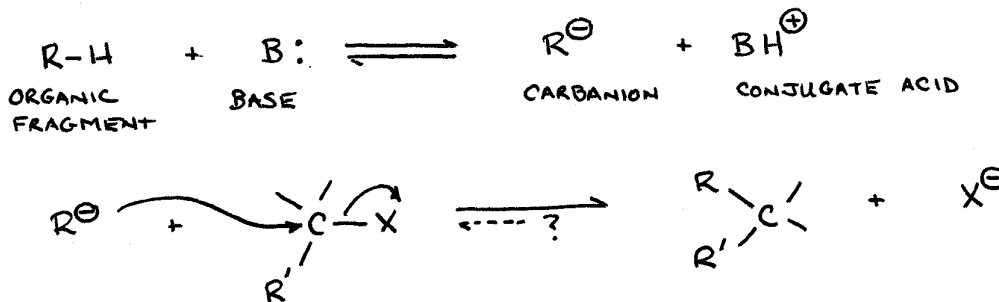# 59-331/333 Organic Synthesis

This course deals predominantly with organic synthesis, which concerns the **construction of larger molecules from smaller parts**, preferably in a rational and predictable manner. As a result, the most important type of reaction type in organic synthesis is **C-C bond formation**. A very important sub-group of these types of reactions are **based induced** (or base catalyzed) **condensation reactions**. The first part of this course will focus on these types of reactions.

In general, all base induced reactions can be simplified schematically as follows:

$$R-H \quad + \quad B: \quad \rightleftharpoons \quad R^{\ominus} \quad + \quad BH^{\oplus}$$

ORGANIC   BASE   CARBANION   CONJUGATE ACID
FRAGMENT

For the above to work, there are several necessities. They are:

i)   A compound with an **acidic H atom** (i.e., the resulting **carbanion** must be **stabilized in some fashion**)

ii)   A **base (B:)** **strong enough** to remove the acidic H

iii)   An **electrophilic centre** present in another organic reagents (R'-C)

iv)   Some way of **eliminating the negative charge** in the carbon containing product.

We'll look at each one of these individually for a bit.

i)   **Stabilization of Carbanions**

What makes a C-H bond acidic (or better still, what makes a carbanion stable)? Really, there are two possible properties, which may or may not be present at the same time.

a)   **Inductive Effects**   - These effects are also called **'through bond'** or (slightly differently) **'field'** effects. They operate solely through the **σ-bonding electrons** (except the field effect, which included though space effects also). So, for example, if you have an electronegative group on a C atom which also bears an H, this electronegative group can relieve the negative charge of the carbon, stabilizing the carbanion.

RELIEVES $\ominus$ CHARGE (PARTIALLY) ON C
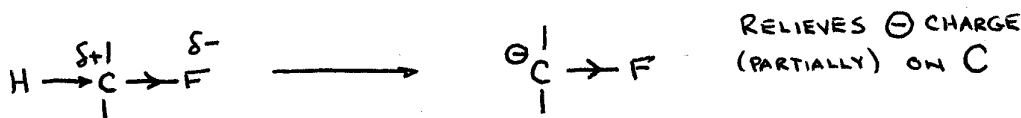
Groups which have this effect are called
**-I** groups if they are **inductively electron withdrawing**
+I groups if they are **inductively electron donating**

1

Examples of -I groups (which we most care about here) include the **halogens**, alkoxy (**-OR**) and amino (**-NR$_2$**) groups. Examples of **+I** groups include **alkyl** groups and silyl (**-SiR$_3$**) groups.

b)   **Resonance Stabilization** - This is also called **mesomeric stabilization**. This is probably the more important of the two types of effects. There are a few **conditions which must** be met for resonance stabilization to occur. They are

1)   - Normally, only the π-**electrons** (meaning **p-orbitals**, usually) are involved; the σ-**electrons and the positions of the atoms themselves must remain the same.** This point is often forgotten.

2)   - The **more atoms** you can spread the charge out over (in this case the negative charge), the **more stable** the charged species (the carbanion)

3)   - Since we're dealing with negative charge here, a resonance process which puts a **negative charge on an electronegative atom** is much more **favourable**
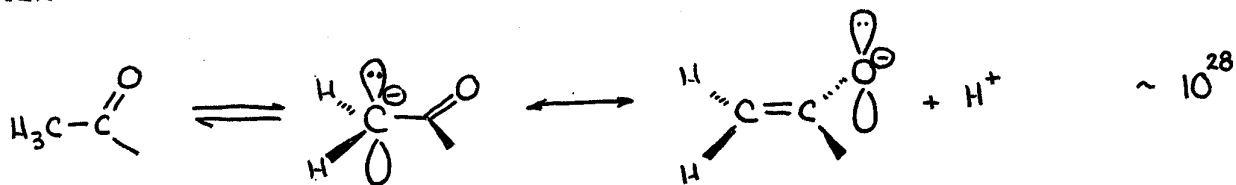
We'll now consider four cases, and see how they rank in anion stabilization, based on the above considerations
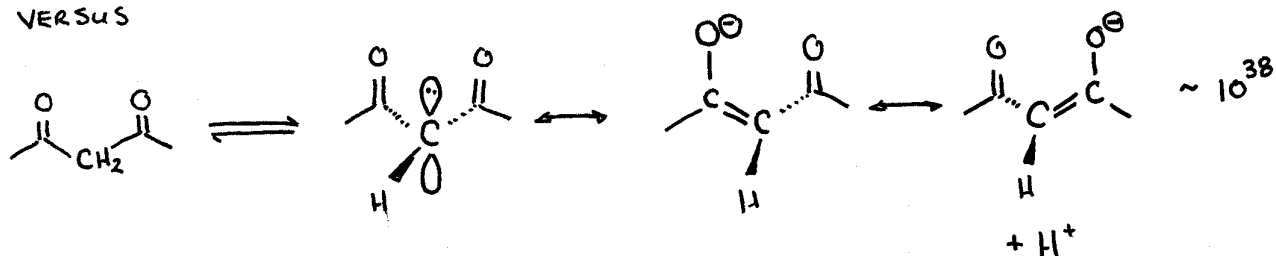

INCREASE IN K_a

$\sim 10^5$

$\sim 10^{28}$

$\sim 10^{38}$

2
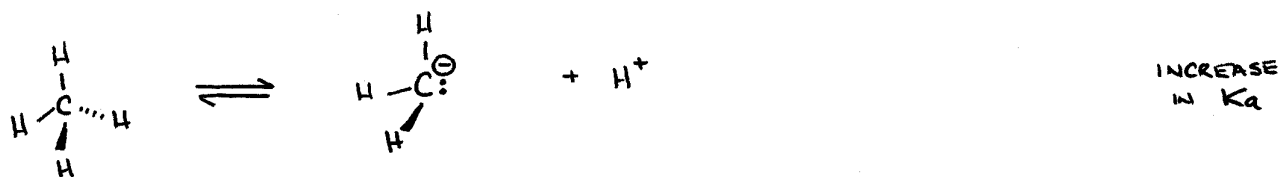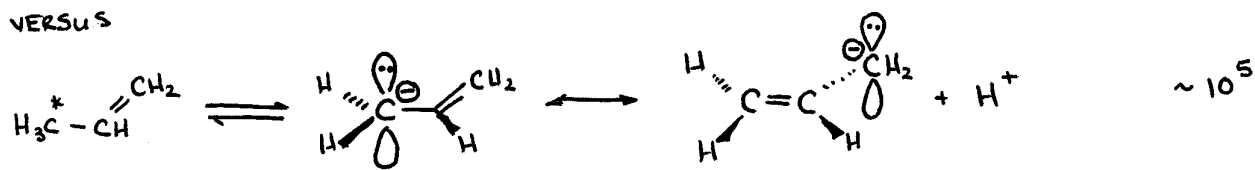
Groups which are involved in resonance are often called M groups:

-M groups are ones which are **electron withdrawing by resonance**. Examples of these are nitro groups (**-NO₂**), carbonyls ($-C\overset{O}{\underset{R}{<}}$), and nitriles ($-C\equiv N$)

+M groups are ones which are **electron donating by resonance**.

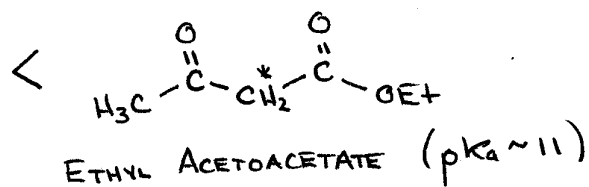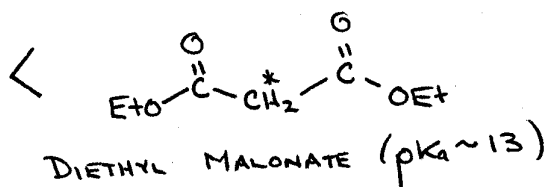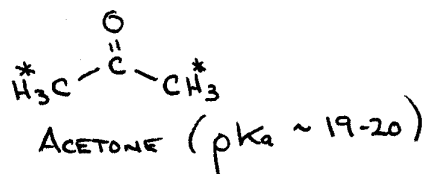Hydrogen atoms which are made acidic in the above two ways are often called **activated H's**.
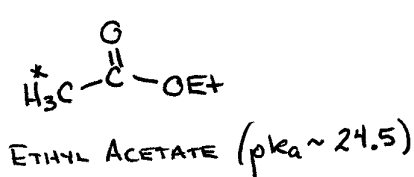
The **relative acidity** of hydrogen atoms are usually discussed in terms of the **pK$_A$** of the substrate from which the proton is removed. A quick refresher of what that means is below....notice that the **lower the pK$_A$** number, the **more acidic** the organic compound.

$$R-H \; + \; H_2O \; \underset{\longleftarrow}{\overset{Ka}{\rightleftharpoons}} \; R^{\ominus} \; + \; H_3O^{\oplus}$$
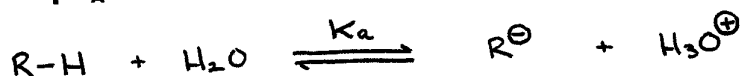
$$K_a = [R^-][H_3O^+]/[R\text{-}H] \qquad\qquad pK_a = \text{-log } K_a$$

For many pK$_a$'s , see Table 1. Note that these pK$_a$'s are measured in water; pK$_a$'s measured in other solvents are sometimes quite different, and that many deprotonation reactions are performed in non-aqueous solvents. Some very common acidic carbon based compounds include the following.

$\overset{*}{H_3}C-\overset{\overset{O}{\|}}{C}-OEt$

ETHYL ACETATE $\left(pKa \sim 24.5\right)$

$<$

$\overset{*}{H_3}C-\overset{\overset{O}{\|}}{C}-\overset{*}{C}H_3$

ACETONE $\left(pKa \sim 19\text{-}20\right)$

$<$ $EtO-\overset{\overset{O}{\|}}{C}-\overset{*}{C}H_2-\overset{\overset{O}{\|}}{C}-OEt$

DIETHYL MALONATE $\left(pKa \sim 13\right)$

$<$ $H_3C-\overset{\overset{O}{\|}}{C}-\overset{*}{C}H_2-\overset{\overset{O}{\|}}{C}-OEt$

ETHYL ACETOACETATE $\left(pKa \sim 11\right)$

* - MOST ACIDIC PROTONS

ii)   **Bases**

Let us consider the deprotonation step again

$$R-H \; + \; B^{\ominus} \; \underset{\longleftarrow}{\overset{Keqm}{\rightleftharpoons}} \; R^{\ominus} \; + \; BH^{\oplus}$$
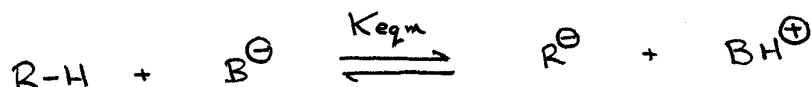
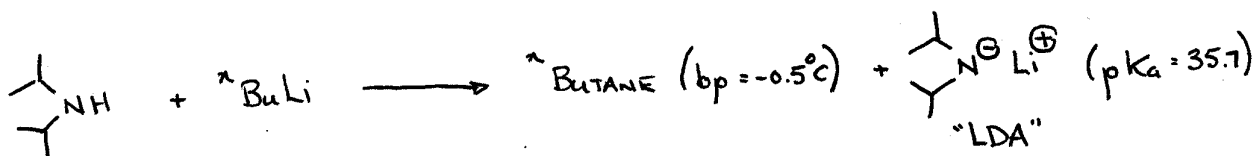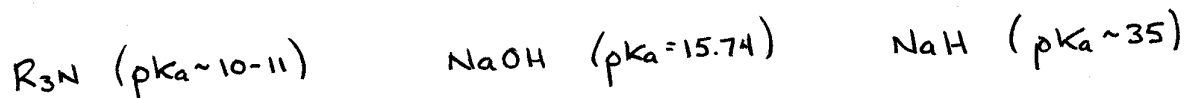Clearly, a stronger acid or a stronger base will push this equilibrium further to the right (meaning a larger K_{eqm}). Information on the strength of bases also comes out of the pK_a values, since the **higher the pK_a value** of a compound the **stronger its conjugate base as a base**. So the pK_a values which I'll give for bases is *actually* the pK_a value of its conjugate acid. Some very common bases, and the most common way of making these is below (note that all of these bases <u>are</u> commercially available).

$$EtOH \; + \; Na \; \longrightarrow \; H_2\uparrow \; + \; EtO^{\ominus} \; Na^{\oplus} \quad (pK_a\sim16)$$

$$(H_3C)_3C\text{-}OH \; + \; K \; \longrightarrow \; H_2\uparrow \; + \; (H_3C)_3C\text{-}O^{\ominus} \; K^{\oplus} \quad (pK_a\sim17)$$

$$R_3N \; (pK_a\sim10\text{-}11) \qquad NaOH \; (pK_a=15.74) \qquad NaH \; (pK_a\sim35)$$

$$\underset{\curlywedge}{\bigwedge}NH \; + \; ^nBuLi \; \longrightarrow \; ^nButane \; (bp=-0.5^\circ C) \; + \; \underset{\text{"LDA"}}{\bigwedge}N^{\ominus}\,Li^{\oplus} \quad (pK_a=35.7)$$

$$H_3C\,CH_2\,CH_2\,CH_2\,Br \; + \; 2\,Li \; \longrightarrow \; Li\,Br \; + \; \underset{\text{"}^nBuLi\text{"}}{CH_3\,CH_2\,CH_2\,CH_2\,Li} \quad (pK_a\sim50)$$
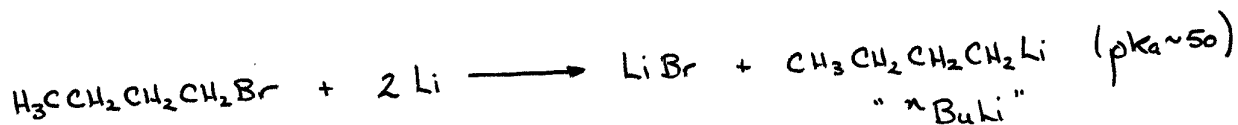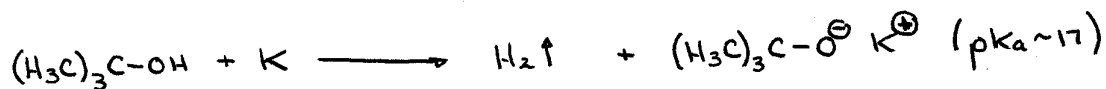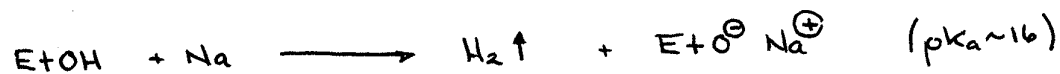
So, to go through these bases, and to make the assumption that pK_a values in water translate 'pretty well' to non-aqueous solvents, the following base strength ordering is useful:

$$\textit{n-}BuLi > LDA > NaH > KO^tBu > NaOEt > NaOH > R_3N$$
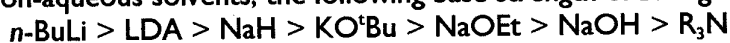
iii)   Electrophilic Centre

Carbon based electrophilic centres with which the carbanion will normally react are usually one of two general types.

      a)   part of C=O or C=N

      b)   attached to a halogen or halogen equivalents ($^{\delta+}C\text{-}Cl^{\delta-}$)

The specifics here will be addressed on a reaction by reaction basis.

iv)   Loss of negative charge

This depends on the type of electrophile, so these will be discussed as we get to each of them.

Prototype of Base-Induced Reactions

Aldol Condensation

The aldol condensation is one of the most fundamental (and important) base induced reactions. It involves the reaction with an aldehyde (or a ketone) with another aldehyde (or a ketone). We will discuss this in some detail, as many of the principles which we use here will be applicable to most other base induced reactions.
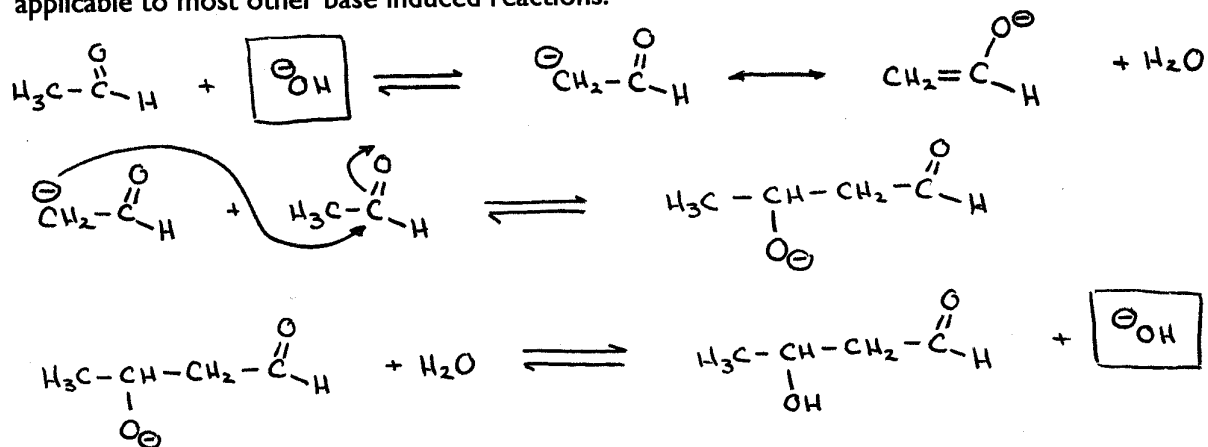
So, some general points about this reaction.

OVERALL

$$2 \; CH_3CHO \; \underset{}{\overset{HO^{\ominus}}{\rightleftharpoons}} \; H_3C-\overset{\overset{\textstyle OH}{|}}{CH}-CH_2CHO$$

1) Note that the HO⁻ used in the beginning is regenerated at the end of the reaction. HO⁻ is therefore a true catalyst (the terminology is sometimes thrown around loosely, but not here.

2) At least to this point, every step of the reaction is reversible, so the entire reaction is reversible.

3) The observed rate is

$$v = k \, [HO^-] \, [CH_3CHO]$$

this means that the first step is the slowest (rate determining) one.

4) In this case, the loss of negative charge is due to protonation of an alkoxide ion.

There is a problem here, however. When a series of steps are all reversible, the product which one gets depends on the equilibrium constants. This can be difficult to control (to make the reaction go to completion). For a good synthetic result, we'd prefer an irreversible reaction, so the reaction is driven entirely to completion (there are other alternatives, too). This can be achieved in