17: Oxidation and Reduction

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Some Comments about this Chapter

Although we introduced oxidation and reduction reactions of organic compounds in earlier chapters, they are so important that we bring them together in this chapter. Chemists use "redox" reactions extensively in synthsis of organic compounds, and they are of immense biological importance.

When we first wrote this chapter, a combined presentation of redox reactions in a basic organic text was unusual. They typically appeared in chapters on the functional groups of the reactants or products. This functional group organization has merits, but a combined presentation of redox reactions of a variety of functional groups in one chapter allows us to more easily compare reagents and reaction mechanisms.

17.1 Oxidation and Reduction Occur Together

We cannot oxidize a chemical species using a chemical reaction without simultaneously reducing another chemical species. As a result, organic *oxidation* requires a simultaneous *reduction* reaction usually of inorganic reagents. Similarly, *reduction* of an organic compound generally involves concomitant *oxidation* of inorganic reagents.

Redox Reactions Involve Electron Transfer (17.1A)

Oxidation and reduction reactions (**redox** reactions) involve the overall *transfer of electrons* from one species to another species. The chemical species being *oxidized* loses electrons to the chemical species being *reduced*.

Inorganic Redox Reactions. The ionic inorganic **redox** reaction involving Fe and Cu ions (Figure 17.001) illustrates this electron transfer.

Figure 17.001

$$Fe^{+3} + Cu^{+1} = Fe^{+2} + Cu^{+2}$$

The two balanced ionic half-reactions (Figure 17.002) that make up this overall reaction show that Cu^{+1} loses an electron (e^-) when it is oxidized to Cu^{+2}.

Figure 17.002

$$Cu^{+1} = Cu^{+2} + e^-$$
$$Fe^{+3} + e^- = Fe^{+2}$$

At the same time, Fe^{+3} gains an electron when it is reduced to Fe^{+2}. The electron gained by Fe^{+3} comes from Cu^{+1}.

> **Remembering How the Electrons Flow.** If you have trouble remembering the way electrons flow in oxidation and reduction reactions, the following observations help me: The word *Oxidation* starts with the letter "O" and that is also the second letter of the word *pOsitive*. Things become more *pOsitive* when they are *Oxidized*. Similarly, both *rEduction* and *nEgative* have the same second letter "E" and things become more *nEgative* when they are *rEduced*.

Organic Redox Reactions. Electron transfer is usually difficult to see in the organic reactant(s) and product(s) in an organic redox reaction. For example the conversion of a 2° alcohol to a ketone (Figure 17.003) is oxidation, but it is not obvious that electron transfer has occurred by looking at the alcohol and ketone structures.

Figure 17.003

This electron transfer is generally visible, however, in the inorganic reagents and products of redox reactions. In the case of oxidation of an alcohol to a ketone, an oxidizing agent can be a chromium compound with Cr in its +6 oxidation state (Cr(VI)). During the reaction, Cr is reduced to Cr(III) in a +3 oxidation state showing that it gains electrons from the alcohol as it is oxidzed to the ketone.

Oxidation Levels of Organic Compounds (17.1B)

We can demonstrate the oxidation or reduction of an organic compound by calculating oxidation numbers for the C atoms that are oxidized or reduced.

Carbon Oxidation Numbers. We showed calculations for C oxidation numbers in Chapter 13 for alcohols, ketones and aldehydes, and carboxylic acids. Similar calculations for other organic compounds allow us to place them at the various **oxidation levels** that we show in Table 17.01.

Table 17.01. Relative Oxidation Levels of Organic Compounds

Relative Carbon Oxidation Number

← (More Reduced) ***(More Oxidized) →***

-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
	$R\underline{C}H_2\underline{C}H_2R$	$R\underline{C}H=\underline{C}HR$	$R\underline{C}\equiv\underline{C}R$			
			$R\underline{C}(OH)H-\underline{C}(OH)HR$			
$R\underline{C}H_3$		$R\underline{C}H_2OH$		$R\underline{C}(=O)H$		$R\underline{C}(=O)OH$
			$R\underline{C}H(OH)R$		$R\underline{C}(=O)R$	
		$R\underline{C}H_2Z$				$R\underline{C}(=O)Z$
	Oxidation →					
					← Reduction	

The relative oxidation numbers are at the top of the table for the underlined C atoms in the structures below them. As the oxidation number becomes more positive (less negative), the C atom becomes more oxidized. As the oxidation number becomes less positive (more negative) the C atom becomes more reduced. Do not memorize these oxidation numbers since they will change depending on the R group. But do learn the relative locations of compounds in each row, in order to understand which compounds are in higher or lower oxidation states.

Definitions of Organic Oxidation and Reduction. You can see by looking at the compounds in Table 17.01, that oxidation of a C atom in an organic compound involves one or more of the following changes:

(1) *an increase in the multiple bond order of the C*

(2) *addition of O to a C*

(3) *replacement of an H on a C by O*

We combine these criteria in the statement that *"oxidation of organic molecules involves a gain in oxygen and/or loss of hydrogen"*. Look at each oxidation reaction in the following sections to see that one or more of these criteria are met.

Presentation of Redox Reactions in this Chapter. We begin our discussions of redox reactions with oxidation reactions. They are in sections corresponding to the functional group that we oxidize. Their titles are *Oxidation of Alcohols and Aldehydes* (17.2), *Oxidation of Carbon-Carbon Multiple Bonds* (17.3), *Oxidation of Alkyl Groups* (17.4), and*Formation of Phenols and Quinones* (17.5).

17.2 Oxidation of Alcohols and Aldehydes

Oxidation of alcohols gives ketones or aldehydes, and oxidation of aldehydes gives carboxylic acids as we show in Figure 17.004 where the designation [O] signifies that the reaction is an oxidation.

Figure 17.004

$R\underline{C}H_2OH$	$\xrightarrow{[O]}$	$R\underline{C}(=O)H$
1°-Alcohol		Aldehyde
$R_2\underline{C}HOH$	$\xrightarrow{[O]}$	$R_2\underline{C}=O$
2°-Alcohol		Ketone
$R\underline{C}(=O)H$	$\xrightarrow{[O]}$	$R\underline{C}(=O)OH$
Aldehyde		Carboxylic Acid

We described these reactions in Chapter 13, but give more detailed information about them here. You can see that they fit the criteria for oxidation that we listed above. In the first two reactions, the multiple bond order of $\underline{C}$ increases due to a "loss of H". In the third reaction, there is replacement of an H on $\underline{C}$ by O with a "gain in O".

Oxidation Using Cr(VI) Reagents (17.2A)

Common oxidizing agents for these oxidations are Cr(VI) compounds (Figure 17.005)(next page). Cr(VI) is reduced to Cr(III) during oxidation of the alcohol or aldehyde.

Figure 17.005

				Ketone		
Alcohol		Cr(VI)		or		Cr(III)
or	and	Reagent	→	Aldehyde	and	Reagent
Aldehyde				or		
				Carboxylic Acid		

Chromate and Dichromate Reagents. We prepare these Cr(VI) reagents by adding sodium or potassium dichromate ($Na_2Cr_2O_7$ or $K_2Cr_2O_7$), or chromium trioxide (CrO_3), to aqueous solutions of sulfuric or acetic acid. Several Cr(VI) species are present in these solutions in equuilibria with each other (Table 17.02 and Figure 17.006).

Figure 17.006

Table 17.02. Cr(VI) Species Present in Solutions of $K_2Cr_2O_7$, $Na_2Cr_2O_7$, or CrO_3 in Sulfuric or Acetic Acid.

Chromate Species	Dichromate Species
H_2CrO_4	$H_2Cr_2O_7$
$HCrO_4^{-1}$	$HCr_2O_7^{-1}$
CrO_4^{-2}	$Cr_2O_7^{-2}$

We can imagine that chromate ion (CrO_4^{-2}) forms from dichromate ($Cr_2O_7^{-2}$) as we show in Figure 17.006, or that it forms from addition of H_2O to CrO_3 followed by deprotonation. The three "chromate" species, and three "dichromate" species, are simply differently protonated froms of CrO_4^{-2} or $Cr_2O_7^{-2}$.

Unwanted Oxidation of Aldehydes. Cr(VI) reagents are powerful oxidizing agents useful for oxidizing 2° alcohols to ketones (Figure 17.005) because ketones are resistant to further oxidation. However aldehydes formed from oxidation of 1° alcohols using Cr(VI) reagents are usually further oxidized to carboxylic acids (Figure 17.004).

We can prevent this by using modified Cr(VI) reagents that we describe later in this section. We can also distill the intermediate aldehyde from the reaction mixture as it forms before it is oxidized further. This is often possible because boiling points of aldehydes are usually much lower than those of the 1° alcohols from which they are formed.

Oxidation of Cyclic Ketones. When ketones react with Cr(VI) reagents at high temperatures, the result is a complicated mixture of products. An exception is oxidation of cyclic ketones that give good yields of dicarboxylic acids (Figure 17.007).

Figure 17.007

Jones Oxidation. Because acyclic ketones are relatively stable to Cr(VI) oxidations, acetone is frequently used as the solvent for Cr(VI) oxidations of alcohols. In these reactions, a $CrO_3/H_2SO_4/H_2O$ mixture is slowly added to an acetone solution of the alcohol, or the alcohol is mixed with an acetone solution of $CrO_3/H_2SO_4/H_2O$. Both the $CrO_3/H_2SO_4/H_2O$ mixture and that mixture in acetone are called the **Jones reagent** while the resultant oxidation reaction is called a **Jones oxidation**.

Besides being stable to oxidation, acetone dissolves many higher molecular mass alcohols that have relatively low solubility in water, and it is easy to remove from the reaction mixture because of its low boiling point (56°C). We symbolize a Jones oxidation by the set of reagents shown in the example in Figure 17.008.

Figure 17.008

Modified Cr(VI) Reagents. Organic chemists have developed modified Cr(VI) reagents that are weaker oxidizing agents than the Jones reagent and permit the formation of aldehydes without their subsequent oxidation to carboxylic acids. Three of these are complexes of pyridine with Cr(VI) species (Figure 17.009).

Figure 17.009

When used with the solvent dichloromethane (CH_2Cl_2), they conveniently convert 1° alcohols to aldehydes (Figure 17.010).

Figure 17.010

Organic chemists also use these pyridine complexes to convert 2° alcohols to ketones when another part of the molecule may be sensitive to the more vigorous conditions of acidic dichromate or acidic CrO_3 oxidizing agents.

Oxidation of Allylic Alcohols. Although milder oxidizing agents such as PCC are preferable, the Jones Reagent oxidizes 1° allylic alcohols to α,β-unsaturated aldehydes (Figure 17.011) without further conversion to carboxylic acids. This is because the conjugated C=O group of α,β-unsaturated aldehydes is less susceptible to further oxidation than C=O groups of unconjugated aldehydes..

Figure 17.011

Cr(VI) Oxidation Mechanisms. Mechanisms of Cr(VI) oxidations are complex with many steps. We show the general transformations that occur in oxidation of an alcohol to an aldehyde or ketone in Figure 17.012.

Figure 17.012

This summary shows there are intermediate Cr(V) and Cr(IV) species, and intermediate organic free radicals on the paths from alcohol to ketone or aldehyde.

The "overall reaction" includes a series of steps in which the alcohol and Cr(VI) reagent form a "chromate ester" that subsequently gives a carbonyl compound and Cr(IV) via an elimination reaction (Figure 17.013).

Figure 17.013

The further oxidation of an aldehyde to a carboxylic acid has mechanistic steps analogous to those in Figures 17.012 and 17.013 for alcohol oxidation.

The reactions in Figure 17.013 are similar to nucleophilic acyl substitution reactions in Chapter 16. The alcohol adds to a Cr=O bond to give a pentavalent intermediate that subsequently loses hydroxide ion (Figure 17.014).

Figure 17.014

The intermediate reacts further to give the ketone product and the Cr(IV) species.

Other Inorganic Oxidizing Agents (17.2B)

Besides Cr(VI) reagents, there are a variety of other inorganic oxidizing reagents that oxidize alcohols and aldehydes. We describe two of these below.

MnO_2. This Mn(IV) reagent selectively oxidizes allylic and benzylic alcohols to ketones or aldehydes (Figure 17.015) and the Mn(IV) is reduced to Mn(II).

Figure 17.015

OH groups that are not allylic or benzylic are not oxidized, and the aldehyde products do not further oxidize to carboxylic acids.

Sodium Hypochlorite (NaOCl). This simple inorganic reagent is frequently used in commercial applications of oxidation such as conversion of 2° alcohols to ketones (Figure 17.016).

Figure 17.016

$$R_2CHOH \xrightarrow[CH_3CO_2H]{NaOCl} R_2C{=}O$$

NaOCl is the active ingredient in commercial liquid bleach, so it is inexpensive and readily available.

Organic Oxidizing Agents (17.2C)

Several different types of organic oxidizing agents oxidize alcohols or carbonyl compounds.

Ketones to Esters. Although inorganic oxidizing agents generally do not oxidize ketones to useful products, we can transform ketones into esters by reactions with **peroxycarboxylic acids** such as **peroxytrifluoroacetic acid** (**trifluoroperacetic acid**) (Figure 17.017).

Figure 17.017

Synthesis of Peroxycarboxylic Acids. Peroxycarboxylic acids (or peracids) from reactions of carboxylic acids with hydrogen peroxide (H_2O_2) as we show in Figure 17.018 for trifluoroperacetic acid.

Figure 17.018

In the **Baeyer-Villiger rearrangement** (Figure 17.017), it appears that the peroxyacid inserts an O into the C-R' bond of the ketone (RC(=O)-R'). It is an oxidation reaction because O is added to the C=O carbon to give C(=O)-O while the oxidation number of the O transferred from the peracid decreases from -1 to -2 indicating that it is reduced.

We show the mechanism of the reaction in Figure 17.019.

Figure 17.019

A key step is migration of the R' group with its bonding electron pair from C to O (fourth step in Figure 17.019). The relative rate (*relative ease*) of migration of this R' group is R' = H > 3° > 2°, aryl > 1° > CH_3.

This migration selectivity has synthetic utility. For example, we can convert compounds of the structure R-C(=O)-CH_3 exclusively into the alcohols R-OH by the sequence of reactions that we show in Figure 17.020.

Figure 17.020

In contrast the facile migration ability of H transforms aldehydes R-C(=O)-H into the corresponding carboxylic acids R-C(=O)-OH. The Baeyer-Villiger rearrangement also allows us to synthesize lactones from cycloalkanones (Figure 17.021).

Figure 17.021

Aldehydes to Carboxylic Acids and Alcohols. We can convert aldehydes that have no α-H's into an equimolar mixture of their corresponding carboxylic acid and alcohol using a strong base such as sodium hydroxide (Figure 17.022).

Figure 17.022

In this **Cannizzaro reaction**, the carboxylic acid is an oxidation product of the aldehyde while the alcohol is a reduction product. As is the case in the *Baeyer-Villliger* reaction, one organic molecule is the reducing agent (and gets *oxidized*) while another organic molecule is the oxidizing agent (and gets *reduced*).

We outline the detailed mechanism in Figure 17.023.

Figure 17.023

The key step is the transfer of an H with its bonding electron pair (a hydride transfer) from the intermediate anion to another molecule of aldehyde. There is evidence that the intermediate anion can react again with $^-$OH to give the even more powerful hydride transfer agent that we show in Figure 17.024.

Figure 17.024

Alcohols to Ketones or Aldehydes. A simple ketone such as acetone ((CH_3)$_2$C=O) can serve as an oxidizing agent for the oxidation of a 1° or 2° alcohol to an aldehyde or ketone (Figure 17.025).

Figure 17.025

The mechanism of this **Oppenauer oxidation** reaction involves conversion of the alcohol ($R_2C\underline{H}OH$) to be oxidized into an alkoxide species ($R_2C\underline{H}O^-$) that transfers a hydride ion (the underlined $\underline{H}$) to acetone. As a result, acetone is reduced and the alkoxide ion becomes a carbonyl compound (Figure 17.026).

Figure 17.026

Both the alkoxide species ($R_2C\underline{H}O^-$) and acetone are bonded to Al in an aluminum trialkoxide molecule (Figure 17.027) formed by reaction of R_2CHOH with a molecule such as $Al(O\text{-}C(CH_3)_3)$.

Figure 17.027

This hydride transfer reaction is similar to that in the *Cannizzaro reaction* shown earlier.

Dimethylsulfoxide. A more recent organic oxidizing agent is *dimethylsulfoxide* (*DMSO*) that can oxidize primary alcohols and halogenated compounds to aldehydes or ketones (Figure 17.028).

Figure 17.028

The mechanism of this **Swern oxidation** is complex and we show part of it in Figure 17.029.

Figure 17.029 (see handwritten, M4, 1194)

The alcohol is first converted to an intermediate sulfoxonium ion that decomposes to dimethylsulfide and the desired aldehyde.

17.3 Oxidation of Carbon-Carbon Multiple Bonds

There are a variety of oxidation reactions in which C=C bonds add oxygen or are cleaved to oxygenated products (Figure 17.030).

Figure 17.030

Addition of Oxygen to C=C Bonds (17.3A)

When oxygen adds to C=C bonds, the products are epoxides or 1,2-diols (Figure 17.030).

Epoxide Formation Using Peroxyacids. Epoxides (oxacyclopropanes) are products of oxidation of C=C bonds using *peroxycarboxylic acids* such as *m-chloroperbenzoic* acid, *perbenzoic* acid, or *peracetic* acid, (e.g. Figure 17.031).

Figure 17.031

The reaction mechanism is a single step (concerted) transfer of an oxygen atom to the C=C (Figure 17.032).

Figure 17.032

The transition state is the structure in the brackets.

Formation of syn-1,2-Diols Using OsO_4 or MnO_4^-. **Osmium tetroxide** (OsO_4), or *potassium permanganate* ($KMnO_4$) in aqueous base, react with alkenes to yield 1,2-diols (Figure 17.033).

Figure 17.033

These reactions give stereospecific ***syn*** addition of the two OH groups because they involve the formation of intermediate cyclic inorganic "esters" shown in Figure 17.034 that decompose to the diol in subsequent steps.

Figure 17.034

Osmium tetratoxide gives excellent yields of 1,2-diols, but it is toxic (it causes blindness) and expensive. *Potassium permanganate* is inexpensive and safer to use, but it gives much lower yields of diols. This is partly because it can cleave the C-C bond of the diol as we describe in a subsequent section.

Formation of anti-1,2-Diols. In order to obtain overall *anti* addition of two OH groups to a C=C bond, we first synthesize an epoxide and then open the 3-membered ring using aqueous acid (Figure 17.035).

Figure 17.035

We can isolate the epoxide, but do not usually do this. We convert the alkene directly to the diol by treating it with an aqueous mixture of H_2O_2 and formic acid (a source of *performic acid*), or with *m-chloroperbenzoic* acid in H_2O. The acidic aqueous reaction mixture causes ring opening of the intermediate epoxide.

Oxidative Cleavage of Carbon-Carbon Multiple Bonds (17.3B)

Oxidizing reagents that cleave C=C or C≡C bonds as they add oxygen to the C atoms include ozone (O_3), CrO_3, and $KMnO_4$ (in <u>neutral</u> or <u>acidic</u> solution) (Figure 17.036).

Figure 17.036

Cleavage Using Ozone (O_3). The mechanism of the reaction between ozone (O_3) and an alkene involves direct addition of O_3 to give an unstable intermediate that decomposes to an **ozonide** intermediate (Figure 17.037).

Figure 17.037

We do not isolate the ozonide (it usually is an explosive compound), but react it with zinc metal in acetic acid to give the product carbonyl compounds (Figure 17.038).

Figure 17.038

These carbonyl compounds are ketones or aldehydes depending on the substitution pattern on the double bondAldehyde products do not oxidize to carboxylic acids under these reaction conditions.

Cleavage Using CrO_3 or $KMnO_4$. The aldehyde products do oxidize further when they arise in reactions of alkenes with the powerful oxidizing agents CrO_3, or $KMnO_4$ in neutral or acidic solution. These reagents cleave the C=C bond, and oxidize each of the C=C carbons to the highest oxidation state consistent with their substitution patterns (Figure 17.039).

Figure 17.039

We obtain the highest yields of carbonyl compound products using KMnO4 dissolved in benzene containing a Crown ether. It permits $KMnO_4$ to dissolve in benzene by solvating the K^+ ion as we show in Figure 17.040.

Figure 17.040

It is important for you to remember that $KMnO_4$ in basic solution yields 1,2-diols without cleavage of the original C=C bond. These 1,2-diols are likely intermediates when we react CrO_3, or $KMnO_4$, with alkenes in neutral or acidic solution. However, under these reaction conditions they further oxidize to ketones and/or aldehydes, and aldehydes further oxidize to carboxylic acids (Figure 17.041.)

Figure 17.041

Cleavage of 1,2-Diols Using HIO_4 or $Pb(OAc)_4$. We can also oxidatively cleave C=C bonds using the sequence of two reactions in Figure 17.042.

Figure 17.042

The 1,2-diols, from reaction of OsO_4 with alkenes, further oxidize to carbonyl compounds with **HIO_4** (**periodic acid**) or **$Pb(OAc)_4$** (**lead tetraacetate**) (Figure 17.042). This sequence of two separate reactions gives high yields of relatively pure products in each step. Once again, aldehydes are stable to further oxidation under these reaction conditions.

Oxidation Using Singlet Oxygen. Molecular oxygen (O_2) in air is an oxidizing agent and we describe one of its oxidation reactions ("**autoxidation**") in the next section on oxidation of alkyl groups. This atmospheric O_2 exists in a "triplet" electronic state (symbolized as $^3O_2$). In that electronic state, the O_2 molecule acts like it is a free radical •O-O• with an unpaired electron on each O atom. [Note that there are two unshared pairs of electrons on each O atom that we do not show here.]

O_2 can also exist in a "singlet" electronic state ($^1O_2$) that has no unpaired electrons. We can represent it as O=O, and it has very different chemical properties than triplet oxygen [Note that once again we have omitted the two unshared pairs of electrons on each oxygen.].

We show three types of reactions of singlet oxygen with molecules containing C=C bonds in Figure 17.043.

Figure 17.043

In the first reaction, *singlet* O_2 reacts with an alkene to form a hydroperoxide in which the C=C bond has rearranged. In the second reaction, *singlet* oxygen adds to the end carbons of a conjugated diene to give a cyclic peroxide. Finally in the third reaction, *singlet* oxygen adds across a C=C bond to give a four-membered cyclic peroxide called a **dioxetane**. The *dioxetane* is an unstable intermediate that fragments into carbonyl compounds as we show in the figure.

We can form *singlet* O_2 chemically by reaction between H_2O_2 and NaOCl. It also forms photochemically by irradiation of O_2 with light in the presence of organic molecules called **photosensitizers**.

17.4 Oxidation of Alkyl Groups

Several different reagents oxidize alkyl groups (R) bonded to double bonds (allylic R groups), or to aromatic rings (benzylic R groups). The products can be alcohols, ketones or aldehydes, and carboxylic acids (Figure 17.044).

Figure 17.044

Metal Oxide Oxidations (17.4A)

Oxidizing agents include *potassium permanganate* ($KMnO_4$), *chromium trioxide* (CrO_3), *chromyl chloride* (Cl_2CrO_2), and *selenium dioxide* (SeO_2).

$KMnO_4$ and CrO_3. The strong oxidizing agents $KMnO_4$ or CrO_3 oxidize alkyl groups on aromatic rings to carboxylic acid groups (directly attached to the ring) if there is at least one H on the C attached to the ring (Figure 17.045).

Figure 17.045

These reagents are so powerful that we limit their use to simple aromatic systems with no other oxidizable functional groups.

Cl_2CrO_2. In contrast, the milder oxidizing agent *chromyl chloride* (Cl_2CrO_2) oxidizes methyl groups on aromatic rings to aldehyde groups without further oxidation to carboxylic acids (Figure 17.046).

Figure 17.046

SeO_2 Oxidations. Even more selectively, *selenium dioxide* (SeO_2) oxidizes allylic R groups to alcohols, and benzylic R groups to alcohols or carbonyl compounds (Figure 17.047).

Figure 17.047

This reagent is particularly useful because it does not oxidize other functional groups that may be oxidized by $KMnO_4$ or CrO_3. For example, the double bonds in the allylic systems above are easily oxidized by either $KMnO_4$ or CrO_3 as we previously described, but are stable to SeO_2. SeO_2 also selectively oxidizes CH_2 groups attached (α) to carbonyl groups (Figure 17.048).

Figure 17.048

O_2 Oxidations (Autoxidation) (17.4B)

Atmospheric oxygen (O_2) sometimes reacts with organic compounds to give peroxides (Figure 17.049).

Figure 17.049

This **autoxidation** reaction is generally an unwanted occurrence that organic chemists try to avoid by keeping reaction mixtures or stored samples of organic compounds free of oxygen. *Autooxidation* is catalyzed by light so organic compounds are usually packaged in bottles that are opaque or made of dark brown glass.

Autoxidation Mechanism. *Autoxidation* has a free radical chain mechanism that we partially outline in Figure 17.050.

Figure 17.050

(We showed other examples of free radical chain reactions in Chapter 11).

While the two "propagation" steps (Figure 17.050) are fast reactions, autoxidation is usually not a rapid process because we need to use catalysts (**free radical initiators**) to generate the initial R· or RO_2· that start an oxidation chain. Atmospheric oxygen is usually not sufficiently reactive to spontaneously generate these radicals by direct reaction with an organic compound.

Synthetic Utility. Autoxidation has only limited synthetic utility because so many types of C-H bonds can be converted to C-OOH groups that it is difficult to have selective reactions. However, one important industrial process using autoxidation is the conversion of **2-propylbenzene** (commonly named **cumene**) to *phenol* and *acetone* (Figure 17.051).

Figure 17.051

The particular C-H of *cumene* that is abstracted is much more reactive than any of the other C-H's because it is both 3° and *benzylic* (on a C directly attached to an aromatic ring). The formation of the hydroperoxide (usually called **cumene hydroperoxide**) is the actual autooxidation process. The decomposition of this peroxide to phenol and acetone involves subsequent ionic reactions that occur after oxidation.

17.5 Phenols, Hydroquinones, and Quinones

We can think of phenols, hydroquinones, and quinones (Figure 17.052), as successive oxidation products of benzene.

Figure 17.052

Formation of Phenols (17.5A)

It is difficult to directly add an OH group to a benzene ring, so we usually synthesize phenols by transforming another functional group, already on an aromatic ring, into an OH group. We summarize several such reaction sequences in Figure 17.053 and describe them in the following sections.

Figure 17.053

In each case, we form the intermediate substituted benzene directly or indirectly by an electrophilic aromatic substitution reaction on benzene.

From Cumene. Organic chemists prepare *phenol* commercially by autoxidation of cumene as we just described (Figure 17.051). Cumene comes from the Friedel-Crafts alkylation (Chapter 12) of benzene (Figure 17.054).

Figure 17.054

This procedure also gives substituted *phenols* by autoxidation of ring-substituted *cumenes*.

From Aryl Halides. Another commercial preparation of phenol involves reaction of chlorobenzene with sodium hydroxide at high temperature and pressure (Figure 17.055).

Figure 17.055

While it looks as if HO^- displaces Cl^- by nucleophilic substitution , this reaction has an elimination-addition mechanism (Figure 17.056) in which benzyne (C_6H_4) (Chapter 12) is an intermediate.

Figure 17.056

We synthesize chlorobenzene from benzene by electrophilic aromatic chlorination (Chapter 12). and show the overall reaction sequence for the conversion of benzene to phenol *via* chlorobenzene in Figure 17.057.

Figure 17.057

From Arylsulfonic Acids. When we "fuse" arylsulfonic acid salts ($Ar-SO_3^-$ Na^+) with sodium hydroxide at high temperatures, we replace the SO_3^- group with an O^- group. Subsequent protonation with acid gives phenols as shown in Figure 17.058.

Figure 17.058

We synthesize arylsulfonic acids from the aromatic compound by electrophilic aromatic sulfonation. and show an overall reaction sequence for conversion of benzene to phenol *via* arylsulfonic acids in Figure 17.059.

Figure 17.059

From Diazonium Ions. The most general laboratory method for substituting OH on an aromatic ring is replacement of an N_2^+ group (a **diazonium** group) by an OH group (Figure 17.060).

Figure 17.060

We form N_2^+ groups from NH_2 groups by a *nitrosation* reaction (Figure 17.061).

Figure 17.061

While there is no synthetically useful direct method to place an NH_2 group on an unsubstituted aromatic ring, we can synthesize amino benzenes and other amino arenes by reducing a nitro group on an aromatic ring (Chapter 12) (Figure 17.062).

Figure 17.062

We describe this conversion of NO_2 into NH_2 in the section on reduction reactions later in this chapter.

Formation of Quinones and Hydroquinones (17.5B)

Quinones are oxidation products of phenol or *p*-substituted phenols (Figure 17.063).

Figure 17.063

Fremy's salt ($(KSO_3)_2N\text{-}O\cdot$) is a free radical that oxidizes phenol by a free radical reaction mechanism. We oxidize the *p*-substituted phenols (Y = OH, NH_2, X, OR, R), with $Cr_2O_7^{-2}$ in H_2SO_4.

We can reduce quinones to hydroquinones using lithium aluminum hydride (Figure 17.064).

Figure 17.064

We describe this reaction and the reducing reagent ($LiAlH_4$) in a later section. We can reoxidize hydroquinones to quinones as we previously showed in Figure 17.063.

> **Quinones and Hydroquinones are Biologically Important**. The quinone **ubiquinone** also known as **coenzyme Q** (**CoQ**) (Figure 17.065) is important in biological electron transport processes.
>
> Figure 17.065
>
> It accepts an electron (is reduced) forming an intermediate *semiquinone* that can also accept an electron (be reduced) to give the hydroquinone **ubiquinol** shown above. *Ubiquinol* donates electrons to *cytochromes* that give electrons to molecular oxygen thereby reducing it.

17.6 Reduction Reactions

The reverse of each oxidation reaction in the previous sections is a reduction reaction

General Features (17.6A)

The characteristics of reduction reactions are opposite to those of oxidation reactions. As a result, organic molecules *lose* oxygen and/or *gain* hydrogen in reduction reactions.

While oxidation and reduction are equally important processes, we often describe *reduction* reactions using terms associated with *oxidation.* For example, when we reduce a molecule , we say it is in a "lower *oxidation* state" rather than in a "higher reduction state". Similarly, we measure the extent of reduction of a C atom by its "*oxidation* number". Finally, we describe the relative levels of reduction of various compounds using their "relative *oxidation* levels" as in Table 17.01.

Types of Reduction Reactions (17.6B)

We show important types of reduction reactions in Figure 17.066 [next page]. We use the general symbol [H] to designate reduction because usually we add one or more H's to the molecule during its reduction. These H's typically come from molecular hydrogen (H_2) or from metal hydride reagents that we describe below.

Figure 17.066

$RC\equiv CR$ or $R_2C=CR_2$ Alkynes or Alkenes	$\xrightarrow{[H]}$	$RCH=CHR$ or $R_2CH\text{-}CHR_2$ Alkenes or Alkanes
$R_2C=O$ Ketones or Aldehydes	$\xrightarrow{[H]}$	R_2CHOH or R_2CH_2 Alcohols or Alkyl Groups
$R\text{-}C(=O)\text{-}Z$ Carboxylic Acid Derivatives	$\xrightarrow{[H]}$	$R\text{-}C(=O)\text{-}H$ or $R\text{-}CH_2OH$ Aldehydes or Alcohols
$R\text{-}C\equiv N$ or $R\text{-}NO_2$ Nitriles or Nitro compounds	$\xrightarrow{[H]}$	$R\text{-}CH_2\text{-}NH_2$ or $R\text{-}NH_2$ Amines

Reduction Using H_2. In many of these reactions, it appears that one or more molecules of H_2 adds across a multiple bond (Figure 17.067).

Figure 17.067

In fact, molecular H_2 in the presence of various metal catalysts can *reduce* most multiple bonds. We describe this **catalytic hydrogenation** at the end of Chapter 10 for reduction of C=C and C≡C bonds and show examples in Figure 17.068.

Figure 17.068

Since catalytic hydrogenation also reduces C=O, C=N, and C≡N bonds, this process often simultaneously reduces most or all of the multiple bonds in a molecule. Because of this lack of selectivity, we generally use catalytic hydrogenation to reduce C=C and C≡C bonds in molecules where other types of multiple bonds are not present or are protected.

Metal Hydride Reagents. Organic chemists have developed a variety of metal hydride reagents that specifically reduce various types of multiple bonds. We show some particularly important examples that we describe in this chapter in Figure 17.069.

Figure 17.069

All of these reagents contain a boron (B) or aluminum (Al) atom bonded to one or more H atoms. They reduce multiple bonds by transferring an H with its bonding electron pair (a *hydride ion*) from B or Al to the positively polarized C atoms in C=O, C=N, and C≡N bonds. We show a general representation of this type of reaction for an "Al-H" reagent and a C=O bond in Figure 17.070.

Figure 17.070

Presentation of Reduction Reactions. We describe the use of these reducing agents to carry out particular types of reduction reactions in the following sections titled *Reduction of Ketones and Aldehydes* (17.7), *Reduction of R-C(=O)-Z and Related Compounds* (17.8), and *Reduction of C=C and C≡C Bonds* (17.9).

We gave a detailed presentation of the reduction reactions of alkenes and alkynes in Chapter 10, however, we review these reactions again in section 17.9 along with a discussion of related reduction reactions of benzenoid aromatic systems (arenes).

17.7 Reduction of Ketones and Aldehydes

Reduction of ketones or aldehydes transforms their C=O groups to alcohol groups (HC-OH), or to CH_2 groups (Figure 17.066). We list the specific reactions in this section in Figure 17.071 .

Figure 17.071

Alcohols from Metal Hydride Reductions (17.7A)

We show typical reaction conditions for $LiAlH_4$, $NaBH_4$, or B_2H_6 reductions of aldehydes or ketones to give alcohols in Figure 17.072.

Figure 17.072

Because of the relatively low reactivity of $NaBH_4$, we can use a protic solvent such as ethanol when $NaBH_4$ is the reducing agent. In contrast, for $LiAlH_4$ reductions we must use aprotic solvents such as ethers. $LiAlH_4$ reacts violently with alcohols or other protic solvents giving molecular H_2 (Figure 17.073) that subsequently undergoes combustion with atmospheric oxygen.

Figure 17.073

$LiAlH_4$ Mechanism. The mechanism for $LiAlH_4$ reduction of a C=O group is complex with many reaction intermediates. In the first step, AlH_4^- transfers an H atom with its electron pair (a "hydride") to the C=O carbon (Figure 17.074).

Figures 17.074

In this step, the C=O double bond becomes an H-C-O single bond and the carbon atom is reduced.

The resultant intermediate $R_2CH-O-AlH_3^-$ is probably complexed with Li^+ and solvent molecules (usually diethyl ether or THF) (Figure 17.075).

Figure 17.075

This intermediate can add hydride to unreacted $R_2C=O$ because it has Al-H bonds. However, it can also participate in a series of reactions that ultimately leads to the formation of $(R_2CH-O)_4Al^-$ and AlH_4^- (Figure 17.076).

Figure 17.076

As a result, hydride transfer can occur from a variety of species. The alcohol product ultimately forms by hydrolysis of $(R_2CH-O)_4Al^-$ (Figure 17.077).

Figure 17.077

$NaBH_4$ Mechanism. In the $NaBH_4$ mechanism, ethanol (shown as R-OH) may transfer a proton to the O of the ketone or aldehyde simultaneously with hydride transfer from BH_4^- to the C (Figure 17.078).

Figure 17.078

After reduction of the carbonyl compound, aqueous acid neutralizes the basic reaction mixture (Figure 17.072). Intermediates such as $CH_3CH_2O\text{-}BH_3^-$ may also serve as hydride ion donors to unreacted carbonyl compound.

Alcohols from Diborane Reduction. Organic chemists use **diborane** (**B_2H_6**) less frequently than either $LiAlH_4$ or $NaBH_4$ to reduce ketones or aldehydes, but it is a useful reagent because of its selectivity (Figure 17.079).

Figure 17.079

The hydride transfer reagent is probably BH_3 that forms from B_2H_6 in the reaction mixture as we described in Chapter 10 and show again in Figure 17.080.

Figure 17.080

We give a mechanism for diborane reduction of a C=O group in Figure 17.081.

Figure 17.081

Neutral *versus* Complex Metal Hydrides. Organic chemists classify lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) as *complex metal hydrides* because they are ionic compounds with negatively charged AlH_4^- and BH_4^- ions. In contrast, neutral metal hydrides such as BH_3 (that exists in its dimeric form B_2H_6), have no charge. As a result, there is a profound difference in their reactivity and selectivity.

Both AlH_4^- and BH_4^- are electron rich species that react by initially donating a hydride to the carbon atom of the multiple bond (Figures 17.074 and 17.078). In contrast, BH_3 is an electron deficient *Lewis Acid*. In the first step of its reactions with C=O, C=N, and C≡N bonds, it bonds to an unshared electron pair on the heteroatom O or N. Subsequently, there is an intramolecular hydride transfer to C as we showed in Figure 17.081.

Because BH_3 is electron deficient (*electrophilic*), it also reacts with C=C and C≡C bonds as we described in Chapter 10. C=C and C≡C bonds prefer to donate electron density to electrophilic species rather than accept it from electron rich nucleophilic species such as BH_4^- and AlH_4^- (Figure 17.082).

Figure 17.082

Alcohols from Organic Reducing Agents (17.7B)

We can form alcohols by reduction of ketones or aldehydes using two organic reactions that we have previously discussed as oxidation reactions. These are the *Cannizzaro reaction* and the **Meerwein-Ponndorf-Verley reduction** that is the reverse of the *Oppenauer oxidation*.

Cannizzaro Reaction. We show the Cannizzaro reaction again in Figure 17.083.

Figure 17.083

In this reaction, two molecules of an aldehyde (without α-H's) simultaneously oxidize and reduce giving an alcohol and a carboxylic acid. You can see in the mechanism that we show again here (Figure 17.023) that a hydride transfer reaction occurs that is analogous to those in metal hydride reductions.

Figure 17.023

However, in this case the hydride transfer agent is a negatively charged organic compound.

Meerwein-Ponndorf-Verley Reduction. This reduction reaction is the reverse of the *Oppenauer oxidation* presented earlier. Treatment with $Al(O-CH(CH_3)_2)_3$ (aluminum triisopropoxide) in isopropyl alcohol (2-propanol) reduces ketones or aldehydes to alcohols (Figure 17.084).

Figure 17.084

As in the Cannizzaro reaction, there is a hydride transfer to the carbonyl compound that forms the alkoxide ion of the desired product alcohol (Figure 17.085).

Figure 17.085

You can see that the hydride comes from the isopropoxide group (1-methylethoxide group) in aluminum triisopropoxide.

Alkyl Groups from C=O Reduction (17.7C)

We can convert the C=O group of ketones and aldehydes into a CH_2 group (Figure 17.086), by the **Clemmensen reduction** or the **Wolff-Kishner reaction**.

Figure 17.086

Clemmensen Reduction
$R_2C=O$ → → → → R_2CH_2
or
Wolff-Kishner Reaction

Clemmensen Reduction. We carry out this reaction by treating an aldehyde or ketone with **zinc amalgam** (Zn treated with mercury metal (Hg)) in aqueous HCl (Figure 17.087).

Figure 17.087

Because this reaction uses aqueous HCl, it is not useful for compounds that are sensitive to acid. (In those cases we can use the reaction described in the next section.) While its mechanism is uncertain, the corresponding alcohol R_2CHOH is not formed as an intermediate.

Wolff-Kishner Reaction. In this reaction, treatment of an aldehyde or ketone with $H_2N\text{-}NH_2{\cdot}H_2O$ (hydrazine hydrate) and NaOH in a high boiling solvent such as refluxing diethylene glycol ($HOCH_2CH_2OCH_2CH_2OH$) (Figure 17.088) transforms their C=O groups into CH_2 groups.

Figure 17.088

We briefly described the *Wolff-Kishner reaction* in Chapter 16 because its mechanism involves nucleophilic addition of hydrazine to the C=O group to form the intermediate hydrazone (Figure 17.089).

Figure 17.089

This intermediate reacts further with HO^- in the reaction mixture to form N_2 and the final organic product (Figure 17.090).

Figure 17.090

Because the reaction medium is basic, we can use the *Wolff-Kishner reaction* with compounds sensitive to the acidic conditions of the *Clemmensen reduction*.

17.8 Reduction of R-C(=O)-Z and Related Compounds

When we reduce *esters, amides,* or other compounds of the structure *R-C(=O)-Z,* possible products are *alcohols, amines,* or *aldehydes*. The type of product depends on the structure of R-C(=O)-Z and that of the metal hydride reducing agent (Figure 17.091).

Figure 17.091

We describe reductions of R-C(=O)-Z in this section along with those of *nitriles* (*R-C≡N*) and *nitro compounds* (*$R\text{-}NO_2$*).

Alcohol Formation (17.8A)

$LiAlH_4$ reduction of R-C(=O)-Z compounds except amides (Z = NR'_2) gives *alcohols* (R-CH_2-OH) (Figure 17.091). *Aldehydes* are intermediates in these reactions (Figure 17.092).

Figure 17.092

General $\boldsymbol{LiAlH_4}$ ***Mechanism***. We show a general mechanism for $LiAlH_4$ reduction of R-C(=O)-Z other than amides in Figure 17.093.

Figure 17.093

After the initial hydride addition to the C(=O)-Z group, Z^- leaves to give an aldehyde intermediate that AlH_4^-, or another other reactive intermediate with Al-H bonds, reduces further to an alcohol (Figure 17.074).

Carboxylic Acid Reduction. When we reduce carboxylic acids with $LiAlH_4$, a carboxylate intermediate initially forms in an acid/base reaction (Figure 17.094).

Figure 17.094

You can see in Figure 17.094 that the reagent subsequently reduces the carboxylate to an aldehyde, and then an alcohol (Figure 17.074).

Diborane Reduction of Carboxylic Acids. We can also reduce carboxylic acids to alcohols using B_2H_6 (Figure 17.095).

Figure 17.095

While $LiAlH_4$ reduces acids, it also reacts with any other C=O groups that are present in the molecule. In contrast, diborane does not reduce other R-C(=O)-Z groups that may be present.

Amine Formation (17.8B)

Amines are the products when we reduce amides (R-C(=O)-NR'_2), nitriles (R-C≡N), or nitro compounds (R-NO_2) with $LiAlH_4$ (Figure 17.091).

Reduction of Amides. $LiAlH_4$ reduction of amides (R-C(=O)-NR'_2) gives 1° amines (R-CH_2-NH_2), 2° amines (R-CH_2-NHR') or 3° amines (R-CH_2-NR'_2) depending on the the number of H's on N. The intermediate formed in the first reaction of $LiAlH_4$ with an amide (Figure 17.096)(next page) is equivalent to that formed in the first reaction when $LiAlH_4$ reacts with other R-C(=O)-Z compounds (Figure 17.093).

Figure 17.096

However in the case of amides, the Z group is NR'_2 and the $^-NR'_2$ anion is such a poor leaving group that an "O-Al" anion leaves instead (the second reaction in Figure 17.096) giving an intermediate iminium ion. Subsequent reduction of that iminium ion (or its imine form) gives the amine as we show in the third reaction in that figure.

Reduction of R-C≡N and R-NO$_2$. Reduction of nitriles (R-C≡N) has a stepwise mechanism in which a C≡N bond becomes a C=N double bond and then a C-N single bond (Figure 17.097).

Figure 17.097

Although we present no mechanism for reduction of nitro compounds (R-NO_2), this reaction is particularly useful for reduction of *nitrobenzenes* to give *anilines* (Figure 17.098).

Figure 17.098

Aldehyde Formation (17.8C)

We obtain *aldehydes* as final products when we use the modified aluminum hydride reagents in Figure 17.091 to reduce *acid halides* ((R-C(=O)-Cl), *esters* ((R-C(=O)-OR'), or *nitriles* (R-C≡N).

Acid Halides and LiAlH(O-C(CH$_3$))$_3$. One of these modified reagents is **lithium *tri-t*-butoxyaluminum hydride** ($LiAlH(O\text{-}C(CH_3))_3$) that we form by reaction of $LiAlH_4$ with t-butyl alcohol (Figure 17.099).

Figure 17.099

This reaction stops after three $OC(CH_3)_3$ groups replace three of the four H's on Al. This is a result of a combination of steric crowding at the Al atom, and reduced reactivity of the final Al-H hydride because of electronic effects of the new t-butoxy group substituents.

This metal hydride probably reacts with acid halides according to the general scheme in Figure 17.100.

Figure 17.100

The intermediate must decompose to give aldehyde after all of the $AlH(O\text{-}t\text{-}bu)_3^-$ reagent has reacted since unreacted reactant will reduce aldehydes to alcohols.

Esters and Diisobutylaluminum Hydride (DIBAL). DIBAL is a metal hydride with the general structure R_2AlH where R = isobutyl (Figure 17.101).

Figure 17.101

It reacts with esters as we show in Figure 17.102.

Figure 17.102

The intermediate gives an aldehyde when we react the reaction mixture with aqueous acid. An intermediate hemiacetal also forms as shown in that figure.

Nitriles and DIBAL. DIBAL reduces nitriles (Figure 17.103).

Figure 17.103

The intermediate in the first reaction does not react further with DIBAL because of steric hindrance. During treatment of the reaction mixture with aqueous acid, it hydrolyzes to give an aldehyde. This reaction is equivalent to the formation of an aldehyde from an imine by hydrolysis (Chapter 16).

Rosenmund Reduction. We can also reduce *acid halides* to *aldehydes* using molecular H_2 instead of metal hydrides. We show this **Rosenmund reduction** in Figure 17.104. The second set of reaction conditions involving Pd(C) is often the best choice.

Figure 17.104

H_2, Pd($BaSO_4$)
→
R-C(=O)-Cl } or { R-C(=O)-H
H_2, Pd(C)
→
Et(i-Pr)$_2$N, acetone

17.9 Reduction of C=C and C≡C Bonds

We discussed reduction of alkenes and alkynes (Figure 17.105) in Chapter 10.

Figure 17.105

We review that material again here along with a brief discussion of arene reduction.

Reduction of Alkenes and Alkynes (17.9A)

Reductions of alkenes and alkynes generally involve catalytic hydrogenation. In the case of alkyne reduction to alkenes, catalytic hydrogenation takes place with *cis* addition of H_2. We can also reduce alkynes using Na in liquid NH_3 with different stereochemical results then catalytic hydrogenation (Figure 17.106.)

Figure 17.106

The reaction of alkenes with diborane to give alkylboranes (Chapter 10) (Figure 17.107) is also a reduction reaction.

Figure 17.107

We convert the alkylboranes to alkanes by reacting them with aqueous carboxylic acids (Figure 17.108).

Figure 17.108

Reduction of Arenes (17.9B)

Reduction of arenes (benzenes) *via* catalytic hydrogenation gives cyclohexanes (Figure 17.109).

Figure 17.109

In contrast, reaction of arenes with Li, Na, or K metal dissolved in liquid NH_3 in the presence of an alcohol, gives 1,4-cyclohexadienes. This **Birch reduction** is applicable to a variety of aromatic rings as we show in the examples in Figure 17.110.

Figure 17.110