Organic Chemistry, *Fourth Edition*

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Chapter 21
Lecture Outline

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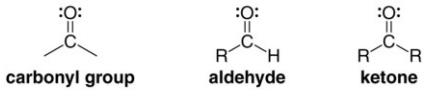
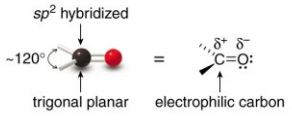
Aldehydes and Ketones

- **Aldehydes and ketones contain a carbonyl group.**
- **An aldehyde contains at least one H atom bonded to the carbonyl carbon, whereas the ketone has two alkyl or aryl groups bonded to it.**



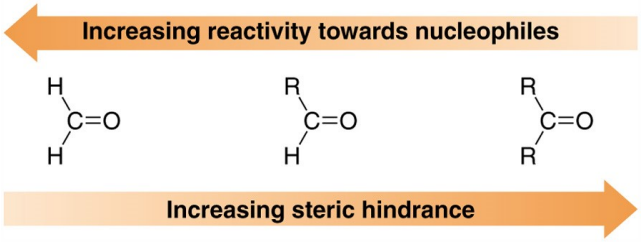
- **Two structural features determine the chemistry and properties of aldehydes and ketones.**



- The carbonyl group is sp^2 hybridized and trigonal planar, making it relatively uncrowded.
- The electronegative oxygen atom polarizes the carbonyl group, making the carbonyl carbon electrophilic.

Reactions of Aldehydes and Ketones

- **Aldehydes and ketones react with nucleophiles.**
- **As the number of R groups around the carbonyl carbon increases, the reactivity of the carbonyl compound decreases, resulting in the following order of reactivity:**



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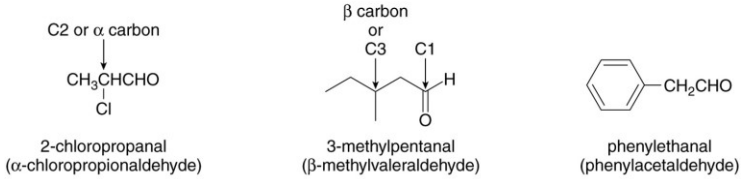
Nomenclature of Aldehydes

- **If the CHO is bonded to a chain of carbons, find the longest chain containing the CHO group, and change the –e ending of the parent alkane to the suffix *–al*.**
- **If the CHO group is bonded to a ring, name the ring and add the suffix *–carbaldehyde*.**
- **Number the chain or ring to put the CHO group at C1, but omit this number from the name.**
- **Apply all the other usual rules of nomenclature.**

Figure 21.1



(Common names are in parentheses.)

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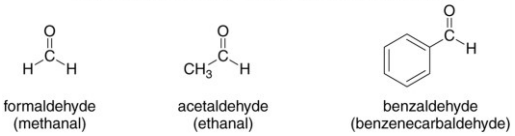
Common Names of Aldehydes

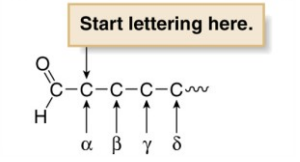
- **Like carboxylic acids, many simple aldehydes have common names that are widely used.**
- **A common name for an aldehyde is formed by taking the common parent name and adding the suffix *–aldehyde*.**



formaldehyde (methanal) | acetaldehyde (ethanal) | benzaldehyde (benzenecarbaldehyde)

(IUPAC names are in parentheses.)

- **Greek letters are used to designate the location of substituents in common names.**



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Nomenclature of Ketones

- **In the IUPAC system, all ketones are identified by the suffix "one".**
- **Find the longest continuous chain containing the carbonyl group, and change the *–e* ending of the parent alkane to the suffix *-one*.**
- **Number the carbon chain to give the carbonyl carbon the lowest number.**
- **Apply all of the usual rules of nomenclature.**
- **With cyclic ketones, numbering always begins at the carbonyl carbon, but the "1" is usually omitted from the name.**
- **The ring is then numbered clockwise or counterclockwise to give the first substituent the lower number.**

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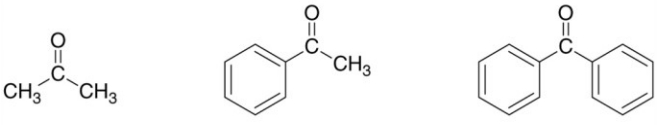
Common Names of Ketones

- **Most common names for ketones are formed by naming both alkyl groups on the carbonyl carbon, arranging them alphabetically, and adding the word "ketone".**

IUPAC name: **2-butanone** Common name: **ethyl methyl ketone**

- **Three widely used common names for some simple ketones do not follow this convention:**



acetone acetophenone benzophenone

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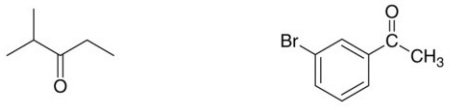
Naming Ketones and Acyl Groups

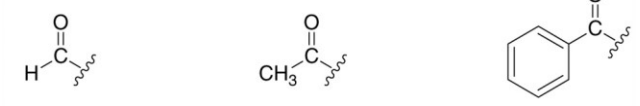
Figure 21.2



IUPAC name: 2-methyl-3-pentanone
Common name: ethyl isopropyl ketone

m-bromoacetophenone
or
3-bromoacetophenone

- **Sometimes, acyl groups must be named as substituents.**
- **The three most common acyl groups are shown below:**



formyl group acetyl group benzoyl group benzyl group

Do not confuse a **benzyl** group with a **benzoyl** group.

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Naming Enals and Enones

- **Compounds containing both a C-C double bond and an aldehyde are named as enals.**
- **Compounds that contain both a C-C double bond and a ketone are named as enones.**
- **The chain is numbered to give the carbonyl the lower number.**

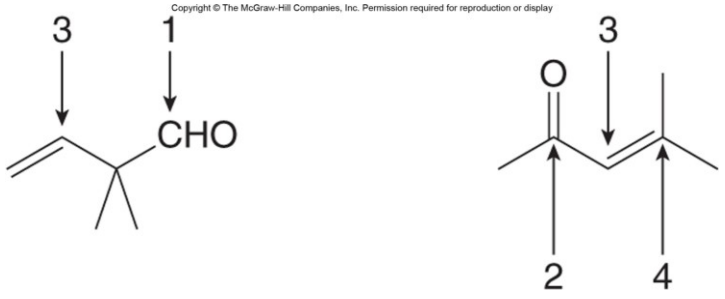

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Table 21.1 Physical Properties of Aldehydes and Ketones

Property	Observation
Boiling point and melting point	• For compounds of comparable molecular weight, bp's and mp's follow the usual trend: The stronger the intermolecular forces, the higher the bp or mp. $CH_3CH_2CH_2CH_2CH_3$ VDW MW = 72 bp 36 °C $CH_3CH_2CH_2CHO$ VDW, DD MW = 72 bp 76 °C $CH_3CH_2COCH_3$ VDW, DD MW = 72 bp 80 °C $CH_3CH_2CH_2CH_2OH$ VDW, DD, HB MW = 74 bp 118 °C Increasing strength of intermolecular forces Increasing boiling point
Solubility	• RCHO and RCOR are soluble in organic solvents regardless of size. • RCHO and RCOR having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • RCHO and RCOR having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

- **Aldehydes and ketones have strong dipoles, but lack hydrogen bonding, resulting in boiling points between nonpolar molecules and alcohols of similar size.**
- **Water solubility mimics that of alcohols and ethers of similar size.**

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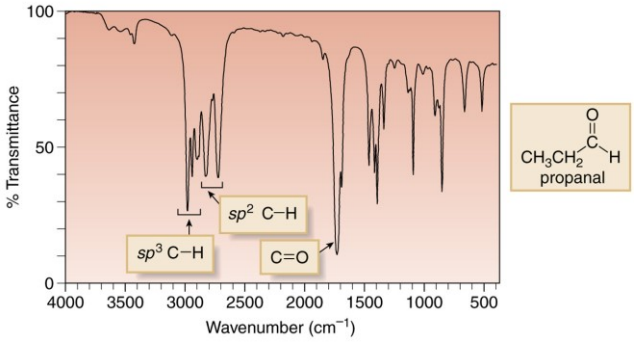
Spectroscopic Properties—IR Spectra

- **Aldehydes and ketones exhibit a strong peak at ~1700 cm^{-1} due to the C=O.**
- **The sp^2 hybridized C–H bond of an aldehyde shows one or two peaks at ~2700 –2830 cm^{-1}.**

Figure 21.3
The IR spectrum of propanal, CH_3CH_2CHO



- A strong C=O occurs at 1739 cm^{-1}.
- The sp^2 C–H of the CHO appears as two peaks at 2813 and 2716 cm^{-1}.

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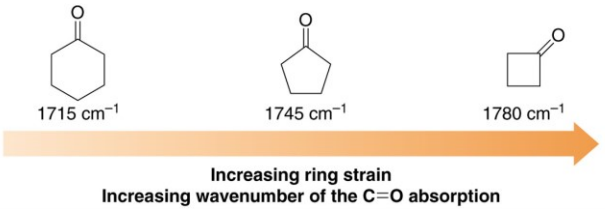
IR—Carbonyl Absorption

- **Most aldehydes have a carbonyl peak around 1730 cm^{-1}, whereas for ketones, it is typically around 1715 cm^{-1}.**
- **Ring size affects the carbonyl absorption in a predictable manner.**

[1] The carbonyl absorption of cyclic ketones shifts to higher wavenumber as the size of the ring decreases and the ring strain increases.



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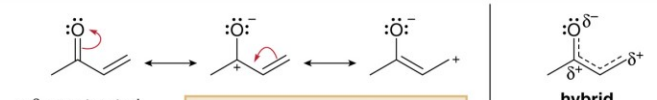
IR—Conjugation Effects

- **Conjugation leads to a somewhat weaker C=O bond, thus shifting the carbonyl absorption to longer wavelengths.**

[2] Conjugation of the carbonyl group with a C=C or a benzene ring shifts the absorption to lower wavenumber by ~30 cm^{-1}.



α,β-unsaturated carbonyl group

Two resonance contributors have **a C–O single bond.**

hybrid

The π bonds are delocalized.

Figure 21.4
The effect of conjugation on the carbonyl absorption in an IR spectrum

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^{1}H and ^{13}C NMR absorptions

- **The *sp*^{2} hybridized C–H proton of an aldehyde is highly deshielded and absorbs far downfield at 9–10 ppm.**
- **Splitting occurs with protons on the α carbon, but the coupling constant is often very small (*J* = 1–3 Hz).**
- **Protons on the α carbon to the carbonyl group absorb at 2–2.5 ppm.**
- **Methyl ketones, for example, give a characteristic singlet at ~2.1 ppm.**
- **In a ^{13}C NMR spectrum, the carbonyl carbon is highly deshielded, appearing in the 190–215 ppm region.**

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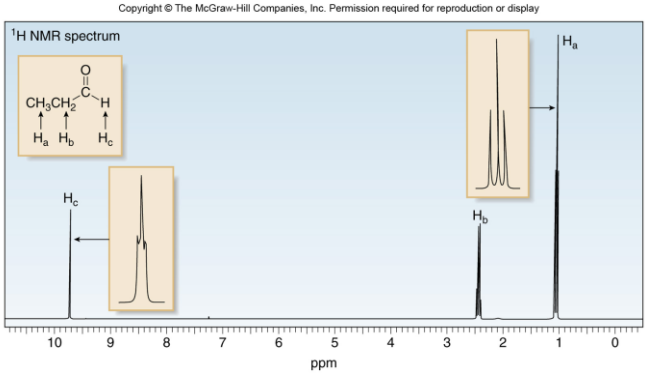
^{1}H NMR of Propanal

Figure 21.5



- There are three signals due to the three different kinds of hydrogens, labeled H_a, H_b, and H_c.
- The deshielded CHO proton occurs downfield at 9.8 ppm.
- The H_c signal is split into a triplet by the adjacent CH_2 group, but the coupling constant is small.

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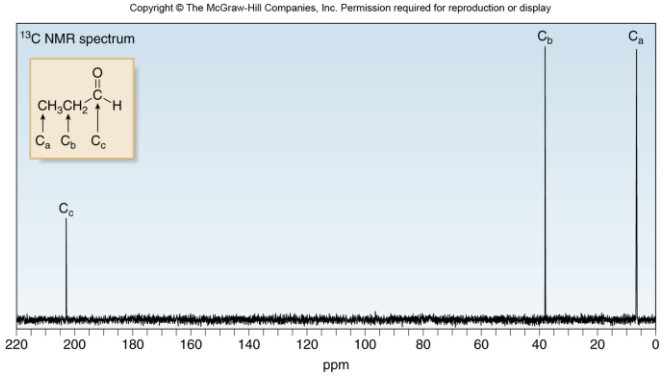
^{13}C NMR absorptions



- There are three signals due to the three different kinds of carbons, labeled C_a, C_b, and C_c.
- The deshielded carbonyl carbon absorbs downfield at 203 ppm.

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Interesting Aldehydes and Ketones—Formaldehyde

formaldehyde

$CH_2=O$

- **Billions of pounds of formaldehyde are produced annually by the oxidation of methanol.**
- **It is sold as a 37% aqueous solution called formalin which is used as a disinfectant, antiseptic, and preservative for biological specimens.**
- **It is a product of incomplete combustion of coal, and is partly responsible for the irritation caused by smoggy air.**

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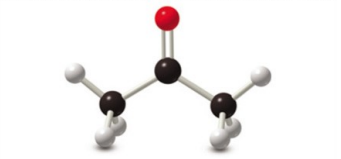
Interesting Aldehydes and Ketones—Acetone



acetone

$(CH_3)_2C=O$

- **Acetone is an industrial solvent.**
- **It is also produced in vivo during breakdown of fatty acids.**
- **Diabetics often have unusually high levels of acetone in their blood streams.**
- **Thus, its characteristic odor can be detected on the breath of diabetic patients when the disease is poorly controlled.**

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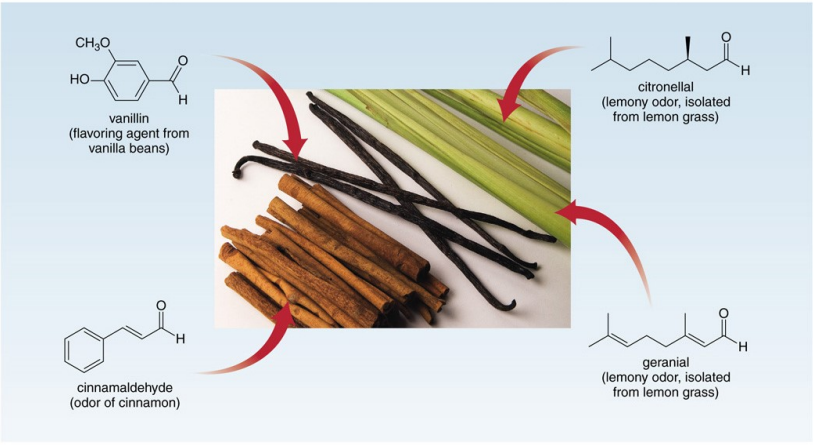
Natural Aldehydes and Ketones with Strong Odors

Figure 21.6



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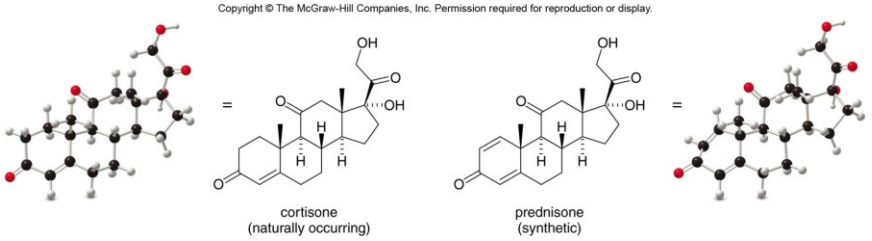
Steroids with Carbonyls

- **Many steroid hormones contain a carbonyl along with other functional groups.**
- **Cortisone and prednisone are two anti-inflammatory steroids with closely related structures.**
- **Cortisone is secreted by the body's adrenal gland, whereas prednisone is the synthetic analogue and is used as an anti-inflammatory for asthma and arthritis.**



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Preparation of Aldehydes

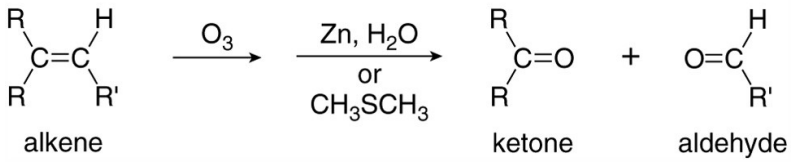
• **By oxidation of 1° alcohols with PCC**	$RCH_2{-}OH$ (1° alcohol) $\xrightarrow{PCC}$ $R{-}C(=O){-}H$	(Section 12.12B)
• **By reduction of esters and acid chlorides**	$R{-}C(=O){-}OR'$ (ester) $\xrightarrow[[2]\ H_2O]{[1]\ DIBAL\text{-}H}$ $R{-}C(=O){-}H$	(Section 20.7A)
	$R{-}C(=O){-}Cl$ (acid chloride) $\xrightarrow[[2]\ H_2O]{[1]\ LiAlH[OC(CH_3)_3]_3}$ $R{-}C(=O){-}H$	
• **By hydroboration–oxidation of an alkyne**	$R{-}C{\equiv}C{-}H$ (alkyne) $\xrightarrow[[2]\ H_2O_2,\ ^-OH]{[1]\ BH_3}$ $RCH_2{-}C(=O){-}H$	(Section 11.10)

Preparation of Ketones

• **By oxidation of 2° alcohols with Cr^{6+} reagents**	$R{-}CH(OH){-}R'$ (2° alcohol) $\xrightarrow[Na_2Cr_2O_7\ or\ K_2Cr_2O_7\ or\ PCC]{CrO_3\ or}$ $R{-}C(=O){-}R'$	(Section 12.12A)
• **By reaction of acid chlorides with organocuprates**	$R{-}C(=O){-}Cl$ (acid chloride) $\xrightarrow[[2]\ H_2O]{[1]\ R'_2CuLi}$ $R{-}C(=O){-}R'$	(Section 20.13)
• **By Friedel–Crafts acylation**	$C_6H_6 + R{-}C(=O){-}Cl$ (acid chloride) $\xrightarrow{AlCl_3}$ $C_6H_5{-}C(=O){-}R$	(Section 18.5)
• **By hydration of an alkyne**	$R{-}C{\equiv}C{-}H$ (alkyne) $\xrightarrow[H_2SO_4\ HgSO_4]{H_2O}$ $R{-}C(=O){-}CH_3$	(Section 11.9)

Oxidative Cleavage of Alkenes

- **Aldehydes and ketones are also both obtained as products of the oxidative cleavage of alkenes.**



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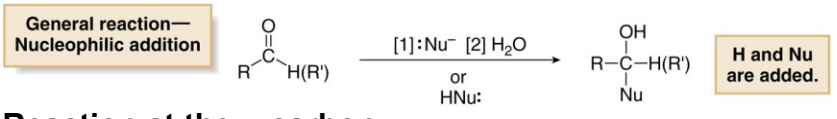
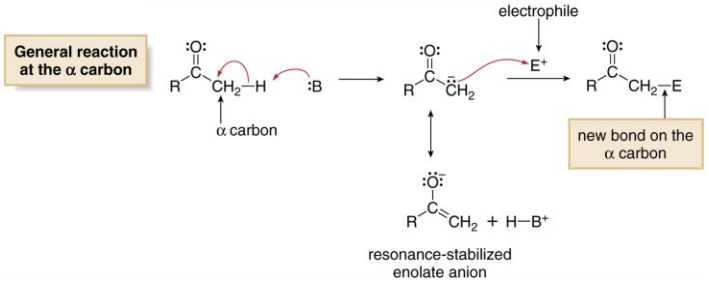
General Reactions of Aldehydes and Ketones

[1] Reaction at the carbonyl carbon—the elements of H and Nu are added to the carbonyl group.



[2] Reaction at the α carbon.



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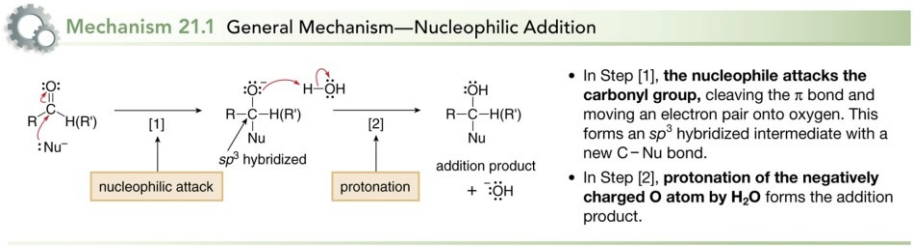
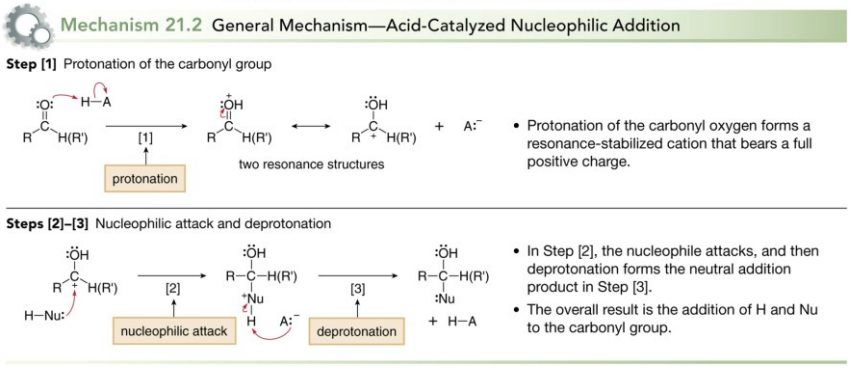
Nucleophilic Addition

- **In this process, nucleophilic attack precedes protonation.**
- **This mechanism occurs with negatively charged or strong neutral nucleophiles.**



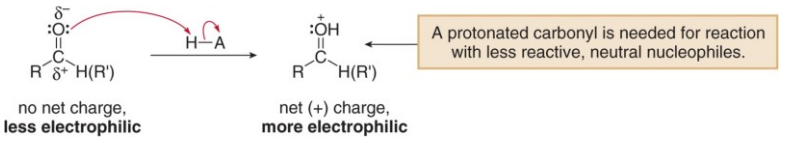
Acid-Catalyzed Nucleophilic Addition



- **In this mechanism, protonation precedes nucleophilic attack as shown above.**
- **With some neutral nucleophiles, nucleophilic addition only occurs if an acid is present to activate the carbonyl by protonation.**

Acid-Catalyzed Nucleophilic Addition

- **The effect of protonation is to convert a neutral carbonyl group to one having a net positive charge.**
- **This protonated carbonyl is much more electrophilic and susceptible to attack by a nucleophile.**



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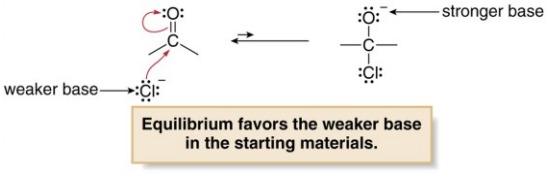
Good Nucleophiles

- **Nucleophilic trends in carbonyl attack are not the same as in straightforward substitution reactions at sp^3 carbon atoms.**
- **Cl^-, Br^-, and I^- are good nucleophiles in substitution reactions at *sp*^{3} hybridized carbons, but they are ineffective nucleophiles in addition.**
- **When these nucleophiles add to the sp^2 carbonyl carbon, they cleave the C–O π bond, forming an alkoxide.**
- **Since X^- is a much weaker base than the alkoxide formed, equilibrium favors the starting materials, not the addition product.**



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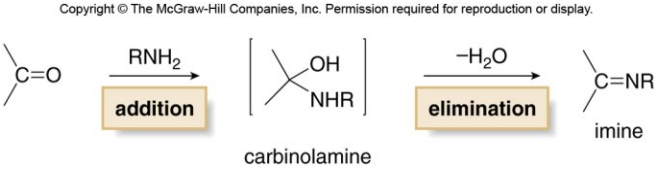
Effective Nucleophiles in Nucleophilic Addition

- **Other nucleophiles add to carbonyl groups to form unstable intermediates which rapidly undergo elimination.**
- **This addition–elimination process, particularly with amine-related nitrogen nucleophiles, replaces a C=O with a C=N.**
- **For example, amines (RNH_2) add to carbonyl groups in the presence of mild acid to form unstable carbinolamines, which readily lose water to form imines.**



- **In cases in which the initial addition adduct is unstable, it is enclosed within brackets, followed by the final product.**

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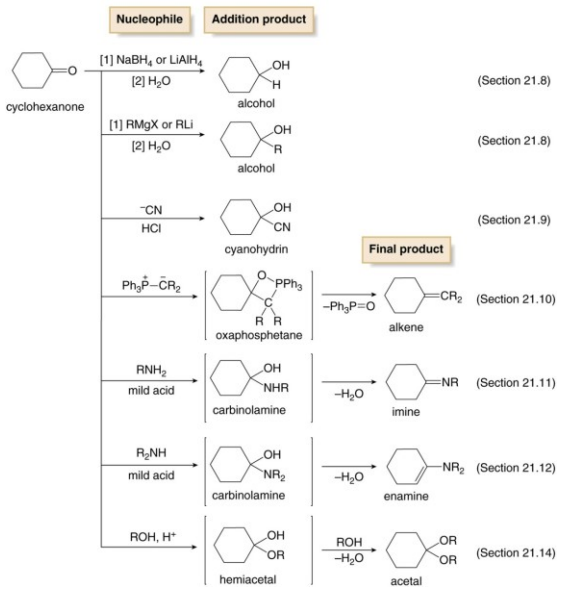
Nucleophilic Addition Reactions

Figure 21.7



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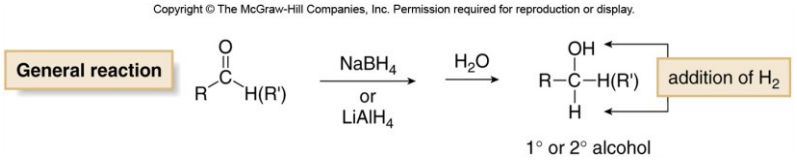
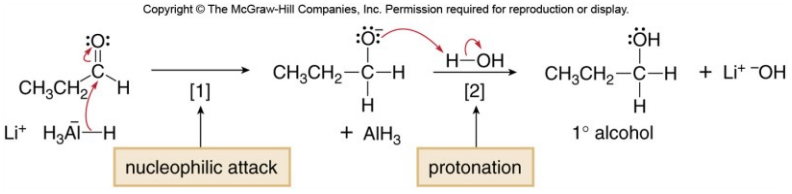
Nucleophilic Addition of Hydride

- **Treatment of an aldehyde or ketone with either $NaBH_4$ or $LiAlH_4$ followed by protonation forms a 1° or 2° alcohol.**



- **Hydride reduction occurs via a two-step mechanism.**



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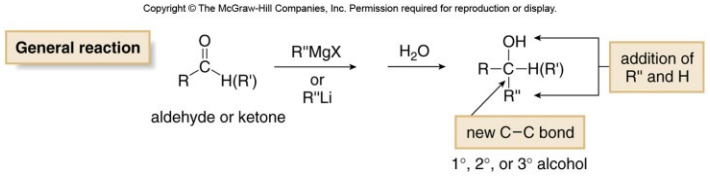
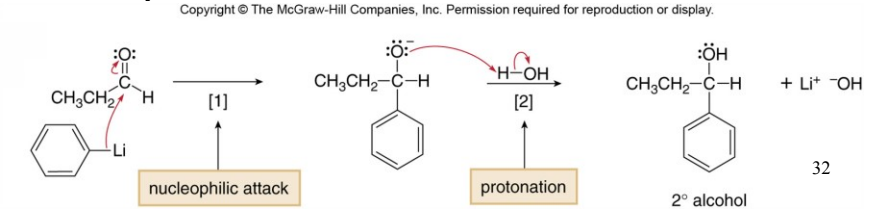
Nucleophilic Addition of R^-

- **Treatment of an aldehyde or ketone with either an organolithium (R″Li) or Grignard reagent (R″MgX) followed by water forms a 1°, 2°, or 3° alcohol containing a new C–C bond.**



- **Nucleophilic addition of the carbanion-like species occurs via a two-step mechanism.**



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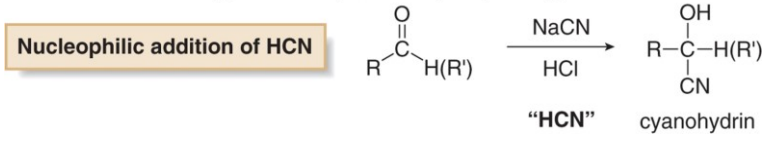
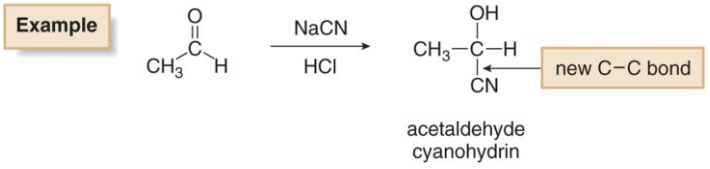
Nucleophilic Addition of $^{-}$CN

- **Treatment of an aldehyde or ketone with NaCN and a strong acid such as HCl adds the elements of HCN across the C–O π bond, forming a cyanohydrin.**
- **This is also a C-C bond forming reaction.**





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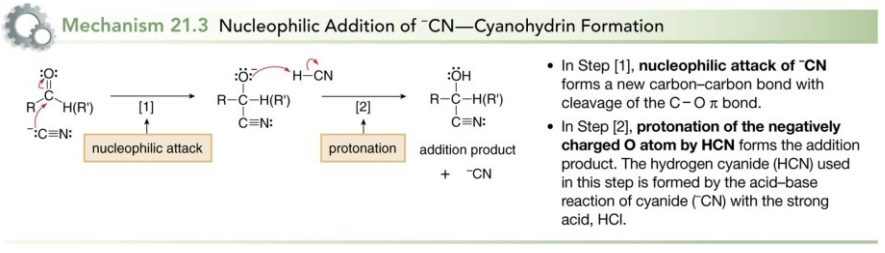
Nucleophilic Addition of $^{-}$CN

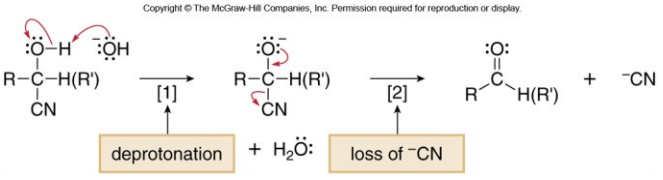
- **The mechanism involves the usual two steps of nucleophilic addition—nucleophilic attack followed by protonation.**
- **This reaction does not occur with HCN alone, it requires $^{-}$CN, which is a strong nucleophile.**



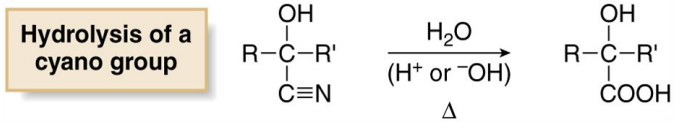
34

Hydrolysis of Cyanohydrins

- **Cyanohydrins can be reconverted to carbonyl compounds by treatment with base.**
- **This process is just the reverse of the addition of HCN: deprotonation followed by elimination of $^{-}$CN.**



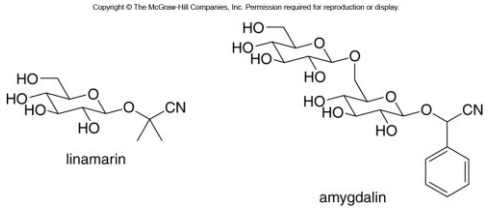
- **The cyano group of a cyanohydrin is readily hydrolyzed to a carboxy group by heating with aqueous acid or base.**



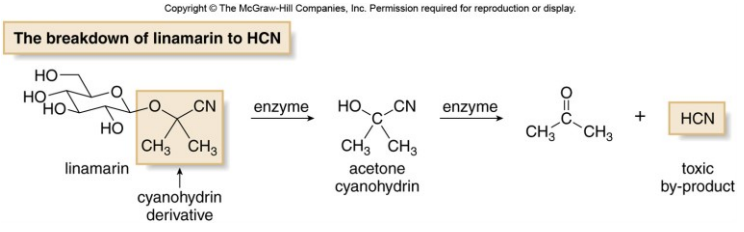
35

Cyanohydrins in Nature

- **Linamarin and amygdalin are two naturally occurring cyanohydrin derivatives.**



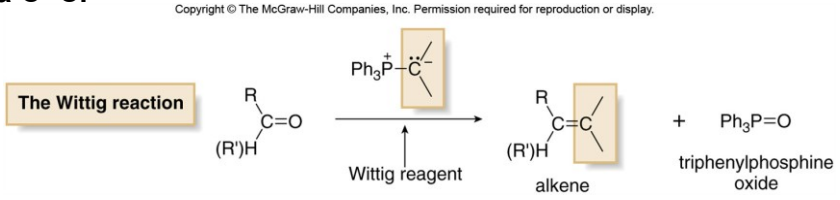
- **Both compounds are toxic because they are metabolized to cyanohydrins, which are hydrolyzed to carbonyl compounds and HCN gas.**

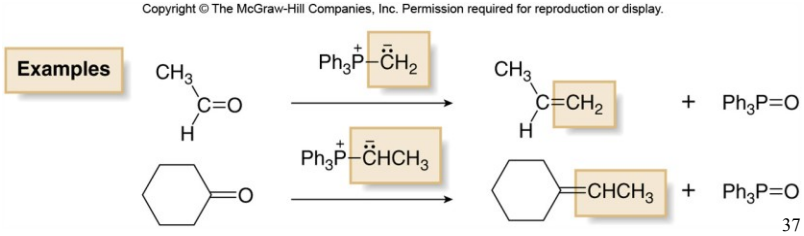


36

Wittig Reaction

- **The Wittig reaction uses a carbon nucleophile (the Wittig reagent) to form alkenes—the carbonyl group is converted to a C=C.**

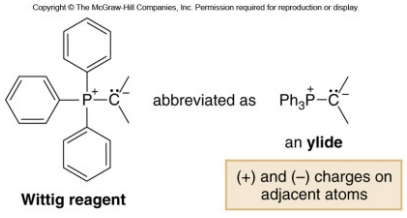




37

Wittig Reagents

- **The Wittig reagent is an organophosphorus reagent.**
- **A typical Wittig reagent has a phosphorus atom bonded to three phenyl groups, plus another alkyl group that bears a negative charge.**



- **A Wittig reagent is an ylide, a species that contains two oppositely charged atoms bonded to each other, with both atoms having octets.**
- **Phosphorus ylides are also called phosphoranes.**

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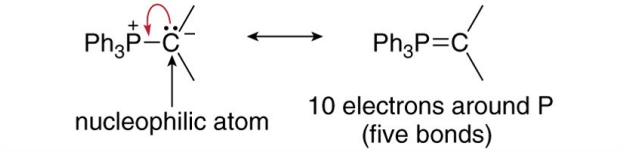
Wittig Reagents

- **Since phosphorus is a second-row element, it can be surrounded by more than eight electrons.**
- **Thus, a second resonance structure can be drawn that places a double bond between carbon and phosphorus.**
- **Regardless of which resonance structure is drawn, a Wittig reagent has no net charge.**
- **However, in one resonance structure, the carbon bears a net negative charge, making it nucleophilic.**

Two resonance structures for the Wittig reagent



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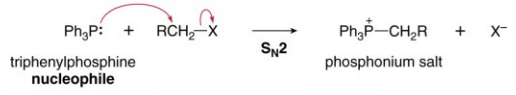
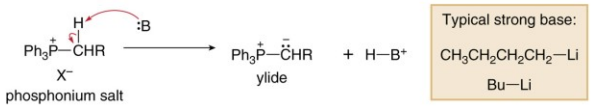
Synthesis of Wittig Reagents

- **Wittig reagents are synthesized by a two-step procedure.**

Step [1] S_N2 reaction of triphenylphosphine with an alkyl halide forms a phosphonium salt.



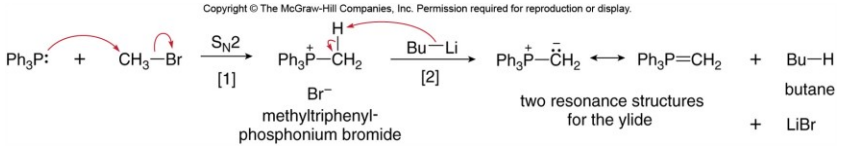
Step [2] Deprotonation of the phosphonium salt with a strong base (:B) forms the ylide.



40

Nucleophilic Addition of R^-

- **To synthesize the Wittig reagent $Ph_3P{=}CH_2$, use the following two steps:**

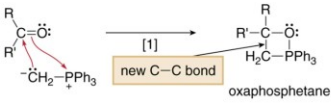


Step [1] Form the phosphonium salt by S_N2 reaction of Ph_3P: and CH_3Br.

Step [2] Form the ylide by removal of a proton using BuLi as a strong base.

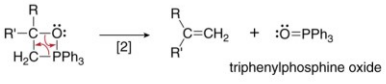
Mechanism 21.4 The Wittig Reaction

Step [1] Nucleophilic addition forms a four-membered ring.



- Step [1] forms two bonds and generates a four-membered ring. The negatively charged carbon atom of the ylide attacks the carbonyl carbon to form a new carbon–carbon σ bond, while the carbonyl O atom attacks the positively charged P atom.
- This process generates an **oxaphosphetane,** a four-membered ring containing a strong P–O bond.

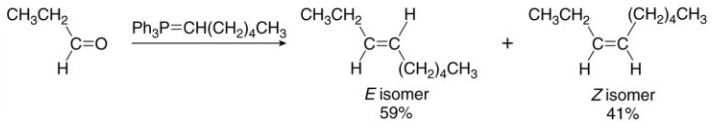
Step [2] Elimination of $Ph_3P{=}O$ forms the alkene.



- In Step [2], **$Ph_3P{=}O$ (triphenylphosphine oxide) is eliminated,** forming two new π bonds. The formation of the very strong P–O double bond provides the driving force for the Wittig reaction.

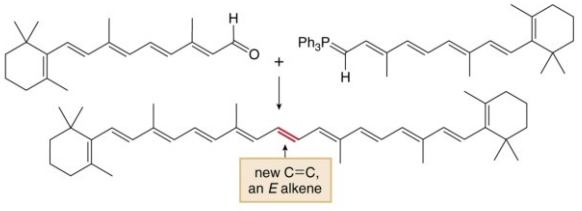
Use of the Wittig Reaction

- **One limitation of the Wittig reaction is that a mixture of stereoisomers sometimes forms.**



- **The Wittig reaction has been used to synthesize many natural products.**

Figure 21.8
A Wittig reaction used to synthesize β-carotene



β-carotene
orange pigment found in carrots
(vitamin A precursor)

- The more stable *E* alkene is the major product in this Wittig reaction.

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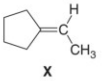
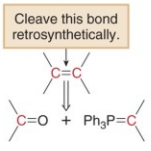
How To Determine the Starting Materials for a Wittig Reaction Using Retrosynthetic Analysis

Example What starting materials are needed to synthesize alkene X by a Wittig reaction?



X

Step [1] Cleave the carbon–carbon double bond into two components.



- Part of the molecule becomes the carbonyl component and the other part becomes the Wittig reagent.

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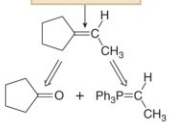
Retrosynthetic Analysis of Wittig Reactions

How To, continued . . .

There are usually two routes to a given alkene using a Wittig reaction:

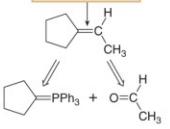
Possibility [1]

Cleave this bond.



Possibility [2]

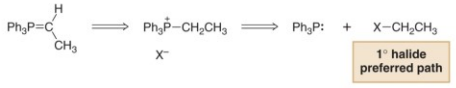
Cleave this bond.



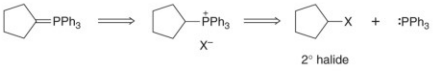
Step [2] Compare the Wittig reagents. The preferred pathway uses a Wittig reagent derived from an unhindered alkyl halide—CH_3X or RCH_2X.

Determine what alkyl halide is needed to prepare each Wittig reagent:

Possibility [1]



Possibility [2]



Because the synthesis of the Wittig reagent begins with an S_N2 reaction, **the preferred pathway begins with an unhindered methyl halide or 1° alkyl halide.** In this example, retrosynthetic analysis of both Wittig reagents indicates that only one of them ($Ph_3P{=}CHCH_3$) can be synthesized from a 1° alkyl halide, making Possibility [1] the preferred pathway.

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The Wittig Reaction Leads to Precise Placement of the Double Bond

- **An advantage of the Wittig reaction over elimination methods used to synthesize alkenes is that the Wittig reaction always gives a single constitutional isomer.**
- **Consider the two methods that can be used to convert cyclohexanone into cycloalkene B.**

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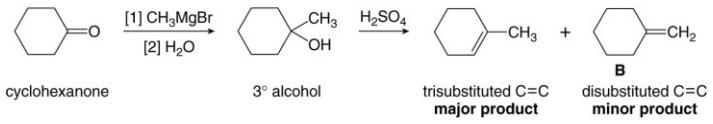
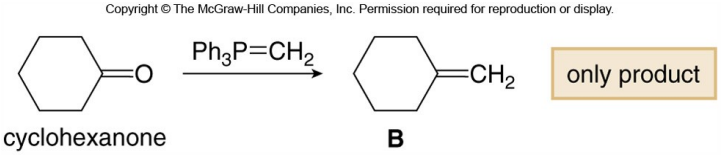
Comparison of Alkene Formation Methods

- **Addition of a Grignard reagent followed by dehydration gives a mixture of products with the desired compound being the minor product.**



- **Using the Wittig reaction to achieve the same synthesis gives only the desired compound.**



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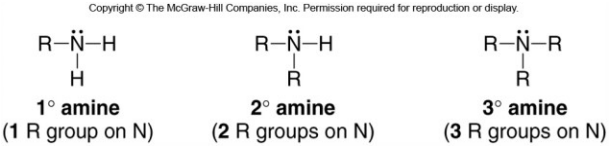
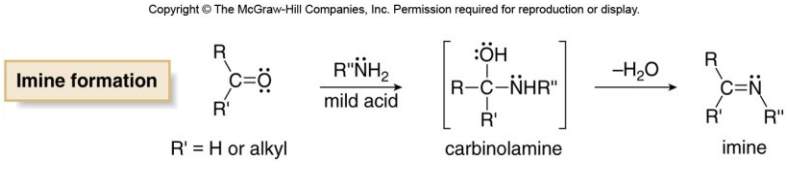
Formation of Imines

- **Amines are classified as 1°, 2°, or 3° by the number of alkyl groups bonded to the nitrogen atom.**



- **Treatment of an aldehyde or a ketone with a 1° amine affords an imine (also called a Schiff base).**



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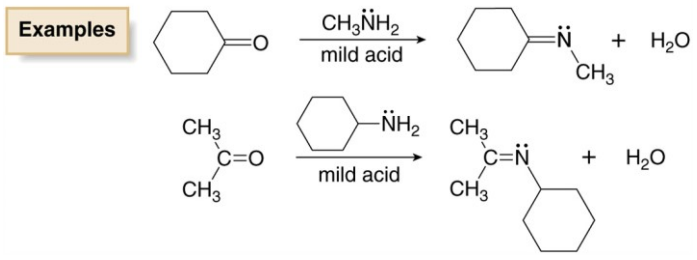
Imine Properties

- **Because the N atom of an imine is surrounded by three groups (two atoms and a lone pair), it is *sp*^{2} hybridized, making the C–N–R bond angle 120°, (not 180°).**
- **Imine formation is fastest when the reaction medium is weakly acidic (pH 4–5).**



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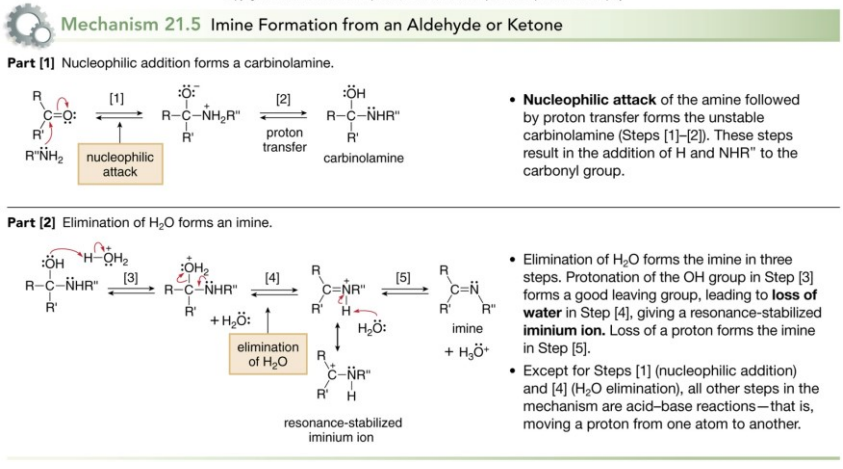

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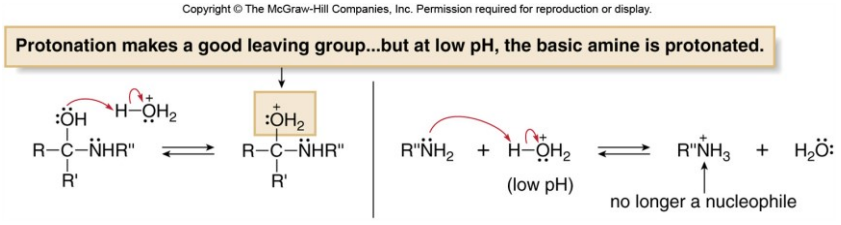
Role of Acidity in Imine Formation

- **In imine formation, mild acid is needed for protonation of the hydroxy group in step 3 to form a good leaving group.**
- **Under strongly acidic conditions, the reaction rate decreases because the amine nucleophile is protonated.**
- **With no free electron pair, it is no longer a nucleophile, and so nucleophilic addition cannot occur.**



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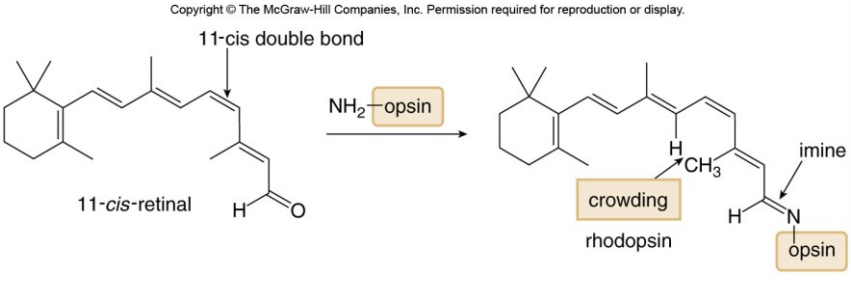
Imines in Nature

- **Many imines play vital roles in biological systems.**
- **A key molecule in the chemistry of vision is the highly conjugated imine rhodopsin, which is synthesized by the rod cells of the eye from 11-*cis*-retinal and a 1° amine in the protein opsin.**



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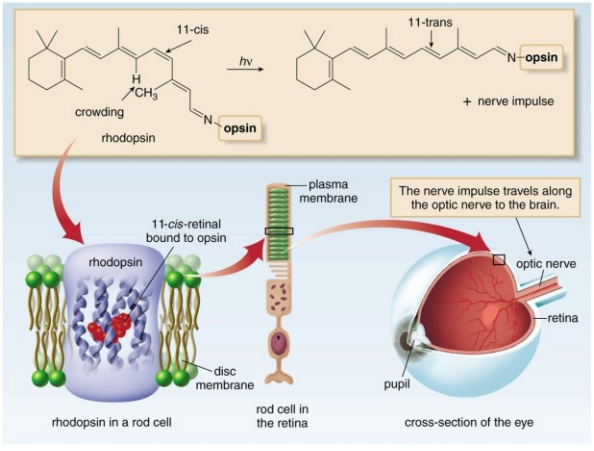
The Key Reaction in the Chemistry of Vision

Figure 21.9



- Rhodopsin is a light-sensitive compound located in the membrane of the rod cells in the retina of the eye. Rhodopsin contains the protein opsin bonded to 11-*cis*-retinal via an imine linkage. When light strikes this molecule, the crowded 11-cis double bond isomerizes to the 11-trans isomer, and a nerve impulse is transmitted to the brain by the optic nerve.

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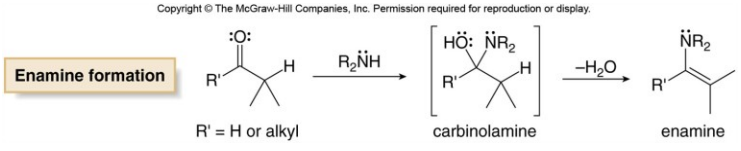
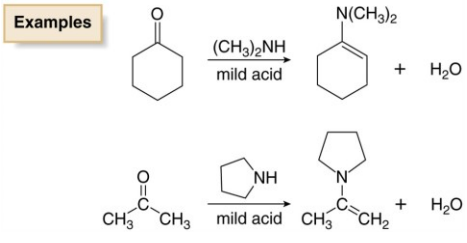
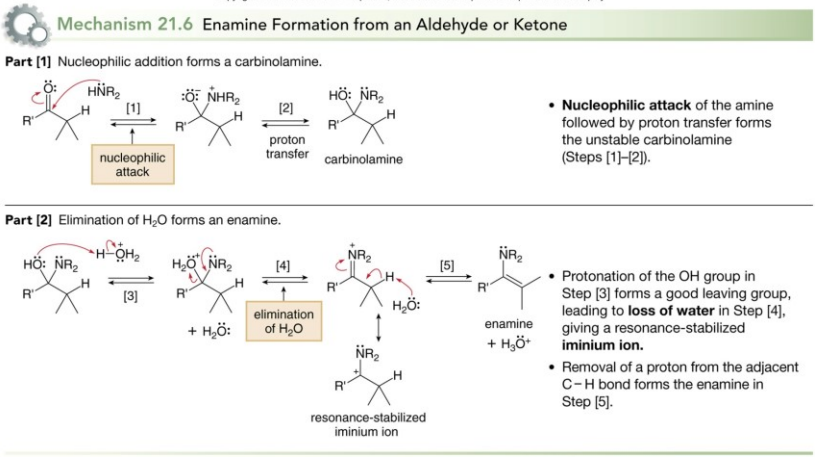
Formation of Enamines

- **A 2° amine reacts with an aldehyde or ketone to give an enamine.**
- **Enamines have a nitrogen atom bonded to a C–C double bond.**



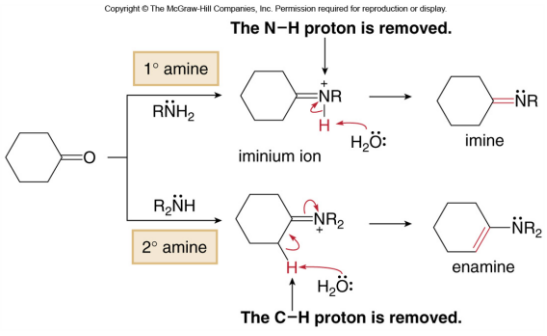


54



Formation of Imines vs. Enamines

Figure 21.10

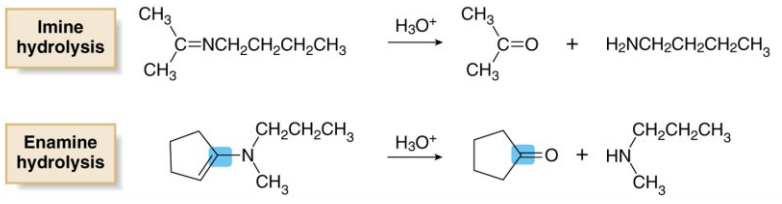


- **With a 1° amine, the intermediate iminium ion still has a proton on the N atom that may be removed to form a C=N.**
- **With a 2° amine, the intermediate iminium ion has no proton on the N atom.**
- **A proton must be removed from an adjacent C–H bond, and this forms a C=C.**

Hydrolysis of Imines and Enamines

- **Because imines and enamines are formed by a reversible set of reactions, both can be converted back to carbonyl compounds by hydrolysis with mild acid.**
- **The mechanism of hydrolysis is the exact reverse of the mechanism written for formation of imines and enamines.**

- Hydrolysis of imines and enamines forms aldehydes and ketones.



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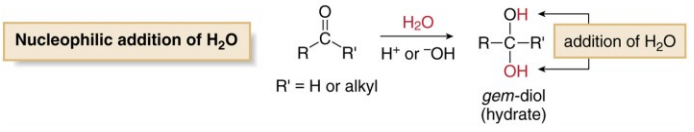
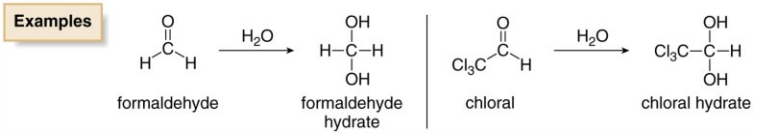
Hydration of Aldehydes and Ketones

- **Treatment of a carbonyl compound with H_2O in the presence of an acid or base catalyst adds the elements of H and OH across the C–O π bond, forming a *gem*-diol or hydrate.**



- ***Gem*-diol product yields are good only when unhindered aldehydes or aldehydes with nearby electron withdrawing groups are used.**



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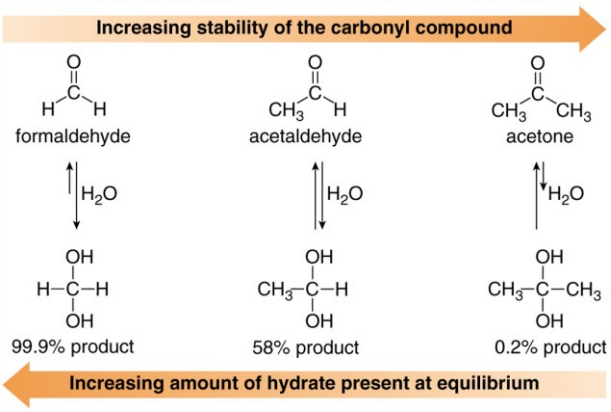
Hydration Level vs. Stability

- **Increasing the number of alkyl groups on the carbonyl carbon decreases the amount of hydrate at equilibrium.**
- **This can be illustrated by comparing the amount of hydrate formed from formaldehyde, acetaldehyde and acetone.**



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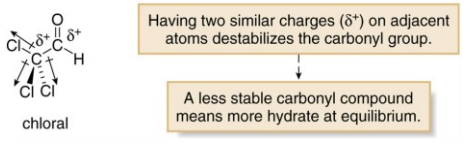
Electronic Factors Affecting Hydrate Stability

- **Electron-donating groups near the carbonyl carbon stabilize the carbonyl group, decreasing the amount of the hydrate at equilibrium.**
- **Electron-withdrawing groups near the carbonyl carbon destabilize the carbonyl group, increasing the amount of hydrate at equilibrium.**
- **This explains why chloral forms a large amount of hydrate at equilibrium.**
- **Three electron-withdrawing Cl atoms result in a partial positive charge on the α carbon of the carbonyl, destabilizing the carbonyl group, and therefore increasing the amount of hydrate at equilibrium.**



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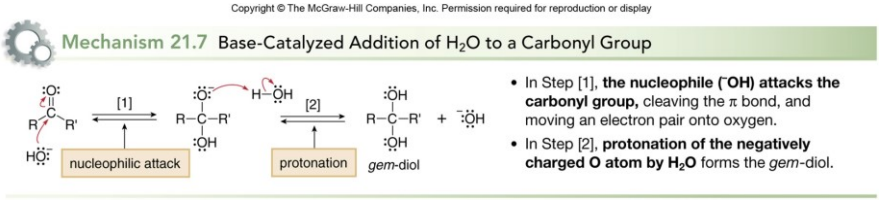
Base Catalyzed Hydration

- **Both acid and base catalyze the addition of H_2O to the carbonyl group.**
- **With base, the nucleophile is ^-OH, and the mechanism follows the usual two steps: nucleophilic attack followed by protonation.**
- **The reaction rate increases under basic conditions because of the higher concentration of ^-OH, a stronger nucleophile.**



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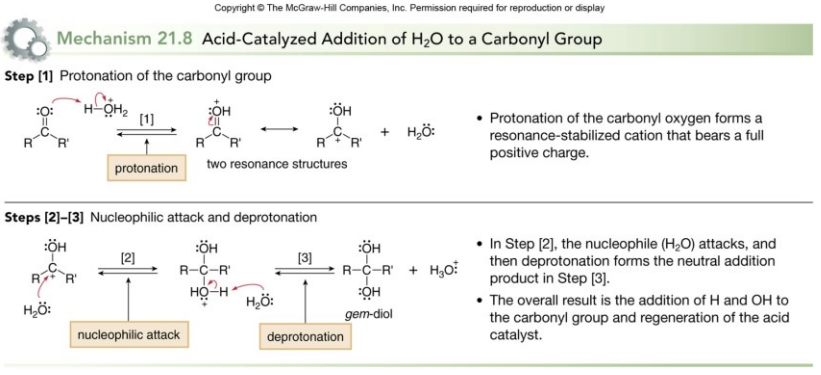
Acid Catalyzed Hydration

- **The reaction rate increases in the presence of acid because the acid protonates the carbonyl group, making it more electrophilic and thus more susceptible to nucleophilic attack.**



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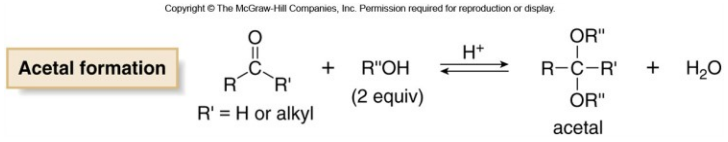
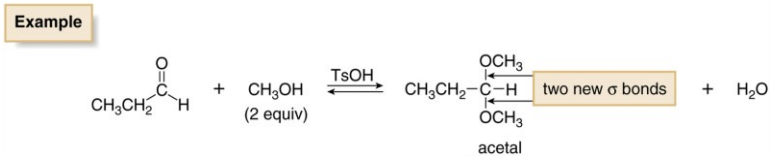
Addition of Alcohols—Acetal Formation

- **Aldehydes and ketones react with two equivalents of alcohol to form acetals.**
- **Acetal formation is catalyzed by acids, such as TsOH.**
- **Note that acetals are not ethers.**





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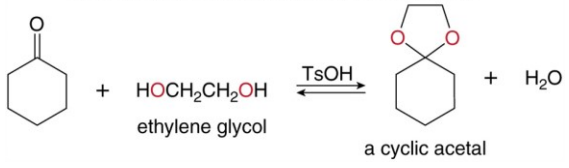
Addition of Alcohols—Acetal Formation

- **When a diol such as ethylene glycol is used in place of two equivalents of ROH, a cyclic acetal is formed.**



- **Like *gem*-diol formation, the synthesis of acetals is reversible, and often, the equilibrium favors the reactants.**
- **In acetal synthesis, since water is formed as a by-product, the equilibrium can be driven to the right by removing H_2O as it is formed using distillation or other techniques.**
- **Driving an equilibrium to the right by removing one of the products is an application of Le Châtelier's principle.**

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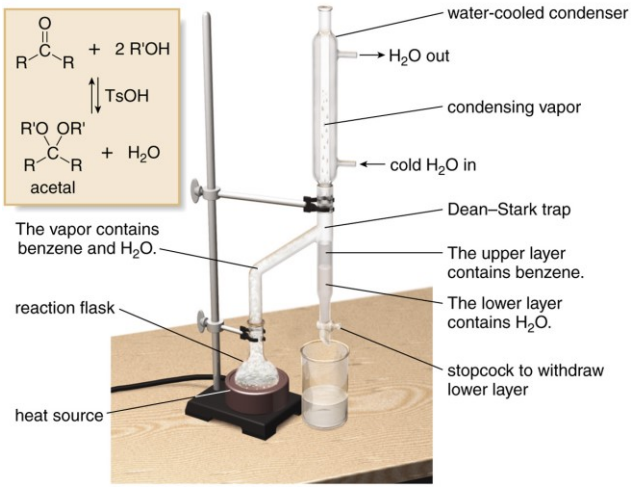
Dean-Stark Trap for Removing Water

Figure 21.11



A Dean–Stark trap is an apparatus used for removing water from a reaction mixture. To use a Dean–Stark trap to convert a carbonyl compound to an acetal:

The carbonyl compound, an alcohol, and an acid are dissolved in benzene. As the mixture is heated, the carbonyl compound is converted to the acetal with water as a by-product. Benzene and water co-distill from the reaction mixture. When the hot vapors reach the cold condenser, they condense, forming a liquid that then collects in the glass tube below. Water, the more dense liquid, forms the lower layer, so that as it collects, it can be drained through the stopcock into a flask. In this way, water can be removed from a reaction mixture, driving the equilibrium.

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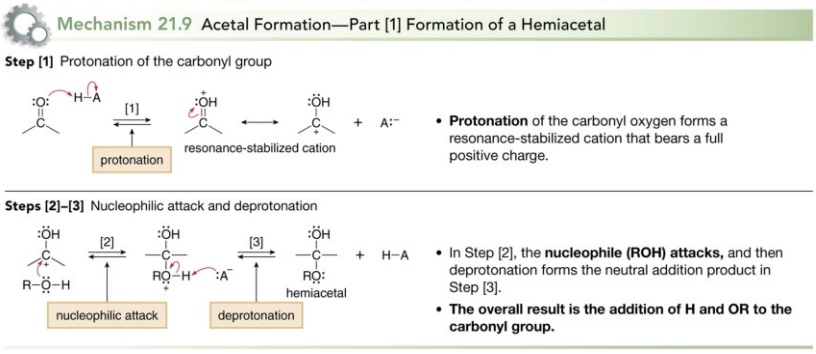
Addition of Alcohols—Hemiacetal Formation

- **The mechanism for acetal formation can be divided into two parts, the first of which is addition of one equivalent of alcohol to form the hemiacetal.**



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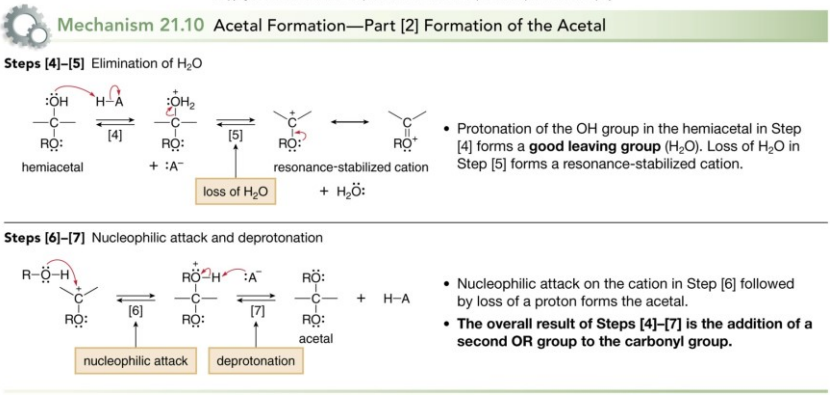
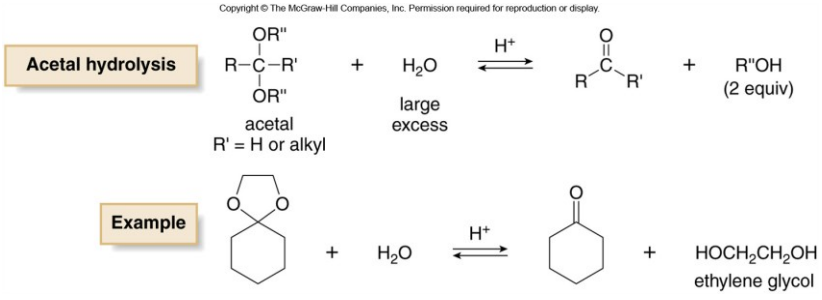
Acetal Formation from a Hemiacetal

- **The second part of the mechanism involves conversion of the hemiacetal into the acetal.**



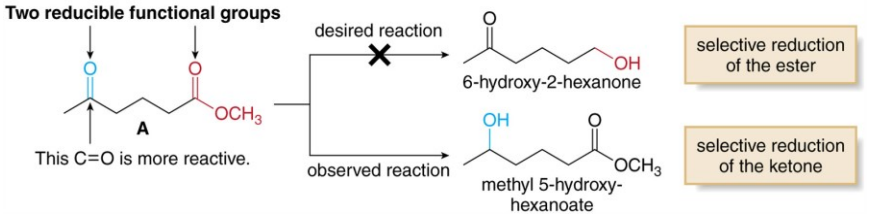
Hydrolysis of Acetals

- **Because conversion of an aldehyde or ketone to an acetal is a reversible reaction, an acetal can be hydrolyzed to an aldehyde or ketone by treatment with aqueous acid.**
- **Since the reaction is also an equilibrium process, it is driven to the right by using a large excess of water for hydrolysis.**



Acetals as Protecting Groups

- **Acetals are valuable protecting groups for aldehydes and ketones.**
- **Suppose we wish to selectively reduce the ester to an alcohol in compound A, leaving the ketone untouched.**
- **Because ketones are more readily reduced, methyl-5-hydroxyhexanoate is formed instead.**
- **To solve this problem, we can use a protecting group to block the more reactive ketone carbonyl.**



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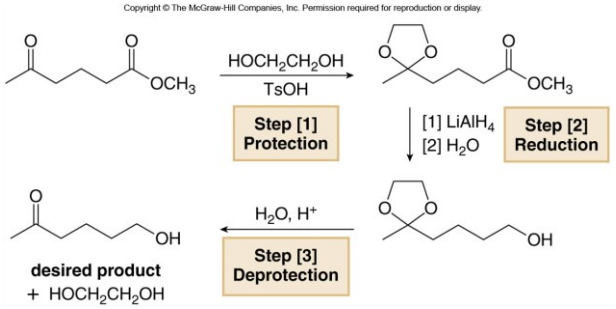
Protection–Deprotection Process

- **The overall process requires three steps.**

[1] Protect the interfering functional group—the ketone carbonyl.

[2] Carry out the desired reaction.

[3] Remove the protecting group.



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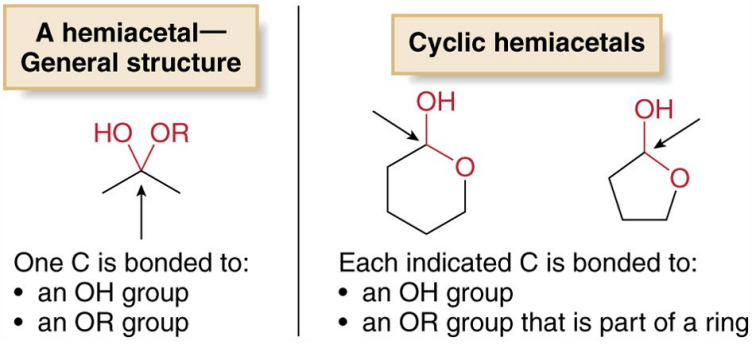
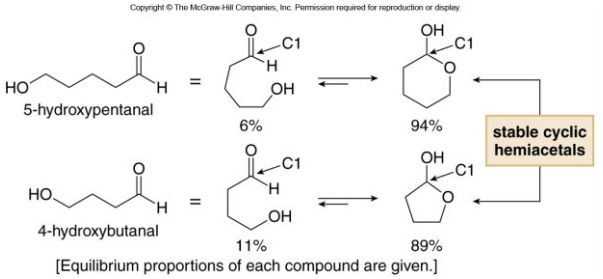
Cyclic Hemiacetals

- **Cyclic hemiacetals containing five- and six-membered rings are stable compounds that are readily isolated.**



Formation of Cyclic Hemiacetals

- **Cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.**

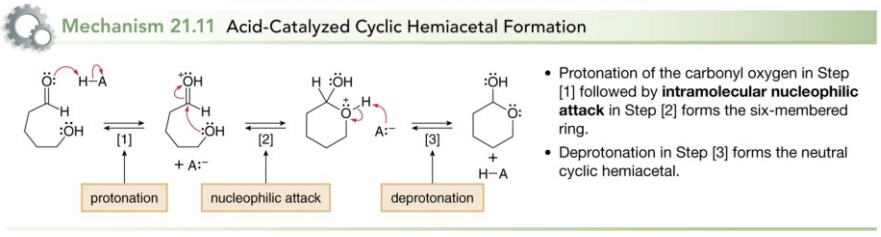


[Equilibrium proportions of each compound are given.]

- **Such intramolecular reactions to form five- and six-membered rings are faster than the corresponding intermolecular reactions.**
- **The two reacting functional groups (OH and C=O), are held in close proximity, increasing the probability of reaction.**

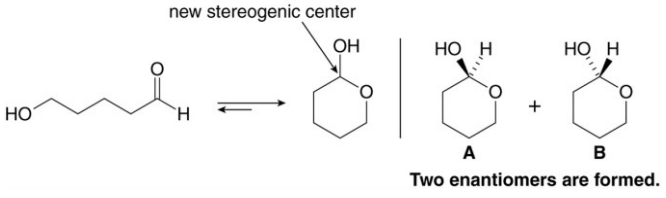
Acid-Catalyzed Hemiacetal Formation

- **Hemiacetal formation is catalyzed by both acid and base.**

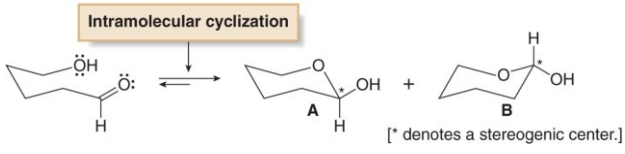


Intramolecular Hemiacetal Formation

- **Intramolecular cyclization of a hydroxy aldehyde forms a hemiacetal with a new stereogenic center, so that an equal amount of two enantiomers results.**

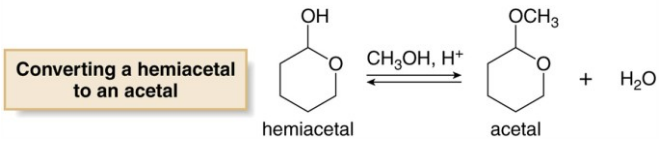


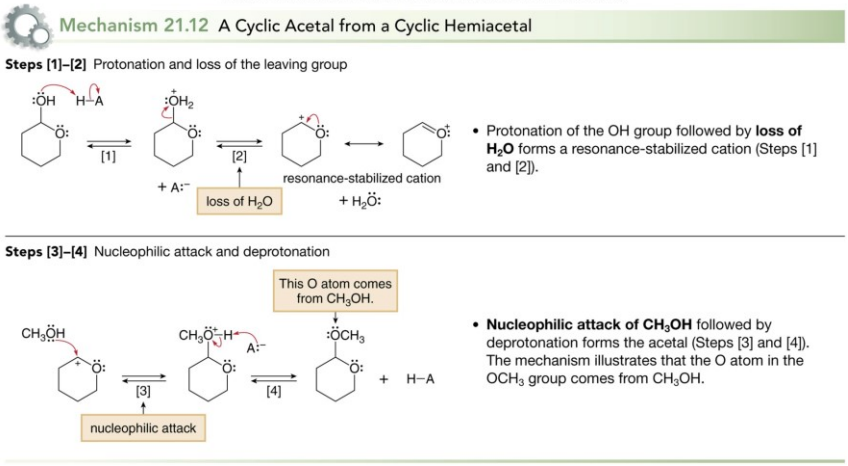
- **Re-drawing the starting material and products in a 3-dimensional representation results in the following:**



Intramolecular Hemiacetal Formation

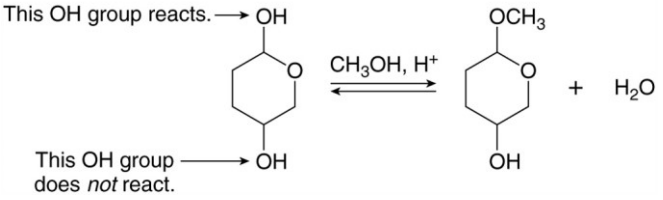
- **Cyclic hemiacetals can be converted to acetals by treatment with an alcohol and acid.**
- **This converts the OH of the hemiacetal into the OR group of an acetal.**





Cyclic Hemiacetals

- **In the conversion of hemiacetals to acetals, the overall result is the replacement of the hemiacetal OH group by an OCH_3 group.**
- **This reaction occurs readily because the carbocation formed in step 2 is stabilized by resonance, making the hemiacetal OH group different from the hydroxy group in other alcohols.**
- **Thus, when a compound with both an alcohol OH and a hemiacetal OH is treated with an alcohol and acid, only the hemiacetal OH reacts to form the acetal.**



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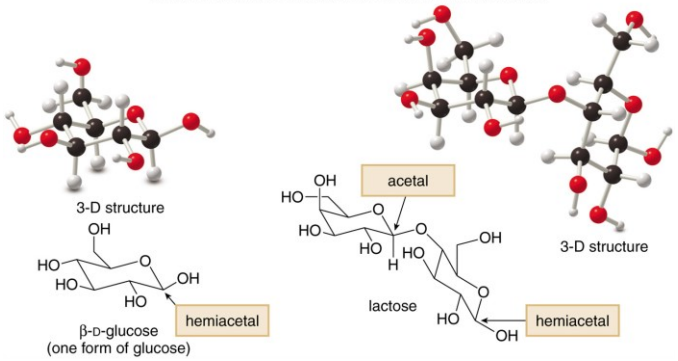
Introduction to Carbohydrates

- **Carbohydrates, commonly referred to as sugars and starches, are polyhydroxy aldehydes and ketones, or compounds that can be hydrolyzed to them.**
- **Many carbohydrates contain cyclic acetals or hemiacetals.**
- **Examples include glucose and lactose.**



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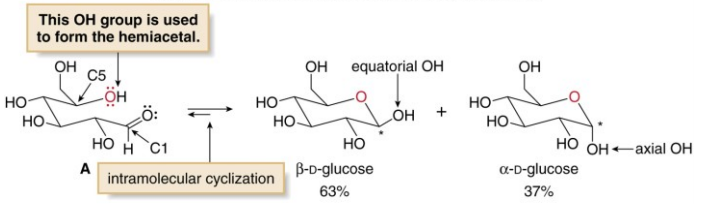
Introduction to Carbohydrates

- **Hemiacetals in sugars are formed by cyclization of hydroxy aldehydes.**
- **The hemiacetal in glucose is formed by cyclization of an acyclic polyhydroxy aldehyde (A), as shown.**



[* denotes a new stereogenic center.]

- **When the OH group on C5 is the nucleophile, cyclization yields a six-membered ring, and this ring size is preferred.**
- **Cyclization forms a new stereogenic center—the new OH group of the hemiacetal can occupy the equatorial or axial position.**

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