18: Reactions of Enolate Ions and Enols

- *Enolate Ions and Enols*
- *Halogenation Reactions*
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- *Condensation Reactions*
- *Enolate Ions from β-Dicarbonyl Compounds*
- *Other Reactions of Enolate Ions and Enols*

18.1 Enolate Ions and Enols

We described in Chapters 13 and 16 that the C=O group of carbonyl compounds is reactive to attack by both nucleophiles (N:) and electrophiles (E^+). We also saw in Chapter 13 that the C=O group causes Hs attached to its α-C (H-C_α-C=O) to be unusually acidic. As a result, these α-CH's are removed by bases giving **enolate ions** ($^-$:C_α-C=O) Figure 18.01) that can react as nucleophiles with different electrophiles (E+) to form compounds with the general structure E-C_α-C=O.

Figure 18.01

Carbonyl compounds with α-CHs (H-C_α-C=O) can also isomerize to enol forms with the general structure C_α=C-O-H (Figure 18.02).

Figure 18.02

In the enol form, the H-C_α-C group becomes a C_α=C double bond while the C=O double bond becomes a C-O-H group. The C_α in enol forms is particularly reactive toward electrophilic species (E^+) and reacts with them in a manner similar to enolate ions to give compounds containing E-C_α-C=O.

Halogenation, Alkylation, and Condensation Reactions (18.1A)

Enolate ions react with a variety of different substrates, but three types of reactions of major importance are those with (a) molecular halogens (X_2), (b) haloalkanes (R'X), and (c) carbonyl compounds (R'C(=O)R") (Figure 18.03).

Figure 18.03

Reaction (a) gives compounds in which a halogen atom replaces the H on an α-C-H so it is referred to as α-**halogenation**. In reaction (b), an alkyl group R' in the reactant R'-X replaces the H on an α-C-H and is referred to as α-**alkylation**. In

reaction (c), the nucleophilic α-C of an enolate ion adds to the C of C=O groups in a variety of carbonyl compounds.

Reactions (c) are often referred to as **condensation reactions**. They are nucleophilic addition reactions to C=O like those in Chapter 16 (16.1) and give an intermediate tetrahedral addition product whose subsequent reactions depend on the structure of the initial carbonyl compound reactant (R'C(=O)R"). Because of the wide variety of possible enolate ions, and carbonyl compounds that can react with enolate ions, there are many different types of *condensation* reactions.

Acidity of α-C-H's (18.1B)

Enolate ions are in equilibrium with carbonyl compounds as we show in Figure 18.04 for reaction of ketones or aldehydes with bases such as hydroxide ion ($HO:^-$)or alkoxide ion ($R'O:^-$).

Figure 18.04

However, hydroxide and alkoxide ions are much less basic than enolate ions, so enolate ions are present in only low concentrations in these equilibria.

Acetone and Ethoxide Ions. We use the reaction of ethoxide ion and acetone to illustrate enolate ion-carbonyl compound equilibria (Figure 18.05).

Figure 18.05

Ethoxide ion (the base) removes a proton from acetone (the acid) to give the conjugate acid ethanol and the enolate ion as the conjugate base.

The pK_a value of the α-C-H of acetone ($CH_3(C=O)CH_3$) and other simple ketones is about 20 ($K_a = 10^{-20}$) while the pK_a value of the O-H of ethanol (CH_3CH_2OH) and other simple alcohols is about 16 ($K_a = 10^{-16}$). Ethanol is a stronger acid by a factor of 10^4 compared to acetone, so the basicity of ethoxide ion (from ethanol) is 10^4 less than the basicity of the enolate ion (from acetone). As a result, the equilibrium mixture (Figure 18.05) resulting from treating acetone with ethoxide ion has a much higher concentration of acetone relative to enolate ion.

Resonance Stabilization. The acidity of the α-C-H of a carbonyl compound such as acetone (pKa = 20) is relatively low compared to a variety of other acids, but it is much greater than that of a C-H in an alkane such as propane (pKa = 50) (13.5B) (Figure 18.06).

Figure 18.06

This enormous difference in C-H acidity between acetone and propane arises because the negative charge (electron pair) on the enolate ion is delocalized as we show with the two resonance structures in Figure 18.07 .

Figure 18.07

In contrast, the negative charge on C, formed by removing a proton from propane, cannot delocalize. Neither the resultant $CH_3CH_2CH_2^-$ nor $(CH_3)_2CH^-$ have resonance structures.

The delocalization of charge in an enolate ion makes it sufficiently stable so that a base such as hydroxide or alkoxide forms it in low concentration by removing an α-C-H from the parent carbonyl compound. We will see later in this chapter that stronger bases than ^-OH or ^-OR quantitatively convert the carbonyl compound to its enolate ion.

Enol Form of the Carbonyl Compound (18.1C)

Enol forms of carbonyl compounds, as well as the carbonyl compound, are in equilibria with enolate ions.

Protonation on C or O. Protonation of the enolate ion on the α-C gives the original carbonyl compound. But the enolate ion resonance structures also show that its negative charge is delocalized on the O of the C=O group. As a result, protonation on O gives an **enol** as we show in Figure 18.08 where we represent electron delocalization in the enolate ion using dotted bonds and partial negative charges (δ-).

Figure 18.08

The enol form and the carbonyl compound are always in equilibrium with each other as we described earlier in Chapter 13 (13.5B). In the presence of a base, the enolate ion is an intermediate in this equilibrium.

Acid Catalyzed Enol Formation. Formation of enols from carbonyl compounds is also catalyzed by acids (Figure 18.09).

Figure 18.09

Protonation of the C=O group of the carbonyl compound on O gives a carbocation that is stabilized by the attached OH group. Subsequent loss of a proton from the OH group gives the unprotonated carbonyl compound. However, loss of a proton from the α-C (as shown by the curved arrows in Figure 18.09) gives rise to an enol.

Enol Content. Generally, the amount of enol form present in equilibrium with its isomeric carbonyl compound is very small but there are exceptions. We show some examples of the equilibrium percentages of enol forms in several different carbonyl compounds from Chapter 13 (13.5B) in Table 18.1.

Table 18.1. Approximate Percentage of Enol Form in some Carbonyl Compounds at Equilibrium.

Carbonyl Compound	%Enol Form
$C\underline{H}_3C(=O)C\underline{H}_3$	0.000006
$C\underline{H}_3C(=O)H$	0.00006
$CH_3CH_2C\underline{H}_2C(=O)H$	0.0006
$(CH_3)_2C\underline{H}C(=O)H$	0.01
$Ph_2C\underline{H}C(=O)H$	9
$CH_3C(=O)C\underline{H}_2C(=O)CH_3$	80

The relatively large amounts of enol form present in the last two carbonyl compounds result from conjugation of the C=C-OH double bond with the phenyl groups (Ph) in the former, and with the second C=O group in the latter (Figure 18.10).

Figure 18.10

We will see that both the enolate ion and the enol form of carbonyl compounds are important in reactions of carbonyl compounds.

Other Types of "Enolate" Ions (18.1D)

The term "enolate ion" originally referred specifically to the anion ($^-$:C-C=O) formed from removal of a C-H proton α to a C=O group. However, the terms "enolate ion" or "enolate-type ion" are now frequently used to refer to a number of different anions with a C:$^-$ center attached to functional groups, other than the C=O group, that can stabilize the (-) charge.

Active Hydrogen Compounds. Compounds that give "enolate ions" or "enolate-type ions" are said to have an "active" hydrogen and we show some general examples in Figure 17.8.

Figure 17.8. Active Hydrogen Compounds

$R_2C_\alpha H\text{-}Z$ and $Z'\text{-}C_\alpha HR\text{-}Z$

Z and/or Z' = C(=O)R, C(=O)Z, C≡N, NO_2, S(=O)R, $S(=O)_2R$

The Z and/or Z' groups attached to the "C_α" stabilize its negative charge by electron delocalization (Figure 18.12).

Figure 18.12

The C(=O)R or C(=O)Z groups can be aldehyde (C(=O)H), ketone (C(=O)R'), ester (C(=O)OR'), amide (C(=O)NR_2'), or even carboxylate ion (C(=O)O^-) groups.

Reactions of Active Hydrogen Compounds. The $R_2ZC:^-$ and $RZ_2C:^-$ "enolate-type" ions formed by removal of the proton from the "α-C" can undergo reactions that are similar to those mentioned earlier for enolate ions from aldehydes and ketones. We will specifically discuss examples of their alkylation and condensation reactions later in this chapter.

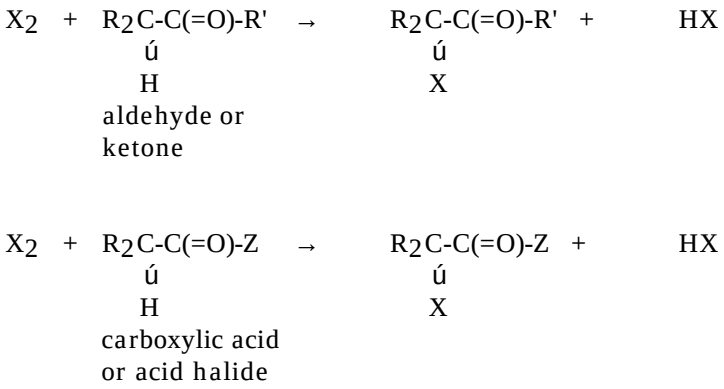
18.2 Halogenation Reactions

Enolate ions, as well as enol forms of carbonyl compounds, react with the molecular halogens Cl_2, Br_2 and I_2 (X_2) to form α-halocarbonyl compounds.

The General Halogenation Reaction (18.2A)

We show general halogenation reactions for an aldehyde (R' = H) or a ketone (R' = alkyl or aryl) as well as for a carboxylic acid (Z = OH) and or acid halide (Z = X) in Figure 18.13.

Figure 18.13



This regiospecific substitution of the α-CH by halogen (X) allows organic chemists to increase the number of functional groups in a molecule by subsequently replacing the α-C-X with another functional group. A specific example is this conversion of an α-halocarboxylic acid (Figure 18.13) into an α-amino acid (Figure 18.14).

Figure 18.14

NH_3 + R_2C-C(=O)-OH → R_2C-C(=O)-Z + HX
ú ú
X NH_2

α-halocarboxylic acid — α-amino acid

α-Amino Acids. α-Amino acids are the building blocks of protein and peptide molecules as you will see in Chapter 22. We do not need this type of amino acid synthesis to make "naturally occurring" amino acids because they are readily available from hydrolysis of naturally occuring peptide and protein molecules (Chapter 22). However, we use it to make "unnatural" amino acids that organic chemists and biochemists sometimes find useful in the synthesis of "non-naturally occurring" peptides and modified proteins.

Acid Catalyzed Halogenation of Ketones and Aldehydes (18.2B)

The α-halogenation of ketones and aldehydes is catalyzed by either acid or base. We describe the acid catalyzed reaction here.

Mechanism. During halogenation of a ketone or aldehyde catalyzed by acid, molecular halogen reacts with the enol form of the ketone or aldehyde (Figure 18.15).

Figure 18.15

Formation of the carbocation intermediate (Step 2) and its subsequent deprotonation (Step 3) are both rapid steps. The slow step of the reaction sequence in Figure 18.15 is acid-catalyzed formation of the enol from the aldehyde or ketone (Step 1) that we previously showed in Figure 18.09 .

Consistent with this mechanism, the rate of formation of α-haloaldehyde or α-haloketone depends only on the concentration of the aldehyde or ketone and not the concentration of the molecular halogen. As a result, the rate of the halogenation reaction is the same for chlorination, bromination, or iodination under the same reaction conditions.

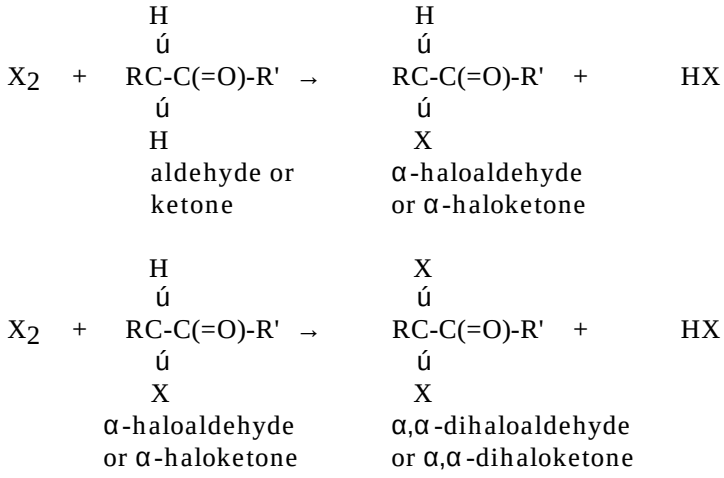
No Halonium Ions. Bromination and chlorination of alkenes occur *via* intermediate cyclic halonium ion intermediates that subsequently react with nucleophiles such as bromide or chloride ion (10.2).

Figure 18.16

In contrast, halonium ions are not considered to be intermediates in bromination or chlorination of enols bbecause the cation formed in Step 2 (Figure 18.15) is resonance stabilized by the attached OH group.

Polyhalogenation. When an aldehyde or ketone has two or more α-H's more than one may be replaced with halogen.

Figure 18.17



Multiple substitution of H by X occurs by mechanisms analogous to that for monohalogenation (Figure 18.15) starting with the α-haloaldehyde or α-haloketone. We can favor monohalogenation by using an excess of carbonyl compound compared to the molecular halogen because the relatively high concentration favors its reaction over that of the monohalo product.

Regiospecificity. While there is only one type of α-C-H in an aldehyde, there are two different types of α-CH's in unsymmetrical ketones (Figure 18.18).

Figure 18.18

$R_2C\underline{H}$-C(=O)-H	$R_2C\underline{H}$-C(=O)-$C\underline{H}R'_2$
aldehyde	unsymmetical ketone
(one type of α-C-H)	(two types of α-C-H)

Since the reactivities of these two α-C-Hs will differ one will be more likely to be replaced than the other.

The reactivity order for acid catalyzed halogenation of unsymmetrical ketones is $R_2C\underline{H}(C=O)R' > RC\underline{H}_2(C=O)R' > C\underline{H}_3(C=O)R'$. This is because the rate of rate-determining enol formation has the same reactivity order. In spite of these

reactivity differences, mixtures of α-halogenated products are often formed from unsymmetrical ketones.

α-Halogenation of Ketones and Aldehydes Using Base (18.2C)
Halogenation of aldehydes and ketones using base to facilitate the reaction can occur by reaction of X_2 with either the enol form or the enolate ion.

Figure 18.19

Mechanisms. In basic solution, reaction of X_2 with the enol is the same as its reaction with the enol in acidic solution (Steps 2 and 3 of Figure 18.15). The only difference is that formation of the enol is catalyzed by the base (Figure 18.08) rather than an added acid.

Reaction of X_2 with the enolate ion follows the mechanism outlined in Figure 18.20.

Figure 18.20
The enolate ion is formed by removal of an α-CH in the slow Step 1, and rapidly reacts with X_2 in Step 2.

Polyhalogenation. If the α-halo carbonyl product formed in Step 2 has additional α-C-H's, it reacts rapidly with base to form a halo substituted enolate ion (Figure 18.21).

Figure 18.21
This ion will also react with X_2, so it is difficult to stop the reaction after only one α-C-H has been replaced by X.. In fact, the reactivity of an α-CH is increased by an X attached to the α-C since the halogen atom stabilizes the negative charge by an inductive effect (Chapter 14)(14.2A,B) (Figure 18.22) .

Figure 18.22

The Haloform Reaction. Base catalyzed halogenation of the α-CH_3 groups of methyl ketones ($CH_3C(=O)R$) and acetaldehyde ($CH_3C(=O)H$) readily transforms them into CX_3 groups. Since halogen atoms stabilize negative charge on their attached C atoms, these CX_3 groups leave as $^{-}{:}CX_3$ anions (Figure 18.23) under the reaction conditions.

Figure 18.23
The last three steps in this reaction are analogous to nucleophilic substitution reactions in Chapter 15 and 16 where a $^{-}{:}Z$ group leaves from the tetrahedral

intermediate formed by addition of $^{-}$OH to the C=O of acid halides, esters, amides or anhydrides with the general structure RC(=O)Z. In this case, CX_3 is the Z group. Since the final trihalomethane products (H-CX_3) formed by protonation of $^{-}$:CX_3 are commonly named *chloroform* (X = Cl), *bromoform* (X = Br), or *iodoform* (X=I), the reaction in Figure 18.23 is called the **haloform reaction**.

> ***Some Historical Information***. *Before the advent of modern spectrometry (Chapter 5), the haloform reaction was widely used to identify the presence of the $CH_3C(=O)$ group in molecules. I_2 was usually used as the molecular halogen in this reaction because the product CHI_3 (iodoform) is a bright orange solid with a characteristic odor that readily precipitates from the aqueous reaction mixture. Since molecular I_2 can oxidize* alcohols of the structure $CH_3CH(OH)R$ to methyl ketones of the structure $CH_3C(=O)R$ (Chapter xx), these alcohols also lead to the formation of CHI_3 when treated with aqueous base in the presence of I_2.*

Regiospecificity. Like acid catalyzed halogenation, two different enols and enolate ions can form when unsymmetrical ketones react with base. Generally, the least substituted α-C is halogenated more rapidly than the more substituted α-C.

This is opposite what occurs in acid catalyzed α-halogenation where the most substituted C is preferentially halogenated. The relative reactivity of α-C-H's toward base (their relative acidity) is $C\underline{H}_3(C=O)R' > RC\underline{H}_2(C=O)R' > R_2C\underline{H}(C=O)R'$ and formation of the enolate ion is the rate-determining step.

> ***Kinetic and Thermodynamic Enolates***. When two different enolate ions can form from reaction of a carbonyl compound and base(18.24), the less substituted enolate ion (A) forms *more rapidly* than the more substituted enolate ion (B).
>
> Figure 18.24
>
> As a result, when an unsymmetrical ketone is treated with base, the initial concentration of (A) is higher then that of (B). However, the more substituted enolate ion (B) is more thermodynamically stable than than the less substituted enolate (A). So after the enolate ions equilibrate, the equilibrium concentration of (B) is higher than that of (A).

Enolate (A) is called the "kinetic" enolate because its early predominant formation depends on relative rate constants for enolate formation. Enolate (B) is called the "thermodynamic" enolate because its ultimate predominance depends on equilibrium constants. Products from the "kinetic" enolate are said to arise from "kinetic control", while products arising from the "thermodynamic" enolate are said to arise from "thermodynamic control". Kinetic *versus* thermodynamic control of product distributions occurs in other reactions besides those involving enolate ions.

α-*Halogenation of Carbonyl Compounds R-C(=O)-Z* (18.2D)

Carbonyl compounds other than aldehydes and ketones can also be α-halogenated by way of their enol forms or enolate ions.

Carboxylic Acids, Acid Halides, and Anhydrides. Reaction of a carboxylic acid (R-C(=O)-Z where Z = OH) with Br_2 and a catalytic amount of PBr_3, or with Cl_2 and a catalytic amount of PCl_3, leads to the formation of the corresponding α-bromocarboxylic acid or α-chlorocarboxylic acid in a process known as the **Hell-Volhard-Zelinskii reaction** (H-V-Z reaction) (Figure 18.25).

Figure 18.25

PBr_3 or PCl_3 convert carboxylic acids into acid halides* (*14.x) and the enol forms of these acid halides are α-halogenated by Br_2 or Cl_2 (Figure 18.26).

Figure 18.26

The α-halogenated acid halide then reacts in an exchange reaction with unreacted carboxylic acid present in the reaction mixture to give α-halocarboxylic acid and unhalogenated acid halide (Figure 18.27).

Figure 18.27

This unhalogenated acid halide then reacts with Cl_2 or Br_2 to give more α-halogenated acid halide and the whole process is repeated.

The H-V-Z reaction takes advantage of the fact that acid halides have larger enol concentrations than carboxylic acids or some other compounds of the structure RC(=O)-Z such as esters or amides. As a result, acid halides themselves can be directly α-halogenated (Figure 18.28).

Figure 18.28

Since anhydrides have a relatively high enol content, they can also be directly α-halogenated with Br_2 or Cl_2.

The H-V-Z reaction cannot be used for iodination or fluorination. However, it is possible to α-iodinate acid chlorides by treatment with I_2 and a catalytic amount of HI (Figure 18.29).

Figure 18.29

18.3 Alkylation Reactions

Alkyl groups can be substituted for α-C-Hs on carbonyl compounds by reaction of the carbonyl compound with base followed by reaction with 1° or 2° haloalkanes.

Figure 18.30

$$R_2CH\text{-}C(=O)R' \xrightarrow[2)\ R''X]{1)\ \text{base}} R_2C(R'')\text{-}C(=O)R'$$

If one or more R group is H, the α-alkylated product can be further alkylated.

α-Alkylation Mechanism (18.3A)

We illustrate a general mechanism for α-alkylation of ketones or aldehydes in Figure 18.31.

Figure 18.31

A base removes an α-H in Step 1 giving an enolate ion. In Step 2 the α-C of the enolate ion reacts in an S_N2 reaction with the haloalkane to give the α-alkylated ketone or aldehyde.

C versus O Alkylation. The O atom of the enolate ion can also serve as the nucleophilic center in the S_N2 reaction leading to the formation of the O-alykylated product (enol ether) shown here.

Figure 18.32

Since C is the more nucleophilic atom, the products are primarily C-alkylated ketones ro aldehydes.

Bases and Solvents

All of the carbonyl reactant must be converted to its enolate ion to prevent its reaction with enolate ion to give *condensation* products as we describe in the next section of this chapter.

Bases. Hydroxide ions (HO^-) and alkoxide ions such as ethoxide ($CH_3CH_2O^-$) or t-butoxide ($(CH_3)_3CO^-$) ions, and hydroxide ion (HO^-), are much less basic than

the enolate ion. As a result, they convert only a small fraction of a ketone, aldehyde, or other carbonyl compound RC(=O)-Z, to their corresponding enolate ions. In contrast stronger bases such as those in Table 18.2 quantitavtively convert carbonyl compounds to enolates.

Table 18.2. Stong Bases Used for Quantitative Enolate Formation

Structure	Name
$(CH_3CH_2)_2NLi$	lithium diethylamide
$((CH_3)_2CH)_2NLi$	lithium diisopropylamide (LDA)
$NaNH_2$	sodium amide
NaH	sodium hydride

Solvents. Solvents for these reactions must not have acidic protons. They must be aprotic since protic solvents like alcohols or water act as acids and protonate enolate ions. Some aprotic solvents are 1,2-dimethoxyethane, tetrahydrofuran, N,N-dimethylformamide, and liquid NH_3 (Figure 18.33).

Figure 18.33

Alkylation of Ketones and Aldehydes (18.3C)

α-Alkylation of ketones is usually more successful than α−alkylation of aldehydes. With aldehydes, it is difficult to avoid condensation reactions because we see later they are readily attacked by enolate ions. We describe indirect reactions that α-alkylate aldehydes later in this section.

Ketones. We can alkylate ketones using the bases and solvents described above (Figure 18.34).

Figure 18.34

The haloalkane reactants can be 1° or 2°, as well as allylic or benzylic, as we see in this example. The S_N2 displacement mechanism makes 3° haloalkanes unsuitable since they primarily undergo E2 elimination with enolate ion serving as the base (Figure 18.35).

Figure 18.35

Some elimination can occur even with 1° and 2° haloalkanes. In place of haloalkanes, other substrates (R-L) can be used where L is a sulfonate group (L = OSO_2R) described in Chapter 7 (7.7).

Regioselective alkylation of an unsymmetrical ketone requires that only one enolate ion is present.

Figure 18.36

This is difficult to achieve if both α-C's are similarly substituted since strong base will give significant amounts of both enolate ions. However, it is possible to separately synthesize each of the two enolate ions of unsymmetrical ketones by indirect methods so that regiospecific α-alkylation of that ketone can be accomplished.

Synthesis of Specific Enolate Ions of Unsymmetrical Ketones. We show a procedure to individually synthesize the two different enolate ions from an unsymmetrical ketone as outlined in Figure 18.37.

Figure 18.37

Reaction of an unsymmetrical ketone with acetyl chloride gives a mixture of the enol acetates (A) and (B). Acetyl chloride reacts with both enol forms present in equilibrium, and the resulting enol acetates are separated by physical methods such as chromatography or distillation.

Reaction of each enol acetate with CH_3Li (Steps 2a and 2b) gives the corresponding lithium enolates. Subsequent alkylation of each of these lithium enolates gives the corresponding α-alkylated carbonyl compound (Figure 18.38).

Figure 18.38

Aldehydes. Since direct alkylation of aldehydes leads to unwanted side reactions, we can use the indirect sequence in Figure 18.39 to obtain the desired α-alkylated products.

Figure 18.39

We convert the aldehyde to an imine and then react the imine with a strong base to give an "enolate-type" ion. Reaction of this ion with haloalkanes gives an α-alkylated imine that we can hydrolyze to give the desired α-alkylated aldehyde.

Alkylation of Esters and Carboxylic Acids (18.3D)

Both esters and carboxylic acids can be directly alkylated.

Esters. α-Alkylation of esters (RC(=O)-OR) is analogous to α-alkylation of ketones.

Figure 18.40

They can be directly alkylated since they give just one enolate ion on reaction with base, and are even less reactive than aldehydes in condensation reactions.

Carboxylic Acids. When a carboxylic acid is reacted with a base, it is quantitatively converted into its carboxylate ion (Chapters 13 and 14) (13.5A and 14.2)

Figure 18.41

In spite of this, strong bases such as those in Table 18.2 will go on to remove an α-H from that carboxylate ion to give an enolate dianion.

Figure 18.42

This dianion will react with haloalkanes to give the α-alkylated carboxylate ion shown above that can be protonated to give the α-alkylcarboxylic acid.

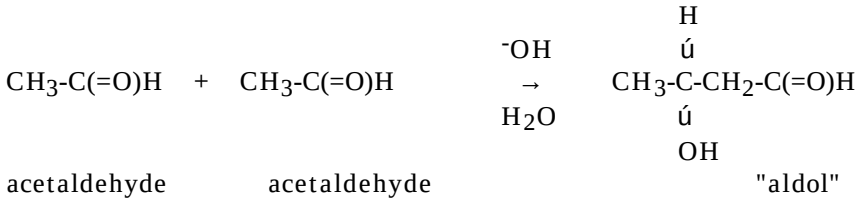
18.4 Condensation Reactions

Although reaction between an enolate ion and its parent aldehyde during α-alkylation is an unwanted side reaction, this **condensation** reaction is a very useful way to convert smaller organic molecules into larger organic molecules with multiple functional groups.

The Aldol Reaction (18.4A)

If you treat acetaldehyde with a base such as hydroxide or alkoxide in the absence of other reactants, the product is a four carbon compound with an OH and C=O group (Figure 18.43).

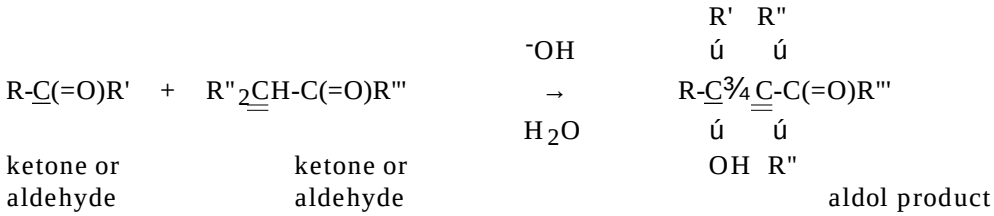
Figure 18.43



The common name of this hydroxy aldehyde product (Figure 18.43) is **aldol** and the reaction is the simplest example of a large group of condensation reactions called **aldol reactions**.

In aldol reactions, two aldehydes, two ketones, or an aldehyde and a ketone react together to form a new C-C bond (Figure 18.44).

Figure 18.44



The Base. A base frequently employed for the aldol reaction is aqueous sodium (or potassium) hydroxide ($^-OH/H_2O$). Hydroxide ion converts only a small fraction of the carbonyl compound to the enolate ion, but that is all that is necessary. The enolate ion reacts with unreacted carbonyl compound and more enolate ion forms as it is used in the reaction.

Hemiacetal Formation. Independent of all the other reactions we have been describing in this chapter, aldehydes always react with aqueous hydroxide ion to form hydrates as we described in Chapter 16 (16.2B) (Figure 18.45).

Figure 18.45

This reaction does not interfere with the aldol reaction since it is an equilibrium and regenerates the aldehyde reactant as needed.

The New C-C Bond. It's important to carefully examine what happens in the aldol reaction in Figure 18.44. The new C-C bond forms between the C(=O) carbon of a ketone or aldehyde molecule and the $R"_2C$ carbon (the α-C) of another ketone or aldehyde molecule. These C's have been underlined in the reactants and in the products for the purpose of identification.

Because of this new C-C bond, the C(=O) group of the first ketone or aldehyde has been transformed into a C(-OH) group and the two original carbonyl compounds join together into a single molecule.

Aldol Reaction Mechanism. We show the mechanism of the aldol reaction for acetaldehyde in Figure 18.46.

Figure 18.46

Base forms an enolate ion from acetaldehyde in Step 1. The nucleophilic enolate then adds to the C=O group of a second acetaldehyde molecule in Step 2. In Step 3, the resultant tetrahedral intermediate from Step 2 is protonated to give the aldol product.

Steps 2 and 3 are completely analogous to the many examples of nucleophilic addition to C=O groups in Chapter 16 (16.2). The important difference between this mechanism and the examples in Chapter 16 is that the nucleophile in the aldol reaction is formed from a carbonyl compound.

We show the general mechanism for the aldol reaction in Figure 18.47.

Figure 18.47

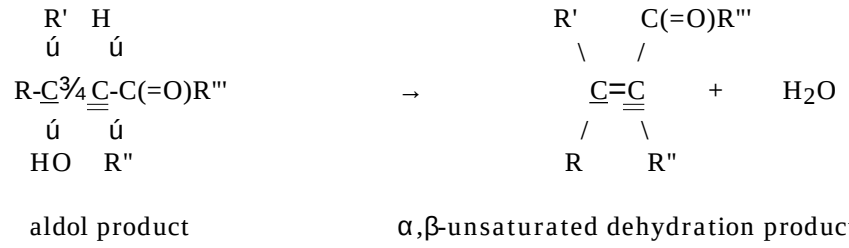
It has the same three steps shown in Figure 18.46 and we arbitrarily choose one of the two carbonyl compounds as the source of the enolate ion. We can identify the enolate and the carbonyl compound that is attacked by examining the aldol product (Figure 18.48).

Figure 18.48

The $\underline{\underline{C}}$ in the atomic grouping HO-$\underline{C}$-$\underline{\underline{C}}$-C=O in the product corresponds to the α-$\underline{\underline{C}}$ of the enolate ion. The HO-$\underline{C}$ group forms from the O=$\underline{C}$ group of the carbonyl compound attacked by the enolate ion. The C=O group of the carbonyl compound giving the enolate ion is the C=O in the final aldol product.

Dehydration of the Aldol Product. Aldol products readily lose water if there is an H on the α-$\underline{C}$ (Figure 18.49).

Figure 18.49



The dehydration product contains a $C_\beta=C_\alpha$-C=O conjugated system where the α and β labels show the origin of the term α, β-unsaturated carbonyl compound. The favorable stability resulting from conjugation in the α,β-unsaturated carbonyl product often causes it to form spontaneously from the aldol product during the aldol reaction.

If dehydration does not occur under basic conditions, it can be accomplished with acid catalysis. We show the mechanisms for base and acid catalyzed dehydration of aldols in Figure 18.50 and 18.51.

Figure 18.50 and 18.51

Aldol Condensation. The *aldol reaction* is often called the **aldol *condensation* reaction**, and the term *condensation* is commonly applied to all reactions in which enolate ions add to C=O groups. But in fact, the term *condensation* is correctly used only when the product isolated from the reaction mixture is the α,β-unsaturated compound.

Aldol Reactions are Equilibria. Each step of the aldol reaction is an equilibrium process. The reaction can go in the "forward" direction beginning with aldehydes and/or ketones, or it can go in the "reverse" direction starting with the aldol addition product (or α,β-unsaturated dehydration product) (Figure 18.52).

Figure 18.52

aldehyde + aldehyde → → aldol addition product (or dehydration product)
← (favored)

ketone + ketone → aldol addition product (or dehydration product)
(favored) ← ←

The equilibrium favors the aldol addition product from two aldehydes, but this is not the case when the starting carbonyl compounds are both ketones. The aldol product formed from two ketones has steric strain that is not present in the aldol product from two aldehydes (Figure 18.53).

Figure 18.53

$R_2CH\text{-}C(=O)R'$ + $R_2CH\text{-}C(=O)R'$ → ← ← $R_2CH\text{-}C(R')(OH)\text{-}C(=O)R'$

ketone ketone aldol product (not favored)
(significant steric strain)

$R_2CH\text{-}C(=O)H$ + $R_2CH\text{-}C(=O)H$ → → ← $R_2CH\text{-}C(H)(OH)\text{-}C(=O)H$

aldehyde aldehyde aldol product (favored)
(less steric strain)

This steric strain in the product from two ketones arises because the C-C bond is fully substituted (has no C-H bonds). In contrast, the R' group is H in the aldol

product from two aldehydes so there is significantly less steric strain across the new C-C bond.

Acid Catalyzed Aldol Reactions. While aldol reactions are usually carried out using a base to form the enolate ion, it is possible to catalyze the reaction with acid (Figure 18.54).

Figure 18.54

A protonated C=O group reacts with the enol form of another carbonyl compound as we show in Figure 18.55.

Figure 18.55

Formation of both the enol form (A) and protonated carbonyl compound (B) is catalyzed by acid (Steps 1a and 1b) and they react in Step 2 via an electrophilic addition reaction on the C=C. Subsequent deprotonation gives the aldol addition product (Step 3a). If it contains an α-CH, rapid dehydration occurs to give the α,β-unsaturated carbonyl compound as we show in Step 3b.

Variations on the Aldol Reaction (18.4B)

Only one product can form when the aldol reaction involves a single aldehyde. However there are a number of possible variations that include reactions between two different aldehydes and/or ketones, as well as "aldol-like" reactions where an aldehyde or ketone reacts with an enolate ion or "enolate-type" ion that does not arise from a ketone or an aldehyde. Also if a molecule contains two C=O groups, intramolecular aldol reactions leading to cyclic products are possible.

Mixed Aldol Reactions. If two different aldehydes are present in the reaction mixture, four aldol products are possible if each aldehyde has an α-CH.

Figure 18.56

There are two possible enolate ions (from A or B), and two possible carbonyl compounds (A or B) for reaction with each enolate ion. The situation is more complicated for an aldol reaction between two different ketones (or between a ketone and an aldehyde) if one or both of the ketones has two different α-CH's. As a result, such **mixed** (or **crossed**) aldol reactions are not feasible without special restrictions.

The most common restriction is that one carbonyl compound has no α-H's. This reduces the number of possible aldol products from reaction of two aldehydes

from 4 to 2 since the aldehyde without the α-H's can never be an enolate ion (Figure 18.57).

Figure 18.57

The experimental procedure can be further controlled to favor formation of only one product by dissolving the aldehyde without α-H's in the basic reaction mixture, and then slowly adding the aldehyde with α-H's to the basic solution.

Figure 18.58

In this case, there is only a small concentration of the aldehyde with α-H's (B) in the reaction mixture at any time compared to a large concentration of the aldehyde without α-H's (A). Each enolate ion (from B) as it forms in the reaction mixture then reacts predominantly with the much larger concentration of (A) already in the reaction mixture.

The same strategy favors single products from reaction of two different carbonyl compounds whether they are ketones or mixtures of aldehydes and ketones. However, the carbonyl compound dissolved in the basic solution cannot have α-H's.

> ***Steric Strain and Mixed Aldol Reactions***. The steric strain that causes aldol reactions between two ketones to be unfavorable (see Figures 18.52 and 18.53) similarly affects aldol reactions between an *aldehyde enolate* and a *ketone*. However, this is not the case for the reaction between a *ketone enolate* and an *aldehyde*. This latter mixed reaction is particularly good when the aldehyde has no α-CH's and cannot condense with itself since the aldol reaction (which is an equilibrium) is very unfavorable for the two ketone molecules.

Intramolecular Aldol. We can use the aldol reaction to make five- and six-membered rings and show an example of the formation of a five-membered ring in Figure 18.59.

Figure 18.59

The enolate ion formed in Step 1 reacts with the other C=O group to give a five-membered ring intermediate in Step 2. Subsequent protonation in Step 3 gives the cyclic aldol product.

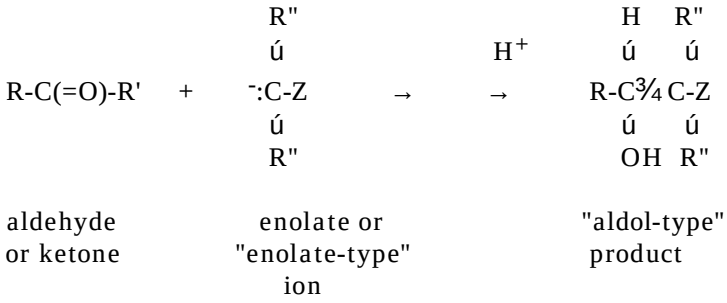
It is also possible to form the alternate enolate that we show in Figure 18.60.

Figure 18.60

However, it forms less rapidly than that in Figure 18.59 because α-CH_2 protons are less reactive than α-CH_3 protons (see section 18.xx). Moreover, this alternate enolate ion (Figure 18.60) does not cyclize because this would form a highly strained three-membered ring (Figure 18.60).

The Enolate Ion is Not from a Ketone or Aldehyde. There are several types of condensation reactions where aldehydes or ketones react with enolate ions formed from carbonyl compounds other than aldehydes or ketones, or with "enolate-type ions" from compounds that are not carbonyl compounds.

Figure 18.61

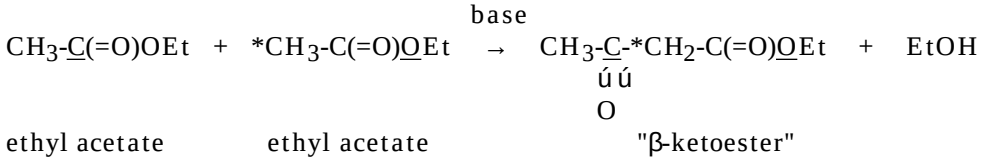


These are not formally "aldol reactions", but they are frequently called that (or called "aldol-type reactions") if the nucleophilic carbon species ($R_2ZC:^-$)) attacks an aldehyde or a ketone (R-C(=O)-R'). We show some examples in Figure 18.62 (next page).

The Claisen Condensation (18.4C)

An aldol-type reaction between two ester molecules is called a **Claisen Condensation** (Figure 18.63)**.**

Figure 18.63

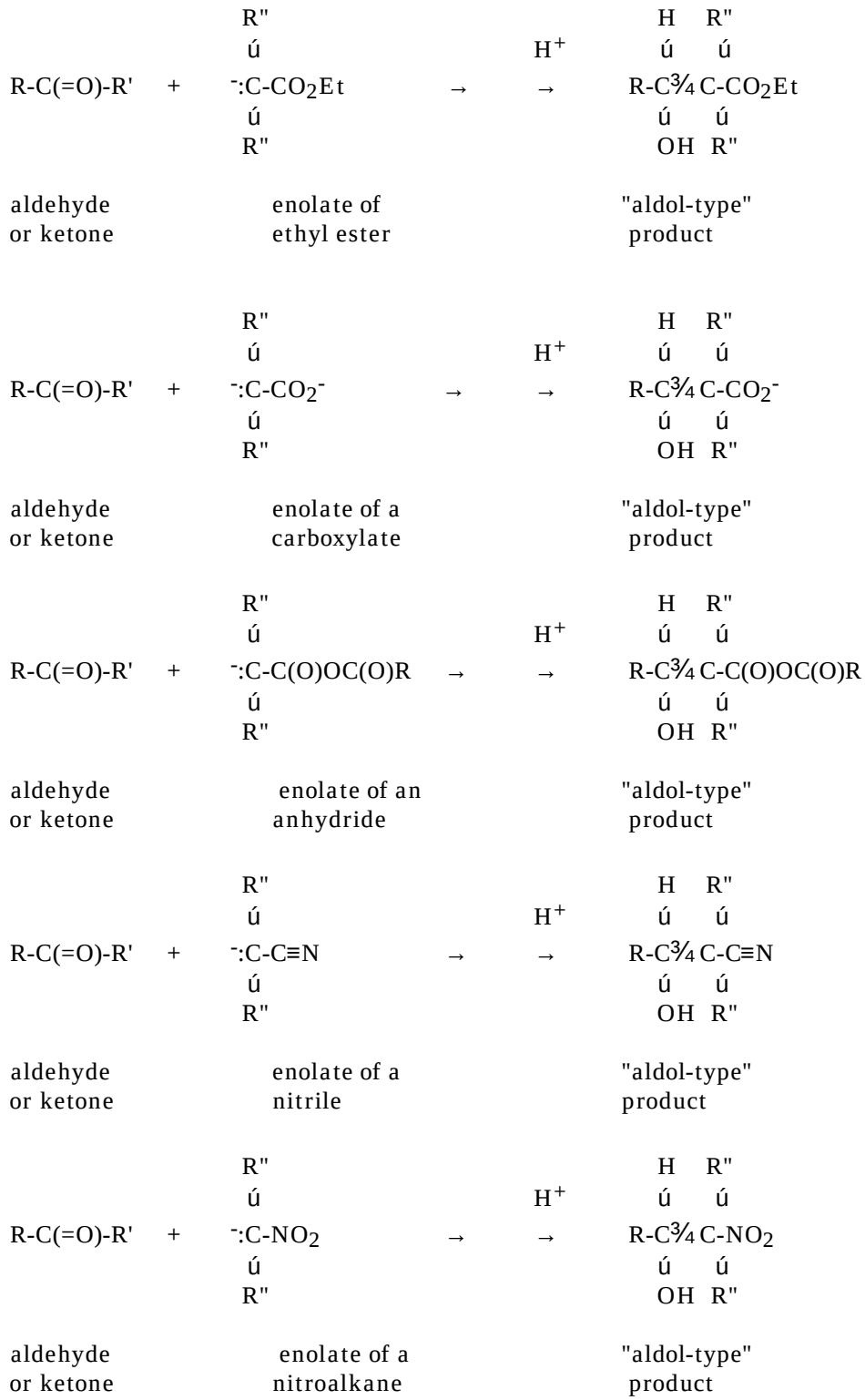


This example is the base catalyzed reaction between two molecules of ethyl acetate that forms the new C-C* bond shown in the β-ketoester product.

Claisen Condensation Mechanism. We show the mechanism of this reaction in Figure 18.64.

Figure 18.64

Figure 18.62. Examples of Reactions of Enolate or "Enolate-Type" Ions ($^-CZR"_2$) with Aldehydes or Ketones.

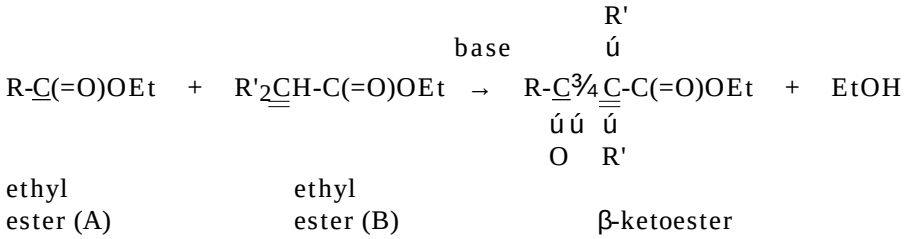


The enolate ion formed in Step 1 adds to the C=O group of a second ethyl acetate molecule in Step 2. The resulting tetrahedral intermediate then loses ethoxide ion in Step 3 to give the β-ketoester product.

Steps 1 and 2 are analogous to aldol reaction mechanisms (Figure 18.46), but Step 3 is different. The loss of ethoxide ion in Step 3 is analogous to what occurs when a variety of nucleophiles add to esters as we outlined in Chapter 15? (15?.x). The difference between the Claisen condensation mechanism and the examples in Chapter 15 is that the nucleophile in the Claisen condensation is an enolate ion formed from a carbonyl compound.

General Examples. We show a general representation of the Claisen condensation between two esters in Figure 18.65.

Figure 18.65



Ester (B) is the source of the enolate ion and the new C-C bond forms between the underlined C's. Reactions where enolate ions from molecules other than esters react with the C=O group of esters are also referred to as *Claisen condensations* and we illustrate some of those later in this section.

> ***A Cautionary Note about the Names of these Reactions***. The reaction in which an ester enolate reacts with an aldehyde or ketone (first example in Figure) is sometimes referred to as a "Claisen reaction". This nomenclature is confusing since in addition the reaction of a ketone enolate with an aldehyde, is called a "Claisen-Schmidt" reaction.
>
> To minimize confusion in this text we will refer to reactions of all enolates with (a) ketones and aldehydes as "aldol" or "aldol-type" condensations or reactions, and (b) with esters as "Claisen" condensations or reactions.

General Claisen Condensation Mechanism. We outline the mechanism for the general Claisen condensation reaction in Figure 18.66.

Figure 18.66

It has the same three-step sequence that we showed in Figure 18.64. We have arbitrarily chosen one of the two carbonyl reactants as the source of the enolate ion and we can identify it from the Claisen condensation product.

Figure 18.67

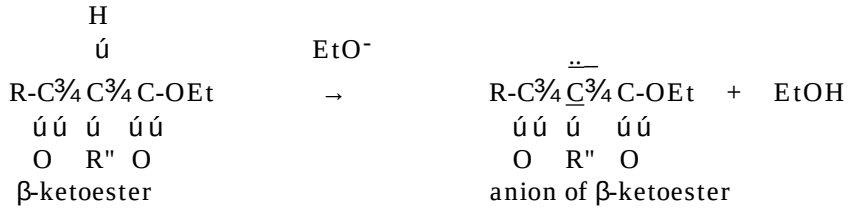
The C in the atomic grouping O=C-C-C(=O)OEt in the product corresponds to the α-C of the original enolate ion reactant while the C=O keto group in the product corresponds to the C(=O)OEt group of the ester that was attacked by the enolate ion. Note that the C(=O)OEt group of the ester giving the enolate ion remains unchanged in the final Claisen condensation product, while the C(=O)OEt group that is attacked by the enolate ion loses -OEt.

The Choice of -OEt as the Base. Claisen condensations are frequently carried out in the solvent ethanol (EtOH) specifically using ethoxide ion (EtO^-) as the base. Since the ethyl esters used in these reactions can react by nucleophilic substitution with any RO^- base (*15?.x), when this reaction occurs with EtO^- there is no change in the ester functional group (Figure 18.68).

Figure 18.68

The Claisen Condensation Product is "Acidic". The Claisen condensation reaction is an equilibrium process like the aldol reaction. However, the β-ketoester product usually cannot revert to the starting esters by cleavage of the newly formed C-C bond. This is because β-ketoesters with α-CHs rapidly react with base in the reaction mixture to form an anion that is α to two C=O groups (Figure 18.69).

Figure 18.69



This anion is particularly stable because of electron delocalization into both C=O groups.

Figure 18.70

This resonance stabilized anion is unreactive toward further reaction by the EtO^- ion. Since attack by EtO^- at the keto C=O group is necessary to reverse the last step of the Claisen condensation, this reaction is effectively irreversible in most cases.

The Dieckmann Condensation. When two ester functional groups are present in the same molecule and separated by 4 to 6 C's, an *intramolecular* Claisen condensation can occur to give a cyclic system. We show formation of a six-membered ring in Figure 18.71.

Figure 18.71

This intramolecular condensation is called a **Dieckmann condensation** and it can give 5, 6, or 7-membered rings.

> ***Ring-Forming Reactions***. Reactions that make rings by forming C-C bonds, such as the Dieckmann condensation or an intramolecular aldol reaction, are very important in synthetic organic chemistry. We describe other ring-forming reactions in Chapter 19?.

Variations of the Claisen Condensation. As we saw with the aldol reaction, mixed or crossed Claisen condensations where two different esters react with each other are best carried out when only one of the esters has α-H's.

Figure 18.72

Esters also can react with enolate ions or "enolate-type" ions from sources other than esters (Figure 18.73).

Figure 18.73

18.5 Enolate Ions from β-Dicarbonyl Compounds

In our discussion of Claisen condensations we saw that α-CHs flanked by two C=O groups are particularly acidic.

Figure 18.74

As a result, it is easy to make enolate ions of such compounds and they are particularly useful in organic synthesis.

Acidity of α-H's in β-Dicarbonyl Compounds (18.5A)

We compare the relative acidities of several types of both C-H and O-H protons in Table 18.3 [next page]. You can see that the acidities (or pK_a values) for α-CHs between two C=O groups (numbers 2-4) fall between those of carboxylic acids (number 1) and simple alcohols (number 5). As a result, alkoxide ions RO^- react quantitatively with the β-dicarbonyl compounds (numbers 2-4) to form enolate ions as we described for the Claisen condensation in the previous section (see Figure 18.69).

Table 18.3 . Acidity of β-Ketoesters and other Selected Compounds

Number	Acidic Proton	K_a	pK_a
1	R-C(=O)O<u>H</u>	10^{-5}	5
2	R-C(=O)-C<u>H</u>$_2$-C(=O)R'	10^{-9}	9
3	R-C(=O)-C<u>H</u>$_2$-C(=O)OR'	10^{-11}	11
4	RO-C(=O)-C<u>H</u>$_2$-C(=O)OR'	10^{-13}	13
5	R-CH$_2$-O<u>H</u>	10^{-16}	16
6	R-C(=O)-C<u>H</u>$_2$-R'	10^{-20}	20
7	RO-C(=O)-C<u>H</u>$_2$-R'	10^{-24}	24

In contrast, the acidity of alcohols (number 5) is greater than that of the α-H's of simple ketones or esters (numbers 6 and 7). As a result, alkoxide ions (RCH_2-O^-) convert only a small fraction of a ketone or ester to its enolate ion. Although β-ketoesters (number 3) (and β-diesters (number 4)) are more acidic than alcohols, they are still much less acidic than carboxylic acids (number 1).

α-*Alkylation of* β-*Dicarbonyl Compounds* (18.5B)

The acidity of an α-C-H between two C=O groups allows that α-C to be easily alkylated (Figure 18.75).

Figure 18.75

We show two specific examples in the next section.

Figure 18.76

In these examples the α-alkylation products undergo further reactions that give substituted carboxylic acids or substituted ketones.

Malonic Ester and Acetoacetic Ester Synthesis. The overall conversion of the β-diester (A) to the substituted carboxylic acid (B) in Figure 18.76 is called the **malonic ester synthesis** because the starting material is an *ester* of *malonic* acid (diethyl malonate).

Figure 18.76

The conversion of the β-ketoester (C) to the substituted ketone (D) in Figure 18.76 is called the **acetoacetic ester synthesis** because the β-ketoester starting material is commonly referred to as an *ester* of *acetoacetic* acid (ethyl acetoacetate).

Their Mechanisms are Similar. Each of these two reactions has several successive steps and they have very similar mechanisms. To show this similarity, we can represent both starting esters as Y-C(=O)-CH_2-C(=O)-OEt (Y = EtO for diethyl malonate and Y = CH_3 for ethyl acetoacetate). The single mechanistic scheme in (Figure 18.77) then applies to both the malonic ester synthesis and the acetoacetic ester synthesis.

Figure 18.77

The enolate ion formed in Step 1 is alkylated in Step 2 to form Y-C(=O)-CHR-C(=O)-OEt. This intermediate is then hydrolyzed in Step 3 so that all ester functional groups are converted into carboxylic acid groups. The resulting β-keto carboxylic acid then undergoes decarboxylation to form compounds of the general structure Y'-C(=O)-CH_2R and CO_2 (Step 4).

We describe the decarboxylation mechanism in Step 4 below. But first you need to note that we have changed the Y group to Y' in the hydrolysis step (Step 3). This is because the Y-C(=O) group in the *malonic ester synthesis* hydrolyzes in Step 3 from EtO-C(=O) to the HO-C(=O). In contrast in the *acetoacetic ester synthesis*, Y-C(=O) remains unchanged in Step 3 as CH_3-C(=O). After hydrolysis in Step 3, Y' = HO in the *malonic ester synthesis*, while Y' = CH_3 in the *acetoacetic ester synthesis*.

Decarboxylation of Carboxylic Acids with β-C=O Groups. In Step 4 of the mechanism in Figure 18.77, Y'-C(=O)-CHR-C(=O)-OH loses CO_2 by the cyclic mechanism in Figure 18.78 to form Y'-C(=O)-CH_2R.

Figure 18.78

The intermediate enol that forms after loss of CO_2 subsequently isomerizes to a keto form (the carboxylic acid form).

Further Alkylation. We can further alkylate the mono-alkylated product in Step 2 whether it is from malonic ester or acetoacetic ester.

Figure 18.79

This means we can substitute two different alkyl groups on the original α-C. The alkylating agent R-X can be any haloalkane that undergoes S_N2 reactions.

Alkylation of Other Z-CH_2-Z'. Besides groups that contain C=O, there are several other Z and Z' groups, such as those in Figure 17.8, that can activate α-

CHs to removal by base. When one of them is an ester group (eg. Z' = C(=O)OEt), decarboxylation occurs after alkylation to give the product Z-CH_2R (Figure 18.80).

Figure 18.80

18.6 Other Reactions of Enolate Ions and Enols

In addition to the wide variety of reactions we have seen in this chapter there are many analogous reactions involving structurally similar reactants. We show some of these in this section.

Michael Addition Reactions (18.6A)

We have seen many reactions where enolate or "enolate-type" ions (represented as $N:^-$) add to C=O groups to give tetrahedral intermediates (Figure 18.81).

Figure 18.81

When the C=O group is conjugated with a C=C, the enolate ion ($N:^-$) can also add to the C=C (Figure 18.81). This conjugate addition reaction is called a **Michael addition reaction**.

Mechanism. We show the mechanism of a Michael addition reaction in Figure 18.82 using a general example.

Figure 18.82

Addition of the nucleophilic enolate ion ($N:^-$) to the C=C-C=O group (Step 1) gives an anion that is also an enolate ion. Subsequent protonation on oxygen gives the enol form (Step 2a), while protonation on carbon gives the keto form (Step 2b). The keto form is the final reaction product, but initial protonation of the intermediate anion occurs mainly on O (Step 2a). The resulting enol rapidly isomerizes to the keto form (Step 3). As a result, the Michael Addition reaction is a 1,4-addition reaction like those described for other conjugated systems (Chapter 12 (12.2)).

1,2-versus 1,4-Addition. When a nucleophilic species $N:^-$ adds to a C=O group to form N-C-O-H, we refer to this 1,2-addition on C=O as "direct" addition.

Figure 18.83

In contrast, when $N:^-$ adds to the β-C of the C_β=C_α-C=O group to ultimately give N-C_β-C_α(H)-C=O, we say the addition is a "Michael" addition or "1,4" addition. Although it appears from the final product that N and H have simply added in a 1,2-fashion across the C=C bond, the reaction is actually a 1,4-addition. The first formed

product is the enol N-C_β-C_α=C-O-H (Figure 18.83) that subsequently isomerizes to the final product.

In Chapter 10, you learned that C=C bonds are much more reactive toward electrophiles (E^+) than nucleophiles ($N:^-$) such as enolate ions. In this case the reason that the C=C is reactive to $N:^-$ is because the conjugated C=O group stabilizes the (-) charge on the intermediate anion as shown by the resonance structures above.

Examples. We show an example of a Michael addition reaction where the enolate ion from malonic ester reacts with an α,β-unsaturated ketone in Figure 18.84.

Figure 18.84

Another example is the addition of an enolate ion to the α,β-unsaturated ketone cyclohexene-3-one in Figure 18.85.

Figure 18.85

While the major product of this reaction at room temperature is the Michael addition product, a small amount of aldol addition product forms from 1,2-addition of the enolate ion on the C=O group. Generally speaking, Michael addition reactions (1,4-addition) predominate over 1,2-addition.

Robinson Annulation (18.6B)

The **Robinson Annulation** begins with a *Michael addition* reaction , followed by an *aldol condensation* reaction (Figure 18.86).

Figure 18.86

The term *annulene* means *ring* so an *annulation* reaction is one in which a ring is formed.

Mechanism. The enolate ion from 3-pentanone (Step 1) adds by a Michael addition to the α, β-unsaturated ketone (methyl vinyl ketone) in Step 2 giving the intermediate enolate ion product.

Figure 18.87

That product then equilibrates in Step 3 with a 1° enolate ion that cyclizes *via* an intramolecular aldol reaction (Step 4) to give the six-membered cyclic β-hydroxyketone. This cyclic compound undergoes acid-catalyzed dehydration (Step 5) giving the cyclic α,β-unsaturated ketone as the final product.

Some Comments about the Robinson Annulation. The enolate ion from Step 2 can conceivably form a four-membered ring (Figure 18.88).

Figure 18.88

However four membered rings are highly strained so while the enolate ion formed in Step 3 is less stable than that from Step 2, it can cyclize to give a more stable six-membered ring (Step 4).

Enamine Alkylation (18.6C)

Enamines (Chapter 16 (16.5)) can react like enolate ions (Figure 18.89).

Figure 18.89

Delocalization of the electron pair on N into the C=C double bond places excess electron density on the C that is α to the C=N as in an enolate ion.

Stork Enamine Reaction. Enamines are used to facilitate α-alkylation of ketones *via* the **Stork enamine reaction** as we show for the α-alkylation of cyclohexanone (Figure 18.90).

Figure 18.90

Reaction of the cyclic 2° amine *pyrrolidine* (*azacyclopentane*) with cyclohexanone in Step 1 of this sequence gives the enamine. It reacts with a haloalkane to form an intermediate aminium ion (Step 2) that is hydrolyzed to form the α-substituted cyclohexanone (Step 3).

Dialkylation. The intermediate aminium ion is in equilibrium with a tautomeric enamine (Figure 18.91).

Figure 18.91

This enamine can add another alkyl group by a second alkylation reaction with the haloalkane (Figure 18.92).

Figure 18.92

Dialkylation occurs if two equivalents of haloalkane are present in the reaction mixture, but it is not a significant side reaction if only one equivalent of haloalkane is used. Although two different enamines can form from the monosubstituted aminium ion, the less substituted enamine is formed most rapidly because the C-H on the less substituted C is more acidic.

Reformatsky Reaction (18.6D)

Organozinc compounds arising from reaction of α-haloesters and zinc metal (Figure 18.93) react like enolate ions.

Figure 18.93

The C-Zn bond is polarized (δ-)C-Zn(δ+) by the attached electropositive Zn as we described in Chapter 7 (7.9) for other organozinc and organometallic compounds in general.

Products and Mechanism. Reactions of these organozinc enolates with carbonyl compounds are called **Reformatsky reactions**. We show an example using the reactants ethyl α-bromoacetate and acetophenone in Figure 18.94.

Figure 18.94

Reaction of the α-bromoester with activated Zn metal gives the organozinc compound (Step 1) that then reacts with the ketone (Step 2). The resulting product is protonated to give a β-hydroxy ester (Step 3).

Unlike most other organometallic reactions, the haloester, Zn metal, and carbonyl compound can be mixed together in the same reaction vessel. Otherwise the overall mechanism is analogous to those described in Chapter 16 (16.6) for nucleophilic addition reactions of organometallic compounds to carbonyl compounds.

The Mannich Reaction (18.6E)

The reaction of an enol or enolate ion with an iminium ion as shown below is the last step of the **Mannich reaction**.

Figure 18.95

The iminium ion forms from the reaction between an amine (R = H or alkyl) and an aldehyde which is often formaldehyde.

Figure 18.96

The reaction in Figure 18.96 occurs as described in Chapter 16 (16.5) and involves a nucleophilic addition of the free amine to the aldehyde, followed by loss of water to give the iminium ion. It is catalyzed by both dilute acid and dilute base. While it has been proposed that under basic conditions the enolate ion directly attacks the intermediate $R_2N\text{-}CH_2\text{-}OH$ displacing hydroxide ion (^-OH), this seems unlikely under the typically mild reaction conditions because ^-OH is a very poor leaving group.