19 Aldehydes and Ketones: Nucleophilic Addition Reactions

Organic KNOWLEDGE TOOLS

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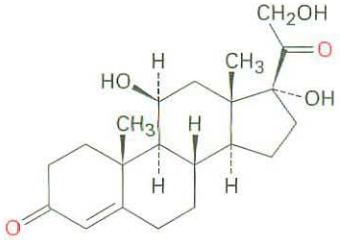
Online homework for this chapter may be assigned in Organic OWL.

Aldehydes (RCHO) and **ketones** (R_2CO) are among the most widely occurring of all compounds. In nature, many substances required by living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions; the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.

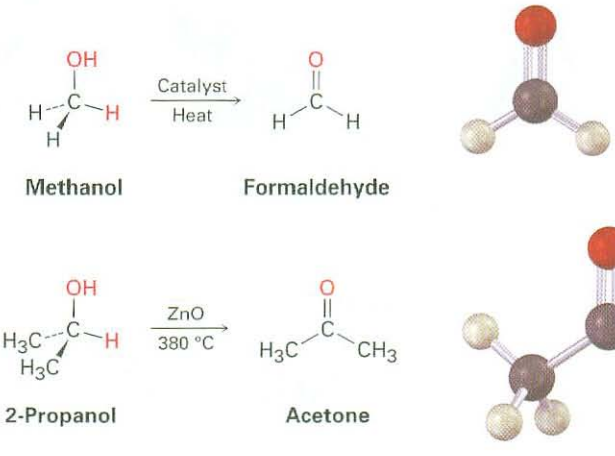
Pyridoxal phosphate (PLP)



Hydrocortisone

In the chemical industry, simple aldehydes and ketones are produced in large quantities for use as solvents and as starting materials to prepare a host of other compounds. For example, more than 1.9 million tons per year of formaldehyde, $H_2C{=}O$, is produced in the United States for use in building insulation materials and in the adhesive resins that bind particle board and plywood. Acetone, $(CH_3)_2C{=}O$, is widely used as an industrial solvent; approximately 1.2 million tons per year is produced in the United States. Formaldehyde is synthesized industrially by catalytic oxidation of methanol, and one method of acetone preparation involves oxidation of 2-propanol.

Sean Duggan



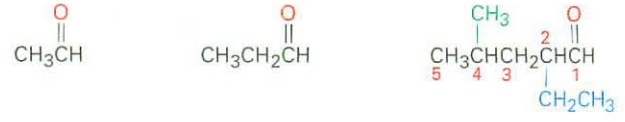
WHY THIS CHAPTER?

Much of organic chemistry is simply the chemistry of carbonyl compounds. Aldehydes and ketones, in particular, are intermediates in the synthesis of many pharmaceutical agents, in almost all biological pathways, and in numerous industrial processes, so an understanding of their properties and reactions is essential. We'll look in this chapter at some of their most important reactions.

19.1 Naming Aldehydes and Ketones

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to draw structures of aldehydes and ketones based on their IUPAC names.**

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the −CHO group, and the −CHO carbon is numbered as carbon 1. For example:



Ethanal (acetaldehyde) **Propanal (propionaldehyde)** **2-Ethyl-4-methylpentanal**

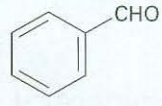
Note that the longest chain in 2-ethyl-4-methylpentanal is a hexane, but this chain does not include the −CHO group and thus is not considered the parent.

For cyclic aldehydes in which the −CHO group is directly attached to a ring, the suffix *-carbaldehyde* is used.

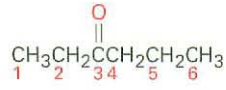
Cyclohexanecarbaldehyde **2-Naphthalenecarbaldehyde**

A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in Table 19.1.

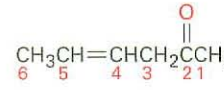
Table 19.1 Common Names of Some Simple Aldehydes

Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$H_2C{=}CHCHO$	Acrolein	Propenal
$CH_3CH{=}CHCHO$	Crotonaldehyde	2-Butenal
	Benzaldehyde	Benzenecarbaldehyde

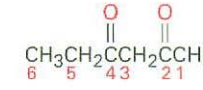
Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that contains the ketone group, and the numbering begins at the end nearer the carbonyl carbon. As with alkenes (Section 6.3) and alcohols (Section 17.1), the locant is placed before the parent name in older rules but before the suffix in newer IUPAC recommendations. For example:



3-Hexanone
(New: Hexan-3-one)

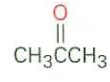


4-Hexen-2-one
(New: Hex-4-en-2-one)

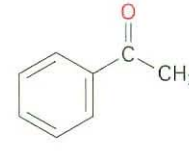


2,4-Hexanedione
(New: Hexane-2,4-dione)

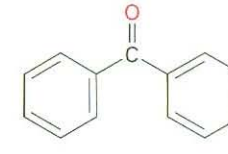
A few ketones are allowed by IUPAC to retain their common names.



Acetone

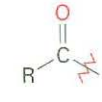


Acetophenone

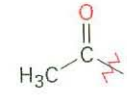


Benzophenone

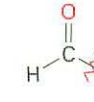
When it's necessary to refer to the R–C=O as a substituent, the name **acyl** (**a**-sil) **group** is used and the name ending *-yl* is attached. Thus, CH_3CO is an *acetyl* group, CHO is a *formyl* group, and C_6H_5CO is a *benzoyl* group.



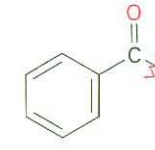
An acyl group



Acetyl

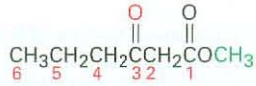


Formyl



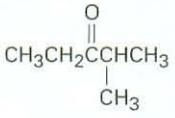
Benzoyl

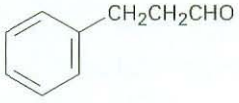
If other functional groups are present and the doubly bonded oxygen is considered a substituent on a parent chain, the prefix *oxo-* is used. For example:

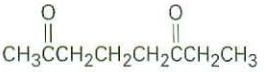


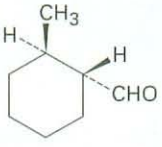
Methyl 3-oxohexanoate

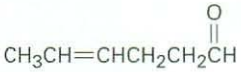
Problem 19.1 Name the following aldehydes and ketones according to IUPAC rules:

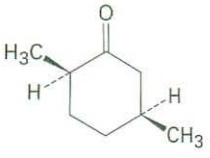
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Problem 19.2 Draw structures corresponding to the following names:

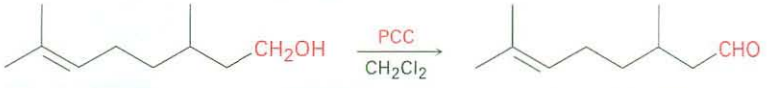
(a) 3-Methylbutanal
(b) 4-Chloro-2-pentanone
(c) Phenylacetaldehyde
(d) *cis*-3-*tert*-Butylcyclohexanecarbaldehyde
(e) 3-Methyl-3-butenal
(f) 2-(1-Chloroethyl)-5-methylheptanal

19.2 Preparation of Aldehydes and Ketones

Preparing Aldehydes

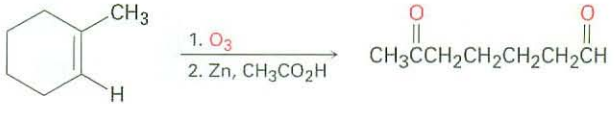
We've already discussed two methods of aldehyde synthesis: oxidation of primary alcohols and oxidative cleavage of alkenes.

- Primary alcohols can be oxidized to give aldehydes (Section 17.7). The reaction is often carried out using pyridinium chlorochromate (PCC) in dichloromethane solvent at room temperature.



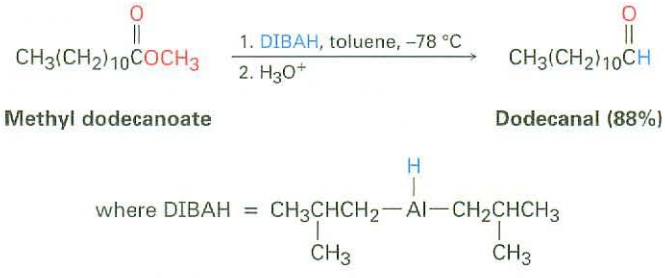
Citronellol **Citronellal (82%)**

- Alkenes with at least one vinylic hydrogen undergo oxidative cleavage when treated with ozone, yielding aldehydes (Section 7.9). If the ozonolysis reaction is carried out on a cyclic alkene, a dicarbonyl compound results.



1-Methylcyclohexene **6-Oxoheptanal (86%)**

A third method of aldehyde synthesis is one that we'll mention here just briefly and then return to in Section 21.6. Certain carboxylic acid derivatives can be *partially* reduced to yield aldehydes. The partial reduction of an ester by diisobutylaluminum hydride (DIBAH), for instance, is an important laboratory-scale method of aldehyde synthesis, and mechanistically related processes also occur in biological pathways. The reaction is normally carried out at −78 °C (dry-ice temperature) in toluene solution.

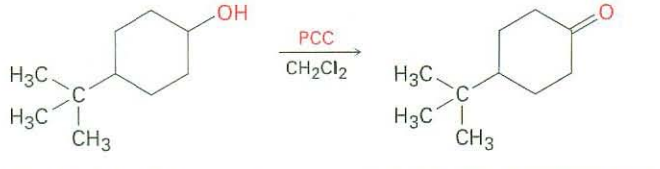


Problem 19.3 How would you prepare pentanal from the following starting materials?
(a) $CH_3CH_2CH_2CH_2CH_2OH$ (b) $CH_3CH_2CH_2CH_2CH{=}CH_2$
(c) $CH_3CH_2CH_2CH_2CO_2CH_3$

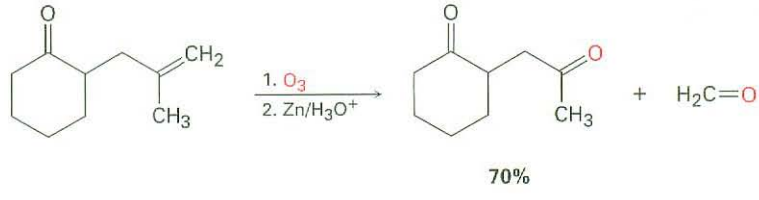
Preparing Ketones

For the most part, methods of ketone synthesis are similar to those for aldehydes.

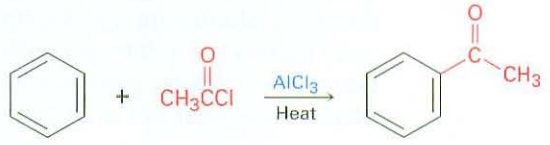
- Secondary alcohols are oxidized by a variety of reagents to give ketones (Section 17.8). The choice of oxidant depends on such factors as reaction scale, cost, and acid or base sensitivity of the alcohol.



- Ozonolysis of alkenes yields ketones if one of the unsaturated carbon atoms is disubstituted (Section 7.9).

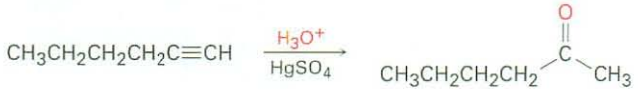


- Aryl ketones are prepared by Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of $AlCl_3$ catalyst (Section 16.3).



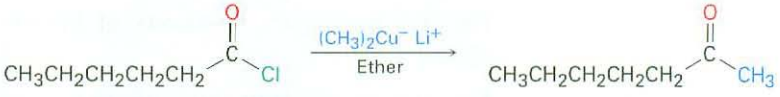
Benzene **Acetyl chloride** **Acetophenone (95%)**

- Methyl ketones are prepared by hydration of terminal alkynes in the presence of Hg^{2+} catalyst (Section 8.4).



1-Hexyne **2-Hexanone (78%)**

In addition to those methods already discussed, ketones can also be prepared from certain carboxylic acid derivatives, just as aldehydes can. Among the most useful reactions of this type is that between an acid chloride and a Gilman diorganocopper reagent such as we saw in Section 10.8. We'll discuss this subject in more detail in Section 21.4.



Hexanoyl chloride **2-Heptanone (81%)**

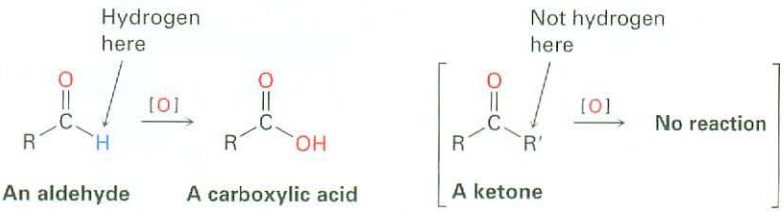
Problem 19.4 How would you carry out the following reactions? More than one step may be required.

(a) 3-Hexyne → 3-Hexanone
(b) Benzene → *m*-Bromoacetophenone
(c) Bromobenzene → Acetophenone
(d) 1-Methylcyclohexene → 2-Methylcyclohexanone

19.3 Oxidation of Aldehydes and Ketones

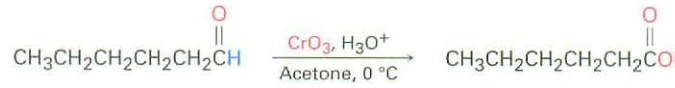
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of oxidation reactions involving aldehydes and ketones.**

Aldehydes are easily oxidized to yield carboxylic acids, but ketones are generally inert toward oxidation. The difference is a consequence of structure: aldehydes have a –CHO proton that can be abstracted during oxidation, but ketones do not.



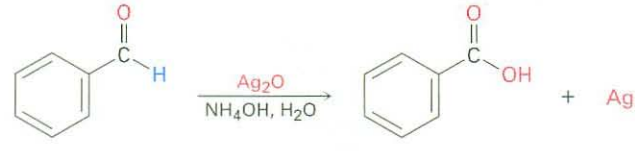
An aldehyde **A carboxylic acid** **A ketone**

Many oxidizing agents, including $KMnO_4$ and hot HNO_3, convert aldehydes into carboxylic acids, but CrO_3 in aqueous acid is a more common choice. The oxidation occurs rapidly at room temperature and generally results in good yields.



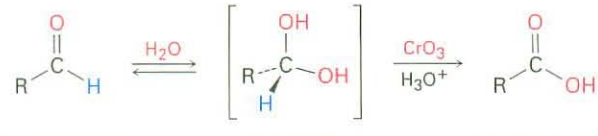
Hexanal **Hexanoic acid (85%)**

One drawback to this CrO_3 oxidation is that it takes place under acidic conditions, and sensitive molecules sometimes undergo side reactions. In such cases, the laboratory oxidation of an aldehyde can be carried out using a solution of silver oxide, Ag_2O, in aqueous ammonia, the so-called Tollens' reagent. Aldehydes are oxidized by Tollens' reagent in high yield without harming carbon–carbon double bonds or other acid-sensitive functional groups in a molecule.



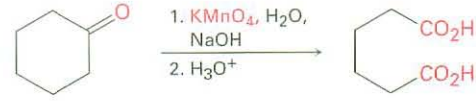
Benzaldehyde **Benzoic acid**

Aldehyde oxidations occur through intermediate 1,1-diols, or *hydrates*, which are formed by a reversible nucleophilic addition of water to the carbonyl group. Even though formed to only a small extent at equilibrium, the hydrate reacts like any typical primary or secondary alcohol and is oxidized to a carbonyl compound (Section 17.7).



An aldehyde **A hydrate** **A carboxylic acid**

Ketones are inert to most oxidizing agents but undergo a slow cleavage reaction when treated with hot alkaline $KMnO_4$. The C–C bond next to the carbonyl group is broken, and carboxylic acids are produced. The reaction is useful primarily for symmetrical ketones such as cyclohexanone because product mixtures are formed from unsymmetrical ketones.



Cyclohexanone **Hexanedioic acid (79%)**

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

As we saw in *A Preview of Carbonyl Compounds*, the most general reaction of aldehydes and ketones is the **nucleophilic addition reaction**. A nucleophile, :Nu$^-$, approaches along the C=O bond from an angle of about 75° to the plane of the carbonyl group and adds to the electrophilic C=O carbon atom. At the same time, rehybridization of the carbonyl carbon from sp^2 to sp^3 occurs, an electron pair from the C=O bond moves toward the electronegative oxygen atom, and a tetrahedral alkoxide ion intermediate is produced (Figure 19.1).

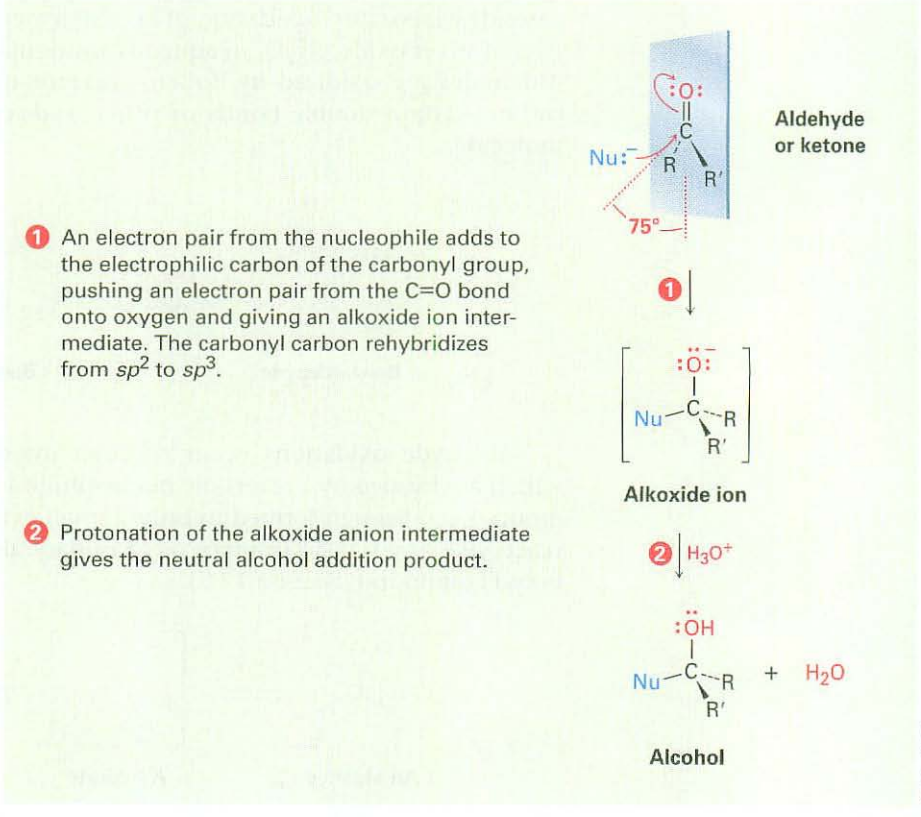


Figure 19.1 MECHANISM: A nucleophilic addition reaction to an aldehyde or ketone. The nucleophile approaches the carbonyl group from an angle of approximately 75° to the plane of the sp^2 orbitals, the carbonyl carbon rehybridizes from sp^2 to sp^3, and an alkoxide ion is formed.

The nucleophile can be either negatively charged (:Nu$^-$) or neutral (:Nu). If it's neutral, however, it usually carries a hydrogen atom that can subsequently be eliminated, :Nu–H. For example:

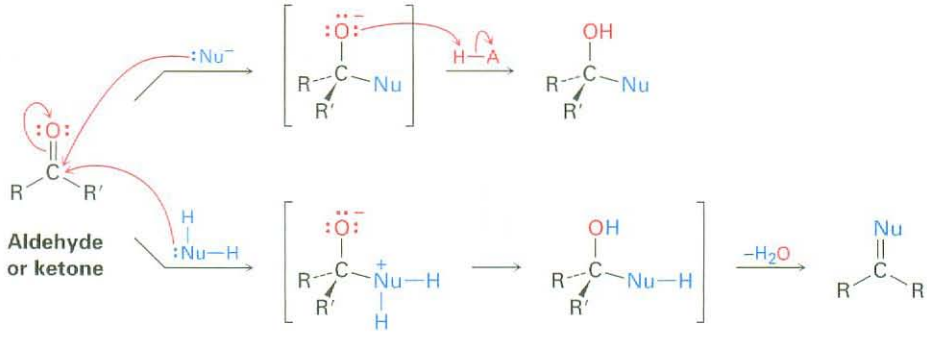
Some negatively charged nucleophiles

- $HO:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $RO:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)

Some neutral nucleophiles

- $H\ddot{O}H$ (water)
- $R\ddot{O}H$ (an alcohol)
- H_3N: (ammonia)
- $R\ddot{N}H_2$ (an amine)

Nucleophilic additions to aldehydes and ketones have two general variations, as shown in Figure 19.2. In one variation, the tetrahedral intermediate is protonated by water or acid to give an alcohol as the final product; in the second variation, the carbonyl oxygen atom is protonated and then eliminated as HO^- or H_2O to give a product with a C=Nu bond.



Active Figure 19.2 Two general reaction pathways following addition of a nucleophile to an aldehyde or ketone. The top pathway leads to an alcohol product; the bottom pathway leads to a product with a C=Nu bond. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons. Sterically, the presence of only one large substituent bonded to the C=O carbon in an aldehyde versus two large substituents in a ketone means that a nucleophile is able to approach an aldehyde more readily. Thus, the transition state leading to the tetrahedral intermediate is less crowded and lower in energy for an aldehyde than for a ketone (Figure 19.3).

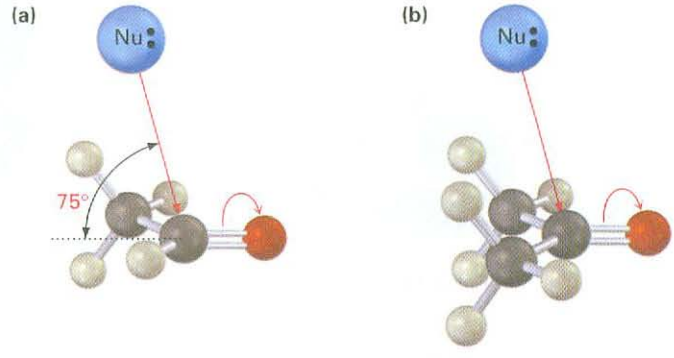
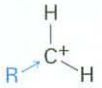


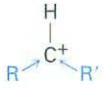
Figure 19.3 **(a)** Nucleophilic addition to an aldehyde is sterically less hindered because only one relatively large substituent is attached to the carbonyl-group carbon. **(b)** A ketone, however, has two large substituents and is more hindered.

Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde carbonyl groups. To see this polarity difference, recall the stability order of carbocations (Section 6.9). A primary carbocation is higher in energy and thus more reactive than a secondary carbocation because

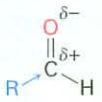
it has only one alkyl group inductively stabilizing the positive charge rather than two. In the same way, an aldehyde has only one alkyl group inductively stabilizing the partial positive charge on the carbonyl carbon rather than two, is a bit more electrophilic, and is therefore more reactive than a ketone.



1° carbocation
(less stable, more reactive)



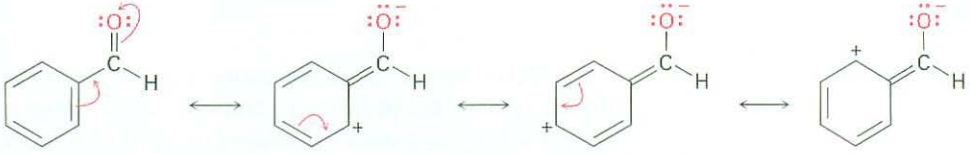
2° carbocation
(more stable, less reactive)

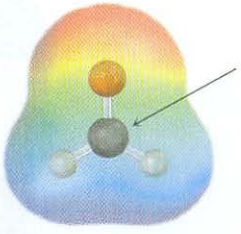


Aldehyde
(less stabilization of δ+, more reactive)

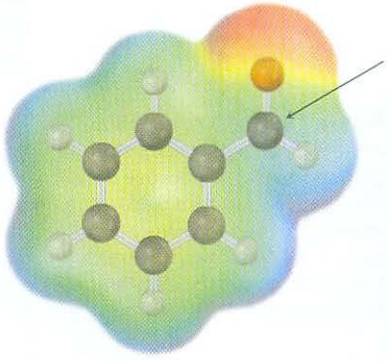
Ketone
(more stabilization of δ+, less reactive)

One further comparison: aromatic aldehydes, such as benzaldehyde, are less reactive in nucleophilic addition reactions than aliphatic aldehydes because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic. Comparing electrostatic potential maps of formaldehyde and benzaldehyde, for example, shows that the carbonyl carbon atom is less positive (less blue) in the aromatic aldehyde.





Formaldehyde



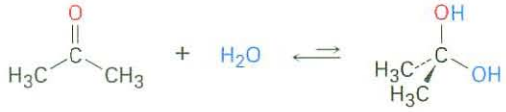
Benzaldehyde

Problem 19.5 Treatment of an aldehyde or ketone with cyanide ion ($^-$:C≡N), followed by protonation of the tetrahedral alkoxide ion intermediate, gives a *cyanohydrin*. Show the structure of the cyanohydrin obtained from cyclohexanone.

Problem 19.6 *p*-Nitrobenzaldehyde is more reactive toward nucleophilic additions than *p*-methoxybenzaldehyde. Explain.

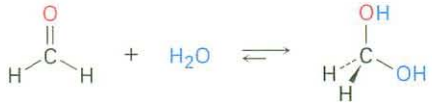
19.5 Nucleophilic Addition of H_2O: Hydration

Aldehydes and ketones react with water to yield 1,1-diols, or *geminal (gem)* diols. The hydration reaction is reversible, and a gem diol can eliminate water to regenerate an aldehyde or ketone.



Acetone (99.9%) **Acetone hydrate (0.1%)**

The position of the equilibrium between a gem diol and an aldehyde or ketone depends on the structure of the carbonyl compound. The equilibrium generally favors the carbonyl compound for steric reasons, but the gem diol is favored for a few simple aldehydes. For example, an aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde, whereas an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.

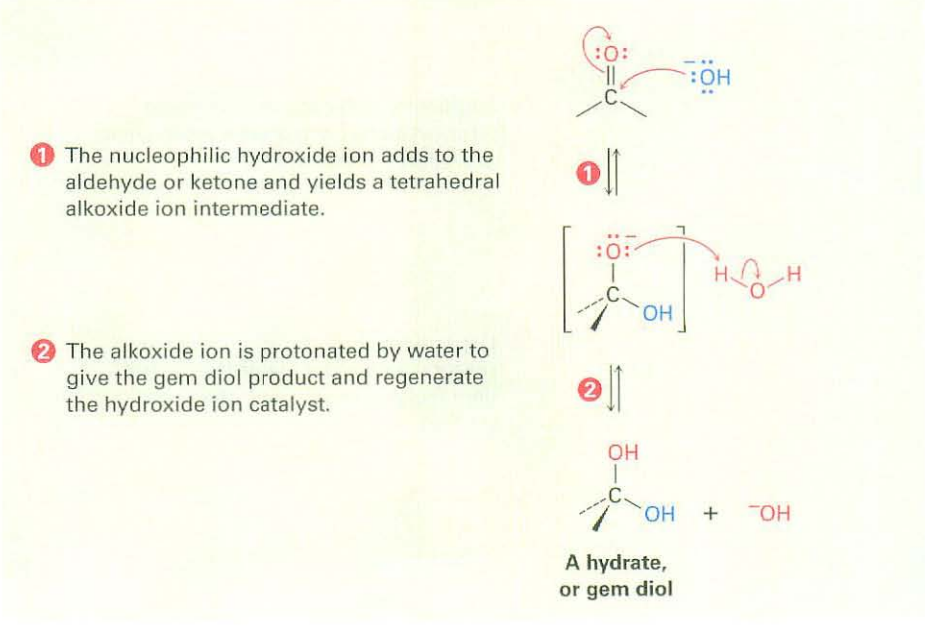


Formaldehyde (0.1%) **Formaldehyde hydrate (99.9%)**

The nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. The base-catalyzed hydration reaction takes place as shown in Figure 19.4. The nucleophile is the

Figure 19.4 MECHANISM: The mechanism of base-catalyzed hydration of an aldehyde or ketone. Hydroxide ion is a more reactive nucleophile than neutral water.

ThomsonNOW Click *Organic Process* to **view an animation of the base-catalyzed hydration of a carbonyl.**



hydroxide ion, which is much more reactive than neutral water because of its negative charge.

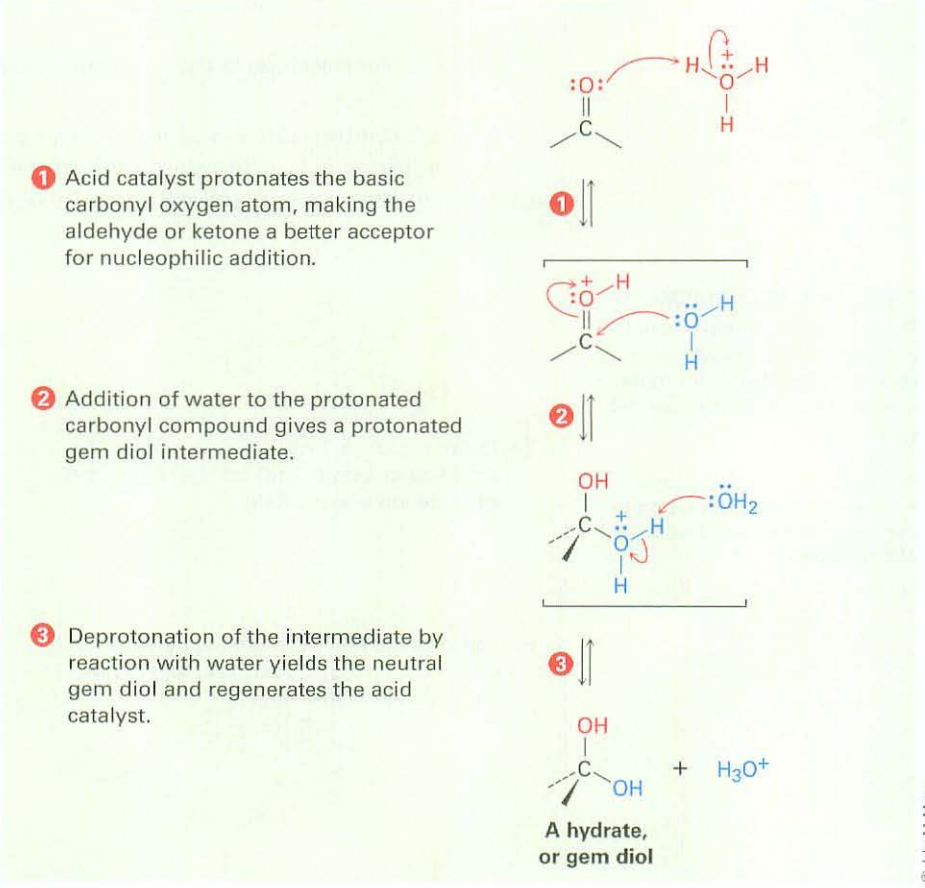
The acid-catalyzed hydration reaction begins with protonation of the carbonyl oxygen atom, which places a positive charge on oxygen and makes the carbonyl group more electrophilic. Subsequent nucleophilic addition of water to the protonated aldehyde or ketone then yields a protonated gem diol, which loses H^+ to give the neutral product (Figure 19.5).

Note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction takes place rapidly because water is converted into hydroxide ion, a much better *nucleophile*. The acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation into a much better *electrophile*.

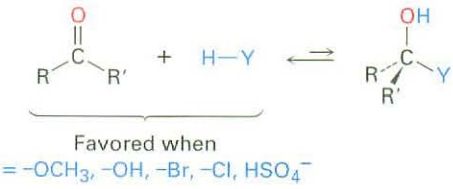
The hydration reaction just described is typical of what happens when an aldehyde or ketone is treated with a nucleophile of the type H–Y, where the Y atom is electronegative and can stabilize a negative charge (oxygen, halogen, or sulfur, for instance). In such reactions, the nucleophilic addition is reversible, with the equilibrium generally favoring the carbonyl reactant rather than the tetrahedral addition product. In other words, treatment of an aldehyde or

Figure 19.5 MECHANISM: The mechanism of acid-catalyzed hydration of an aldehyde or ketone. Acid protonates the carbonyl group, making it more electrophilic and more reactive.

ThomsonNOW Click *Organic Process* to **view an animation of the acid-catalyzed hydration of a carbonyl.**



ketone with CH_3OH, H_2O, HCl, HBr, or H_2SO_4 does not normally lead to a stable alcohol addition product.



Problem 19.7 When dissolved in water, trichloroacetaldehyde (chloral, CCl_3CHO) exists primarily as chloral hydrate, $CCl_3CH(OH)_2$, better known as "knockout drops." Show the structure of chloral hydrate.

Problem 19.8 The oxygen in water is primarily (99.8%) ^{16}O, but water enriched with the heavy isotope ^{18}O is also available. When an aldehyde or ketone is dissolved in ^{18}O-enriched water, the isotopic label becomes incorporated into the carbonyl group. Explain.

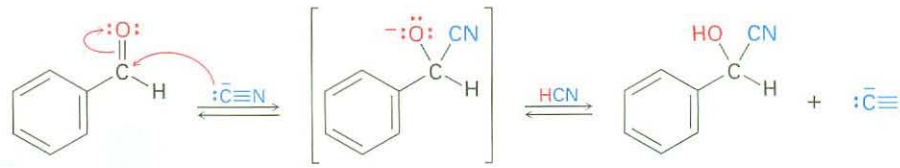
$$R_2C{=}O + H_2O \rightleftharpoons R_2C{=}O + H_2O \qquad \text{where O} = {}^{18}O$$

19.6 Nucleophilic Addition of HCN: Cyanohydrin Formation

Arthur Lapworth

Arthur Lapworth (1872–1941) was born in Galashiels, Scotland, and received a D.Sc. at the City and Guilds Institute, London. He was professor of chemistry at the University of Manchester from 1909 until his retirement in 1937.

Aldehydes and unhindered ketones undergo a nucleophilic addition reaction with HCN to yield **cyanohydrins**, **RCH(OH)C≡N**. Studies carried out in the early 1900s by Arthur Lapworth showed that cyanohydrin formation is reversible and base-catalyzed. Reaction occurs slowly when pure HCN is used but rapidly when a small amount of base is added to generate the nucleophilic cyanide ion, CN^-. Alternatively, a small amount of KCN can be added to HCN to catalyze the reaction. Addition of CN^- takes place by a typical nucleophilic addition pathway, yielding a tetrahedral intermediate that is protonated by HCN to give cyanohydrin product plus regenerated CN^-.

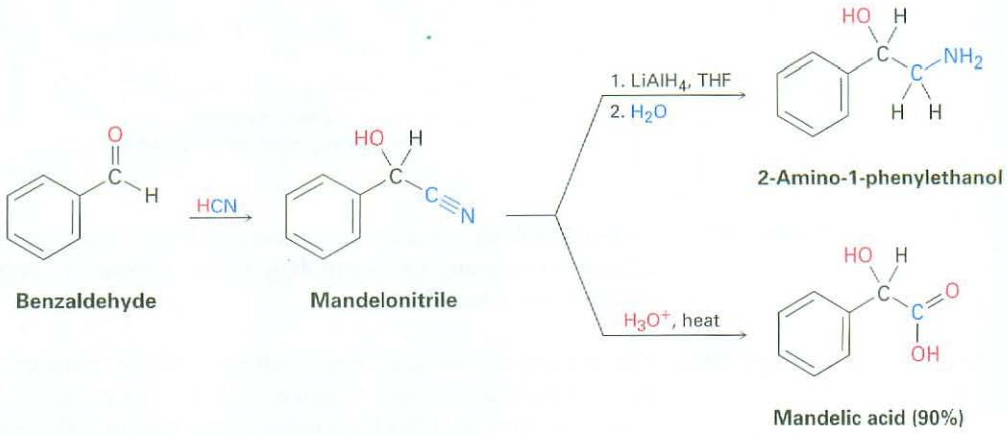


Benzaldehyde **Tetrahedral intermediate** **Mandelonitrile (88%)**

Cyanohydrin formation is somewhat unusual because it is one of the few examples of the addition of a protic acid (H–Y) to a carbonyl group. As noted in the previous section, protic acids such as H_2O, HBr, HCl, and H_2SO_4 don't normally yield carbonyl addition products because the equilibrium constants are unfavorable. With HCN, however, the equilibrium favors the cyanohydrin adduct.

Cyanohydrin formation is useful because of the further chemistry that can be carried out on the product. For example, a nitrile (R–C≡N) can be reduced with $LiAlH_4$ to yield a primary amine (RCH_2NH_2) and can be hydrolyzed by hot

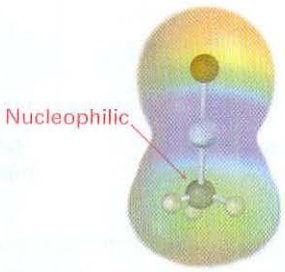
aqueous acid to yield a carboxylic acid. Thus, cyanohydrin formation provides a method for transforming an aldehyde or ketone into a different functional group.



Problem 19.9 Cyclohexanone forms a cyanohydrin in good yield but 2,2,6-trimethylcyclohexanone does not. Explain.

19.7 Nucleophilic Addition of Grignard and Hydride Reagents: Alcohol Formation

We saw in Section 17.5 that treatment of an aldehyde or ketone with a Grignard reagent, RMgX, yields an alcohol by nucleophilic addition of a carbon anion, or **carbanion**. A carbon–magnesium bond is strongly polarized, so a Grignard reagent reacts for all practical purposes as $R:^{-}\ ^{+}MgX$.



Methylmagnesium chloride

A Grignard reaction begins with an acid–base complexation of Mg^{2+} to the carbonyl oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better electrophile. Nucleophilic addition of $R:^{-}$ then produces a tetrahedral magnesium alkoxide intermediate, and protonation by addition of water

or dilute aqueous acid in a separate step yields the neutral alcohol (Figure 19.6). Unlike the nucleophilic additions of water and HCN, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

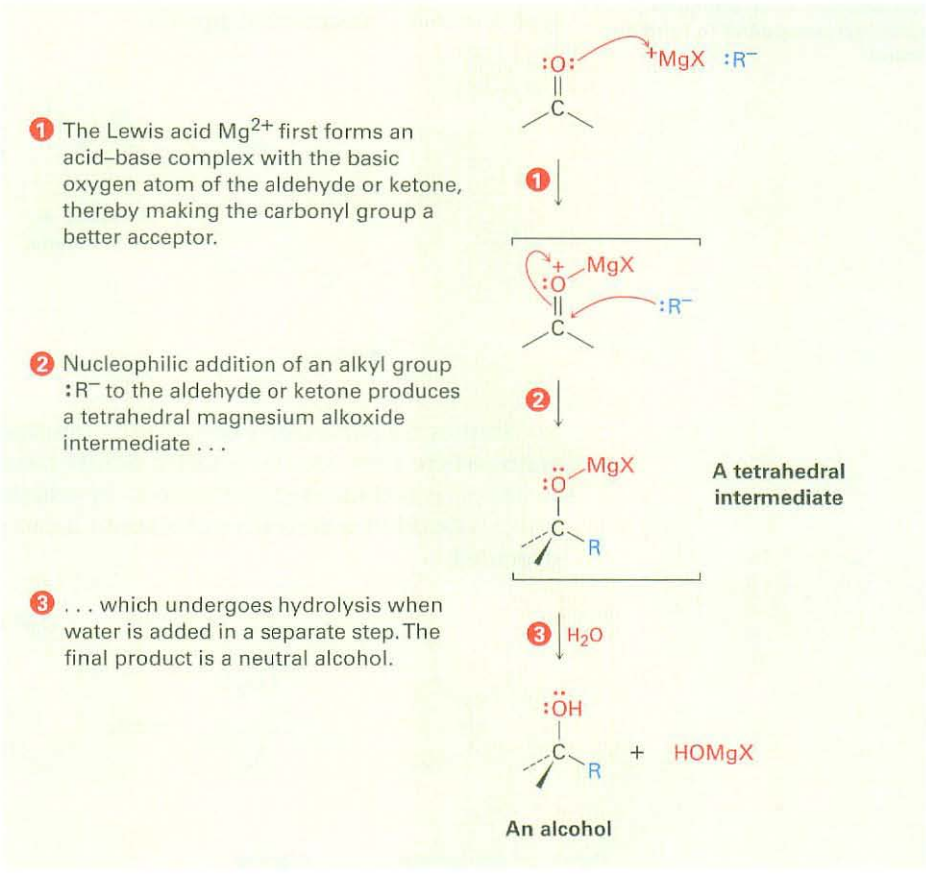


Figure 19.6 MECHANISM: Mechanism of the Grignard reaction. Nucleophilic addition of a carbanion to an aldehyde or ketone, followed by protonation of the alkoxide intermediate, yields an alcohol.

Just as addition of a Grignard reagent to an aldehyde or ketone yields an alcohol, so does addition of hydride ion, $:H^-$ (Section 17.4). Although the details of carbonyl-group reductions are complex, $LiAlH_4$ and $NaBH_4$ act as if they were donors of hydride ion in a nucleophilic addition reaction (Figure 19.7). Addition of water or aqueous acid after the hydride addition step protonates the tetrahedral alkoxide intermediate and gives the alcohol product.

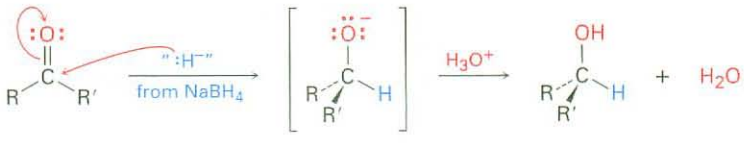
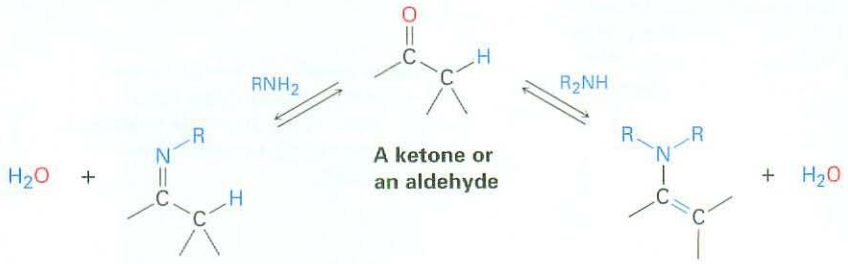


Figure 19.7 Mechanism of carbonyl-group reduction by nucleophilic addition of "hydride ion" from $NaBH_4$ or $LiAlH_4$.

19.8 Nucleophilic Addition of Amines: Imine and Enamine Formation

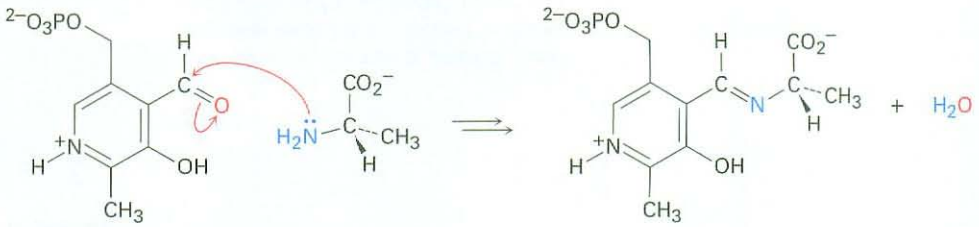
ThomsonNOW Click *Organic Process* to view an animation of the addition of an amine to a carbonyl compound to form an imine.

Primary amines, RNH_2, add to aldehydes and ketones to yield **imines**, $R_2C{=}NR$. Secondary amines, R_2NH, add similarly to yield **enamines**, $R_2N{-}CR{=}CR_2$ (*ene* + *amine* = unsaturated amine).



An imine — An enamine

Imines are particularly common as intermediates in many biological pathways, where they are often called **Schiff bases**. The amino acid alanine, for instance, is metabolized in the body by reaction with the aldehyde pyridoxal phosphate (PLP), a derivative of vitamin B_6, to yield a Schiff base that is further degraded.

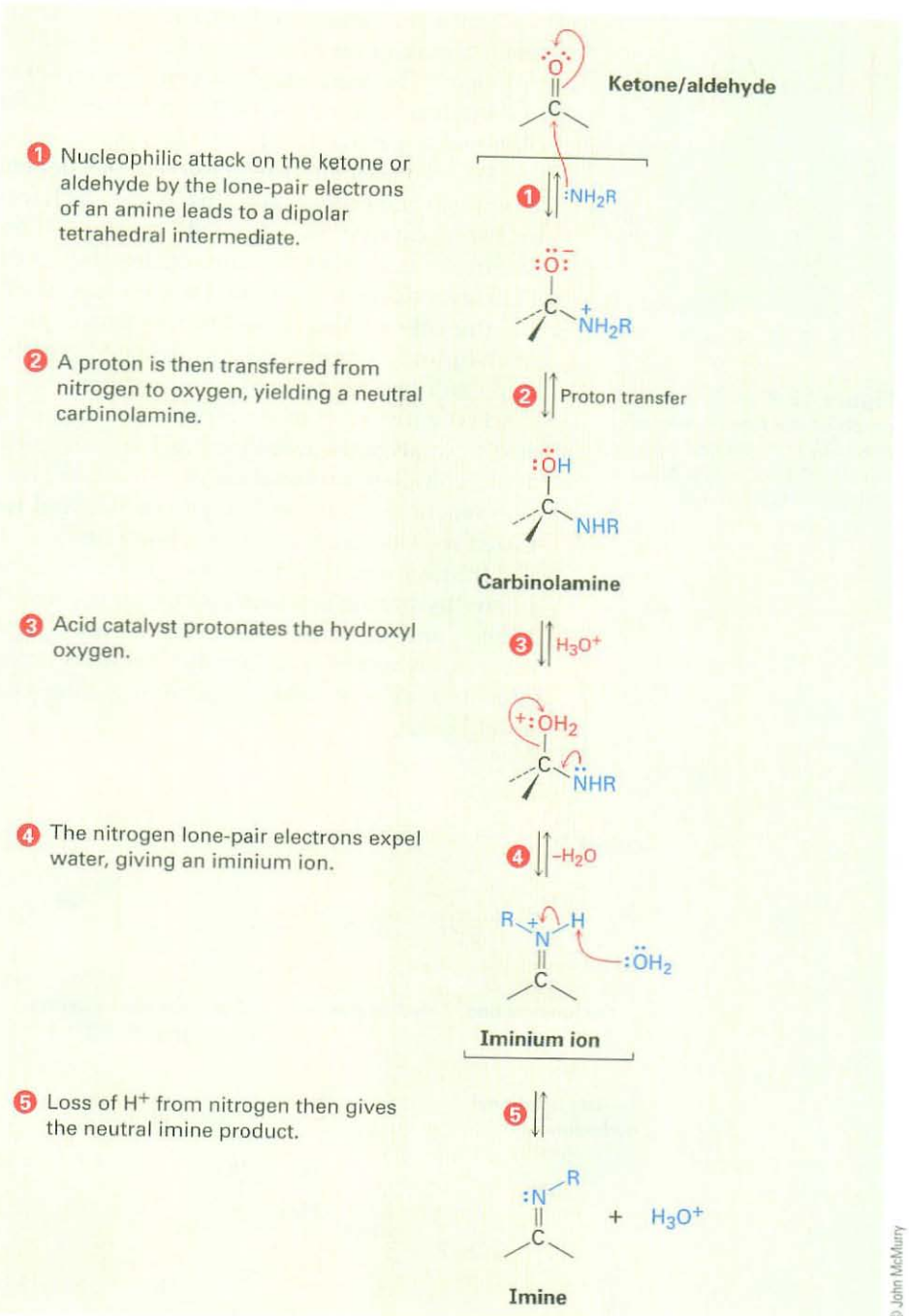


Pyridoxal phosphate — Alanine — An imine

Imine formation and enamine formation appear different because one leads to a product with a C=N bond and the other leads to a product with a C=C bond. Actually, though, the reactions are quite similar. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new C=Nu bond is formed.

Imines are formed in a reversible, acid-catalyzed process that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or *carbinolamine*. Protonation of the carbinolamine oxygen by an acid catalyst then converts the $-OH$ into a better leaving group ($-OH_2^+$), and E1-like loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst (Figure 19.8).

Figure 19.8 MECHANISM: Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is nucleophilic addition to yield a carbinolamine intermediate, which then loses water to give the imine.



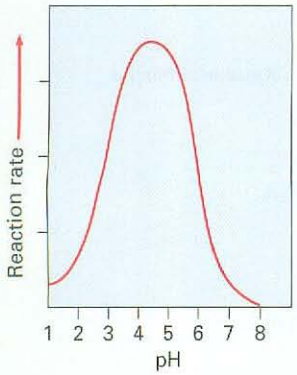


Figure 19.9 Dependence on pH of the rate of reaction between acetone and hydroxylamine: $(CH_3)_2C{=}O + NH_2OH \rightarrow (CH_3)_2C{=}NOH + H_2O$.

Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. For example, the profile of pH versus rate shown in Figure 19.9 for the reaction between acetone and hydroxylamine, NH_2OH, indicates that the maximum reaction rate is obtained at pH 4.5.

We can explain the observed pH dependence of imine formation by looking at the individual steps in the mechanism. As indicated in Figure 19.8, an acid catalyst is required in step 3 to protonate the intermediate carbinolamine, thereby converting the $-OH$ into a better leaving group. Thus, reaction will be slow if not enough acid is present (that is, at high pH). On the other hand, if too much acid is present (low pH), the basic amine nucleophile is completely protonated, so the initial nucleophilic addition step can't occur.

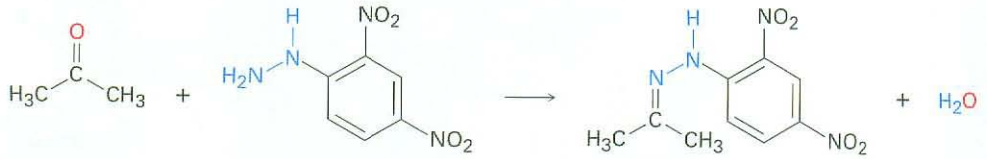
Evidently, a pH of 4.5 represents a compromise between the need for *some* acid to catalyze the rate-limiting dehydration step but *not too much* acid so as to avoid complete protonation of the amine. Each individual nucleophilic addition reaction has its own requirements, and reaction conditions must be optimized to obtain maximum reaction rates.

Imine formation from such reagents as hydroxylamine and 2,4-dinitrophenylhydrazine is sometimes useful because the products of these reactions—*oximes* and *2,4-dinitrophenylhydrazones (2,4-DNPs)*, respectively—are often crystalline and easy to handle. Such crystalline derivatives are occasionally prepared as a means of purifying and characterizing liquid ketones or aldehydes.

Oxime

Cyclohexanone **Hydroxylamine** **Cyclohexanone oxime (mp 90 °C)**

2,4-Dinitrophenylhydrazone



Acetone **2,4-Dinitrophenylhydrazine** **Acetone 2,4-dinitrophenylhydrazone (mp 126 °C)**

Reaction of an aldehyde or ketone with a secondary amine, R_2NH, rather than a primary amine yields an enamine. The process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the α carbon), yielding an enamine (Figure 19.10).

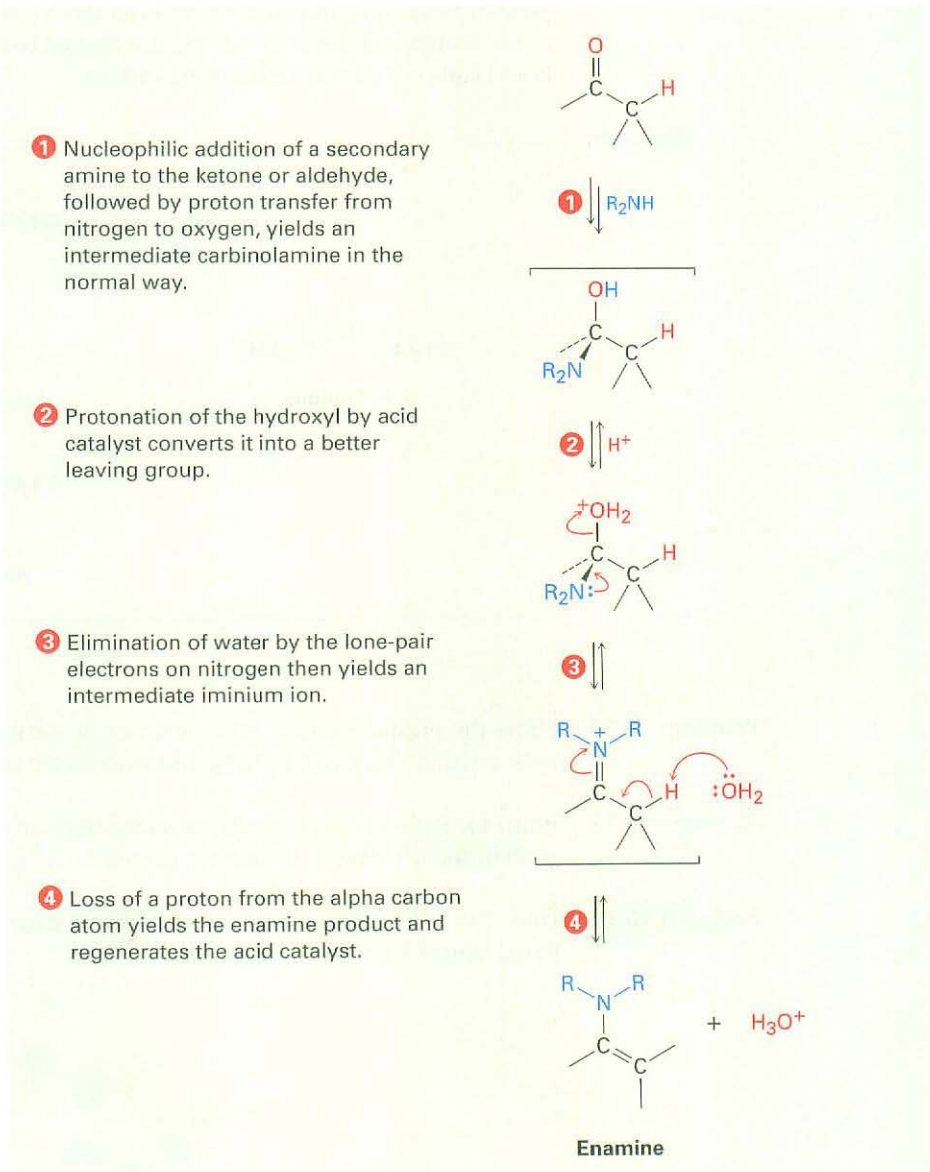


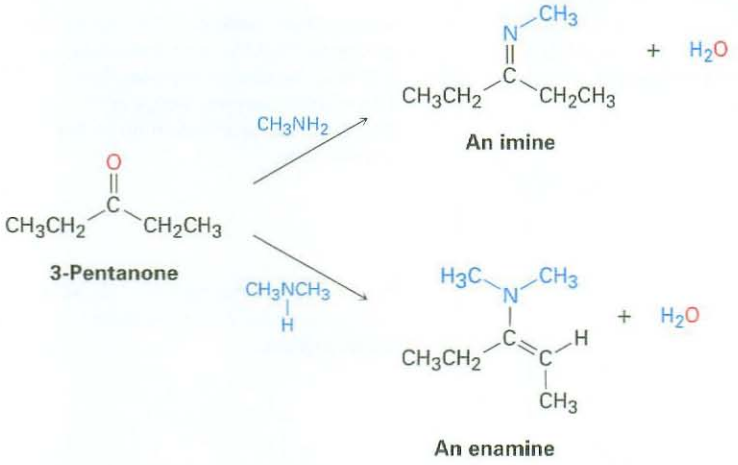
Figure 19.10 MECHANISM: Mechanism of enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH. The iminium ion intermediate has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.

WORKED EXAMPLE 19.1 ***Predicting the Product of Reaction between a Ketone and an Amine***

Show the products you would obtain by acid-catalyzed reaction of 3-pentanone with methylamine, CH_3NH_2, and with dimethylamine, $(CH_3)_2NH$.

Strategy An aldehyde or ketone reacts with a primary amine, RNH_2, to yield an imine, in which the carbonyl oxygen atom has been replaced by the =N–R group of the amine. Reaction of the same aldehyde or ketone with a secondary amine, R_2NH, yields an enamine, in which the oxygen atom has been replaced by the $-NR_2$ group of the amine and the double bond has moved to a position between the former carbonyl carbon and the neighboring carbon.

Solution



Problem 19.10 Show the products you would obtain by acid-catalyzed reaction of cyclohexanone with ethylamine, $CH_3CH_2NH_2$, and with diethylamine, $(CH_3CH_2)_2NH$.

Problem 19.11 Imine formation is reversible. Show all the steps involved in the acid-catalyzed reaction of an imine with water (hydrolysis) to yield an aldehyde or ketone plus primary amine.

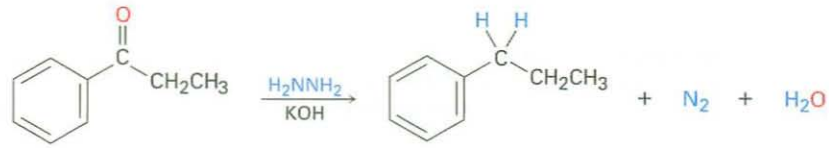
Problem 19.12 Draw the following molecule as a line-bond structure, and show how it can be prepared from a ketone and an amine.

19.9 Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction

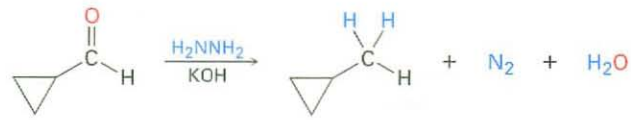
Ludwig Wolff

Ludwig Wolff (1857–1919) was born in Neustadt/Hardt, Germany, and received his Ph.D. from the University of Strasbourg working with Rudolf Fittig. He was professor of chemistry at the University of Jena.

A useful variant of the imine-forming reaction just discussed involves the treatment of an aldehyde or ketone with hydrazine, H_2NNH_2, in the presence of KOH. Called the **Wolff–Kishner reaction**, the process is a useful and general method for converting an aldehyde or ketone into an alkane, $R_2C{=}O \rightarrow R_2CH_2$.



Propiophenone **Propylbenzene (82%)**



Cyclopropane-carbaldehyde **Methylcyclo-propane (72%)**

N. M. Kishner

N. M. Kishner (1867–1935) was born in Moscow and received his Ph.D. at the University of Moscow working with Vladimir Markovnikov. He became professor, first at the University of Tomsk and then at the University of Moscow.

The Wolff–Kishner reaction involves formation of a *hydrazone* intermediate, $R_2C{=}NNH_2$, followed by base-catalyzed double-bond migration, loss of N_2 gas, and protonation to give the alkane product (Figure 19.11). The double-bond migration takes place when base removes one of the weakly acidic NH protons to generate a hydrazone anion, which has an allylic resonance structure that places the double bond between nitrogens and the negative charge on carbon. Reprotonation then occurs on carbon to generate the double-bond rearrangement product. The next step—loss of nitrogen and formation of an alkyl anion—is driven by the large thermodynamic stability of the N_2 molecule.

Note that the Wolff–Kishner reduction accomplishes the same overall transformation as the catalytic hydrogenation of an acylbenzene to yield an alkylbenzene (Section 16.10). The Wolff–Kishner reduction is more general and more useful than catalytic hydrogenation, however, because it works well with both alkyl and aryl ketones.

Problem 19.13 Show how you could prepare the following compounds from 4-methyl-3-penten-2-one, $(CH_3)_2C{=}CHCOCH_3$.

(a) $CH_3CHCH_2CCH_3$ (with CH3 and O)

(b) $CH_3C{=}CHCH_2CH_3$ (with CH3)

(c) $CH_3CHCH_2CH_2CH_3$ (with CH3)

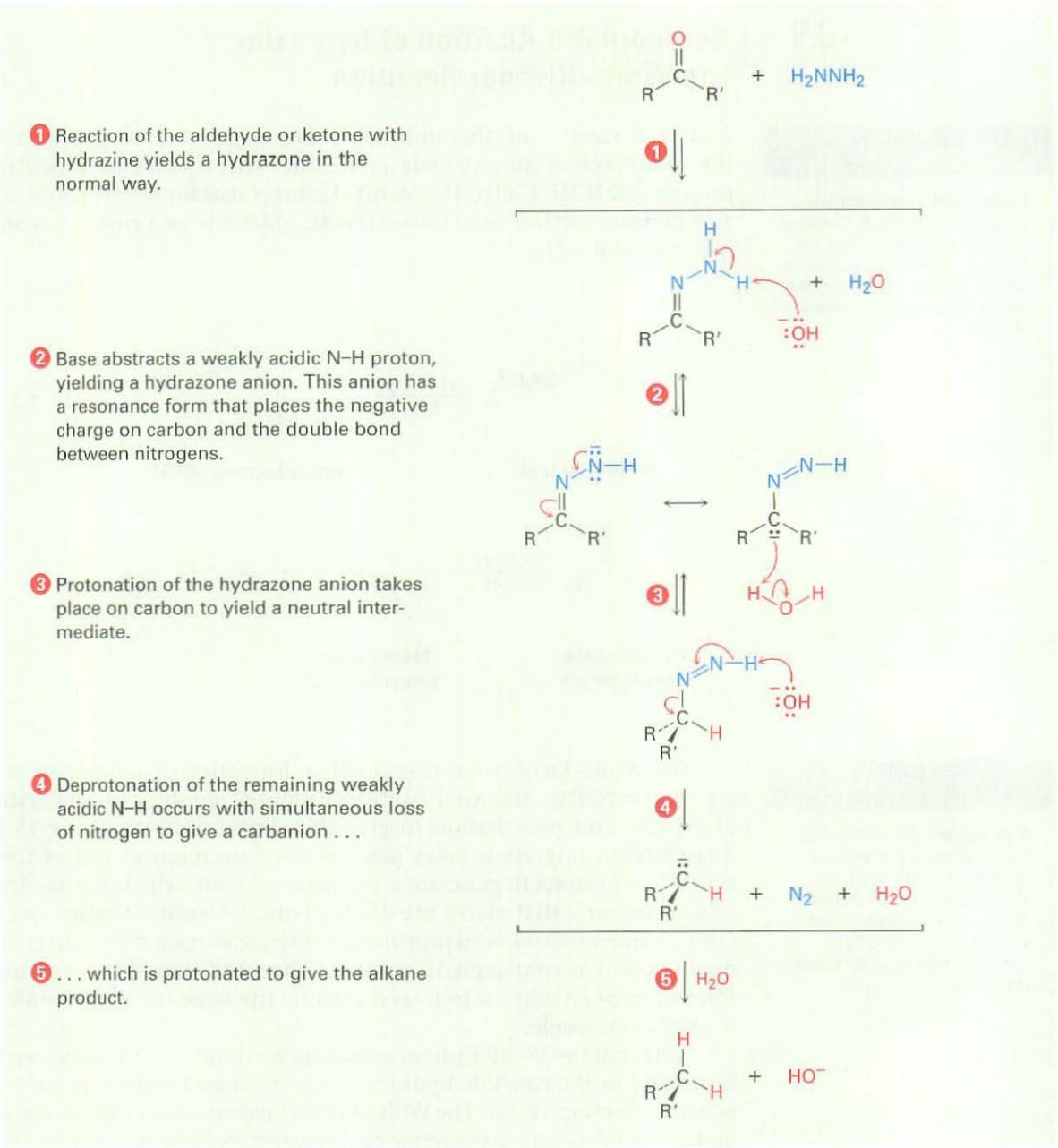
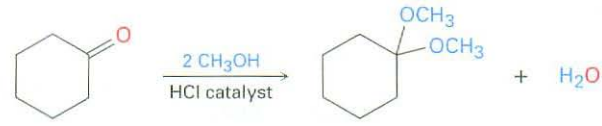


Figure 19.11 MECHANISM: Mechanism of the Wolff–Kishner reduction of an aldehyde or ketone to yield an alkane.

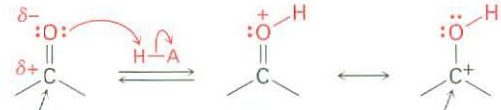
19.10 Nucleophilic Addition of Alcohols: Acetal Formation

Aldehydes and ketones react reversibly with 2 equivalents of an alcohol in the presence of an acid catalyst to yield **acetals**, $R_2C(OR')_2$, sometimes called *ketals* if derived from a ketone. Cyclohexanone, for instance, reacts with methanol in the presence of HCl to give the corresponding dimethyl acetal.



Cyclohexanone **Cyclohexanone dimethyl acetal**

Acetal formation is similar to the hydration reaction discussed in Section 19.5. Like water, alcohols are weak nucleophiles that add to aldehydes and ketones only slowly under neutral conditions. Under acidic conditions, however, the reactivity of the carbonyl group is increased by protonation, so addition of an alcohol occurs rapidly.



A neutral carbonyl group is moderately electrophilic because of the polarity of the C–O bond.

A protonated carbonyl group is strongly electrophilic because of the positive charge on carbon.

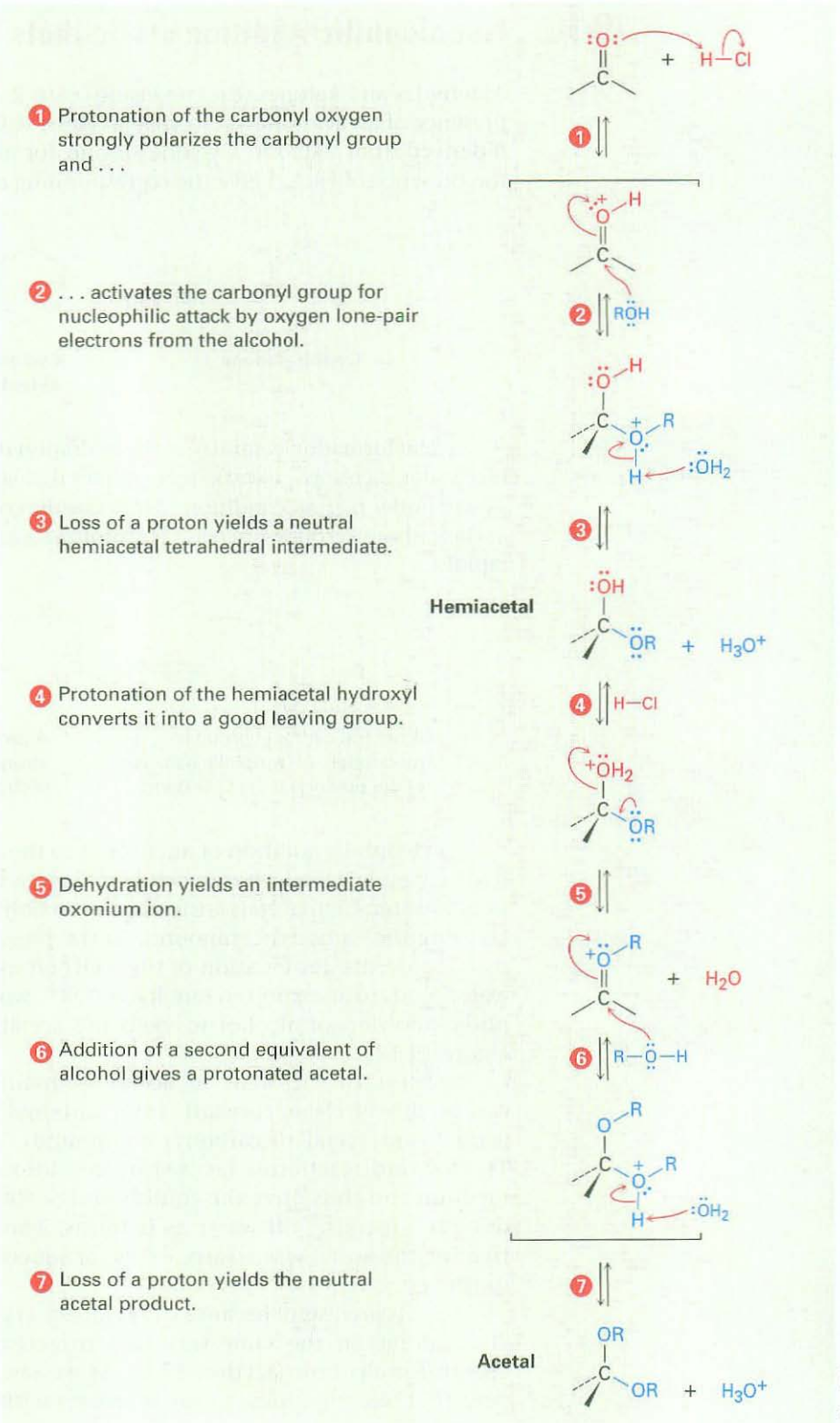
Nucleophilic addition of an alcohol to the carbonyl group initially yields a hydroxy ether called a **hemiacetal**, analogous to the gem diol formed by addition of water. Hemiacetals are formed reversibly, with the equilibrium normally favoring the carbonyl compound. In the presence of acid, however, a further reaction occurs. Protonation of the −OH group, followed by an E1-like loss of water, leads to an oxonium ion, $R_2C{=}OR^+$, which undergoes a second nucleophilic addition of alcohol to yield the acetal. The mechanism is shown in Figure 19.12.

Because all the steps in acetal formation are reversible, the reaction can be driven either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the conditions. The forward reaction is favored by conditions that remove water from the medium and thus drive the equilibrium to the right. In practice, this is often done by distilling off water as it forms. The reverse reaction is favored by treating the acetal with a large excess of aqueous acid to drive the equilibrium to the left.

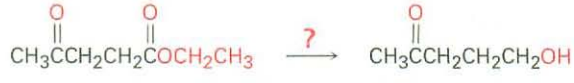
Acetals are useful because they can act as protecting groups for aldehydes and ketones in the same way that trimethylsilyl ethers act as protecting groups for alcohols (Section 17.8). As we saw previously, it sometimes happens that one functional group interferes with intended chemistry elsewhere

Figure 19.12 MECHANISM: Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.

ThomsonNOW Click *Organic Process* to **view an animation of acetal formation from an alcohol and an aldehyde.**

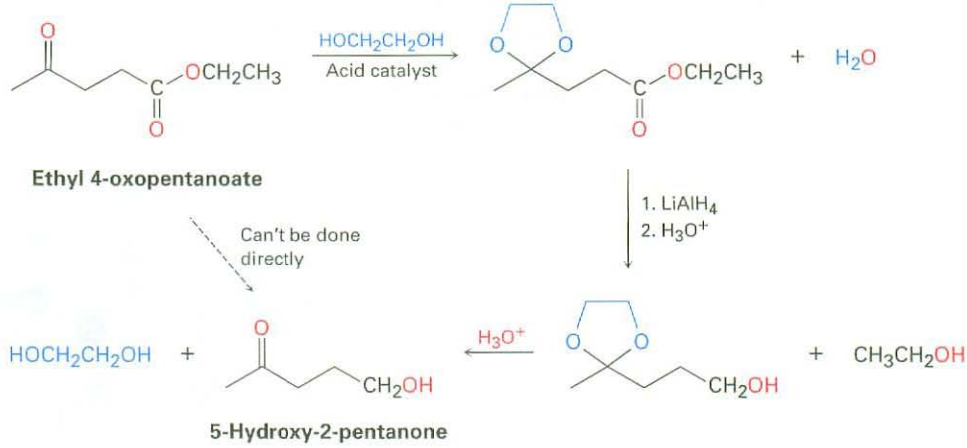


in a complex molecule. For example, if we wanted to reduce only the ester group of ethyl 4-oxopentanoate, the ketone would interfere. Treatment of the starting keto ester with $LiAlH_4$ would reduce both the keto and the ester groups to give a diol product.



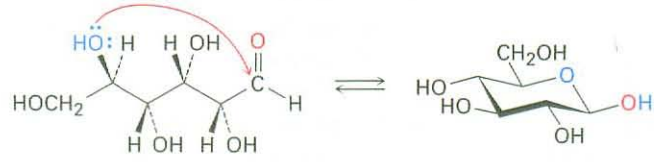
Ethyl 4-oxopentanoate **5-Hydroxy-2-pentanone**

By protecting the keto group as an acetal, however, the problem can be circumvented. Like other ethers, acetals are unreactive to bases, hydride reducing agents, Grignard reagents, and catalytic reducing conditions, but are cleaved by acid. Thus, we can accomplish the selective reduction of the ester group in ethyl 4-oxopentanoate by first converting the keto group to an acetal, then reducing the ester with $LiAlH_4$, and then removing the acetal by treatment with aqueous acid.



In practice, it's convenient to use 1 equivalent of a diol such as ethylene glycol as the alcohol and to form a *cyclic* acetal. The mechanism of cyclic acetal formation using ethylene glycol is exactly the same as that using 2 equivalents of methanol or other monoalcohol. The only difference is that both −OH groups are in the same molecule.

Acetal and hemiacetal groups are particularly common in carbohydrate chemistry. Glucose, for instance, is a polyhydroxy aldehyde that undergoes an *internal* nucleophilic addition reaction and exists primarily as a cyclic hemiacetal.



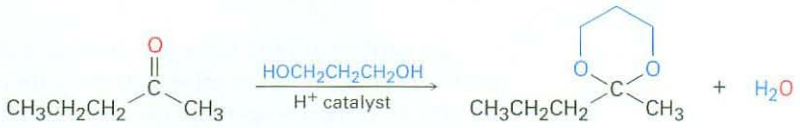
Glucose—open chain **Glucose—cyclic hemiacetal**

WORKED EXAMPLE 19.2 ***Predicting the Product of Reaction between a Ketone and an Alcohol***

Show the structure of the acetal you would obtain by acid-catalyzed reaction of 2-pentanone with 1,3-propanediol.

Strategy Acid-catalyzed reaction of an aldehyde or ketone with 2 equivalents of a monoalcohol or 1 equivalent of a diol yields an acetal, in which the carbonyl oxygen atom is replaced by two —OR groups from the alcohol.

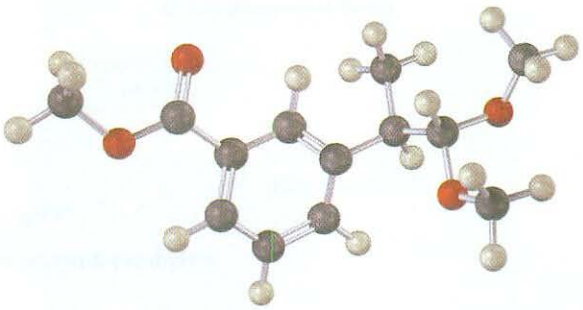
Solution



2-Pentanone

Problem 19.14 Show all the steps in the acid-catalyzed formation of a cyclic acetal from ethylene glycol and an aldehyde or ketone.

Problem 19.15 Identify the carbonyl compound and the alcohol that were used to prepare the following acetal:



19.11 Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction

Georg F. K. Wittig

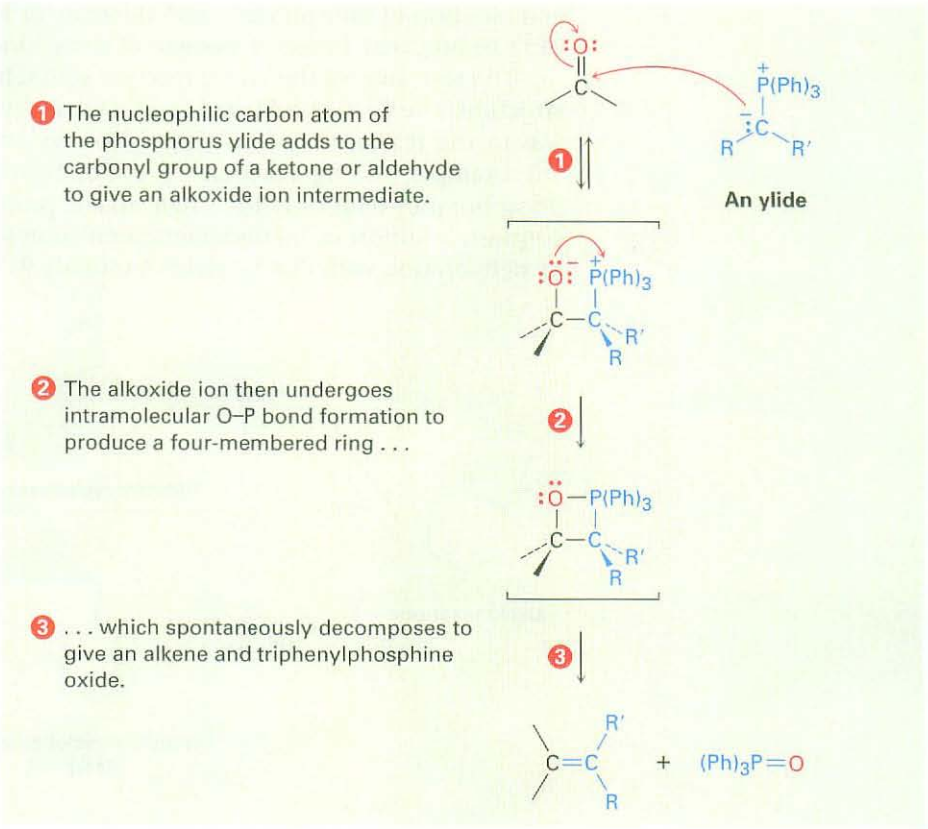
Georg F. K. Wittig (1897–1987) was born in Berlin, Germany, and received his Ph.D. at the University of Marburg in 1926, working with von Auwers. He then became professor of chemistry, first at the University of Braunschweig and later in Freiburg, Tübingen, and Heidelberg. In 1979, he received the Nobel Prize in chemistry for his work on phosphorus-containing organic compounds.

Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition called the **Wittig reaction**. The reaction has no direct biological counterpart but is important both because of its wide use in the laboratory and drug manufacture and because of its mechanistic similarity to reactions of the coenzyme thiamin diphosphate, which we'll see in Section 29.6.

In the Wittig reaction, a phosphorus *ylide*, $R_2\bar{C}-\overset{+}{P}(C_6H_5)_3$, also called a *phosphorane* and sometimes written in the resonance form $R_2C{=}P(C_6H_5)_3$, adds to an aldehyde or ketone to yield a dipolar intermediate called a *betaine*. (An **ylide**—pronounced **ill**-id—is a neutral, dipolar compound with adjacent plus and minus charges. A **betaine**—pronounced **bay**-ta-een—is a neutral, dipolar compound with nonadjacent charges.)

The betaine intermediate is not isolated; rather, it spontaneously decomposes through a four-membered ring to yield alkene plus triphenylphosphine

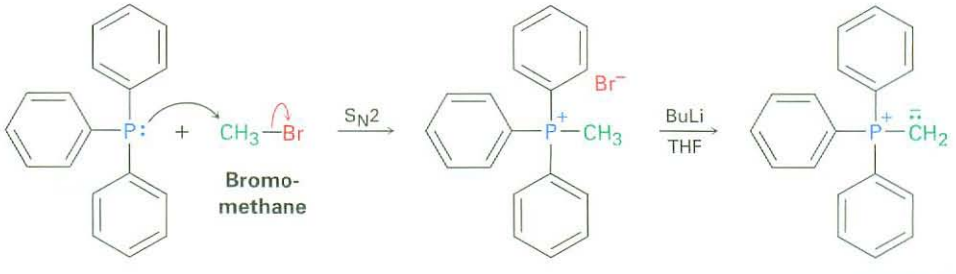
Active Figure 19.13
MECHANISM: The mechanism of the Wittig reaction between a phosphorus ylide and an aldehyde or ketone to yield an alkene. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



ThomsonNOW Click *Organic Interactive* to **use your problem-solving skills to design syntheses involving Wittig reactions.**

oxide, $(Ph)_3P{=}O$. The net result is replacement of the carbonyl oxygen atom by the $R_2C{=}$ group originally bonded to phosphorus (Figure 19.13).

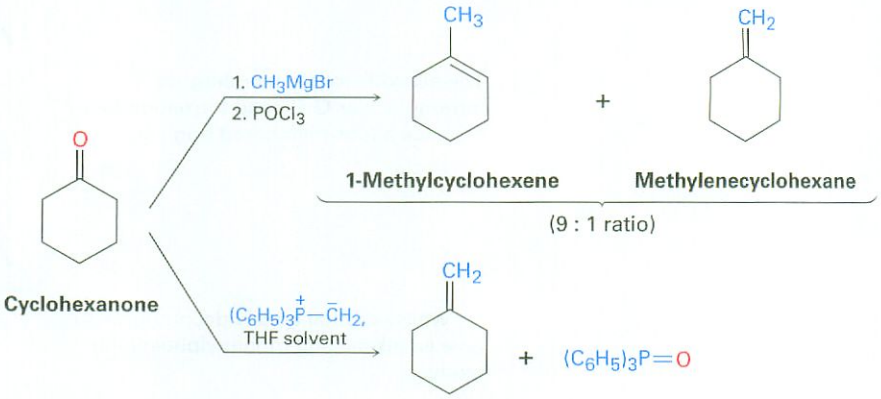
The phosphorus ylides necessary for Wittig reaction are easily prepared by S_N2 reaction of primary (and some secondary) alkyl halides with triphenylphosphine, followed by treatment with base. Triphenylphosphine, $(Ph)_3P$, is a good nucleophile in S_N2 reactions, and yields of the resultant alkyltriphenylphosphonium salts are high. Because of the positive charge on phosphorus, the hydrogen on the neighboring carbon is weakly acidic and can be removed by a strong base such as butyllithium (BuLi) to generate the neutral ylide. For example:



The Wittig reaction is extremely general, and a great many monosubstituted, disubstituted, and trisubstituted alkenes can be prepared from the appropriate

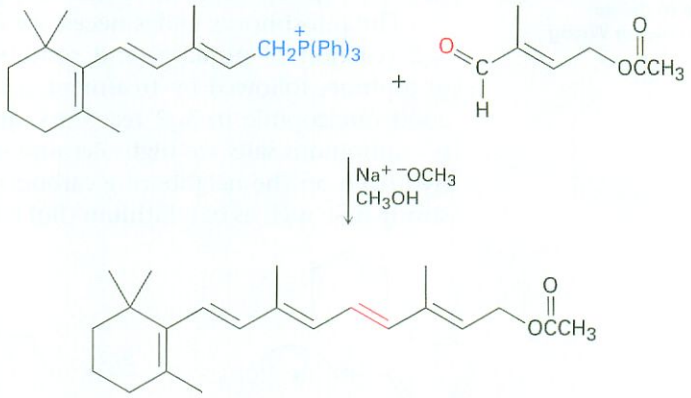
combination of phosphorane and aldehyde or ketone. Tetrasubstituted alkenes can't be prepared, however, because of steric hindrance during the reaction.

The real value of the Wittig reaction is that it yields a pure alkene of defined structure. The C=C bond in the product is always exactly where the C=O group was in the reactant, and no alkene isomers (except *E,Z* isomers) are formed. For example, Wittig reaction of cyclohexanone with methylenetriphenylphosphorane yields only the single alkene product methylenecyclohexane. By contrast, addition of methylmagnesium bromide to cyclohexanone, followed by dehydration with $POCl_3$, yields a roughly 9:1 mixture of two alkenes.



Methylenecyclohexane (84%)

Wittig reactions are used commercially in the synthesis of numerous pharmaceutical agents. For example, the German chemical company BASF prepares vitamin A by Wittig reaction between a 15-carbon ylide and a 5-carbon aldehyde.



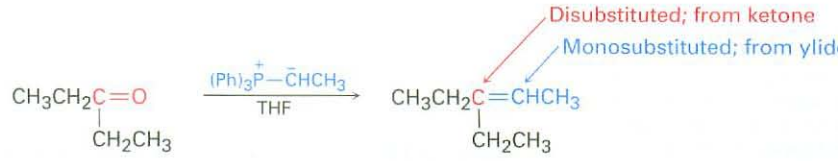
Vitamin A acetate

WORKED EXAMPLE 19.3 ***Synthesizing an Alkene Using a Wittig Reaction***

What carbonyl compound and what phosphorus ylide might you use to prepare 3-ethyl-2-pentene?

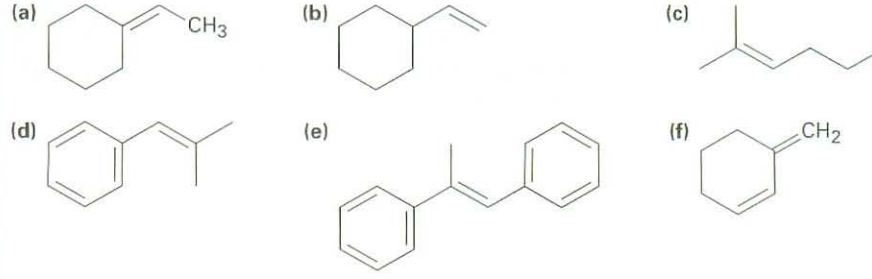
Strategy An aldehyde or ketone reacts with a phosphorus ylide to yield an alkene in which the oxygen atom of the carbonyl reactant is replaced by the $=CR_2$ of the ylide. Preparation of the phosphorus ylide itself usually involves S_N2 reaction of a primary alkyl halide with triphenylphosphine, so the ylide is typically primary, $RCH{=}P(Ph)_3$. This means that the disubstituted alkene carbon in the product comes from the carbonyl reactant, while the monosubstituted alkene carbon comes from the ylide.

Solution

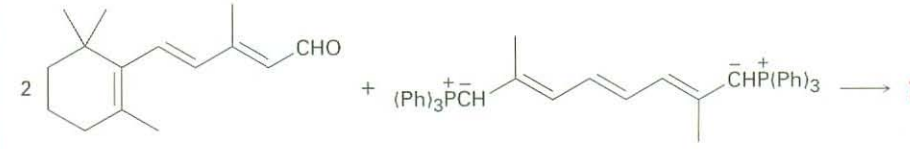


3-Pentanone **3-Ethyl-2-pentene**

Problem 19.16 What carbonyl compound and what phosphorus ylide might you use to prepare each of the following compounds?



Problem 19.17 β-Carotene, a yellow food-coloring agent and dietary source of vitamin A, can be prepared by a *double* Wittig reaction between 2 equivalents of β-ionylideneacetaldehyde and a *diylide*. Show the structure of the β-carotene product.



β-Ionylideneacetaldehyde **A diylide**

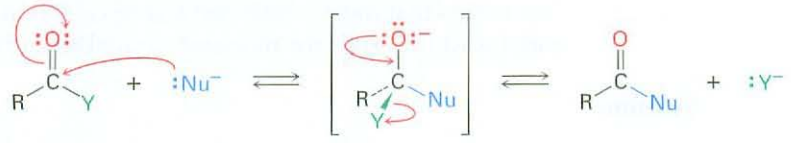
19.12 Biological Reductions

As a general rule, nucleophilic addition reactions are characteristic only of aldehydes and ketones, not of carboxylic acid derivatives. The reason for the difference is structural. As discussed previously in *A Preview of Carbonyl Compounds* and shown in Figure 19.14, the tetrahedral intermediate produced by addition of a nucleophile to a carboxylic acid derivative can eliminate a leaving group, leading to a net nucleophilic acyl substitution reaction. The tetrahedral intermediate

Stanislao Cannizzaro

Stanislao Cannizzaro (1826–1910) was born in Palermo, Sicily, the son of the chief of police. He studied at the University of Pisa under Rafaelle Piria and also worked in Paris with Michel-Eugène Chevreul. As a youth, he took part in the Sicilian revolution of 1848 and was at one point condemned to death. He was professor of chemistry at the universities of Genoa, Palermo, and Rome and is best known for being the first to clarify the distinction between atoms and molecules.

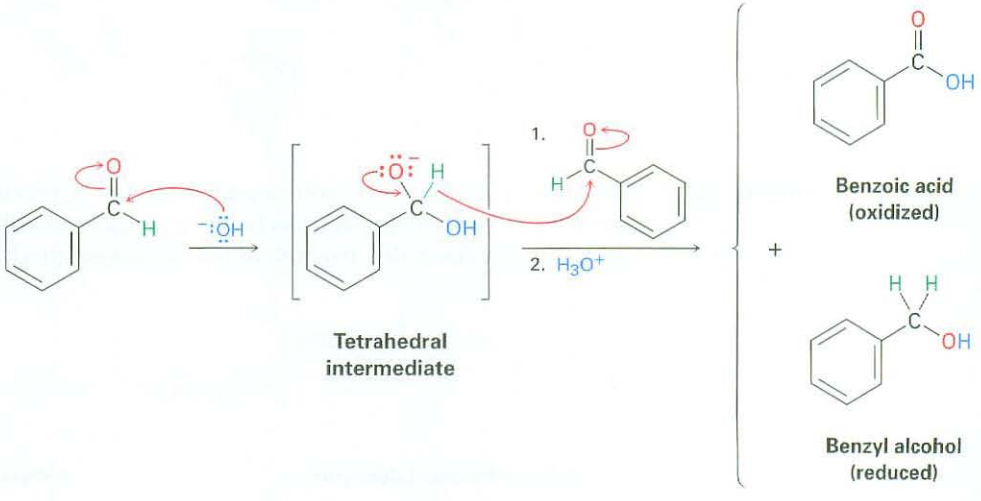
produced by addition of a nucleophile to an aldehyde or ketone, however, has only alkyl or hydrogen substituents and thus can't usually expel a leaving group. One exception to this rule, however, is the **Cannizzaro reaction**, discovered in 1853.



Reaction occurs when: Y = –Br, –Cl, –OR, $-NR_2$
Reaction *does NOT occur* when: Y = –H, –R

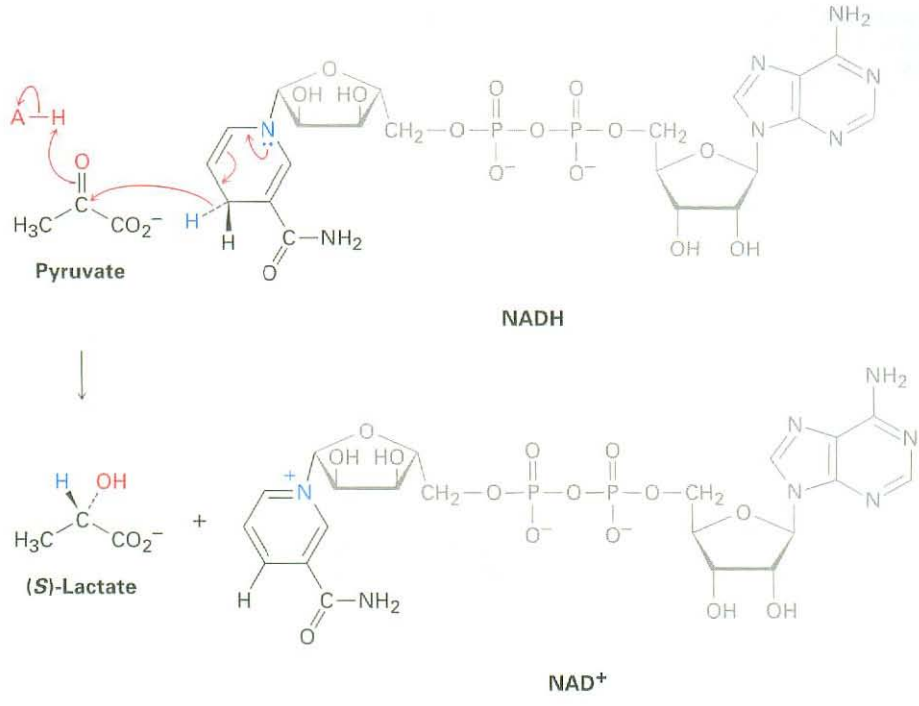
Figure 19.14 Carboxylic acid derivatives have an electronegative substituent Y = –Br, –Cl, –OR, $-NR_2$ that can be expelled as a leaving group from the tetrahedral intermediate formed by nucleophilic addition. Aldehydes and ketones have no such leaving group and thus do not usually undergo this reaction.

The Cannizzaro reaction takes place by nucleophilic addition of OH^- to an aldehyde to give a tetrahedral intermediate, *which expels hydride ion as a leaving group* and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced. Benzaldehyde, for instance, yields benzyl alcohol plus benzoic acid when heated with aqueous NaOH.

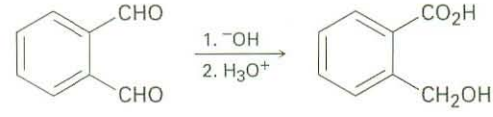


The Cannizzaro reaction has little use but is interesting mechanistically because it is a simple laboratory analogy for the primary biological pathway by which carbonyl reductions occur in living organisms. In nature, as we saw in Section 17.4, one of the most important reducing agents is NADH, reduced nicotinamide adenine dinucleotide. NADH donates H^- to aldehydes and ketones, thereby reducing them, in much the same way that the tetrahedral alkoxide intermediate in a Cannizzaro reaction does. The electron lone pair on a nitrogen atom of NADH expels H^- as leaving group, which adds to a carbonyl group in another molecule (Figure 19.15). As an example, pyruvate is converted during intense muscle activity to (*S*)-lactate, a reaction catalyzed by lactate dehydrogenase.

Figure 19.15 Mechanism of biological aldehyde and ketone reductions by the coenzyme NADH.



Problem 19.18 When *o*-phthalaldehyde is treated with base, *o*-(hydroxymethyl)benzoic acid is formed. Show the mechanism of this reaction.



o-Phthalaldehyde *o*-(Hydroxymethyl)benzoic acid

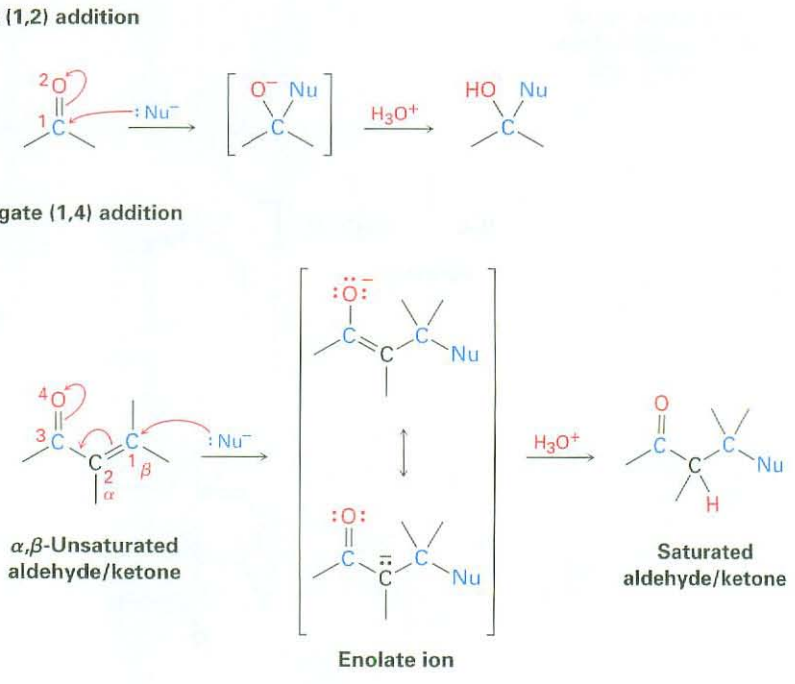
Problem 19.19 What is the stereochemistry of the pyruvate reduction shown in Figure 19.15? Does NADH lose its *pro-R* or *pro-S* hydrogen? Does addition occur to the *Si* face or *Re* face of pyruvate?

19.13 Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

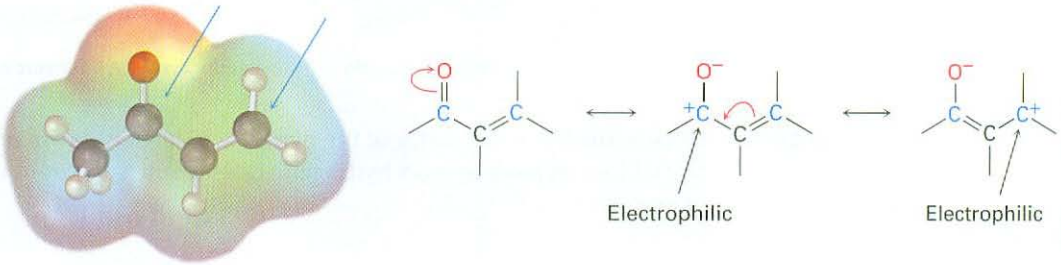
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of conjugate addition reactions.**

All the reactions we've been discussing to this point have involved the addition of a nucleophile directly to the carbonyl group, a so-called **1,2-addition**. Closely related to this direct addition is the **conjugate addition**, or **1,4-addition**, of a nucleophile to the C=C bond of an α,β-unsaturated aldehyde or ketone. (The carbon atom next to a carbonyl group is often called the α *carbon*, the next carbon is the β *carbon*, and so on. Thus, an *α,β-unsaturated* aldehyde or ketone has a double bond conjugated with the carbonyl group.) The initial product of conjugate addition is a resonance-stabilized *enolate ion*, which typically undergoes protonation on the α carbon to give a saturated aldehyde or ketone product (Figure 19.16).

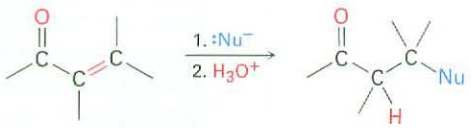
Figure 19.16 A comparison of direct (1,2) and conjugate (1,4) nucleophilic addition reactions.

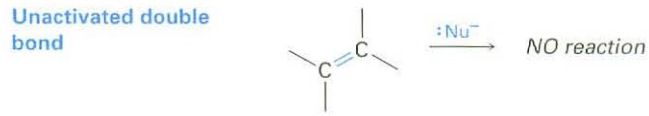


The conjugate addition of a nucleophile to an α,β-unsaturated aldehyde or ketone is caused by the same electronic factors that are responsible for direct addition. The electronegative oxygen atom of the α,β-unsaturated carbonyl compound withdraws electrons from the β carbon, thereby making it electron-poor and more electrophilic than a typical alkene carbon.



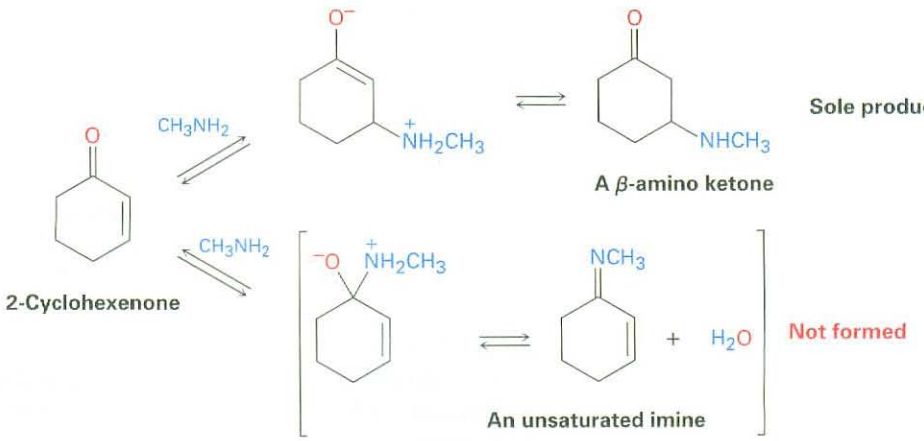
As noted previously, conjugate addition of a nucleophile to the β carbon of an α,β-unsaturated aldehyde or ketone leads to an enolate ion intermediate, which is protonated on the α carbon to give the saturated product (Figure 19.16). The net effect is addition of the nucleophile to the C=C bond, with the carbonyl group itself unchanged. In fact, of course, the carbonyl group is crucial to the success of the reaction. The C=C bond would not be activated for addition, and no reaction would occur, without the carbonyl group.





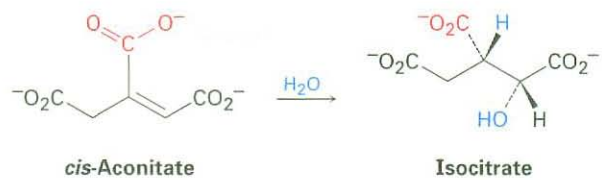
Conjugate Addition of Amines

Both primary and secondary amines add to α,β-unsaturated aldehydes and ketones to yield β-amino aldehydes and ketones rather than the alternative imines. Under typical reaction conditions, both modes of addition occur rapidly. But because the reactions are reversible, they generally proceed with thermodynamic control rather than kinetic control (Section 14.3), so the more stable conjugate addition product is often obtained to the complete exclusion of the less stable direct addition product.



Conjugate Addition of Water

Water can add reversibly to α,β-unsaturated aldehydes and ketones to yield β-hydroxy aldehydes and ketones, although the position of the equilibrium generally favors unsaturated reactant rather than saturated adduct. A related addition to an α,β-unsaturated carboxylic acid occurs in numerous biological pathways, such as the citric acid cycle of food metabolism where *cis*-aconitate is converted into isocitrate by conjugate addition of water to a double bond.



Problem 19.20 Assign *R* or *S* stereochemistry to the two chirality centers in isocitrate, and tell whether OH and H add to the *Si* face or the *Re* face of the double bond.

Conjugate Addition of Alkyl Groups: Organocopper Reactions

Conjugate addition of an alkyl group to an α,β-unsaturated ketone (but not aldehyde) is one of the more useful 1,4-addition reactions, just as direct addition of a Grignard reagent is one of the more useful 1,2-additions.

α,β-Unsaturated ketone

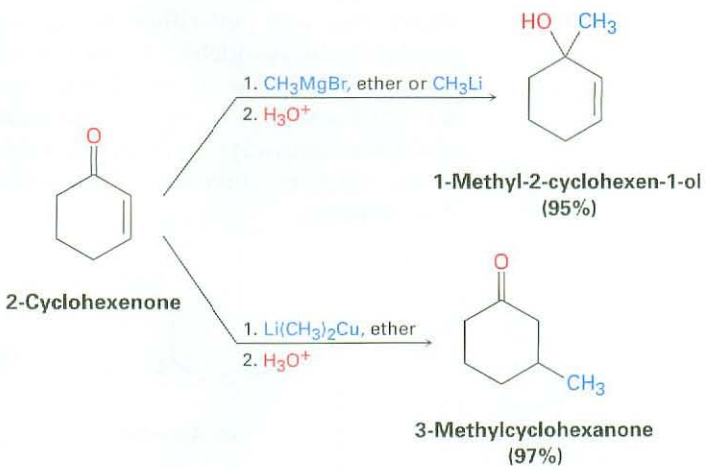
Conjugate addition of an alkyl group is carried out by treating the α,β-unsaturated ketone with a lithium diorganocopper reagent. As we saw in Section 10.8, diorganocopper (Gilman) reagents can be prepared by reaction between 1 equivalent of cuprous iodide and 2 equivalents of organolithium.

$$RX \xrightarrow[\text{Pentane}]{2\ Li} RLi + Li^+\ X^-$$

$$2\ RLi \xrightarrow[\text{Ether}]{CuI} Li^+(R\bar{C}uR) + Li^+\ I^-$$

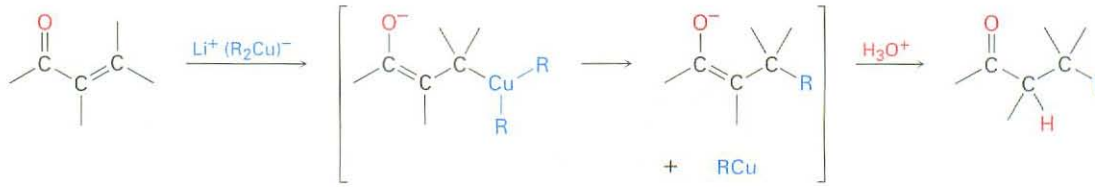
A lithium diorganocopper (Gilman reagent)

Primary, secondary, and even tertiary alkyl groups undergo the addition reaction, as do aryl and alkenyl groups. Alkynyl groups, however, react poorly in the conjugate addition process. Diorganocopper reagents are unique in their ability to give conjugate addition products. Other organometallic reagents, such as Grignard reagents and organolithiums, normally give direct carbonyl addition on reaction with α,β-unsaturated ketones.



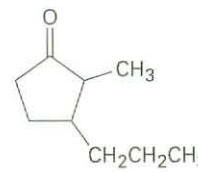
The mechanism of the reaction is thought to involve conjugate nucleophilic addition of the diorganocopper anion, R_2Cu^-, to the enone to give a

copper-containing intermediate. Transfer of an R group and elimination of a neutral organocopper species, RCu, gives the final product.



WORKED EXAMPLE 19.4 *Synthesis Using Conjugate Addition Reactions*

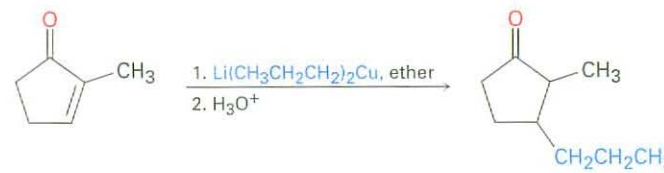
How might you use a conjugate addition reaction to prepare 2-methyl-3-propylcyclopentanone?



2-Methyl-3-propylcyclopentanone

Strategy A ketone with a substituent group in its β position might be prepared by a conjugate addition of that group to an α,β-unsaturated ketone. In the present instance, the target molecule has a propyl substituent on the β carbon and might therefore be prepared from 2-methyl-2-cyclopentenone by reaction with lithium dipropylcopper.

Solution



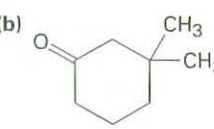
2-Methyl-2-cyclopentenone **2-Methyl-3-propylcyclopentanone**

Problem 19.21 Treatment of 2-cyclohexenone with HCN/KCN yields a saturated keto nitrile rather than an unsaturated cyanohydrin. Show the structure of the product, and propose a mechanism for the reaction.

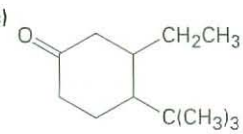
Problem 19.22 How might conjugate addition reactions of lithium diorganocopper reagents be used to synthesize the following compounds?

(a) $CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

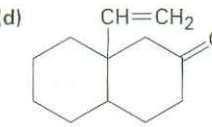
(b)



(c)



(d)



19.14 Spectroscopy of Aldehydes and Ketones

Infrared Spectroscopy

Aldehydes and ketones show a strong C=O bond absorption in the IR region from 1660 to 1770 cm^{-1}, as the spectra of benzaldehyde and cyclohexanone demonstrate (Figure 19.17). In addition, aldehydes show two characteristic C–H absorptions in the range 2720 to 2820 cm^{-1}.

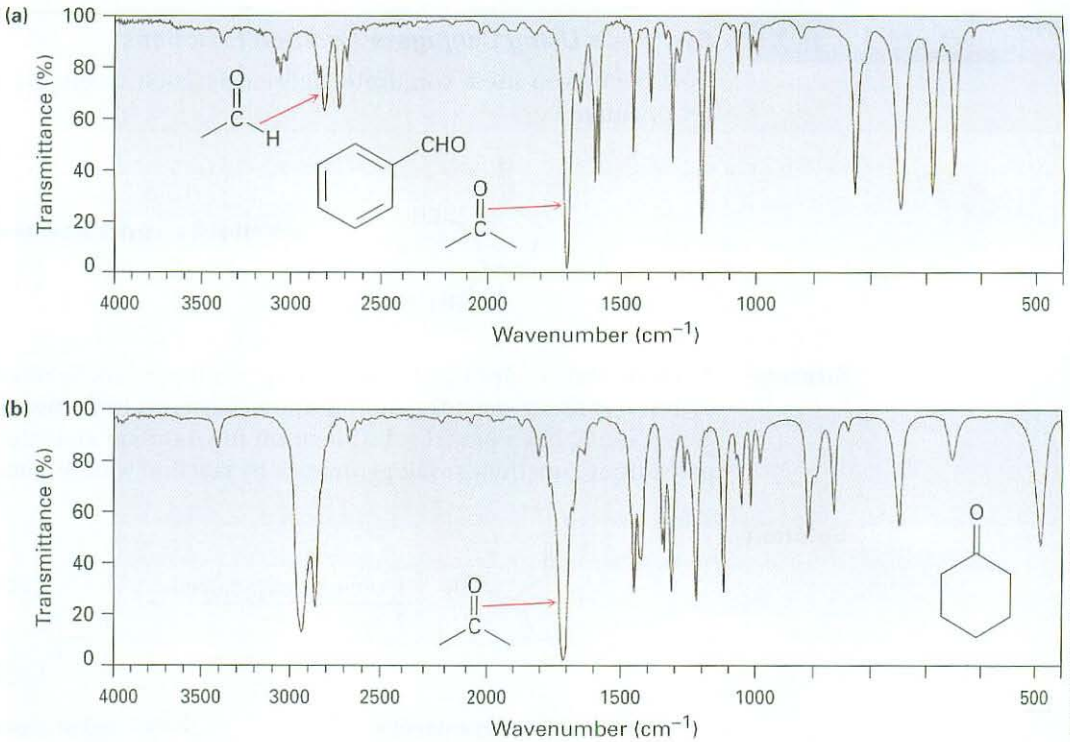


Figure 19.17 Infrared spectra of **(a)** benzaldehyde and **(b)** cyclohexanone.

The exact position of the C=O absorption is diagnostic of the nature of the carbonyl group. As the data in Table 19.2 indicate, saturated aldehydes usually show carbonyl absorptions near 1730 cm^{-1} in the IR spectrum, but conjugation of the aldehyde to an aromatic ring or a double bond lowers the absorption by 25 cm^{-1} to near 1705 cm^{-1}. Saturated aliphatic ketones and cyclohexanones both absorb near 1715 cm^{-1}, and conjugation with a double bond or an aromatic ring again lowers the absorption by 30 cm^{-1} to 1685 to 1690 cm^{-1}. Angle strain in the carbonyl group caused by reducing the ring size of cyclic ketones to four or five raises the absorption position.

The values given in Table 19.2 are remarkably constant from one aldehyde or ketone to another. As a result, IR spectroscopy is a powerful tool for identifying the kind of a carbonyl group in a molecule of unknown structure. An unknown that shows an IR absorption at 1730 cm^{-1} is almost certainly an aldehyde rather than a ketone; an unknown that shows an IR absorption at 1750 cm^{-1} is almost certainly a cyclopentanone, and so on.

Table 19.2 Infrared Absorptions of Some Aldehydes and Ketones

Carbonyl type	Example	Absorption (cm^{-1})
Saturated aldehyde	CH_3CHO	1730
Aromatic aldehyde	PhCHO	1705
α,β-Unsaturated aldehyde	$H_2C{=}CHCHO$	1705
Saturated ketone	CH_3COCH_3	1715
Cyclohexanone		1715
Cyclopentanone		1750
Cyclobutanone		1785
Aromatic ketone	$PhCOCH_3$	1690
α,β-Unsaturated ketone	$H_2C{=}CHCOCH_3$	1705

Problem 19.23 How might you use IR spectroscopy to determine whether reaction between 2-cyclohexenone and lithium dimethylcopper gives the direct addition product or the conjugate addition product?

Problem 19.24 Where would you expect each of the following compounds to absorb in the IR spectrum?

(a) 4-Penten-2-one
(b) 3-Penten-2-one
(c) 2,2-Dimethylcyclopentanone
(d) *m*-Chlorobenzaldehyde
(e) 3-Cyclohexenone
(f) 2-Hexenal

Nuclear Magnetic Resonance Spectroscopy

Aldehyde protons (RCHO) absorb near 10 δ in the ^1H NMR spectrum and are very distinctive because no other absorptions occur in this region. The aldehyde proton shows spin–spin coupling with protons on the neighboring carbon, with coupling constant $J \approx 3$ Hz. Acetaldehyde, for example, shows a quartet at 9.8 δ for the aldehyde proton, indicating that there are three protons neighboring the –CHO group (Figure 19.18).

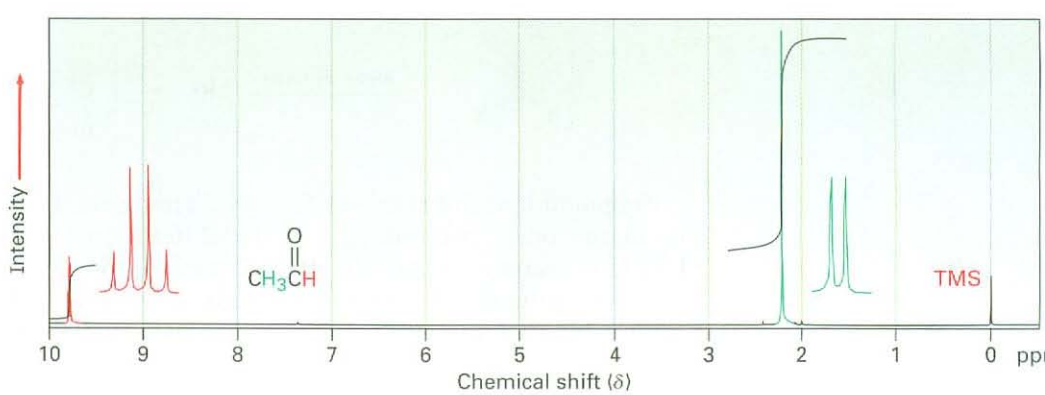
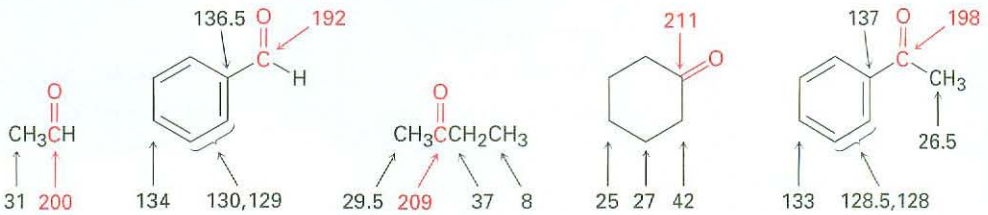


Figure 19.18 ^1H NMR spectrum of acetaldehyde. The absorption of the aldehyde proton appears at 9.8 δ and is split into a quartet.

Hydrogens on the carbon next to a carbonyl group are slightly deshielded and normally absorb near 2.0 to 2.3 δ. The acetaldehyde methyl group in Figure 19.18, for instance, absorbs at 2.20 δ. Methyl ketones are particularly distinctive because they always show a sharp three-proton singlet near 2.1 δ.

The carbonyl-group carbon atoms of aldehydes and ketones have characteristic ^{13}C NMR resonances in the range 190 to 215 δ. Since no other kinds of carbons absorb in this range, the presence of an NMR absorption near 200 δ is clear evidence for a carbonyl group. Saturated aldehyde or ketone carbons usually absorb in the region from 200 to 215 δ, while aromatic and α,β-unsaturated carbonyl carbons absorb in the 190 to 200 δ region.

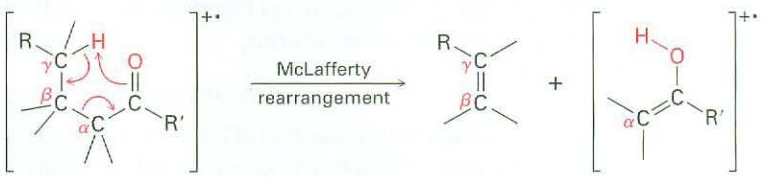


Mass Spectrometry

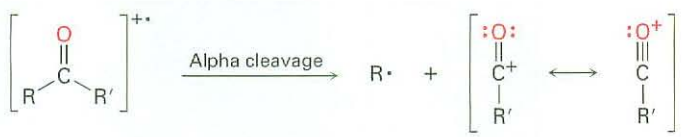
Fred Warren McLafferty

Fred Warren McLafferty (1923–) was born in Evanston, Illinois, and received his Ph.D. in 1950 at Cornell University. He was a scientist at the Dow Chemical Company from 1950 to 1964 before becoming professor of chemistry at Purdue University. In 1968, he returned to Cornell University as professor.

Aliphatic aldehydes and ketones that have hydrogens on their gamma (γ) carbon atoms undergo a characteristic mass spectral cleavage called the **McLafferty rearrangement**. A hydrogen atom is transferred from the γ carbon to the carbonyl oxygen, the bond between the α and β carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition to fragmentation by the McLafferty rearrangement, aldehydes and ketones also undergo cleavage of the bond between the carbonyl group and the α carbon, a so-called α cleavage. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.



Fragment ions from both McLafferty rearrangement and α cleavage are visible in the mass spectrum of 5-methyl-2-hexanone shown in Figure 19.19. McLafferty rearrangement with loss of 2-methylpropene yields a fragment with $m/z = 58$. Alpha cleavage occurs primarily at the more substituted side of the carbonyl group, leading to a $[CH_3CO]^+$ fragment with $m/z = 43$.

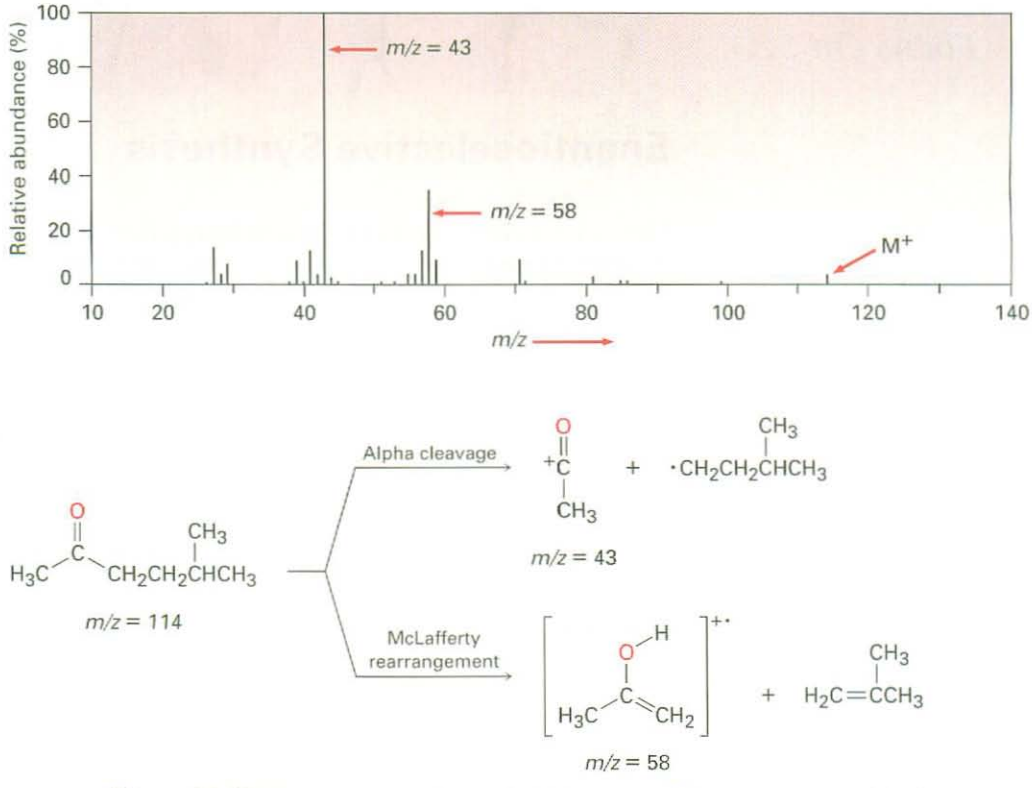


Figure 19.19 Mass spectrum of 5-methyl-2-hexanone. The peak at $m/z = 58$ is due to McLafferty rearrangement. The abundant peak at $m/z = 43$ is due to α cleavage at the more highly substituted side of the carbonyl group. Note that the peak due to the molecular ion is very small.

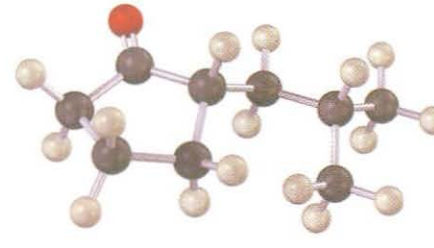
Problem 19.25 How might you use mass spectrometry to distinguish between the following pairs of isomers?

(a) 3-Methyl-2-hexanone and 4-methyl-2-hexanone

(b) 3-Heptanone and 4-heptanone

(c) 2-Methylpentanal and 3-methylpentanal

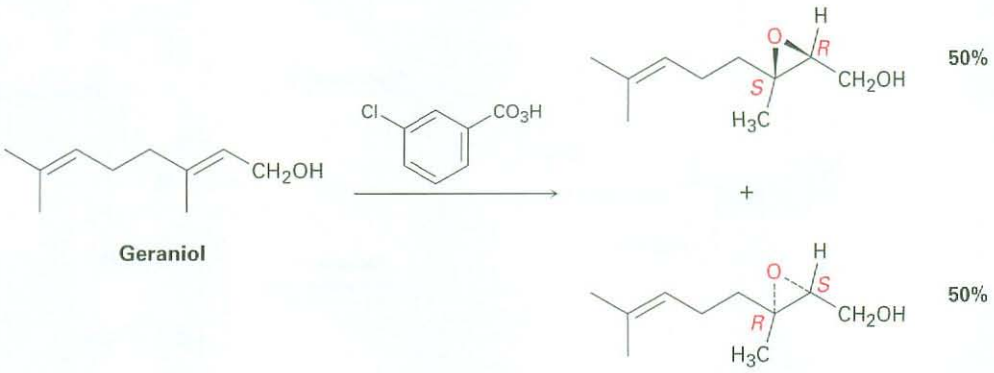
Problem 19.26 Tell the prominent IR absorptions and mass spectral peaks you would expect for the following compound:



Focus On . . .

Enantioselective Synthesis

Whenever a chiral product is formed by reaction between achiral reagents, the product is racemic; that is, both enantiomers of the product are formed in equal amounts. The epoxidation reaction of geraniol with *m*-chloroperoxybenzoic acid, for instance, gives a racemic mixture of (2*R*,3*S*) and (2*S*,3*R*) epoxides.

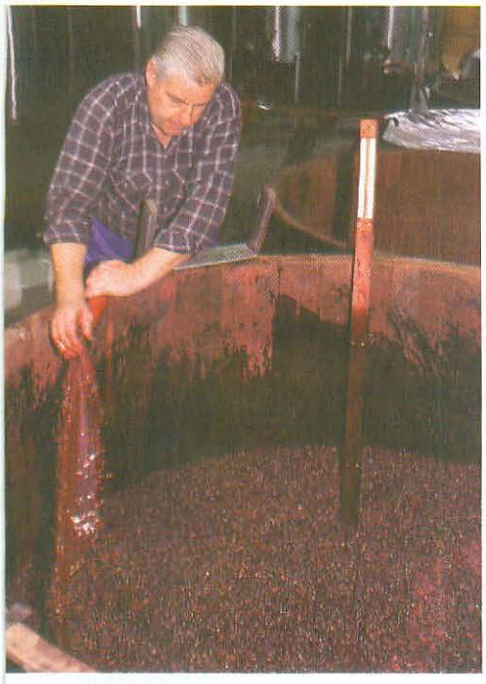


Geraniol

Unfortunately, it's usually the case that only a *single* enantiomer of a given drug or other important substance has the desired biological properties. The other enantiomer might be inactive or even dangerous. Thus, much work is currently being done on developing *enantioselective* methods of synthesis, which yield only one of two possible enantiomers. So important has enantioselective synthesis become that the 2001 Nobel Prize in chemistry was awarded to three pioneers in the field: William S. Knowles, K. Barry Sharpless, and Ryoji Noyori.

Several approaches to enantioselective synthesis have been taken, but the most efficient are those that use chiral catalysts to temporarily hold a substrate molecule in an unsymmetrical environment—exactly the same strategy that nature uses when catalyzing reactions with chiral enzymes. While in that unsymmetrical environment, the substrate may be more open to reaction on one side than on another, leading to an excess of one enantiomeric product over another. As an analogy, think about picking up a coffee mug in your

(continued)



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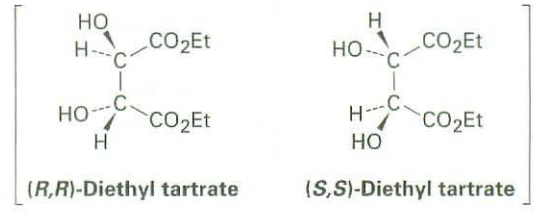
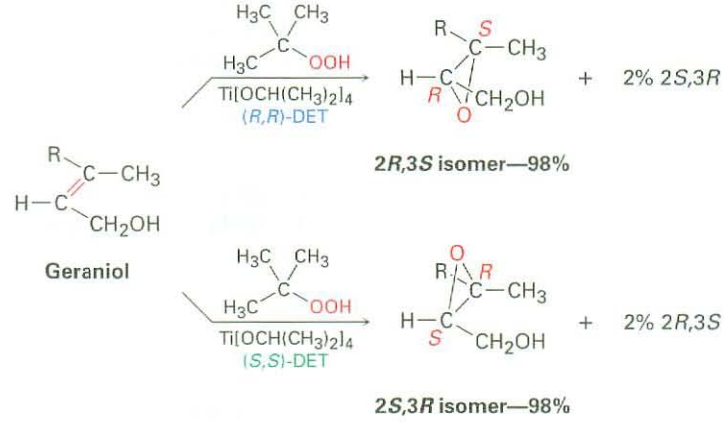
A substance made from the tartaric acid found at the bottom of this wine vat catalyzes enantioselective reactions.

right hand to take a drink. The mug by itself is achiral, but as soon as you pick it up by the handle, it becomes chiral. One side of the mug now faces toward you so you can drink from it, but the other side faces away. The two sides are different, with one side much more accessible to you than the other.

Among the many enantioselective reactions now known, one of the most general is the so-called Sharpless epoxidation, in which an allylic alcohol, such as geraniol, is treated with *tert*-butyl hydroperoxide, $(CH_3)_3C{-}OOH$, in the presence of titanium tetraisopropoxide and diethyl tartrate (DET) as a chiral auxiliary reagent. When the (*R*,*R*) tartrate is used, geraniol is converted into its 2*R*,3*S* epoxide with 98% selectivity, whereas use of the (*S*,*S*) tartrate gives the 2*S*,3*R* epoxide enantiomer. We say that the major product in each case is formed with an *enantiomeric excess* of 96%, meaning that 4% of the product is racemic (2% 2*R*,3*S* plus 2% 2*S*,3*R*) and an extra 96% of a single enantiomer is formed. The mechanistic details by which the chiral catalyst works are a bit complex, although it appears that a chiral complex of two tartrate molecules with one titanium is involved.





SUMMARY AND KEY WORDS

acetal [$R_2C(OR')_2$], 717
acyl group, 697
1,2-addition, 725
1,4-addition, 725
aldehyde (RCHO), 695
betaine, 720
Cannizzaro reaction, 724
carbanion, 708
conjugate addition, 725
cyanohydrin [RCH(OH)C≡N], 707
enamine ($R_2N-CR=CR_2$), 710
hemiacetal, 717
imine ($R_2C=NR$), 710
ketone ($R_2C=O$), 695
McLafferty rearrangement, 732
nucleophilic addition reaction, 702
Schiff base, 710
Wittig reaction, 720
Wolff–Kishner reaction, 715
ylide, 720

Aldehydes and ketones are among the most important of all compounds, both in biochemistry and in the chemical industry. Aldehydes are normally prepared in the laboratory by oxidation of primary alcohols or by partial reduction of esters. Ketones are similarly prepared by oxidation of secondary alcohols or by addition of diorganocopper reagents to acid chlorides.

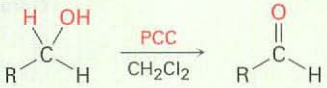
The **nucleophilic addition reaction** is the most common reaction of aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by $NaBH_4$ or $LiAlH_4$ to yield secondary and primary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones also gives alcohols (tertiary and secondary, respectively), and addition of HCN yields **cyanohydrins**. Primary amines add to carbonyl compounds yielding **imines**, and secondary amines yield **enamines**. Reaction of an aldehyde or ketone with hydrazine and base gives an alkane (the **Wolff–Kishner reaction**). Alcohols add to carbonyl groups to yield **acetals**, which are valuable as protecting groups. Phosphoranes add to aldehydes and ketones to give alkenes (the **Wittig reaction**) in which the new C=C bond in the product is exactly where the C=O bond was in the starting material.

α,β-Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4-addition**. Particularly useful is the reaction with a diorganocopper reagent, which results in the addition of an alkyl, aryl, or alkenyl group to the double bond.

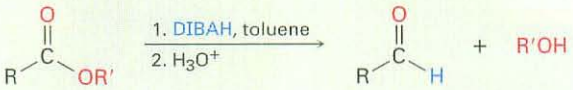
IR spectroscopy is helpful for identifying aldehydes and ketones. Carbonyl groups absorb in the IR range 1660 to 1770 cm^{-1}, with the exact position highly diagnostic of the kind of carbonyl group present in the molecule. ^{13}C NMR spectroscopy is also useful for aldehydes and ketones because their carbonyl carbons show resonances in the 190 to 215 δ range. ^1H NMR is useful for aldehyde −CHO protons, which absorb near 10 δ. Aldehydes and ketones undergo two characteristic kinds of fragmentation in the mass spectrometer: α cleavage and **McLafferty rearrangement**.

SUMMARY OF REACTIONS

1. Preparation of aldehydes (Section 19.2)
   (a) Oxidation of primary alcohols (Section 17.7)

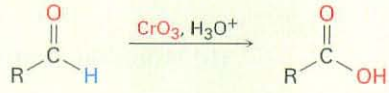


   (b) Partial reduction of esters (Section 19.2)

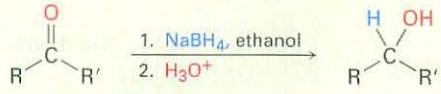


2. Preparation of ketones (Section 19.2)
   Diorganocopper reaction with acid chlorides

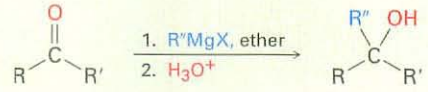
3. Reactions of aldehydes (Section 19.3)
   Oxidation to give carboxylic acids



4. Nucleophilic addition reactions of aldehydes and ketones
   (a) Addition of hydride: alcohols (Section 19.7)

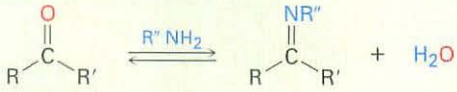


   (b) Addition of Grignard reagents: alcohols (Section 19.7)

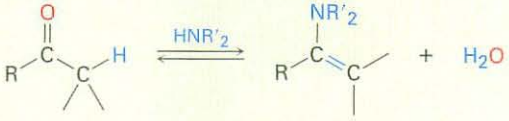


   (c) Addition of HCN: cyanohydrins (Section 19.6)

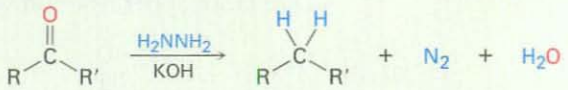
   (d) Addition of primary amines: imines (Section 19.8)



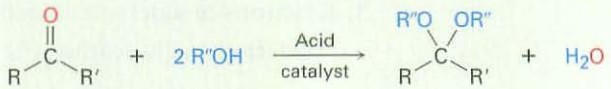
   (e) Addition of secondary amines: enamines (Section 19.8)



(f) Wolff–Kishner reaction (Section 19.9)



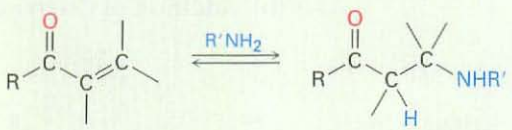
(g) Addition of alcohols: acetals (Section 19.10)



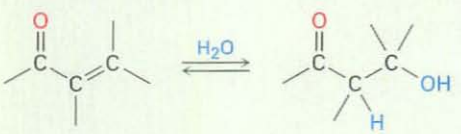
(h) Addition of phosphorus ylides: Wittig reaction (Section 19.11)

5. Conjugate additions to α,β-unsaturated aldehydes and ketones (Section 19.13)

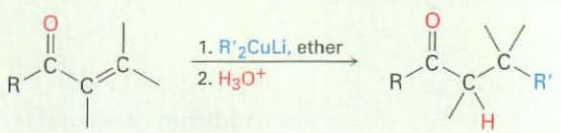
(a) Conjugate addition of amines



(b) Conjugate addition of water



(c) Conjugate addition of alkyl groups: diorganocopper reaction



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

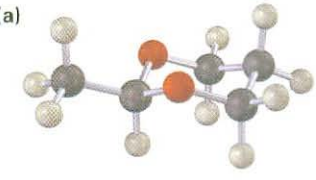
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

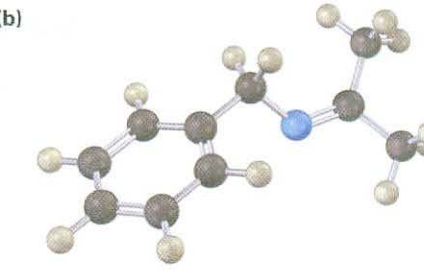
(Problems 19.1–19.26 appear within the chapter.)

19.27 ■ Each of the following substances can be prepared by a nucleophilic addition reaction between an aldehyde or ketone and a nucleophile. Identify the reactants from which each was prepared. If the substance is an acetal, identify the carbonyl compound and the alcohol; if it is an imine, identify the carbonyl compound and the amine; and so forth.

(a)



(b)



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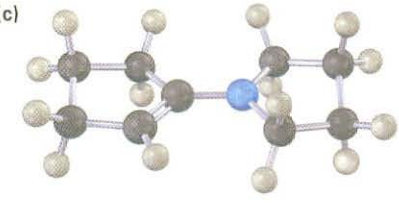

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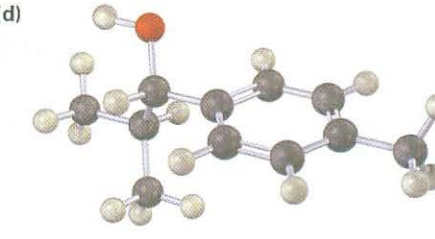
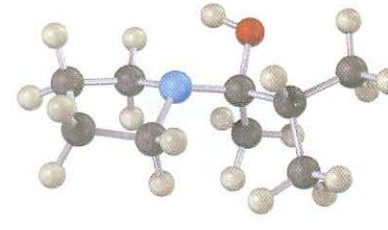


19.28 ■ The following molecular model represents a tetrahedral intermediate resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the structure of the final product when the nucleophilic addition reaction is complete.



19.29 The enamine prepared from acetone and dimethylamine is shown here in its lowest-energy form.

(a) What is the geometry and hybridization of the nitrogen atom?
(b) What orbital on nitrogen holds the lone pair of electrons?
(c) What is the geometric relationship between the *p* orbitals of the double bond and the nitrogen orbital that holds the lone pair? Why do you think this geometry represents the minimum energy?

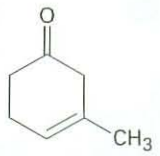
ADDITIONAL PROBLEMS

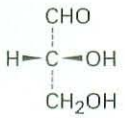
19.30 ■ Draw structures corresponding to the following names:

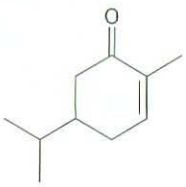
(a) Bromoacetone
(b) (*S*)-2-Hydroxypropanal
(c) 2-Methyl-3-heptanone
(d) (2*S*,3*R*)-2,3,4-Trihydroxybutanal
(e) 2,2,4,4-Tetramethyl-3-pentanone
(f) 4-Methyl-3-penten-2-one
(g) Butanedial
(h) 3-Phenyl-2-propenal
(i) 6,6-Dimethyl-2,4-cyclohexadienone
(j) *p*-Nitroacetophenone

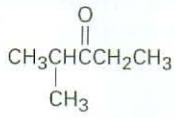
19.31 ■ Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$. Which are chiral?

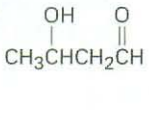
19.32 Give IUPAC names for the following structures:

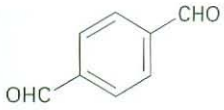
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

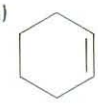
19.33 Give structures that fit the following descriptions:

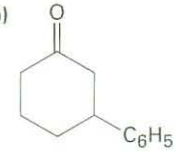
(a) An α,β-unsaturated ketone, C_6H_8O
(b) An α-diketone
(c) An aromatic ketone, $C_9H_{10}O$
(d) A diene aldehyde, C_7H_8O

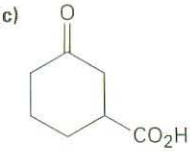
19.34 ■ Predict the products of the reaction of (i) phenylacetaldehyde and (ii) acetophenone with the following reagents:

(a) $NaBH_4$, then H_3O^+
(b) Tollens' reagent
(c) NH_2OH, HCl catalyst
(d) CH_3MgBr, then H_3O^+
(e) 2 CH_3OH, HCl catalyst
(f) H_2NNH_2, KOH
(g) $(C_6H_5)_3P{=}CH_2$
(h) HCN, KCN

19.35 ■ How would you prepare the following substances from 2-cyclohexenone? More than one step may be required.

(a) 

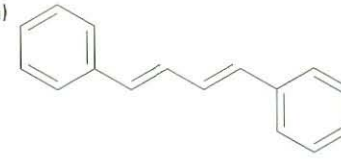
(b) 

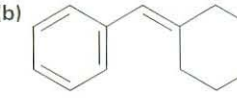
(c) 

(d) 

(Two ways)

19.36 ■ Show how the Wittig reaction might be used to prepare the following alkenes. Identify the alkyl halide and the carbonyl components that would be used.

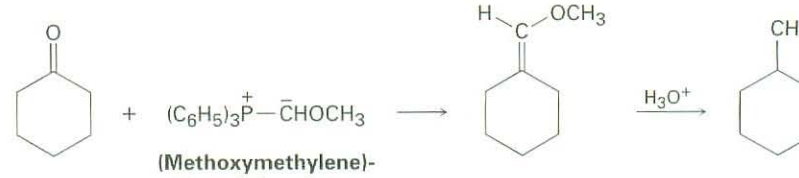
(a) 

(b) 

19.37 ■ How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

(a) 2-Pentanol
(b) 1-Butanol
(c) 1-Phenylcyclohexanol
(d) Diphenylmethanol

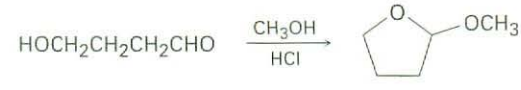
19.38 Aldehydes can be prepared by the Wittig reaction using (methoxymethylene)-triphenylphosphorane as the Wittig reagent and then hydrolyzing the product with acid. For example,



(Methoxymethylene)-triphenylphosphorane

(a) How would you prepare the necessary phosphorane?
(b) Propose a mechanism for the hydrolysis step.

19.39 When 4-hydroxybutanal is treated with methanol in the presence of an acid catalyst, 2-methoxytetrahydrofuran is formed. Explain.



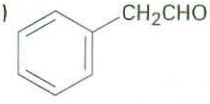
■ Assignable in OWL

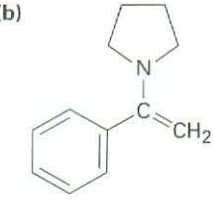
19.40 ■ How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 19.5 that aldehydes are more reactive than ketones toward nucleophilic addition.)

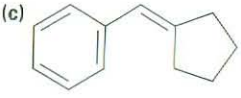
(a) $CH_3CCH_2CH_2CH_2CH \longrightarrow CH_3CCH_2CH_2CH_2CH_2OH$

(b) $CH_3CCH_2CH_2CH_2CH \longrightarrow CH_3CHCH_2CH_2CH_2CH$

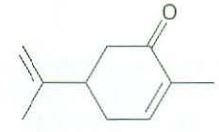
19.41 ■ How would you synthesize the following substances from benzaldehyde and any other reagents needed?

(a) 

(b) 

(c) 

19.42 ■ Carvone is the major constituent of spearmint oil. What products would you expect from reaction of carvone with the following reagents?



Carvone

(a) $(CH_3)_2Cu^-\ Li^+$, then H_3O^+
(b) $LiAlH_4$, then H_3O^+
(c) CH_3NH_2
(d) C_6H_5MgBr, then H_3O^+
(e) H_2/Pd
(f) CrO_3, H_3O^+
(g) $(C_6H_5)_3\overset{+}{P}\overset{-}{C}HCH_3$
(h) $HOCH_2CH_2OH$, HCl

19.43 The S_N2 reaction of (dibromomethyl)benzene, $C_6H_5CHBr_2$, with NaOH yields benzaldehyde rather than (dihydroxymethyl)benzene, $C_6H_5CH(OH)_2$. Explain.

19.44 Reaction of 2-butanone with HCN yields a chiral product. What stereochemistry does the product have? Is it optically active?

19.45 ■ How would you synthesize the following compounds from cyclohexanone?

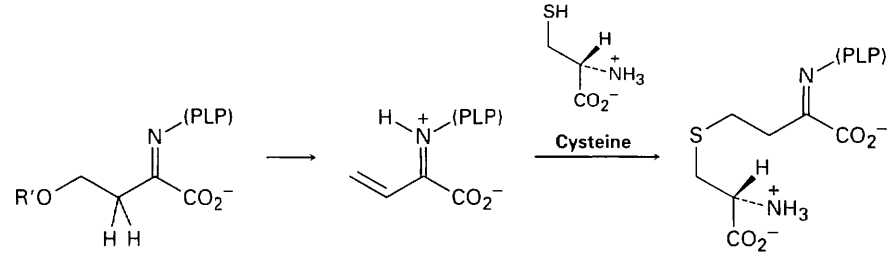
(a) 1-Methylcyclohexene
(b) 2-Phenylcyclohexanone
(c) *cis*-1,2-Cyclohexanediol
(d) 1-Cyclohexylcyclohexanol

19.46 One of the steps in the metabolism of fats is the reaction of an unsaturated acyl CoA with water to give a β-hydroxyacyl CoA. Propose a mechanism.

$$RCH_2CH_2CH{=}CHCSCoA \xrightarrow{H_2O} RCH_2CH_2CH(OH){-}CH_2CSCoA$$

Unsaturated acyl CoA → **β-Hydroxyacyl CoA**

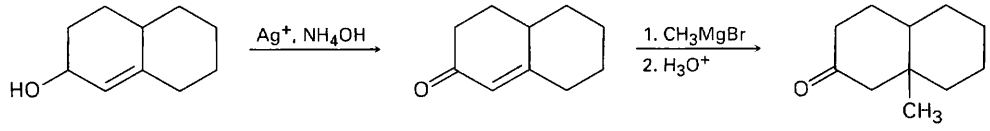
19.47 The amino acid methionine is biosynthesized by a multistep route that includes reaction of an imine of pyridoxal phosphate (PLP) to give an unsaturated imine, which then reacts with cysteine. What kinds of reactions are occurring in the two steps?



***O*-Succinylhomoserine–PLP imine** **Unsaturated imine**

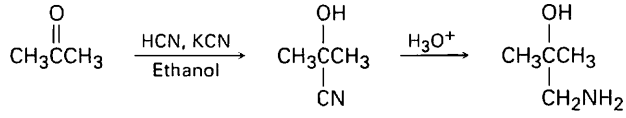
19.48 Each of the following reaction schemes contains one or more flaws. What is wrong in each case? How would you correct each scheme?

(a)

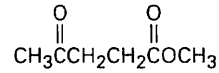


(b) $C_6H_5CH{=}CHCH_2OH \xrightarrow[H_3O^+]{CrO_3} C_6H_5CH{=}CHCHO \xrightarrow{H^+,\ CH_3OH} C_6H_5CH{=}CHCH(OCH_3)_2$

(c)

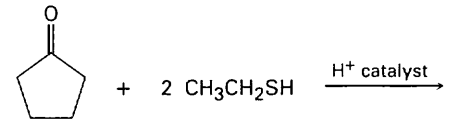


19.49 6-Methyl-5-hepten-2-one is a constituent of lemongrass oil. How could you synthesize this substance from methyl 4-oxopentanoate?

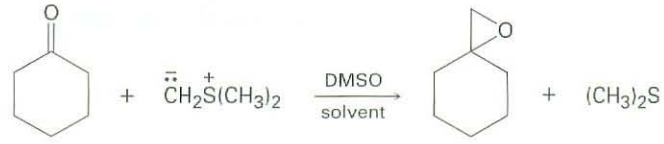


Methyl 4-oxopentanoate

19.50 Aldehydes and ketones react with thiols to yield *thioacetals* just as they react with alcohols to yield acetals. Predict the product of the following reaction, and propose a mechanism:

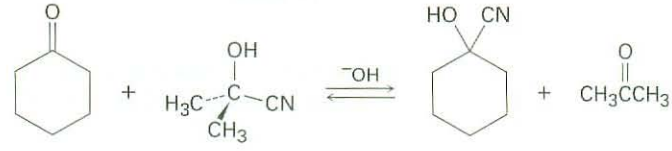


19.51 ■ Ketones react with dimethylsulfonium methylide to yield epoxides. Suggest a mechanism for the reaction.

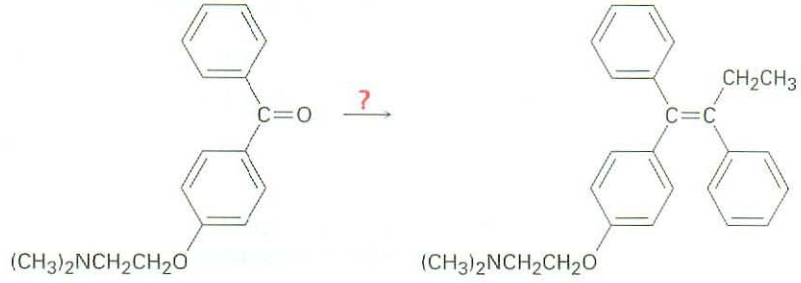


Dimethylsulfonium methylide

19.52 ■ When cyclohexanone is heated in the presence of a large amount of acetone cyanohydrin and a small amount of base, cyclohexanone cyanohydrin and acetone are formed. Propose a mechanism.

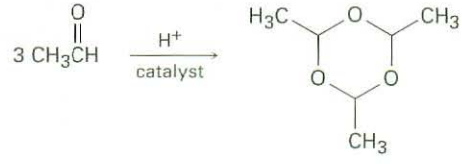


19.53 Tamoxifen is a drug used in the treatment of breast cancer. How would you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?



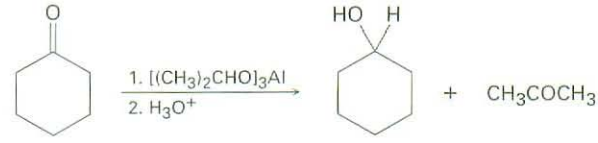
Tamoxifen

19.54 Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism for the reaction.

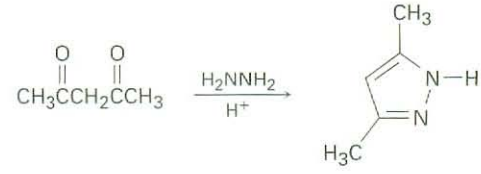


Paraldehyde

19.55 The Meerwein–Ponndorf–Verley reaction involves reduction of a ketone by treatment with an excess of aluminum triisopropoxide. The mechanism of the process is closely related to the Cannizzaro reaction in that a hydride ion acts as a leaving group. Propose a mechanism.

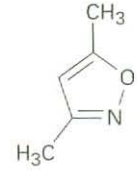


19.56 Propose a mechanism to account for the formation of 3,5-dimethylpyrazole from hydrazine and 2,4-pentanedione. Look carefully to see what has happened to each carbonyl carbon in going from starting material to product.



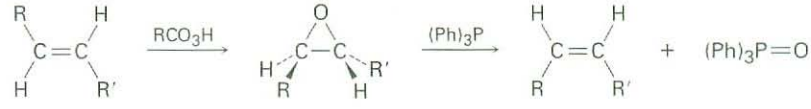
2,4-Pentanedione **3,5-Dimethylpyrazole**

19.57 In light of your answer to Problem 19.56, propose a mechanism for the formation of 3,5-dimethylisoxazole from hydroxylamine and 2,4-pentanedione.

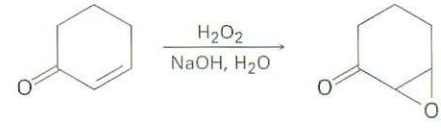


3,5-Dimethylisoxazole

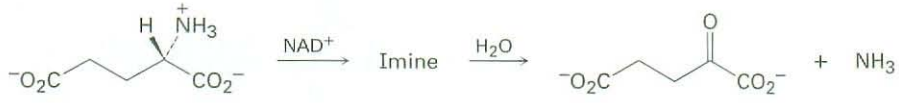
19.58 ■ Trans alkenes are converted into their cis isomers and vice versa on epoxidation followed by treatment of the epoxide with triphenylphosphine. Propose a mechanism for the epoxide → alkene reaction.



19.59 ■ Treatment of an α,β-unsaturated ketone with basic aqueous hydrogen peroxide yields an epoxy ketone. The reaction is specific to unsaturated ketones; isolated alkene double bonds do not react. Propose a mechanism.



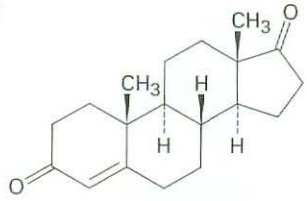
19.60 ■ One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) oxidation of the amine by NAD^+ to give an imine, and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α-ketoglutarate. Show the structure of the imine intermediate, and propose mechanisms for both steps.



Glutamate **α-Ketoglutarate**

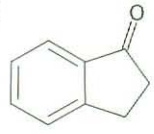
19.61 At what position would you expect to observe IR absorptions for the following molecules?

(a)



4-Androstene-3,17-dione

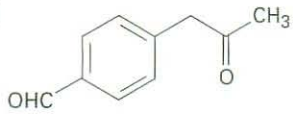
(b)



1-Indanone

(c)

(d)

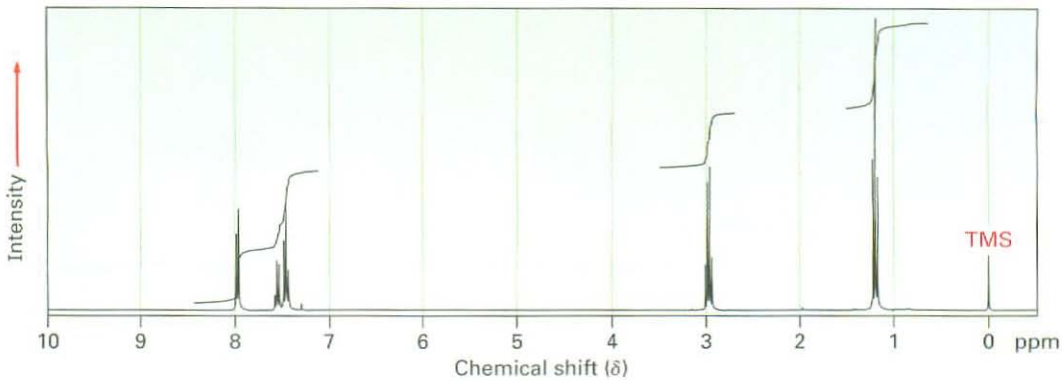


19.62 Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What possible structures are there for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{-1}, what is its structure?

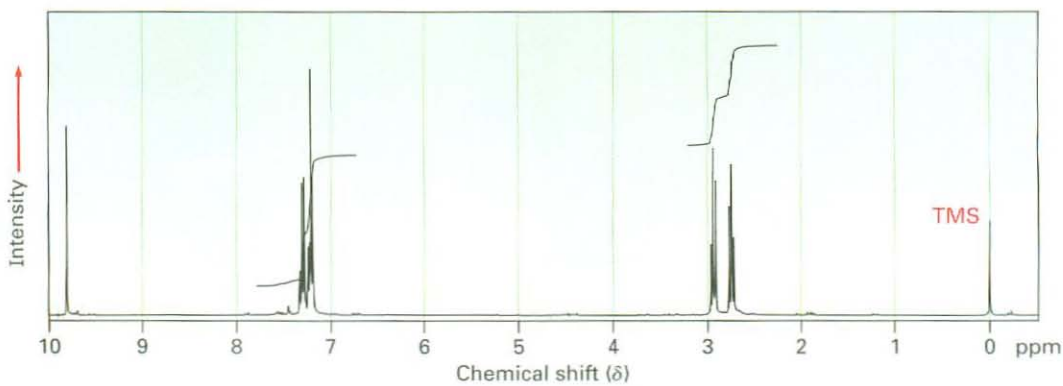
19.63 ■ Compound A, MW = 86, shows an IR absorption at 1730 cm^{-1} and a very simple ^1H NMR spectrum with peaks at 9.7 δ (1 H, singlet) and 1.2 δ (9 H, singlet). Propose a structure for A.

19.64 ■ Compound B is isomeric with A (Problem 19.63) and shows an IR peak at 1715 cm^{-1}. The ^1H NMR spectrum of B has peaks at 2.4 δ (1 H, septet, J = 7 Hz), 2.1 δ (3 H, singlet), and 1.2 δ (6 H, doublet, J = 7 Hz). What is the structure of B?

19.65 ■ The ^{1}H NMR spectrum shown is that of a compound with formula $C_9H_{10}O$. How many double bonds and/or rings does this compound contain? If the unknown has an IR absorption at 1690 cm^{-1}, what is a likely structure?



19.66 The ^{1}H NMR spectrum shown is that of a compound isomeric with the one in Problem 19.65. This isomer has an IR absorption at 1730 cm^{-1}. Propose a structure. [Note: Aldehyde protons (CHO) often show low coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]



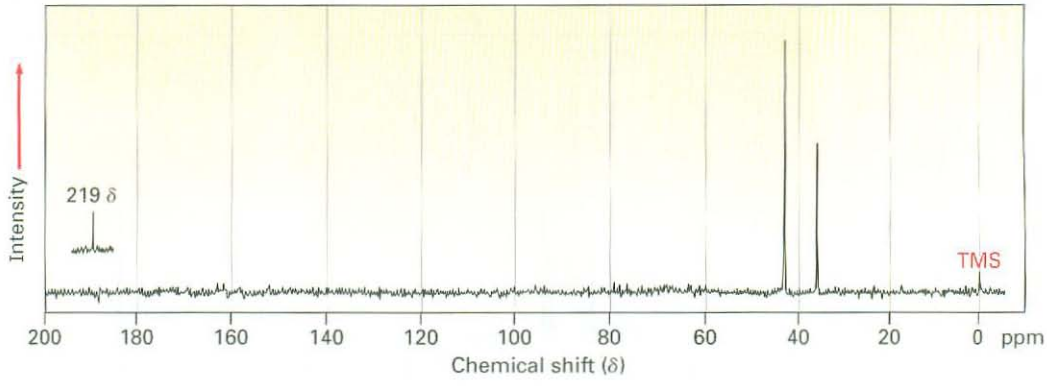
19.67 ■ Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT-NMR.

(a) $C_6H_{12}O$; IR: 1715 cm^{-1}; ^{13}C NMR: 8.0 δ (1°), 18.5 δ (1°), 33.5 δ (2°), 40.6 δ (3°), 214.0 δ (4°)

(b) $C_5H_{10}O$; IR: 1730 cm^{-1}; ^{13}C NMR: 22.6 δ (1°), 23.6 δ (3°), 52.8 δ (2°), 202.4 δ (3°)

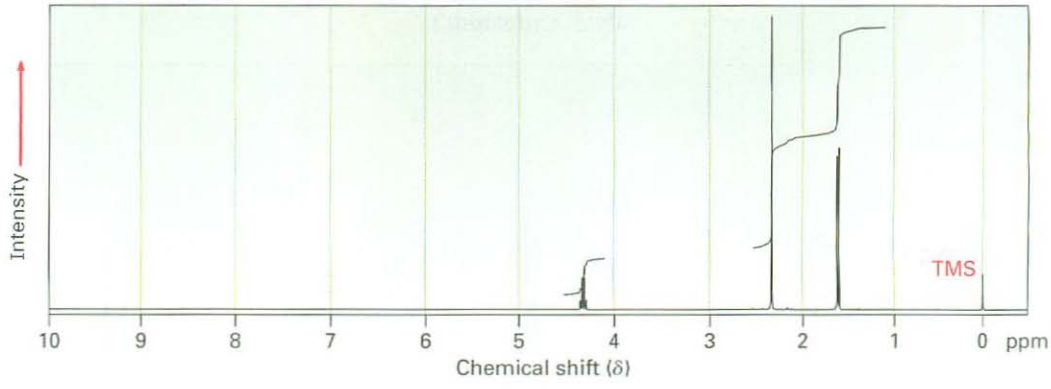
(c) C_6H_8O; IR: 1680 cm^{-1}; ^{13}C NMR: 22.9 δ (2°), 25.8 δ (2°), 38.2 δ (2°), 129.8 δ (3°), 150.6 δ (3°), 198.7 δ (4°)

19.68 Compound A, $C_8H_{10}O_2$, has an intense IR absorption at 1750 cm^{-1} and gives the ^{13}C NMR spectrum shown. Propose a structure for A.

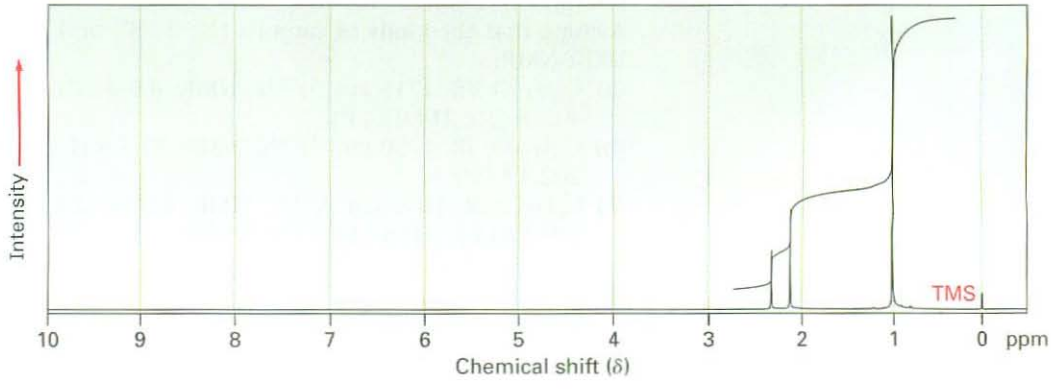


19.69 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

(a) C_4H_7ClO
IR: 1715 cm^{-1}

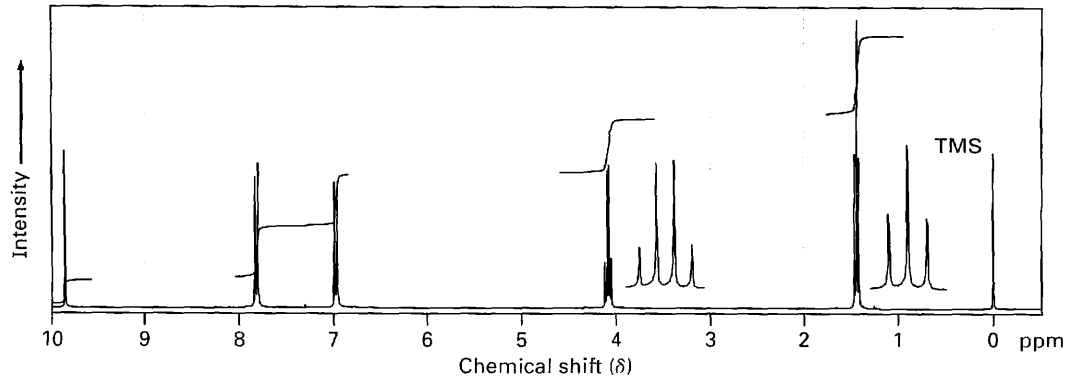


(b) $C_7H_{14}O$
IR: 1710 cm^{-1}



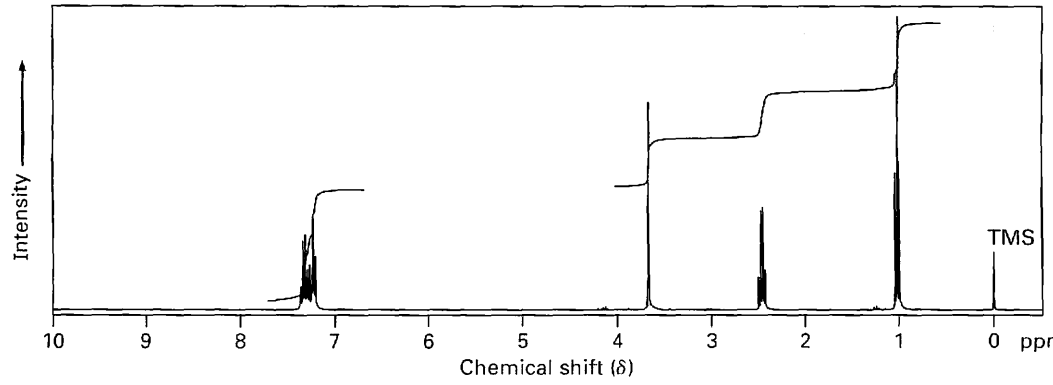
■ Assignable in OWL

(c) $C_9H_{10}O_2$
IR: 1695 cm^{-1}

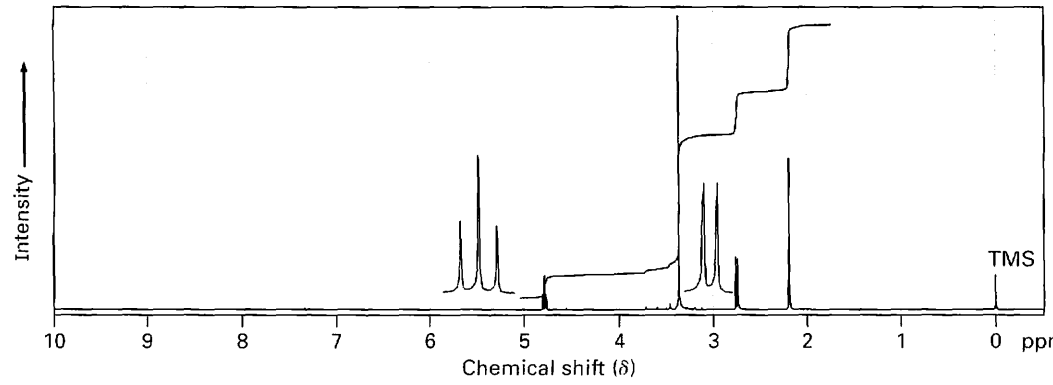


19.70 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra.

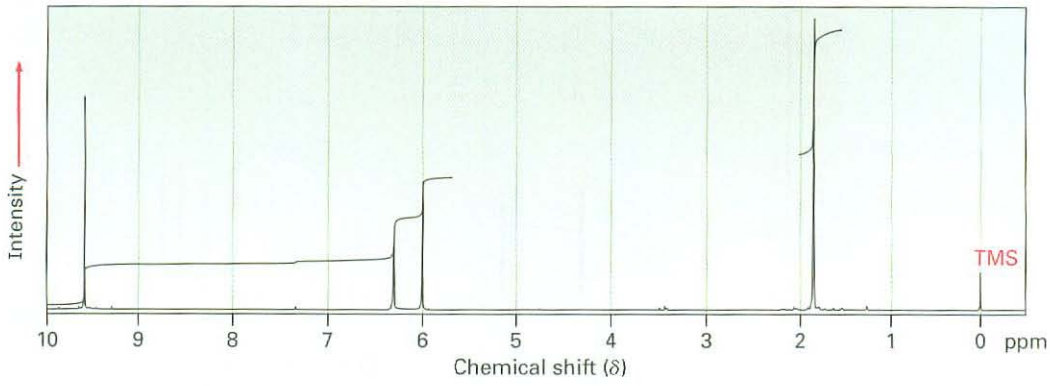
(a) $C_{10}H_{12}O$
IR: 1710 cm^{-1}



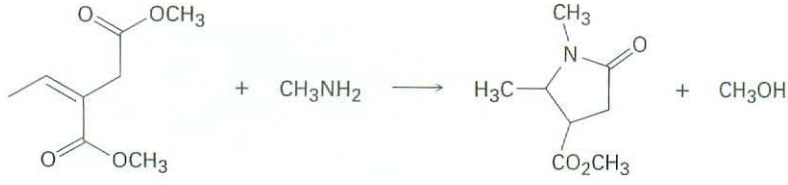
(b) $C_6H_{12}O_3$
IR: 1715 cm^{-1}



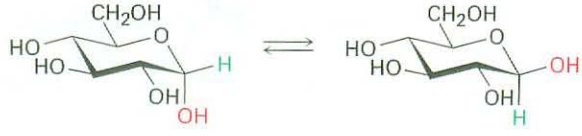
(c) C_4H_6O
IR: 1690 cm^{-1}



19.71 Primary amines react with esters to yield amides: $RCO_2R' + R''NH_2 \rightarrow RCONHR'' + R'OH$. Propose a mechanism for the following reaction of an α,β-unsaturated ester.

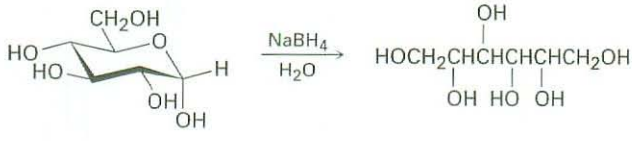


19.72 When crystals of pure α-glucose are dissolved in water, isomerization slowly occurs to produce β-glucose. Propose a mechanism for the isomerization.



α-Glucose **β-Glucose**

19.73 When glucose (Problem 19.72) is treated with $NaBH_4$, reaction occurs to yield *sorbitol*, a polyalcohol commonly used as a food additive. Show how this reduction occurs.



Glucose **Sorbitol**