16: Addition and Substitution Reactions of Carbonyl Compounds

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***Author's Note**: You may think of some additional topics that could be in Chapters 16-19. These were the last Chapters I wrote in preliminary draft form prior to my retirement from UC Riverside in July 1998. I have decided to edit those drafts and post them without adding additional content. I may revisit these later and add more material as appropriate.*

16.1 Carbonyl Groups React with Nucleophiles

Reactions of nucleophiles with carbonyl groups are among the most important reactions in organic chemistry. They are widely used in organic synthesis to make C-C bonds, and we will see them in fundamental bioorganic reactions of carbohydrates, proteins, and lipids.

Overview (16.1A)

The nucleophiles can be neutral or negative (Nu: or $Nu:^-$), and they attack the positively polarized carbon atoms of C=O groups as we show for a negative nucleophile ($Nu:^-$) in the general reaction in Figure 16.001.

Figure 16.001

We have already described some of these reactions in earlier chapters that introduce the various classes of carbonyl compounds. This chapter is a unified presentation of these reactions, along with their mechanisms. It also includes reactions of nucleophiles with C=N and C≡N bonds since they are mechanistically similar to those of the C=O groups.

Addition and Substitution (16.1B)
We broadly classify the overall reactions of nucleophiles with C=O groups as **nucleophilic acyl addition** or **nucleophilic acyl substitution**.

Addition Reactions. In *nucleophilic acyl addition* reactions, the nucleophile binds to the C of the C=O group giving a product where the sp^2 C of the C=O group (with three attached atoms) is transformed into an sp^3 C (with four attached atoms). The C=O bond becomes a C-O bond and more specifically C=O often becomes C-OH as we illustrate in the general example in Figure 16.002.
Figure 16.002

Substitution Reactions. In *nucleophilic acyl substitution* reactions, the C=O group remains in the final reaction product. The overall transformation replaces a group originally attached to the C=O (e.g. the Z group), with a nucleophile such as $Nu:^-$ (Figure 16.003).
Figure 16.003

Addition and Sustitution Mechanisms. The mechanisms for nucleophilic acyl addition or substitution begin with the same first step in which a nucleophile adds to C=O (Figure 16.001). In the addition reactions, an electrophilic species such as a proton is donated to the $Nu\text{-}C\text{-}O^-$ intermediate to give Nu-C-OH (Figure 16.004).
Figure 16.004
In contrast, nucleophilic acyl substitution leads to loss of a Z group from the $Nu\text{-}C\text{-}O^-$ intermediate. The result is that Z is replaced or substituted by Nu.

Nucleophilic acyl substitution reactions primarily occur when the carbonyl compound is an *acid halide, ester, amide,* or other compound of the general structure *R-C(=O)-Z* such as we described in Chapter 15. *Addition* rather than *substitution* occurs when the carbonyl compound is a *ketone* or an *aldehyde,* because R and H are very poor leaving groups (Figure 16.005).
Figure 16.005

Types of Nucleophiles (16.1C)
We list a variety of nucleophiles that react with carbonyl groups in Table 16.01 and underline the nucleophilic atoms that bind to C of the C=O groups.

Table 16.01. Nucleophiles That Add to C=O Groups.

Oxygen-Centered

$H_2\underline{O}$, $H\underline{O}^-$, $R\underline{O}H$

Nitrogen-Centered

$R_2\underline{N}H$, $RNH\text{-}\underline{N}H_2$, $HO\text{-}\underline{N}H_2$

Carbon-Centered

$R_3\underline{C}\text{-}MgX$, $(R_3\underline{C})_2Cu\text{-}Li$, $R_3\underline{C}\text{-}Li$

$^-\underline{C}\equiv N$, $Ph_3P{=}\underline{C}R_2$, "enolate ions" (see text below)

Others

$LiAl\underline{H}_4$, $NaB\underline{H}_4$, $\underline{X}^-$, $H\underline{S}O_3^-$

We described a number of these nucleophiles in Chapter 7 (Nucleophilic Substitution Reactions). They react as nucleophiles with C=O because they provide the electron pair that constitutes the new bond between the nucleophile "Nu" and the C of the C=O group.

In the following sections we discuss the reactions of these individual nucleophiles (Table 16.01) with different classes of carbonyl compounds. For each type of nucleophile, we first discuss its *addition reactions* and follow that with examples of its *substitution reactions.*

Enolate Ions. Enolate ions have a negatively charged C atom attached to a C=O group (they contain the atom grouping O=C-C:$^-$). They are a diverse group of nucleophiles that react with C=O groups in a variety of C-C bond forming reactions. We discuss them and their reactions in Chapter 18(?).

16.2 The Nucleophile HO^-

We illustrate the basic mechanistic features of *nucleophilic addition* and *substitution* reactions on carbonyl compounds using the nucleophile *hydroxide ion* that we write either as HO^- or ^-OH (Figure 16.006).

Figure 16.006

HO^- in HOH (16.2A)

Water is generally the solvent for reactions of the hydroxide nucleophile ^-OH.

Relative Nucleophilicities of HO^- and HOH. Both water and hydroxide ion are nucleophiles, and in aqueous solutions of HO^- the concentration of water is much higher than that of HO^-. However since HO^- is much more nucleophilic than HOH, even at low concentrations HO^- reacts with C=O compounds much faster than HOH.

Nucleophilicity and Reaction Rates. The opposite situation occurs in the competitive reaction of the nucleophiles HOH and HO^- with a carbocation (R_3C^+) (Chapter 7). Intermediate carbocations are highly reactive and react quickly with the nearest nucleophile. Although HO^- is always more nucleophilic than HOH, the relatively high concentration of HOH compared to HO^- in aqueous base favors its reaction with carbocations.

In contrast, carbonyl compounds are stable organic molecules. So they usually react with the more reactive nucleophile even if it is present in relatively low concentration compared to another significantly less reactive nucleophile.

Competitive Enolate Ion Formation. Before we discuss nucleophilic addition of HO^- to C=O compounds, we need to remember that hydroxide ion can also react with an α-H of a carbonyl compound to form an enolate ion as we described in Chapter 13 (Figure 16.007).

Figure 16.007

Enolate ion formation, and nucleophilic addition to C=O, occur simultaneously in reactions with HO^- whenever the C=O compound has α-H's. We discuss this competition, and the reactions of enolate ions, in Chapter 18.

Reaction Notation. When we write *"HO^-, H_2O" or "HO^-/H_2O"* above or below a reaction arrow, we clearly specify that water is the solvent. However, even if we write only *"HO^-"* above the reaction arrow, you can usually assume that the solvent is H_2O.

It is important to remember that the hydroxide ion comes to the water solution with some cation such as Na^+ or K^+ (for example, as NaOH or KOH). But since we do not show these cations as participating in the mechanistic steps of the reaction, we frequently omit them when we specify the reagents in the reaction.

HO^- Addition to Ketones and Aldehydes (16.2B)

Addition of HO^- to the carbonyl group of ketones or aldehydes leads to the formation of 1,1-diols as we show mechanistically in Figure 16.008.

Figure 16.008

1,1-Diols are Called Hydrates. Because the net result is the addition of a molecule of water (think of it as H-OH) across the C=O bond (Figure 16.009), we commonly refer to 1,1-diols as **hydrates** of ketones or aldehydes.

Figure 16.009

Although hydroxide ion is consumed in the first step of the sequence in Figure 16.008, it is regenerated in the second step so we refer to the overall process as "**base** (or **hydroxide ion**) ***catalyzed*** **hydration**" of the ketone or aldehyde. The definition of a *catalyst* is that it facilitates the reaction, but is not used up in that reaction.

Ketones, Aldehydes, and Their Hydrates. Whenever ketones or aldehydes are dissolved in water they are in equilibrium with their hydrates (Figure 16.010).

Figure 16.010

Hydroxide ion facilitates the establishment of this equilibrium, but it does not affect the equilibrium distribution of the carbonyl compound and its hydrate.

Hydrates are only a small fraction of the equilibrium mixture for water solutions of most ketones. However the hydrates of some aldehydes are more stable than their carbonyl compounds. We give examples of equilibrium distributions of hydrates and their parent aldehydes or ketones in Table 16.02.

Table 16.02. Equilibrium Distribution of Hydrates and Their Carbonyl Compounds in Water.

Carbonyl Compound	(Hydrate)/(Carbonyl)
CH_3-C(=O)-CH_3	0.002
CH_3CH_2-C(=O)-H	0.7
CH_3-C(=O)-H	1.3
H-C(=O)-H	2,000
Cl_3C-C(=O)-H	28,000
$ClCH_2$-C(=O)-CH_2Cl	10

HO^- Substitution on R-C(=O)-Z Compounds (16.2C)

Reaction of hydroxide ion with esters, amides, anhydrides, or other compounds of the general structure R-C(=O)-Z leads to substitution of Z by OH.

The Mechanism. The mechanism of this substitution reaction includes several steps (Figure 16.011).

Figure 16.011

Hydroxide ion adds to the C=O group in the first step, followed by loss of Z from the intermediate in the second step of the mechanism.

The carboxylic acid formed in the second step is not the final product. It rapidly reacts with either Z^- or HO^- present in the reaction mixture to yield a carboxylate ion (Figure 16.011). We can isolate the carboxylic acid itself from the reaction mixture after we neutralize the basic solution using excess aqueous hydrochloric or sulfuric acid (Figure 16.012).

Figure 16.012

We refer to the overall reaction in Figure 16.011 as **base catalyzed hydrolysis** even though hydroxide ion is consumed in the reaction. A rationalization is that the hydroxide ion is replaced with Z^- or carboxylate ion.

When Z is OH. Nucleophilic addition of hydroxide ion, followed by elimination of Z, occurs with all compounds of the structure R-C(=O)-Z except carboxylic acids (Z = OH). Carboxylic acids rapidly react with HO^- to form negatively charged *carboxylate ions* that are unreactive to C=O addition of nucleophiles such as HO^-. For example, the product that would result from hydroxide addition to a carboxylate ion is the highly unstable dianion shown in Figure 16.013.

Figure 16.013

More powerful nucleophiles than hydroxide ion do react with carboxylate ions in nucleophilic addition reactions and we describe some of them later in this chapter.

16.3 The Nucleophile HOH

Water is a much weaker nucleophile than hydroxide ion, so its rate of addition to carbonyl groups is much less than that of hydroxide ion. However, we can increase its nucleophilic addition rate by activating the carbonyl group with an acid catalyst. For this reason, many reactions of carbonyl compounds with water are catalyzed by acids. We describe these acid catalyzed reactions before our discussion of uncatalyzed additions of water to C=O groups.

Activation of C=O by Protonation (16.3A)

Carbonyl compounds are protonated on oxygen by acids such as HCl, H_2SO_4, or H_3PO_4 (Figure 16.014).

Figure 16.014

Protonated C=O Group. The carbonyl group is a weak base, so the equilibrium concentration of protonated carbonyl compound is very low compared to that of the uprotonated carbonyl compound. However, a protonated carbonyl group is much more reactive toward nucleophiles than an unprotonated carbonyl group.

This enhanced reactivity results from the full positive charge imparted to the carbonyl group by protonation. Resonance structures in Figure 16.015 show that this positive charge is delocalized on both the C and the O of the protonated carbonyl group.

Figure 16.015

While the C of an unprotonated C=O is positively polarized, that of the $C{=}OH^+$ group is much more positively polarized because of the full + charge on the group.

Reaction with HOH. When water adds to a protonated carbonyl group the single positive charge is transferred to the oxygen atom of the water molecule (Figure 16.016).

Figure 16.016

In contrast, when water adds to an unprotonated carbonyl group, a less favorable separated intermediate forms that has a positively charged "water" oxygen and a negatively charged "carbonyl" oxygen (Figure 16.016).

Acid Catalyzed Addition of HOH to Aldehydes and Ketones (16.3B)

We can describe the overall mechanism for acid catalyzed addition of water to aldehydes or ketones (**acid catalyzed hydration**) as the following three steps:

(a) The C=O group is protonated on O.

(b) Water adds to the C of the protonated C=O group.

(c) The resultant addition product "loses" a proton from the water O.

We illustrate these in Figure 16.017.

Figure 16.017

Alternate Ways to Write the Same Mechanism. The equations in Figure 16.017 are one way of depicting the written mechanism outlined as (a)-(c) above. However there are other ways to write equations for this mechanism that look different than those in Figure 16.017, but mean the same thing. Organic chemists have individual preferences as to how these steps should be represented and your instructor may have a preference that is different than that shown here.

For students, these equivalent alternatives are usually confusing so we individually discuss some of these below. These alternate mechanistic illustrations will help you understand comparable mechanistic alternatives for later reactions.

Carbonyl Protonation. We might show protonation of the carbonyl group (Step (a)) using any one of the four equations in Figure 16.018.

Figure 16.018

They all signify the transfer of a a proton to the carbonyl group to give the protonated carbonyl group.

The only difference between the first and second reactions is that they show alternate resonance structures (Figure 16.015) for the protonated carbonyl group. The same is true for the third and fourth reactions.

Addition of Water. We can also show either resonance structure of the protonated carbonyl group reacting with the nucleophile water (Step (b)) to give the protonated product (Figure 16.019).

Figure 16.019

Loss of the Proton (Deprotonation). There are different ways to indicate removal of the proton from a protonated intermediate (deprotonation) (Figure 16.017, Step (c)). Several different bases are usually simultaneously present in the reaction

mixture and any of them might accept the proton from the protonated intermediate. They can include *water*, the *conjugate base (A:⁻)* of an acid catalyst (H-A), or even the *aldehyde* or *ketone* itself (Figure 16.020).

Figure 16.020

For this reason, we often write the deprotonation step in Figure 5.13 as a proton transfer to some generic base "B:", or just as a "proton loss" ($-H^+$) without specifying where the proton goes.

Figure 16.021

Reversible Steps. All steps we have shown for these hydration reactions are reversible. As a result, these acid catalyzed reactions of carbonyl compounds are equilibria as we show for hydrate formation (Figure 16.022).

Figure 16.022

We will consider this reversibility in more detail in subsequent sections.

Acid Catalyzed Addition of Water to R-C(=O)-Z (16.3C)

Acid catalysis also facilitates the reaction of water with a variety of other carbonyl compounds with the general structure R-C(=O)-Z. In these reactions, the Z group becomes OH and we call the reaction *hydrolysis*. The mechanisms of these acid catalyzed hydrolysis reactions of R-C(=O)-Z involve many intermediate steps. However, each individual step is relatively simple as we see below.

The Overall Mechanism. We can generally describe the individual mechanistic steps for all acid catalyzed hydrolysis reactions of R-C(=O)-Z as follows:

(a) Protonation of the carbonyl oxygen
(b) Addition of water to the protonated carbonyl carbon
(c) Proton "shifts" in the intermediate
(d) Loss of Z-H from the intermediate
(e) Deprotonation of the product

We discuss each of these steps in detail below.

The Tetrahedral Intermediate. Steps (a) and (b) are completely analogous to those for acid catalyzed hydration of ketones and aldehydes as we show in equation form in Figure 16.023.

Figure 16.023

We call the intermediate "I" the **tetrahedral intermediate** because the sp^2 C of the C(=O)-Z group becomes "tetrahedral" (sp^3) upon HOH addition in Step (b). A similar *tetrahedral intermediate* forms in the base catalyzed reaction (Figure 16.011), and both the intermediate and the final hydrate product in the hydration reaction of ketones and aldehydes (Figure 16.008) are also tetrahedral.

Loss of the Z Group. These tetrahedral intermediates formed in base (Figure 16.011) or acid (Figure 16.008) catalyzed hydrolysis lose the Z group transforming R-C(=O)-Z into R-C(=O)-OH. However, the way that Z leaves from the *tetrahedral intermediate* "I" differs in the two mechanisms.

In the acid catalyzed mechanism, Z is protonated prior to its loss so the actual leaving group is Z-H as we show in in Step (d) of Figure 16.024.

Figure 16.024

Z is protonated in a sequence of deprotonation and protonation steps. In the first part of Step (c), a base (B:) removes a proton from the H-O-H^+ group. Then Z is protonated by an acid BH^+. The protonated ZH^+ group then leaves as ZH (Step (d)) and the protonated product "loses" a proton (Step (e)).

Proton Shifts. Although we often refer to the "O deprotonation" and "Z protonation" steps on the tetrahedral intermediate (Figure 16.024) as *proton shifts*, this is not accurate. The proton on oxygen must be removed by a base before, or as, the Z is protonated by another acid. However if we keep this in mind, it is often convenient to represent this deprotonation/protonation sequence by the single reaction in Figure 16.025.

Figure 16.025

After examining this reaction (Figure 16.025), you may wonder why the proton doesn't "shift" to the other oxygen atom in the tetrahedral intermediate. In fact it does, and we show all of the possible protonated intermediates in Figure 16.026 [next page].

Figure 16.026

While each of these protonated intermediates can lose its protonated group, only that intermediate with a protonated Z group gives a product that is different than the starting carbonyl compound. As a result, these steps not on the path to product formation are not included. In general, we show only those steps in mechanisms that actually lead sequentially to the desired reaction product.

Amide Hydrolysis as an Example. The general mechanistic steps that we just described apply to acid catalyzed hydrolysis of *esters*, *amides*, *anhydrides*, and other compounds of the general structure R-C(=O)-Z. We show how they specifically describe acid catalyzed hydrolysis of an *amide* in Figure 16.027.

Figure 16.027

The Benefits of Acid Catalysis. Acid catalysis facilitates hydrolysis reactions of amides or other compounds R-C(=O)-Z in two important ways: (1) protonation of the carbonyl group in the first step of the reaction (see Figure 16.027) makes the carbonyl group more reactive to attack by the nucleophile, and (2) protonation of the Z group (also see Figure 16.027) allows it to leave as the more stable ZH species instead of the less stable $Z:^-$ ion. We previously described this situation for nucleophilic substitution reactions on alcohols in Chapter 7.

"Uncatalyzed" Addition of HOH to Carbonyl Compounds (16.3D)

Aldehydes and ketones form hydrates in water even without added acids or bases. Similarly, esters, amides, anhydrides, acid halides, and other R-C(=O)-Z compounds will hydrolyze in water without these catalysts. We refer to such reactions as "**uncatalyzed**" reactions, but detailed mechanistic studies that we describe below indicate that this designation is misleading.

Uncatalyzed Aldehyde Hydration. When water adds directly to an unprotonated C=O group in the absence of acid or base, that process is probably catalyzed by at least one other water moleculeas we show for hydration of an aldehyde in water in Figure 16.028.

Figure 16.028

In this mechanism, a second water molecule "assists" the nucleophilic addition of the first water molecule by simultaneously donating a proton to the carbonyl

oxygen. The resultant hydroxide ion subsequently removes the proton from the protonated oxygen of the intermediate.

> **A Mechanistic Caveat**. The steps in Figure 16.028 represent the collective wisdom of a variety of chemists interested in the mechanisms of organic reactions. While this may appear reasonable as shown, the possible timing of nucleophilic attack and proton transfer in aldehyde hydration has many variations. This picture is the one most generally accepted. But perhaps someday you will develop and justify an alternate proposal to this or some other mechanism presented in this text.

Uncatalyzed Hydrolysis of R-C(=O)-Z. The precise mechanisms of "uncatalyzed" hydrolysis of amides, esters, anhydrides, acid halides, and other compounds of the structure R-C(=O)-Z are uncertain. As a result, we often write a less detailed mechanism for uncatalyzed hydrolysis of these compounds such as that in Figure 16.029.

Figure 16.029

The addition of the nucleophile is probably assisted by proton donation from water, but you can simply think of the addition as giving the tetrahedral intermediate in the first reaction. We then show this intermediate losing the Z group as Z^- followed by proton transfer in the third step.

This mechanism reasonably describes hydrolysis of acid halides since halide ions are good leaving groups. However, loss of Z^- groups such as RO^- from esters, and R_2N^- from amides, are not energetically favorable. Their departure is most certainly assisted by "proton shifts" so that the leaving group is ZH (Figure 16.030).

Figure 16.030

> **Uncatalyzed Reactions are Hard to Find**. Even if the first molecule of R-C(=O)-Z reacts with water in the absence of a catalyst, the reaction products H-Z and R-C(=O)-OH can serve as catalysts. For acid halides such as R-C(=O)-Cl or R-C(=O)-Br, H-Z is the mineral acid HCl or HBr. For amides, H-Z is an amine (H-NR_2) that is basic. And for all of these systems, R-C(=O)-Z hydrolysis forms a carboxylic acid R-C(=O)-OH that is acidic. All of these products can serve as catalysts for hydrolysis of R-C(=O)-Z.

16.4 Alcohols (ROH) as Nucleophiles

Alcohols (RO-H) are also nucleophiles for carbonyl compounds. We can catalyze their addition and substitution mechanisms with acids or bases, or they can be "uncatalyzed", as just described for water. However, from a practical standpoint, nucleophilic reactions of alcohols with carbonyl compounds are generally acid catalyzed reactions.

ROH Addition to Aldehydes and Ketones gives Hemiacetals (16.4A)

We show the overall addition reaction of an alcohol to the carbonyl group of an aldehyde or a ketone in Figure 16.031.

Figure 16.031

The resultant product that contains both an OH and an OR group on the same carbon is a **hemiacetal**.

> **Hemiacetals *versus* Hemiketals**. Originally, the name hemiacetal was reserved for the alcohol addition product formed from an *aldehyde*, while that from a *ketone* was called a **hemiketal**. The name *hemiacetal* is now used for both types of compounds.

Hemiacetal Formation Mechanism. We outline a mechanism in Figure 16.032 for the acid catalyzed reaction that gives *hemiacetals*.

Figure 16.032

These steps are analogous to those we showed in Figure 16.017 for acid catalyzed hydration of an aldehyde or a ketone. It is particularly important to note that protonation of the carbonyl oxygen is the first step in this mechanism as we have seen it is for all acid catalyzed reactions of carbonyl groups!

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Cyclic Hemiacetals. When an alcohol functional group and a carbonyl group are in the same molecule, they generally react with each other to form **cyclic hemiacetals** (Figure 16.033).

Figure 16.033

> **A Biologically Important Hemiacetal**. An important biological example of cyclic hemiacetal formation is the equilibrium between the acyclic and cyclic forms of simple sugars such as **glucose**. The cyclic compounds **α-D-glucose** and **β-D-glucose** (Figure 16.034) are such hemiacetals.
>
> Figure 16.034

They are in equilibrium with the acyclic carbonyl form of **D-glucose** that we also show in that figure. The OH group on C5 adds to the aldehyde group to give these two isomeric cyclic hemiacetals.

We show the C5 OH as the reactive OH group, but you can see that there are four other OH groups in the acyclic carbonyl form of D-glucose. In fact, each of these OH groups reacts reversibly with the aldehyde group to a small extent. The six-membered cyclic hemiacetal products formed by reaction of the C5 OH are simply more thermodynamically stable than 3, 4, 5, or 7-membered ring systems formed by reactions of C=O with OH groups on C2, C3, C4, or C6, respectively.

Acid Catalyzed Formation of Acetals (16.4B)

Under strongly acidic conditions, hemiacetals react further with alcohols as we show in Figure 16.035.

Figure 16.035

The OH group of the hemiacetal is replaced by another RO group from the alcohol and we call the resulting products **acetals**.

Acetals versus Ketals. Originally, *acetals* that formed specifically from *ketones* were called **ketals**, but like *hemiketals*, the name *ketal* is no longer recommended systematic nomenclature.

Acetal Formation Mechanism. We outline the mechanism for transformation of a *hemiacetal* into an *acetal* in Figure 16.036.

Figure 16.036

After protonation of the hemiacetal, a water molecule leaves to form an intermediate carbocation. This S_N1 ionization (see Chapter 7) is facilitated by the resonance stabilization of the intermediate carbocation that we show in brackets in that figure.

The resultant carbocation reacts with an alcohol molecule to yield a "nucleophilic substitution" product that subsequently loses a proton to give the acetal. Since the intermediate carbocation is resonance stabilized we can also view its reaction with an alcohol as the addition of the alcohol to the C=O bond of an activated "carbonyl-like" group as we show in Figure 16.037.

Figure 16.037

Since all steps are reversible, acetal formation is an equlibrium process as we indicate in Figure 16.038.

Figure 16.038

We can shift the position of that equilibrium toward the acetal by removal of the product water, and shift it back to the original carbonyl compound by adding water to the acetal.

Acetals Serve as Protecting Groups. Acetals are important functional groups because they are relatively unreactive and can be easily converted back to the original aldehyde or ketone when desired. Situations arise in organic syntheses where molecules containing aldehyde or ketone functional groups must be exposed to reagents that can react with those carbonyl groups in an undesired side reaction. To prevent these side reactions, carbonyl groups can first be converted to unreactive acetals, then subsequently regenerated by hydrolysis after the reagent is no longer present.

When used this way, the acetals are called **protecting groups**. An alcohol frequently used to form *protecting group acetals* is 1,2-ethanediol (ethylene glycol) that gives a cyclic acetal (Figure 16.039) because it contains two OH groups.

Figure 16.039

ROH Addition to R-C(=O)-Z (16.4C)

Alcohols react with R-C(=O)-Z compounds to form *esters* as we show in Figure 16.040.

Figure 16.040

General Mechanism. When we react ROH with R-C(=O)-Z the Z group leaves from a tetrahedral intermediate and the overall reaction is substitution of Z by OR. This substitution reaction can takes place with all of the R-C(=O)-Z compounds, but particularly important examples are reactions of ROH with *acid halides* (Z = X), *carboxylic acids* (Z = OH), and with other *esters* (Z = OR) as we describe below.

ROH Reaction with Acid Halides. Reactions of alcohols with acid halides (Figure 16.041) occur rapidly without a catalyst.

Figure 16.041

To prevent undesired side reactions caused by the mineral acid H-X that forms in the reaction, we neutralize H-X by adding a base such as *hydroxide ion* or *pyridine* (Figure 16.042).

Figure 16.042

Besides reacting as a base with H-X, *pyridine* also reacts with the R-C(=O)-X (Figure 16.043).

Figure 16.043

The resulting *pyridinium ion* is the species that actually reacts with the alcohol to produce the ester product.

> **Schotten-Baumann Procedure**. When chemists use aqueous base to neutralize HX formed in reactions of alcohols with acid halides, the reaction is called the **Schotten-Baumann Procedure**. Many organic reactions are named after the people who discovered them, or who were significantly responsible for their development. Chemists refer to these reactions as "**name reactions**". Your instructor will tell you when you should memorize these names.
>
> The acid halide does not react directly with $^-$OH to a significant extent because $^-$OH is present in an aqueous phase while the acid halide and alcohol are present in a separate organic phase. The reactive nucleophile is probably not ROH, but is RO^- that reacts very rapidly with the acid halide as it is formed by reaction of ROH with $^-$OH.

ROH Reactions with Carboxylic Acids and Esters. We can also prepare esters by reaction of alcohols with carboxylic acids or even with other esters as we show in Figure 16.044.

Figure 16.044

We call the reaction of an alcohol (ROH) with a carboxylic acid **esterification** while we call reactions of ROH with other esters **transesterification**. These reactions are usually catalyzed by acids.

Both *esterification* and *transesterification* are equilibrium processes. In order to successfully prepare the ester product we must shift the equilibrium toward the product. We can accomplish this by removing the reaction products *water* (in esterification), and *R'OH* (in transesterification). Alternatively we can use a large excess of the reactant ROH.

The acid catalyzed mechanisms of these two reactions are very similar. We can convert the mechanism for *transesterification* (Figure 16.045) to that for *esterification* by simply replacing the R' group with an H throughout the mechanism.

Figure 16.045

This transesterification mechanism is analogous to the acid catalyzed hydrolysis reaction of esters that we described earlier in this chapter.

16.5 Amines (R_2NH) as Nucleophiles

Amines are more nucleophilic than either water or alcohols. As a result, they react with carbon compounds in nucleophilic addition and substitution reactions without acid or base catalysis. In fact, acid protonates amines causing them to be non-nucleophilic (Figure 16.046).

Figure 16.046

Reaction of Amines with Ketones or Aldehydes (16.5A)

Ammonia, or 1° and 2° amines, react by nucleophilic addition with ketones or aldehydes to give intermediate tetrahedral addition products called **hemiaminals** (Figure 16.047).

Figure 16.047

Hemiaminals are analogous to hydrates formed by the addition of water to aldehydes or ketones, but they usually do not represent the final product of the addition reaction.

> **Tertiary Amines (R_3N)**. Tertiary amines add to C=O groups but do not give stable addition products.

Imines. When NH_3 or a 1° amine (RNH_2) reacts with a ketone or an aldehyde, the intermediate *hemiaminal* loses water to give an *imine* as we show in Figure 16.048.

Figure 16.048

Imines are often unstable, or rapidly react with each other, giving undesired side-products. However imines with an aromatic ring on either the C or N of the C=N group are stable and can be isolated.

Substituted imines are also called **Schiff bases**. The chemical reactivity of a C=N bond of an imine is similar to that of a C=O bond and we describe their participation as reactants in nucleophilic addition reactions later in this chapter.

Schiff Bases. An example of a biologically important Schiff base is found in the visual pigment **rhodopsin** that is responsible for vision in animals and humans. Rhodopsin contains an imine (Schiff base) linkage formed from reaction of the aldehyde named **11-*cis*-retinal** with a specific NH_2 group on the protein molecule called **opsin** (Figure 16.049).

Figure 16.049

Rhodopsin absorbs light causing the *cis* double bond of the polyene chain to isomerize to a *trans* configuration (Figure 16.050).

Figure 16.050

The resultant "all-*trans*" imine isomer hydrolyzes to give opsin and "all-*trans*" retinal that is isomerized back to *11-cis retinal* by an *enzyme* called **retinal isomerase** as we also show in Figure 16.050.

Enzymes are protein molecules that catalyze biochemical reactions. We discuss enzymes in Chapter 22 that describes amino acids and proteins.

Enamines. When a 2° amine (R_2NH) reacts with an aldehyde or ketone, *imine* formation is impossible because there are no H's on the N of the hemiaminal (see Figure 16.047). However, if the initial carbonyl compound has an α-hydrogen atom (C<u>H</u>-C=O), the intermediate hemiaminal can lose water to give an **enamine**.

Figure 16.051

Enamines are important in organic synthesis because they behave as if they have a nucleophilic C atom (see the second resonance structure in Figure 16.052).

Figure 16.052

We discuss them further in in Chapter 18.

Imine Formation Mechanism. The rate of imine formation from reaction of a 1° amine (R-NH_2) and an aldehyde or ketone has an unusual pH dependence (Figure 16.053).

Figure 16.053

The reaction rate is fastest at about pH 4, but decreases at pH values that are either lower (more acidic), or higher (less acidic) than pH 4. This is because of the different ways that pH influences reactions (1) and (2) in Figure 16.054.

Figure 16.054

At low pH values (moderate to highly acidic solutions), reaction (2) is very rapid because it is catalyzed by acid. In contrast, reaction (1) is very slow and rate determining because the reactant R-NH_2 is extensively protonated and exists primarily as unreactive R-NH_3^+ as we show in the equilibrium labelled reaction (3).

As we increase pH (make the solution less acidic), the amount of unprotonated R-NH_2 increases. This increases the overall reaction rate until the point is reached where the rate of the acid catalyzed reaction (2) decreases so much that it becomes rate determining. Further increases in pH (decreases in acidity) continue to lower the rate of reaction (2) leading to the observed decrease in rate at pH values above 4.

Reaction of Amines with R-C(=O)-Z (16.5B)

Reaction of NH_3, or 1° and 2° amines (RNH_2 or R_2NH), with compounds of the general structure R-C(=O)-Z gives 1°, 2°, or 3° amides (Figure 16.055).

Figure 16.055

Amines and Acid Halides. We outline a mechanism for the reaction of a *1° amine* (RNH_2) and an *acid chloride* (R-C(=O)-Cl) in Figure 16.056.

Figure 16.056

Since the product *HCl* will protonate the reactant *amine*, we use at least two equivalents of *amine* for each equivalent of *acid chloride.* If we add *aqueous base* to neutralize HCl, we call the reaction the *Schotten-Bauman procedure* that we previously illustrated for alcohol addition to acid halides in the presence of aqueous base.

Reminder. Reactions of amines with acid halides are like those between pyridine and acid halides described earlier. When pyridine is the reactant, the product is not an amide but an intermediate ion that undergoes further reaction as we showed in Figure 16.043

Amines and Anhydrides or Esters. Both anhydrides and esters react with NH_3 or amines to give amides (Figure 16.057).

Figure 16.057

Anhydrides are generally more reactive than esters because the resonance stabilized carboxylate ion ($^-$OC(=O)R) leaving group from anhydrides is better than the alkoxide ion ($^-$OR) leaving group from esters (Figure 16.058).

Figure 16.058

Amines and Carboxylic Acids. *Carboxylic acids* undergo an acid-base reaction with *NH_3* or *amines* to form *ammonium carboxylates*, but we can force these salts to form *amides* by heating them at high temperatures in **pyrolysis** reactions (Figure 16.058a).

Figure 16.058a

This method is generally not used to make acyclic amides, but it readily transforms δ- or γ-*amino acids* into cyclic amides called **lactams** (Figure 16.059).

Figure 16.059

Other Nitrogen Nucleophiles (16.5C)

There are a number of nitrogen nucleophiles with the general structure Y-NH_2 that react with carbonyl compounds. The Y group typically has an N or O directly attached to NH_2.

Hydrazines as Nucleophiles. **Hydrazines** (RNH-NH_2) react with aldehydes and ketones to form **hydrazones** (Figure 16.060).

Figure 16.060

R has a variety of different structures such as those we show in Figure 16.061.

Figure 16.061

> **History**. Before instrumental methods such as NMR and Mass spectrometry were available to help identify organic compounds, chemists used physical characteristics of compounds such as their melting point. However many ketones and aldehydes are liquids, so melting points could not be used for their identification. Fortunately, the various hydrazone products of aldehydes and ketones (Figure 16.061) are easily purified solids with sharp melting points so they served as a way to identify their precursor aldehyde or ketone.

Wolff-Kishner Reaction. The reaction of unsubstituted **hydrazine** (H_2N-NH_2) with *aldehydes* or *ketones*, followed by treatment with strong base, that

converts their C=O groups into CH_2 groups (15.39b), is named the **Wolff-Kishner** reaction.

Figure 16.062

In the presence of strong base, the intermediate *hydrazone* (Figure 16.062) decomposes losing N_2. We describe the mechanism of this *reduction reaction* in the next chapter that covers *oxidations* and *reductions.*

Hydroxylamine as a Nucleophile. Reaction of **hydroxylamine** ($HO\text{-}NH_2$) with *ketones* or *aldehydes* gives **oximes** (Figure 16.063).

Figure 16.063

Oximes are structurally similar to the *hydrazones* already described. Like *hydrazones*, they are solids that can be purified and they have sharp melting points that make them useful for structural identification of their precursor ketones and aldehydes. The mechanism and pH dependence of the reaction of *hydroxylamine* with *carbonyl compounds* is analogous to that we described earler for addition of *amines.*

16.6 Carbon Centered Nucleophiles

So far, all nucleophiles in this chapter have their nucleophilic center on O or N. However many nucleophiles that react with carbonyl compounds have their nucleophilic center on C.

Different Types of C Nucleophiles (16.6A)

Two major types of carbon-centered nucleophiles are **enolate ions**, and **organometallic reagents** (Figure 16.064).

Figure 16.064

Organometallic reagents have negatively polarized C atoms directly bonded to *metal atoms* while *enolate ions* have negatively charged C's bonded to C=O groups that stabilize the $C:^-$ center. We discuss *organometallic reagents* below, but defer our discussion of *enolate ions* until Chapter 18.

Two other carbon-centered nucleophiles are *cyanide ion* ($^-:C{\equiv}N$), and **Wittig Reagents** ($Ph_3P{=}CR_2$). The P=C bond of *Wittig Reagents* behaves as if it is ionic ($^+P\text{-}C:^-$) with a negative charge on the C atom. We describe Wittig reagents and cyanide ion reactions at the end of this section.

Organometallic Reagents (16.6B)

Organometallic reagents have carbon-metal bonds. We show some examples here that we first described in Chapter 7. Since C is more electronegative than these metals, the C-M bond is polarized (δ^-)C-M(δ^+) as we indicate in Figure 16.065.

Figure 16.065

As a result, the C-M carbon is nucleophilic and adds to C=O groups as we show in Figure 16.066.

Figure 16.066

> **Note Added During Editing**. It would have been more accurate to write a general structure such as R_3C-M for an organometallic compound rather than simply R-M. In each organometallic compound there is a C-M bond and it is the C of the R_3C group. That C bonds to C=O to give a new C-C bond and forms a new group with the general structure R_3C-C-O-M.

Overview. An organometallic compound (R-M shown in the general reaction above) can have a wide variety of R groups and several different metals (M). For example, the C directly bonded to the metal atom can be hybridized sp^3, sp^2, or sp, as we show in Figure 16.067.

Figure 16.067

Metals in R-M commonly include Mg, Li, and Zn, but can also be Na, Al, Sn, B, and Cu among others. The choice of the metal often depends on the hybridization of the nucleophilic carbon center and we show common pairings of R and M in Table 16.03.

Table 16.03. Some Common Pairings of R and M in Organometallic Compounds (R-M).

R	M
alkyl	Mg, Li, (Zn), Cu-Li
aryl	Mg, Li
R-C≡C	Na
R-CH=CH	Al
R-CH=CH-CH_2	Si, Sn, (B)

Magnesium, Lithium and Zinc Reagents. Historically, the most popular organometallic reagents had magnesium (Mg) as their metal. These **organomagnesium** reagents are called **Grignard reagents** (pronounced "grin-yard" reagents). We described their formation from reaction of organic halogen compounds and magnesium metal (Figure 16.068) in Chapter 7.

Figure 16.068

Grignard reagents are cheap and will add a wide variety of alkyl and aryl groups to ketones and aldehydes. However **organolithium (R-Li)** compounds are now more widely used. They are easier to prepare and control than Grignard reagents and are also commercially available.

Addition of "R-M" to Aldehydes and Ketones (16.6C)

Organometallic reagents (R-M) add their R group to the C=O group of aldehydes and ketones. The overall result is the formation of a C-C bond and the conversion of the carbonyl compound to an alcohol (Figure 16.069).

Figure 16.069

Stepwise Reactions. These transformations are performed in two stages indicated by the numbered reagents over the reaction arrow in the example above. We form the new C-C bond by reacting the organometallic compound with the ketone or aldehyde while we exclude both moisture and oxygen as we show for CH_3-Mg-Br in Figure 16.070.

Figure 16.070

Hydrolysis of the intermediate with solutions of aqueous acid (dilute HCl or H_2SO_4) or aqueous ammonium chloride ($NH_4^+Cl^-$) gives the desired alcohol (Figure 16.071).

Figure 16.071

We use the weakly acidic ammonium chloride solution when the alcohol product is acid sensitive. We show two examples of organometallic addition reactions of carbonyl compounds in Figure 16.072.

Figure 16.072

Solvents. Grignard reagents are prepared, and reacted with carbonyl compounds, in an ether solvent such as diethyl ether or tetrahydrofuran (THF).

These solvents stabilize the organomagnesium compounds by solvation as we show for diethyl ether in Figure 16.073.

Figure 16.073

In ether solvents, Grignard reagents exist in a variety of different forms (including R-Mg-X and R-Mg-R) that are in equilibrium with each other (Figure 16.074).

Figure 16.074

Organolithium reagents also exist in different forms in solution that are in equilibrium with each other. While ethers can be used as solvents for organolithium reagents, simple hydrocarbons such as pentane and hexane are most frequently used.

Mechanisms. We generally describe reactions of most R-M compounds with C=O compounds as *nucleophilic addition* reactions. However the nucleophilic center on C is generally not a free carbanion. For example, the reaction of Grignard reagents with a C=O group (Figure 16.070) probably involves concerted addition of the R group with its pair of electrons to the C of the carbonyl group as the MgBr group binds to the carbonyl oxygen.

In some cases the mechanism may involve free radical intermediates (Figure 16.075).

Figure 16.075

The organometallic compound and carbonyl compound react to form a pair of free radicals that then combine to give the "addition" product. This **single electron transfer (SET)** mechanism seems to be important for carbonyl compounds in which the R groups are aromatic.

Side Reactions. A number of undesired side reactions can occur in reactions of R-M reagents with C=O compounds (Figure 16.076).

Figure 16.076

For example, R-M reagents react with H_2O or other OH groups present in the reactants or solvents to give hydrocarbons R-H. In addition, two R groups from R-M can couple to give a dimer R-R that probably arises from R· free radical intermediates that can also react with oxygen to form peroxy radicals R-O-O·.

Addition of "R-M" to Carbonyl Compounds R-C(=O)-Z (16.6D)
Organometallic compounds react with R-C(=O)-Z compounds to give ketones that then can react further to give 3° alcohols Figure 16.077.

Figure 16.077

Whether the reaction stops with formation of the *ketone*, or proceeds to the *alcohol*, depends on the type of organometallic reagent, on the Z group, and on the reaction conditions as we briefly describe below.

A General Mechanism. We show these transformations in the general mechanism in Figure 16.078 using CH_3-MgBr as the organometallic reagent.

Figure 16.078

Addition of CH_3-MgBr to the carbonyl group of R-C(=O)-Z followed by loss of Z from the intermediate yields a *ketone*. Subsequent reaction of the *ketone* with CH_3MgBr leads to the formation of the *alcohol*.

3° Alcohol Formation. Grignard reagents (R-Mg-X) convert *esters* (R-C(=O)-OR') to *3° alcohols* (Figure 16.079).

Figure 16.079

3° alcohols are also the principal reaction products when Grignard reagents (R-Mg-X) react with *acid halides* (RC(=O)-X) or *anhydrides* (RC(=O)-O-C(=O)R). *Amides* (RC(=O)-NR_2), give low product yields and are not useful reactants.

Ketone Formation. We can obtain the intermediate *ketone* as our product if the RC(=O)-Z substrate is an *acid halide* (RC(=O)-X) and the organometallic reagent is a *lithium dialkylcopper* reagent that we can represent with the general structure R_2CuLi.

Figure 16.080

> **Other Organometallic Reagents Can be Used**. Besides the R_2CuLi reagent in Figure 16.080, chemists form ketones from acid halides using a wide variety of other organometallic reagents with metals such as Cd, Zn, Sn, Hg, Si, Mn, Tl, B, Li, and Rh. A description of these reagents and their reactions are beyond the scope of this text.

Reactions of "R-M" with Carboxylic Acids (16.6E)
Carboxylic acids (R-C(=O)-Z where Z = OH) initially react with organometallic compounds in an acid-base reaction (Figure 16.081) [next page].

Figure 16.081

But surprisingly, the product of that acid/base reaction (R-C(=O)-OM) can subsequently undergo a nucleophilic addition reaction with the organometallic compound R-M. This occurs with organolithium reagents (M = Li) that react with carboxylic acids to give ketone products (Figure 16.082).

Figure 16.082

After the acid-base reaction, the Li salt of the acid reacts again with R-Li to give the dilithium "salt" of a hydrate that reacts with water to generate the hydrate that is in equilibrium with the ultimate ketone product. The R groups in R-Li, and in the carboxylic acid (R-CO_2H), can be a variety of alkyl or aryl groups.

Reactions with CO_2 (16.6F)

Grignard reagents (R-MgX) and other organometallic compounds (R-M) add to CO_2 (in the form of solid Dry Ice™) to give the metal salt of a carboxylate ion (Figure 16.083).

Figure 16.083

We obtain the corresponding carboxylic acid (R-C(=O)-OH) by extracting it from the reaction mixture that we have acidified. This overall reaction selectively adds one C atom (from CO_2) to the R group in R-M and the resulting carboxylic acid group (R-CO_2H) can be subsequently transformed into a variety of other functional groups.

Reaction of Cyanide Ion with C=O Groups (16.6G)

The cyanide ion ($^-$:C≡N) is a non-organometallic C nucleophile that readily adds to C=O groups in aldehydes and many ketones to form compounds called **cyanohydrins** (Figure 16.084).

Figure 16.084

Cyanohydrins. Cyanohydrins are useful synthetic intermediates because the C≡N group hydrolyzes to give a carboxylic acid (Chapter 15) (Figure 16.085).

Figure 16.085

In addition, we can convert the OH group, as well as the carboxylic acid group resulting from hydrolysis of C≡N, into other functional groups. As a result, these α-hydroxy carboxylic acids (Figure 16.085) can be starting materials for a variety of organic reactions. We describe the mechanism for conversion of C≡N into CO_2H later in this chapter.

Mechanism of Cyanohydrin Formation. The mechanism of formation of cyanohydrins that we show in Figure 16.086 is one of the oldest known organic reaction mechanisms.

Figure 16.086

HCN is a very weak acid, so the reaction needs a basic species ($A:^-$) to generate a small amount of cyanide ion to initiate the reaction. Addition of $^-:CN$ to the C=O group is a slow step that is followed by rapid protonation of the intermediate formed in the second step.

All three steps are reversible, and the yield of cyanohydrin depends on the structure of the carbonyl compound. We show some overall equilibrium constants for addition of HCN to various aldehydes and ketones (Figure 16.084) in Table 16.04.

Table 16.04. Approximate Equilibrium Constants for Cyanohydrin Formation (96% Ethanol, 20°C)

R_1	R_2	K
phenyl	H	200
phenyl	CH_3	1
CH_3	CH_3	30
CH_3	CH_3CH_2	40
cyclopentanone		50
cyclohexanone		1000
cycloheptanone		10

While aldehydes give high yields of cyanohydrin, the yields from acyclic ketones are generally lower. This is particularly true for ketones in which one R group is aromatic. Cyanohydrins do not form when both groups of a ketone are aromatic.

The cyanohydrin yield from HCN addition to cyclic ketones depends on the ring size. That for cyclohexanone is particularly high because converting the the sp^2 C=O carbon of cyclohexanone into an sp^3 center is sterically very favorable.

Reaction of $Ph_3P=CR_2$ with C=O Groups (16.6H)

Reagents with the structure $Ph_3P=CR'_2$, called **Wittig reagents**, react with aldehydes or ketones as we show in Figure 16.087.

Figure 16.087

Wittig Reaction. In this **Wittig reaction**, the O of the C=O is replaced by the CR'_2 group of the reagent $Ph_3P{=}CR'_2$. The *Wittig reagent* reacts with C=O groups because the C of the P=C bond is nucleophilic. We can see this from the second resonance structure for the *Wittig reagent* in Figure 16.088.

Figure 16.088

Formation of the Wittig Reagent. We make *Wittig reagents* by reacting triphenylphosphine (Ph_3P) with haloalkanes of the general structure R_2CHX (Figure 16.089).

Figure 16.089

Triphenylphospine displaces X as a halide ion ($X:^-$) in a nucleophilic substitution reaction that forms an intermediate phosphonium salt.

Reaction of the phosphonium salt with a strong base such as sodium hydride (NaH), butyllithium (BuLi), sodium amide ($NaNH_2$), or a sodium alkoxide (RONa), removes a proton from C giving a zwitterionic compound called an **ylide** (pronounced "ill-ed"). We call this *ylide* the *Wittig reagent* and can represent it using the two resonance structures in Figure 16.088.

Mechanism of the Wittig Reaction. We show a mechanism for the *Wittig reaction* in Figure 16.090.

Figure 16.090

Organic chemists have confirmed the cyclic intermediate shown in this figure using NMR spectrometry. It's ring opens under the reaction conditions to give the alkene product and triphenylphosphine oxide ($Ph_3P{=}O$).

When $R_2C{=}O$ has two different R groups, and the two R's on the *Wittig reagent* also differ from each other, the Wittig reaction can form *E* and *Z* alkene isomers. The *E/Z* ratio depends in a complex way on the R groups and the solvent system. We show examples of Wittig reactions in Figure 16.091.

Figure 16.091

The Tebbe Reagent. A more recent organometallic reagent, that readily converts C=O groups into $C{=}CH_2$ groups is named the **Tebbe Reagent** (Figure 16.092).

Figure 16.092

The "Cp" groups are aromatic cyclopentadienide ions (Chapter 12?) that bind to Ti by a symmetric interaction of an orbital on each C with the Ti atom as we show in Figure 16.093.

Figure 16.093

The *Tebbe reagent* is more reactive than the *Wittig reagent* so it reacts not only with ketones, but also with esters (Figure 16.094).

Figure 16.094

I met Fred Tebbe at UC Riverside when he was a postdoctoral scholar and I was an Assistant Professor of Chemistry.

16.7 Other Nucleophiles

There are several additional nucleophiles that react with C=O groups besides those we have described. We discuss some of these in the following sections while we defer others to later chapters.

The Hydride Nucleophile (16.7A)

A most important nucleophile for C=O groups that we have not yet described is *hydride* (or *hydride ion*) that adds to C=O groups as if it is $H{:}^-$. Sources of *hydride* include *metal hydrides* such as $NaBH_4$ (*sodium borohydride*) and $LiAlH_4$ (*lithium aluminum hydride*) (Chapter 7). They transfer a *hydride* to a variety of C=O groups as we illustrate in Figure 16.095.

Figure 16.095

We can categorize these reactions as *nucleophilic addition* to C=O groups, however they are also *reduction reactions.* For example they reduce *ketones* and *aldehydes* to *alcohols* as we show in Figure 16.096.

Figure 16.096

For this reason we will present them in Chapter 17 where we discuss both *reduction* reactions and *oxidation* reactions.

Oxidation and reduction reactions (also collectively called *redox* reactions) have many different mechanisms, but organic chemists frequently group them together since they permit "reversible" interconversions of *alcohols*, *aldehydes* (or *ketones*), and *carboxlic acids* (Figure 16.097).

Figure 16.097

They Could Have Been Here! Many organic texts put hydride reductions of C=O compounds in chapters like this one that describes nucleophiles adding to C=O groups. This is perfectly acceptable since this chapter includes carbonyl (C=O) to alcohol (C-OH) conversions resulting from reactions with organometallic compounds (R-M).

A justification for treating *organometallic "reductions"* of C=O groups differently than *hydride reductions* is that *hydride reductions* are "reversible" *redox* reactions, while the *organometallic* reactions are not reversible. While *organometallic additions* convert $R_2C=O$ to R_3C-OH, but do not permit the reverse reactions, *hydride additions* convert $R_2C=O$ to R_2CH-OH that we can reoxidize to $R_2C=O$.

Chloride Ion as a Nucleophile (16.7B)

Chloride ion adds as a nucleophile to a C=O group in the reaction (Figure 16.098) where a carboxylic acid is transformed into an acid chloride.

Figure 16.098

We previously described this reaction in Chapter 15. We write the first part of this reaction using the mechanistic steps in Figure 16.099.

Figure 16.099

In the first step, the carboxylic acid adds as a nucleophile to the S=O bond, and this is followed by the loss of the leaving group Cl^- and deprotonation. The overall reaction is a nucleophilic substitution that is very similar to those we showed for compounds of the structure R-C(=O)-Z in previous sections.

The product that forms in the third step then reacts with Cl^- by a nucleophilic substitution mechanism that we can write as in Figure 16.100.

Figure 16.100

These mechanistic steps are analogous to those we showed earlier for nucleophilic substitution reactions except that the leaving group $^-$O-S(=O)-Cl subsequently decomposes into SO_2 and Cl^-.

We can write very similar mechanisms involving nucleophilic addition of chloride and other halide ions for the reactions in Figure 16.101.

Figure 16.101

Bisulfite Addition Products. The **bisulfite ion** (from **sodium bisulfite**) is an unusual nucleophile that reacts with carbonyl compounds in an equilibrium that we show in Figure 16.102 [next page].

Figure 16.102

The resultant *bisulfite addition product,* with its C-S bond, readily forms with most aldehydes. However only sterically unhindered methyl ketones, and cyclic ketones undergo bisulfite addition reactions..

Bisulfite addition products are easily converted back to the starting carbonyl compounds by treatment with aqueous acid or base. They are prepared not as a final reaction product, but because they provide a method of purifying carbonyl compounds. The bisulfite adducts of carbonyl compounds are water soluble, so they dissolve in an aqueous phase permitting other water insoluble impurities in the carbonyl compound to be extracted by organic solvents.

16.8 Nucleophilic Addition to C=N and C≡N Bonds

A number of the nucleophiles that we have described for C=O bonds also add to C=N and C≡N bonds. We outline some of these reactions in the following sections. All of their mechanisms involve a nucleophilic addition step followed by subsequent steps analogous to those we have given for C=O compounds.

Additions to C=N (16.8A)

This section includes reactions of C=N compounds with H_2O, organometallic reagents (R-M), and cyanide ion ($^{-}$:C≡N).

Addition of Water. Most C=N bonds of compounds such as imines, hydrazones, and oximes (represented as R_2C=N-Y) react with H_2O to give the corresponding ketones or aldehydes as we show in Figure 16.103.

Figure 16.103

These reactions are the reverse of those we showed in earlier sections for the formation of these C=N compounds. While they are often acid or base catalyzed, they can sometimes be carried out without those catalysts.

Addition of Organometallic Reagents. Substituted *imines* of *aldehydes* react with *Grignard reagents* and other organometallic compounds such as *organolithiums* to form C-alkylated amines (Figure 16.104)[next page].

Figure 16.104

Substituted *imines* from *ketones* specifically require the use of organolithium compounds. *Iminium* salts such as those in Figure 16.105 [next page] readily react with Grignard reagents to form *3° amines*.

Figure 16.105

Addition of Cyanide Ion. Cyanide ion (⁻:C≡N) adds to C=N bonds as we show using an *imine* as the reactant in Figure 16.106.

Figure 16.106

The resulting compound is an α-*amino nitrile* that we can hydrolyze to an α-*amino acid* (Figure 16.107).

Figure 16.107

We mentioned the C≡N hydrolysis reaction in the preceding chapter and will describe it in detail in the following section.

Strecker Synthesis. We can form unsubstituted α-*amino acids* directly from aldehydes or ketones using the reaction sequence in Figure 16.108.

Figure 16.108

The first step of this reaction is called the **Strecker synthesis** and its mechanism presumably involves formation of an intermediate imine that subsequently reacts with cyanide ion to form an α-amino nitrile (Figure 16.109).

Figure 16.109

We can synthesize N-substituted amino acids if we use N-substituted aminium ions in place of ammonium ion.

Additions to C≡N (16.8B)

This section includes reactions of water (hydrolysis) and organometallic reagents to nitrile (C≡N) groups. We defer hydride reactions to Chapter 18 since they are reduction reactions.

Addition of Water. Addition of water to nitrile groups hydrolyzes them to to amides that subsequently hydrolyze further to carboxylic acids (Figure 16.110).

Figure 16.110

These interconversions indicate why *nitriles* and their reactions are generally discussed along with compounds of the structure R-C(=O)-Z as we do in this chapter and in Chapter 15.

We can perform these hydrolysis reactions using either acid or base catalysis. Nitriles are usually hydrolyzed in order to synthesize the final carboxylic acid product (Figure 16.110). An efficient method utilizes aqueous sodium hydroxide

containing hydrogen peroxide followed by acidification of the reaction mixture as illustrated in Figure 16.111.

Figure 16.111

We can isolate amides as reaction products by hydrolyzing the nitrile with concentrated sulfuric acid (Figure 16.112).

Figure 16.112

However in more dilute aqueous acid , the intermediate amide is further hydrolyzed to the carboxylic acid.

Hydrolysis Reaction Mechanism. We show mechanisms for acid and base catalyzed formation of amides from nitriles in Figures 16.113 and 16.114.

Figure 16.113 and Figure 16.114

We gave mechanistic details for the subsequent hydrolysis of amides to carboxylic acids earlier in this chapter.

When hydrogen peroxide is present in the base catalyzed reaction, the strongly nucleophilic hydroperoxide ion (HOO-) is the reactive nucleophile. It forms in an acid/base reaction between HO- and HOOH.

Addition of Organometallic Reagents. Reaction of nitriles with organometallic reagents such as Grignard reagents followed by hydrolysis leads to the formation of ketones as shown in Figure 16.115.

Figure 16.115