Aldehydes and Ketones

Nomenclature - form text.

The best way to think of an aldehyde or ketone (or just about any carbonyl compound) is with a slight positive charge on carbon, and a slight negative charge on oxygen:

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{R}' & \quad \text{O}^+ \\
\end{align*}
\]

Just about all of the chemistry of carbonyl compounds is explained by the oxygen being slightly nucleophilic (thus easily protonated) and the carbon being strongly electrophilic. Remember this!

**Preparation:**

**Aldehydes:**
1) Oxidation of a primary alcohol with PCC

2) Ozonolysis of an alkene
   REVIEW IT!

3) Reduction of an Acyl Halide.
   Acyl halides can be reduced with a special reagent – lithium tri(t-butoxy)aluminum hydride, LiAl(O-t-Bu)_3H :

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{Cl} & \quad \text{LiAl(O-t-Bu)}_3 \text{H} \\
\text{R} & \quad \text{O} \\
\text{H} & \quad \\
\end{align*}
\]

Your text states that aldehydes can be easily prepared from esters with DIBAH (diisobutylaluminum hydride). Typically, it is easier to reduce all the way to a primary alcohol (you need 2 equivalents of DIBAH for this), then re-oxidize:

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{OR'} & \quad \text{Al} \\
\text{H} & \quad \text{PCC} \\
\text{R} & \quad \text{O} \\
\text{H} & \quad \\
\end{align*}
\]

**Ketones**
1) Oxidation of secondary alcohols – usually be the Swern oxidation, or with PCC
2) Ozonolysis of an alkene.
3) Friedel-Crafts Acylation.

Below is the preparation of a ketone sequentially from a primary alcohol (through an intermediate aldehyde):
Some ketones can also be prepared from acyl halides and organo-copper reagents (called lithium dialkylcuprates), as shown below:

Further oxidation of aldehydes and ketones:
As you might imagine, most ketones are inert to all but the harshest oxidative conditions, and thus there is no synthetic utility in trying to oxidize them. However, aldehydes can generally be oxidized to carboxylic acids under relatively mild conditions:

Reactivity of Aldehydes and Ketones.
These carbonyl compounds generally have two reaction pathways – they react with strong nucleophiles (generally, strong nucleophiles have a formal negative charge) under neutral, generally anhydrous conditions, or with weak nucleophiles (those with lone pairs, but no charge) under mild acid catalysis. If you take a good look at the nucleophile and reaction conditions, you’ll be able to figure out which way it will go...

Reactivity – aldehydes are much more reactive than ketones. ‘nuff said.

Addition of water or alcohols (to from a hydrate or alcoholate (ketal)). Ketones and aldehydes in aqueous or alcoholic media frequently react with the medium to form hydrates (or alcoholates). The extent to which this occurs correlates to many things, including the electrophilicity of the carbonyl carbon. While acetophenone exists mostly as the ketone, trichloroacetaldehyde (chloral) exists almost entirely as the hydrate (if exposed to water):
Similar things happen in neutral alcoholic medium - take chloroacetaldehyde in methanol, for example:

\[
\begin{align*}
\text{Cl-CH}_2\text{CHO} & \quad \text{MeOH} \quad \rightarrow \quad \text{Cl-CH}_2\text{CH(OH)OMe} \\
\end{align*}
\]

Why do these hydrates form better with \(\text{e}^-\)-withdrawing substituents? Remember the first figure shown in these notes.....

The mechanism for these additions is relatively straightforward:

This is the mechanism for the reaction in neutral media. The mechanism in basic media is left as an exercise for the reader (i.e. you!). In acidic alcoholic media, the reaction behaves like the Energizer™ Bunny - it just keeps going and going, until a completely new product is formed. It is called an acetal:

\[
\begin{align*}
\text{Cl-CH}_2\text{CHO} & \quad \text{MeOH} \quad \rightarrow \quad \text{Cl-CH}_2\text{CH(OH)OMe} \\
\end{align*}
\]

The mechanism is quite straightforward:

Basically, a series of protonation, nucleophile attack, deprotonation steps.

Big Note: Acetal formation CANNOT occur under basic catalysis. Convince yourself that this is true...if you can’t, come see me.
Remember that these reactions are all in equilibrium - it can be forced to the acetal by doing it under anhydrous conditions (or by distilling off the water), or forced back to the ketone/aldehyde by the addition of excess water (making it the perfect protecting group!):

\[
\begin{align*}
\text{EtOH} / H^+ & \quad \text{Benzene} \\
\text{Br}_2 & \quad \text{KOH} \\
\text{H}_2\text{O} / H^+ & \quad \text{R}
\end{align*}
\]

In general, simple alcohols like methanol and ethanol are not used in the formation of acetals (particularly from less-reactive ketones!) The main reason is entropy - you’ve got to get three molecules together to form one - that’s not so good! The very common way around this is to use a glycol - ethylene or propylene glycol – to form a cyclic acetal:

As you would expect for ethers, acetals are stable to base and most nucleophiles, such as Grignard reagents and alkylolithiums. They revert back to the carbonyl compound on exposure to aqueous acid.

**Enamines:**

Just as with alcohols, amines can add to ketones and aldehydes. Primary amines add to give imines, while secondary amines give enamines (pronounced ene-amines). The reactions are generally catalyzed by a small amount of acid, and need to be buffered to a pH of ~4.5.

An Imine (in this case, the amine is hydrazine, and the product is called a hydrazone):
In the case of secondary amines, we have a lack of protons that can easily be removed from the amine – the mechanism thus requires that the offending positive charge be neutralized by removing a proton from the alkyl group:

Overall:

De-Oxygenation reactions.
There are two general reactions for the complete de-oxygenation of ketones and aldehydes. The general scheme for de-oxygenation is:

\[
\text{R'} \text{ can } = \text{H} \quad \text{O} \quad \text{De-Oxygenate} \quad \text{R} \quad \text{R'}
\]

The two methods are the Wolff-Kishner (runs under basic conditions) and the Clemmensen (under acidic conditions). Below find an example for each one:
The Greatest Double Bond Forming Reaction Ever Invented:

The Wittig Reaction

This reaction is what I would call “cute” chemistry. One of the cool things about Wittig reactions is that they just about always work.

The most general scheme, an alkyl halide (usually the bromide) and an aldehyde or ketone are taken to an alkene. If an aldehyde is used with a primary alkyl halide, generally the trans product results.

Either R’ or R” MUST be hydrogen

In a more detailed picture of this reaction, the alkyl bromide is allowed to react with triphenyl phosphine to form an alkylphosphonium salt:

These salts are generally quite stable, and can be stored over long periods of time (i.e. many of these salts are even sold commercially). The phosphonium salt is then deprotonated (usually with sodium hydride, or butyllithium) to form the ylide. An ylide is simply a charge-separated species, as shown below:

This ylide is then allowed to react with a ketone or aldehyde, to form a betaine intermediate. This intermediate cyclizes to form another intermediate, an oxaphosphetane:
The oxaphosphetane decomposes rapidly to form the alkene and triphenylphosphine oxide:

The main driving force for this reaction is the formation of the phosphorous-oxygen double bond - this is one of the strongest bonds known, and its formation pulls the reaction to completion. Below are a few examples of the Wittig reaction at work:

A simple modification of the Wittig reaction leads to a dibromo-olefin, which is an excellent precursor to alkynes:
Conjugate Addition

Okay, I’m afraid things are going to get a bit ugly again. We now focus on conjugated carbonyl compounds. If you look at resonance structures for these (particularly in comparison with the figure on the top of page 1):

You see that in conjugated systems, there are TWO sites for nucleophilic attack. Let’s do a little nomenclature before we continue - when we look at carbonyl compounds, the carbonyl carbon is the real center of attraction. Any carbons directly attached to the carbonyl are called the alpha (α) carbons (in the case above, the one with the slight negative charge). As you’ll see in upcoming chapters, the alpha carbon is often quite nucleophilic...

Unsurprisingly, the carbon attached to the alpha carbon is called the beta (β) carbon. And as you can see, in the case of conjugated carbonyl compounds (which are often called alpha,beta unsaturated compounds), the beta carbon is electrophilic.

This leaves us with a bit of a puzzle. If we add a nucleophile to this conjugated compound, will it add to the carbonyl, or to the double bond?:

or ???

or ???
Addition to the carbonyl you’ve seen before. Addition to the double bond (to form an enolate, which tautomerizes to the ketone) is new. This type of addition is called *conjugate addition*, or, more frequently, *Michael addition*.

How can we tell if we’ll be getting carbonyl addition or conjugate addition? Fortunately, it is quite easy. Non-carbon nucleophiles (we frequently call these “soft” nucleophiles) like nitrogen (amines) and oxygen (alcohols) will always add in a conjugate fashion, particularly if the reaction is carried out under neutral conditions. Some examples:

\[
\begin{align*}
\text{CO} & \xrightarrow{\text{H-N}} \text{CO} \\
\text{EtOH} & \xrightarrow{\text{EtOH}} \text{EtOH} \\
\text{NO ACID!!} & \xrightarrow{\text{NO ACID!!}} \text{NO ACID!!}
\end{align*}
\]

A way to force only conjugate addition with a “hard” nucleophile (i.e. \(\text{RM}\)) is to form the copper salt - in this case, a dialkylcuprate. You’ve already seen these used to prepare ketones from acid chlorides – formation of copper salts is a great way to “soften” a hard nucleophile. The dialkyl cuprates are usually formed from alkyllithiums (hence, lithium dialkylcuprates). Your text gives a number of good examples, but I thought I should throw in my two cents on the subject as well:

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{Li}} \text{Li} \\
& \xrightarrow{0.5 \text{CuBr}} \text{Li} \\
& \xrightarrow{\text{CuLi}} \text{Cl}_2 \\
& \xrightarrow{\text{Cl}_2} \text{Cl}_2 \\
\end{align*}
\]

(Think carefully about what’s happening here...)

As you might expect, conjugate addition to an alkynyl ketone leads to a vinyl ketone. Here is an example using a different kind of “soft” nucleophile (we’ll discuss this type in a few weeks):
A highly stabilized (and thus, "soft") nucleophile

Of course, as we have already seen, organolithium (e.g. butyllithium) or magnesium (Grignard) reagents *always* add to the carbonyl.