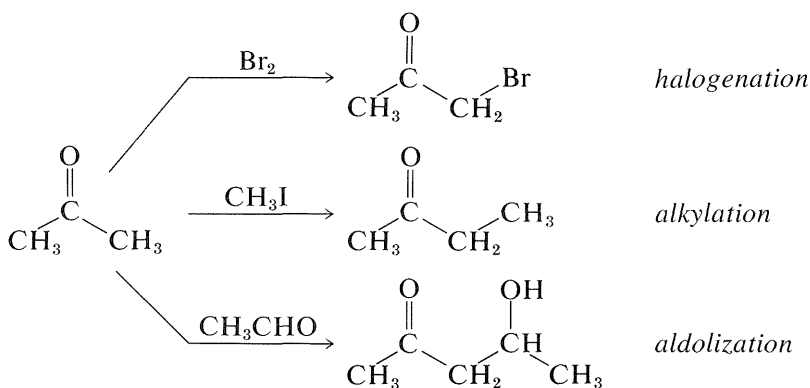


CARBONYL COMPOUNDS II. ENOLS AND ENOLATE ANIONS. UNSATURATED AND POLYCARBONYL COMPOUNDS

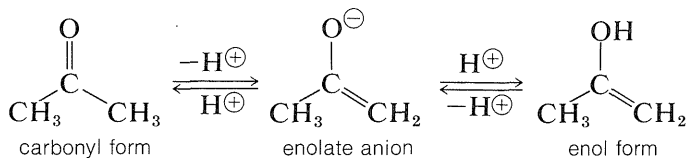
Some of the most useful reactions of carbonyl compounds involve carbon-hydrogen bonds adjacent to the carbonyl group. Such reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of the hydrogen by some other atom or group, as in the

sequence $\text{H}-\underset{\text{|}}{\text{C}}-\underset{\text{|}}{\text{C}}=\text{O} \longrightarrow \text{X}-\underset{\text{|}}{\text{C}}-\underset{\text{|}}{\text{C}}=\text{O}$. The important examples we

will consider in this chapter are halogenation, alkylation, and aldol reactions of aldehydes and ketones, illustrated here for 2-propanone:



Although these reactions lead to many diverse products depending on the reagents and conditions, they have one feature in common—they proceed by way of the enol or the enolate anion of the parent carbonyl compound:



Therefore, to understand the nature of these reactions we first must understand the conditions that convert aldehydes and ketones to their enol forms or the anions of those enol forms.

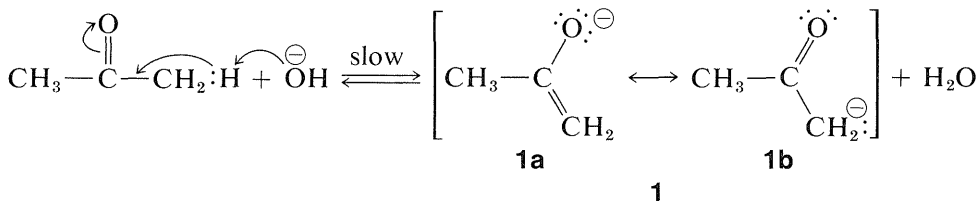
17-1 ENOLIZATION OF ALDEHYDES AND KETONES

Transformation of a carbonyl compound to an enol at a useful rate normally requires either a basic catalyst or an acidic catalyst and, of course, at least one hydrogen on the α carbon. The features of each type of catalysis follow.

17-1A Enolization in Basic Solution.

C—H Acidity of Carbonyl Compounds

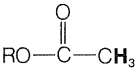
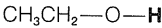
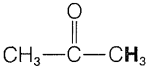
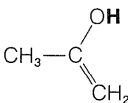
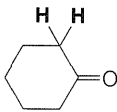
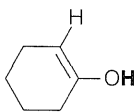
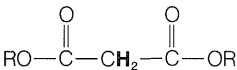
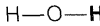
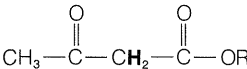
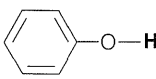
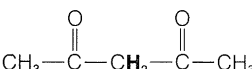
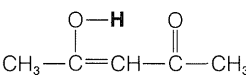

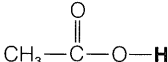

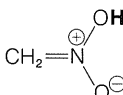
With a basic catalyst such as hydroxide ion, the first step in enolization is removal of a proton from the α position to give the enolate anion **1**:



Normally, C—H bonds are highly resistant to attack by basic reagents, but removal of a proton *alpha* to a carbonyl group results in the formation of a considerably stabilized anion with a substantial proportion of the negative charge on oxygen, as represented by the valence-bond structure **1a**. Carbonyl compounds such as 2-propanone therefore are weak acids, only slightly weaker than alcohols (compare the $\text{p}K_{\text{a}}$ values for some representative compounds in Table 17-1).¹

¹The important difference between 2-propanone and ethanol as acids is that the *rate* of establishment of equilibrium with 2-propanone or similar compounds where ionization involves breaking a C—H bond is very much *slower* than the corresponding reaction with O—H bonds.

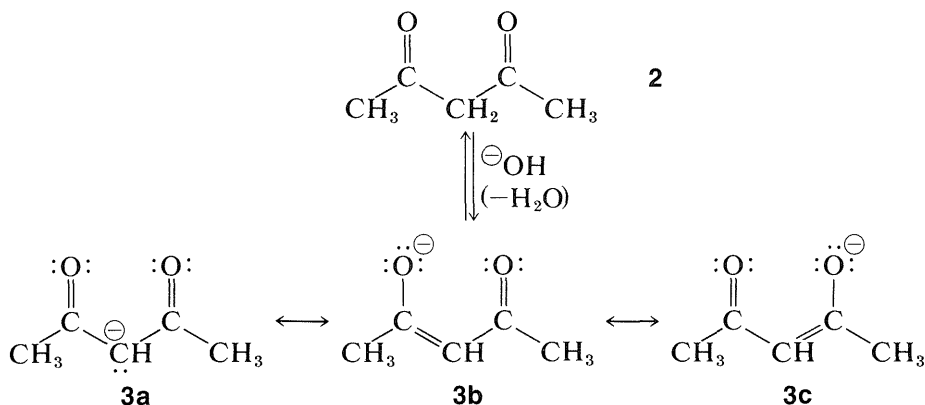
Table 17-1C—H and O—H Acidities of Some Representative Compounds^a

| C—H Acidity | | O—H Acidity | |
|--|-------------------------|---|-------------------------|
| Compound | p <i>K</i> _a | Compound | p <i>K</i> _a |
|  | 25 |  | 18 |
|  | 20 |  | 14 |
|  | 17 |  | 11 |
|  | 13 |  | 16 |
|  | 11 |  | 10 |
|  | 9 |  | 9 |
|  | 10 |  | 5 |
|  | 25 |  | 4 |

^aThese are approximate values; the acidic hydrogen is shown in boldface type; p*K*_a is defined in Section 8-1.

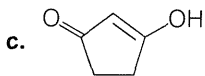
Two carbonyl groups greatly increase the acidity. For example, 2,4-pentanedione (acetylacetone, **2**) has a p*K*_a ≅ 9, which is comparable to the O—H acidity of phenols (see Table 17-1). The reason is that the enolate anion **3** has the charge largely shared by the two oxygen atoms (cf. **3b** and **3c**). As a result, the enolate anion **3** is stabilized more with respect to the

ketone than the enolate anion from 2-propanone is stabilized relative to 2-propanone:



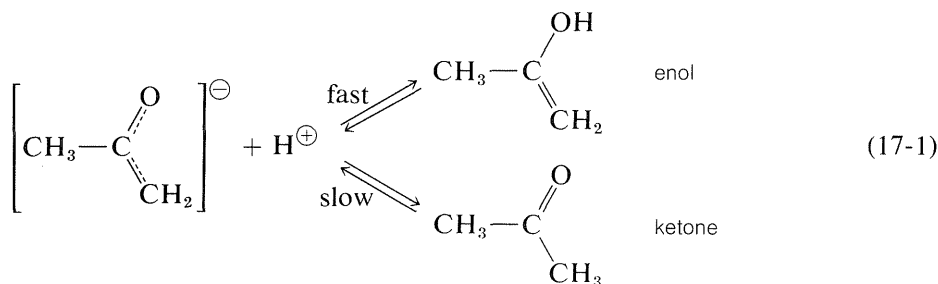
Exercise 17-1 Other groups in addition to carbonyl groups enhance the acidities of adjacent C–H bonds. For instance, nitromethane, CH_3NO_2 , has $\text{p}K_{\text{a}} = 10$; ethanenitrile, CH_3CN , has a $\text{p}K_{\text{a}} \cong 25$. Explain why these compounds behave as weak acids. Why is CH_3COCH_3 a stronger acid than $\text{CH}_3\text{CO}_2\text{CH}_3$?

Exercise 17-2 Draw valence-bond structures to represent the anions derived from the following compounds in the presence of a strong base. Assume that the base functions to remove the most acidic proton.



17-1B Enol Formation from Enolate Anions

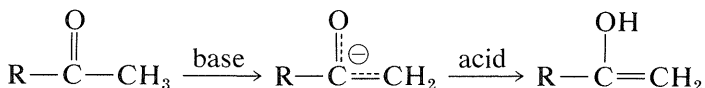
You will notice from Structures **1a** and **1b** that because the negative charge of the enolate anion is distributed on both oxygen and carbon, the ion can, in principle, combine with a proton at either site. If the enolate ion adds a proton to oxygen, the enol is formed; if it adds a proton to carbon, the ketone is formed:



Ions of this type, which can react at either of two different sites, often are called **ambident ions**.

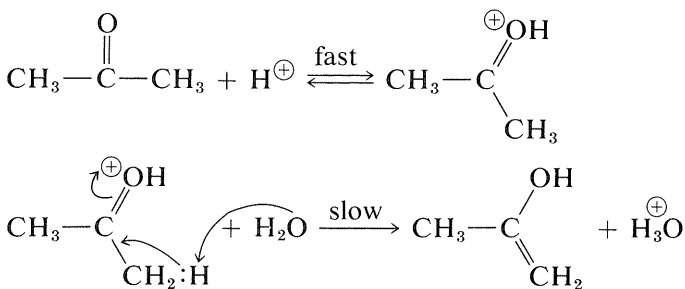
In fact, enolate anions add a proton at oxygen at least 10^{10} times faster than at carbon; the proton also is removed from oxygen much faster than from carbon. Thus the enolate anion of 2-propanone is in rapid equilibrium with the enol, but is converted back and forth to the ketone only slowly (Equation 17-1).

Another important point is that, although enolization by way of enolate anions requires a basic catalyst, both an acid and a base are necessary: a base to form the enolate anion; an acid to donate a proton to the anion to form the enol. If there is no acid available that is strong enough to donate a proton to the anion, then only the enolate anion is formed:



17-1C Enolization in Acid Solution


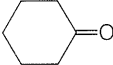
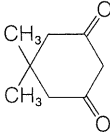
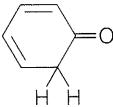
Catalysis of the enolization of 2-propanone by acids involves first, oxonium-salt formation and second, removal of an α proton with water or other proton acceptor (base):



This sequence differs from enolization induced by basic catalysts (as discussed in Section 17-1B) in that the enol is formed directly and not subsequent to the formation of the enolate anion. The proton addition to the carbonyl oxygen greatly facilitates proton removal from the α carbon because of the electron-attracting power of the positively charged oxygen. Nevertheless, this last step is the *rate-determining* step for enolization in acid solution.

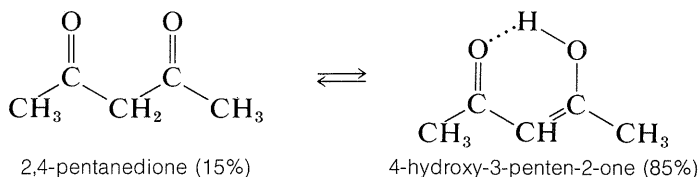
Exercise 17-3 Explain why the D or L enantiomer of a chiral ketone such as 4-phenyl-3-methyl-2-butanone racemizes in the presence of dilute acid or dilute base.

Table 17-2
The Enol Content of Some Carbonyl Compounds

| Compound | Percent enol (solvent) |
|---|---|
| 2-propanone, CH_3COCH_3 | 1.5×10^{-4} (H_2O) |
| cyclopentanone,  | 0.013 (H_2O) |
| cyclohexanone,  | 0.0004 (H_2O) |
| 2,4-pentanedione, $\text{CH}_3\text{COCH}_2\text{COCH}_3$ | 16 (H_2O) 85 (none) |
| 5,5-dimethylcyclohexane-1,3-dione,  | 95 (H_2O) |
| 2,4-cyclohexadienone, (keto form of phenol)  | ~100 |

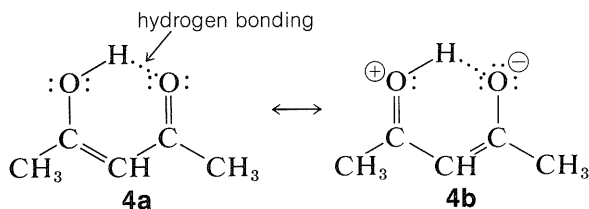
17-1D Stabilities of Enols

The equilibrium position between a simple ketone and its enol usually lies far on the side of the ketone (see Table 17-2). However, there are some interesting and important exceptions to this generalization. For instance, the influence of *two* carbonyl groups on the enol content is very striking, as we can see from the fact that 85% of 2,4-pentanedione is the enol form at equilibrium:



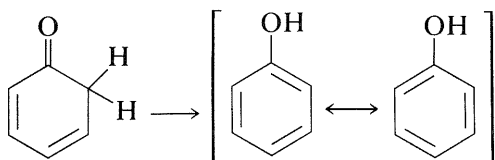
The enol form of 2,4-pentanedione (and of related dicarbonyl compounds of the type $\text{O}=\text{C}-\text{CH}=\text{C}=\text{O}$) not only is stabilized by electron-delocalization,

as shown in Structures **4a** and **4b**, but by hydrogen-bonding of the acidic hydrogen between the two oxygens:



Of course, such stabilization is not possible for the keto form.

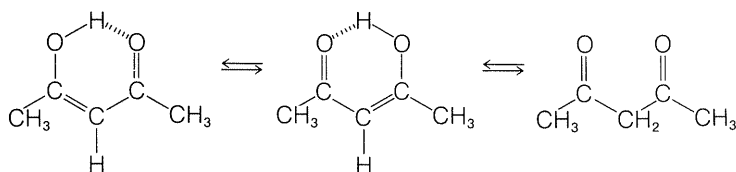
An extreme example of the stabilization of an enol by electron delocalization is benzenol (phenol), which exists 100% in the enol form. In this case the extra stability of the benzene ring is the important factor:



In the succeeding sections of this chapter we will discuss several important reactions that take place by way of enols or enolate anions.

Exercise 17-4 a. The proton nmr spectrum of 2,4-pentanedione is shown in Figure 17-1. Interpret this spectrum by assigning each resonance to a structurally different proton, and explain why the broad resonance at 15 ppm is at unusually low field strengths.

b. What does this spectrum indicate about the *rates* of the establishment of each of the following equilibria?



Give your reasoning (review Sections 9-10E and 9-10C).

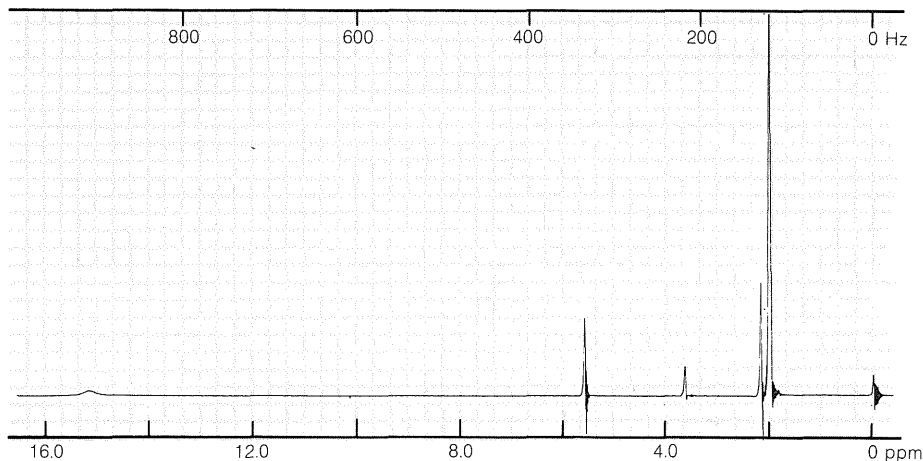
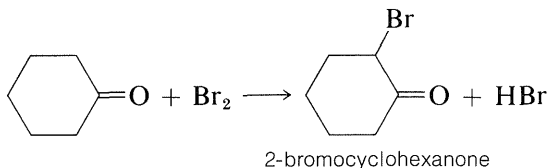
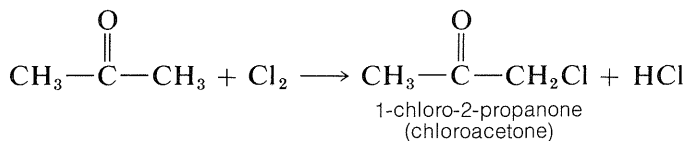


Figure 17-1 Proton nmr spectrum of 2,4-pentanedione at 60 MHz. Calibrations are relative to tetramethylsilane.

17-2 HALOGENATION OF ALDEHYDES AND KETONES

17-2A Synthesis of α -Halo Ketones

Halogenation of saturated aldehydes and ketones usually occurs exclusively by replacement of hydrogens *alpha* to the carbonyl group:



The reagents that commonly are used to halogenate carbonyl compounds are those that are used to halogenate alkanes (e.g., Cl_2 , Br_2 , SO_2Cl_2 , and *N*-bromoamides; see Sections 4-4 and 14-3). However, the characteristics of the two types of halogenation normally are very different. 2-Propanone has been particularly well studied, and the important features of the halogenation of this compound are summarized as follows:

1. 2-Propanone reacts easily with chlorine, bromine, and iodine.

2. 2-Propanone reacts at the *same* rate with *each* halogen. Indeed, the rate of formation of the 1-halo-2-propanone is *independent* of the concentration of the halogen, even at very low halogen concentrations.

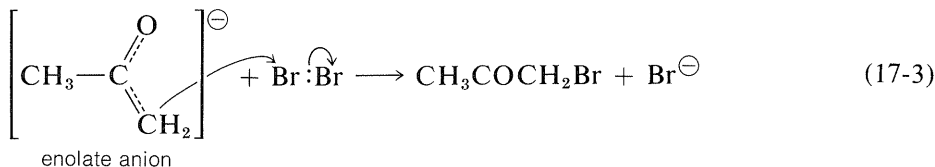
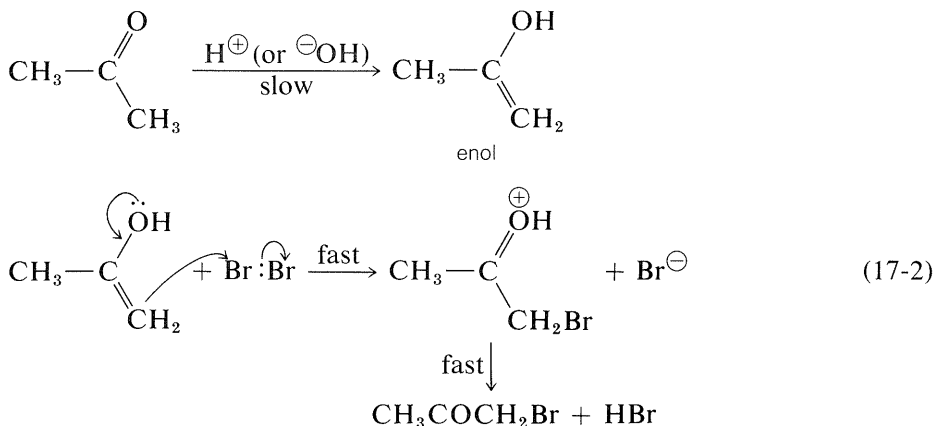
3. The halogenation of 2-propanone is catalyzed by both acids and bases. The rate expressions for formation of 1-halo-2-propanone in water solution are:

$$v = k[\text{CH}_3\text{COCH}_3][\text{OH}^\ominus] \quad \text{at moderate OH}^\ominus \text{ concentrations}$$

$$v = k'[\text{CH}_3\text{COCH}_3][\text{H}^\oplus] \quad \text{at moderate H}^\oplus \text{ concentrations}$$

The ratio of k to k' is 12,000, which means that hydroxide ion is a much more effective catalyst than is hydrogen ion.

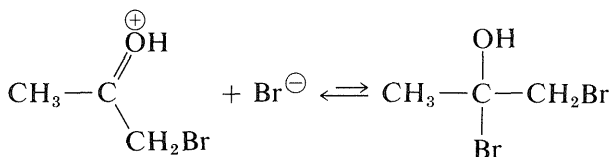
To account for the role of the catalysts and the independence of the rate from the halogen concentration, the ketone necessarily must be slowly converted by the catalysts to something that can react *rapidly* with halogen to give the products. This something is either the enol or the enolate anion of 2-propanone:



As long as the first step is slow compared with the steps of Equations 17-2 and 17-3, the overall rate of reaction will be independent of both the concentration of halogen and whether it is chlorine, bromine, or iodine (cf. Section 4-4C).

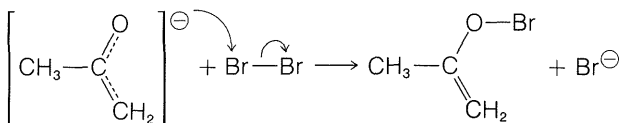
The reaction of either the enol or the enolate anion (Equations 17-2 or 17-3) with Br_2 resembles the first step in the electrophilic addition of halogens to carbon-carbon multiple bonds (Section 10-3A). However, the second step,

addition of the nucleophilic halide, if it occurs at all, does not produce any stable product:



Exercise 17-5 a. Would you expect the enol or the enolate anion of 2-propanone to be more reactive toward bromine if each were present at the same concentration? Why?

b. Would you expect the enolate anion to react with bromine at the oxygen? Explain. (Consider the bond energies involved!)



Exercise 17-6 Would you anticipate any significant difference in the rate of halogenation between CH_3COCH_3 and CD_3COCD_3 under (a) basic conditions and (b) acidic conditions? Explain. (Review Section 15-6B.)

Exercise 17-7 A detailed study of the rate of bromination of 2-propanone in water, in the presence of ethanoic acid and ethanoate ions, has shown that $v = \{6 \times 10^{-9} + 5.6 \times 10^{-4} [\text{H}_3\text{O}^\oplus] + 1.3 \times 10^{-6} [\text{CH}_3\text{CO}_2\text{H}] + 7[\text{OH}^\ominus] + 3.3 \times 10^{-6} [\text{CH}_3\text{CO}_2^\ominus] + 3.5 \times 10^{-6} [\text{CH}_3\text{CO}_2\text{H}] [\text{CH}_3\text{CO}_2^\ominus]\} [\text{CH}_3\text{COCH}_3]$ in which the rate v is expressed in moles liter⁻¹ sec⁻¹ when the concentrations are in moles liter⁻¹.

a. Calculate the rate of the reaction for a 1M solution of 2-propanone in water at pH = 7 in the absence of $\text{CH}_3\text{CO}_2\text{H}$ and $\text{CH}_3\text{CO}_2^\ominus$.

b. Calculate the rate of the reaction for 1M 2-propanone in a solution made by neutralizing 1M ethanoic acid with sufficient sodium hydroxide to give pH = 5.0 (K_a of ethanoic acid = 1.75×10^{-5}).

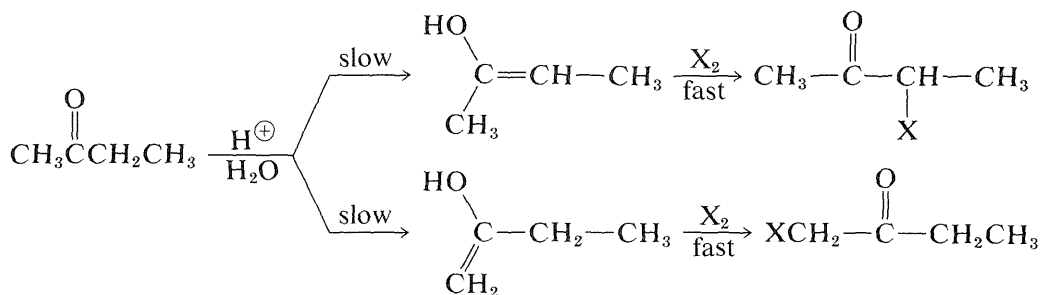
c. Explain how the numerical values of the coefficients for the rate equation may be obtained from observations of the reaction at various pH values and ethanoate ion concentrations.

d. The equilibrium concentration of enol in 2-propanone is estimated to be $\sim 1.5 \times 10^{-4}\%$. If the rate of conversion of 1M 2-propanone to enol at pH 7 (no $\text{CH}_3\text{CO}_2\text{H}$ or $\text{CH}_3\text{CO}_2^\ominus$ present) is as calculated in Part a, calculate the rate of the reverse reaction from enol to ketone at pH 7 if the enol were present in 1M concentration.

e. Suggest a mechanistic explanation for the term $3.5 \times 10^{-6} [\text{CH}_3\text{CO}_2\text{H}] [\text{CH}_3\text{CO}_2^\ominus]$ in the rate expression.

Exercise 17-8 In which of the ketones studied in Section 17-1 would you expect the rate-limiting step in halogenation to be the reaction of the enol with halogen rather than formation of the enol?

Unsymmetrical ketones, such as 2-butanone, can form two different enols that will react with halogens to give isomeric halo ketones:



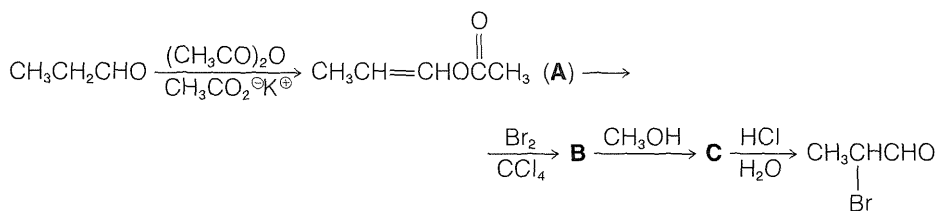
The composition of the product mixture will depend on the relative rates of formation of the isomeric enols, provided that the halogenation step is not a reversible reaction. Barring any serious steric effects that influence the rate of reaction, the more rapidly formed enol generally is the more thermodynamically stable enol.

Exercise 17-9 a. Explain why 2-butanone is halogenated preferentially on the ethyl side with an acidic catalyst. (Review of Section 11-3 should be helpful.)

b. What product would predominate in the acid-catalyzed bromination of 1-phenyl-2-propanone? Give your reasoning.

Exercise 17-10 When a small amount of bromine is added to a solution of cyclohexanone in carbon tetrachloride, the brown-red bromine color persists for quite some time. Subsequent additions of bromine result in more rapid reaction and finally the bromine is decolorized almost as rapidly as it can be poured in (until all of the ketone has reacted). Explain this sequence of events.

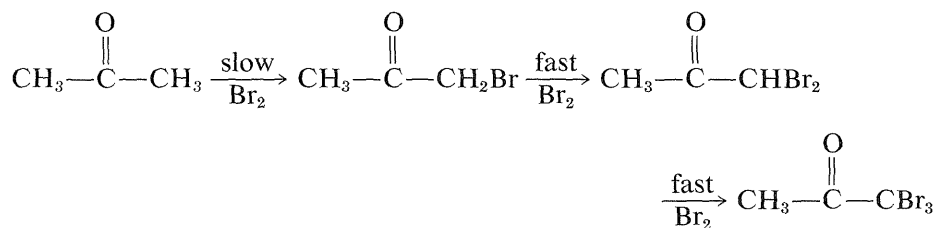
Exercise 17-11 The direct halogenation of aldehydes under either acidic or basic conditions is complicated by side reactions involving either oxidation of the aldehyde $-\text{CHO}$ group or additions to the $-\text{CH}=\text{O}$ double bond. Therefore the synthesis of α -halo aldehydes by the procedure described for ketones is not of much practical value. α -Halo aldehydes can be prepared indirectly from the enol ethanoate of the aldehyde. The enol ethanoate is made by treating the aldehyde with ethanoic anhydride and potassium ethanoate. The overall sequence follows:



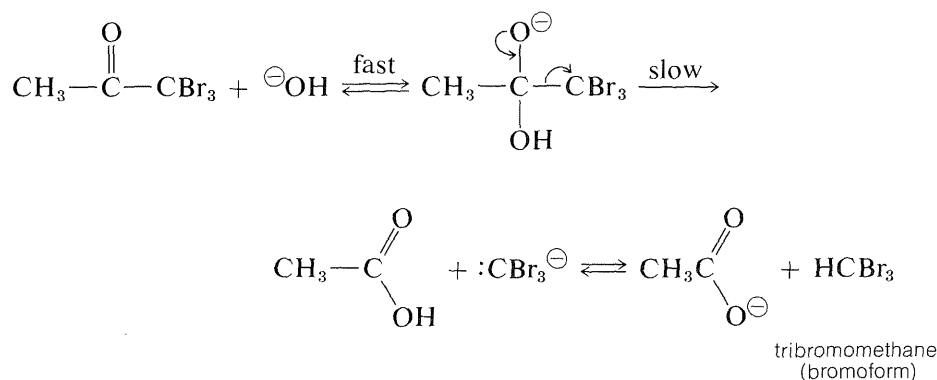
Write the structures of the intermediate products, **B** and **C**, and the steps involved in each of the reactions to produce **A**, **B**, **C**, and 2-bromopropanal. What is the function of potassium ethanoate in the formation of **A**? (You may wish to review Sections 15-4D and 15-4E.)

17-2B The Haloform Reaction

The previous discussion of the halogenation of ketones is incomplete in one important respect concerning *base-induced* halogenation. That is, once an α -halo ketone is formed, the other hydrogens on the same carbon are rendered more acidic by the electron-attracting effect of the halogen and are replaced much more rapidly than the first hydrogen:

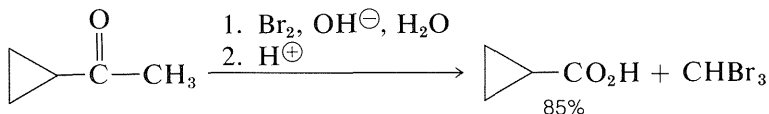


The result is that, if the monobromoketone is desired, the reaction is carried out best with an *acidic* catalyst rather than a basic catalyst. A further complication in the base-catalyzed halogenation of a methyl ketone is that the trihalo-ketone formed is attacked readily by base, thereby resulting in cleavage of a carbon-carbon bond:

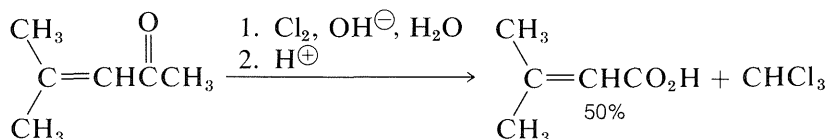


This sequence is called the **haloform reaction** because it results in the production of chloroform, bromoform, or iodoform, depending upon the halogen used. The haloform reaction is a useful method for identification of methyl ketones, particularly when iodine is used, because iodoform is a highly insoluble, bright-yellow solid. The reaction also is very effective for the synthesis of carboxylic

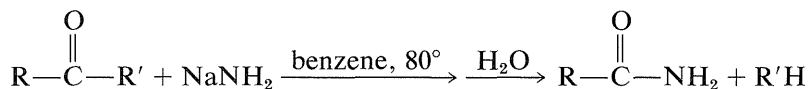
acids when the methyl ketone is more available than the corresponding acid:



Because the haloform reaction is fast, in some cases it can be used to prepare unsaturated acids from unsaturated ketones without serious complications caused by addition of halogen to the double bond:



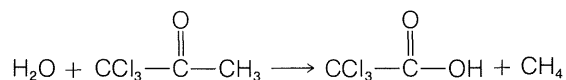
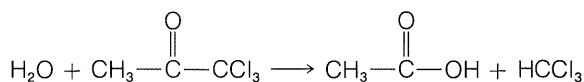
A reaction somewhat similar to the cleavage of haloforms with hydroxide occurs with ketones that do not have α -hydrogens through the action of sodium amide:



This reaction, called the **Haller-Bauer reaction**, has utility for the preparation of amides of the types ArCONH_2 and *tert*- RCONH_2 , and, through hydrolysis, the corresponding carboxylic acids.

Exercise 17-12 Trichloromethane (chloroform) at one time was synthesized commercially by the action of sodium hypochlorite on ethanol. Formulate the reactions that may reasonably be involved. What other types of alcohols may be expected to give haloforms with halogens and base?

Exercise 17-13 The ΔH° values calculated from bond energies for the following reactions in the vapor phase are equal ($-9 \text{ kcal mole}^{-1}$):

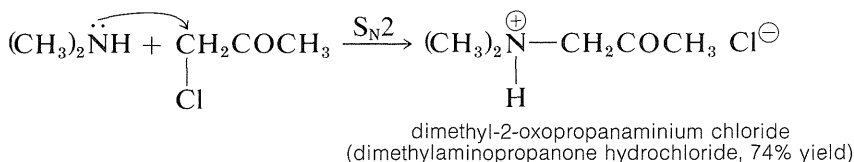


Explain why the first, but not the second, reaction proceeds rapidly with the aid of sodium hydroxide. Would you expect ethanoic acid to undergo the haloform reaction? Explain.

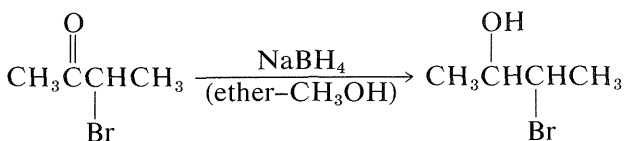
Exercise 17-14* The Haller-Bauer cleavage of 2,2-dimethyl-1-phenyl-1-propanone with sodium amide forms benzenecarboxamide and 2-methylpropane. Write a mechanism for the Haller-Bauer reaction analogous to the haloform cleavage reaction.

17-2C Reactions of α -Halo Ketones

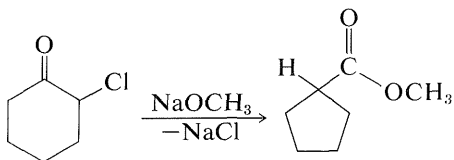
The halogen of an α -halo aldehyde or an α -halo ketone is exceptionally *unreactive* in S_N1 -displacement reactions, but is exceptionally *reactive* in S_N2 displacements, compared with the halogen of alkyl halides having comparable potential steric effects. Similar behavior is observed with α -halo carboxylic acids and is discussed further in Chapter 18.



In some circumstances, the production of a 2-halo alcohol by reduction of the carbonyl group of an α -halo ketone with metal hydrides is a useful synthetic reaction:

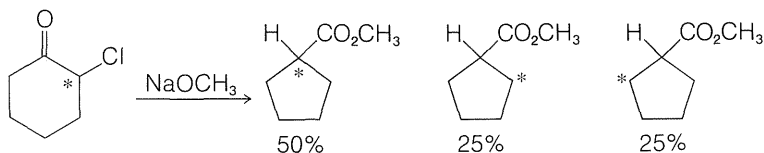


When one attempts E2 reactions with α -halo ketones using strong bases such as alkoxides, an interesting rearrangement pathway may occur called the **Favorskii rearrangement**. In this reaction, the α -halo ketone is converted to an ester. For example, 2-chlorocyclohexanone is converted to the methyl ester of cyclopentanecarboxylic acid by treatment with sodium methoxide in ether:



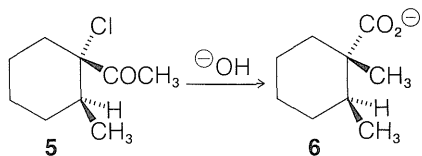
The mechanism of this reaction has been the subject of many investigations and some of the evidence obtained is incorporated into Exercise 17-15.

Exercise 17-15* When 2-chlorocyclohexanone-2- ^{14}C was treated with sodium methoxide, the ^{14}C label in the methyl cyclopentanecarboxylate formed was found at the 1-position (50%) and 2,5-positions (50%) of the ring:

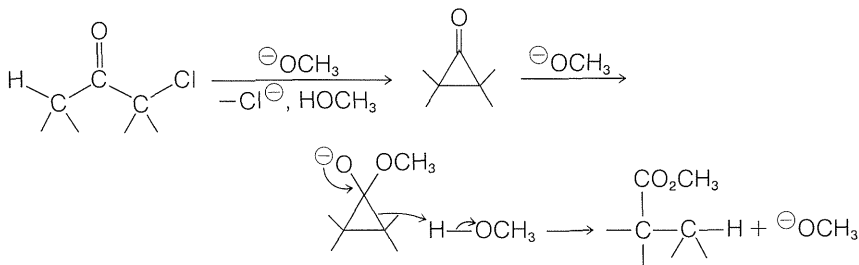


In the related reaction of the chiral chloroketone, **5**, which has the configuration shown,

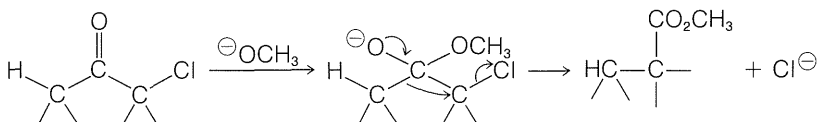
the product is the cyclohexanecarboxylic acid, **6**, with the configuration as shown:



These facts have been interpreted as indicating a mechanism involving the following intermediates (where $\ominus\text{OCH}_3$ is used as the base):



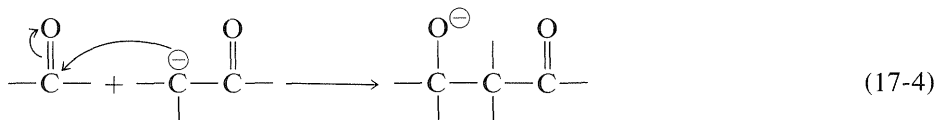
Show in detail how the given results are in accord with this mechanism and how they rule out the following alternative scheme:

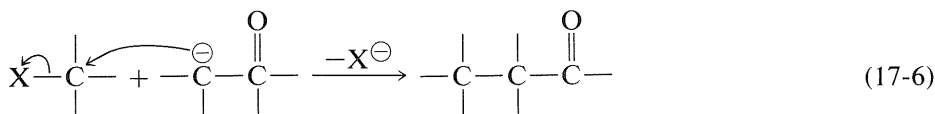
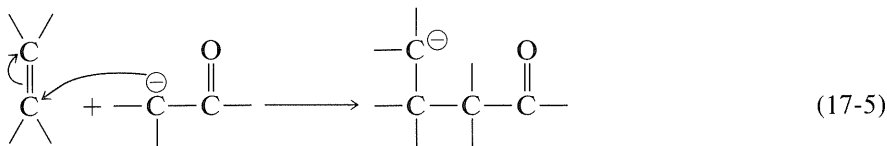


17-3 NUCLEOPHILIC ADDITION REACTIONS OF ENOLATE ANIONS

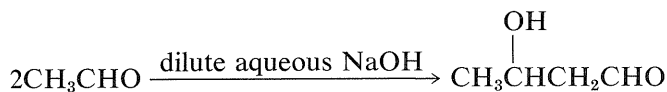
17-3A The Aldol Addition

A most important property of enolate anions, at least as far as synthesis is concerned, is their excellent nucleophilicity, which enables them to *add* to double bonds and to participate in nucleophilic substitution. When the addition is to a carbonyl double bond, it is called an **aldol addition** (Equation 17-4). Additions of enolate anions to carbon-carbon double bonds usually are classified as **Michael additions** (Equation 17-5), and these are discussed in Sections 17-5B and 18-9D. The principles of S_N nucleophilic reactions of enolate anions (Equation 17-6) will be considered in Section 17-4, and their synthetic applications in detail in Chapter 18.



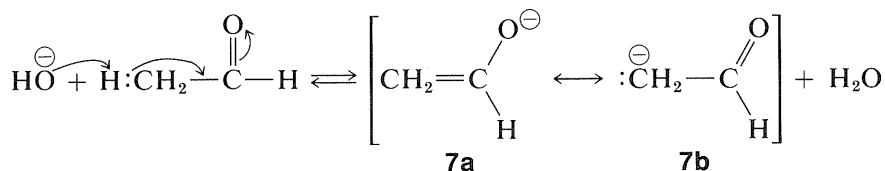


The products of aldol addition are β -hydroxy aldehydes (*ald-ols*) or β -hydroxy ketones (*ket-ols*). A typical example is the reaction of ethanal with base and, if the conditions are reasonably mild, the product is 3-hydroxybutanal:

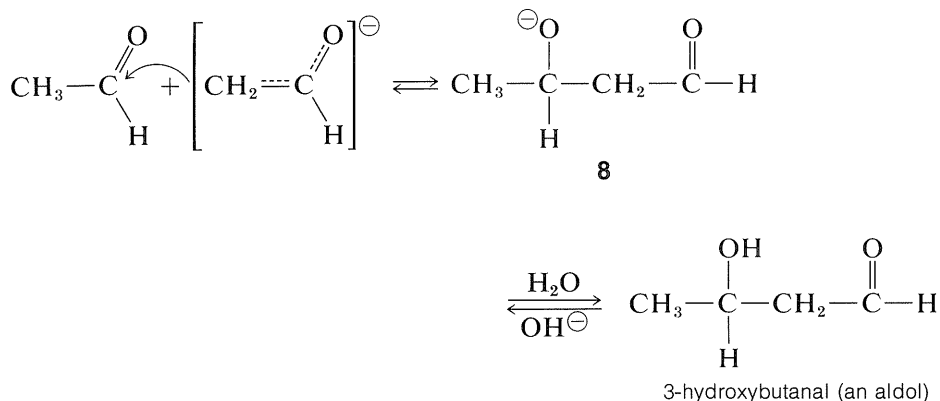


The overall reaction corresponds to a dimerization of ethanal, that is, an addition of one ethanal molecule to another with formation of a new carbon-carbon bond. The synthetic value of the reaction lies in the fact that it can be used to build large molecules from smaller molecules (see Section 13-7).

Formation of the enolate anion, **7**, by removal of an α hydrogen by base is the first step in the aldol addition:

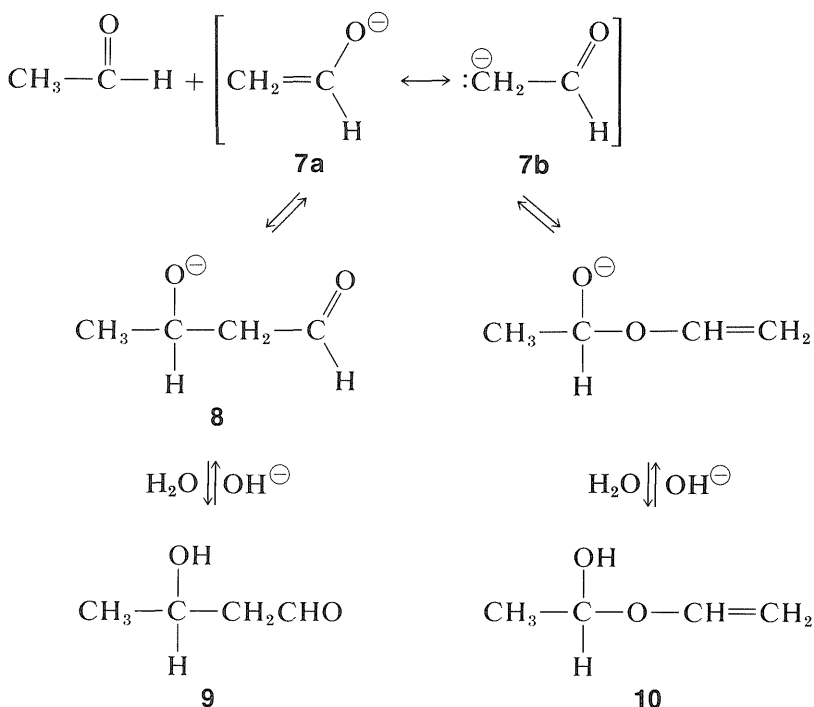


The anion then adds to the carbonyl group of a second molecule of ethanal in a manner analogous to the addition of other nucleophiles to carbonyl groups (e.g., cyanide ion, Section 16-4A). The adduct so formed, **8**, rapidly adds a proton to the alkoxide oxygen to form the aldol, 3-hydroxybutanal. This last step regenerates the basic catalyst, $^\ominus\text{OH}$:



17-3B Ambident Nature of Enolate Ions in Aldol Addition

The two possible valence-bond structures of the enolate anion, **7a** and **7b**, show that the anion should act as an **ambident nucleophile**—a nucleophile with nucleophilic properties associated with *both* carbon and oxygen. The addition step in the aldol reaction therefore may be expected to take place in either of two ways: The anion could attack as a *carbon* nucleophile to form a carbon–carbon bond, **8**, leading ultimately to the aldol **9**, or it might attack as an *oxygen* nucleophile to form a carbon–oxygen bond, thereby leading to the hemiacetal **10**. By this reasoning, we should obtain a mixture of products **9** and **10**. However, the aldol **9** is the only one of these two possible products that can be isolated:



Why is only one of these products formed? To understand this, you must recognize that aldol reactions are reversible and therefore are subject to *equilibrium* rather than *kinetic* control (Section 10-4A). Although the formation of **10** is mechanistically reasonable, it is not reasonable on thermodynamic grounds. Indeed, while the overall ΔH^0 (for the vapor) calculated from bond energies is $-4 \text{ kcal mole}^{-1}$ for the formation of the aldol, it is $+20.4 \text{ kcal mole}^{-1}$ for the formation of **10**.² Therefore, the reaction is overwhelmingly in favor of the aldol as the more stable of the two possible products.

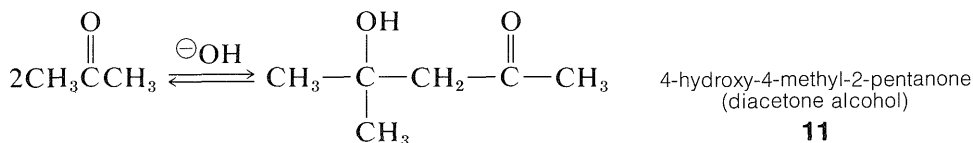
²This value probably is too large by 3 to 4 kcal, because resonance stabilization of alkoxyalkenes has been ignored in this calculation.

Exercise 17-16 When the aldol reaction of ethanal is carried on in D_2O containing OD^\ominus , using moderate concentrations of undeuterated ethanal, the product formed in the *early* stages of the reaction contains *no* deuterium bound to carbon. Assuming the mechanism discussed in this section to be correct, what can you conclude as to which step in the reaction is the *slow* step? What then would be the kinetic equation for the reaction? What would you expect to happen to the kinetics and the nature of the product formed in D_2O at very *low* concentrations of ethanal?

Exercise 17-17 What would be the products expected from aldol additions involving propanal, 2,2-dimethylpropanal, and a mixture of the two aldehydes?

17-3C Position of the Equilibrium in Aldol Additions

The equilibrium constant is favorable for the aldol addition of ethanal, as in fact it is for most aldehydes. For ketones, however, the reaction is much less favorable. With 2-propanone (acetone) only a few percent of the addition product “diacetone alcohol,” **11**, is present at equilibrium:



This is understandable on the basis of steric hindrance and the fact that the ketone-carbonyl bond is about 3 kcal mole⁻¹ stronger than the aldehyde-carbonyl bond. Despite the unfavorable equilibrium constant, it is possible to prepare diacetone alcohol in good yield with the aid of an apparatus such as that shown in Figure 17-2.

The 2-propanone is boiled and the hot condensate from the reflux condenser flows back over solid barium hydroxide contained in the porous thimble and comes to equilibrium with the addition product **11**. The barium hydroxide is retained by the porous thimble and the liquid phase returns to the boiler where the 2-propanone, which boils 110° below the temperature at which **11** boils, is selectively vaporized and returns to the reaction zone to furnish more adduct.

Exercise 17-18 At what point would the system shown in Figure 17-2 cease to produce more **11**? What would happen if some barium hydroxide were to get through a hole in the thimble and pass into the boiler? Why is barium hydroxide more suitable for this preparation than sodium hydroxide?

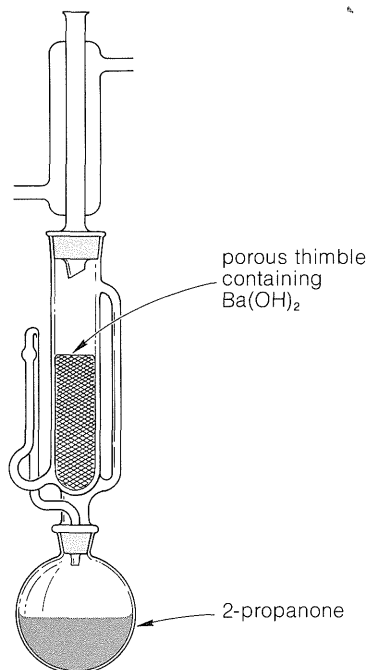
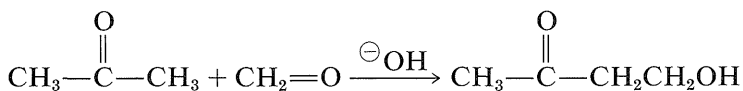


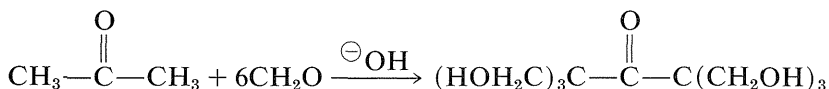
Figure 17-2 Apparatus for the aldol addition of 2-propanone

The key step in aldol addition requires an electron-pair donor (nucleophile) and an electron-pair acceptor (electrophile). In the formation of 3-hydroxybutanal or **11**, both roles are played by one kind of molecule, but there is no reason why this should be a necessary condition for reaction. Many kinds of mixed aldol additions are possible.

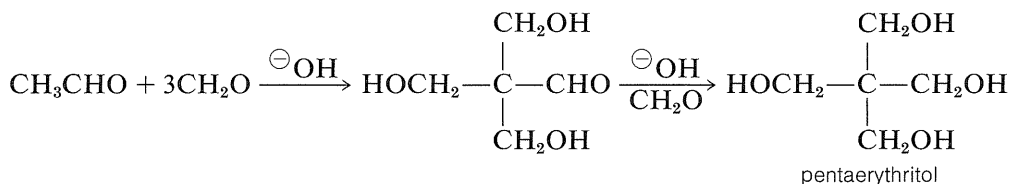
Consider the combination of methanal and 2-propanone. Methanal cannot form an enolate anion because it has no α hydrogens. However, it is expected to be a particularly good electron-pair acceptor because of freedom from steric hindrance and the fact that it has an unusually weak carbonyl bond (166 kcal compared to 179 kcal for 2-propanone). In contrast, 2-propanone forms an enolate anion easily but is relatively poor as the electrophile. Consequently the addition of 2-propanone to methanal should and does occur readily:



The problem is not to get addition, but rather to keep it from going too far. Indeed, all six α hydrogens of 2-propanone can be replaced easily by $-\text{CH}_2\text{OH}$ groups:



A commercially important mixed addition involves ethanal and an excess of methanal in the presence of calcium hydroxide. Addition occurs three times and the resulting trihydroxymethylethanal (which has no α hydrogens) undergoes a “crossed Cannizzaro” reaction (see Exercise 16-33) with more methanal to give a tetrahydroxy alcohol known as “pentaerythritol”:



Pentaerythritol is used widely in the preparation of surface coatings and in the formation of its tetranitrate ester, pentaerythrityl tetranitrate [PETN, $\text{C}(\text{CH}_2\text{ONO}_2)_4$], which is an important high explosive.

Exercise 17-19 To obtain high yields of the *mono* adduct, 4-hydroxy-2-butanone, from aldol addition of 2-propanone to methanal, it usually is necessary to use an apparatus such as that shown in Figure 17-3. The 2-propanone is placed in the round-

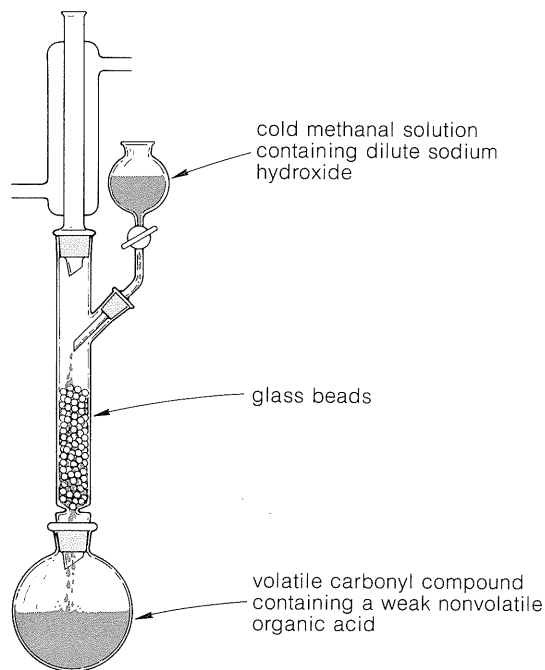
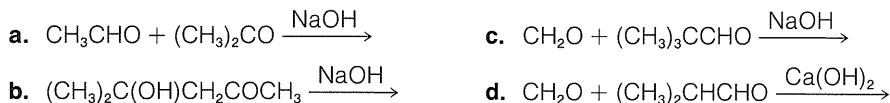


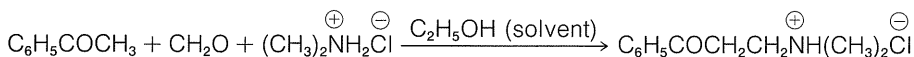
Figure 17-3 Apparatus for the preparation of monohydroxymethylene aldol-addition products from methanal and carbonyl compounds with more than one α hydrogen

bottom flask with a weak *nonvolatile* acid, such as butanedioic (succinic) acid, $(\text{CH}_2\text{CO}_2\text{H})_2$. The 2-propanone is heated in the flask and the vapors are condensed and returned to the flask through the column that is packed with glass beads. When a good flow of 2-propanone is attained through the column, a basic solution of methanal is slowly dripped in. Explain how this arrangement ensures a high conversion to the monohydroxymethyl derivative, $\text{HOCH}_2\text{CH}_2\text{COCH}_3$, with a minimum of reversion to 2-propanone and methanal. Why is $(\text{CH}_3)_2\text{C}(\text{OH})\text{CH}_2\text{COCH}_3$ (**11**) not formed in significant amounts?

Exercise 17-20 Predict the principal products to be expected in each of the following reactions; give your reasoning:



Exercise 17-21 a. A useful modification of aldol addition to methanal, known as the **Mannich reaction**, uses a secondary amine (usually as its hydrochloride salt) to selectively introduce *one* carbon atom at the alpha position of an aldehyde or ketone. The actual product is the salt of an amino ketone. For example,



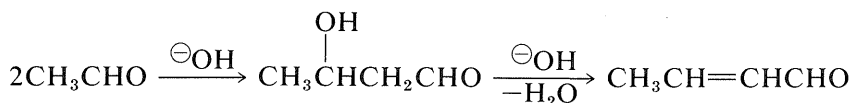
Write the steps involved in this reaction, assuming that an intermediate iminium ion,

$(\text{CH}_3)_2\text{N}^+=\text{CH}_2$, is formed from the amine and methanal.

b. Show how the reaction product—the so-called Mannich base—could be converted to $\text{C}_6\text{H}_5\text{COCH}=\text{CH}_2$.

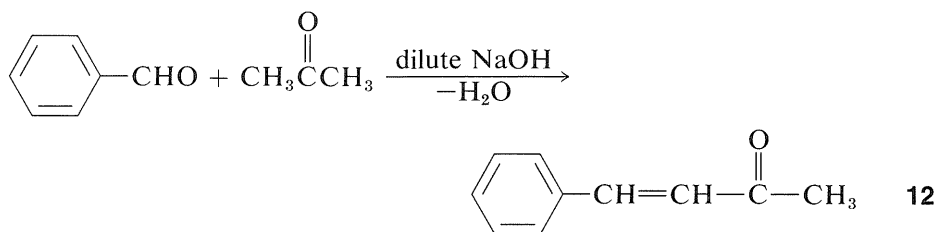
17-3D Dehydration of Aldol Addition Products

An important property of aldol addition products is the ease with which they eliminate water in the presence of either acids or bases. For example, when 3-hydroxybutanal is heated in the basic solution in which it is formed (by aldol addition of ethanal), 2-butenal results:



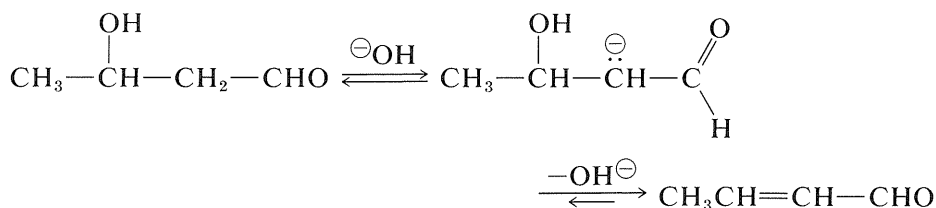
The ease of dehydration compared with simple alcohols is related to the fact that the product is a *conjugated* alkenone. The stabilization energy of the conjugated system makes the equilibrium constant for dehydration especially favorable. In many cases the aldol adduct is only an intermediate in aldol reactions because it dehydrates more rapidly than it can be isolated.

Such is most often the case when the dehydration product is a polyunsaturated conjugated aldehyde or ketone. 2-Propanone and benzencarbaldehyde (benzaldehyde), for instance, give the unsaturated ketone **12** in cold aqueous sodium hydroxide solution:



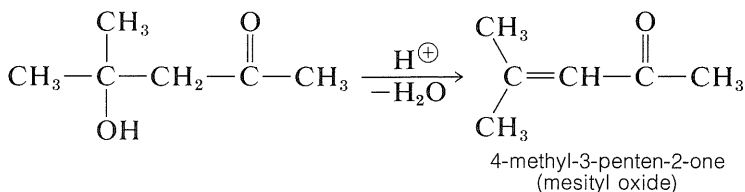
Although the equilibrium for aldol addition may be unfavorable, when dehydration of the aldol product is rapid, C–C bond formation may be pushed to completion by conversion of the aldol to the α,β -unsaturated ketone.

The mechanism of base-catalyzed dehydration of aldols involves formation of an enolate anion by removal of a proton from the C2 or *alpha* carbon and subsequent elimination of the hydroxyl group as hydroxide ion:



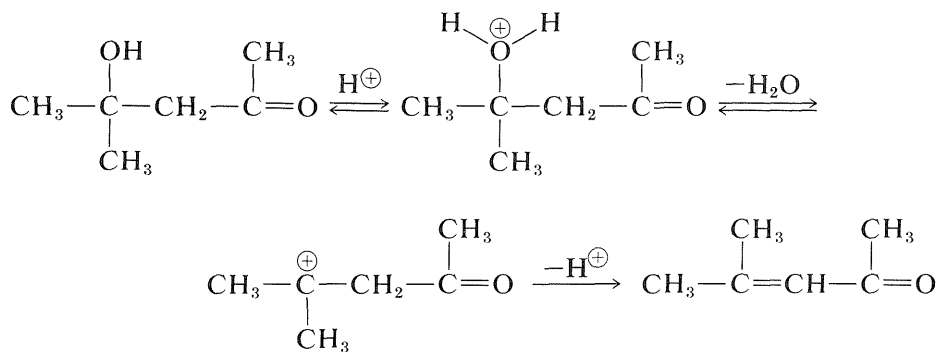
This last step is one of the rare examples in which the leaving group is $\ominus\text{OH}$. Generally, hydroxide is a poor leaving group in substitution ($\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$) or elimination ($\text{E}1$ or $\text{E}2$) reactions (see Section 8-7C).

Dehydration of aldols to α,β -unsaturated carbonyl compounds usually is achieved best with acidic catalysts. An example is the dehydration of the aldol from 2-propanone to give 4-methyl-3-penten-2-one:



If this reaction were attempted under basic conditions, extensive reversion of the aldol to 2-propanone would occur (see Section 17-3C). Under acidic conditions, however, the process is a straightforward proton transfer to oxygen

followed by elimination of water and proton transfer from carbon:



Exercise 17-22 Explain why many β -halo ketones undergo E2 elimination with considerable ease. What kinds of β -halo ketones do not undergo such elimination readily?

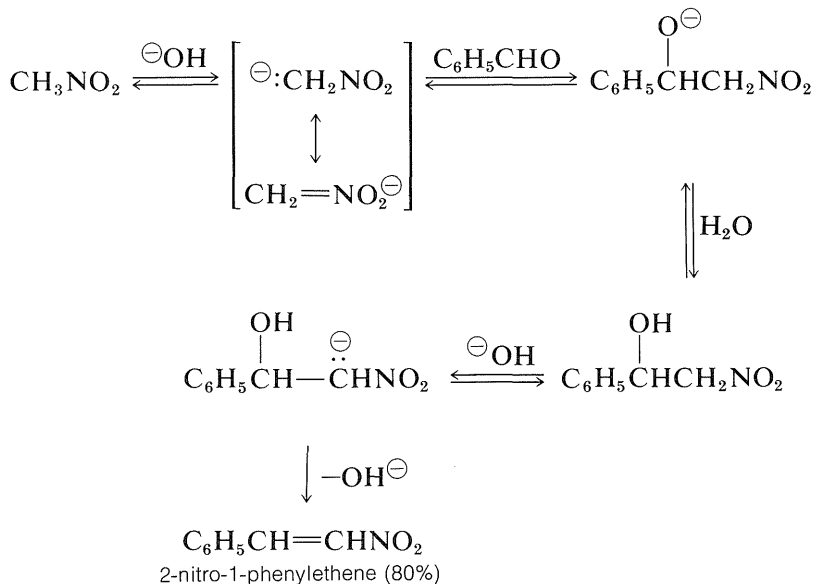
Exercise 17-23 Aldol additions also occur in the presence of acidic catalysts. For example, 2-propanone with dry hydrogen chloride slowly yields $(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$ (mesityl oxide) and $(\text{CH}_3)_2\text{C}=\text{CHCOCH}=\text{C}(\text{CH}_3)_2$ (phorone). Write mechanisms for the formation of these products, giving particular attention to the way in which the new carbon-carbon bonds are formed.

Exercise 17-24 What features of the base-catalyzed dehydration of 3-hydroxybutanal make it a more favorable and faster reaction than would be expected for a base-catalyzed dehydration of 2-butanol? Give your reasoning.

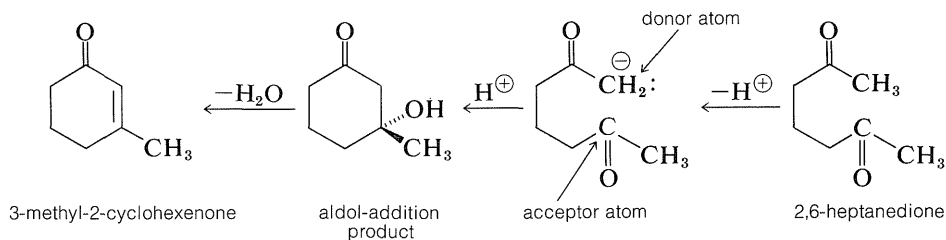
17-3E The Use of Aldol Addition Reactions in Synthesis

Aldol reactions provide a valuable synthetic method for forming carbon-carbon bonds. They can be adapted to extend the length of a carbon chain, to form cyclic compounds, and to provide intermediates that can be transformed into more useful materials. An important feature of these intermediates is that functional groups useful for later reactions are located close to or on the carbons of the newly formed C-C bond. There is an almost bewildering number of variations on the aldol reaction and we shall not mention all of them. The main thing to recognize in all of these reactions is that the acceptor molecule always is a carbonyl compound, best an aldehyde, sometimes a ketone, even an ester (see Section 18-8E). The donor molecule is some type of carbanion; usually, but not always, an enolate anion. However, any substance that has a

C—H acidity in the pK_a range of 25 or less can be converted easily to a carbanion, which in principle may serve as the donor in aldol additions. Examples are listed in Table 17-1 and include not only aldehydes and ketones but esters, nitriles, and nitro compounds. The use of a nitroalkane in aldol addition is shown in the following sequence. The use of esters as the donor is discussed further in Section 18-8E.

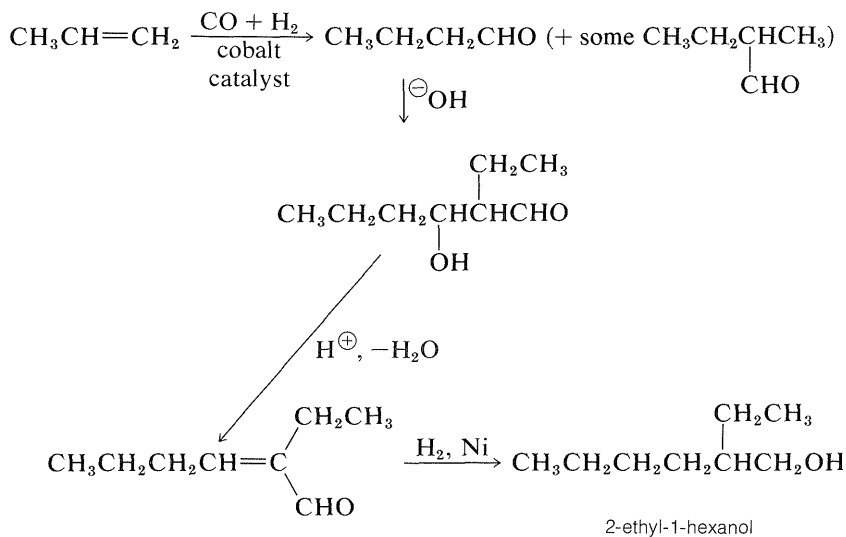
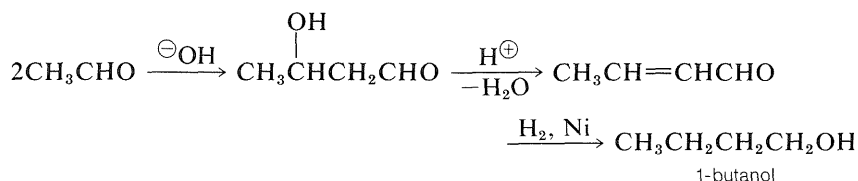


Cyclic products can be formed by aldol additions provided the donor carbanion and acceptor carbonyl are part of the *same* molecule. For example, consider how the synthesis of 3-methyl-2-cyclohexenone could be achieved from acyclic substances. The carbon-carbon bond formed in this process of aldol addition closes the ring and ultimately becomes the double bond in the conjugated system when the aldol product undergoes dehydration. Working backwards, we have the sequence



and the starting material for the synthesis therefore is 2,6-heptanedione. Because ΔG° for the formation of aldol products is not very favorable, cyclizations involving aldol reactions usually will not proceed to give strained carbocyclic rings.

The *industrial* importance of aldol reactions is in the synthesis of alcohols, especially 1-butanol and 2-ethyl-1-hexanol:



Notice that the combination of hydroformylation (Section 16-9F), aldol addition, dehydration, and hydrogenation takes a simple alkene (propene) to an alcohol with more than twice as many carbons.

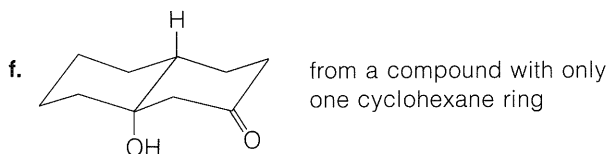
Exercise 17-25 Show how the following compounds can be synthesized from the indicated starting materials by a route having as at least one step an aldol addition:

- a. $\text{CH}_3-\underset{\text{OH}}{\text{CH}}-\text{CH}_2-\underset{\text{OH}}{\text{CH}_2}$ from ethanal
- b. $\text{CH}_3\text{CH}=\text{CH}-\text{CH}_2\text{OH}$ from ethanal
- c. $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CH}_3$ from 2-propanone
- d. $\text{CH}_3\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}(\text{CH}_3)-\text{CH}_2\text{CH}_3$ from propanal
- e. $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$ from benzencarbaldehyde and ethanal

Exercise 17-26 Devise a reasonable synthesis of each of the following compounds from the indicated starting materials. Assume that other needed reagents are available. (Not all of the syntheses involve aldol-addition reactions, but all involve at some stage or the other carbonyl-addition reactions.)

- a. propenenitrile from ethanal

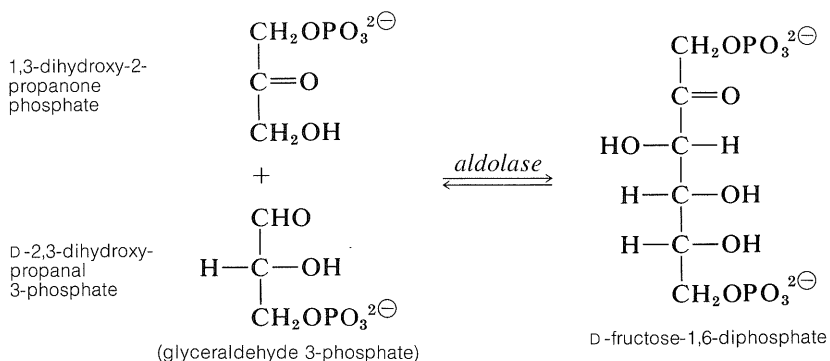
- b. 1-(trichloromethyl)cyclohexanol from cyclohexanone
 c. 2,2-dimethyl-1,3-propanediol from 2-methylpropanal
 d. 2-(phenylmethylidene)cyclohexanone from cyclohexanone
 e. 2,3-diphenylpropenenitrile from phenylethanenitrile



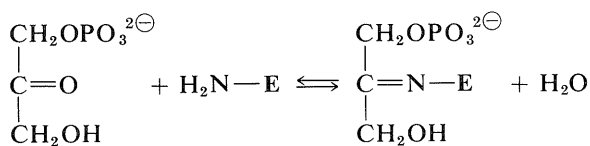
- g. 3-methyl-2-cyclopentenone from an open-chain compound

17-3F A Biological Aldol Addition

One of the reactions in the metabolism of carbohydrates by the glycolytic pathway is a type of aldol addition. In this reaction D-fructose (as the 1,6-diphosphate ester) is formed from D-glyceraldehyde and 1,3-dihydroxypropanone (both as monophosphate esters). The process is readily reversible and is catalyzed by an enzyme known as *aldolase*:

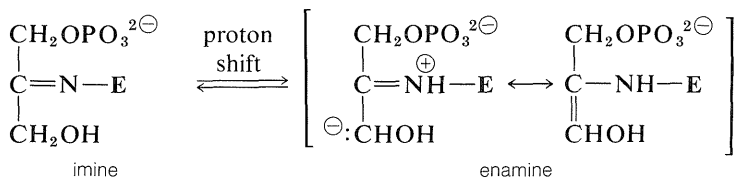


It seems unlikely that this reaction could occur in quite the same way as in the laboratory aldol reactions discussed so far, because the enolate anion of the donor molecule (dihydroxypropanone) is not expected to be formed in significant amount at the pH of living cells. In fact, there is strong evidence that the enzyme behaves as an amino (ENH_2) compound and reacts with the carbonyl group of dihydroxypropanone to form an imine, analogous to the reactions described in Section 16-4C:

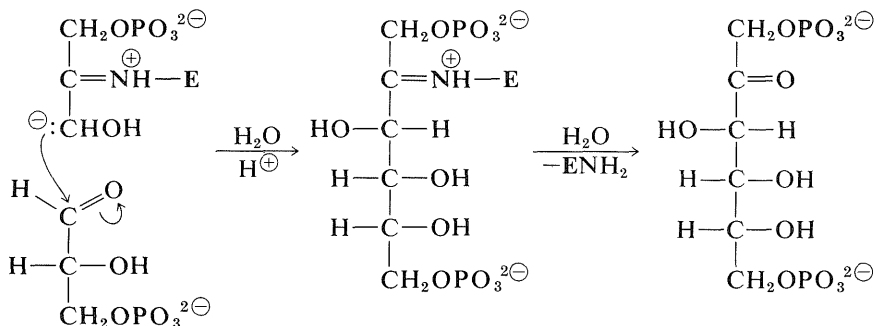


This implies that the imine form of dihydroxypropanone is a key intermediate in the overall aldol-type addition.

How can the imine behave as the carbon *donor* in addition to the aldehyde carbonyl of glyceraldehyde 3-phosphate? It is unlikely to do so directly, but it can rearrange to an enamine which, as we will explain in Section 17-4B, can act as a carbon nucleophile:



Attack of the nucleophilic carbon of the enamine at the aldehyde carbonyl of glyceraldehyde 3-phosphate forms the aldol of the imine which, on hydrolysis, gives the aldol and regenerates the enzyme:

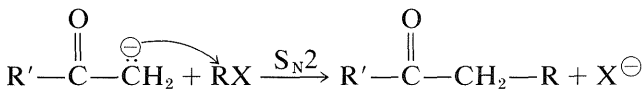


By using the neutral enamine as the carbon nucleophile rather than an enolate anion, the biological system avoids the need for strongly basic reaction conditions in aldol addition.

17-4 NUCLEOPHILIC SUBSTITUTION WITH ENOLATE ANIONS

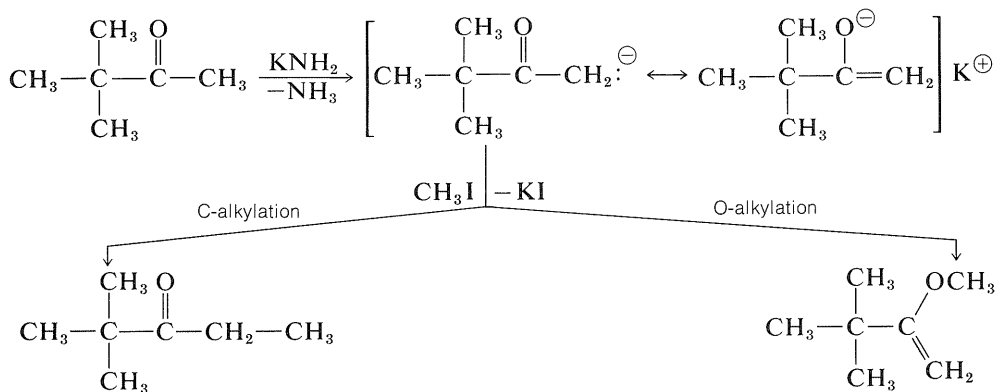
17-4A Alkylation of Ketones

The synthetic chemistry of enolate anions is centered on their nucleophilic and basic properties. Accordingly these ions participate in S_N2 reactions with suitable alkyl compounds:



However, there are a number of complicating factors to consider. First, the basic conditions needed to form the enolate ions often lead to side reactions such as aldol addition and E2 elimination of RX compounds. Aldol addition is minimized if the carbonyl compound is a ketone with a structure unfavorable for aldol addition or if *all* of the carbonyl compound is converted to its enolate. To convert all of a simple carbonyl compound to its enolate usually requires a very strong base, such as $\ominus\text{NH}_2$ in an aprotic solvent or liquid ammonia. Because the enolate anion itself is a strong base, best results are obtained when the halide, RX, does not undergo E2 reactions readily.

The second complication arises if the alkyl compound reacts with both carbon and oxygen of the nucleophilic enolate anion. The carbon product is the result of "C-alkylation," whereas the oxygen product is the result of "O-alkylation":

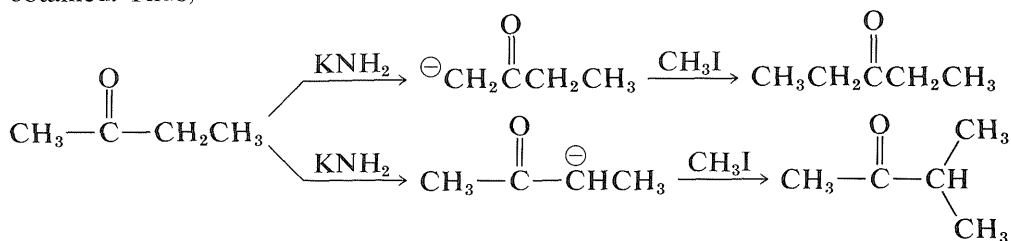


The possibility of the enolate anion acting as if its charge were effectively concentrated on carbon or on oxygen was discussed previously in connection with aldol addition (Section 17-3B). However, the situation there was quite different from the one here, because aldol addition is easily reversible, whereas alkylation is not. Furthermore, while the aldol reaction involving C-O bond formation is unfavorable ($\Delta H^\circ = +20 \text{ kcal mole}^{-1}$) compared to C-C bond formation ($\Delta H^\circ = -4 \text{ kcal mole}^{-1}$), both O- and C-alkylation of the anion have $\Delta H^\circ < 0$ (see Exercise 17-64).

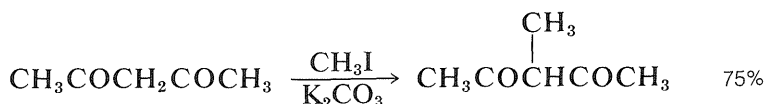
Whether C- or O-alkylation predominates depends on kinetic control (Section 10-4A). It is not a simple matter to predict which of the two positions of the enolate will be more nucleophilic, and in fact, mixtures of products often are obtained in distributions that depend on the solvent used, the temperature, the nature of X, and the nature of the base employed to form the anion. O-Alkylation tends to occur with ketones of high enol content (which usually means that the enolate anion will have especially high charge density on oxygen) and with alkylating agents possessing a high degree of $\text{S}_{\text{N}}2$ reactivity.

There is another correlation that seems to have validity in many situations, at least where kinetic control is dominant; namely, the *freer* (less associated) the ambident anion is from its cation, the *more likely* is the electrophile to attack the atom of the anion with the *highest* negative charge. Thus O-alkylation of the sodium enolate of 2-propanone is favored in aprotic solvents that are good at solvating cations [such as $(\text{CH}_3)_2\text{SO}$, Section 8-7F].

In the alkylation of unsymmetrical ketones, formation of more than one enolate anion is possible, and when this occurs, mixtures of products are obtained. Thus,



However, when one of the possible enolate anions is especially stabilized, either by conjugation or by strong electron-withdrawing groups, that enolate usually is the dominant form and only one product is formed. Thus 2,4-pentanedione is methylated at C3, not at C1:



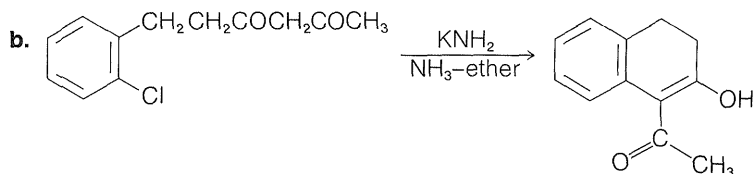
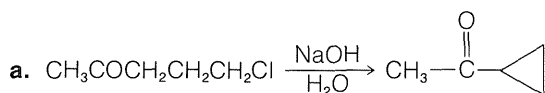
Exercise 17-27 If methyl iodide gives mainly C-alkylation with the enolate anion of 2-propanone, which of the following halides would you expect to be candidates to give O-alkylation: *tert*-butyl chloride, phenylmethyl chloride, 3-chloropropene, neopentyl chloride?

Exercise 17-28 a. Alkylation of ketones is much less successful with ethyl and higher primary halides than for methyl halides. Explain why competing reactions may be particularly important for such cases.

b. What would you expect to happen if you were to try to alkylate ethanal with KNH_2 and CH_3I ?

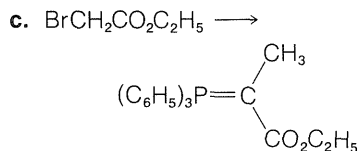
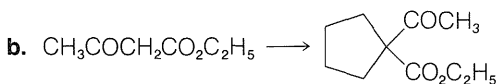
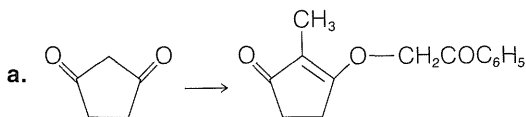
Exercise 17-29 If you wished to prepare the methyl ether of 4-hydroxy-3-penten-2-one by O-alkylation, what base and which of the methylating agents listed would you choose? CH_3Cl , CH_3I , $\text{CH}_3\text{OSO}_2\text{OCH}_3$, $(\text{CH}_3)_3\text{OBF}_4$, or $(\text{CH}_3)_2\text{O}$. Give your reasoning.

Exercise 17-30 Show the steps that are likely to take place in the following transformations:



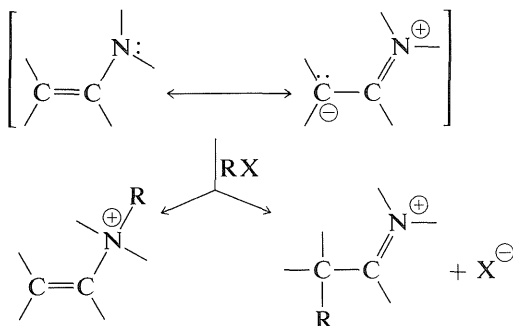
(Review Section 14-6.)

Exercise 17-31 Show how the following transformations can be carried out. Indicate the conditions, particularly the bases used, necessary reagents, and any expected by-products.

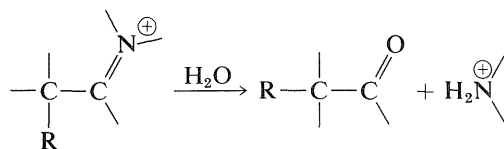


17-4B Alkylation of Enamines

Enamines (Section 16-4C), like enolate anions, have two reactive positions and, in principle, can give either N- or C-alkylation.



Both products may be formed, but they can be separated readily because, on treatment with dilute acid, only the C-alkylation product hydrolyzes to a ketone. Generally, the alkylated ketone is the desired product:



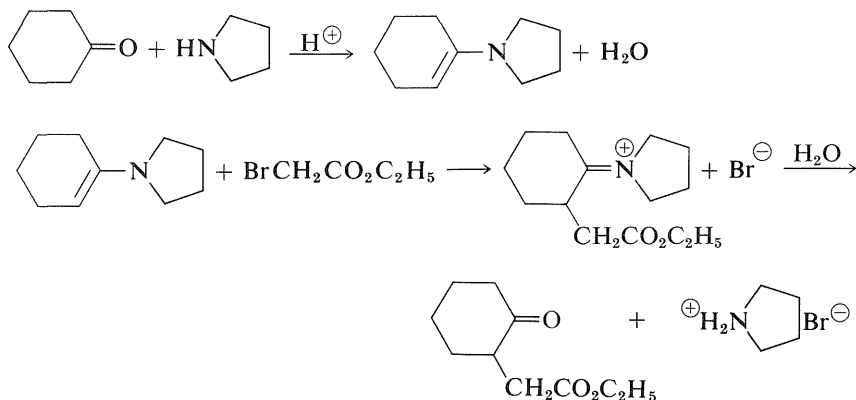
Alkylation of enamines therefore is a feasible, and sometimes much more useful, alternative to the direct alkylation of ketones because it proceeds under less strongly basic conditions. The sequence starts with conversion of a ketone to

an enamine, $-\text{CH}-\text{C}=\text{O} \xrightarrow{\text{R}_2\text{NH}} -\text{C}=\text{C}-\text{NR}_2 + \text{H}_2\text{O}$, followed by

C-alkylation of the enamine, $-\text{C}=\text{C}-\text{NR}_2 \xrightarrow{\text{RX}} \text{RC}-\text{C}=\text{NR}_2 + \text{X}^{\ominus}$, and

ends with hydrolysis to the alkylated ketone, $\text{RC}-\text{C}=\text{NR}_2 + \text{H}_2\text{O} \longrightarrow$

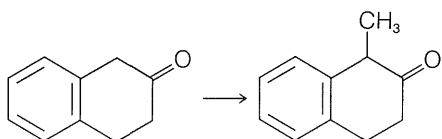
$\text{RC}(\text{R})_2\text{C}=\text{O} + \text{R}_2\text{NH}_2^{\oplus}$. A typical example of the use of enamines for alkylation of a ketone follows:



Several important biological reactions utilize enamine intermediates as carbon nucleophiles in C–C bond-forming reactions. One example is discussed in Section 17-3F.

Exercise 17-32* The immonium ion formed on C-alkylation of an enamine is easily hydrolyzed to a ketone. Write the steps involved and show how this reaction differs from the acid-catalyzed formation of enamines discussed in Section 16-4C.

Exercise 17-33* Show how the following transformation could be achieved by way of an enamine:



Indicate what other alkylation product may be formed and explain why the one shown is the actual product.

17-4C Alkylation of Sulfur-Stabilized Carbanions

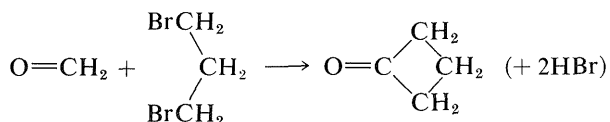
The chemistry of carbanions stabilized by groups other than carbonyl functions is closely analogous to the chemistry of enolate anions. We have seen that

C–H acidity of compounds with the structural feature $\text{X}-\text{C}-\text{H}$ can be significant ($\text{p}K_{\text{a}}$ of 25 or less) when X is an atom or group that can effectively delocalize the negative charge on carbon in $\text{X}-\text{C}^{\ominus}$. Typical X groups are

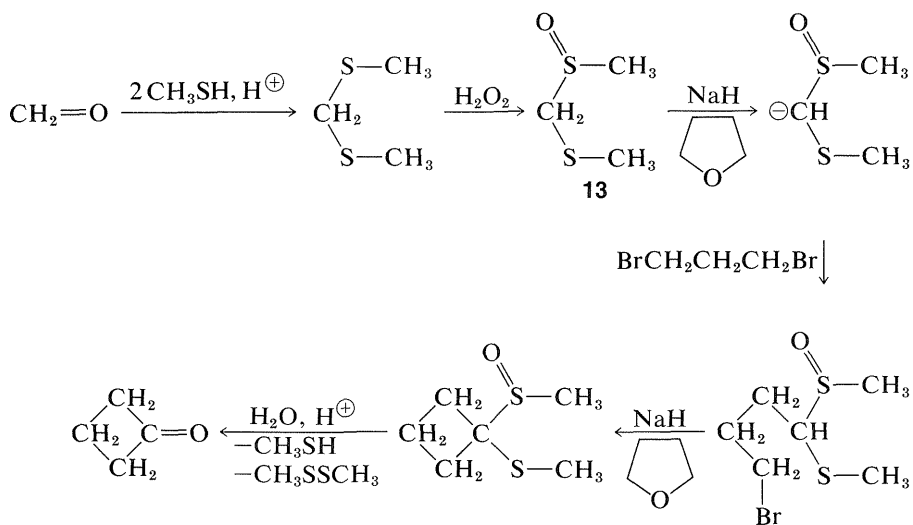
$C=O$, $C\equiv N$, PR_3 , SR_2 , SO_2R , and SR . Consequently, we can expect that carbanions of the type $X-C^{\ominus}$, when formed, will resemble enolate anions and will undergo addition reactions to $C=O$ and $C=C$, and will be alkylated with halides of good S_N2 reactivity. In fact, the reactions of ylides discussed in Section 16-4A are examples of the addition of phosphorus-, sulfur-, and nitrogen-stabilized carbanions to carbonyl groups.

Sulfur in its higher oxidation states (e.g., sulfone, $-SO_2-$) is especially effective in stabilizing adjacent carbanion centers. However, from a synthetic standpoint there are disadvantages to the sulfone grouping in that the better stabilized carbanions also are the least reactive, and subsequent removal of the sulfone grouping can be difficult. A good balance between carbanion stability, carbanion reactivity, and ease of C-S bond cleavage is present in the

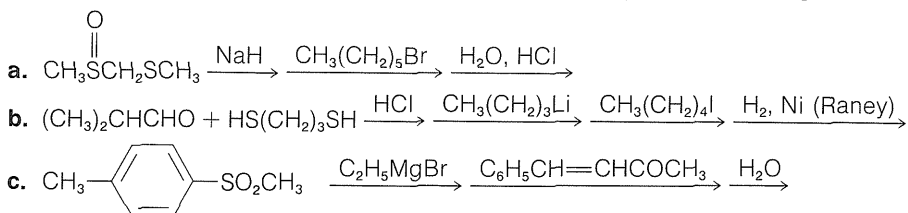
structures $RS-CH_2-SR$ and $RS-CH_2-\overset{O}{\parallel}SR$. This is illustrated below for a strikingly simple concept for preparing cyclobutanone, in which the ring carbons are derived from methanal and 1,3-dibromopropane:



To achieve this synthesis, the methanal first is converted to a thioketal, which then is partially oxidized to give **13**. Treatment of **13** with a strong base converts it to the carbanion, which can be readily alkylated. By using 1,3-dibromopropane and two equivalents of base, a double displacement forms the cyclic product, **14**. The sulfur groups of **14** can be removed easily by acid hydrolysis to give cyclobutanone:



Exercise 17-34* Show the products formed in each step of the following reactions:



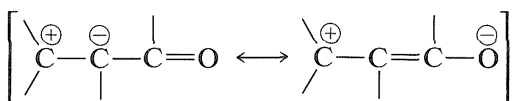
Unsaturated Carbonyl Compounds

The combination of a carbonyl function and a double bond in the same molecule leads to exceptional properties only when the groups are close to one another. The cumulated and conjugated arrangements are of particular interest. We shall consider first the conjugated, or α,β -unsaturated, carbonyl compounds, because their chemistry is related closely to that of the substances already discussed in this chapter and in Chapter 16.

17-5 α,β -UNSATURATED ALDEHYDES AND KETONES

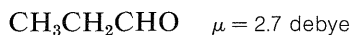
17-5A Structure and Spectral Properties

The most generally useful preparation of α,β -unsaturated carbonyl compounds is by dehydration of aldol addition products, as described in Section 17-3D. Conjugation of the carbonyl group and double bond has a marked influence on spectroscopic properties, particularly on ultraviolet spectra, as the result of stabilization of the excited electron states, which for $\pi \rightarrow \pi^*$ transitions can be described in terms of important contributions of polar resonance structures (see Sections 9-9B and 16-3B):



Such resonance is much less important in the ground state but is still sufficiently

important to account for the moderate differences in dipole moments between saturated and α,β -unsaturated aldehydes and ketones; for example,

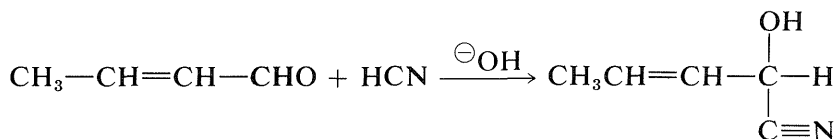
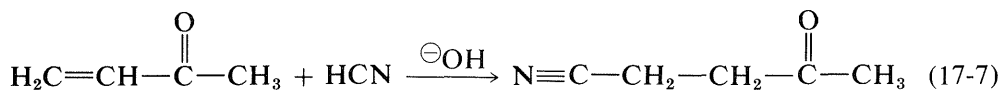


The effect of conjugation also is reflected in infrared carbonyl frequencies (Section 16-3A) and nmr spectra. With respect to the latter, it is found that the protons on the β carbon of α,β -unsaturated carbonyl compounds usually come at 0.7 to 1.7 ppm *lower* fields than ordinary alkenic protons. The effect is smaller for the α protons.

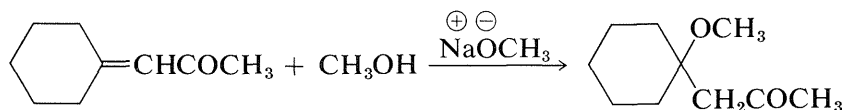
Exercise 17-35 Interpret the proton nmr spectra given in Figure 17-4 in terms of structures of compounds with the molecular formulas $\text{C}_6\text{H}_{10}\text{O}$ and $\text{C}_9\text{H}_8\text{O}$. The latter substance has a phenyl (C_6H_5) group. Show how each compound may be synthesized from substances with fewer carbons.

17-5B Addition Reactions

There are many addition reactions of α,β -unsaturated aldehydes, ketones, and related compounds that are the same as the carbonyl addition reactions described previously. Others are quite different and result in addition to the *alkene* double bond. Organometallic compounds are examples of nucleophilic reagents that can add to either the alkene or the carbonyl bonds of conjugated ketones (see Section 14-12D). Hydrogen cyanide behaves likewise and adds to the carbon-carbon double bond of 3-butene-2-one, but to the carbonyl group of 2-butenal:



All of these reactions may be classified as nucleophilic additions, but when addition occurs at the alkene bond, the orientation always is such that the nucleophile adds at the β carbon. An example is the addition of methanol catalyzed by sodium methoxide:



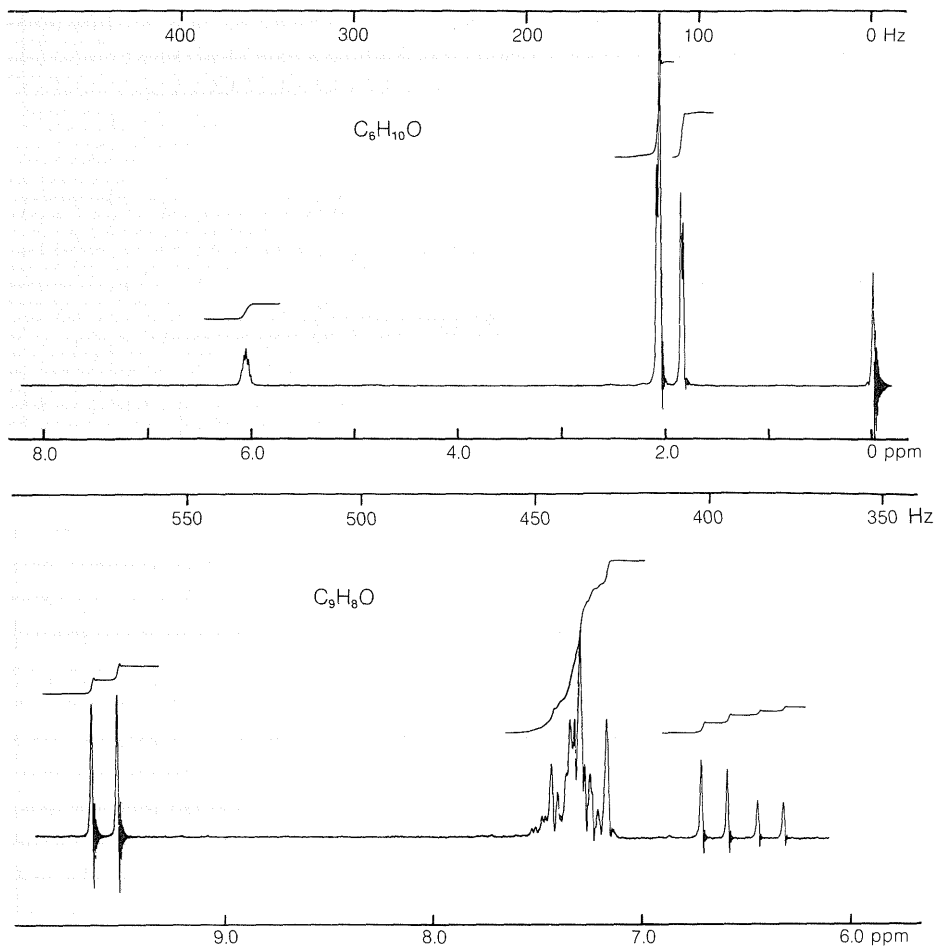
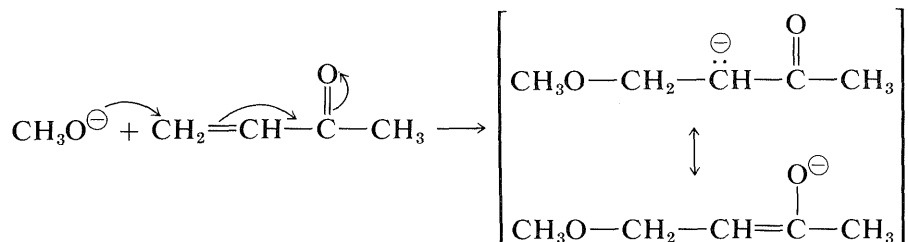
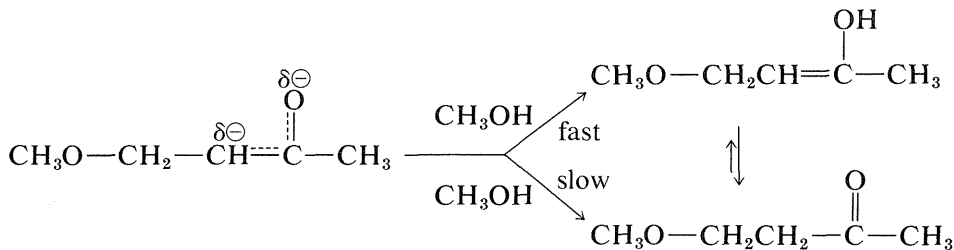


Figure 17-4 Proton nmr spectra at 60 MHz with tetramethylsilane as standard. See Exercise 17-35.

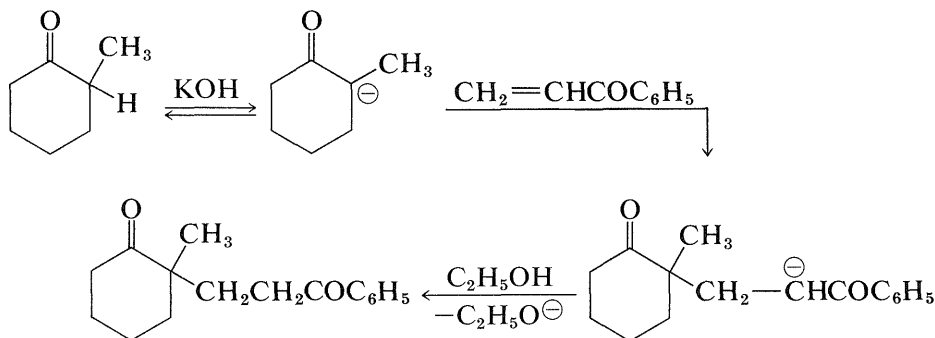
Nucleophilic reagents normally do not attack carbon-carbon double bonds (Section 10-6). The adjacent carbonyl function therefore must greatly enhance the reactivity of the double bond toward such reagents. This enhancement is not surprising when it is realized that the attack of a nucleophile produces a stabilized enolate anion:



The products are formed from the enolate intermediate by proton transfer to either carbon or oxygen. If the proton adds to oxygen the enol is formed, which is unstable with respect to the ketone and ultimately will rearrange:

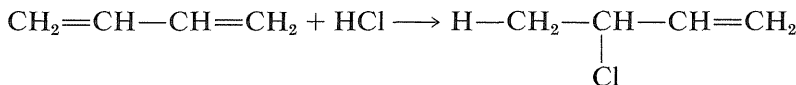


Reactions of this type are referred to in a variety of terms, many of which are rather confusing and nondescriptive. They sometimes are classified as **1,4-additions**, implying that addition occurs across the terminal positions of the conjugated system. A synonymous term is **conjugate addition**. When the nucleophile is a carbanion, the reaction is called a **Michael addition**. Thus, by this definition, Equation 17-7 represents a Michael addition. Another, perhaps more typical, example is the addition of an enolate to a conjugated ketone:



Michael-type additions, like aldol additions, are useful for the formation of carbon-carbon bonds.

Electrophilic addition of hydrogen halides to α,β -unsaturated aldehydes and ketones places the halogen on the β carbon. This orientation is opposite to that observed for related additions to conjugated dienes:



Exercise 17-36 a. Explain why the addition of HCl to propenal gives a different orientation than in the addition of HCl to 1,3-butadiene. (Review Section 13-2.)

b. What product would you expect from the addition of bromine to 3-buten-2-one? Would you expect this addition to be more, or less, rapid than the addition of bromine to 1-butene? Why?

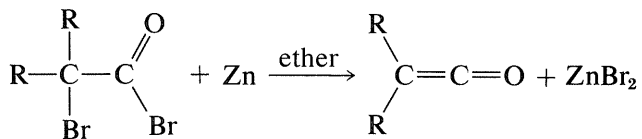
Exercise 17-37 On what basis can you account for the fact that HCN adds to the carbonyl group of 3-butenal and to the double bond of 3-buten-2-one? Would you expect the carbonyl or the double-bond addition product of HCN to 3-buten-2-one to be more thermodynamically favorable? Give your reasoning.

17-6 KETENES

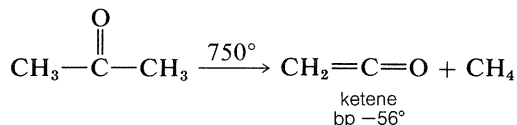
17-6A Preparation of Ketenes

Substances with cumulated carbonyl and carbon-carbon double bonds, $\begin{array}{c} \diagup \\ \text{C}=\text{C}=\text{O} \\ \diagdown \end{array}$, are called ketenes and, as may be expected, have interesting and unusual properties. Ketene itself, $\text{CH}_2=\text{C}=\text{O}$, and its monosubstitution products, $\text{RCH}=\text{C}=\text{O}$ (R = alkyl or aryl), are called **aldoketenes**, whereas disubstituted ketenes, $\text{R}_2\text{C}=\text{C}=\text{O}$, are called **ketoketenes**.

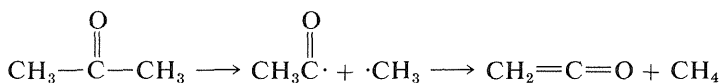
There are relatively few general methods for preparing ketenes. The simplest procedure is to treat an α -bromoacyl bromide with zinc, but the yields usually are not very good:



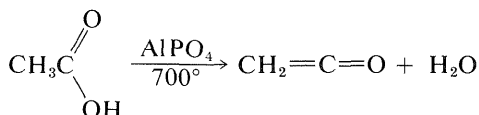
Several special methods are available for the preparation of ketene itself. The most convenient laboratory preparation is to pass 2-propanone vapor over a coil of resistance wire heated electrically to a dull red heat; air is excluded to avoid simple combustion:



The weakest bonds are the C-C bonds and, at 750°, fragmentation yields a methyl radical and an ethanoyl radical:

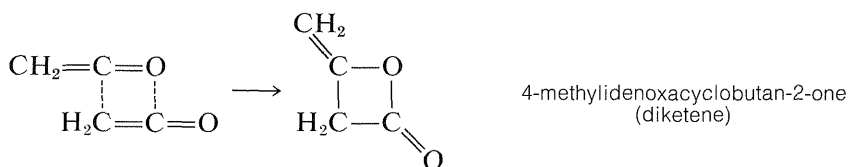


Transfer of a hydrogen atom (i.e., disproportionation) gives methane and ketene. Industrially, ketene is best prepared by dehydration of ethanoic acid:



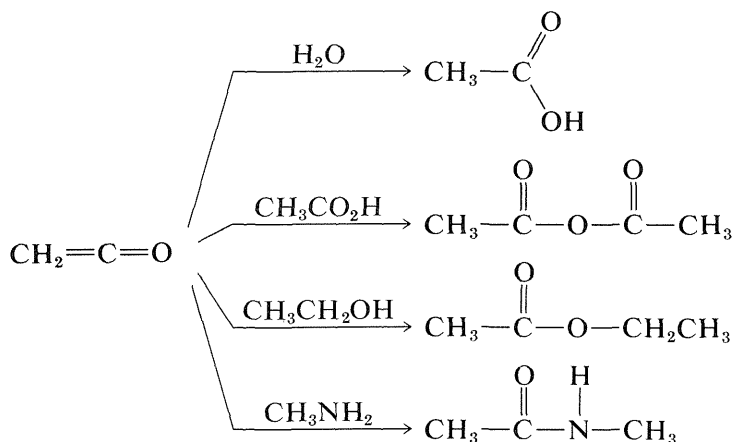
17-6B Reactions of Ketenes

Ketene has a boiling point of -56° and normally would be stored under pressure in steel cylinders. However, this is not possible because ketene is unstable with respect to formation of a dimer known as “diketene”:

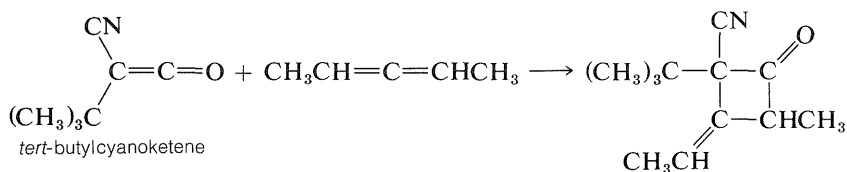


The dimer also is a highly reactive substance with such unusual characteristics that its structure was not firmly established until 1956, almost 48 years after it first was prepared.

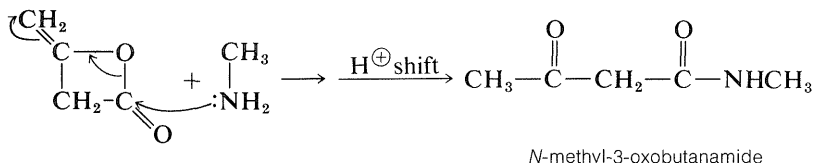
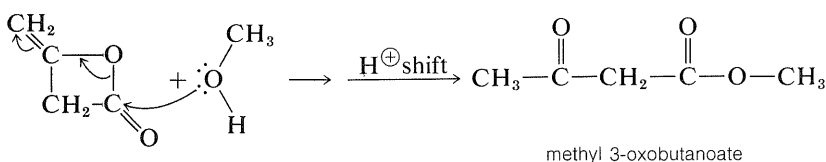
Ketenes in general are useful reagents for acylating alcohols, ROH, and amines, RNH₂, because the reactions involve additions; there are no by-products to be separated:



Ketenes also can be used for the synthesis of cyclobutane derivatives through [2 + 2] cycloadditions with suitably active alkenes (Section 13-3D):



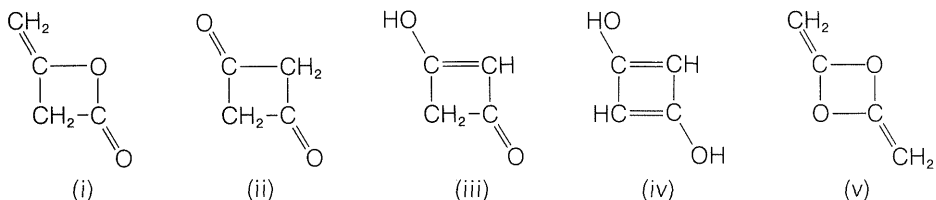
Diketene is very useful in synthesis, particularly through its reactions with alcohols and amines to give derivatives of 3-oxobutanoic acid:

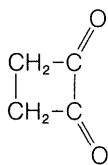


Exercise 17-38 Write reasonable mechanisms for the reaction of ketene with alcohols and amines. Would you expect these reactions to be facilitated by acids, or by bases?

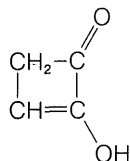
Exercise 17-39 Write a mechanism for the acid-catalyzed reaction of methanol with diketene that accords with the nature of the reagents involved.

Exercise 17-40 The following structures have been proposed, or could be proposed, for diketene. Show how infrared, Raman, ultraviolet, and nmr spectroscopy may be used to distinguish between the possibilities (if necessary review Chapter 9).

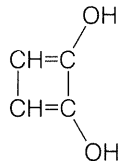




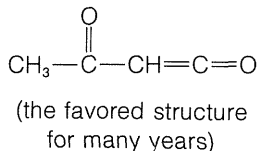
(vi)



(vii)



(viii)



(ix)

Exercise 17-41 1-Propen-1-one (methylketene) forms a dimer, $\text{C}_6\text{H}_8\text{O}_2$, by [2 + 2] cycloaddition with itself. The nmr spectrum of the dimer is shown in Figure 17-5. Assign a structure to the dimer consistent with the spectrum.

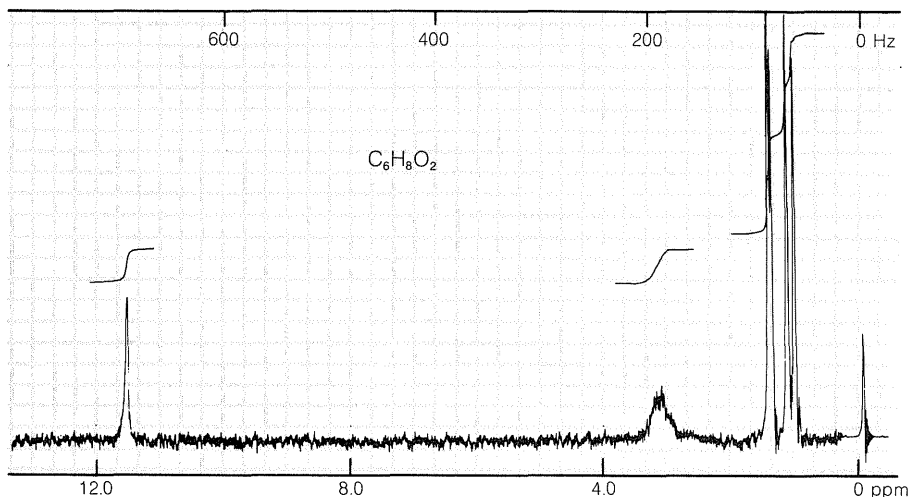
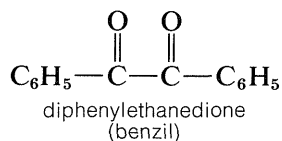
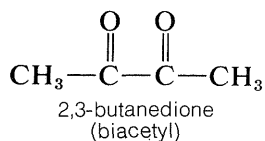
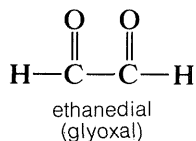


Figure 17-5 Proton nmr spectrum at 60 MHz with tetramethylsilane as standard

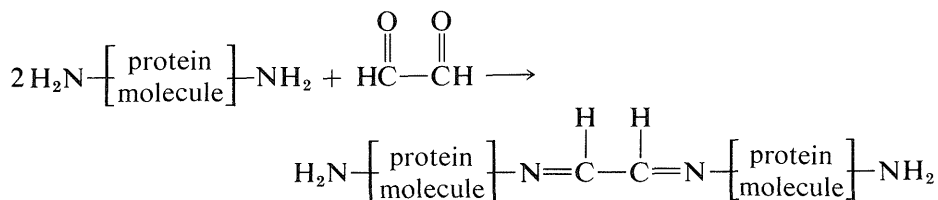
Polycarbonyl Compounds

17-7 1,2-DICARBONYL COMPOUNDS

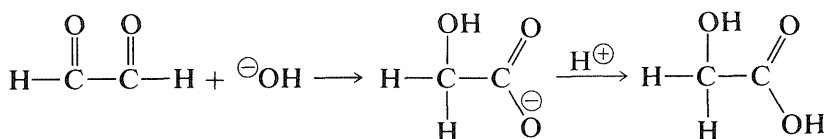
Some typical and important members of this class have structures as follows:



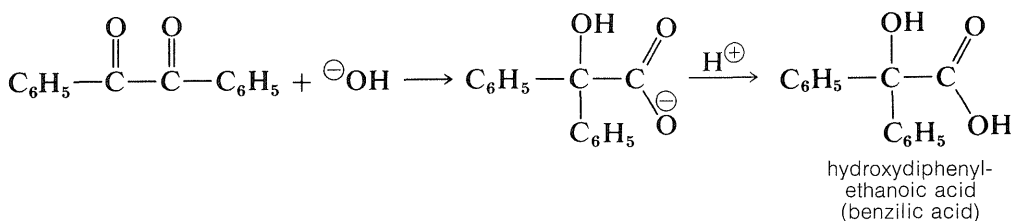
Most of the 1,2-dicarbonyl compounds are yellow. Ethanedial is unusual in being yellow in the liquid state, but green in the vapor state. It has very reactive aldehyde groups and is employed in the manufacture of plastics and as a component of embalming fluids to harden proteins by linking together their amino groups through imine formation:



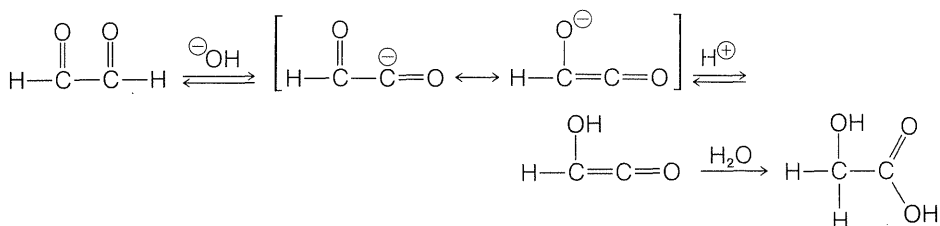
Ethanedial undergoes an internal Cannizzaro reaction with alkali to give hydroxyethanoic (glycolic) acid:



An analogous reaction occurs with diphenylethanedione, which results in carbon-skeleton rearrangement. This is one of the few carbon-skeleton rearrangements brought about by basic reagents, and is known as the “**benzilic acid rearrangement.**”

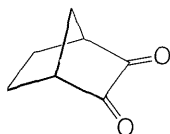


Exercise 17-42 What experiments may be done to prove or disprove the following mechanism for rearrangement of ethanedial to hydroxyethanoic acid?



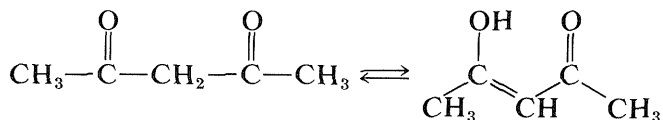
Exercise 17-43 Write a mechanism analogous to that for the Cannizzaro reaction for the benzylic acid transformation. What product would you expect to be formed from diphenylethanedione with potassium *tert*-butoxide in *tert*-butyl alcohol? Would you expect a benzylic acid-type rearrangement to occur with 2,3-butanedione? Give your reasoning.

Exercise 17-44 1,2-Cyclopentanedione exists substantially as the monoenol, whereas 2,3-butanedione exists as the diketo form. Suggest explanations for this behavior that take into account possible conformational differences between the two substances. How easily would you expect dione **15** to enolize? Why?

**15**

17-8 1,3-DICARBONYL COMPOUNDS

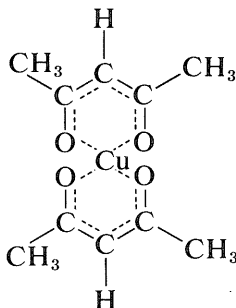
Much of the chemistry of 1,3-dialdehydes, aldehyde ketones, and diketones already has been mentioned in this chapter and is well illustrated in the properties of 2,4-pentanedione,



The liquid ketone exists 85% in the enol form and is moderately acidic. The K_a in water is $\cong 10^{-9}$. The enol form is stabilized significantly by both electron delocalization and hydrogen bonding. The amount of enol present at equilibrium depends on the solvent, and is smallest in hydrogen-bonding solvents and largest in nonpolar solvents such as carbon tetrachloride.

The reactions discussed in this chapter that depend on the formation of enolate anions (i.e., halogenation, aldol addition, and alkylation) often proceed smoothly and under milder conditions with 1,3-diketones than with mono-ketones. This is because the 1,3-diketones are stronger acids and therefore can form the enolate anions with weaker bases. The principal synthetic methods for preparing 1,3-dicarbonyl compounds will be discussed in Chapter 18.

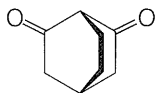
With 2,4-pentanedione, polyvalent metal cations often form very stable and only slightly polar enolate salts, better known as **metal chelates**. Cupric ion forms a particularly stable dark-blue chelate:



2,4-pentanedionatocopper(II)
(cupric acetylacetonate)

The beryllium chelate of 2,4-pentanedione is another example of a stable chelate; it melts at 108°, boils at 270°, and is soluble in many organic solvents. By replacing the methyl groups of 2,4-pentanedione with *tert*-butyl groups, a diketone is obtained which, with many metals including transition and rare-earth metals, forms complexes that often are highly soluble in nonpolar organic solvents. The interior of these chelates is saltlike but the exterior is hydrocarbonlike and nonpolar, which accounts for the substantial solubility in nonpolar solvents.

Exercise 17-45 2,6-Bicyclo[2.2.2]octanedione, **16**, exhibits no enolic properties. Explain.



16

Exercise 17-46* If the keto form of 2,4-pentanedione is more stable than the enol form in water solution, why does it also have to be a weaker acid than the enol form in water solution?

Exercise 17-47 Interpret the proton nmr spectrum shown in Figure 17-6 in terms of possible structures of compounds with molecular formula $C_{10}H_{10}O_2$ with one phenyl group, C_6H_5- .

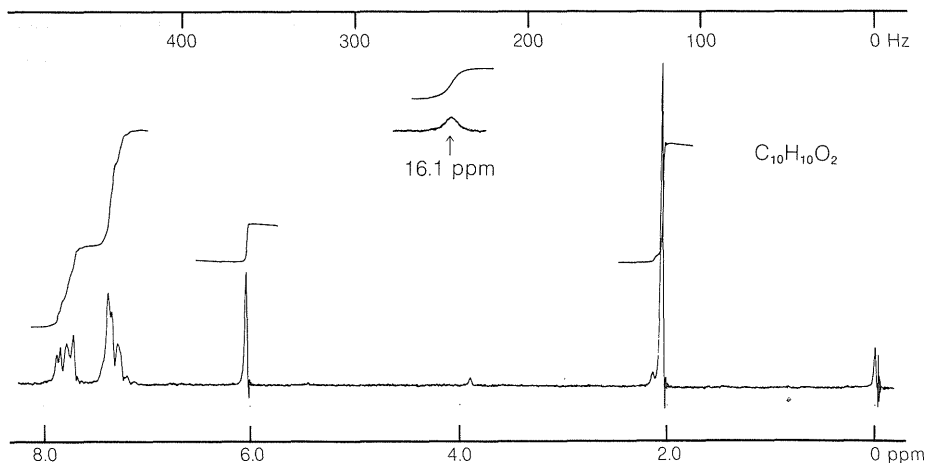
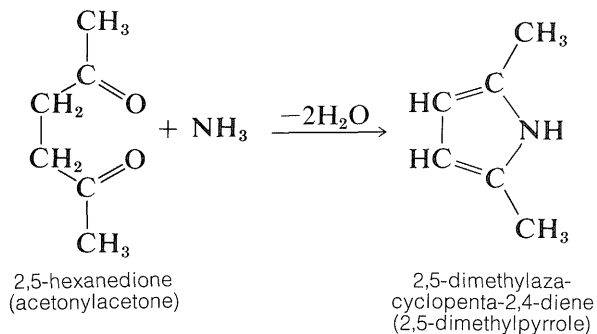


Figure 17-6 Proton nmr spectrum of $C_{10}H_{10}O_2$ at 60 MHz with tetramethylsilane as the standard. The integral of the offset peak at 16.1 ppm has the same vertical scale as the other integral lines. See Exercise 17-47.

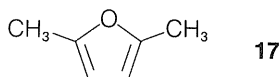
17-9 1,4-DICARBONYL COMPOUNDS

Most of the reactions of the 1,4-dicarbonyl compounds are the conventional reactions expected for isolated carbonyl groups. An important exception is formation of azacyclopentadiene (pyrrole) derivatives from 1,4-dicarbonyl compounds and ammonia or primary amines:



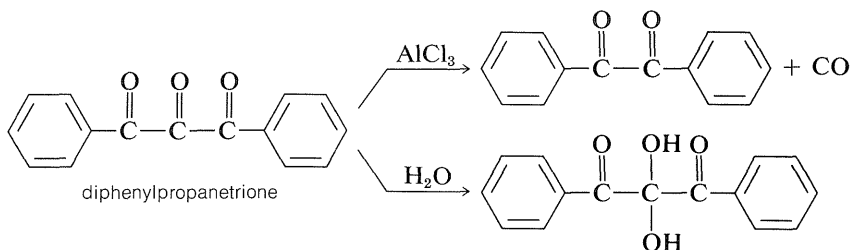
These reactions are reasonably general and also can be used to prepare compounds with oxygen and sulfur in five-membered rings.

Exercise 17-48 Write a reasonable mechanism, supported by analogy, for the acid-catalyzed dehydration of 2,5-hexanedione to 2,5-dimethyloxacyclopenta-2,4-diene, **17**.

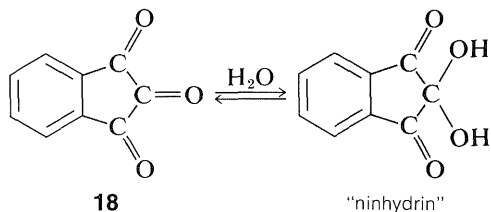


17-10 TRICARBONYL COMPOUNDS

The properties of tricarbonyl compounds are for the most part as expected, except when the three groups are contiguous to one another, as in diphenylpropanetrione. With such compounds, the central carbonyl group is highly reactive; it is lost, as carbon monoxide, in the presence of acidic catalysts such as aluminum chloride, and adds water readily to give a monohydrate:



We shall consider the hydrate of the cyclic triketone, **18**, known as “ninhydrin,” later in connection with amino acids:

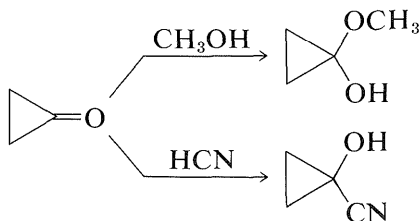


Exercise 17-49* Devise a synthesis of diphenylpropanetrione from 1,3-diphenyl-1,3-propanedione, $(C_6H_5CO)_2CH_2$. How could you determine whether the center or one of the flanking carbonyl groups is lost, as carbon monoxide, with aluminum chloride?

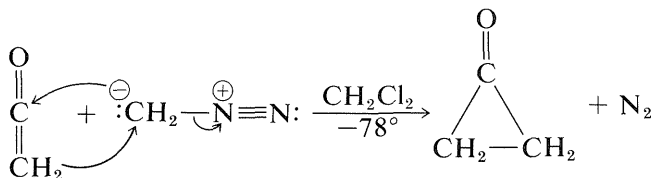
Exercise 17-50* What properties would you expect for 1,3,5-cyclohexanetrione?

17-11 CYCLOPROPANONES AND CYCLOPROPENONES

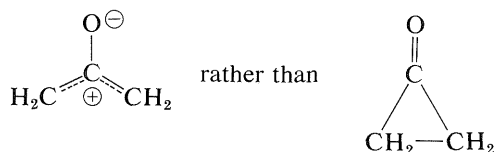
Cyclopropanones deserve special comment, not because of their practical importance (they have no commercial value at this time), but because of their novel behavior and reactivity. No unambiguous synthesis of cyclopropanones was known prior to 1965, and the older textbooks usually contained statements such as "cyclopropanones apparently cannot exist." However, they had been postulated as intermediates in various reactions (see, for example, the Favorskii rearrangement, Section 17-2C and Exercise 17-15), but until recently had defied isolation and identification. The problem is that the three-ring ketone is remarkably reactive, especially towards nucleophiles. Because of the associated relief of angle strain, nucleophiles readily add to the carbonyl group without the aid of a catalyst and give good yields of adducts from which the cyclopropanone is not easily recovered:



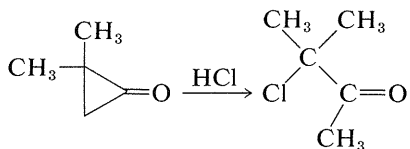
To avoid destructive side reactions, cyclopropanones have to be prepared at low temperatures in the absence of nucleophiles. A good example is the synthesis of cyclopropanone itself from ketene and diazomethane (see Section 16-4A):



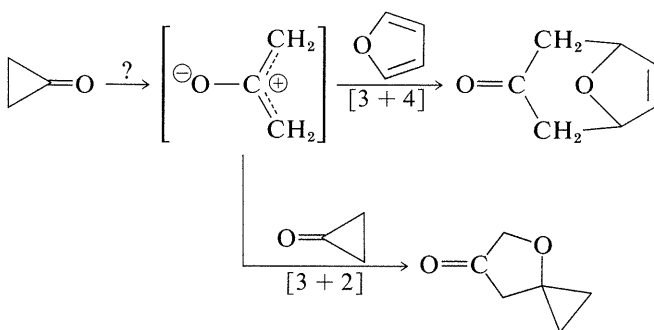
When seemingly simple organic structures defy isolation, this usually stimulates many theoretical and experimental studies in an effort to rationalize anomalous behavior. In the case of cyclopropanone, the possibility was considered that the molecule might preferably exist as an open-chain dipolar structure rather than as the cyclic ketone:



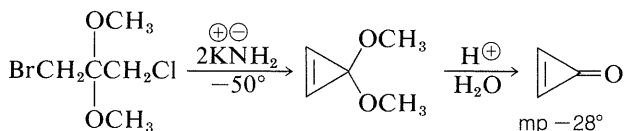
Although the spectral properties of cyclopropanones and the easy formation of hydrates and hemiketals are inconsistent with the dipolar form, some reactions of cyclopropanones do indicate that the ring carbons are much more electrophilic than in other cyclic or acyclic ketones. For example, nucleophilic ring opening often occurs easily:



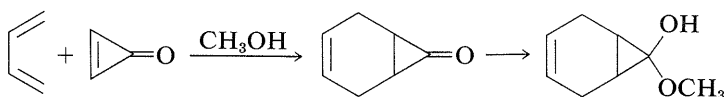
Also, both [3 + 4] cycloadditions of cyclopropanone to dienes and [3 + 2] additions to carbonyl groups have been observed. These reactions seem easiest to understand if cyclopropanone can behave as if it had, or could be converted to, a dipolar open-chain structure:



Cyclopropenone has been prepared by a route that illustrates the value of the acetal grouping in protecting ketone groups (Section 16-8):



Cyclopropenone undergoes many interesting reactions—one example is Diels-Alder addition, the product of which in methanol solution is a hemiketal. That the hemiketal is favored for the adduct, but not for cyclopropenone, indicates that the double bond of cyclopropenone has a considerable effect on the reactivity of the carbonyl group.



Additional Reading

H. O. House, *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Inc., Menlo Park, Calif., 1972, Chapters 8, 9, and 10.

H. H. Wasserman, G. M. Clark, and P. C. Turley, "Recent Aspects of Cyclopropanone Chemistry," in *Topics in Current Chemistry I, No. 47*, Springer Verlag, New York, 1974.

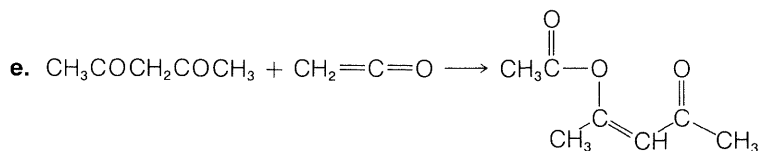
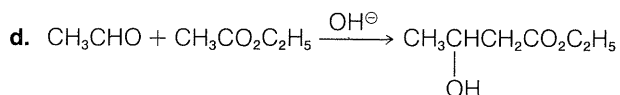
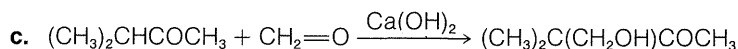
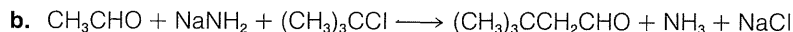
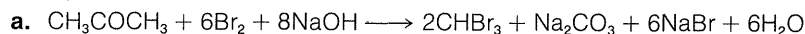
A. T. Nielsen and W. J. Houlihan, "The Aldol Condensation," *Organic Reactions* **16**, 1 (1968).

A. S. Kende, "The Favorskii Rearrangement of Haloketones," *Organic Reactions* **11**, 261 (1960).

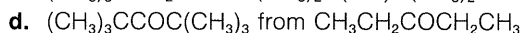
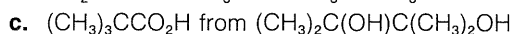
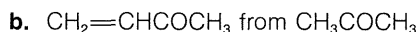
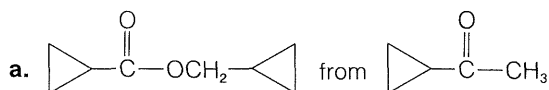
T. Kato, "Recent Synthetic Studies using Diketenes," *Accounts of Chemical Research* **7**, 265 (1974).

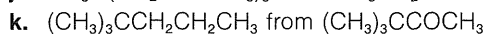
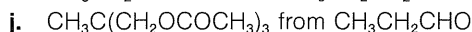
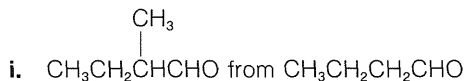
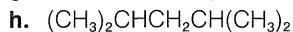
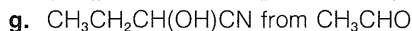
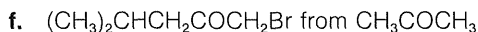
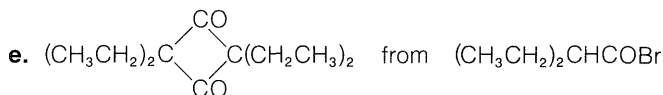
Supplementary Exercises

17-51 It is just as important to be able to recognize reactions which do not work as it is to recognize reactions that do work. The following equations represent "possible" synthetic reactions. Consider each carefully and decide whether it will proceed as written. *Show your reasoning*. If you think a different reaction will take place, write an equation for it.

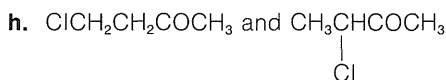
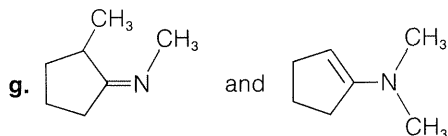
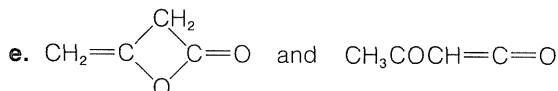
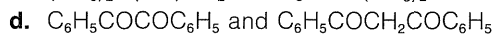
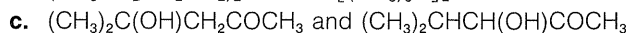
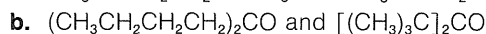
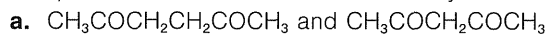


17-52 Write equations for a practical laboratory synthesis of each of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions.



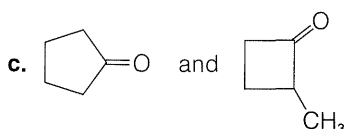
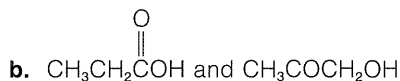
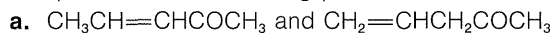


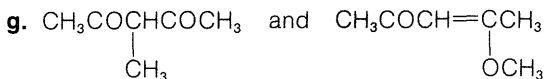
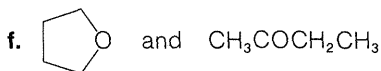
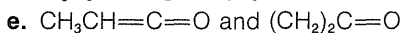
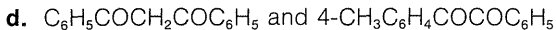
17-53 For each of the following pairs of compounds show explicitly how a chemical test, preferably a test-tube reaction, can be used to distinguish between the two compounds. Describe the observation by which the distinction is made.



17-54 How many spectroscopic means be used to distinguish between the pairs of compounds in Exercise 17-53?

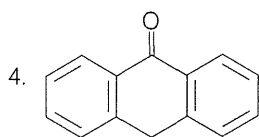
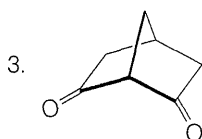
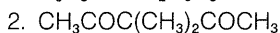
17-55 How many spectroscopic methods be used to distinguish between the isomeric compounds in the following pairs:



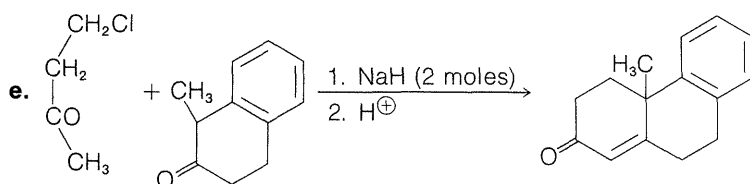
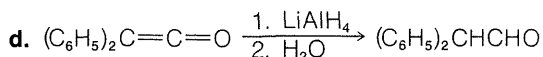
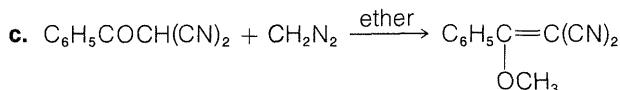
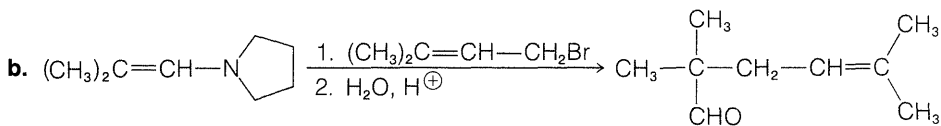
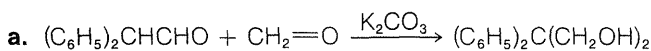


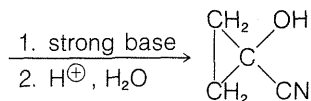
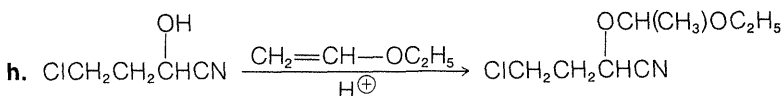
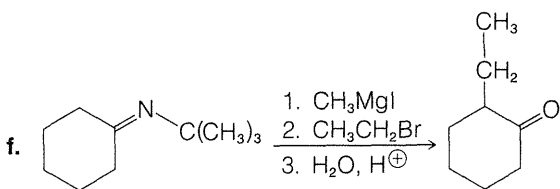
17-56 a. Calculate the percentage of enol present in 1-phenyl-1,3-butanedione from its proton nmr spectrum (Figure 17-6).

b. Estimate the amount of enol expected to be present at equilibrium as either small, medium, or large for each of the following compounds. Give your reasoning.

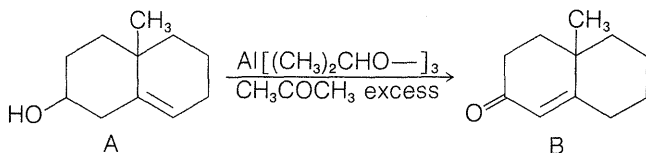


17-57 Write the steps involved, showing probable mechanisms, for each of the following reactions:



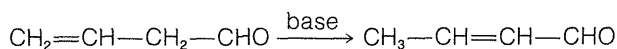


17-58 Explain why oxidation of compound A leads to the α,β -unsaturated ketone B.

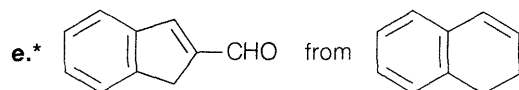
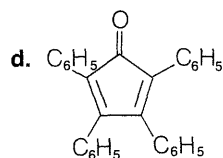
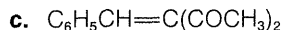
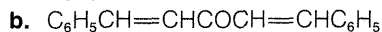
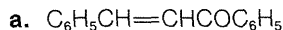


17-59 The proton nmr spectra of two compounds of formulas $\text{C}_4\text{H}_7\text{OCl}$ and $\text{C}_4\text{H}_7\text{OBr}$ are shown in Figure 17-7. Assign to each compound a structure that is consistent with its spectrum. Show your reasoning. Give a concise description of the chemical properties to be expected for each compound.

17-60 Explain why β,γ -unsaturated aldehydes and ketones usually are relatively difficult to synthesize and are found to rearrange readily to the α,β -unsaturated isomers, particularly in the presence of basic reagents:



17-61 Devise a synthesis of each of the following compounds using as a key step an aldol-type addition reaction:



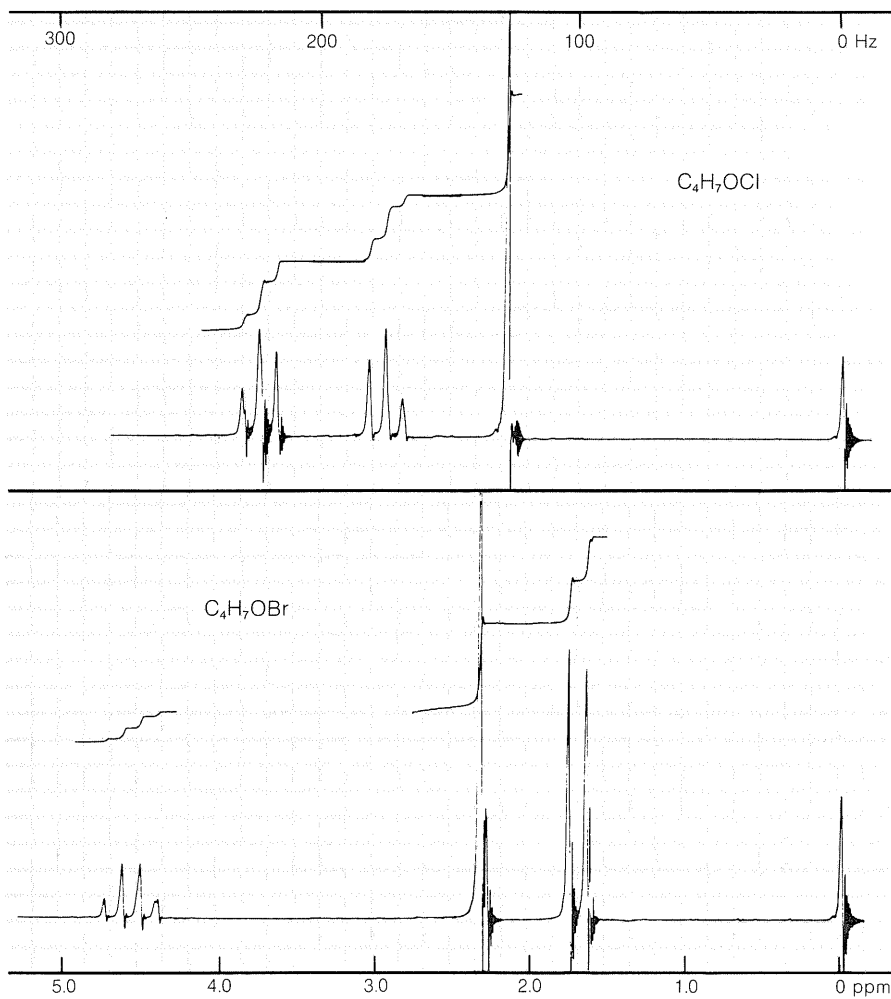
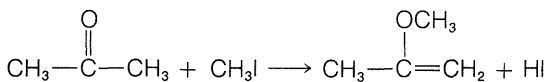
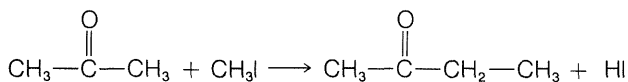


Figure 17-7 Proton nmr spectra at 60 MHz with TMS as standard. See Exercise 17-59.

17-62 Alkenyl ethers (enol ethers) of the type $ROCH=CH_2$ are more stable to rearrangement to $O=CH-CH_2R$ than is an enol such as $HOCH=CH_2$ to $O=CH-CH_3$. Why? What conditions would you expect to be favorable for rearrangement of an alkenyl ether?

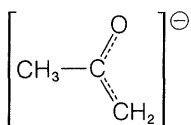
17-63 How would you expect the proton nmr spectrum of cyclopropanone in the cyclic ketone and dipolar ion structures (Section 17-11) to differ? Show your reasoning.

Exercise 17-64* Calculate ΔH° from bond energies (Table 4-3) for C- and O-alkylation of 2-propanone with CH_3I in accord with the following equations:



Compare your answers with the ΔH° values calculated for O- and C-addition in the aldol reaction (Section 17-3B).

How can it be that *both* C- and O-alkylation of the anion



with CH_3I have $\Delta H < 0$? (Notice that the $\text{p}K_a$ of 2-propanone is about 20 and that of HI is about -9 .)