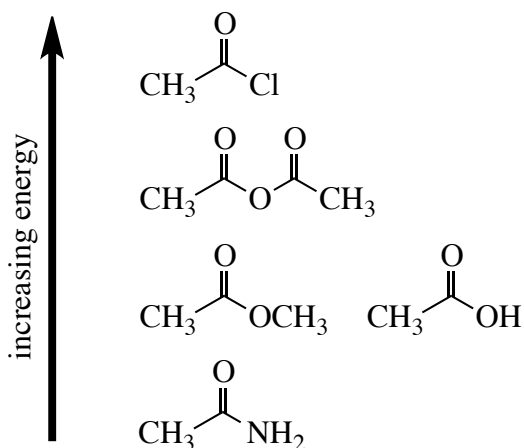
A. Reaction of Esters with Water: Hydrolysis of Esters

The hydrolysis of esters is a very slow reaction because water is a poor nucleophile, and esters have a poor leaving group, RO^-. These reactions are therefore always catalyzed in the lab using *acid* or *base*. Also, because the stability of esters and carboxylic acids are similar, the reaction has to be driven to completion using Le Chatelier's principles.

Acid **catalyzed reaction:**

$$H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3 \quad + \quad H_2O \quad \underset{\xrightarrow{\hspace{2cm}}}{\xleftarrow{\hspace{2cm}}} \quad \overset{H_3O^+}{}$$
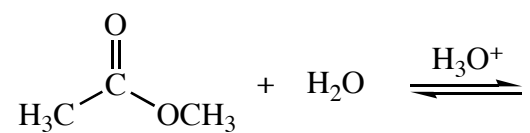
Mechanism:

- In the first step of the mechanism, the carbonyl oxygen is protonated to make it more electrophilic, so that the weak nucleophile, H_2O can attack:

- The reaction is reversible and must be driven to completion. ***How?***

Base **promoted reaction:**

The reaction can also be done using base, and is driven to completion by ***deprotonation of the carboxylic acid*** in the last step. Base promoted hydrolysis of esters is called **Saponification.**

$$H_3C\overset{\overset{\textstyle O}{\|}}{C}OCH_3 \ + \ H_2O \ \underset{\longleftarrow}{\overset{HO^-}{\longrightarrow}}$$
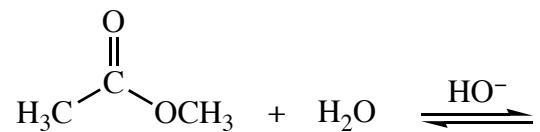
Mechanism:

NOTE!!! Alkoxide ion is a leaving group in this reaction!

Q. ***How*** can an alkoxide act as a L.G???
A. The bond energy of a carbonyl group is so high (179 kcal/mole), that there is a powerful driving force for the expulsion of the alkoxide and the formation of a carbonyl group in this type of reaction.
In an S$_N$2 reaction:

Nu $\overset{\textstyle H}{\underset{\textstyle H}{\underset{H}{C}}}$—OR

Compare with:

$$CH_3CH_2 - \underset{\underset{OH}{|}}{\overset{\overset{O^{\ominus}}{|}}{C}} - OCH_3$$
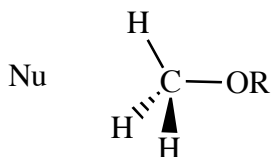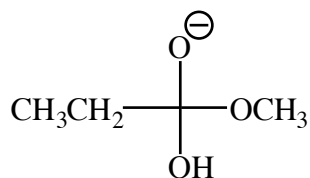
Another reaction where we've seen an alkoxide act as a L.G.:

Q. How do we know that the base-catalyzed mechanism proceeds by this mechanism? Why can't it proceed by direct attack of HO^- on the *alkyl carbon* rather than the *acyl carbon*??

*Possible
Pathway:*

$$H_3C - \overset{\overset{O}{\|}}{C} - O - CH_2CH_3 \xrightarrow{S_N2 \; ??}$$
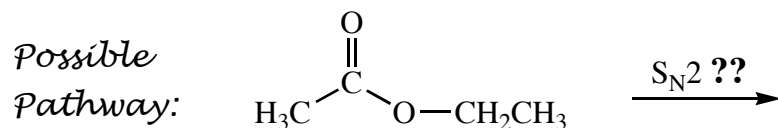
A. There are two clues that eliminate this possible pathway

Clue #1: Labeling studies

$$H_3C - \overset{\overset{O}{\|}}{C} - {}^{18}O - CH_2CH_3 \xrightarrow{HO^-}$$
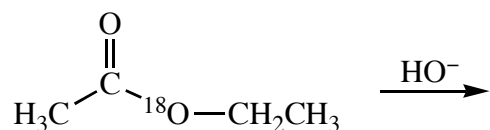
If the mechanism involved direct nucleophilic attack on the alkyl:

$$H_3C - \overset{\overset{O}{\|}}{C} - {}^{18}O - CH_2CH_3 \xrightarrow{HO^-}$$
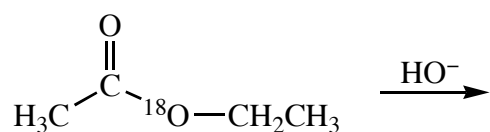
Clue #2: Studies using esters of chiral alcohols

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle R'}{/}}{\underset{\overset{|}{H}}{C}}{\cdots R''} \xrightarrow{\text{NaOH}}$$
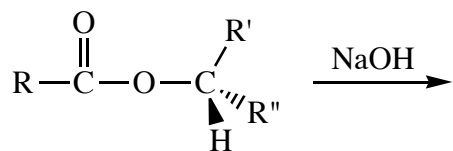
This is consistent with a mechanism involving nucleophilic substitution at the acyl carbon:

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle R'}{/}}{\underset{\overset{|}{H}}{C}}{\cdots R''} \xrightarrow{\text{NaOH}}$$
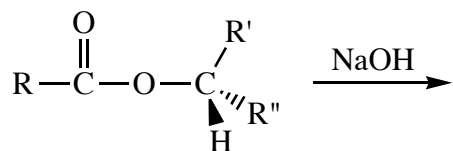
If: The mechanism involved nucleophilic substitution at the alkyl carbon
Then: inversion of configuration would be expected:

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle R'}{/}}{\underset{\overset{|}{H}}{C}}{\cdots R''} \longrightarrow$$
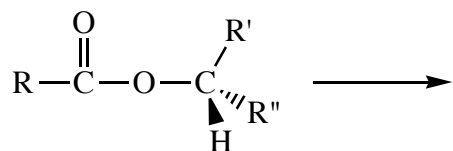
B. Application: Lipid Hydrolysis

The most prevalent naturally occurring esters are triacylglycerols (chapter 10). Triacylglycerols are the lipids that comprise animal fats and vegetable oils.
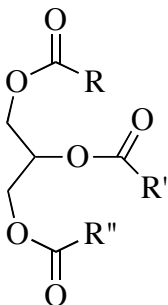
triacylglycerol

Fats & Oils: are hydrolyzed in the body with enzymes called lipases to form glycerol and three fatty acids. In the lab, fats and oils are hydrolyzed in either acid (*to produce fatty acids*) or in base (*to produce carboxylate salts.*)

glycerol   *fatty acids*

glycerol   *carboxylate salts (soaps)*
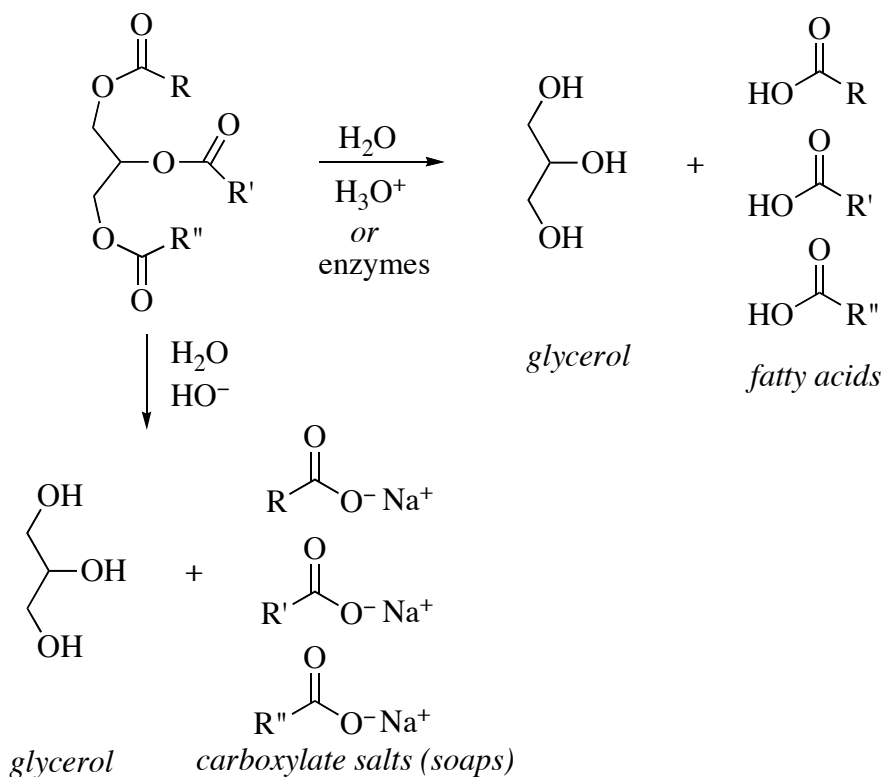
Recall: Soaps are surface-active compounds (*surfactants*), with hydrophilic (*ionic*) heads and hydrophobic tails (≥ *12 carbons in a chain*).

The type of the fatty acid and the length of the carbon chain determines the unique properties of the various soaps. Tallow or animal fats give primarily sodium stearate (*18 carbons*), a very hard, insoluble soap.

sodium stearate
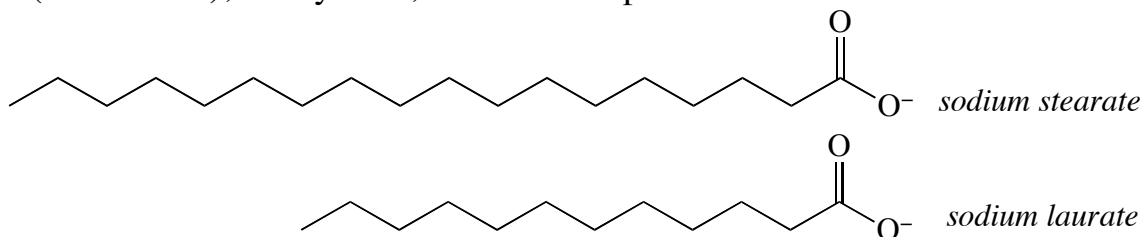
sodium laurate

Fatty acids with longer chains are even more insoluble. Coconut oil is a source of lauric acid which can be made into sodium laurate (*12 carbons*). This soap is very soluble and will lather easily even in seawater. Fatty acids with ten or fewer carbons are not used in soaps because they irritate the skin and have objectionable odors.

Percent Fatty Acids in Triacylglycerols

Fat or oil	saturated		unsaturated		
	palmitic	stearic	oleic	linoleic	other
Animal origin:					
butter	29	9	27	4	31
lard	30	18	41	6	5
beef	32	25	38	3	2
Vegetable origin:					
corn	10	4	34	48	4
soybean	7	3	25	56	9
peanut	7	5	60	21	7
olive	6	4	83	7	-

B. Reaction of Esters with Alcohols: Transesterification

Conversion of one ester into another by reaction of an ester with an alcohol is known as transesterification. Alcohols are poor nucleophiles, so acid or base catalysis must be used. The mechanism is the same as the two ester hydrolysis mechanisms above, except that ROH is used instead of H_2O as a nucleophile.

$$H_2C{=}CH-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3 \quad + \quad CH_3CH_2OH \quad \underset{\triangle}{\overset{TsOH}{\rightleftarrows}}$$
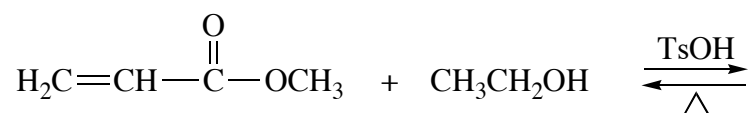
Mechanism:

- The equilibrium must be driven or a mixture of both esters will be obtained! ***How?***

C. Reaction of Esters with Amines: Aminolysis

Esters can be converted into amides by treatment with amines. Since amines are good nucleophiles, the reaction is ***not*** catalyzed by acid or base. The reaction can be driven to completion by using excess amine, or distilling off the alcohol as it is formed. The mechanism is addition/elimination.
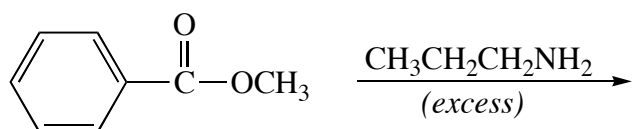
IX. Reactions of Carboxylic Acids

You may predict that carboxylic acids could be easily converted to esters using acid/base catalysis *(this is simply the reverse of hydrolysis of an ester – you just have to drive the equilibrium the other way)*, and that they could easily be converted into amides. The only reaction that works is acid-catalyzed esterification!

Problem:
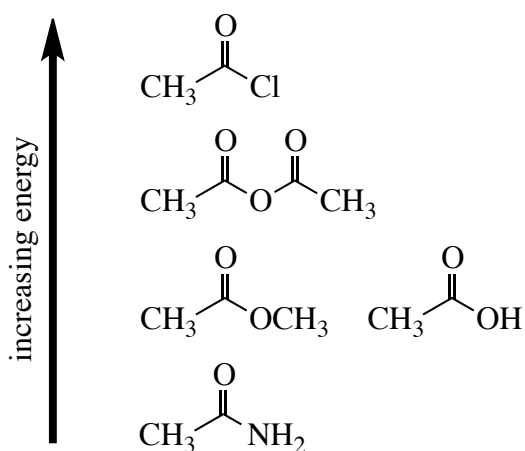
✱ Carboxylic acids, in the presence of base, are deprotonated to make a carboxylate anion, which is the *least electrophilic* of all the carboxylic acid derivatives!

$$H_3C-\overset{\overset{O}{\|}}{C}-O-H \quad + \quad NH_3 \quad \longrightarrow$$

✱ Even if excess NH_3 is used, it is *not* nucleophilic enough to attack the very stable carboxylate anion.
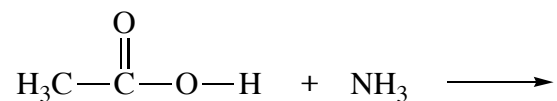
A. Acid Catalyzed Esterification

Carboxylic acids do undergo acid-catalyzed reaction with alcohols to form esters. The reaction is also known as **Fischer esterification**.

$$C_6H_5-\overset{\overset{O}{\|}}{C}-OH \quad + \quad CH_3OH \quad \underset{\longleftarrow}{\overset{H_3O^+ (cat)}{\longrightarrow}}$$
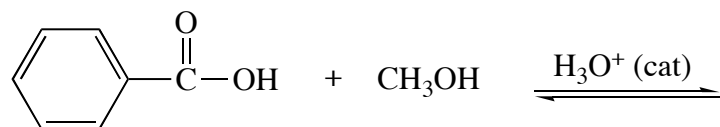
Mechanism:

☛ The reaction is reversible and must be driven to completion (the reverse reaction is *acid catalyzed hydrolysis of an ester*.

To favor esterification of an acid:

To favor hydrolysis of an ester:

B. Conversion of Carboxylic Acids into Acid Chlorides

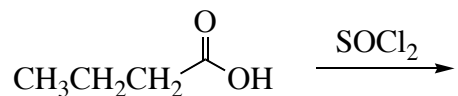The last reaction you would expect carboxylic acids to undergo is conversion into acid chlorides, since acid chlorides are so much less stable than carboxylic acids. If you imagine the tetrahedral intermediate formed when chloride ion attacks a carboxylic acid, chloride ion will be eliminated since it is the best leaving group.

But wait! A carboxylic acid has an –OH group, and we saw in Chapter 9 that OH groups could be converted into good leaving groups by treatment with reagents such as $SOCl_2$, and PBr_3. These same reagents react with carboxylic acids to form acid halides.

$$CH_3CH_2CH_2 \overset{\displaystyle O}{\underset{}{\|}}{\!\!\!-\!\!} OH \xrightarrow{SOCl_2}$$

How?

$$CH_3CH_2CH_2 \overset{\overset{\displaystyle O}{\|}}{C} OH \quad \xrightarrow[\text{(or } PCl_3\text{)}]{PBr_3}$$
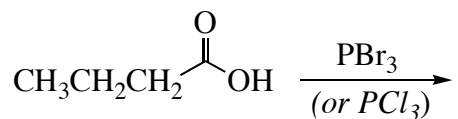
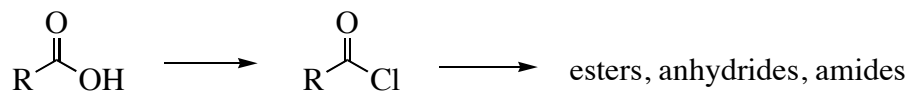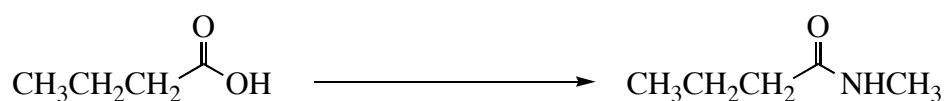★ *So, indirectly, carboxylic acids can be converted into every carboxylic acid derivative by first converting them into acid halides!*

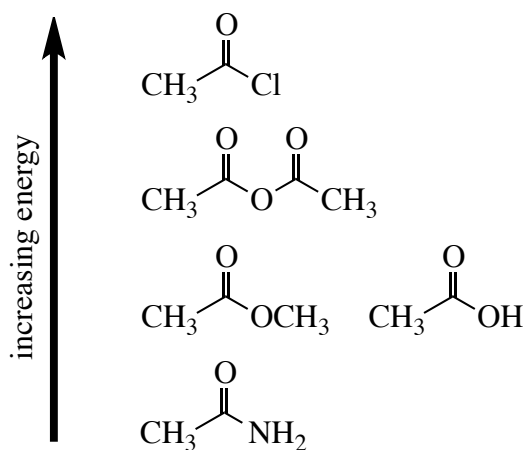$$R \overset{\overset{\displaystyle O}{\|}}{C} OH \quad \longrightarrow \quad R \overset{\overset{\displaystyle O}{\|}}{C} Cl \quad \longrightarrow \quad \text{esters, anhydrides, amides}$$

Example from a previous exam:

$$CH_3CH_2CH_2 \overset{\overset{\displaystyle O}{\|}}{C} OH \quad \longrightarrow \quad CH_3CH_2CH_2 \overset{\overset{\displaystyle O}{\|}}{C} NHCH_3$$

X. Reactions of Amides

Here we are at the bottom of the barrel. Can amides be converted into any other carboxylic acid derivatives, since all of them are less stable than amides? They don't react with halide ions or carboxylate ions, but *will* react with water and alcohols using strong acid catalysis and heat.

increasing energy ↑

$$CH_3 \overset{\overset{\displaystyle O}{\|}}{C} Cl$$

$$CH_3 \overset{\overset{\displaystyle O}{\|}}{C} O \overset{\overset{\displaystyle O}{\|}}{C} CH_3$$

$$CH_3 \overset{\overset{\displaystyle O}{\|}}{C} OCH_3 \quad CH_3 \overset{\overset{\displaystyle O}{\|}}{C} OH$$

$$CH_3 \overset{\overset{\displaystyle O}{\|}}{C} NH_2$$

A. Acid Catalyzed Hydrolysis of Amides

$$R - \overset{\overset{\displaystyle O}{\|}}{C} - NH_2 \quad \xrightarrow[\text{H}_2\text{O}]{\text{H}_3\text{O}^+}$$
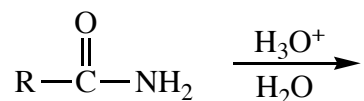
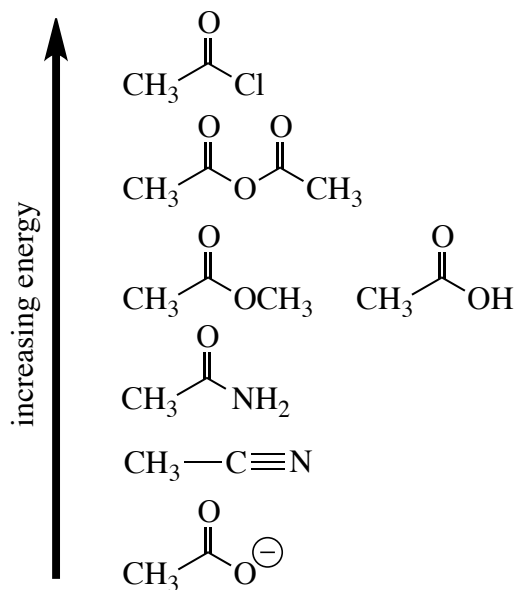**Mechanism:**

B. Acid Catalyzed Esterification
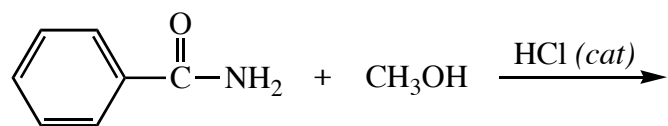
XI. Reactions of Nitriles

Nitriles are considered carboxylic acid derivatives, because, like all Type 2 compounds, they react with water to form carboxylic acids.

    Q. How reactive are nitriles?

    A. Nitriles are less reactive than amides. Reactions in base are slower because nitrogen is less electronegative than oxygen and accepts electrons less readily. Nitriles are less reactive in acid because they are so much less basic. Nitriles hydrolyze even more slowly than amides.

increasing energy →

$$CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-Cl$$

$$CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-O-\underset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

$$CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-OCH_3 \qquad CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-OH$$

$$CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-NH_2$$

$$CH_3-C\equiv N$$

$$CH_3-\underset{\overset{\displaystyle O}{\|}}{C}-O^{\ominus}$$

Nitriles hydrolyze in the presence of acid or base to produce carboxylic acids. They have to be heated higher than amides because they are less reactive than amides.

Acid catalyzed reaction:

$$R-C\equiv N \xrightarrow[\text{H}_2\text{O},\,\Delta]{\text{H}_3\text{O}^+}$$
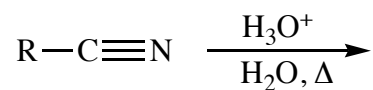
Mechanism:

Base catalyzed mechanism: (*see page 866 in text*)

Because nitriles can be prepared from the reaction of an alkyl halide with cyanide ion, we now have a synthesis of carboxylic acids from alkyl halides. Notice the carboxylic acid has one more carbon than the alkyl halide.
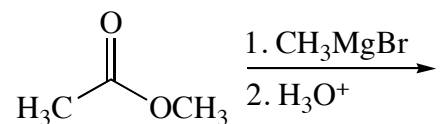
$$CH_3CH_2Br \quad \xrightarrow{\overset{\ominus}{:}C\equiv N} \qquad\qquad \xrightarrow[\Delta]{HCl,\ H_2O}$$
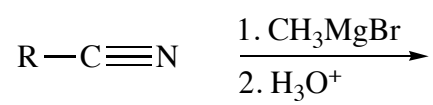
Another way to do this:

XII. Irreversible Addition Reactions of Type 2 Carbonyl Compounds

Notice that most of the reactions we have done in this chapter involve weaker nucleophiles that do reversible addition reactions. Powerful nucleophiles, on the other add to carbonyl compounds irreversibly. Using what you learned in chapter 20, we can now make predictions about what will happen with nitriles, the newest Type 2 carbonyl:
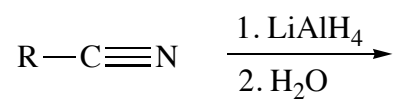
Review reaction: (*reason through it*)

$$H_3C\overset{\overset{\textstyle O}{\|}}{\quad}OCH_3 \quad \xrightarrow[2.\ H_3O^+]{1.\ CH_3MgBr}$$

New reaction: (*predict what the product will be*)

$$R-C\equiv N \quad \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr}$$
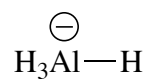
Mechanism for imine conversion into ketone:

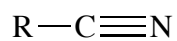New reaction: (*predict what the product will be*)

$$R-C\equiv N \quad \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4}$$

Don't use book mechanism for this reaction!

Problems with book mechanism:

2nd edition:

$$R-C\equiv N$$

$$\overset{\ominus}{H_3Al}-H$$

3rd & 4th edition:

$$R-C\equiv N$$

$$\overset{\ominus}{H_3Al}-H$$
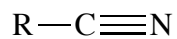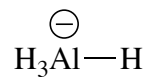
If you want to stop at one addition**, use DIBAL-H:**

$$R-C\equiv N \quad \xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. DIBAL-H}}$$